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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 October 2016 (13.10.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/164669 A3

(51) International Patent Classification:
*A61K 39/395* (2006.01) *C07K 16/28* (2006.01)
*A61K 51/10* (2006.01) *C07K 16/18* (2006.01)
*C07K 16/46* (2006.01) *C12P 21/08* (2006.01)

(21) International Application Number:
PCT/US2016/026567

(22) International Filing Date:
8 April 2016 (08.04.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/144,901 8 April 2015 (08.04.2015) US

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(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, 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).

**Declarations under Rule 4.17**:

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

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

**Published**:

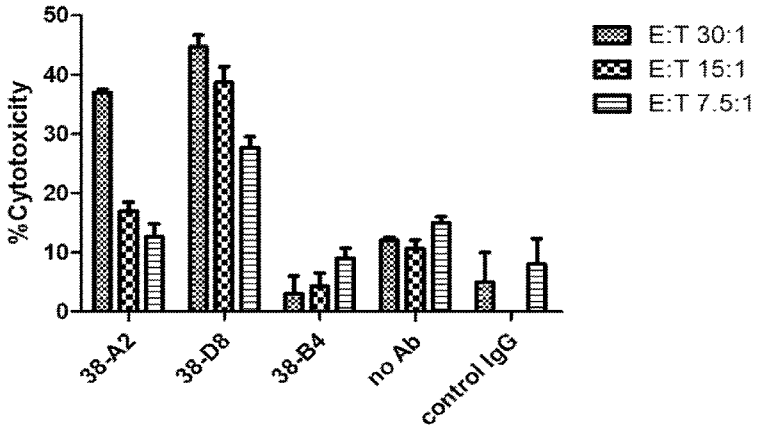
— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
12 January 2017

(54) Title: ANTIBODY THERAPEUTICS THAT BIND CD38

Figure 1




(57) Abstract: There is disclosed compositions and methods relating to or derived from anti-CD38 antibodies. More specifically, there is disclosed fully human antibodies that bind CD38, CD38-antibody binding fragments and derivatives of such antibodies, and CD38-binding polypeptides comprising such fragments. Further still, there is disclosed nucleic acids encoding such antibodies, antibody fragments and derivatives and polypeptides, cells comprising such polynucleotides, methods of making such antibodies, antibody fragments and derivatives and polypeptides, and methods of using such antibodies, antibody fragments and derivatives and polypeptides, including methods of treating a disease.

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/26567

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/395, 51/10; C07K 16/46, 16/28, 16/18; C12P 21/08 (2016.01)
CPC - A61K 39/39533, 51/1027, 51/1087, 51/1075; C07K 16/46
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): A61K 39/395, 51/10; C07K 16/46, 16/28, 16/18, 16/24; C12P 21/08; A61P 35/00; C12N 1/19, 1/21
CPC: A61K 39/39533, 51/1027, 51/1087, 51/1075; C07K 16/46, 16/2815, 2317/55, 2317/732, 2317/21, 2317/73, 2317/565, 2317/76

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, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google Scholar; Pubmed; EBSCO; The Lens PatSeq Finder; NCBI BLAST; Keywords: human, antibod*, immunoglobulin, CD38, heavy chain, light chain, cancer, variable, domain

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 2013/0171154 A1 (TAKEDA PHARMACEUTICAL COMPANY LIMITED.) 04 July, 2013; paragraph [0271] | 1-2, 3/1-2, 4-5, 6/4-5, 7-8, 9/7-8, 12-14 |
| A | US 2003/0059937 A1 (RUBEN, SM et al.) 27 March, 2003; paragraph [0251]; page 134, table 1; SEQ. ID NO. 1156 | 1-2, 3/1-2, 4-5, 6/4-5, 7-8, 9/7-8, 12-14 |
| A | (TIAN, C et al.) Immunodominance of the VH1-46 Antibody Gene Segment in the Primary Repertoire of Human Rotavirus-Specific B Cells is Reduced in the Memory Compartment Through Somatic Mutation of Nondominant Clones. The Journal of Immunology. 01 March, 2008; Vol. 180, No. 5; pages 3279-3288; page 3282, column 2, paragraph 1; Genbank Supplement pages 1-2. | 1-2, 3/1-2, 4-5, 6/4-5, 7-8, 9/7-8, 12-14 |
| A | (KRAMER, RA et al.) The human Antibody Repertoire Specific for Rabies Virus Glycoprotein as Selected from Immune Libraries. European Journal of Immunology. 01 July 2005; Vol. 35, No. 7; pages 2131-2145; abstract; page 2132, column 1, paragraph 2; Genbank Supplement pages 1-2. | 1-2, 3/1-2, 4-5, 6/4-5, 7-8, 9/7-8, 12-14 |

☐ 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 |
|---|---|
| 20 August 2016 (20.08.2016) | 30 SEP 2016 |
| Name and mailing address of the ISA/<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer<br>Shane Thomas<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (January 2015)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/26567

**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.: 10, 11, 15
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:
**-Please See Supplemental Page-***-

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.:
Groups I+, Claims 1-9, 12-14 and SEQ ID NOs: 1 and 2

**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**
Information on patent family members

International application No.
PCT/US16/26567

-***-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 1-9, 12-14 and SEQ ID NOs: 1 and 2 are directed toward an isolated, fully human antibody of an IgG class, fully human antibody Fab fragment, and single chain human antibody comprising a heavy chain variable domain and a light chain variable domain which are connected by a peptide linker; wherein the antibody and/or fragments thereof bind to CD38; and a method of treating cancer therewith.

The antibodies, fragments thereof, and method will be searched to the extent they encompass a heavy chain variable domain encompassing SEQ ID NO: 1 (first exemplary VH) and a light chain variable domain encompassing SEQ ID NO: 2 (first exemplary VL). Applicant is invited to elect additional pair(s) of heavy and light chain variable domains, with specified SEQ ID NO: for each, or specified substitution(s) at specified site(s) of a SEQ ID NO: in order to provide fully specified variable domain sequence(s), to be searched. Additional pair(s) of variable domain 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), 6 (in-part), 7 (in-part), 8 (in-part), 9 (in-part), 12 (in-part), 13 (in-part) and 14 (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: 1 (VH) and SEQ ID NO: 2 (VL). 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 or fragment thereof encompassing a heavy chain variable domain encompassing SEQ ID NO: 3 (first exemplary elected VH), and a light chain variable domain encompassing SEQ ID NO: 4 (first exemplary elected VL).

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

Groups I+ share the technical features including: an isolated, fully human antibody of an IgG class that binds to a CD38 epitope, wherein said antibody comprises a heavy chain variable domain sequence and a light chain variable domain sequence; an anti-CD38 fully human antibody Fab fragment comprising a heavy chain variable domain and a light chain variable domain; an anti-CD38 single chain human antibody comprising a heavy chain variable domain and a light chain variable domain which are connected by a peptide linker; an isolated anti-CD38 human antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain comprising complementarity determining regions (CDRs) as set forth in a heavy chain variable domain amino acid sequence and comprising a light chain variable domain comprising CDRs as set forth in a light chain variable region amino acid sequence; and a method of treating cancer in a human subject in need thereof, comprising administering an effective amount of the anti-CD38 antibody, or antigen-binding fragment thereof to the subject, such that cancer is treated.

However, these shared technical features are previously disclosed by US 2013/0171154 A1 to Takada Pharmaceutical Company Limited (hereinafter 'Takada').

Takada discloses an isolated, fully human antibody (an isolated, fully human antibody; paragraph [0063]) of an IgG class (of an IgG class; paragraph [0063]) that binds to a CD38 epitope (that binds to a CD38 epitope; paragraph [0012]), wherein said antibody comprises a heavy chain variable domain sequence (wherein said antibody comprises a heavy chain variable domain sequence; paragraph [0013]) and a light chain variable domain sequence (a light chain variable domain sequence; paragraph [0013]); an anti-CD38 fully human antibody (an anti-CD38 fully human antibody; paragraph [0063]) Fab fragment (Fab fragment; paragraph [0082]) comprising a heavy chain variable domain (comprising a heavy chain variable domain; paragraphs [0013], [0082]) and a light chain variable domain (and a light chain variable domain; paragraphs [0013], [0082]); an anti-CD38 (anti-CD38; paragraph [0012]) single chain human antibody (single chain human antibody; paragraphs [0063], [0082]) comprising a heavy chain variable domain (comprising a heavy chain variable domain; paragraphs [0013], [0082]) and a light chain variable domain (a light chain variable domain; paragraphs [0013], [0082]) which are connected by a peptide linker (which are connected by a peptide linker; paragraph [0082]); an isolated anti-CD38 human antibody (an isolated anti-CD38 human antibody; paragraphs [0012], [0063]) comprising a heavy chain variable domain (comprising a heavy chain variable domain; paragraph [0013]) comprising complementarity determining regions (CDRs) (comprising complementarity determining regions (CDRs); paragraph [0013]) as set forth in a heavy chain variable domain amino acid sequence (as set forth in a heavy chain variable domain amino acid sequence; paragraphs [0013], [0014]) and comprising a light chain variable domain (comprising a light chain variable domain; paragraph [0013]) comprising CDRs (comprising CDRs; paragraph [0013]) as set forth in a light chain variable region amino acid sequence (as set forth in a light chain variable region amino acid sequence; paragraphs [0013], [0014]); and a method of treating cancer in a human subject in need thereof (and a method of treating cancer in a human subject in need thereof; paragraphs [0011], [0012], [0164]), comprising administering an effective amount of the anti-CD38 antibody to the subject (comprising administering an effective amount of the anti-CD38 antibody to the subject; paragraph [0164]), such that cancer is treated (such that the cancer is treated; paragraphs [0011], [0012], [0164]).

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 Takada reference, unity of invention is lacking.