



(51) International Patent Classification:

C07K 14/00 (2006.01) C07K 16/00 (2006.01)
C07K 14/54 (2006.01) C07K 16/10 (2006.01)

(21) International Application Number:

PCT/US2014/047315

(22) International Filing Date:

18 July 2014 (18.07.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/856,010 18 July 2013 (18.07.2013) 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, LT, 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, 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).

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))
- with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:
25 June 2015



WO 2015/010100 A3

(54) Title: HUMANIZED ANTIBODIES WITH ULTRALONG COMPLEMENTARITY DETERMINING REGIONS

Figure 1

BLW1K2	CTVHC	RIKRVQ	QSPRHYRNSICSRNRCQTRRQYVSPVPCNLTLPQYSSYTYWYEW	IPVWPCZGLLVVSS	(SEQ ID NO : 360)
BLVSD3	CTVHC	RIKRVQ	QSPRHYRNSICSRNRCQTRRQYVSPVPCNLTLPQYSSYTYWYEW	IPVWPCZGLLVVSS	(SEQ ID NO : 361)
BLVSD3	CSYVC	RIKRVQ	QSPRHYRNSICSRNRCQTRRQYVSPVPCNLTLPQYSSYTYWYEW	IPVWPCZGLLVVSS	(SEQ ID NO : 362)
BLVSD11	CTVHC	RIKRVQ	QSPRHYRNSICSRNRCQTRRQYVSPVPCNLTLPQYSSYTYWYEW	IPVWPCZGLLVVSS	(SEQ ID NO : 363)
BF4B9	CTVHC	RIKRVQ	QSPRHYRNSICSRNRCQTRRQYVSPVPCNLTLPQYSSYTYWYEW	IPVWPCZGLLVVSS	(SEQ ID NO : 364)
BF1H1	CTVHC	RIKRVQ	QSPRHYRNSICSRNRCQTRRQYVSPVPCNLTLPQYSSYTYWYEW	IPVWPCZGLLVVSS	(SEQ ID NO : 365)
P18	CTVHC	RIKRVQ	QSPRHYRNSICSRNRCQTRRQYVSPVPCNLTLPQYSSYTYWYEW	IPVWPCZGLLVVSS	(SEQ ID NO : 366)

(57) Abstract: The present disclosure provides humanized antibodies, including antibodies comprising an ultralong CDR3 and uses thereof.

INTERNATIONAL SEARCH REPORT

International application No PCT/US2014/047315

A. CLASSIFICATION OF SUBJECT MATTER INV. C07K14/00 C07K14/54 C07K16/00 C07K16/10 ADD.				
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) C07K				
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) EPO-Internal, BIOSIS, EMBASE, WPI Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	FENG WANG ET AL: "Reshaping Antibody Diversity", CELL, vol. 153, no. 6, 1 June 2013 (2013-06-01), pages 1379-1393, XP055169986, ISSN: 0092-8674, DOI: 10.1016/j.cell.2013.04.049 figures 1-5	1-140, 145-225		
A	----- WO 93/20210 A1 (SCOTGEN LTD [GB]; TAYLOR GERALDINE [GB]; STOTT EDWARD JAMES [GB]) 14 October 1993 (1993-10-14) figure 10; example 20 ----- <div style="text-align: center;">-/--</div>	1-140, 145-225		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.				
* Special categories of cited documents : <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> </tr> </table>			"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
"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			
7 May 2015	13/05/2015			
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Cilensek, Zoran			

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/047315

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2014/110368 A1 (CALIFORNIA INST FOR BIOMEDICAL RES [US]) 17 July 2014 (2014-07-17) paragraphs [[0004]] - [[0006]]; figures 1, 2	1-140, 145-225
X,P	WO 2013/106485 A2 (SCRIPPS RESEARCH INST [US]; BAZIRGAN OMAR A [US]; MAO HONGYUAN HELEN S) 18 July 2013 (2013-07-18) claims 1-188	1-140, 145-225
X,P	WO 2013/106489 A1 (SCRIPPS RESEARCH INST [US]) 18 July 2013 (2013-07-18) examples 1-10	1-140, 145-225
X,P	SMIDER VV: "Cow Antibodies: A New Structural Class of Antibody Using Ultralong CDR3s", 16 October 2013 (2013-10-16), XP055170029, Retrieved from the Internet: URL:http://adc-summit.com/uploads/files/2463_ADC/Vaughn Smider.pdf [retrieved on 2015-02-16] the whole document	1-140, 145-225
A	SURINDER S. SAINI ET AL: "Exceptionally long CDR3H region with multiple cysteine residues in functional bovine IgM antibodies", EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 29, no. 8, 1 August 1999 (1999-08-01) , pages 2420-2426, XP055158026, ISSN: 0014-2980, DOI: 10.1002/(SICI)1521-4141(199908)29:08<2420: :AID-IMMU2420>3.0.CO;2-A the whole document	1-140, 145-225
A	WO 2005/056759 A2 (XENCOR INC [US]; LAZAR GREGORY ALAN [US]; DESJARLAIS JOHN R [US]; HAMM) 23 June 2005 (2005-06-23) figure 1a	1-140, 145-225
T	YONG ZHANG ET AL: "Rational Design of Humanized Dual-Agonist Antibodies", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 137, no. 1, 14 January 2015 (2015-01-14), pages 38-41, XP055170033, ISSN: 0002-7863, DOI: 10.1021/ja510519u the whole document	1-140, 145-225

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/047315

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.:
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 additional sheet

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 an 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.:

1-140, 145-225

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-140, 145-225

A humanized antibody or binding fragment thereof comprising a heavy chain variable region comprising: (a) an amino acid sequence selected from the group consisting of:

- (i) SEQ ID NO: 734 or SEQ ID NO: 735,
 - (ii) SEQ ID NO: 736 or SEQ ID NO: 737,
 - (iii) SEQ ID NO: 738 or SEQ ID NO: 739,
 - (iv) SEQ ID NO: 740 or SEQ ID NO: 741 ,
 - (v) SEQ ID NO: 742 or SEQ ID NO: 743,
 - (vi) SEQ ID NO: 744 or SEQ ID NO: 745,
 - (vii) SEQ ID NO: 746 or SEQ ID NO 747, and
 - (viii) SEQ ID NO: 748 or SEQ ID NO:749; and
- (b) an ultralong CDR3.

Subject-matter related thereto.

2. claim: 141

A library of humanized antibodies or binding fragments thereof comprising an ultralong CDR3 that comprises a non-antibody sequence.

3. claims: 142, 143

A method of generating a library of humanized antibodies or binding fragments thereof comprising an ultralong CDR3 that comprises a cysteine motif, the method comprising:

- a.) combining a human variable region framework (FR) sequence, and a nucleic acid sequence encoding an ultralong CDR3 and a cysteine motif;
- b.) introducing one or more nucleotide changes to the nucleic acid sequence encoding one or more amino acid residues that are positioned between one or more cysteine residues in the cysteine motif for nucleotides encoding different amino acid residues to produce nucleic acids encoding humanized antibodies or binding fragments thereof comprising an ultralong CDR3 and a cysteine motif with one or more nucleotide changes introduced between one or more cysteine residues in the cysteine domain ; and
- c.) expressing the nucleic acids encoding humanized antibodies or binding fragments thereof comprising an ultralong CDR3 and a cysteine motif with one or more nucleotide changes introduced between one or more cysteine residues in the cysteine domain to generate a library of humanized antibodies or binding fragments thereof comprising an ultralong CDR3 and a cysteine motif with one or more amino acid changes introduced between one or more cysteine residues in the cysteine domain.

A library of humanized antibodies or binding fragments thereof comprising an ultralong CDR3 that comprises a

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

cysteine motif, wherein the antibodies or binding fragments comprise one or more substitutions of amino acid residues that are positioned between cysteine residues in the cysteine motif.

4. claim: 144

A method of generating a library of humanized antibodies or binding fragments thereof comprising a bovine ultralong CDR3, the method comprising:

- a.) combining a nucleic acid sequence encoding a human variable region framework (FR) sequence and a nucleic acid encoding a bovine ultralong CDR3, and
- b.) expressing the nucleic acids encoding a human variable region framework (FR) sequence and a nucleic acid encoding a bovine ultralong CDR3 to generate a library of humanized antibodies or binding fragments thereof comprising a bovine ultralong CDR3.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2014/047315

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