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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:

13 August 2020 (13.08.2020)

(54) Title: LEUCOCYTE IMMUNOGLOBULIN-LIKE RECEPTOR 2 NEUTRALIZING ANTIBODIES

(57) Abstract: This invention relates to agents that bind and neutralize the inhibitory activity of human ILT2 proteins having inhibitory activity in NK cells, T cells and/or other immune cells. Such agents can be used for the treatment of cancers or infectious disease.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A61K39/395 A61P35/00
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 A61K A61P

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/065329 A1 (UNIV LELAND STANFORD JUNIOR [US]) 28 April 2016 (2016-04-28)	1-17, 29-43, 45,46, 54,60,61
Y	paragraphs [0251], [0263], [0270], [0083] ----- -/--	47

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 5 March 2020	Date of mailing of the international search report 24/06/2020
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 Bumb, Peter

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EMILIE LESPORT ET AL: "Inhibition of human VÎ39VÎ 2 T-cell antitumoral activity through HLA-G: implications for immunotherapy of cancer", CELLULAR AND MOLECULAR LIFE SCIENCES, BIRKHÄUSER-VERLAG, BA, vol. 68, no. 20, 20 February 2011 (2011-02-20), pages 3385-3399, XP019957638, ISSN: 1420-9071, DOI: 10.1007/S00018-011-0632-7	3,5-17, 29-36, 45,46,62
Y	figure 6	47

X	NICHOLAS L. LI ET AL: "Cis association of leukocyte Ig-like receptor 1 with MHC class I modulates accessibility to antibodies and HCMV UL18 : Molecular immunology", EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 43, no. 4, 1 April 2013 (2013-04-01), pages 1042-1052, XP055452844, Weinheim ISSN: 0014-2980, DOI: 10.1002/eji.201242607	3,5-10, 12-17, 29-36, 45,46
Y	page 1047, left-hand column	47

X	FAVIER BENOIT ET AL: "ILT2/HLA-G interaction impairs NK-cell functions through the inhibition of the late but not the early events of the NK-cell activating synapse.", FASEB JOURNAL : OFFICIAL PUBLICATION OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY MAR 2010, vol. 24, no. 3, March 2010 (2010-03), pages 689-699, XP002798138, ISSN: 1530-6860	3,5-10, 12-17, 29-36, 45,46
Y	page 691, right-hand column figure 1	47

X	BANHAM A H ET AL: "Identification of the CD85 antigen as ILT2, an inhibitory MHC class I receptor of the immunoglobulin superfamily", JOURNAL OF LEUKOCYTE BIOLOGY, FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, US, vol. 65, no. 6, 1 June 1999 (1999-06-01), pages 841-845, XP002546229, ISSN: 0741-5400	3,5-10, 12-17, 29-36, 45,46
Y	page 843, left-hand column	47

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LIN A ET AL: "Aberrant human leucocyte antigen-G expression and its clinical relevance in hepatocellular carcinoma.", JOURNAL OF CELLULAR AND MOLECULAR MEDICINE AUG 2010, vol. 14, no. 8, August 2010 (2010-08), pages 2162-2171, XP002798139, ISSN: 1582-4934	3,5-10, 12-17, 29-36, 45,46,48
Y	figure 5C	47
X	----- GONEN-GROSS T ET AL: "COMPLEXES OF HLA-G PROTEIN ON THE CELL SURFACE ARE IMPORTANT FOR LEUKOCYTE IG-LIKE RECEPTOR-1 FUNCTION", THE JOURNAL OF IMMUNOLOGY,, vol. 171, no. 3, 1 August 2003 (2003-08-01), pages 1343-1351, XP008043177, ISSN: 0022-1767	3,5-10, 12-17, 29-36, 45,46
Y	page 1346, last line - page 1347, line first	47
X	----- VILLA-ÁLVAREZ MÓNICA ET AL: "Ig-like transcript 2 (ILT2) suppresses T cell function in chronic lymphocytic leukemia.", ONCOIMMUNOLOGY 2017, vol. 6, no. 10, 2017, page e1353856, XP002798140, ISSN: 2162-4011	3,5-10, 12-17, 29-36, 45,46
Y	abstract page 2, right-hand column page 10, left-hand column	47
X	----- SILKE HEIDENREICH ET AL: "Impact of the NK Cell Receptor LIR-1 (ILT-2/CD85j/LILRB1) on Cytotoxicity against Multiple Myeloma", CLINICAL & DEVELOPMENTAL IMMUNOLOGY, vol. 171, no. 3, 1 January 2012 (2012-01-01), pages 1343-13, XP055232336, US	3,5-10, 12-17, 29-36, 45,46
Y	ISSN: 1740-2522, DOI: 10.1155/2012/652130 paragraph [02.2]	47
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International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROBERTI MARÍA P ET AL: "Overexpression of CD85j in TNBC patients inhibits Cetuximab-mediated NK-cell ADCC but can be restored with CD85j functional blockade", HIGH-FREQUENCY AND ADAPTIVE-LIKE DYNAMICS OF HUMAN CD1 SELF-REACTIVE T CELLS,, vol. 45, no. 5, 1 May 2015 (2015-05-01), pages 1560-1569, XP002784224, ISSN: 1521-4141, DOI: 10.1002/EJI.201445353	3,5-10, 12-17, 29-36, 45,46
Y	figure 4 page 1567, left-hand column	47
X	FARAH KETROUSSI ET AL: "Lymphocyte Cell-Cycle Inhibition by HLA-G Is Mediated by Phosphatase SHP-2 and Acts on the mTOR Pathway", PLOS ONE, vol. 6, no. 8, 24 August 2011 (2011-08-24), page e22776, XP055465313, DOI: 10.1371/journal.pone.0022776	3,5-10, 12-17, 29-36, 45,46
Y	the whole document figure 1 page 2, left-hand column	47
X	ZHONG MAOHUA ET AL: "Dimerization of soluble HLA-G by IgG-Fc fragment augments ILT2-mediated inhibition of T-cell alloresponse", TRANSPLANTATION, WILLIAMS AND WILKINS, GB, vol. 87, no. 1, 15 January 2009 (2009-01-15), pages 8-15, XP002530629, ISSN: 0041-1337, DOI: 10.1097/TP.0B013E31818B6141	3,5-10, 12-17, 29-36, 45,46
Y	figure 6 page 12, right-hand column page 10, right-hand column	47
X	R. BAHRI ET AL: "Soluble HLA-G Inhibits Cell Cycle Progression in Human Alloreactive T Lymphocytes", THE JOURNAL OF IMMUNOLOGY, vol. 176, no. 3, 19 January 2006 (2006-01-19), pages 1331-1339, XP055178776, ISSN: 0022-1767, DOI: 10.4049/jimmunol.176.3.1331	3,5-10, 12-17, 29-36, 45,46
Y	page 1332, left-hand column figure 3	47
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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>GODAL R ET AL: "Natural Killer Cell Killing of Acute Myelogenous Leukemia and Acute Lymphoblastic Leukemia Blasts by Killer Cell Immunoglobulin-Like Receptor-Negative Natural Killer Cells after NKG2A and LIR-1 Blockade", BIOLOGY OF BLOOD AND MARROW TRANSPLANTATION, KLUGE CARDEN JENNINGS PUBLISHING, CHARLOTTESVILLE, VA, US, vol. 16, no. 5, 1 May 2010 (2010-05-01), pages 612-621, XP027017558, ISSN: 1083-8791 [retrieved on 2010-02-06] page 614, left-hand column page 617</p>	1,3
T	<p>-----</p> <p>AIFEN LIN ET AL: "Human Leukocyte Antigen-G (HLA-G) Expression in Cancers: Roles in Immune Evasion, Metastasis and Target for Therapy", MOLECULAR MEDICINE, vol. 21, no. 1, 1 January 2015 (2015-01-01), page 1, XP055365402, WASHINGTON, DC; US ISSN: 1076-1551, DOI: 10.2119/molmed.2015.00083 the whole document figure 1 page 783, middle column - right-hand column</p>	1,2, 47-49
Y	<p>-----</p> <p>BUKUR JÜRGEN ET AL: "Functional role of human leukocyte antigen-G up-regulation in renal cell carcinoma.", CANCER RESEARCH 15 JUL 2003, vol. 63, no. 14, 15 July 2003 (2003-07-15), pages 4107-4111, XP002798141, ISSN: 0008-5472 page 4110</p>	47
X,P	<p>-----</p> <p>WO 2019/144052 A1 (ADANATE INC [US]) 25 July 2019 (2019-07-25)</p> <p>the whole document</p>	3,5-10, 12-17, 29-36, 45,46
E	<p>-----</p> <p>WO 2020/023268 A1 (AMGEN INC [US]) 30 January 2020 (2020-01-30)</p> <p>the whole document</p> <p>-----</p>	3,5-10, 12-17, 29-36, 45,46

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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.:
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.:

1-21, 34-36(completely); 23-33, 37-48, 54, 57, 60-62(partially)

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: 1-21, 34-36(completely); 23-33, 37-48, 54, 57, 60-62(partially)

Means for neutralizing human ILT2 and thereby enhance T or NK cell cytotoxicity, wherein the means is a monoclonal antibody or fragment thereof, that does not bind or block ILT6.

2. claims: 22(completely); 23-33, 37-48, 54, 57, 60-62(partially)

Antibody binding human ILT2-protein, comprising the six CDRs of one of (a) mAb 2H2B, (b) 48F12 or (c) 3F5, i.e. wherein these block HLA-G and bind domain D1. Note: (lack of) crossreactivity with ILT6 is not shown for these.

3. claims: 49-53, 58, 59(all partially)

Method of treating urothelial carcinoma using neutralizing anti-ILT2 antibody.

4. claims: 49-53, 58, 59(all partially)

Method of treating HNSCC using neutralizing anti-ILT2 antibody.

5. claims: 49-53, 58, 59(all partially)

Method of treating lung cancer or NSCLC using neutralizing anti-ILT2 antibody.

6. claims: 49-53, 58, 59(all partially)

Method of treating RCC using neutralizing anti-ILT2 antibody.

7. claims: 49-53, 58, 59(all partially)

Method of treating ovarian cancer using neutralizing anti-ILT2 antibody.

8. claim: 55

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Means of treating tumor in a human using (a) means for inducing NMK-cell mediated ADCC and (b) means for neutralizing ILT-2 without binding human CD16A.

9. claim: 56(partially)

Method of treating tumor in a human comprising (i) means for binding an epitope in SEQ. 55 (domain D1).

10. claim: 56(partially)

INVENTION 10:

claims (completely):

claims (completely): 56

Method of treating tumor in a human comprising (i) means for binding an epitope in SEQ. 56 (domain D4).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2019/086858

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016065329	A1	28-04-2016	CA 2959821 A1 28-04-2016
			EP 3209769 A1 30-08-2017
			US 2018251558 A1 06-09-2018
			WO 2016065329 A1 28-04-2016

WO 2019144052	A1	25-07-2019	NONE

WO 2020023268	A1	30-01-2020	NONE
