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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 November 2015 (05.11.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/166105 A3

(51) **International Patent Classification**:
C07K 16/28 (2006.01)

(21) **International Application Number**:
PCT/EP2015/059633

(22) **International Filing Date**:
2 May 2015 (02.05.2015)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/987,929 2 May 2014 (02.05.2014) 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).

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**:
30 December 2015

WO 2015/166105 A3

(54) **Title**: ION CHANNEL MODULATORS AND USES THEREOF

(57) **Abstract**: The invention provides antibodies that specifically bind a P2X4 polypeptide and modulate P2X4 channel activity, recombinant P2X4 polypeptides and methods for generating such polypeptides, as well as compositions and methods for generating anti-P2X4 antibodies, and methods of using P2X4 antibodies for the treatment of neuropathic pain and other indications.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/059633

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/286 C07K16/28
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, Sequence Search, 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	M. T. YOUNG ET AL: "Molecular Shape, Architecture, and Size of P2X4 Receptors Determined Using Fluorescence Resonance Energy Transfer and Electron Microscopy", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 283, no. 38, 19 September 2008 (2008-09-19), pages 26241-26251, XP055205467, ISSN: 0021-9258, DOI: 10.1074/jbc.M804458200	1
Y	the whole document	2,5-8, 25-29, 41-51
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[X] Further documents are listed in the continuation of Box C.

[X] 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
12 November 2015	18/11/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Scheffzyk, Irmgard

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/059633

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/48395 A1 (BIOSCEPTRE PTY LTD [AU]; BARDEN JULIAN [AU]; SLATER MICHAEL [AU]) 20 June 2002 (2002-06-20)	1
Y	example 3	2,5-8, 25-29, 41-51

X	TSUDA MAKOTO ET AL: "P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury", NATURE, NATURE PUBLISHING GROUP, UNITED KINGDOM, vol. 424, no. 6950, 14 August 2003 (2003-08-14), pages 778-783, XP002376086, ISSN: 0028-0836, DOI: 10.1038/NATURE01786	1
Y	the whole document	2,5-8, 25-29, 41-51

X	E. TOULME ET AL: "P2X4 receptors in activated C8-B4 cells of cerebellar microglial origin", THE JOURNAL OF GENERAL PHYSIOLOGY, vol. 4, no. 1, 1 April 2010 (2010-04-01), pages 4.19-353, XP055142775, ISSN: 1934-2616, DOI: 10.1006/bbrc.1996.0380	1
Y	the whole document	2,5-8, 25-29, 41-51

X	US 2005/074819 A1 (INOUE KAZUHIDE [JP] ET AL) 7 April 2005 (2005-04-07) [0017]; the whole document	1,3-6, 25-27, 41-43

X	US 6 242 216 B1 (LYNCH KEVIN J [US] ET AL) 5 June 2001 (2001-06-05) the whole document	1,2,5-8, 25-29, 41-51

A	GARCIA-GUZMAN M ET AL: "CHARACTERIZATION OF RECOMBINANT HUMAN P2X4 RECEPTOR REVEALS PHARMACOLOGICAL DIFFERENCES TO THE RAT HOMOLOGUE", MOLECULAR PHARMACOLOGY, AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, US, vol. 51, 1 January 1997 (1997-01-01), pages 109-118, XP002059398, ISSN: 0026-895X the whole document	1,2,5-8, 25-29, 41-51

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/059633

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/287467 A1 (TAMURA GEN [JP] ET AL) 20 November 2008 (2008-11-20) the whole document	1,3-6, 25-27, 41-51
A	REBECCA J GUM ET AL: "P2X receptor antagonists for pain management: examination of binding and physicochemical properties", PURINERGIC SIGNALLING, KLUWER ACADEMIC PUBLISHERS, DO, vol. 8, no. 1, 16 November 2011 (2011-11-16), pages 41-56, XP035006784, ISSN: 1573-9546, DOI: 10.1007/S11302-011-9272-5 the whole document	1-22, 25-29, 41-51
X	MARIA VALENTE ET AL: "Expression, purification, electron microscopy, N-glycosylation mutagenesis and molecular modeling of human P2X4 andP2XA", BIOCHIMICA ET BIOPHYSICA ACTA (BBA) - BIOMEMBRANES, ELSEVIER, AMSTERDAM, NL, vol. 1808, no. 12, 19 August 2011 (2011-08-19), pages 2859-2866, XP028316556, ISSN: 0005-2736, DOI: 10.1016/J.BBAMEM.2011.08.025 [retrieved on 2011-08-26] the whole document	1-22, 25-29, 41-51

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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.:

2-4, 9-22(completely); 1, 5-8, 25-29, 41-51(partially)

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.:

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: 2(completely); 1, 5-8, 25-29, 41-51(partially)

   Antibody specifically binding human P2X4 wherein the antibody is a P2X4 potentiator

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2. claims: 3, 4(completely); 1, 5-8, 25-29, 41-51(partially)

   Antibody specifically binding P2X4 wherein the antibody is a P2X4 antagonist

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3. claims: 9-16(completely); 1, 5-8, 25-29, 41-51(partially)

   Antibody specifically binding human P2X4 wherein the antibody is characterised by the presence of the heavy chain variable region CDR1,CDR2,CDR3 as recited in claims 9-16

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4. claims: 17-22(completely); 1, 5-8, 25-29, 45-51(partially)

   Antibody specifically binding human P2X4 wherein he antibody is characterised by th presence of the light chain variable region CDR1,CDR2,CDR3 as defined in claims 17-22

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5. claims: 23, 24(completely); 1, 5-8, 25-29, 45-51(partially)

   Antibody specifically binding P2X4 wherein the antibody comprises the heavy chain variable region sequences as recited in claims 23 and 24

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6. claims: 30-36(completely); 1, 5-8, 25-29, 41-51(partially)

   Antibody specifically binding to P2X4 wherein the antibody comprises the heavy chain variable region sequences as recited in claims 30-36

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7. claims: 37-40(completely); 1, 5-8, 25-29, 41-51(partially)

   Antibody specifically binding to P2X4 wherein the antibody comprises the light chain variable regions as defined in claims 37-40

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8. claims: 52-59

   Method for large scale production of recombinant P2X4 polypeptide

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/059633

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0248395 A1	20-06-2002	AT 428803 T	15-05-2009
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