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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 December 2012 (13.12.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/170438 A3

(51) International Patent Classification:
C07K 16/28 (2006.01) *A61P 3/10* (2006.01)
A61P 3/00 (2006.01) *C07K 14/71* (2006.01)
A61P 3/04 (2006.01)

(21) International Application Number:
PCT/US2012/040941

(22) International Filing Date:
5 June 2012 (05.06.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/493,933	6 June 2011 (06.06.2011)	US
61/501,133	24 June 2011 (24.06.2011)	US
61/537,998	22 September 2011 (22.09.2011)	US
13/487,061	1 June 2012 (01.06.2012)	US

(71) Applicant *(for all designated States except US)*: **AMGEN INC.** [US/US]; One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LI, Yang** [US/US]; 1142 Cuesta Drive, Mountain View, CA 94040 (US). **STEVENS, Jennitte** [US/US]; 9820 West Olympic Boulevard, Beverly Hills, CA 90212 (US). **KING, Chadwick, Terence** [CA/CA]; 1325 Moody Avenue, North Vancouver, British Columbia V7L 3T5 (CA). **FOLTZ, Ian** [CA/CA]; 2108 Knightswood Place, Burnaby, British Columbia V5A 4B9 (CA). **KANNAN, Gunasekaran** [US/US]; 1168 Westlake Boulevard, Unit B, Westlake Village, CA 91361 (US). **YIE, Junming** [US/US]; 2623 Capella Way, Thousand Oaks, CA 91362 (US). **HU, Shaw-Fen, Sylvia** [US/US]; 986 Lynnmere Drive, Thousand Oaks, CA 91360 (US).

(74) Agent: **BERNSTEIN, Scott**; AMGEN INC., One Amgen Center Drive, Patent Operations/MS 28-2-C, Thousand Oaks, CA 91320-1799 (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, 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, IS, JP, KE, KG, KM, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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, 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))*

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:
11 April 2013

(54) Title: HUMAN ANTIGEN BINDING PROTEINS THAT BIND TO A COMPLEX COMPRISING β-KLOTHO AND AN FGF RECEPTOR

(57) Abstract: The present invention provides compositions and methods relating to or derived from antigen binding proteins capable of inducing B-Klotho, and or FGF21-like mediated signaling. In embodiments, the antigen binding proteins specifically bind to a complex comprising β-Klotho and at least one of (i) FGFR1c, (ii) FGFR2c and (iii) FGFR3c. In some embodiments the antigen binding proteins induce FGF21-like signaling. In some embodiments, an antigen binding protein is a fully human, humanized, or chimeric antibodies, binding fragments and derivatives of such antibodies, and polypeptides that specifically bind to a complex comprising β-Klotho and at least one of (i) FGFR1c, (ii) FGFR2c and (iii) FGFR3c. Other embodiments provide nucleic acids encoding such antigen binding proteins, and fragments and derivatives thereof, and polypeptides, cells comprising such polynucleotides, methods of making such antigen binding proteins, and fragments and derivatives thereof, and polypeptides, and methods of using such antigen binding proteins, fragments and derivatives thereof, and polypeptides, including methods of treating or diagnosing subjects suffering from type 2 diabetes, obesity, NASH, metabolic syndrome and related disorders or conditions.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/040941

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A61P3/00 A61P3/04 A61P3/10 C07K14/71
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, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/066211 A2 (FIVE PRIME THERAPEUTICS INC [US]; ZENG CHANGJIANG [US]; HESTIR KEVIN []) 21 July 2005 (2005-07-21) page 16, last paragraph; claims 1-5, 195; sequences 9, 10	1,2,11, 12,14, 15,21-23
E	WO 2012/158704 A1 (GENENTECH INC [US]; HOFFMANN LA ROCHE [CH]; SONODA JUNICHIRO [US]; WU) 22 November 2012 (2012-11-22) the whole document	1,2,11, 12,14, 15,21-23

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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
14 January 2013	01/02/2013

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	Lechner, Oskar

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Form PCT/ISA/210 (second sheet) (April 2005)

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 2008/261236 A1 (KURO-O MAKOTO [US] ET AL) 23 October 2008 (2008-10-23) paragraph [0010] paragraph [0013] paragraph [0003] paragraph [0017] paragraph [0021]; claim 6	1,2,11, 12,14, 15,21-23
X	WO 2010/139741 A1 (NOVARTIS AG [CH]; CHAU DINH LE MARY [US]; GROMADA JESPER [US]; WU ZHID) 9 December 2010 (2010-12-09) claims 1-4	1,2,11, 12,14, 15,21-23
X,P	WO 2011/071783 A1 (AMGEN INC [US]; HU SHAW-FEN SYLVIA [US]; FOLTZ IAN [CA]; KING CHADWICK) 16 June 2011 (2011-06-16) the whole document claims 1-26	1,2,11, 12,14, 15,21-23
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X,P	WO 2012/059873 A2 (COVX) 10 May 2012 (2012-05-10) claims 1, 36-38	1,2,11, 12,14, 15,21-23
A	BERNHARD M KAESS ET AL: "FGF21 signalling pathway and metabolic traits - genetic association analysis", EUROPEAN JOURNAL OF HUMAN GENETICS, vol. 18, no. 12, 1 December 2010 (2010-12-01), pages 1344-1348, XP055038861, ISSN: 1018-4813, DOI: 10.1038/ejhg.2010.130 abstract	1,2,11, 12,14, 15,21-23
A	XU JING ET AL: "Fibroblast Growth Factor 21 Reverses Hepatic Steatosis, Increases Energy Expenditure, and Improves Insulin Sensitivity in Diet-Induced Obese Mice", DIABETES, AMERICAN DIABETES ASSOCIATION, US, vol. 58, no. 1, 1 January 2009 (2009-01-01), pages 250-259, XP009144078, ISSN: 0012-1797, DOI: 10.2337/DB08-0392 abstract	1,2,11, 12,14, 15,21-23

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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	XINLE WU: "Role of FGF19 induced FGFR4 activation in the regulation of glucose homeostasis", AGING, vol. 1, no. 12, 1 December 2009 (2009-12-01), pages 1023-1027, XP055049191, abstract	1,2,11, 12,14, 15,21-23
T	XUNSHAN DING ET AL: "[beta]Klotho Is Required for Fibroblast Growth Factor 21 Effects on Growth and Metabolism", CELL METABOLISM, vol. 16, no. 3, 1 September 2012 (2012-09-01), pages 387-393, XP055038849, ISSN: 1550-4131, DOI: 10.1016/j.cmet.2012.08.002 abstract	1,2
A	MASASHI SUZUKI ET AL: "betaKlotho is required for fibroblast growth factor (FGF) 21 signaling through FGF receptor (FGFR) 1c and FGFR3c", MOLECULAR ENDOCRINOLOGY, THE ENDOCRINE SOCIETY, US, vol. 22, no. 4, 1 April 2008 (2008-04-01), pages 1006-1014, XP002624718, ISSN: 0888-8809, DOI: 10.1210/ME.2007-0313 [retrieved on 2008-01-10] abstract	1,2,11, 12,14, 15,21-23
T	WU AI-LUEN ET AL: "Amelioration of type 2 diabetes by antibody-mediated activation of fibroblast growth factor receptor 1", SCIENCE / SCIENCE TRANSLATIONAL MEDICINE, WASHINGTON, DC : AAAS, US, vol. 3, no. 113 (112-114), 14 December 2011 (2011-12-14), page 66, XP008153178, ISSN: 1946-6242 the whole document	1,2,11, 12,14, 15,21-23
T	FOLTZ IAN N ET AL: "Treating Diabetes and Obesity with an FGF21-Mimetic Antibody Activating the [beta] Klotho/FGFR1c Receptor Complex", SCIENCE / SCIENCE TRANSLATIONAL MEDICINE, WASHINGTON, DC : AAAS, US, vol. 4, no. 162 (162ra153), 28 November 2012 (2012-11-28), pages 1-10, XP009166047, ISSN: 1946-6242, DOI: 10.1126/SCITRANSLMED.3004690 the whole document	1,2,11, 12,14, 15,21,22

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INTERNATIONAL SEARCH REPORT

International application No.
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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.: 3-10, 13, 16-20(completely); 11, 12, 14, 15, 21-23(partially)
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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:

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.:

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

Continuation of Box II.2

Claims Nos.: 3-10, 13, 16-20(completely); 11, 12, 14, 15, 21-23(partially)

This search report takes into account those claims for which no Sequence Listing is necessary (PCT Rule 13ter, PCT Rule 5.2 and Art. 17(2)(a)PCT). The specific sequences of claim(s) have, according to PCT Rule 13ter.1 .d, not been searched since the Sequence Listing as present in the description does not comply with WIPO Standard ST 25 prescribed in the administrative instructions under Rule 5.2. The Sequence Listing has been furnished neither in paper form nor in machine readable form as provided for in the same instructions and the applicant has not remedied the disclosed deficiencies within the time limit fixed in the invitation pursuant to PCT Rule 13ter.1.a. Moreover, it is also noted that the sequence listing as originally filed covers a total of 330 sequences, whereas already in the claims reference is made to e.g. SeqID 1827.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/040941

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