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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:
8 March 2012

(54) Title: HUMAN FGF RECEPTOR AND β-KLOTHO BINDING PROTEINS

(57) Abstract: The present invention provides compositions and methods relating to or derived from antigen binding proteins and antigen binding protein-FGF21 fusions that specifically bind to β-Klotho, or β-Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In some embodiments the antigen binding proteins and antigen binding protein-FGF21 fusions induce FGF21-like signaling. In some embodiments, an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding component is a fully human, humanized, or chimeric antibody, binding fragments and derivatives of such antibodies, and polypeptides that specifically bind to β-Klotho, or β-Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Other embodiments provide nucleic acids encoding such antigen binding proteins and antigen binding protein-FGF21 fusions, and fragments and derivatives thereof, and polypeptides, cells comprising such polynucleotides, methods of making such antigen binding proteins and antigen binding protein-FGF21 fusions, and fragments and derivatives thereof, and polypeptides, and methods of using such antigen binding proteins and antigen binding protein-FGF21 fusions, 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/US2011/032333

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.:

1-17(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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/032333

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A61P3/10 A61K39/395
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

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 practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, PAJ, 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	ITO SHINJI ET AL: "Impaired negative feedback suppression of bile acid synthesis in mice lacking .beta.Klotho", JOURNAL OF CLINICAL INVESTIGATION, AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, US, vol. 115, no. 8, 1 August 2005 (2005-08-01), pages 2202-2208, XP002542526, ISSN: 0021-9738, DOI: DOI:10.1172/JCI23076 the whole document -----	1-17
X	US 2008/261236 A1 (KURO-O MAKOTO [US] ET AL) 23 October 2008 (2008-10-23) the whole document -----	1-17

☐ 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 document 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
27 June 2011	13/01/2012

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/032333

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2008261236 A1	23-10-2008	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-17(partially)

Invention 1 relates to an anti-beta-Klotho antibody or antibody fragment comprising the light chain variable domain L1 and the heavy chain variable domain H1 consisting of SEQ. ID. NO. 17 and 28 respectively, pharmaceutical composition comprising the same, nucleic acid encoding said antibody and expression vector comprising said nucleic acid, cells comprising the said vector and method for the production of said antibody expressed by said cells.

2-11. claims: 1-17(partially)

Invention 2-11 relates to an anti-beta-Klotho antibody or antibody fragment comprising the light chain variable domain L2-L11 respectively and the heavy chain variable domain H2-H11 respectively consisting of SEQ. ID. NO. 18-27 and 29-38 respectively, pharmaceutical composition comprising the same, nucleic acid encoding said antibody and expression vector comprising said nucleic acid, cells comprising the said vector and method for the production of said antibody expressed by said cells.

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12. claims: 18-51(completely); 1-10(partially)

Invention 12 relates to polypeptides or more specifically to anti-beta-Klotho antibody characterized in that it comprises either within its heavy chain polypeptide sequence chosen among the peptide sequences consisting of SEQ. ID. NOs 184-215, or fused to it, a polypeptide sequence that binds to one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, such as FGF21. Invention 12 further relates to pharmaceutical composition comprising said polypeptides, nucleic acid encoding said polypeptides and expression vector comprising said nucleic acid, cells comprising the said vector and method for the production of said antibody expressed by said cells, and use of said polypeptide in therapy.
