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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))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

(88) Date of publication of the international search report:
31 March 2016

(54) Title: METHODS TO MANIPULATE ALPHA-FETOPROTEIN (AFP)

(57) Abstract: As demonstrated herein, soluble human FcRn binds to AFP with affinities greater than observed with albumin, and is able to interfere with FcRn-mediated protection of and functional associations with IgG. Accordingly, provided herein, in some aspects, are compositions and methods to inhibit FcRn and AFP interactions in diseases or disorders where elevated AFP levels are associated with immunosuppression. Also provided herein, in some aspects, are compositions and methods to enhance or potentiate FcRn and AFP interactions in diseases or disorders with decreased AFP levels or diseases or disorders where increasing AFP levels increasing with immunosuppression.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/26860

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/16, A61K 38/00, A61K 35/14, C07K 1/00, C07K 14/00, C07K 16/00, C07K 17/00 (2015.01)
CPC - A61K 38/00, C07K 14/4717, C07K 14/4721, C07K 14/47, C07K 2319/00, A01K 2217/05
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)
IPC(8) - A61K 38/16, A61K 38/00, A61K 35/14, C07K 1/00, C07K 14/00, C07K 16/00, C07K 17/00 (2015.01)
CPC- A61K 38/00, C07K 14/4717, C07K 14/4721, C07K 14/47, C07K 2319/00, A01K 2217/05

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC- A61K 38/177, C07K 14/705, A61K 39/00, A61K 2123/00, C07K 16/3015, C07K 14/8125, C07K 16/18, A61K 35/16
USPC- 514/21.2, 530/350, 530/392, 530/386

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(PGPB,USPT,USOC,EPAB,JPAB); PatBase, Google/Scholar: AFP, Alpha-1-fetoprotein, Alpha-fetoglobulin, FETA, ADM31, 1352C>T, Thr451Ile, chromosome 4; 4:74316394 C/T, rs138531623, Thr451Ile; 4:74318296 A/T, rs140758670, Asp536Val, neonatal Fc receptor, FcRn..... GenCore 6.4.1: SEQ ID NO: 3 with substitutions

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/0107845 A1 (Blumberg, et al.) 03 May 2012 (03.05.2012) para [0081]-[0083], [0100], [00360], [00361]	1
A	Pyzik, Michal. Identification of a novel immunosuppressive FcRn ligand: implications for cancer . Modified: 14 May 2012. [Retrieved from the Internet 08 October 2015: <http://webcache.googleusercontent.com/search?q=cache:W9G9Ic7Q2WcJ:http://webapps.cihr-irsc.gc.ca/funding/detail_e%3FpResearchId%3D5226533%26p_version%3DCIHR%26p_language%3DE%26p_session_id%3D%2BAFP+FcRn+Blumberg&hl=en&gbv=2&prmd=ivns&strip=1&vwsrc=0>]; in entirety	2, 3
A	Posypanova, et al. The receptor binding fragment of alpha-fetoprotein is a promising new vector for the selective delivery of antineoplastic agents. J Drug Target. 2013, 21(5):458-65; pg 464, col 2	2, 3
A	Mizejewski. Review of the adenocarcinoma cell surface receptor for human alpha-fetoprotein; proposed identification of a widespread mucin as the tumor cell receptor. Tumor Biology 2013, 34(3):1317-1336; pg 4 [according to the posted document], col 1	2, 3
A	Li, et al. Alpha-fetoprotein receptor as an early indicator of HBx-driven hepatocarcinogenesis and its applications in tracing cancer cell metastasis. Cancer Lett. 2013, 330(2):170-80; Abstract	2, 3

☒ Further documents are listed in the continuation of Box C. ☐

* 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
07 October 2015 (07.10.2015)	04 NOV 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/26860

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Sand, et al. Dissection of the neonatal Fc receptor (FcRn)-albumin interface using mutagenesis and anti-FcRn albumin-blocking antibodies. J Biol Chem. Epub 24 April 2014, 289(24):17228-39; Abstract, pg 17237, Fig 8	2, 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/26860

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.: 4-19, 23-61
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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I: claims 1-3, directed to a pharmaceutical composition comprising an inhibitor of AFP-FcRn and a carrier.

Group II: claims 20-22, directed to a pharmaceutical composition comprising an AFP-FcRn potentiator and a carrier.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

********** See Supplemental Sheet to continue **********

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 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.:
1-3

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.

********** Supplemental Sheet **********

In Continuation of Box III. Observations where unity of invention is lacking:

Special Technical Features
The inventions of Group I do not include the shared or common technical feature of an AFP-FcRn potentiator, as required by Group II.

The inventions of Group I do not include the shared or common technical feature of an inhibitor of AFP-FcRn, as required by Group I. In addition, an inhibitor of AFP-FcRn interaction was known in the art at the time of the invention. Specifically, US 2012/0107845 A1 to Blumberg, et al. (hereinafter "Blumberg") discloses "a mouse anti-hFcRn antibody that blocks the hFcRn-albumin binding site (but not hFcRn-IgG binding site) (the ADM31 antibody, described in Qiao et al...)" (para [0100]).
Blumberg does not disclose that the ADM31 antibody is an inhibitor of the AFP-FcRn interaction. However, this limitation is met by/inherently present in Blumberg for the following reasons:
Per Applicant, "ADM31 blocks AFP-FcRn-mediated inhibitory functions" (instant application, para [00360], " FIG. 8 demonstrates that ADM31 blocks AFP-FcRn-mediated inhibitory functions. ADM31, a monoclonal anti-hFcRn antibody blocks hAFP inhibition of CD8+ T cell IL-2 secretion in response to antigen in IgG-IC... [00361] FIG. 9 demonstrates that ADM31 blocks AFP-FcRn-mediated inhibitory functions. ADM31 blocks hAFP inhibition of CD8+ T cell proliferation in response to antigen in IgG-IC..."). Thus, the ADM31 antibody of Blumberg being identical to the ADM31 disclosed by Applicant is an inhibitor of the AFP-FcRn interaction.

Common Technical Features
The inventions of Groups I and II share the technical feature of a pharmaceutical composition comprising an AFP-FcRn modulator and a pharmaceutically acceptable carrier. However, this shared technical feature does not represent a contribution over prior art as being obvious over Blumberg, as above.

Blumberg discloses "a mouse anti-hFcRn antibody that blocks the hFcRn-albumin binding site (but not hFcRn-IgG binding site) (the ADM31 antibody, described in Qiao et al...)" (para [0100]). Blumberg does not disclose that the ADM31 antibody is an inhibitor of the AFP-FcRn interaction. However, this limitation is met by/inherently present in Blumberg for the following reasons:
Per Applicant, "ADM31 blocks AFP-FcRn-mediated inhibitory functions" (instant application, para [00360] FIG. 8 demonstrates that ADM31 blocks AFP-FcRn-mediated inhibitory functions. ADM31, a monoclonal anti-hFcRn antibody blocks hAFP inhibition of CD8+ T cell IL-2 secretion in response to antigen in IgG-IC... [00361] FIG. 9 demonstrates that ADM31 blocks AFP-FcRn-mediated inhibitory functions. ADM31 blocks hAFP inhibition of CD8+ T cell proliferation in response to antigen in IgG-IC"). Thus, the ADM31 antibody of Blumberg being identical to the ADM31 disclosed by Applicant is an inhibitor of the AFP-FcRn interaction.

Blumberg does not disclose a specific embodiment of a pharmaceutical composition comprising the ADM31 antibody and a pharmaceutically acceptable carrier. However, Blumberg does disclose using the ADM31 antibody in a mouse (para [0100], "Mice deficient in mouse FcRn that express human FcRn (hFcRn) and h.beta.2m are administered a lethal dose of acetaminophen with (Group I) or without (Group II) a compound that blocks the interaction between FcRn and albumin. The compound is a mouse anti-hFcRn antibody that blocks the hFcRn-albumin binding site (but not hFcRn-IgG binding site) (the ADM31 antibody, described in Qiao et al...)", and further generally discloses how to formulate a pharmaceutical composition comprising "[c]ompounds useful in decreasing the concentration of albumin-binding toxins or treating disorders associated with albumin-binding toxins" (para [0081], "Such compositions typically include the compound and a pharmaceutically acceptable carrier"; see also para [0082]-[0083]).
It would have been obvious therefore to one of ordinary skill in the art how to, in the course of routine experimentation and with a reasonable expectation of success, formulate a pharmaceutical composition comprising the ADM31 antibody and a pharmaceutically acceptable carrier. As said technical feature would have been obvious to one of ordinary skill in the art at the time of the invention, this cannot be considered special technical feature that would otherwise unify the groups.

The inventions of Group I and II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.