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— 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))

[Continued on next page]

(54) Title: METHODS AND COMPOSITIONS RELATING TO MODULATION OF THE PERMEABILITY OF THE BLOOD BRAIN BARRIER

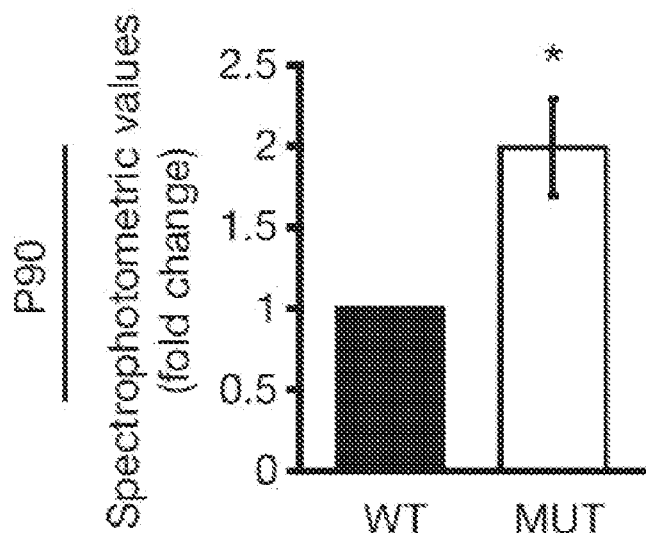


Fig. 15

(57) Abstract: Described herein are methods and compositions relating to modulating the permeability of the blood-brain barrier, e.g. increasing or decreasing the permeability of the blood-brain barrier for therapeutic purposes.



— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:

26 March 2015

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/43395

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 25/00, A61K 38/00, A61K 31/00, G01N 33/53 (2014.01)

CPC - A61K 38/00, A61K 31/00, G01N 33/6896

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) - A61P 25/00, A61K 38/00, A61K 31/00, G01N 33/53 (2014.01)

CPC - A61K 38/00, A61K 31/00, G01N 33/6896

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CPC: A61K47/48507, C07K7/06, C07K7/08

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, Google Scholar, Google Web, search terms: blood-brain barrier, increased permeability, Mfsd2A, Slc12A1, Slc38A5, LRP8, Slc3A2, Slc7A5, Slc7A1, Slc6A6, IGFBP7, Glut1, Slc40A1, Slc30A1, inhibitor, antagonist, agonist, gene expression, antibody, decreased permeability, kidney, glomerular, modulate permeability

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHESNEY et al., Taurine and the renal system. J Biomed Sci.(24 August 2010) vol 17, Suppl 1, S4 pp1-10, pg 3 col 1, para 5 - col 2 para 1, pg 7, col 2, para 5, pg 8, col 1, para 3	41-43
Y	US 2010/0199362 A1 (MCMAHON et al.) 05 August 2010 (05.08.2010) para [0007], [0039], [0065], [0075], [0085], [0087], [0130], [0152]	1-3, 9
Y	ZHENG et al., Glut1/SLC2A1 is crucial for the development of the blood-brain barrier in vivo. Ann Neurol (December 2010) vol 68, no 6, pp 835-844, abstract	1-3, 9
Y	ABU-SAFIEH et al., Mutation of IGFBP7 Causes Upregulation of BRAF/MEK/ERK Pathway and Familial Retinal Arterial Macroaneurysms. Am J Hum Genet. (12 August 2011) vol 89, no 2, pp 313-319, abstract, pg 313, col 2 para 2, pg 316 col 1 para 2, pg 318, col 1, para 1	37-39
Y	US 2008/0287341 A1 (CHEN) 20 November 2008 (20.11.2008) para [0001], [0004], [0073], [0077]	37-39
Y	US 2008/0038237 A1 (SAPOLSKY et al.) 14 February 2008 (14.02.2008) para [0042]	9
A	US 2005/0170391 A1 (ZERANGUE) 04 August 2005 (04.08.2005) para [0061]	41-43

☐ 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

09 January 2015 (09.01.2015)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/43395

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.: 4-8, 10-11, 16, 22-25, 29-32, 40, 44-48
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. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-3, 9, 37-39, 41-43, drawn to methods comprising administering an inhibitor or agonist of a gene or gene expression product

Group II: Claims 12-15, 17-18, drawn to pharmaceutical compositions comprising an inhibitor or agonist of a gene or gene expression product

—please see continuation on extra 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 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, 9, 37-39, 41-43

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/US 14/43395

Continuation of:

Box No. III Observations where unity of invention is lacking

Group III: Claims 19-21, 26-28, drawn to methods for determining the permeability of the blood-brain barrier and screening methods for agents that modulate the permeability of the blood-brain barrier

Group IV: Claims 33-36, drawn to methods and compositions comprising antibody reagents that binds to a polypeptide

The inventions listed as Groups I-IV 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:

Special Technical Features

Group I requires the administration an inhibitor or agonist of a gene or gene expression product, not required by Groups II-IV.

Group II requires a pharmaceutical composition comprising an inhibitor or agonist of a gene or gene expression product; not required by Groups I and III-IV.

Group III requires the method steps of injecting the liver of an embryo with a detectable agent while the embryo is connected to the maternal circulation via the umbilical cord; allowing the dye to circulate in the bloodstream; detecting a signal from the detectable agent in blood vessels within the brain and within brain tissue separated from the bloodstream by the blood-brain barrier; not required by Groups I-II and IV.

Group IV requires an antibody reagent, not required gy Groups I-III.

Common Technical Features

The feature shared by Groups I and III is the permeability of the blood-brain barrier. The feature shared by Groups I-II and IV is a gene or gene expression product selected from the group consisting of: Mfsd2A; Slc10Cl; Slc38A5; LRP8; Slc3A2; Slc7A5; Slc7A1; Slc6A6; IGFBP7; Glut1; Slc40A1; and Slc30A1. More specifically, the feature shared by Groups I and II is an inhibitor or agonist of said gene or gene expression product. The feature shared by Groups I-II and IV is a pharmaceutical composition and pharmaceutically-acceptable carrier.

However, these shared technical features do not represent a contribution over prior art, because the shared technical features are taught by US 2005/0170394 A1 to (Zerangue). Zerangue discloses methodds related to permeability of the blood-brain barrier (para [0007] - "blood-brain barrier permeability"; para [0010] - "Disclosed herein are methods of screening agents, conjugates or conjugate moieties for the ability to enter the CNS by crossing the blood brain barrier in order to treat or diagnose conditions within the CNS"). Zerangue further teaches the gene or gene expression product Glut1 (para [0012]) and an inhibitor of Glut1 (para [0024]; para [0068] - "inhibitors of GLUT1") as well as ligands that bind to GLUT1 (para [0048]) wherein these compounds (Glut1 ligand and/or substrates) can be incorporated into a pharmaceutical composition comprising pharmaceutically-acceptable carrier (para [0102]-[0103]). As the technical feature was known in the art at the time of the invention, it cannot be considered a special technical feature that would otherwise unify the groups.

Groups I-IV therefore lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.