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(71) Applicant: UNIVERSITY OF PITTSBURGH-OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION [US/US]; 200 Gardner Steel Conference Center, Thackeray & O'Hara Streets, Pittsburgh, Pennsylvania 15260 (US).

(72) Inventors: JACKSON, Travis, C.; River Vue Apartments, Apartment #1106, 300 Liberty Avenue, Pittsburgh, Pennsylvania 15222 (US). KOCHANEK, Patrick, M.; 114 Altadena Drive, Pittsburgh, Pennsylvania 15228 (US).

(74) Agents: HIRSHMAN, Jesse, A. et al.; The Webb Law Firm, One Gateway Center, 420 Ft. Duquesne Blvd., Suite 1200, Pittsburgh, Pennsylvania 15222 (US).

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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))
- 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))

[Continued on next page]

(54) Title: METHOD TO IMPROVE NEUROLOGIC OUTCOMES IN TEMPERATURE MANAGED PATIENTS

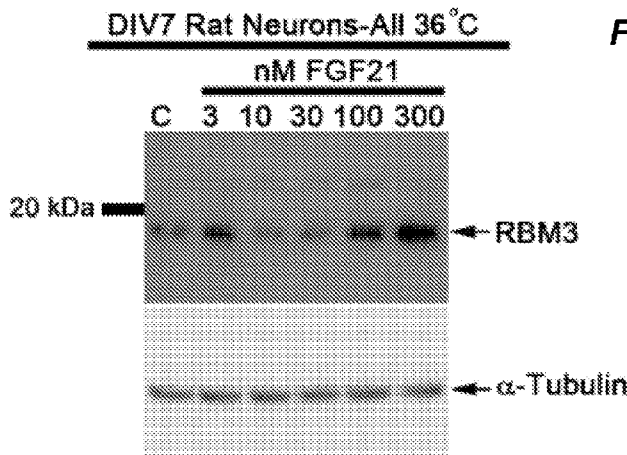
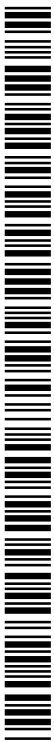


Fig. 6C

(57) Abstract: A method of improving brain function in a hypothermic patient is provided. The method comprises administering to the patient an amount of a fibroblast growth factor 21 (FGF21) effective to increase RNA binding motif 3 (RBM3) production in nerve cells of the patient. The method is useful, for example, where the patient is or will be undergoing cardiac surgery or spinal surgery, such as requiring deep hypothermia circulatory arrest (DHCA), or is subject to an emergency preservation and resuscitation (EPR) method, or where a patient suffers from mild/moderate/severe traumatic brain injury (TBI), ventricular fibrillation cardiac arrest (VFCA), subarachnoid hemorrhage (SAH), subdural hematoma (SH), cerebral vasospasm, neonatal abusive head trauma (a.k.a. shaken baby syndrome), neonatal hypoxic ischemic encephalopathy (HIE), asphyxia cardiac arrest (ACA), treatment of spinal injury, prophylaxis in spinal surgery, stroke, and drug overdose.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/33563

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A61K 38/18, C07K 14/50, A61P 25/00 (2016.01)
 CPC - A61K 38/1825, C07K 14/50
 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 38/18, C07K 14/50, A61P 25/00 (2016.01)
 CPC - A61K 38/1825, C07K 14/50

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 USPC - 514/9.1
 Keyword limited; search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 PatBase, Google Scholar, Google Patents. hypothermia, body temperature, fibroblast growth factor, FGF21, traumatic brain injury, subdural hematoma, head trauma, subarachnoid hemorrhage, RNA binding motif 3, RBM3, human growth hormone, protein synthesis, microarray, transcriptome, brain, neuron, transplant kidney, delayed graft function, cerebral in

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHIP et al. The RNA-binding protein RBM3 is involved in hypothermia induced neuroprotection. 17 April 2011 (17.04.2011), Volume 43, Issue 2, pp 388-396. Especially Abstract.	1-20
Y	KERN et al. The Effects of Temperature and Seasons on Subcutaneous White Adipose Tissue in Humans: Evidence for Thermogenic Gene Induction. J Clin. Endocrinol. Metab. 31 December 2014 (31.12.2014), Volume 99, Issue 12, pp E2772-9. Especially E 2776 col 2 para 2 to col 2 para 1.	1-20
Y	DOURIS et al. Central Fibroblast Growth Factor 21 Browns White Fat via Sympathetic Action in Male Mice. Endocrinology. 29 April 2015 (29.04.2015), Volume 156, Issue 7, pp 2470-81. Especially page 1 col 1 para 2 to col 2 para 1, page 3 col 1 para 5 to col 2 para 1, page 6 col 1 para 1, page 6 col 2 para 2.	1-20
Y	GAICH et al. The Effects of LY2405319, an FGF21 Analog, in Obese Human Subjects with Type 2 Diabetes. Cell Metab. 03 September 2013 (03.09.2013), Volume 18, Issue 3, pp 333-40. Especially Page 334 col 1 para 2.	4, 18
Y	US 2002/0091431 A1 (GUNN et al.). 11 July 2002 (11.07.2002) abstract, para [0025], [0026]	5, 6, 8
Y	US 6,156,057 A (FOX). 05 December 2000 (05.12.2000) Col 9 ln 9-16	9, 13

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

12 September 2016

Date of mailing of the international search report

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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
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/33563

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:
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 1-20, drawn to methods of improving brain function or inducing RBM3 in a nerve cell by using fibroblast growth factor 21 (FGF21) protein effective to increase RBM3 production in a nerve cell.

Group II Claims 21-27, drawn to a composition comprising an FGF21 protein.

Group III: Claim 28, drawn to a method of preparing a kidney for transplantation by using FGF21 to reduce the prevalence of delayed graft function in a recipient patient of a kidney.

-----See 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.:
1-20

- 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 16/33563

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P ✓	JACKSON et al. Cold stress protein RBM3 responds to temperature change in an ultra-sensitive manner in young neurons. <i>Neuroscience</i> . 08 August 2015 (08.08.2015), Volume 305, pp 268-78. Entire document, especially abstract	1-20
A ✓	Fisher et al. "FGF21 regulates PGC-1alpha and browning of white adipose tissues in adaptive thermogenesis" <i>Genes Dev.</i> 1 February 2012, Vol 26, No 3, pp 271-81 (abstract)	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/33563

Continuation of Box III Observations where Unity of Invention is Lacking.

The inventions listed as Groups I, II, and III 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 an increase in RBM3 production that is induced by FGF21, not required by Groups II and III.

Group II requires a composition, not required by the methods of Groups I and III.

Group III requires a reduction in prevalence of delayed graft function in a recipient patient of a kidney by use of FGF21, not required by Groups I and II.

Common Technical Features

The feature shared by Groups I-III is FGF21 protein, more specifically administration of FGF21 protein to a patient under hypothermic conditions.

However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is taught by the article entitled "FGF21 regulates PGC-1alpha and browning of white adipose tissues in adaptive thermogenesis" by Fisher et al. (Genes Dev. 1 February 2012, Vol 26, No 3, pp 271-81) (hereinafter 'Fisher').

Fisher discloses FGF21 protein (abstract), and further teaches that FGF21 plays a physiologic role in cold exposure, acting to provide a robust defense against hypothermia (abstract "We show here that fibroblast growth factor 21 (FGF21) plays a physiologic role in this thermogenic recruitment of WATs. In fact, mice deficient in FGF21 display an impaired ability to adapt to chronic cold exposure, with diminished browning of WAT ... We conclude that FGF21 acts to activate and expand the thermogenic machinery in vivo to provide a robust defense against hypothermia"). Given that FGF21 is protective under hypothermic conditions, one of ordinary skill in the art would have found it obvious to administer FGF21 protein to a patient under hypothermic conditions.

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.

Another feature shared by Groups I and II is use of FGF21 in the treatment of neurological diseases or disorders.

However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is taught by US 2014/0287996 A1 to Northwestern University (hereinafter 'Northwestern Univ').

Northwestern Univ discloses use of FGF21 protein for treatment of stroke (para [0003] "compositions (e.g., hepatocyte secretory factors) for alleviating and/or protecting against neuronal damage (e.g., resulting from stroke)"; para [0006] "the composition comprises at least one isolated hepatocyte secretory factor."; Claim 9 "...said human hepatocyte secretory factor is selected from the group comprising: human FGF21 or a biologically active fragment or variant thereof").

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, II, and III therefore lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.