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(54) Title: REAGENTS AND METHODS FOR ALZHEIMER'S DISEASE AND COMORBIDITIES THEREOF

(57) Abstract: Methods for using gene expression changes and mutations in neural organoids to identify neural networks that predict the onset of Alzheimer's disease and associated comorbidities are disclosed.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/30998

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C12N 5/1079, C12N 5/00 (2020.01)

CPC - C12N 5/0622, 5/0062, 5/0618, 5/0621

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2013/0116132 A1 (SHARMA, P et al.) 09 May 2013; paragraph [0037], [0084]-[0085], [0098], Table 2, page 45	19, 20, 22/19- 22/20, 23/22/19-23/22/20 ---- 1-18, 22/6-7, 22/17-18, 23/22/6-7, 23/22/17-23/22/18, 24/6-7, 24/12-24/15, 25/24/6-7, 25/24/12-25/24/15, 26/25/24/6-7, 26/25/24/12-26/25/24/15, 27/24/6-7, 27/24/12-27/24/15, 29, 38, 40, 44/1, 44/16, 45/44/1, 45/44/16, 46/45/44/1, 46/45/44/16, 47/16, 48
X -- Y	(RAJA, WK et al.) Self-Organizing3D Human Neural Tissue Derived from Induced Pluripotent Stem Cells Recapitulate Alzheimer's Disease Phenotype. PLoS ONE. 2016, 11(9): e0161969, pages 1-18; abstract; page 3, first paragraph, page 8, second paragraph, page 10, second paragraph; doi:10.1371/journal.pone.0161969	21 --- 1-18, 22/6-7, 22/17, 22/18, 23/22/6-7, 23/22/17-23/22/20, 24/6-7, 24/12-24/15, 25/24/6-7,

☒ 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
"D" document cited by the applicant in the international application
"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
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INTERNATIONAL SEARCH REPORT

International application No.
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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.
		25/24/12-25/24/15, 27/24/6-7, 27/24/12-27/24/15, 29, 48
X -- Y	US 2019/0017018 A1 (OHIO STATE INNOVATION FOUNDATION) 17 January 2019; Figures 21A, 21B paragraphs [0068], [0069], [0183], [0188]-[0189], [0191]	19-21, 22/19-22/20, 30-32, 34-37, 39, 43, 46/34, 47/34 ---- 1-3, 5-6, 8-10, 14 -20, 22/6, 22/15-20, 23/22/6, 23/22/15-23/22/20, 24/6, 24/14-24/15, 25/24/6, 25/24/14-25/24/15, 26/25/24/6, 26/25/24/14-26/25/24/15, 27/24/6, 27/24/14-27/24/15, 33, 38, 40-41, 43, 44/1, 44/16, 44/34, 45/44/1, 45/44/16, 45/44/34, 46/45/44/1, 46/45/44/16
Y	(KOUROU, K et al.) Machine learning applications in cancer prognosis and prediction. Computational and Structural Biotechnology Journal. 2015, Vol. 13, pages 8–17; abstract; DOI: 10.1016/j.csbj.2014.11.005	47/1, 47/16 33
Y	(ISRAEL, MA et al.) Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells. Nature. 2012, Vol. 482, No. 7384, pages 216–220; abstract, page 6, third paragraph; doi:10.1038/nature10821	44/34, 45/44/1, 45/44/16, 45/44/34, 46/45/44/1, 46/45/44/16
Y	(WANG, H) Modeling Neurological Diseases With Human Brain Organoids. Front. Synaptic Neurosci. 2018, Vol. 10, No. 15, pages 1-14; page 1, second paragraph; figure 1, page 7, first column, second paragraph; doi: 10.3389/fnsyn.2018.00015	11-15, 24/12-24/15, 25/24/12-25/24/15, 26/25/24/12-26/25/24/15, 27/24/12-27/24/15
Y	(ABATE, G et al.) Nutrition and AGE-ing: Focusing on Alzheimer's Disease. Hindawi. Oxidative Medicine and Cellular Longevity. Vol. 2017, Article ID 7039816, pages 1-10; page 4, first column, second and third paragraphs, second column, first paragraph; https://doi.org/10.1155/2017/7039816	14-15, 24/14-24/15, 25/24/14-25/24/15, 26/25/24/14-26/25/24/15, 27/24/14-27/24/15
Y	(LIU, C et al.) Modeling human diseases with induced pluripotent stem cells: from2D to 3D and beyond. Development. 01 March 2018, Vol. 145, No. 5, pages 1-13; Liu, page 5, second paragraph DOI: 10.1242/dev.156166	44/1, 44/16, 45/44/1, 45/44/16, 45/44/34, 46/45/44/1, 46/45/44/16
Y	(BOUHENNI, RA et al.) Identification of differentially expressed proteins in the aqueous humor of primary congenital glaucoma. Exp Eye Res. 2011, Vol. 92, No. 1, pages 67-75; pages 1-2; abstract; DOI: 10.1016/j.exer.2010.11.004.	3, 5-6, 15, 17-20, 22/17-20, 24/6, 24/14-24/15, 25/24/6, 25/14-25/15, 26/25/24/6, 26/25/24/14-26/25/24/15, 27/24/6, 27/24/14-27/24/15, 38, 43
Y	WO 2017/191274 A2 (CUREVAC AG) 09 November 2017; paragraphs [0191], [0592], [1022], [1033]	3, 5-6, 15, 17-20, 22/6, 22/17-20, 23/22/6, 23/22/17-23/22/20, 24/6, 24/14-24/15, 25/24/6, 25/14-25/15, 26/25/24/6, 26/25/24/14-26/25/24/15, 27/24/6, 27/24/14-27/24/15, 38, 41, 43
Y	(COLE, GB et al.) Specific estrogen sulfotransferase (SULT1E1) substrates and molecular imaging probe candidates. PNAS. 2010, Vol. 107, No. 14, pages 6222–6227; page 6224, first column, second paragraph. DOI: 10.1073/pnas.0914904107	3, 5-6, 15, 17-20, 22/6, 22/17-20, 23/22/6, 23/22/17-23/22/20, 24/6, 24/14-24/15, 25/24/6, 25/14-25/15, 26/25/24/6, 26/25/24/14-26/25/24/15, 27/24/6,

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/30998

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.: 28
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:

-***-Please See Supplemental Box-***-

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.:

Group I (Claims 1-20, 22-27, 29, 34-41, 43-48, AND ABCAI0), Group II (Claim 21), Group III (Claims 30-33), and additional biomarkers AIM2, GUCY2D, RBP3, SULTIEI, SLC2AI2, CENPA, and ALCAM

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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US20/30998

-***-Continuation of Box No. III - Observations where unity of invention is lacking:

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.

Groups I+, Claims 1-20, 22-27, 29, 34-41, 43-48, and ABCA10 (biomarker) are directed toward methods for predicting a risk for developing Alzheimer's disease, treating Alzheimer's disease, and reducing the risk for developing Alzheimer's disease-related comorbidities; and kits and diagnostic panels associated therewith.

The methods, diagnostic panels, and kits will be searched to the extent they encompass ABCA10 (biomarker). Applicant is invited to elect additional biomarker(s) to be searched. Additional biomarkers will be searched upon the payment of additional fees. It is believed that claims 1, 2, 3 (in-part), 4, 5 (in-part), 7-9, 10 (in-part), 11-14, 15 (in-part), 16, 17-20 (each in-part), 22-27 (each in-part), 29, 34-36, 38 (in-part), 39, and 44-48 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass ABCA10 (biomarker). Applicants must specify the searchable claims that encompass any additionally elected biomarker(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be ABCA4 (biomarker).

Group II, Claim 21 is directed toward a method of pharmaceutical testing for drug screening, toxicity, safety, and/or pharmaceutical efficacy studies using a patient specific neural organoid.

Group III, Claims 30-33 are directed toward a method for detecting one or a plurality of biomarkers from different human chromosomes associated with Alzheimer's disease using data analytics that obviates the need for whole genome sequence analysis of patient genomes

Group IV, Claim 42 is directed toward a method of using a neural organoid along with confirmatory data, and novel data to develop signature algorithms with machine learning, artificial intelligence and deep learning.

The inventions listed as Groups I+ and II-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: the special technical features of Groups I+ include ABCA10, not present in any other Group; the special technical features of Group II include a method of pharmaceutical testing, not present in any other Group; the special technical features of Group III include data analytics that obviate the need for whole genome sequence analysis, not present in any other Group; the special technical features of Group IV include signature algorithms, not present in any other Group.

There is no single technical feature that is shared by all of Groups I+ and II-IV. Groups I+, II and IV share the technical features including: a neural organoid. Groups I+ and III share the technical features including: detecting biomarkers from humans associated with Alzheimer's disease.

However, these shared technical features are previously disclosed by US 2019/0017018 A1 to Ohio State Innovation Foundation (hereinafter 'Ohio').

Ohio discloses a neural organoid (a neural organoid; abstract); and detecting biomarkers from humans associated with Alzheimer's disease (assessing changes in gene expression (detecting biomarkers) from humans associated with Alzheimer's disease; Fig. 21A, paragraph [0188]).

No technical features are shared between the biomarkers of Groups I+ and, accordingly, these groups lack unity a priori.

-***-Continued on Next Supplemental Page-***-

-***-Continued from Previous Supplemental Page-***-:

Groups I+ share the technical features including: a method for treating Alzheimer's disease in a human, using a patient-specific pharmacotherapy, the method comprising a) procuring one or a plurality of cell samples from a human, comprising one or a plurality of cell types; b) reprogramming the one or the plurality of cell samples to produce one or a plurality of induced pluripotent stem cell samples; c) treating the one or the plurality of induced pluripotent stem cell samples to obtain one or more patient specific neural organoids; d) collecting a biological sample from the patient specific neural organoid; e) detecting changes in Alzheimer's disease biomarker expression from the patient specific neural organoid sample that are differentially expressed in humans with Alzheimer's disease: i) performing assays on the patient specific neural organoid to identify therapeutic agents that alter the differentially expressed Alzheimer's disease biomarkers in the patient-specific neural organoid sample; and g) administering a therapeutic agent for Alzheimer's disease to treat the human; a kit comprising an array containing the sequences of one or a plurality of biomarkers in a human patient; a patient-specific pharmacotherapeutic method for reducing risk for developing Alzheimer's disease-associated co-morbidities in a human, the method comprising: a) procuring one or a plurality of cell samples from a human, comprising one or a plurality of cell types; b) reprogramming the one or the plurality of cell samples to produce one or a plurality of induced pluripotent stem cell samples; c) treating the one or the plurality of induced pluripotent stem cell samples to obtain one or more patient specific neural organoids; d) collecting a biological sample from the patient specific neural organoid; e) detecting biomarkers of an Alzheimer's disease related co-morbidity in the patient specific neural organoid sample; f) administering an anti-Alzheimer's disease therapeutic agent to the human; method for detecting at least one biomarker, the method comprising: a) obtaining a biological sample from a human patient; and b) contacting the biological sample with an array comprising specific-binding molecules for the at least one biomarker and detecting binding between the at least one biomarker and the specific binding molecules; and a method for predicting a risk for developing Alzheimer's disease in a human, the method comprising: a) procuring one or a plurality of cell samples from the human, comprising one or a plurality of cell types; b) reprogramming the one or the plurality of cell samples to produce one or a plurality of induced pluripotent stem cell samples; c) treating the one or the plurality of induced pluripotent stem cell samples to obtain a neural organoid; d) collecting a biological sample from the neural organoid; e) measuring biomarkers in the neural organoid sample; and f) detecting measured biomarkers from the neural organoid sample that are differentially expressed in humans with Alzheimer's disease.

However, these shared technical features are previously disclosed by Ohio, as above, in view of US 2018/0284139 A1 to Rai et al. (hereinafter 'Rai'), in view of US 2018/0067133 A1 to Electrophoretics Limited (hereinafter 'Electrophoretics').

Ohio discloses a method for treating Alzheimer's disease in a human ((a method for) treating Alzheimer's disease in a human; paragraphs [0003], [0035], [0036], [0191]), (), the method comprising a) procuring one or a plurality of cell samples from a human, comprising one or a plurality of cell types (the method comprising a) procuring one or a plurality of cell samples from a human, comprising one or a plurality of cell types; paragraph [0184]); b) reprogramming the one or the plurality of cell samples to produce one or a plurality of induced pluripotent stem cell samples (reprogramming the one or the plurality of cell samples to produce one or a plurality of induced pluripotent stem cell samples; paragraph [0184]); c) treating the one or the plurality of induced pluripotent stem cell samples to obtain one or more patient specific neural organoids (treating the one or the plurality of induced pluripotent stem cell samples to obtain one or more patient specific neural organoids; paragraphs [0006], [0118]); d) collecting a biological sample from the patient specific neural organoid (subjecting normal and APP mutant organoid to whole genome transcriptomic analysis (collecting a biological sample from the patient specific neural organoid); paragraph [0188]; wherein, in order to perform the analysis a sample of the organoid must have been used); e) detecting changes in Alzheimer's disease biomarker expression from the patient specific neural organoid sample that are differentially expressed in humans with Alzheimer's disease (detecting changes in Alzheimer's disease biomarker expression from the patient specific neural organoid sample that are differentially expressed in humans with Alzheimer's disease; paragraph [0188]); a kit (a kit; paragraph [0079]) comprising an array containing the sequences of one or a plurality of biomarkers in a human patient (comprising an array containing the sequences of one or a plurality of biomarkers in a human patient; paragraphs [0070], [0188]); Alzheimer's disease-associated co-morbidities in a human (Alzheimer's disease-associated adenosine deficiency, x-chromosome aneuploidy in the brain, and impaired neurogenesis (co-morbidities) in a human; Figures 21A and 21B); a method for detecting at least one biomarker (a method for transcriptome analysis (detecting at least one biomarker); paragraph [0188]), the method comprising: a) obtaining a biological sample from a human patient (the method comprising: a) obtaining a biological sample from a human patient; paragraph [0184]); and b) contacting the biological sample with an array comprising specific-binding molecules for the at least one biomarker and detecting binding between the at least one biomarker and the specific binding molecules (contacting the biological sample with a microarray for transcriptomic expression analysis (an array comprising specific-binding molecules for the at least one biomarker and detecting binding between the at least one biomarker and the specific binding molecules); paragraphs [0070], [0188]); and performing assays on the patient specific neural organoid (performing assays on the patient specific neural organoid; paragraph [0071]) to identify therapeutic agents that alter the differentially expressed Alzheimer's disease biomarkers in the patient-specific neural organoid sample (to identify therapeutic agents that alter the differentially expressed Alzheimer's disease biomarkers in the patient-specific neural organoid sample; paragraphs [0071], [0188]).

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Ohio does not disclose: using a patient-specific pharmacotherapy; and g) administering a therapeutic agent for Alzheimer's disease to treat the human; a patient-specific pharmacotherapeutic method for reducing risk for developing Alzheimer's disease-associated co-morbidities in a human, the method comprising: a) procuring one or a plurality of cell samples from a human, comprising one or a plurality of cell types; b) reprogramming the one or the plurality of cell samples to produce one or a plurality of induced pluripotent stem cell samples; c) treating the one or the plurality of induced pluripotent stem cell samples to obtain one or more patient specific neural organoids; d) collecting a biological sample from the patient specific neural organoid; e) detecting biomarkers of an Alzheimer's disease related co-morbidity in the patient specific neural organoid sample; f) administering an anti-Alzheimer's disease therapeutic agent to the human; and a method for predicting a risk for developing Alzheimer's disease in a human, the method comprising: a) procuring one or a plurality of cell samples from the human, comprising one or a plurality of cell types; b) reprogramming the one or the plurality of cell samples to produce one or a plurality of induced pluripotent stem cell samples; c) treating the one or the plurality of induced pluripotent stem cell samples to obtain a neural organoid; d) collecting a biological sample from the neural organoid; e) measuring biomarkers in the neural organoid sample; and f) detecting measured biomarkers from the neural organoid sample that are differentially expressed in humans with Alzheimer's disease.

Rai discloses a method for risk prediction and therapy of Alzheimer's disease (a method for risk prediction and therapy of Alzheimer's disease; abstract), and Alzheimer's disease-associated co-morbidities (disease states associated with AD (Alzheimer's disease-associated co-morbidities); paragraph [0035]), comprising measuring the amount of specific biomarkers in a sample from the patient (comprising measuring the amount of specific biomarkers in a sample from the patient; abstract); and for patient-specific pharmacotherapy (to select therapies for use in a subject (patient-specific pharmacotherapy); paragraph [0035]).

Electrophoretics discloses identifying a panel of biomarkers to diagnose and determine the likelihood of developing Alzheimer's disease (identifying a panel of biomarkers to diagnose and determine the likelihood of developing Alzheimer's disease; abstract); as well as administering to a subject a therapeutic agent for Alzheimer's disease (administering to a subject a therapeutic agent for Alzheimer's disease; paragraph [0037]).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the disclosure of Ohio to have used the organoids developed by Ohio for risk prediction and personalized therapy selection for Alzheimer's disease, and Alzheimer's associated co-morbidities, as disclosed by Rai, in order to better determine the likelihood of a person developing Alzheimer's disease, and providing preventative treatment. It further would have been obvious to a person of ordinary skill in the art at the time the invention was made to have administered an effective treatment for Alzheimer's disease, as disclosed by Electrophoretics, in order to enable actual treatment and symptom amelioration.

Since none of the special technical features of the Groups I+ and II-IV inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Ohio, Rai and Electrophoretics references, unity of invention is lacking.