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(54) Title: TARGETS AND METHODS OF DIAGNOSING, MONITORING AND TREATING FRONTOTEMPORAL DEMENTIA

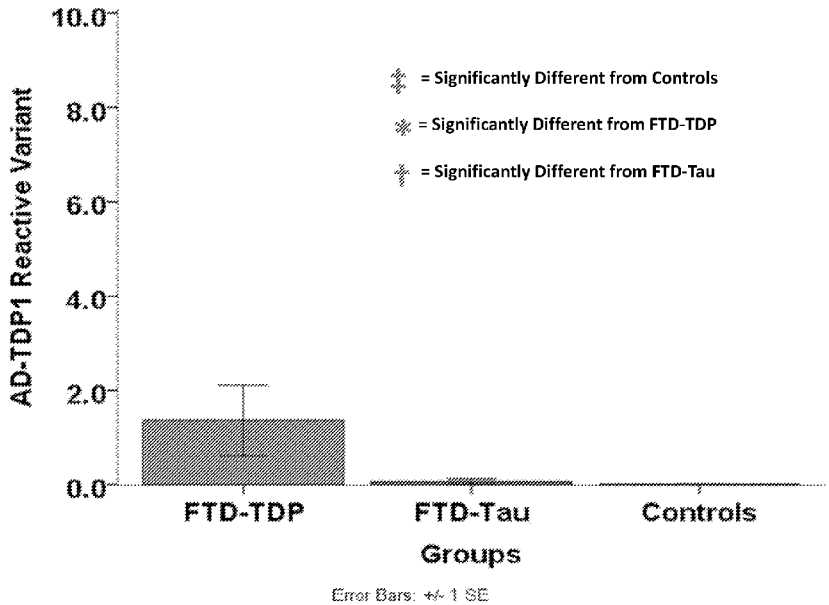

Figure 1A

(57) Abstract: Disclosed herein are antibodies, antibody fragments, binding agents, and compositions that specifically recognize protein variant biomarkers associated with frontotemporal dementia, kits and methods of use, including diagnosing, monitoring and treating frontotemporal dementia.

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[Continued on next page]

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/37603

A. CLASSIFICATION OF SUBJECT MATTER

IPC - G01N 33/68; C07K 16/18; A61K 39/395 (2020.01)

CPC - G01N 33/6896; C07K 16/18; A61K 39/3955; G01N 2800/2814; C07K 2317/569

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 – A	WO 2015/117088 A2 (ARIZONA BOARD OF REGENTS ON BEHALF OF ARIZONA STATE UNIVERSITY) 06 August 2015; page 4, lines 18-24, 32-33; page 8, lines 17-21, 27-32; page 10, lines 19-21; page 11, lines 10-25; page 12, lines 20-31; page 16, lines 5-8	1, 5-6, 10 – 19 – 2, 3/2, 11, 12/11, 20, 21/20
Y	WO 2005/025516 A2 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 24 March 2005; page 4, lines 14-26; page 6, lines 6-9; page 11, lines 6-15; page 16, lines 21-26; page 17, lines 12-21; claims 1, 69, 77-78	1, 3/1, 10, 12/10, 19, 21/19
Y	FANG, Y et al. Full-length TDP-43 forms toxic amyloid oligomers that are present in frontotemporal lobar dementia-TDP patients. Nature Communications. 12 September 2014. Vol. 5, No. 4824; abstract. DOI: 10.1038/ncomms5824	1, 3/1, 10, 12/10, 19, 21/19
Y – A	US 2019/0169274 A1 (BIOGEN MA INC. et al.) 06 June 2019; abstract; paragraphs [0006], [0008], [0288]	19 – 20, 21/20
Y	US 2017/0234891 A1 (ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE) 17 August 2017; paragraphs [0309]-[0310]	19, 21/19
A	WO 2012/058334 A1 (ARIZONA BOARD OF REGENTS, A BODY CORPORATE OF THE STATE OF ARIZONA ACTING FOR AND ON BEHALF OF ARIZONA STATE UNIVERSITY) 03 May 2012; page 6, lines 17-22; table 6; SEQ ID NO: 6	2, 3/2, 11, 12/11, 20, 21/20

☒ 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)
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"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 application No.
PCT/US20/37603

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2016/0320412 A1 (ARIZONA BOARD OF REGENTS ON BEHALF OF ARIZONA STATE UNIVERSITY) 03 November 2016; paragraphs [0088]-[0089]; table 1; SEQ ID NO: 6	2, 3/2, 11, 12/11, 20, 21/20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/37603

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, 7-9, 13-18
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 Page-***-

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, 2-3 (each in-part), 5, 6, 10, 11-12 (each in-part), 19, and 20-21 (each in-part)

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/US20/37603

-***-Continued from 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 1-3, 5, 6, 10-12, 19-22 and SEQ ID NO: 1 (scFv sequence) are directed toward methods of diagnosing and monitoring a subject with frontotemporal dementia, and kits therefor.

The methods and kits will be searched to the extent they encompass SEQ ID NO: 1 (first exemplary scFv sequence). Applicant is invited to elect additional scFv(s), with specified SEQ ID NO: for each, or with specified substitution(s) at specified site(s) of a SEQ ID NO:, such that the sequence of each elected species is fully specified (i.e. no optional or variable residues or substituents), where available as an option within at least one searchable claim, to be searched. Additional scFv sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1, 2-3 (each in-part), 5, 6, 10, 11-12 (each in-part), 19, and 20-21 (each in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 1 (scFv sequence). Applicants must specify the searchable claims that encompass any additionally elected scFv sequence(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 SEQ ID NO: 2 (scFv sequence).

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

Groups I+ share the technical features including: a method of diagnosing a subject with frontotemporal dementia (FTD), comprising: contacting a biological sample from a subject at risk or suspected of having FTD with one or more single-chain variable fragments (scFvs) at least reactive with one or more oligomeric beta amyloid variants, TDP-43 variants and/or tau variants; and detecting binding between one or more scFvs and one or more oligomeric beta amyloid variants, TDP-43 protein variants and/or tau protein variants; a method of monitoring a subject with frontotemporal dementia (FTD), comprising: contacting a first biological sample from a subject diagnosed with FTD with one or more single-chain variable fragments (scFvs) at least reactive with one or more oligomeric beta amyloid variants, TDP-43 variants and/or tau variants; detecting binding between one or more scFvs and one or more oligomeric beta amyloid variants, TDP-43 protein variants and/or tau protein variants; and a kit for detecting FTD, comprising one or more reagents reactive with one or more oligomeric beta amyloid variants, TDP-43 variants and/or tau variants and one or more controls and instructions for using the kit.

However, these shared technical features are previously disclosed by US 2019/0169274 A1 to Biogen MA, Inc. et al. (hereinafter 'Biogen'), in view of US 2018/0298086 A1 to Arizona Board of Regents on Behalf of Arizona State University (hereinafter 'Arizona').

Biogen discloses a method of diagnosing a subject with a neurodegenerative disease, including frontotemporal dementia (a method of diagnosing a subject with a neurodegenerative disease, including frontotemporal dementia; paragraphs [0013], [0014], [0303]), comprising: contacting a biological sample from a subject at risk or suspected of having FTD (comprising: determining the presence of tau in a biological sample from the subject with an antibody or fragment thereof (contacting a biological sample from a subject at risk or suspected of having the disease; paragraph [0303]) with one or more single-chain variable fragments (scFvs) (with one or more single-chain variable fragments (scFvs); paragraphs [0006], [0008]) at least reactive with tau variants (at least reactive with tau variants; paragraph [0006]); and detecting binding between one or more scFvs and tau protein variants (detecting binding between one or more scFvs and tau protein variants; paragraphs [0276], [0303]); a method of monitoring a subject with a neurodegenerative disease, including frontotemporal dementia (a method of monitoring a subject with a neurodegenerative disease, including frontotemporal dementia; paragraphs [0061], [0284], Claim 72), comprising: contacting a first biological sample from a subject diagnosed with the disease with one or more single-chain variable fragments (comprising: contacting a first biological sample from a subject diagnosed with the disease with one or more single-chain variable fragments; paragraph [0008], Claim 72) at least reactive with tau variants (at least reactive with tau variants; paragraph [0006], Claim 72); detecting binding between one or more scFvs and one or more tau protein variants (detecting binding between one or more scFvs and tau protein variants; paragraph [0276], Claim 72); and a kit for detecting neurodegenerative diseases (a kit for detecting neurodegenerative diseases; abstract, paragraph [0288]), comprising one or more reagents reactive with one or more tau variants and one or more controls and instructions for using the kit (comprising one or more antibodies (reagents) reactive with one or more tau variants and one or more controls and instructions for using the kit; abstract, paragraph [0288]).

Biogen does not disclose a specific embodiment directed toward frontotemporal dementia (FTD).

Arizona discloses antibodies and fragments thereof that bind to tau (antibodies and fragments thereof that bind to tau; abstract) for detecting tau in frontotemporal dementia (paragraphs [0036], [0145]).

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 Biogen to have included the use of antibodies to tau for detection of frontotemporal dementia, as disclosed by Arizona, in order to enable the detection and diagnosis of the disorder at as early a stage as possible, in order to enable the selection of an effective treatment therefor.

Since none of the special technical features of the Groups I+ 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 Biogen and Arizona references, unity of invention is lacking.