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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))*

(54) Title: ANTIBODY-BASED METHODS OF DETECTING AND TREATING ALZHEIMER'S DISEASE

(57) Abstract: Disclosed herein are antibodies and antigen binding fragments that bind phosphorylated and dephosphorylated tau and methods of use in detecting and treating Alzheimer's disease and other tauopathies. Also included are methods for determining the stage of Alzheimer's disease in a human subject and monitoring the effectiveness of an anti-tau therapy.

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/18 A61P25/28
ADD.

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)
A61P C07K

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

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

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/041962 A1 (AXON NEUROSCIENCE SE [SK]; NOVAEK MICHAL [SK] ET AL.) 28 March 2013 (2013-03-28) page 35, paragraph 0106 page 121, paragraph 0363 - page 122 figure 7D page 127, paragraph 0374 page 128; example 6 page 149 - page 152; example 18 ----- -/--	1-12, 15-22, 24-26, 28-49, 51, 107-109, 138,139, 173-176

[X] Further documents are listed in the continuation of Box C.

[X] 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

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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
5 December 2019	03/01/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Malamoussi, A

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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.
X	DAVID SINGER ET AL: "Characterization of Phosphorylation Dependent Antibodies To Study the Phosphorylation Status of the Tau Protein", INTERNATIONAL JOURNAL OF PEPTIDE RESEARCH AND THERAPEUTICS, vol. 11, no. 4, 1 December 2005 (2005-12-01), pages 279-289, XP055546131, NL ISSN: 1573-3149, DOI: 10.1007/s10989-005-9269-4 abstract -----	1-10, 15-22, 24, 30-49, 51,108, 109,138, 173,174
X	Nicolas R. Barthélemy ET AL: "Tau hyperphosphorylation on T217 in cerebrospinal fluid is specifically associated to amyloid-[beta] pathology", bioRxiv, 30 November 2017 (2017-11-30), pages 1-20, XP055621444, DOI: 10.1101/226977 Retrieved from the Internet: URL:https://www.biorxiv.org/content/biorxiv/early/2017/11/30/226977.full.pdf [retrieved on 2019-09-12]	152-156, 168
Y	abstract Methods: point 2.1 Results: point 3.1 Discussion: second paragraph -----	98-106, 125-137, 141-143, 145-151, 157-162, 164-170
Y	BARTHÉLEMY NICOLAS R ET AL: "HIGHLY SPECIFIC CSF TAU HYPERPHOSPHORYLATION ON T217 OCCURS SIMULTANEOUSLY WITH AMYLOIDOSIS", ALZHEIMER'S & DEMENTIA: THE JOURNAL OF THE ALZHEIMER'SASSOCIATION, vol. 13, no. 7, 17 July 2017 (2017-07-17), XP085216689, ISSN: 1552-5260, DOI: 10.1016/J.JALZ.2017.06.911 Background Conclusions -----	98-106, 125-137, 141-143, 145-151, 157-162, 164-170

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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.
X	US 2008/220449 A1 (VASAN SARA [US] ET AL) 11 September 2008 (2008-09-11)	1-12, 15-22, 24-26, 28-60, 62-64, 66,67, 69-106, 108-116, 118-120, 122,123, 139-152, 156, 163-165, 173,174
Y	page 15; examples 2-3 figure 4	98-106, 125-137, 141-143, 145-151, 157-162, 164-170

X	HIROTAKA YOSHIDA ET AL: "Sequential phosphorylation of tau protein by cAMP-dependent protein kinase and SAPK4/p38? or JNK2 in the presence of heparin generates the AT100 epitope", JOURNAL OF NEUROCHEMISTRY, vol. 99, no. 1, 1 October 2006 (2006-10-01), pages 154-164, XP055621450, GB ISSN: 0022-3042, DOI: 10.1111/j.1471-4159.2006.04052.x page 155, right-hand column, paragraph 2	1-10, 15-22, 24, 30-49, 51,108, 109,138, 173,174

X	WO 2013/096380 A2 (JANSSEN BIOTECH INC [US]) 27 June 2013 (2013-06-27) page 18 - page 19; example 2 page 19, paragraph 2 page 16, paragraph 2 page 22; table 2 page 21, paragraph 2 figures 6A-6B	1-12, 15-22, 24-26, 28-60, 69-97, 108,109, 138-140, 144,152, 156,163, 173,174

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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.
X	WO 98/22120 A1 (WISTAR INST [US]; UNIV PENNSYLVANIA [US] ET AL.) 28 May 1998 (1998-05-28) page 22; table 2	1-10, 15-22, 24, 30-49, 51,108, 109,138, 173,174
X	US 2014/234214 A1 (GRISWOLD-PRENNER IRENE [US] ET AL) 21 August 2014 (2014-08-21) page 30 - page 31; example 10 page 31; examples 11,12	15,16, 48,49, 107, 173-176
X	CHRISTOPHER M. ACKER ET AL: "Sensitive quantitative assays for tau and phospho-tau in transgenic mouse models", NEUROBIOLOGY OF AGING, vol. 34, no. 1, 1 January 2013 (2013-01-01), pages 338-350, XP055621423, US ISSN: 0197-4580, DOI: 10.1016/j.neurobiolaging.2012.05.010 page 340, left-hand column, paragraph 2	11,12, 15-18, 25-47, 50-56, 69,70, 73, 79-82, 87,89, 95,96, 108,109, 139,140, 144
X	JAN TORLEIF PEDERSEN ET AL: "Tau immunotherapy for Alzheimer's disease", TRENDS IN MOLECULAR MEDICINE, vol. 21, no. 6, 1 June 2015 (2015-06-01), pages 394-402, XP055307560, GB ISSN: 1471-4914, DOI: 10.1016/j.molmed.2015.03.003 in particular table 1; the whole document	15-19, 48,49, 107, 173-176
X	JERE E. MEREDITH JR. ET AL: "Characterization of Novel CSF Tau and ptau Biomarkers for Alzheimer's Disease", PLOS ONE, vol. 8, no. 10, 7 October 2013 (2013-10-07), page e76523, XP055395393, DOI: 10.1371/journal.pone.0076523 abstract figure 2 page 2; table 1	11,12, 15-17, 25,26, 28-47, 50-56, 69-97, 108,109, 139,140, 144

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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:

see additional 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 an 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.:

1-12, 25-29, 62-64, 66, 67, 119, 120, 122, 123, 138, 139(completely); 15-22 24, 30-60, 69-116, 118, 125-137, 140-170, 173-176(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10, 62-64, 66, 67, 119, 120, 122, 123, 138(completely); 15-22, 24, 30-60, 69-116, 118, 125-137, 140-170, 173-176(partially)

   An antibody or antigen binding fragment thereof capable of binding tau, relating to clone DC2E7, comprising the heavy and light chain variable region CDR1-3 sequences with SEQ ID No 1-6, respectively, or having substitutions at the recited positions and its use in the methods of treatment or diagnosis/ detection and other as claimed.

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2. claims: 11, 12, 25-29, 139(completely); 15-17, 30-56, 69-112, 118, 125-137, 140-151, 164, 165, 168, 173-176(partially)

   An antibody or antigen binding fragment thereof capable of binding tau, relating to clone DC2E2, comprising the heavy and light chain variable region CDR1-3 sequences with SEQ ID No 15-20, respectively, and its use in the methods of treatment or diagnosis/ detection and other as claimed.

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3. claims: 13, 14, 65, 68, 121, 124(completely); 15-22, 24, 30-60, 69-116, 118, 125-137, 140-170, 173-176(partially)

   An antibody or antigen binding fragment thereof capable of binding tau, relating to clone DC149, comprising the heavy and light chain variable region CDR1-3 sequences with SEQ ID No 23-28, respectively, and its use in the methods of treatment or diagnosis/ detection or other as claimed.

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4. claims: 23, 61, 117, 171, 172(completely); 15-22, 24, 30-60, 69-116, 118, 125-137, 140-170, 173-176(partially)

   An antibody or antigen binding fragment thereof capable of binding tau, relating to clone DC807, comprising the heavy and light chain variable region CDR1-3 sequences with SEQ ID No 101-106, respectively, and its use in the methods of treatment, diagnosis/ detection or other as claimed.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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