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[Continued on next page]

(54) Title: PHOSPHOSPECIFIC ANTIBODIES RECOGNISING TAU

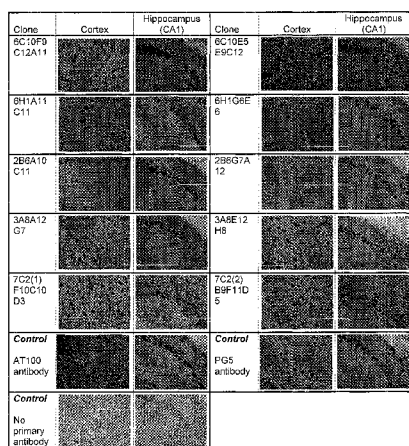


FIGURE 1-1

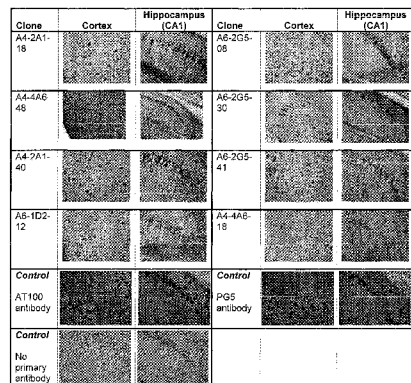


FIGURE 1-2

(57) Abstract: The present invention relates to methods and compositions for the therapeutic and diagnostic use in the treatment of diseases and disorders which are caused by or associated with neurofibrillary tangles. In particular, the invention relates to antibodies, which specifically recognize and bind to phosphorylated pathological protein tau-conformers and to methods and compositions involving said antibodies for the therapeutic and diagnostic use in the treatment of tauopathies including Alzheimer's Disease (AD).



(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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 (an) indication(s) in relation to deposited biological material furnished under Rule 13bis separately from the description (Rules 13bis.4(d)(i) and 48.2(a)(viii))
- with sequence listing part of description (Rule 5.2(a))

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

31 May 2012

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/067604

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/18 G01N33/68 A61K39/00
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)
C07K G01N A61K

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 practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEE G ET AL: "Phosphorylation of tau by fyn: implications for Alzheimer's disease", JOURNAL OF NEUROSCIENCE, THE SOCIETY, WASHINGTON, DC, US, vol. 24, no. 9, 3 March 2004 (2004-03-03), pages 2304-2312, XP002350398, ISSN: 1529-2401, DOI: 10.1523/JNEUROSCI.4162-03.2004 the whole document page 2305, column 1 - column 2 figures 1-2,5-7 ----- -/-	1-120



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
"E" earlier document 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

26 March 2012

Date of mailing of the international search report

03/04/2012

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/067604

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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X	US 2008/050383 A1 (SIGURDSSON EINAR [US] ET AL) 28 February 2008 (2008-02-28) the whole document claims 1,6,31,37,38 page 11; sequence 6 -----	1-120
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X	US 2005/221391 A1 (DAVIES PETER [US]) 6 October 2005 (2005-10-06) the whole document paragraph [0081] -----	1-120
X	US 2002/086009 A1 (ISHIGURO KOICHI [JP] ET AL) 4 July 2002 (2002-07-04) the whole document claims 1,2,7 -----	1-120
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INTERNATIONAL SEARCH REPORT

International application No

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/067604

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International application No

PCT/EP2011/067604

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X,P	WO 2011/013034 A1 (PFIZER VACCINES LLC [US]; SMITH III GEORGE JOSEPH [US]; WILLS KENNETH) 3 February 2011 (2011-02-03) the whole document claim 1 page 8 pages 18-20 page 82; table 5 -----	1-120
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/067604

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZEMLAN F P ET AL: "MONOCLONAL ANTIBODY PHF-9 RECOGNIZES PHOSPHORYLATED SERINE 404 OF TAU PROTEIN AND LABELS PAIRED HELICAL FILAMENTS", JOURNAL OF NEUROSCIENCE RESEARCH, WILEY-LISS, US, vol. 46, no. 1, 1 October 1996 (1996-10-01), pages 90-97, XP000646724, ISSN: 0360-4012, DOI: 10.1002/(SICI)1097-4547(19961001)46:1<90::AID-JNR11>3.0.CO;2-G the whole document table 1 figure 3 -----	1-120
X	RODER H M ET AL: "PHOSPHORYLATION-DEPENDENT MONOCLONAL TAU ANTIBODIES DO NOT RELIABLY REPORT PHOSPHORYLATION BY EXTRACELLULAR SIGNAL-REGULATED KINASE 2 AT SPECIFIC SITES", JOURNAL OF BIOLOGICAL CHEMISTRY, THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, INC, US, vol. 272, no. 7, 14 February 1997 (1997-02-14), pages 4509-4515, XP000979104, ISSN: 0021-9258, DOI: 10.1074/JBC.272.34.21616 the whole document tables 1,2 -----	1-120
X	HIRATA-FUKAE C ET AL: "Levels of soluble and insoluble tau reflect overall status of tau phosphorylation in vivo", NEUROSCIENCE LETTERS, LIMERICK, IE, vol. 450, no. 1, 23 January 2009 (2009-01-23), pages 51-55, XP025800599, ISSN: 0304-3940, DOI: 10.1016/J.NEULET.2008.11.023 [retrieved on 2008-11-13] the whole document figure 1 -----	1-120
X	US 2008/220449 A1 (VASAN SARA [US] ET AL) 11 September 2008 (2008-09-11) the whole document paragraph [0071] example 6 ----- -/--	1-120

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/067604

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S. ODDO ET AL: "Reduction of Soluble Abeta and Tau, but Not Soluble Abeta Alone, Ameliorates Cognitive Decline in Transgenic Mice with Plaques and Tangles", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 281, no. 51, 1 January 2006 (2006-01-01), pages 39413-39423, XP55022863, ISSN: 0021-9258, DOI: 10.1074/jbc.M608485200 the whole document page 39417 -----	1-120

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2011/067604

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.:
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: 19, 36, 50, 79, 80, 89, 90(completely); 1-18, 24-31, 43-45, 53-78, 105-114(partially)

The claims in so far as they relate to the epitope comprising Tau 15-20, pY18.

- 2-5. claims: 1-18, 20-35, 37-49, 51-78, 81-88, 91-114(all partially)

The claims in so far as they relate to the epitopes comprising residue pS409, pT212+pS214, pS396, pS404, respectively.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/067604

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