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24 April 2008

(54) Title: ASSAY FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE BASED ON THE DETERMINATION OF THE RATIO OF GAMMA-SECRETASE ABETA CLEAVAGE PRODUCTS

(57) Abstract: Described is a method for the diagnosis of Alzheimer's disease (AD) or a particular stage of the disease which is based on the determination of the ratio of at least two gamma-secretase cleavage products, Abeta48, Abeta45, Abeta42, Abeta38 and Abeta35, preferably the ratio of Abeta38: Abeta42. A decreased ratio of Abeta38: Abeta42 as compared to the normal ratio is indicative of AD. Moreover, kits suitable for carrying out said diagnostic method are described.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/003505

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/68

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)
G01N

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, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WILTFANG J ET AL: "Highly conserved and disease-specific patterns of carboxyterminally truncated Abeta peptides 1-37/38/39 in addition to 1-40/42 in Alzheimer's disease and in patients with chronic neuroinflammation" JOURNAL OF NEUROCHEMISTRY, vol. 81, no. 3, May 2002 (2002-05), pages 481-496, XP002397538 ISSN: 0022-3042 the whole document	1-14
X	see "Materials and methods" page 482 - page 483	15,16
Y	WO 02/02769 A (VLAAMS INTERUNIVERSITAIR INSTITUUT VOOR BIOTECHNOLOGIE VZW; CRUTS, MAR) 10 January 2002 (2002-01-10)	1-14
X	the whole document	15

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[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

"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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2008	14/03/2008

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pilch, Bartosz

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/21589 A (THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA; LEE, VIRGINIA, M.-Y; D) 22 May 1998 (1998-05-22)	1-14
A	claim 2 page 4, line 12 - page 5, line 9; claim 1	17
X	WO 03/103593 A (BUCK INSTITUTE; HOOK, VIVIAN Y.H) 18 December 2003 (2003-12-18) example 5	15
Y	BLENNOW ET AL: "Cerebrospinal Fluid Protein Biomarkers for Alzheimer's Disease" JOURNAL OF THE AMERICAN SOCIETY FOR EXPERIMENTAL NEUROTHERAPEUTICS, XX, XX, vol. 1, no. 2, April 2004 (2004-04), pages 213-225, XP005321033 ISSN: 1545-5343 page 215, left-hand column, line 7 - page 216, right-hand column, line 12; table 1 page 218, left-hand column, last paragraph - page 219, left-hand column, line 2; table 5	1-14
Y	ANDREASEN N ET AL: "CSF biomarkers for mild cognitive impairment and early Alzheimer's disease" CLINICAL NEUROLOGY AND NEUROSURGERY, ELSEVIER, AMSTERDAM, NL, vol. 107, no. 3, April 2005 (2005-04), pages 165-173, XP004917240 ISSN: 0303-8467 page 166, left-hand column, last paragraph - page 168, left-hand column, line 7	1-14
Y	GOLDE T E ET AL: "Biochemical detection of Abeta isoforms: implications for pathogenesis, diagnosis, and treatment of Alzheimer's disease" BIOCHIMICA ET BIOPHYSICA ACTA. MOLECULAR BASIS OF DISEASE, AMSTERDAM, NL, vol. 1502, no. 1, 26 July 2000 (2000-07-26), pages 172-187, XP004276984 ISSN: 0925-4439 the whole document	1-14
X	WO 2005/116640 A2 (LUDWIG MAXIMILIANS UNI MUENCHE [DE]; MAX PLANCK GESELLSCHAFT [DE]; BER) 8 December 2005 (2005-12-08) claims 1,6 page 1, line 1 - line 12 page 19, line 20 - line 22	17

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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 03/040183 A2 (ABETA GMBH [DE]; MULTAUP GERD [DE]; SCHEUERMANN STEFAN [DE] ABETA GMBH) 15 May 2003 (2003-05-15) claims 19,20 page 2, last paragraph - page 3, line 10 page 5, line 6 - line 8 page 19, line 10 - page 22, line 17	17
A	CHANG L ET AL: "FEMTOMOLE IMMUNODETECTION OF SYNTHETIC AND ENDOGENOUS AMYLOID-BETA OLIGOMERS AND ITS APPLICATION TO ALZHEIMER'S DISEASE DRUG CANDIDATE SCREENING" JOURNAL OF MOLECULAR NEUROSCIENCE, BIRKHAEUSER, CAMBRIDGE, MA, US, vol. 20, no. 3, 2003, pages 305-313, XP008062752 ISSN: 0895-8696 the whole document	17
A	WO 03/001881 A2 (NEW YORK STATE OFFICE OF MENTA [US]; MATHEWS PAUL M [US]; NIXON RALPH) 9 January 2003 (2003-01-09) claims	17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/003505

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. [X] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable 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 reportcovers 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.

[X] 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: 1-16

Method for the diagnosis of Alzheimer's DIsease comprising the determination of the ration of two gamma secretase cleavage products A.beta48, 45, 42, 38 and 35

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2. claim: 17

Method of screening for a therapeutic agent useful in the prophylaxis or treatment of AD comprising the determination of the formation of oligomers or homodimers from the monomers or the formation of monomers from the homodimers or oligomers of (i) amyloid precursor protein, (ii) beta-CTF, (iii) APP-TMS or (iv) a protein comprising an APP-TMS monomer, homodimer or oligomer

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/003505

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2412925 A1	10-01-2002
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		JP 2004536600 T	09-12-2004