(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 May 2006 (26.05.2006)

PCT

(10) International Publication Number
WO 2006/055178 A3

(51) International Patent Classification:
A61K 39/395 (2006.01)

(21) International Application Number:
PCT/US2005/038125

(22) International Filing Date: 21 October 2005 (21.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/621,776	25 October 2004 (25.10.2004)	US
60/652,538	14 February 2005 (14.02.2005)	US

(71) Applicants *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 E. Lincoln Avenue, Rahway, NJ 07065-0907 (US). **NORTHWESTERN UNIVERSITY** [US/US]; 633 Clark Street, Evanston, IL 60208 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ACTON, Paul** [US/US]; 1770 Red Bud Road, Quakertown, PA 18951 (US). **AN, Zhiqiang** [US/US]; 315 Gentry Lane, Ambler, PA 19002 (US). **BETT, Andrew, J.** [CA/US]; 1402 Oxford Circle, Lansdale, PA 19446 (US). **BREESE, Robert** [US/US]; 2360 Witchazel Drive, Quakertown, PA 18951 (US). **DODSON, Elizabeth, Chen** [US/US]; 505 Cherry Drive, Souderton, PA 18964 (US). **KINNEY, Gene** [US/US]; 4125 Justin Court, Collegeville, PA 19426 (US). **KLEIN, William** [US/US]; 1145 Chatfield Road, Winetka, IL 60093 (US). **LAMBERT, Mary, P.** [US/US]; 1956 Linneman Street, Glenview, IL 60025 (US). **LIANG, Xiaoping** [CA/US]; 2054 Woodgate Lane, Collegeville, PA 19426 (US). **SHUGHRUE, Paul** [US/US]; 16 Maentel Drive, West Chester, PA 19382 (US). **STROHL, William, R.** [US/US]; 1086 Tullo Farm Road, Bridgewater, NJ 08807 (US). **VIOLA, Kirsten, L.** [US/US]; 850 N. DeWitt Place, 6K, Chicago, IL 60611 (US). **CHANG, Lei** [CN/US]; 5602 King Arthur Court, Apartment 2, Westmont, IL 60559 (US).

(74) Agents: **LICATA, Jane, Massey** et al.; Licata & Tyrrell P.C., 66 E. Main Street, Marlton, NJ 08053 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
3 May 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTI-ADDL ANTIBODIES AND USES THEREOF

(57) Abstract: The present invention relates to antibodies that differentially recognize multi-dimensional conformations of Aβ-derived diffusible ligands, also known as ADDLs. The antibodies of the invention can distinguish between Alzheimer's Disease and control human brain extracts and are useful in methods of detecting ADDLs and diagnosing Alzheimer's Disease. The present antibodies also block binding of ADDLs to neurons, assembly of ADDLs, and tauphosphorylation and are there useful in methods for the preventing and treating diseases associated with soluble oligomers of amyloid β 1-42.

WO 2006/055178 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/38125

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8): **A61K 39/395**(2006.01)

USPC: 424/146.1
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)
U.S. : 424/146.1

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)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20030068316 A1 (KLEIN et al) 10 April 2003 (10.04.2003), entire document	1-3, 6 and 10

☐ 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 application or patent 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
20 December 2006 (20.12.2006)

Date of mailing of the international search report
22 JAN 2007

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Gregory S. Emch
Telephone No. (571) 272-1600

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/38125

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:
Please See Continuation 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 additional fees, this Authority did not invite payment of any 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.: 1-3,6 and 10

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.

BOX 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.

Group I, claim(s) 1, 2, 3, 6 and 10 are drawn to an isolated antibody capable of differentially recognizing a multi-dimensional conformation of one or more Abeta-derived diffusible ligands, a kit and pharmaceutical composition comprising the antibody, a method for preventing binding of Abeta-derived diffusible ligands to a neuron comprising contacting the neuron with the antibody and a method for treating a disease associated with Abeta-derived diffusible ligands with the composition.

Group II, claim(s) 4 is drawn to a method for inhibiting assembly of Abeta-derived diffusible ligands comprising contacting a sample containing amyloid beta 1-42 peptides with the antibody.

Group III claim(s) 5 is drawn to a method for blocking the phosphorylation of tau protein at Ser202/Thr205 comprising contacting a sample containing a tau protein with the antibody of claim 1.

Group IV claim(s) 7 is drawn to a method for identifying a therapeutic agent that prevents the binding of Abeta-derived diffusible ligands to a neuron.

Group V claim(s) 8 is drawn to a method for detecting Abeta-derived diffusible ligands in a sample.

Group VI claim(s) 9 is drawn to a method for diagnosing a disease associated with Abeta-derived diffusible ligands.

The inventions listed as Groups I-VI 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: Groups I-VI are drawn to separate, distinct inventions and are distinguished from each other because the special technical features which define them by chemical and physical characteristics i.e. the structure/function are different. These special technical features are not shared by each invention as evidenced by the different methods recited by the claims. Since these special technical features are not shared by each invention and since the common features do not establish an advance over the prior art, the inventions of Groups I-VI do not form a single inventive concept within the meaning of Rule 13.2.
It is noted that the original lack of unity mailed 20 November 2006 contained improper descriptions of claims 4 and 5. However, the claims still lack unity for same reasons as set forth previously and as set forth above. The PCT rules allow for examination of the international application on those parts of the application, which relate to the invention first mentioned in the claims. Claims 4 and 5 do not relate to the invention first mentioned in the claims; thus, the holding for unity of invention still applies and is maintained.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/38125

Continuation of B. FIELDS SEARCHED Item 3:
USPAT, USOCR, PGPUBS, EPO, JPO, DERWENT, MEDLINE, BIOSIS, LIFESCI, EMBASE, SCISEARCH and CAPLUS