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14/47(74) Agent: **NATAUPSKY, Steven, J.**; Knobbe, Martens, Ol-
son and Bear, LLP, 620 Newport Center Drive, 16th floor,
Newport Beach, CA 92660 (US).

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60/215,729 28 June 2000 (28.06.2000) US(71) Applicant (for all designated States except US): **SCIOS
INC.** [US/US]; 749 North Mary Ave., Sunnyvale, CA
94086 (US).

(72) Inventors; and

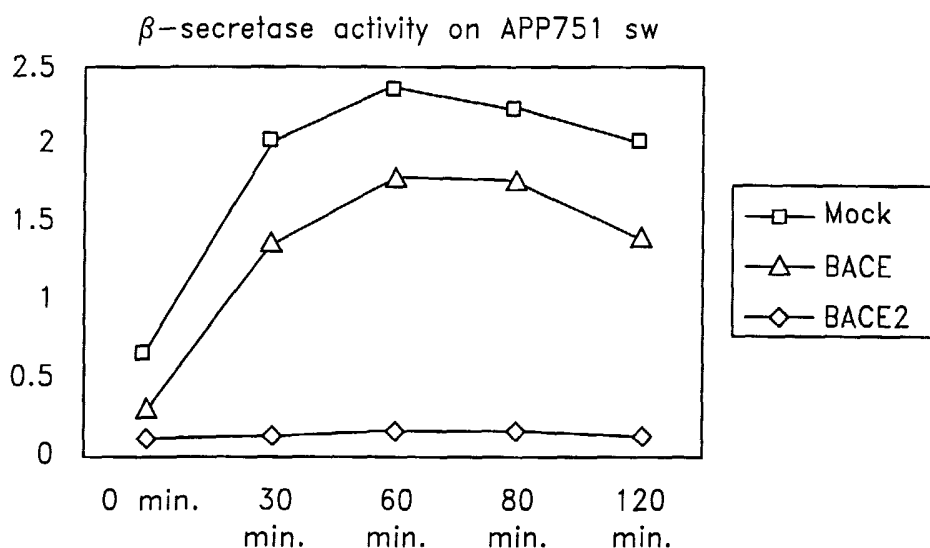
(75) Inventors/Applicants (for US only): **CORDELL, Bar-
bara** [US/US]; 4051 Ben Lomond Drive, Palo Alto, CA
94306 (US). **SCHIMMOLLER, Frauke** [DE/US]; 311
Waverly Street, Apt. #1, Menlo Park, CA 94025 (US).
LIU, Yu-Wang [US/US]; 2349 Roosevelt Court, Santa
Clara, CA 95051 (US). **QUON, Diana, Hom** [US/US]; 51
Hillview Avenue, Redwood City, CA 94062 (US).(81) Designated States (national): AE, AG, AL, AM, AT
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[Continued on next page]

(54) Title: MODULATION OF β -AMYLOID LEVELS BY β -SECRETASE BACE2(57) Abstract: The present invention is based on the findings that BACE2, a homolog of β -secretase BACE, is able to stimulate processing of APP in a non-amyloidogenic pathway, thereby suppressing the level of A β . Accordingly, the present invention provides methods and means for the identification and use of modulators of this unique activity of BACE2 to suppress A β production. The compounds identified using the methods and means provided herein may be used as potential candidates for the treatment of Alzheimer's disease and other neurological diseases.



(15) Information about Correction:

Previous Correction:

see PCT Gazette No. 43/2002 of 24 October 2002, Section II

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.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/20465

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/48 G01N33/50 A61P25/28 //C12N15/57,C12N9/64,
C07K14/47

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)

IPC 7 A61K C12N

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, WPI Data, PAJ, MEDLINE, BIOSIS, SEQUENCE SEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 848 062 A (SMITHKLINE BEECHAM PLC ;SMITHKLINE BEECHAM CORP (US)) 17 June 1998 (1998-06-17) page 1, line 25 - line 38 page 9, line 29 - line 33 page 12, line 11 - line 12; claims ---	1-27, 51-56
P,X	WO 01 23533 A (GURNEY MARK ;BIENKOWSKI MICHAEL JEROME (US); UPJOHN CO (US)) 5 April 2001 (2001-04-05) page 1, line 14 - line 17 page 2, line 14 - line 17 page 3, line 9 - line 10 page 10 -page 26; claims; examples 13-15 --- -/--	1-31, 36-45, 51-56

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in 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.
- *G* document member of the same patent family

Date of the actual completion of the international search

10 October 2002

Date of mailing of the international search report

24/10/2002

Name and mailing address of the ISA

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

Authorized officer

Bayrak, S

INTERNATIONAL SEARCH REPORT

Inter.  al Application No

PCT/US 01/20465

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BENNETT BRIAN D ET AL: "Expression analysis of BACE2 in brain and peripheral tissues." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 27, 7 July 2000 (2000-07-07), pages 20647-20651, XP002214379 ISSN: 0021-9258 cited in the application the whole document ----	1-45, 51-56
A	ACQUATI F ET AL: "The gene encoding DRAP (BACE2), a glycosylated transmembrane protein of the aspartic protease family, maps to the Down critical region" FEBS LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 468, no. 1, 18 February 2000 (2000-02-18), pages 59-64, XP004260998 ISSN: 0014-5793 cited in the application the whole document -----	1-45, 51-56

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/20465

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:
Although claims 1-27 (as far as in vivo application is concerned) and claims 51-56 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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 fee, this Authority did not invite payment of any additional fee.
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.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

1. Claims 1-45, 51-56 relate to compounds defined by reference to a desirable characteristic or property, namely "antagonist", "agonist", "modulator", "fragment thereof", "an enzyme having a pH optimum at about pH 6.5-7.0, and an estimated MW of about 32-39 kDa as calculated from radiation inactivation analysis of HEK293 cell membrane extracts, or about 20-26 kDa as calculated from radiation inactivation analysis of human brain samples, with a candidate compound", "an enzyme having a pH optimum at about pH 4.5-5.0, and an estimated MW of about 50-60 kDa as calculated from radiation inactivation analysis of HEK293 cell membrane extracts, or human brain samples (BACE1)". The claims 1-45, 51-56 cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity because the expressions "antagonist", "agonist", "modulator", "fragment thereof", "an enzyme having a pH optimum at about pH 6.5-7.0, and an estimated MW of about 32-39 kDa as calculated from radiation inactivation analysis of HEK293 cell membrane extracts, or about 20-26 kDa as calculated from radiation inactivation analysis of human brain samples, with a candidate compound", "an enzyme having a pH optimum at about pH 4.5-5.0, and an estimated MW of about 50-60 kDa as calculated from radiation inactivation analysis of HEK293 cell membrane extracts, or human brain samples (BACE1)" used in claims 1-45, 51-56 are unclear and leave the reader in doubt as to the meaning of the technical feature to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT). Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

1.2 Claims 1-27, 51-56 relate to the use of a pharmaceutical preparation for prophylaxis or treatment of a disease involving "modulating/inhibiting the enzymatic production of beta-amyloid peptide from APP", "of beta-amyloid deposits in the CNS", or "an AD-type pathology", "inhibiting the release of a full-length beta-amyloid polypeptide from beta-amyloid precursor protein (APP) or a fragment thereof, comprising cleaving said APP or APP fragment by a BACE2 polypeptide or an agonist thereof at a site interfering with beta-secretase processing of said APP or APP fragment" which encompass a multitude of different diseases. The claims thus cover a rather large number of diseases, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Art. 5 PCT for only a very limited number of diseases. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims 1-27, 46-56 also lack clarity because it is not fully possible to determine the diseases for which protection might legitimately be sought (Art. 6 PCT). Again, this lack of clarity in the present case is such as to render a meaningful

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the use of BACE2 or Asp1 or SEQ ID No 1 in the treatment of Alzheimer's disease and cerebral amyloid angiopathy.

3. Claims 46-50 encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. Therefore, no search has been performed for claims 46-50 (Art. 5 and 6 PCT).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/20465

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0848062	A	17-06-1998	EP 0848062 A2	17-06-1998
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