

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
26 January 2006 (26.01.2006)

PCT

(10) International Publication Number  
**WO 2006/008294 A3**

(51) International Patent Classification:

*C12Q 1/68* (2006.01)      *G01N 33/53* (2006.01)  
*C12N 9/02* (2006.01)      *A01K 67/027* (2006.01)  
*C07K 16/18* (2006.01)

(21) International Application Number:

PCT/EP2005/053468

(22) International Filing Date: 19 July 2005 (19.07.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/590,372      23 July 2004 (23.07.2004)      US

(71) Applicant (for all designated States except US): **EVOTEC NEUROSCIENCES GMBH** [DE/DE]; Schnackenburgallee 114, 22525 Hamburg (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **VON DER KAMMER, Heinz** [DE/DE]; Verbindungsstr. 6d, 22607 Hamburg (DE). **POHLNER, Johannes** [DE/DE]; Quittenweg 11, 22175 Hamburg (DE).

(74) Agents: **MEYERS, Hans-Wilhelm** et al.; P.O. Box 10 22 41, 50462 Cologne (DE).

(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, 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:

19 October 2006

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: DIAGNOSTIC AND THERAPEUTIC USE OF SLIM3 FOR NEURODEGENERATIVE DISEASES

(57) Abstract: The present invention provides a protein encoded by the SLIM3 gene and discloses the differential expression of the gene SLIM3 coding for SLIM3 proteins in specific brain regions of Alzheimer's disease patients. Based on this finding, the invention provides a method for diagnosing or prognosticating Alzheimer's disease in a subject, or for determining whether a subject is at increased risk of developing Alzheimer's disease. Furthermore, this invention provides therapeutic and prophylactic methods for treating or preventing Alzheimer's disease and related neurodegenerative disorders using the SLIM3 gene and its corresponding gene products. A method of screening for modulating agents of neurodegenerative diseases is also disclosed.



WO 2006/008294 A3

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2005/053468

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. C12Q1/68 C12N9/02 C07K16/18 G01N33/53 A01K67/027

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)  
 C12Q G01N A01K

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, BIOSIS, EMBASE, MEDLINE, Sequence Search

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/100092 A (EVOTEC NEUROSCIENCES GMBH; HESTERKAMP, THOMAS; VON DER KAMMER, HEINZ;) 4 December 2003 (2003-12-04) the whole document	1-8, 10-12
Y	WO 02/16636 A (EVOTEC NEUROSCIENCES GMBH ;HIPFEL RAINER (DE); KRAPPA RALF (DE); P) 28 February 2002 (2002-02-28) the whole document	1-8, 10-12
	----- -/--	

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

19 April 2006

Date of mailing of the international search report

26. 07. 2006

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  
  
 Hagenmaier, S

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2005/053468

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ALBRECHT C ET AL: "Spatio - temporal gene expression profiling in Alzheimer's disease." SOCIETY FOR NEUROSCIENCE ABSTRACT VIEWER AND ITINERARY PLANNER, vol. 2003, 2003, pages Abstract No. 202.18 URL-http://sf, XP008062372 & 33RD ANNUAL MEETING OF THE SOCIETY OF NEUROSCIENCE; NEW ORLEANS, LA, USA; NOVEMBER 08-12, 2003 abstract	1-8, 10-12
Y	TANAHASHI H ET AL: "Alzheimer's disease-associated presenilin 2 interacts with DRAL, an LIM-domain protein." HUMAN MOLECULAR GENETICS. 22 SEP 2000, vol. 9, no. 15, 22 September 2000 (2000-09-22), pages 2281-2289, XP002374761 ISSN: 0964-6906 cited in the application the whole document	1-8, 10-12
Y	CHAN K K ET AL: "Molecular cloning and characterization of FHL2, a novel LIM domain protein preferentially expressed in human heart" GENE: AN INTERNATIONAL JOURNAL ON GENES AND GENOMES, ELSEVIER, AMSTERDAM, NL, vol. 210, no. 2, 14 April 1998 (1998-04-14), pages 345-350, XP004118187 ISSN: 0378-1119 cited in the application the whole document	1-8, 10-12
Y	DATABASE UniProt [Online] 1 November 1997 (1997-11-01), "Four and a half LIM domains protein 2 (FHL-2) (Skeletal muscle LIM- protein 3) (SLIM 3) (LIM-domain protein DRAL)." XP002377336 retrieved from EBI accession no. UNIPROT:FHL2_HUMAN Database accession no. FHL2_HUMAN the whole document	1-8, 10-12
A	WO 03/087768 A (MITOKOR; THE BUCK INSTITUTE FOR AGE RESEARCH; GHOSH, SOUMITRA, S; FAHY) 23 October 2003 (2003-10-23) claims 1-19; sequence 169 the whole document	

-/--

INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2005/053468

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 03/054152 A (HYSEQ, INC; TANG, Y., TOM; ASUNDI, VINOD; GOODRICH, RYLE, W; REN, FEIY) 3 July 2003 (2003-07-03) claims 1-26; sequence 1020 pages 1-114</p>	
A	<p>LORING J F ET AL: "A gene expression profile of Alzheimer's disease." DNA AND CELL BIOLOGY. UNITED STATES NOV 2001, vol. 20, no. 11, November 2001 (2001-11), pages 683-695, XP002233087 ISSN: 1044-5498 the whole document</p>	
A	<p>"Consensus report of the Working Group on: "Molecular and Biochemical Markers of Alzheimer's Disease". The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group." NEUROBIOLOGY OF AGING. UNITED STATES 1998 MAR-APR, vol. 19, no. 2, March 1998 (1998-03), pages 109-116, XP002233088 ISSN: 0197-4580 the whole document</p>	
P,X	<p>EP 1 491 895 A (UNIVERSITAETSKLINIKUM FREIBURG) 29 December 2004 (2004-12-29) abstract page 6, line 34 - page 7, line 5</p>	3

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2005/053468

## Box 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 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 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.:  
  
1-8, 10-12 (completely)

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

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

1. claims: 1-8,10-12 (all completely)

A method of diagnosing or prognosticating Alzheimer's disease comprising determining the level and/or activity of a transcription/translation product of the SLIM3 gene in a sample; use of a kit for diagnosing or prognosticating Alzheimer's disease comprising at least one reagent that selectively detects a transcription/translation product of the SLIM3 gene; a recombinant non-human animal comprising a non-native gene sequence coding for a SLIM3 protein with Seq. ID 1; methods for screening for a modulator of Alzheimer's disease using the SLIM3 gene or a transcription/translation product of the SLIM3 gene; use of a protein molecule being a translation product of the SLIM3 gene for use as a diagnostic/screening target for Alzheimer's disease; use of an antibody specifically immunoreactive with a protein molecule of SLIM3 having Seq. ID 1 for detecting Alzheimer's disease.

---

2. claim: 9 (completely)

A method for testing a compound, preferably for screening a plurality of compounds to determine the degree of binding of said compounds to a SLIM3 protein having Seq. ID 1 or to a fragment or derivative thereof.

---

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2005/053468

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0310092	A	04-12-2003	AU	2003242588 A1	12-12-2003
WO 0216636	A	28-02-2002	AU	8983401 A	04-03-2002
WO 03087768	A	23-10-2003	AU	2003223520 A1	27-10-2003
WO 03054152	A	03-07-2003	AU	2002366951 A1	09-07-2003
			CA	2469941 A1	03-07-2003
			EP	1504099 A2	09-02-2005
EP 1491895	A	29-12-2004	CA	2530130 A1	06-01-2005
			WO	2005001482 A1	06-01-2005