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- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/206,428 (CON)
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- (88) Date of publication of the international search report:
29 August 2002
- (72) Inventor; and
- (75) Inventor/Applicant (*for US only*): **ZLOKOVIC, Berislav, V.** [US/US]; 3345 Elmwood Avenue, Rochester, NY 14610 (US).
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.



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(54) Title: DIAGNOSIS OF ALZHEIMER'S DISEASE LDL RECEPTOR PROTEIN-1

(57) Abstract: Brain endothelial low-density lipoprotein receptor related protein-1 (LRP-1) mediates vascular clearance of Alzheimer's amyloid- β peptide (A β) from the brain. Transport of A β occurs across the blood-brain barrier (BBB) to the systemic circulation, but the brain endothelium is compromised in Alzheimer's disease. The invention is used to diagnose the disease in symptomatic and asymptomatic individuals, to identify those at risk for disease or already affected thereby, to determine the stage of disease or its progression, to intervene earlier in or alter the disease's natural history, to provide a target for therapeutic or prophylactic treatments, to screen drugs or compare medical regimens, to determine the effectiveness of a drug or medical regimen, or any combination thereof.

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 G01N33/92 A61P25/28 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)

IPC 7 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)

BIOSIS, MEDLINE, CHEM ABS Data, EMBASE, EPO-Internal, 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.
X	WO 97 04794 A (GEN HOSPITAL CORP ; AMERICAN NAT RED CROSS (US)) 13 February 1997 (1997-02-13) page 4, line 17,18 page 12, line 7 - line 11 page 23, line 20 - line 23 --- -/--	1-3, 14

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.
- *&* document member of the same patent family

Date of the actual completion of the international search

13 June 2002

Date of mailing of the international search report

24/06/2002

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INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US 01/16561

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>QIU ZHIHUA ET AL: "alpha2-Macroglobulin enhances the clearance of endogenous soluble beta-amyloid peptide via low-density lipoprotein receptor-related protein in cortical neurons." JOURNAL OF NEUROCHEMISTRY, vol. 73, no. 4, October 1999 (1999-10), pages 1393-1398, XP008003745 ISSN: 0022-3042 page 1393, left-hand column, paragraph 1 -right-hand column, paragraph 2 page 1395, left-hand column, paragraph 2 -right-hand column, paragraph 1 page 1397, right-hand column, paragraph 3 ---</p>	4-6,8,14
X	<p>JORDAN J ET AL: "ISOFORM-SPECIFIC EFFECT OF APOLIPOPROTEIN E ON CELL SURVIVAL AND BETA-AMYLOID-INDUCED TOXICITY IN RAT HIPPOCAMPAL PYRAMIDAL NEURONAL CULTURES" JOURNAL OF NEUROSCIENCE, NEW YORK, NY, US, vol. 18, no. 1, 1 January 1998 (1998-01-01), pages 195-204, XP002930147 ISSN: 0270-6474 page 197, left-hand column, paragraph 2 -right-hand column, paragraph 2 ---</p>	4-7,14
A	<p>NARITA M ET AL: "ALPHA2-MACROGLOBULIN COMPLEXES WITH AND MEDIATES THE ENDOCYTOSIS OF BETA-AMYLOID PEPTIDE VIA CELL SURFACE LOW-DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN" JOURNAL OF NEUROCHEMISTRY, NEW YORK, NY, US, vol. 69, no. 5, 1997, pages 1904-1911, XP000921049 ISSN: 0022-3042 cited in the application page 1908, right-hand column, paragraph 2 ---</p>	12
P,X	<p>SHIBATA MASAYOSHI ET AL: "Clearance of Alzheimer's amyloid-beta1-40 peptide from brain by LDL receptor-related protein-1 at the blood-brain barrier." JOURNAL OF CLINICAL INVESTIGATION, vol. 106, no. 12, December 2000 (2000-12), pages 1489-1499, XP001077700 ISSN: 0021-9738 page 1490, left-hand column, line 4 - paragraph 2 figure 6 --- -/--</p>	1-12,14

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/16561

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>ZLOKOVIC B V ET AL: "Role of low-density lipoprotein receptor related protein-1 in vascular clearance of amyloidbeta1-40 peptide from brain." SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 26, no. 1-2, 2000, pages Abstract No.-275.18, XP001077059 30th Annual Meeting of the Society of Neuroscience; New Orleans, LA, USA; November 04-09, 2000 ISSN: 0190-5295 abstract</p> <p style="text-align: center;">-----</p>	1-12,14

INTERNATIONAL SEARCH REPORT

International application No.
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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:
see FURTHER INFORMATION sheet PCT/ISA/210

2. Claims Nos.: 13
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.1

Although claims 1-3 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound.

Although claims 4-12 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.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

Continuation of Box I.2

Claims Nos.: 13

Present claim 13 relates to a compound (drug) defined by reference to a desirable characteristic or property, namely being identifiable by the method of claim 12.

The claims cover all drugs having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for no such products. 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 (Article 6 PCT). An attempt is made to define the drug by reference to a result to be achieved. 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. 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 screening method per se (claim 12).

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 01/16561

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9704794	A	13-02-1997	CA 2246561 A1
			WO 9704794 A1
			US 6156311 A
			13-02-1997
			05-12-2000
