

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
17 January 2008 (17.01.2008)

PCT

(10) International Publication Number  
**WO 2008/008846 A3**

(51) International Patent Classification:  
*C12Q 1/68* (2006.01)

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(21) International Application Number:  
PCT/US2007/073272

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

(22) International Filing Date: 11 July 2007 (11.07.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/807,027 11 July 2006 (11.07.2006) US

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(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, MT, 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).

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Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:  
14 August 2008

(54) Title: DIFFERENTIAL EXPRESSION OF MOLECULES ASSOCIATED WITH INTRA-CEREBRAL HEMORRHAGE

(57) Abstract: Methods are provided for evaluating a stroke, for example for determining whether a subject has had a hemorrhagic stroke, determining the severity or likely neurological recovery of a subject who has had a hemorrhagic stroke, and determining a treatment regimen for a subject who has had a hemorrhagic stroke, as are arrays and kits that can be used to practice the methods. In particular examples, the method includes screening for expression of hemorrhagic stroke related genes (or proteins), such as genes (or proteins) involved in suppression of the immune response, genes (or proteins) involved in vascular repair, genes (or proteins) involved in the acute inflammatory response, genes (or proteins) involved in cell adhesion, genes (or proteins) involved in hypoxia, genes (or proteins) involved in signal transduction, and genes (or proteins) involved in the response to the altered cerebral microenvironment. Arrays and kits are provided that can be used in the disclosed methods. Also provided are methods of identifying one or more agents that alter the activity (such as the expression) of a hemorrhagic stroke-related molecule.



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**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/US2007/073272

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. C12Q1/68

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)  
C12Q

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, MEDLINE, BIOSIS, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/017523 A (UNIV GENEVE [CH]; LUCAS BRIAN [GB]; LESCUYER PIERRE [FR]; HOCHSTRASSER) 24 February 2005 (2005-02-24) claims 1,5,24,32 example 1 figures 1-3	1-60
X	US 2005/130230 A1 (DAVALOS ANTONI [ES] ET AL) 16 June 2005 (2005-06-16) page 3, paragraph 26 page 3, paragraph 30 page 29, paragraphs 195,197,199	1-60
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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

13 June 2008

Date of mailing of the international search report

24/06/2008

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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2007/073272

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 2006/036220 A (PREDICTION SCIENCES LLC [US]; CASTELLANO MAR [ES]; DAVALOS ANTONI [ES]) 6 April 2006 (2006-04-06) page 6, paragraph 23 page 8, paragraph 30	1-60
X	US 2003/219807 A1 (LUBBERT HERMANN [DE] ET AL) 27 November 2003 (2003-11-27) page 4, paragraph 63 claims 1,16-21	1-60
X	US 2003/119064 A1 (VALKIRS GUNARS E [US] ET AL) 26 June 2003 (2003-06-26) page 2, paragraph 14 page 3, paragraph 24 page 9, paragraphs 80,81 figure 1	1-60
X	US 2004/209307 A1 (VALKIRS GUNARS [US] ET AL) 21 October 2004 (2004-10-21) page 2, paragraphs 15,19,20 page 3, paragraphs 22,26 page 12, paragraph 108 page 36, paragraph 256 tables 4-6	1-60
X	US 2004/219509 A1 (VALKIRS GUNARS E [US] ET AL) 4 November 2004 (2004-11-04) examples 5,6,10	1-60
X	US 2005/255484 A1 (VALKIRS GUNARS E [US] ET AL) 17 November 2005 (2005-11-17) example 6	1-60
X	US 2005/136496 A1 (JACKOWSKI GEORGE [CA]) 23 June 2005 (2005-06-23) table 3 figures 1-10 page 9, paragraphs 58,65	1-60
X	US 6 780 606 B1 (JACKOWSKI GEORGE [CA]) 24 August 2004 (2004-08-24) table 3 column 17, line 64 - column 18, line 21	1-60
X	"Affimetrix GeneChip Human Genome U133 Array Set HG-U133A" GEO,, 1 January 1900 (1900-01-01), XP002254749 the whole document	50-60

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2007/073272

## Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
  - a. type of material
    - a sequence listing
    - table(s) related to the sequence listing
  - b. format of material
    - on paper
    - in electronic form
  - c. time of filing/furnishing
    - contained in the international application as filed
    - filed together with the international application in electronic form
    - furnished subsequently to this Authority for the purpose of search
2.  In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 65

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

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Continuation of Box II.2

Claims Nos.: 65

The subject-matter of claim 65 relates to a method of treating a mammal who has had a haemorrhagic stroke comprising administering the agent identified using the method of claim 61 to the mammal. Present claim 65 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claim attempts to define the agent used in the treatment only in that it is able to treat a patient who has had a haemorrhagic stroke. However, this sole indication does not allow the skilled person to identify any structural feature of the "agent" which could allow its unambiguous definition. Hence, claim 65 so lacks clarity that no complete search over its scope can be done.

The applicant's attention is drawn to the fact that 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. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2007/073272

## 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.: 65  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy**
  
2.  Claims Nos.: 65  
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 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.  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 report covers only those claims for which fees were paid, specifically claims Nos.:  
**1-60**
  
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.
- 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:

Invention 1: claims 1-24, 27-42, 44, 47, 49-50, 51-55, 57-60

- A method of evaluating haemorrhagic stroke in a subject comprising detecting differential expression of at least four molecules listed in any of Tables 2-8 and 15-16 and in particular of IL1R2, amphiphysin, TAP2 and haptoglobin.
- An array.
- A kit.

Invention 2: claims 1-24, 26-42, 51-60

- Same method, array and kit as herein above, wherein the differential expression profile of the 47 genes listed in Tab. 2 is detected.

Invention 3: claims 1-24, 26-42, 51-60

- Same method, array and kit as herein above, wherein the differential expression profile of the 1263 genes listed in Tab. 3 is detected.

Invention 4: claims 1-24, 26-42, 51-60

- Same method, array and kit as herein above, wherein the differential expression profile of the 119 genes listed in Tab. 4 is detected.

Invention 5: claims 1-42, 43, 45-46, 48, 51-60

- Same method, array and kit as herein above, wherein the differential expression profile of the 30 genes listed in Tab. 5 is detected.

Invention 6: claims 1-24, 26-42, 51-60

- Same method, array and kit as herein above, wherein the differential expression profile of the 446 genes listed in Tab. 6 is detected.

Invention 7: claims 1-24, 26-42, 51-60

- Same method, array and kit as herein above, wherein the differential expression profile of the 25 genes listed in Tab. 7 is detected.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 8: claims 1-42, 51-60

- Same method, array and kit as herein above, wherein the differential expression profile of the 316 genes listed in Tab. 8 is detected.

Invention 9: claims 1-42, 51-60

- Same method, array and kit as herein above, wherein the differential expression profile of the 5 genes listed in Tab. 15 is detected.

Invention 10: claims 1-42, 51-60

- Same method, array and kit as herein above, wherein the differential expression profil of the 18 genes listed in Tab. 16 is detected.

Inventions 11-2279: claims 61-64.

- A method of identifying an agent that alters an activity of one haemorrhagic stroke-related molecule listed in Tab. 2-8 and 15-16.

Invention 2280: claims 66-67

- A method of imaging a mammalian brain in a subject.

Invention 2281: claims 68-71

- A method of determining whether a subject has suffered a stroke wherein the differential expression of any combination of at least four molecules listed in Tab. 14 is detected.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2007/073272
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005017523	A	24-02-2005	AU 2004264560 A1 24-02-2005
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US 2005255484	A1	17-11-2005	NONE
US 2005136496	A1	23-06-2005	NONE
US 6780606	B1	24-08-2004	NONE