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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: BIOMARKERS OF NEURODEGENERATIVE DISEASE

(57) Abstract: Disclosed are biomarkers for neurodegenerative diseases. Methods of identifying such biomarkers and methods of using such biomarkers to, for example, diagnose neurodegenerative disease and monitor disease progression and treatment. Assays, kits, and solid supports related to the biomarkers are also disclosed.



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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/025491

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/50 G01N33/68 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)
G01N 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, BIOSIS, WPI Data, PAJ, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2001, KVETNOY I M ET AL: "Diagnostic value of immunocytochemical identification of tau-protein in human peripheral blood lymphocytes in Alzheimer's disease" XP002383727 Database accession no. PREV200200142139 abstract & IMMUNOLOGIYA, no. 2, 2001, pages 46-48, XP009067325 ISSN: 0206-4952</p> <p style="text-align: center;">-/--</p>	<p>1-5, 9-20, 24-33, 38-43, 47-53, 57-66,70</p>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the International filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the International filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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.</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 9 June 2006	Date of mailing of the international search report 13. 10. 2006
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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 <p style="text-align: center; font-size: 1.2em;">Hinchliffe, Philippe</p>
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/025491

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>& KVETNOY I M ET AL: "Diffuse neuroendocrine system and mitochondrial diseases: Molecular and cellular bases of pathogenesis, new approaches to diagnosis and therapy" NEUROENDOCRINOLOGY LETTERS 2000 SWEDEN, vol. 21, no. 2, 2000, pages 83-99, XP009067319 ISSN: 0172-780X page 95, column 1, paragraph 6</p> <p>-----</p>	1-5, 9-20, 24-33, 38-43, 47-53, 57-66,70
X	<p>LEVITE M ET AL: "Dopamine interacts directly with its D3 and D2 receptors on normal human T cells, and activates beta1 integrin function" EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 31, no. 12, December 2001 (2001-12), pages 3504-3512, XP002383728 ISSN: 0014-2980 the whole document</p> <p>-----</p>	1-5, 9-20, 24-33, 38-43, 47-53, 57-66,70
X	<p>CARONTI B ET AL: "Dopamine transporter immunoreactivity in peripheral blood lymphocytes in Parkinson's disease" JOURNAL OF NEURAL TRANSMISSION, vol. 108, no. 7, 2001, pages 803-807, XP002383729 ISSN: 0300-9564 the whole document</p> <p>-----</p>	1-5, 9-20, 24-33, 38-43, 47-53, 57-66,70
X	<p>SCHIPPER H M ET AL: "EVALUATION OF HEME OXYGENASE-1 AS A SYSTEMIC BIOLOGICAL MARKER OF SPORADIC AD" NEUROLOGY, LIPPINCOTT WILLIAMS & WILKINS, PHILADELPHIA, US, vol. 6, no. 54, 28 March 2000 (2000-03-28), pages 1297-1304, XP001064649 ISSN: 0028-3878 abstract</p> <p>-----</p>	1-5, 9-20, 24-33, 38-43, 47-53, 57-66,70
X	<p>INESTROSA N C ET AL: "Blood markers in Alzheimer disease: Subnormal acetylcholinesterase and butyrylcholinesterase in lymphocytes and erythrocytes" JOURNAL OF THE NEUROLOGICAL SCIENCES, vol. 122, no. 1, 1994, pages 1-5, XP002383730 ISSN: 0022-510X the whole document</p> <p>-----</p>	1-5, 9-20, 24-33, 38-43, 47-53, 57-66,70
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/025491

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GIUBILEI F ET AL: "INTERACTION BETWEEN CHOLINERGIC AND CATECHOLAMINERGIC SYSTEMS IN NEURODEGENERATIVE COGNITIVE IMPAIRMENT." SOCIETY FOR NEUROSCIENCE ABSTRACT VIEWER AND ITINERARY PLANNER, vol. 2002, 2002, pages Abstract No. 786.15 URL-http://sf, XP002383732 & 32ND ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE; ORLANDO, FLORIDA, USA; NOVEMBER 02-07, 2002 abstract	1-5, 9-20, 24-33, 38-43, 47-53, 57-66,70
X	----- TSUJI T ET AL: "Proteomic profiling and neurodegeneration in Alzheimer's disease." NEUROCHEMICAL RESEARCH, vol. 27, no. 10, October 2002 (2002-10), pages 1245-1253, XP002383733 ISSN: 0364-3190 the whole document -----	1-5, 9-20, 24-33, 38-43, 47-53, 57-66,70

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/025491

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.: 8, 23, 36, 46, 56, 69, 72
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.: 8, 23, 36, 46, 56, 69, 72
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 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.:
1-5, 9-20, 24-33, 37-43, 47-53, 57-66, 70

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 II.1

Although claims 1-70 could be 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/composition.

The dependencies of the claims are incorrect. For example claim 16 should be dependent upon claim 15 and not claim 12. The same applies to claims 18 and 19 analogously.

Continuation of Box II.2

Claims Nos.: 8,23,36,46,56,69,72

The definition of proteins found in these claims is not specific enough to allow a search to be made because the molecular weight and isoelectric points provided do not provide sufficient information to characterise one protein uniquely. MW is not regarded as reliable data when the method of calculating it is not provided.

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, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-5,9-20,24-33,37-43,47-53,57-66,70

A method of diagnosing a neurodegenerative disorder in a subject wherein a biomarker is sought in a leukocyte population or lysate thereof. No specific biomarker is suggested.

2. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part), 67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein an HSP60 biomarker is sought in a leukocyte population or lysate thereof.

3. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part), 67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein an dihydrolipoamide dehydrogenase biomarker is sought in a leukocyte population or lysate thereof.

4. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part), 67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein an ER-60 biomarker is sought in a leukocyte population or lysate thereof.

5. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part), 67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a Glucose-6-phosphate dehydrogenase biomarker is sought in a leukocyte population or lysate thereof.

6. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part), 67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein an ATP synthase beta chain biomarker is sought in a leukocyte population or lysate thereof.

7. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part), 67 (part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of diagnosing a neurodegenerative disorder in a subject wherein an Annexin I biomarker is sought in a leukocyte population or lysate thereof.

8. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part), 67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a 14-3-3-epsilon biomarker is sought in a leukocyte population or lysate thereof.

9. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part), 67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a Prohibitin biomarker is sought in a leukocyte population or lysate thereof.

10. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part), 67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a Phosphoglycerate mutase 1 biomarker is sought in a leukocyte population or lysate thereof.

11. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part), 67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein an Apo A1 biomarker is sought in a leukocyte population or lysate thereof.

12. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part), 67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a superoxide dismutase biomarker is sought in a leukocyte population or lysate thereof.

13. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part), 67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a RNA binding protein reg. subunit biomarker is sought in a leukocyte population or lysate thereof.

14. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part),

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a Chain A thioredoxin peroxidase B biomarker is sought in a leukocyte population or lysate thereof.

15. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part),
67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a RAS related protein biomarker is sought in a leukocyte population or lysate thereof.

16. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part),
67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a tumour rejection antigen biomarker is sought in a leukocyte population or lysate thereof.

17. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part),
67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a Haptoglobin biomarker is sought in a leukocyte population or lysate thereof.

18. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part),
67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a Fibrin beta biomarker is sought in a leukocyte population or lysate thereof.

19. claims: 6 (part), 21 (part), 34 (part), 44 (part), 54 (part),
67 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein all of the above are used in combination as biomarkers and are sought in a leukocyte population or lysate thereof.

20. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a cyclin D1 transcript biomarker is sought in a leukocyte population or lysate thereof.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

21. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a cyclin B transcript biomarker is sought in a leukocyte population or lysate thereof.

22. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a cyclin G1 transcript biomarker is sought in a leukocyte population or lysate thereof.

23. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a weel transcript biomarker is sought in a leukocyte population or lysate thereof.

24. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a hTR2 transcript biomarker is sought in a leukocyte population or lysate thereof.

25. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a CDC25b transcript biomarker is sought in a leukocyte population or lysate thereof.

26. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a GSK3 beta transcript biomarker is sought in a leukocyte population or lysate thereof.

27. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of diagnosing a neurodegenerative disorder in a subject wherein a protein kinase C alpha transcript biomarker is sought in a leukocyte population or lysate thereof.

28. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a C5 transcript biomarker is sought in a leukocyte population or lysate thereof.

29. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a C1 inhibitor transcript biomarker is sought in a leukocyte population or lysate thereof.

30. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a IL-17r transcript biomarker is sought in a leukocyte population or lysate thereof.

31. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a IL-8 transcript biomarker is sought in a leukocyte population or lysate thereof.

32. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a LIF transcript biomarker is sought in a leukocyte population or lysate thereof.

33. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a TNF alpha transcript biomarker is sought in a leukocyte population or lysate thereof.

34. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a IL-10r transcript biomarker is sought in a leukocyte population or lysate thereof.

35. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a Alpha 1 antichymotrypsin transcript biomarker is sought in a leukocyte population or lysate thereof.

36. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a HSP 27 transcript biomarker is sought in a leukocyte population or lysate thereof.

37. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a HSP90 transcript biomarker is sought in a leukocyte population or lysate thereof.

38. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a crystalline transcript biomarker is sought in a leukocyte population or lysate thereof.

39. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a GADPH transcript biomarker is sought in a leukocyte population or lysate thereof.

40. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a ferritin H transcript biomarker is sought in a leukocyte population or lysate thereof.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

41. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a Ferritin L transcript biomarker is sought in a leukocyte population or lysate thereof.

42. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a cox 1 transcript biomarker is sought in a leukocyte population or lysate thereof.

43. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a cox 2 transcript biomarker is sought in a leukocyte population or lysate thereof.

44. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a transferrin transcript biomarker is sought in a leukocyte population or lysate thereof.

45. claims: 7 (part), 22 (part), 35 (part), 45 (part), 55 (part),
68 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein combinations of the above transcripts are sought as biomarkers in a leukocyte population or lysate thereof.

46. claims: 8 (part), 23 (part), 36 (part), 46 (part), 56 (part),
69 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a protein of MW 27,100 biomarker is sought in a leukocyte population or lysate thereof.

47. claims: 8 (part), 23 (part), 36 (part), 46 (part), 56 (part),
69 (part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of diagnosing a neurodegenerative disorder in a subject wherein a protein of MW 25,400 biomarker is sought in a leukocyte population or lysate thereof.

48. claims: 8 (part), 23 (part), 36 (part), 46 (part), 56 (part),
69 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a protein of MW 27,600 biomarker is sought in a leukocyte population or lysate thereof.

49. claims: 8 (part), 23 (part), 36 (part), 46 (part), 56 (part),
69 (part)

A method of diagnosing a neurodegenerative disorder in a subject wherein a combination of the above MW proteins are used as biomarkers in a leukocyte population or lysate thereof.

50. claims: 71-74

Solid supports comprising any one of the above proteins/transcripts or combinations thereof. Effectively a gene chip or a microtitre plate is covered and these need not be used exclusively for neurodegenerative disorder screening.
