(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 May 2005 (26.05.2005)

PCT

(10) International Publication Number
WO 2005/047484 A3

(51) International Patent Classification:
G01N 33/50 (2006.01)

(21) International Application Number:
PCT/US2004/037994

(22) International Filing Date:
6 November 2004 (06.11.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/518,360	7 November 2003 (07.11.2003)	US
60/526,753	2 December 2003 (02.12.2003)	US
60/546,423	19 February 2004 (19.02.2004)	US
60/547,250	23 February 2004 (23.02.2004)	US
60/558,896	2 April 2004 (02.04.2004)	US
60/572,617	18 May 2004 (18.05.2004)	US
60/586,503	8 July 2004 (08.07.2004)	US

(71) Applicant *(for all designated States except US)*: **CIPHERGEN BIOSYSTEMS, INC.** [US/US]; 6611 Dumbarton Circle, Fremont, CA 94555 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DAVIES, Huw, Alun** [GB/GB]; 27 Bunburry Way, Epsom Downs Surrey KT17 4JP (GB). **MCGUIRE, James** [US/DK]; Hummeltoftevej 108, DK-2830 Virum (DK). **SIMONSEN, Anja, Hviid** [DK/DK]; 11 Lauritz Soerensens Vej, DK-2000 Frederiksberg (DK). **BLENNOW, Kaj** [SE/SE]; Molndal, Sweden (SE). **PODUST, Vladimir** [RU/US]; 1140 Chopin Terrace, #202, Fremont, CA 94538 (US).

(74) Agents: **ULLSPERGER, Chris** et al.; Townsend And Townsend And Crew LLP, Two Embarcadero Center, Eighth Floor, San Francisco, CA 94111-3834 (US).

(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, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, 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, LU, 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*
— *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:
7 June 2007

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 FOR ALZHEIMER'S DISEASE

(57) Abstract: The present invention provides protein-based biomarkers and biomarker combinations that are useful in qualifying Alzheimer's disease status in a patient. In particular, the biomarkers of this invention are useful to classify a subject sample as Alzheimer's or non-Alzheimer's dementia or normal. The biomarkers can be detected by SELDI mass spectrometry. In addition, the invention provides appropriate treatment interventions and methods for measuring response to treatment. Certain biomarkers of the invention may also be suitable for employment as radio-labeled ligands in non-invasive imaging techniques such as Positron Emission Tomography (PET).

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/37994

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.:
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 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:
Please See Continuation 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 additional fees, this Authority did not invite payment of any 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.:

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, 8-27, and 67, to the extent they encompass hemopexin

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/37994

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8): **G01N 33/50**(2007.01)

USPC: 435/7.1
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)
U.S. : 435/7.1

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 practicable, search terms used)
EAST, Pubmed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	YU H et al. Aberrant profiles of native and oxidized glycoproteins in Alzheimer plasma Proteomics 2003 Vol 3, pages 2240-2248.	1,3,5,14,16,18-19,67 ---------- 9-11,21-23
X,P,E --- Y	US 2004/0072261 (KOSTANJEVECKI et al) 15 April 2004 (15.04.2004)	1-5,12-14,16,18-20,24-25,67 ---------- 9-11,21-23
Y	KAWANO M. et al Marked decrease of plasma apolipoprotein AI and AII in Japanese patients with late-onset non-familiar Alzheimer's disease Clinca Chimica Acta 1995 Vol 239. pages 209-211	9
Y, E	US 2004/0072251 (ANDERSON) 15 April 2004 (15.04.2004), paragraph [0008]	11,22

☒ 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 application or patent 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	Date of mailing of the international search report
13 December 2006 (13.12.2006)	09 APR 2007
Name and mailing address of the ISA/US *Mail Stop PCT, Attn: ISA/US* Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Daniel Kolker Telephone No. (571) 272-1600

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/37994

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WILLIAMS A. Overview of Conventional Chromatography Current Protocols in Protein Science 1995, pages 8.1.1 - 8.1.9	21,25
A	IGUCHI H et al Evidence for a novel pituitary protein (7B2) in human brain, cerebrospinal fluid and Plasma: Brain concentration in controls and patients with Alzheimer's disease Peptide 1987 Vol 8 pages 593-598.	10

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1 - 5, 8 - 27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring Hemopexin.

Group 2, claim(s) 1 - 4, 8 - 27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring 7B2 CT fragment.

Group 3, claim(s) 1 - 4, 8 - 27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring Ubiquitin-3aa from CT.

Group 4, claim(s) 1 - 4, 8 - 27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring EA-92 ChrA peptide.

Group 5, claim(s) 1 - 4, 8 - 27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring pancreatic ribonuclease.

Group 6, claim(s) 1 - 4, 8 - 27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring transerythrin S-glutathionylated.

Group 7, claim(s) 1 - 4, 8 - 27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring transerythrin S-Cys/S-CysGly.

Group 8, claim(s) 1 - 4, 8 - 27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring cystatin-C-8aa from NT.

Group 9, claim(s) 1-4, 8-27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring ubiquitin -4aa from CT.

Group 10, claim(s) 1-4,8-27, and 67 each in part drawn to methods for qualifying Alzheimer's disease comprising measuring secretoneurin ChrC/SGII peptide.

Group 11, claim(s) 1-4,8-27, and 67 each in part drawn to methods for qualifying Alzheimer's disease comprising measuring Vasostatin II ChrA peptide.

Group 12, claim(s) 1-4,8-27, and 67 each in part drawn to methods for qualifying Alzheimer's disease comprising measuring chromogranin B peptide.

Group 13, claim(s) 1-4,8-27, and 67 each in part drawn to methods for qualifying Alzheimer's disease comprising measuring A-beta 1-40.

Group 14, claim(s) 1-4, 7-27, and 67 each in part drawn to methods for qualifying Alzheimer's disease comprising measuring apolipoprotein A-II dimer.

Group 15, claim(s) 1-4,8-27 and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring C3a des-Arg.

Group 16, claim(s) 1-4, 8-27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring prostaglandin-D synthase.

Group 17, claim(s) 1-4, 8-27 and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring alpha-1-antichymotrypsin CT fragment).

Group 18, claim(s) 1-4,8-27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring osteopontin CT fragment.

Group 19, claim(s) 1-4,8-27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring VGF(NCBI) peptide.

Group 20, claim(s) 1-4,8-27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring thymosin beta-4-acetylated.

Group 21, claim(s) 1-4, 6, and 8-27, and 67 each in part, drawn to methods for qualifying Alzheimer's disease comprising measuring 10.3kDa.

Groups 22 - 42, claim(s) 28 - 41, drawn kits comprising capture agents which bind to biomarkers as set forth in groups 1 - 21 respectively

Group 43, claim(s) 42 - 45, drawn to software products.

Group 44, claim(s) 46, drawn to an isolated polypeptide.

Group 45, claim(s) 47 - 61, drawn to a method for qualifying Alzheimer's disease comprising measuring SEQ ID NO:2.

Group 46, claim(s) 62 - 63, drawn to screening methods.

Group 47, claim(s) 64 - 65, drawn to methods for treating disease.

Group 48, claim(s) 66, drawn to methods for qualifying Alzheimer's disease comprising measuring beta2 microglobulin.

Group 49, claim(s) 68-69, drawn to methods for qualifying Alzheimer's disease comprising labeling and administering a compound.

The inventions listed as Groups 1 - 49 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group 1 is directed to methods for qualifying Alzheimer's disease comprising measuring Hemopexin. However, because Yu et al. (2003. Proteomics 3(11):2240-2248, published online 11 July 2003) teach measuring hemopoxin in biological samples and teach that it is significantly elevated in patients with Alzheimer's disease, no special technical feature as defined by PCT rule 13.2 exists for Group 1 because it does not define a contribution over the prior art. Groups 2 - 21 and 45 - 49 are drawn to methods which require different technical features as they require different starting materials and detection steps than Group 1. Groups 22 - 44 are drawn to specific products none of which has the same or corresponding technical feature as Group 1. Note that PCT Rule 13 does not provide for multiple products of methods within a single application. Because the technical feature of Group 1 is not a special technical feature and because the technical features of the remaining groups are not present in Group 1, unity of invention is lacking.