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**Declarations under Rule 4.17**:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

**Published**:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
18 December 2014

(54) Title: SYSTEMS AND METHODS FOR CHARACTERIZATION OF MULTIPLE SCLEROSIS

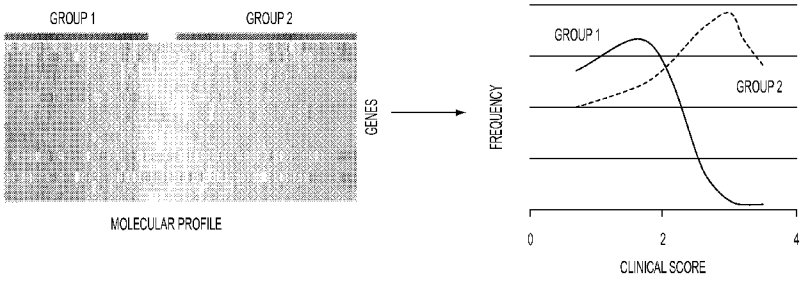


FIG. 1

(57) Abstract: Methods and systems to characterize multiple sclerosis in a subject, e.g., in a subject a progressive form of MS are disclosed.

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# INTERNATIONAL SEARCH REPORT PCT/US2014/029925 23.10.2014

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PCT/US14/29925

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07K 16/28; C12N 5/071; G01N 33/53; A61K 9/00 (2014.01)

USPC - 435/6.12, 6.17, 372.3, 372.2, 372, 366; 436/506

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 (8): C07K 16/28; C12N 5/071; G01N 33/53, 33/564, 33/68; A61K 9/00 (2014.01)
USPC: 435/6.12, 6.17, 372.3, 372.2; 436/506; CPC: C07K 16/28; C12N 5/0634; A61K 9/00, 38/00; G01N 33/564, 33/68

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)

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Espacenet; Google; Google Scholar; PubMed; 'secondary progressive multiple sclerosis,' '(T OR B) ADJ (cell* OR lymphocyte*),' '(erythrocyte* OR e-ERY),' '((granulocyte OR monocyte) near2 (progenitor* OR precursor*)),' 'CFU-GM,' '(genes OR markers OR biomarkers), (expression* OR level*),' therapy

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y<br>---<br>A | US 2010/0062471 A1 (KANTOR, AB et al.) March 11, 2010; paragraphs [0001], [0009], [0045]-[0048], [0053], [0054], [0056], [0057], [0059], [0060], [0065], [0070], [0071], [0092], [0168], [0170], [0177], [0179]-[0181], [0191], [0193], [0199], [0200], [0215], [0251]-[0253], [0267]-[0300]; Table 5 | 69, 74<br>-----<br>1-65 |
| Y<br>---<br>A | US 2006/0088836 A1 (WOHLGEMUTH, J et al.) April 27, 2006; paragraphs [0029], [0032], [0125], [0126], [0129], [0131], [0135], [0212], [0215], [0243], [0247], [0259], [0279]; Tables 10, 11 | 69, 74<br>-----<br>1-65 |

☐ Further documents are listed in the continuation of Box C. ☐

* 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 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 | Date of mailing of the international search report |
|---|---|
| 25 September 2014 (25.09.2014) | 23 OCT 2014 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Shane Thomas<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

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**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 Supplemental Page-***-

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 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.:

Group I+: Claims 1-65, 69, 74

**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 application No.
PCT/US14/29925

-***-Continued from Box No. 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 I: Claims 1-65, 69 and 74 are directed toward methods and a kit for identifying a subject having multiple sclerosis, or at risk of developing secondary progressive multiple sclerosis, comprising determining the expression levels of two or more genes associated with B cells, two or more genes associated with T cells, two or more genes associated with e-ERYs, and two or more genes associated with GMPs in a sample from the subject.

Group II: Claims 66-68 are directed toward a method of determining a gene expression profile for a subject having MS, e.g., SPMS, comprising one or more of: (1) stratifying a subject population; (2) identifying or selecting the subject as likely or unlikely to respond to an MS therapy; (3) selecting an MS therapy; (4) treating the subject; or (5) prognosticating the time course and/or severity of the disease in the subject.

Group III: Claims 70-73 are directed toward system for evaluating a subject population having MS, e.g., SPMS, the system comprising at least one processor operatively connected to a memory.

The inventions listed as Groups I-III 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: the special technical features of Group I include a method of treating or preventing one or more symptoms associated with MS, which is not present in either of Groups II or III; the special technical features of Group II including stratifying a subject population, which is not present in either of Groups I or III; the special technical features of Group III including a system comprising at least one processor operatively connected to a memory.

Group I-III share the technical features including expression of genes in association with MS or SPMS, including genes associated with T cells, B cells, e-ERYs and GMPs (granulocyte/monocyte progenitors), and progression of MS or SPMS. Group I and II share the technical features including selecting an MS therapy.

However, these shared technical features are previously disclosed by US 2010/0055722 A1 to Nayak, et al. (hereinafter 'Nayak') in view of US 2005/0282234 A1 to Ahearn, et al. (hereinafter 'Ahearn'). Nayak discloses the expression of genes in association with MS or SPMS (monitoring or detecting multiple sclerosis in a fluid sample containing circulating phagocytes by detecting biomarkers in the phagocytes, including proteins (expression of genes in association with MS or SPMS); paragraphs [0008], [0030], [0037]), including genes associated with T cells (T-lymphocyte marker (genes associated with T cells); paragraph [0068]), B cells (B-lymphocyte marker; paragraph [0068]), and macrophages or monocytes (monocyte/macrophage cell surface marker; paragraph [0068]); progression of MS or SPMS (monitoring progression of MS; paragraph [0054]); and an MS appropriate therapy (MS appropriate therapy; paragraph [0058]). Nayak does not disclose the expression of genes in e-ERYs or GMPs (granulocyte/monocyte progenitors), or selecting an MS therapy. Ahearn discloses the diagnosis and monitoring of patients with inflammatory diseases (diagnosis and monitoring of patients with inflammatory diseases; abstract), including MS (including MS; paragraph [0027]) comprising determining the level of a marker in an e-ERY (comprising determining the level of a complement pathway component of immature red blood cells i.e. reticulocytes (comprising determining the level of a marker in an e-ERY); paragraphs [0022], [0023]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previous disclosure of Nayak, for integrating the determination of the levels of markers in additional cells in fluid samples, such as in early erythrocytes, as previously disclosed by Ahearn, for effectively characterizing the disease, and enabling an early diagnosis. Furthermore, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have readily determined the levels of biomarkers in cells related to those previously disclosed by Nayak, such as GMPs, depending upon the prevalence of these cells in the sample, as an alternative or supplemental means of characterizing the disease in the subject, using the methods previously disclosed by Nayak. Additionally, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have applied the methods of MS therapy initiation and monitoring previously disclosed by Nayak, in order to have implemented the selection of an alternative therapy for MS when monitoring indicates that the present therapy does not improve the levels of measured biomarkers, in an effort to effectively treat the patient.

Since none of the special technical features of the Groups I-III inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Nayak and Ahearn references, unity of invention is lacking.