Title: DIAGNOSIS AND MONITORING OF DISEASES

Abstract: The present invention relates to the diagnosis and monitoring of diseases and conditions by quantifying markers, including degradation products of disease-associated proteins, such as diketopiperazines composed of the two N-terminal amino acids or the two C-terminal amino acids of such proteins. The methods are useful for diagnosing or monitoring various diseases, including multiple sclerosis, Alzheimer’s disease and ischemia. The invention further provides binding partners specific for the markers and compositions and kits for conducting the methods of the invention.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

<table>
<thead>
<tr>
<th>IPC(7)</th>
<th>US CL.</th>
</tr>
</thead>
<tbody>
<tr>
<td>G01N 35/53, 33/576; A01N 1/00, 1/02, 37/18; A61K 38/00</td>
<td>435/6, 7.1, 7.2, 7.21; 435/501; 514/1, 2</td>
</tr>
</tbody>
</table>

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)

| US: | 435/6, 7.1, 7.2, 7.21; 435/501; 514/1, 2 |

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)

Please See Continuation Sheet

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>MONTINESE et al. Cerebrospinal Fluid Ab-42, Tau, and P2-Dependent Concentrations in Patients with Alzheimer Disease, Other Dementias, and In Age-Matched Controls. Arch Pathol Lab Med. April 2001, Vol. 125, pages 510-512, Figure 1.</td>
<td>1, 2, 13, 14</td>
</tr>
</tbody>
</table>

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

Date of the actual completion of the international search: 14 JUN 2005

Name and mailing address of the ISA/US

- Mail: P.O. Box, Alexandria, Virginia 22313-1450
- Facsimile: (703) 308-5350

Form PCT/ISA/210 (second sheet) (July 1998)
INTERNATIONAL SEARCH REPORT

**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim 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. ☐ Claim 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:

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 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.: 1-15 (Myelin basic protein)

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant’s protest.

☐ No protest accompanied the payment of additional search fees.
BOX II. 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) 1-15, drawn to a method for diagnosing or monitoring a disease or condition including C-reactive protein.

Group 2, claim(s) 16-19, drawn to a method of diagnosing or monitoring multiple sclerosis in a patient.

Group 3, claim(s) 20-21, drawn to a method of diagnosing or monitoring Alzheimer’s disease in a patient.

Group 4, claim(s) 22-32, drawn to a method of diagnosing or monitoring placental ischemia in a pregnant patient.

Group 5, claim(s) 33-46, drawn to an isolated binding partner.

According to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The inventions listed as Groups 1-5 do not relate to a single general inventive concept because they lack the same or corresponding special technical feature.

The technical feature of Group 1 is a method of diagnosing or monitoring a disease or condition comprising obtaining a target marker including a truncated disease-associated protein lacking its two C-terminal amino acids. This special technical feature is shown by Montine et al. (April 2001) "Cerebrospinal Fluid Ab42, Tau, and F2-Isoprostone Concentrations in Patients with Alzheimer Disease, Other Dementias, and in Age-Matched Controls. Arch Pathol Lab Med Vol. 125, pp. 510-512. Montine et al. teaches that measuring Ab42 in cerebrospinal fluid is indicative of Alzheimer’s disease. Ab42 is a truncated version of the full-length APP which is 770 amino acids long thus Ab42 lacks two C-terminal amino acids (Figure 1). Thus the special technical feature of Group 1 lacks novelty thus does not make it a contribution over the prior art.

Group 1 is has the special technical feature of diagnosing diseases via C-reactive proteins, which is not shared by the other groups.

Group 2 is has the special technical feature of multiple sclerosis diagnosis, which is not shared by the other groups.

Group 3 is has the special technical feature of Alzheimer’s disease diagnosis, which is not shared by the other groups.

Group 4 is has the special technical feature of placental ischemia diagnosis, which is not shared by the other groups.

Group 5 has the special technical feature of isolated binding partner, which is not shared by the other groups.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

- Myelin basic protein
- Beta-amyloid
- Rh factor
- Pulmonary surfactant-associated protein A, B, or D
- Insulin
- Tau protein
- Alpha-synuclein
- Albumin

Form PCT/ISA/210 (second sheet) (July 1998)
C-reactive protein
Interleukin 8
S100 proteins
Beta-chorionic gonadotropin
Fetal erythropoietin
Pregnancy-associated protein A
Myoglobin
Tropinin I
Tropinin T
Prostate specific antigen
Amylase
Lipase
Alpha-1-antitrypsin
Erythropoietin
Activated protein C
Tethal chain
Zeta chain
Alpha chain
Beta chain
Delta chain
Epsilon chain
Gamma AG
Brain natriuretic peptide

Continuation of B. FIELDS SEARCHED Item 3:
WEST (USPT, PGPUB, USOCR, JPO, EPO, DERTWENT); NCBI (PUBMED); STN (BIOSCIENCE)
APP770, Ab42, Ab40, diketopiperoxine, DKP, His-Pro-KDP, MBP, myelin basic protein, multiple sclerosis