Title: METHOD AND ANALYTICAL REAGENTS FOR IDENTIFYING THERAPEUTICS USING BIOMARKERS RESPONSIVE TO THIAZOLIDINEDIONES

Abstract: The present invention relates to methods for screening for therapeutics on the basis of biomarkers responsive to treatment with thiazolidinediones, in particular therapeutics having activities analogous to thiazolidinediones. Such therapeutics may be useful, for example, in therapy of Type II diabetes, insulin resistance, obesity, impaired glucose tolerance, metabolic syndrome (syndrome x), cardiovascular diseases, atherosclerosis and dyslipidemia. Furthermore, the invention relates to methods for testing whether an individual will benefit from treatment with the afore mentioned therapeutics. The biomarkers are selected from Fnl4, HMGAl, apelin, fragments and variants thereof.
**INTERNATIONAL SEARCH REPORT**

International application No

PCT/EP2006/009324

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**A. CLASSIFICATION OF SUBJECT MATTER**

INV. G01N33/68 C07K14/705 C07K14/47

ADD. C07K16/28 C07K16/18

According to International Patent Classification (IPC) and both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

GOIN C07K

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, Sequence Search, CHEM ABS Data

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tbody>
<tr>
<td></td>
<td>abstract; lines 33-39 of the left-hand column on page 4; paragraphs [0061]-[0068], [0073][0074] and [0117]-[0124]; example 2; Seq. IDs 4-5, 17, 24 and 25</td>
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<td>X</td>
<td>WO 2005/080972 A (AXARON BIOSCIENCE AG [DE]; SCHNEIDER ARMIN [DE]; ROSSNER MORITZ [DE]); 1 September 2005 (2005-09-01)</td>
<td>1-19, 22-28, 31-34</td>
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<td>* abstract; page 1, line 35; page 7, last paragraph; page 12, third paragraph; example 3 *</td>
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Further special categories of cited documents

* "A" document defining the general state of 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 after the priority date claimed

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**Date of the actual completion of the International search**

18 January 2007

**Date of mailing of the international search report**

20/04/2007

Name and mailing address of the ISA/

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Authorized officer

Fausti, Simone
<table>
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<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>WO 01/94410 A (METCON MEDICIN AB [SE]; SMITH ULF [SE]) 13 December 2001 (2001-12-13) abstract; claims 5,32</td>
<td>1-18, 22-27</td>
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</table>
### 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. **X** Claims Nos.:
   - because they relate to subject matter not required to be searched by this Authority, namely:
     - see **FURTHER INFORMATION** sheet PCT/ISA/210

2. **I** 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 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. **D** As all required additional search fees were timely paid by the applicant, this International Search Report covers all 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. **X** 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.:

   1-18 (partially), 19, 22-27 (partially), 28, 31-34 (partially)

**Remark on Protest**

- **□** The additional search fees were accompanied by the applicant's protest
- **□** No protest accompanied the payment of additional search fees.
Continuation of Box II.1

The subject-matter of claims 1-12 and 18-30 might involve diagnostic methods practised on the human/animal body, because the definition of independent claim 1 does not explicitly exclude the possibility of carrying out the determination step in vivo. In addition, claims 13-30 relates to medical trials for testing experimental drugs, which involve methods of treatment of the human/animal body and could cause harm without benefits, e.g. to human subjects. The search for these claims has been based on the alleged effects of the candidate substance on the (expression) level of the marker protein/peptide.
This International Searching Authority found multiple inventions in this international application, as follows:

1. claims: 1-18 (partially), 19, 22-27 (partially), 28, 31-34 (partially)

   Methods involving the determination of Fn14, peptides having any of Seq. IDs 7-10, nucleic acids encoding these peptides and antibodies against the peptides.

2. claims: 1-18 (partially), 20, 22-27 (partially), 29, 31-34 (partially)

   Methods involving the determination of HMGAI, peptides having Seq. ID 11, nucleic acids encoding these peptides and antibodies against the peptides.

3. claims: 1-18 (partially), 21, 22-27 (partially), 30, 31-34 (partially)

   Methods involving the determination of Apelin, peptides having any of Seq. IDs 12-13, nucleic acids encoding these peptides and antibodies against these peptides or a peptides having Seq. ID 14.
<table>
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<th>Publication date</th>
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<td>US 2005208046 A1</td>
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