Abstract:

MONOCLONAL ANTIBODY DRUG TREATMENT

Title: GENE EXPRESSION MARKERS FOR PREDICTING RESPONSE TO INTERLEUKIN-6 RECEPTOR-INHIBITING MONOCLONAL ANTIBODY DRUG TREATMENT

(57) Abstract: This invention provides methods, compositions, and kits relating to gene product biomarkers where gene expression levels are correlated with therapeutic response of rheumatoid arthritis patients to treatment with an IL-6 receptor antagonist, such as an IL6 antibody. The methods, compositions, and kits of the invention can be used to identify rheumatoid arthritis patients who are likely, or not likely, to respond to IL-6 receptor antagonist treatments.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68 G01N33/50

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)
C12Q G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and where practical, search terms used)
EPO-Internal, BIOSIS, Sequence Search, EMBASE, WPI Data

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>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>JP 2009 092508 A (NISHIMOTO N0RIHI R0; MIMA KYO; DNA CHI P RES INC; CHUGAI PHARMACEUTICAL) 30 April 2009 (2009-04-30) the whole document</td>
<td>1-9</td>
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* 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 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 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 of 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.

"A" document member of the same patent family

Date of the actual completion of the international search
11 January 2012

Date of mailing of the international search report
06/02/2012

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer
Schmitt, Anja

Form PCT/ISA/210 (second sheet) (April 2005)
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INTERNATIONAL SEARCH REPORT

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. X Claims Nos.: 10  
   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 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:

   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 fees, this Authority did not invite payment of additional fees.

3. X 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.: Impartially)

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.:  

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.  
X□ No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9 (partially)

A method of identifying a rheumatoid arthritis patient that is a candidate for treatment with an human interleukin-6 receptor anti body or a rheumatoid arthritis patient that should be excluded from treatment, the method comprising: providing an RNA nucleic acid sample obtained from peripheral blood lymphocytes (or a serum sample comprising protein(s) from peripheral blood lymphocytes) from the patient; determining the level of expression of at least one gene product encoded by the first gene set forth in Table 1 (Affymetrix probe set number 240934_at; Accession number AI801975; Gene Symbol PI P5K1B) that is associated with a therapeutic response to treatment with IL-6 receptor anti body; wherein when the level exceeds the threshold value, the level of the biomarker is indicative of a patient that is a candidate for treatment with the human interleukin-6 receptor anti body; or that a patient that should be excluded from treatment.

A diagnostic device comprising two or more nucleic acid probes attached to a solid surface to detect RNA expression levels of two or more biomarkers set forth in Table 1, Table 2, or Table 3, wherein at least one of the probes is specific for the first gene set forth in Table 1 (Affymetrix probe set number 240934_at; Accession number AI801975; Gene Symbol PI P5K1B).

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2-280. claims: 1-9 (partially)

Method and device as defined in invention 1, wherein the at least one gene product is encoded by gene number 2 (3-95) of Table 1; (genes 1-104 of Table 2; genes 1-81 of Table 3).

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Contingent on of Box II.2

Claims Nos.: 10

Present claim 10 relates to an extremely large number of possible methods, namely methods of identifying a rheumatoid arthritis patient that is a candidate for treatment with an human interleukin-6 receptor antibody or a rheumatoid arthritis patient that should be excluded from treatment, the method comprising determining in an RNA nucleic acid sample obtained from peripheral blood lymphocytes from the patient the level of expression of at least two gene products having a value > 0 in columns C or D or E or F or G or H or I or J of Table 5. In view of said large number of possible methods, the scope of said claim is neither concisely nor clearly defined and thus does not fulfill the requirements of Art. 6 PCT. Already in view of this reason, the search with respect to claim 10 would have to be limited to those methods falling within the scope of said claim, which are, in view of the description, clear (Art. 6 PCT).

However, the description does not disclose any such combinations of at least two gene products from columns D-J of Table 5. This non-compliance with the substantial provisions is to such an extent that no meaningful search of claim 10 could be carried out at all (Art. 17(2) PCT).

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 Internationa l Preliminary Examination Authority is normally not to carry out a preliminary examination on any 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 applicant proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination on before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2) declaration be overcome.
<table>
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