Abstract:

Methods for identifying subjects having a cancer or pre-malignant condition that will benefit from anti-CD40 therapeutic agents that modulate CD40L-mediated CD40 signaling are provided. The methods comprise the use of biomarkers of cellular apoptosis, cell proliferation and survival, and CD40 signaling pathways to monitor ex vivo response to one or more anti-CD40 therapeutic agents of interest that modulate CD40 signaling on CD40-expressing neoplastic cells. The ex vivo prognostic assays can be used alone or in conjunction with other prognostic assays to identify candidate subjects who will benefit from treatment with anti-CD40 therapeutic agents. Methods of the invention also comprise the use of these biomarkers to monitor in vivo efficacy of treatment with an anti-CD40 therapeutic agent.
INTERNATIONAL SEARCH REPORT

PCT/US2006/019414

A. CLASSIFICATION OF SUBJECT MATTER

G01N 33/574  A61K 39/395

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)

G01N A61K

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, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<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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* Further documents are listed in the continuation of Box C.

X See patent family annex.

"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 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.

"A" document member of the same patent family

Date of the actual completion of the international search 29 September 2006

Date of mailing of the international search report 30 Oct 2006

Name and address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
Fax: (+31-70) 340-3016

Authorized officer

Hoesel, Heidi
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<th>Relevant to claim No.</th>
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</table>
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:

   Although claims 44, 61-113, 117 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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).

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 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.:

   1-44, 65-99, 116, 117

Remark on Protest

- [ ] The additional search fees were accompanied by the applicant's protest,
- [ ] 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: 1-44, 65-99, 116, 117

   method for predicting the therapeutical response towards the efficacy of a cancer therapy using an anti CD40 agent by way of quantification of an CD40 associated biomarker in biopsies incubated with or without the therapeutical agent

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2. claims: 45-61, 100-113

   method for predicting the therapeutical response towards the efficacy of a cancer therapy using an anti-CD40 agents by way of determining the expression of CD40 or its cognate ligand on the surface of neoplastic cells

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3. claims: 114, 115

   prevention of progression of a gammoathia (MGUS) into multiple myeloma by administration of an antagonistic anti-CD40 monoclonal anti body.
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