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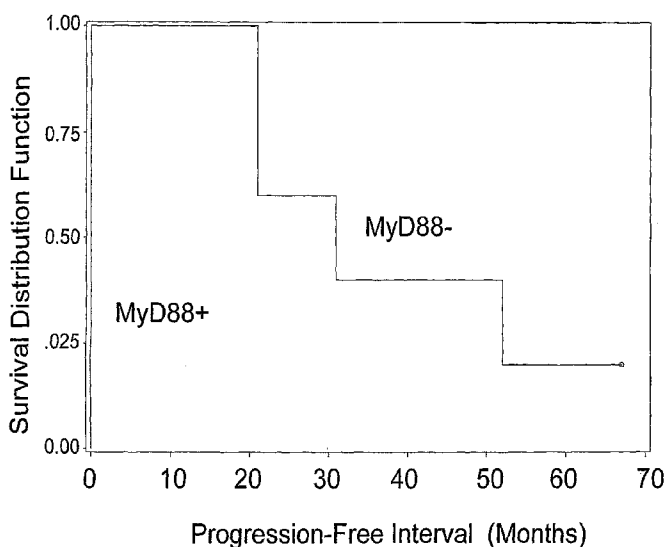
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(54) Title: DRUG RESISTANCE TO PLANT ALKALOIDS BASED UPON MYD88 STATUS IN A CELL AND METHODS OF INHIBITING SIGNALING THROUGH THE TLR-4:MYD88 PATHWAY



(57) Abstract: Described herein is a cellular marker, MyD88, useful for assessing an individual's (patient's) sensitivity (or resistance) to chemotherapy, particularly sensitivity (or resistance) to chemotherapeutic drugs, such as plant alkaloids (e.g., a taxane, such as paclitaxel or docetaxel). As described herein, Applicants provide a method by which it is possible to determine whether an individual (cancer cells in an individual) is sensitive to chemotherapy with plant alkaloids (e.g., a taxane, such as paclitaxel or docetaxel). Early identification of chemoresistance in patients with cancer is of utmost importance, particularly since it makes it possible to provide the most appropriate therapy.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/004707

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/50 G01N33/574

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

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, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WANG JINGXIN ET AL: "MyD88 is involved in the signalling pathway for taxol-induced apoptosis and TNF-alpha expression in human myelomonocytic cells" MEDLINE, 1 August 2002 (2002-08-01), XP002968401 the whole document	1-17, 53-57, 60-63
Y	SAPI E ET AL: "RESISTANCE OF OVARIAN CARCINOMA CELLS TO DOCETAXEL IS XIAP DEPENDENT AND REVERSIBLE BY PHENOXODIOL" ONCOLOGY RESEARCH, PERGAMON PRESS, NEW YORK, NY, US, vol. 14, no. 11/12, 2004, pages 567-578, XP009049252 ISSN: 0965-0407 abstract	1-17, 53-57, 60-63

Further documents are listed in the continuation of Box C.

See patent family annex.

* 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 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

23 November 2007

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/004707

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FLICK MARYANN B ET AL: "Apoptosis-based evaluation of chemosensitivity in ovarian cancer patients." JOURNAL OF THE SOCIETY FOR GYNECOLOGIC INVESTIGATION MAY 2004, vol. 11, no. 4, May 2004 (2004-05), pages 252-259, XP009088472 ISSN: 1071-5576 the whole document	1-17, 53-57, 60-63
Y	WO 2005/054814 A (UNIV YALE [US]; MOR GUILLERMO [US]) 16 June 2005 (2005-06-16) page 1, lines 22,23	1-17, 53-57, 60-63
A	BYRD-LEIFER CYNTHIA A ET AL: "The role of MyD88 and TLR4 in the LPS-mimetic activity of Taxo1" EUROPEAN JOURNAL OF IMMUNOLOGY, WEINHEIM, DE, vol. 31, no. 8, August 2001 (2001-08), pages 2448-2457, XP002199843 ISSN: 0014-2980 cited in the application abstract	1-17, 53-57, 60-63

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 53-57 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.

Although claims 60-63 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

The term "plant alkaloid", found in claim 1 and subsequent independent claims, has not been searched as it covers a huge class of compounds. The search has therefore been restricted to taxane, paclitaxel or docetaxel (as found in cl.2-4).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/004707

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:
see FURTHER INFORMATION sheet PCT/ISA/210

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:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable 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. 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.:

1-17, 53-57, 60-63

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-17,53-57,60-63

A method of assessing the sensitivity/responsiveness of an ovarian cancer cell/patient suffering from ovarian cancer to taxane wherein the status of the marker MyD88 is checked. If the cell/patient is MyD88 negative then the patient will be sensitive to the drug and vice versa. Genetic screening of the MyD88 status is also covered. Those with elevated levels of MyD88, compared to normals, are more likely to have a pre-cancerous lesion or an increased chance of getting cancer.

2. claims: 18-52,58,59,64

A method of inhibiting proliferation of any cancer cell which involves inhibiting the interaction between MyD88 and TLR4. Treatments of patients with any cancer are covered along with any drugs that may block/inhibit said interaction.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/004707

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005054814 A	16-06-2005	CA 2547213 A1	16-06-2005
		EP 1697718 A1	06-09-2006
		US 2007275434 A1	29-11-2007
