Title: BIOMARKER: COMPOUND CORRELATIONS IN CANCER DIAGNOSIS AND THERAPY

Abstract: The present invention provides methods and reagents relating to establishing and using biomarker: chemical compound correlations. The invention provides correlated biomarker: compound pairs, and further provides methods of using such pairs, for example, in the identification of tumors or tumor cells likely to be responsive or resistant to particular therapy, and/or the identification of chemical compounds likely (or unlikely) to be useful in the treatment of particular tumors.
Published:

- with international search report

(88) Date of publication of the international search report:
24 August 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

C12Q1/68, 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)

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

**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>WO 03/087761 A (CELL SIGNALING TECHNOLOGY, INC; CROSBY, KATHERINE; SMITH, BRADLEY)</td>
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<td>23 October 2003 (2003-10-23) the whole document -----</td>
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Further documents are listed in the continuation of box C.

* 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)
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* O document member of the same patent family

**Date of the actual completion of the international search**

30 November 2005

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

01.03.2006

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 540-2040, Tx. 31 661 epo nl, Fecx (+31-70) 340-3016

Authorized officer

Ludemann, S
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<td>X</td>
<td>WO 02/101357 A (IRM LLC; SU, ANDREW, I; HAMPTON, GARRET, M)</td>
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<td>19 December 2002 (2002-12-19) the whole document</td>
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<td>X</td>
<td>WO 03/004989 A (MILLENIUM PHARMACEUTICALS, INC; LILLIE, JAMES; GANNAVARAPU, MANJULA; G) 16 January 2003 (2003-01-16) the whole document</td>
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### 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. ☐ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

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 8.4(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. ☐ 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.:

   1-6 and 18 (all partially)

**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:

Invention 1: claims 1-6 and 18 (all partially)

A method of classifying a tumor as likely or unlikely to respond to therapy with a chemical compound comprising steps of: (i) providing a tumor sample from a patient; (ii) detecting in the tumor sample a correlated biomarker characterized in that presence or absence of the biomarker has been correlated with responsiveness or lack of responsiveness to a selected chemical compound; and (iii) classifying the tumor as likely or unlikely to respond to therapy with the selected chemical compound based on the results of the detection step; wherein the biomarker is Hs.23643 and the chemical compound is methotrexate.

Inventions 2-111: claims 1-6, 18 and 19 (all partially)

A method of classifying a tumor as likely or unlikely to respond to therapy with a chemical compound comprising steps of: (i) providing a tumor sample from a patient; (ii) detecting in the tumor sample a correlated biomarker characterized in that presence or absence of the biomarker has been correlated with responsiveness or lack of responsiveness to a selected chemical compound; and (iii) classifying the tumor as likely or unlikely to respond to therapy with the selected chemical compound based on the results of the detection step; wherein the biomarker is Hs.279949 and the chemical compound is methotrexate, further biomarker Hs. 3566 and methotrexate, biomarker Hs. 151903 and methotrexate, biomarker Hs. 274453 and 8-azaguanine, etc.

Invention 112: claim 7

A method of identifying biomarkers that are predictive of tumor responsiveness to particular chemical compounds, the method comprising steps of: providing an expression or activity dataset for a predetermined collection of tumor cells; providing a chemical compound toxicity dataset for the tumor cells; and establishing a correlation between expression of at least one biomarker and toxicity of at least one compound such that expression of the at least one biomarker is predictive of tumor responsiveness to the at least one compound.

Invention 113: claims 8-17
A method of identifying chemical compounds whose ability to inhibit tumor cell growth correlates with expression of a particular biomarker, the method comprising steps of: providing an expression or activity dataset for a predetermined collection of tumor cells; providing a chemical compound toxicity dataset for the tumor cells; and establishing a correlation between expression of at least one biomarker and toxicity of at least one compound such that the compound is predicted to effectively inhibit growth of tumor cells expressing the biomarker.
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