Title: COMPOSITIONS AND METHODS FOR TREATING AND DIAGNOSING CANCER

Abstract: The present invention relates to compositions and methods for treating, characterizing, and diagnosing cancer. In particular, the present invention provides gene expression profiles associated with solid tumor stem cells, as well as novel stem cell cancer gene signatures useful for the diagnosis, characterization, prognosis and treatment of solid tumor stem cells.
A. CLASSIFICATION OF SUBJECT MATTER

IPC: C12Q 1/68 (2006.01); G01N 33/53 (2006.01), 33/574 (2006.01); C07K 1/00(2006.01), 16/00(2006.01); C07H 21/02(2006.01)

USPC: 530/350,387.1; 536/23.1; 435/6,7.1,7.23

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)

U.S.: 530/350,387.1; 536/23.1; 435/6,7.1,7.23

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 practicable, search terms used)

EAST, MEDLINE, BIOSIS, EMBASE, CAPLUS, SCISEARCH, BIOTECHNO, DISSABS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 2003/0086934 A1 (Botstein et al.) 8 May 2003 (08.05.2003), Examples 6 and 7.</td>
<td>1-5, 36, 37, and 40</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search
04 June 2008 (04.06.2008)

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
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Date of mailing of the international search report
08 JUL 2008

Authorized officer
/Karen A. Canella/
Telephone No. 571-272-1600
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. ☐ 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:

Please See Continuation 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 additional fees, this Authority did not invite payment of any 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.: 1-6,10,36,37 and 40

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.

Form PCT/ISA/210 (continuation of first sheet(2)) (April 2007)
BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-6, 10-22, 36, 37, and 40, drawn to a method of classifying a cancer, the method comprising: a. determining expression levels of one or more genes in a cancer sample in comparison to expression levels of the gene(s) in a reference sample, wherein the gene(s) are selected from a cancer stem cell gene signature; b. comparing the expression levels of the gene(s) in the cancer sample to the expression levels of the gene(s) comprising the cancer stem cell gene signature; and, c. classifying the cancer to either a high risk or low risk group based on the comparison in (b), wherein determining the expression levels of one or more genes selected from the cancer stem cell gene signature is by measuring expression of the corresponding protein or polypeptide.

Group 2, claim(s) 1, 7-22 and 36-39, drawn to a method of classifying a cancer, the method comprising: a. determining expression levels of one or more genes in a cancer sample in comparison to expression levels of the gene(s) in a reference sample, wherein the gene(s) are selected from a cancer stem cell gene signature; b. comparing the expression levels of the gene(s) in the cancer sample to the expression levels of the gene(s) comprising the cancer stem cell gene signature; and, c. classifying the cancer to either a high risk or low risk group based on the comparison in (b), wherein determining the expression levels of one or more genes selected from the cancer stem cell gene signature is by measuring expression of corresponding mRNA.

Group 3, claim(s) 23 drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 9A immobilized on a solid surface.

Group 4, claim(s) 24, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 10A immobilized on a solid surface.

Group 5, claim(s) 25, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 11A immobilized on a solid surface.

Group 6, claim(s) 26, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 12A immobilized on a solid surface.

Group 7, claim(s) 27, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 13A immobilized on a solid surface.

Group 8, claim(s) 28, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 17A immobilized on a solid surface.

Group 9, claim(s) 29, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 18A immobilized on a solid surface.

Group 10, claim(s) 30, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 19A immobilized on a solid surface.

Form PCT/ISA/210 (extra sheet) (April 2007)
Group 11, claim(s) 31, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 20A immobilized on a solid surface, classified in class 536, subclass 23.1.

Group 12, claim(s) 32, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 21A immobilized on a solid surface.

Group 13, claim(s) 33, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 22A immobilized on a solid surface.

Group 14, claim(s) 34, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 23A immobilized on a solid surface.

Group 15, claim(s) 35, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 24A immobilized on a solid surface.

Group 16, claim(s) 41-46, 50-52, and 55, drawn to a method of classifying a cancer, the method comprising: a. determining expression levels of two or more genes in a cancer sample in comparison to expression levels of the genes in a reference sample wherein the genes are selected from a cancer stem cell gene signature and a wound-response gene signature; b. comparing the expression levels of the genes in the cancer sample to the expression levels of the genes comprising the cancer stem cell gene signature and a wound-response gene signature; and, c. classifying the cancer to either a high risk or low risk group based on the comparison in (b), wherein determining the expression levels of one or more genes selected from the cancer stem cell gene signature is by measuring expression of the corresponding protein or polypeptide.

Group 17, claim(s) 41, 47-49, 50-52, 53 and 54, drawn to a method of classifying a cancer, the method comprising: a. determining expression levels of two or more genes in a cancer sample in comparison to expression levels of the genes in a reference sample wherein the genes are selected from a cancer stem cell gene signature and a wound-response gene signature; b. comparing the expression levels of the genes in the cancer sample to the expression levels of the genes comprising the cancer stem cell gene signature and a wound-response gene signature; and, c. classifying the cancer to either a high risk or low risk group based on the comparison in (b), wherein determining the expression levels of one or more genes selected from the cancer stem cell gene signature is by measuring expression of corresponding mRNA.

Group 18, claim(s) Claim 56, drawn to an array comprising polynucleotides hybridizing to cancer stem cell gene signature genes in Table 11A and wound-response signature genes in Table 26 immobilized on a solid surface.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows

**Species Elections for Groups 1 and 2**

A. Claim 1 is generic to the following disclosed patentably distinct species of cancer stem cell gene signature found in the following tables:
   - Table 9A, Table 10A, Table 11A, Table 12A, Table 13A, Table 17A, Table 18A, Table 19A, Table 20A, Table 21A, Table 22A, Table 23A, Table 24A
B. Claim 1 is generic to the disclosed patentably distinct species of genes found in the elected cancer stem cell signature. Applicants must elect ONE gene or A SPECIFIC, DEFINED COMBINATION OF GENES from the elected cancer stem cell signature that has support in the specification as originally filed.

**Species Elections for Groups 16 and 17**

A. Claim 41 is generic to the following disclosed patentably distinct species of cancer stem cell gene signature found in the following tables:
   - Table 9A, Table 10A, Table 11A, Table 12A, Table 13A, Table 17A, Table 18A, Table 19A, Table 20A, Table 21A, Table 22A, Table 23A, Table 24A
B. Claim 41 is generic to the disclosed patentably distinct species of genes found in the elected cancer stem cell signature and the wound response gene signature of Table 26. Applicants must elect TWO genes or A SPECIFIC, DEFINED COMBINATION OF GENES OF MORE THAN TWO GENES from the elected cancer stem cell signature and the wound response gene signature of Table 26 that has support in the specification as originally filed.

The inventions listed as Groups 1-18 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

A national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features which define a contribution over the prior art. If there is no special technical feature, if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(d).

The technical feature linking Groups 1-18 appears to be cancer stem cell gene signature genes.
However, US Patent App. Pub.: 2003/0225528 (Jaffé et al. Dec 4, 2003) teaches arrays comprising BCL2, a cancer stem cell gene found in table 11A, and a method for classifying cancer comprising, determining the expression level of two or more genes selected from the group consisting of Bcl2, hepatocyte nuclear factor 3, ER, ErbB2 and Grb7, or their expression products, in a cancer tissue, normalized against a control gene or genes, and compared to the amount found in a reference cancer tissue set, wherein (i) tumors expressing at least one of Bcl2, hepatocyte nuclear factor 3, and ER, or their expression products, above the mean expression level in the reference tissue set are classified as having a good prognosis for disease free and overall patient survival following treatment; and (ii) tumors expressing elevated levels of ErbB2 and Grb7, or their expression products, at levels ten-fold or more above the mean expression level in the reference tissue set are classified as having poor prognosis of disease free and overall patient survival following treatment for breast cancer wherein the expression level is determined using RNA from a formalin fixed paraffin embedded tissue sample, see claims 25-29, 39 and 40 and para 0019.

Therefore, the technical feature linking the inventions of Groups 1-18 does not constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art.