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(72) Inventors; and


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(54) Title: METHODS AND COMPOSITIONS FOR ASSESSING ALTERATIONS IN GENE EXPRESSION PATTERNS IN CLINICALLY NORMAL TISSUES OBTAINED FROM HETEROZYGOUS CARRIERS OF MUTANT GENES ASSOCIATED WITH CANCER AND METHODS OF USE THEREOF

(57) Abstract: Compositions, kits, and methods are provided for assessing alterations in gene expression in heterozygous carriers of mutant genes associated with cancer.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/047222

A. CLASSIFICATION OF SUBJECT MATTER

INT. CL. C12Q 1/68 (2006.01) A61B 5/00 (2006.01)
US.CL. 435/6

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)

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)

WPIDS, CA MEDLINE BIOSIS: breast, mammary, ovarian, ovary, cancer, carcinoma, tumour, tumor, neoplasms, sarcoma, mammaglobin, mammoglobin, SCGB2A2, mgb#, secretoglobulin, UGB2, lipophilin, lipHB, SCGB1D#, tensin 4, TNS4, mucin 16, MUC16, CA125, keratin 14, cytokeratin 14, cdc2, cdk1, p34cdc2, nups, cenu, centromere protein a, centromere 17k, cd24, nectadrin, SAA2, serum amyloid A2, pnsin, sorbs 1, SII3 protein, CHISL1, HCGP39, YKL40, cartilage gp39, HCGP39, chitinase 3 like 1, chondrex, MMP3, matrix metalloproteinase 3, stromelysin, transin, COX1, cyclooxygenase, prostaglandin H synthase, BRCA, BRCA1, BRCA2, array, microarray, chip, differential expression, up regulated, down regulated, expression profile, expression signature

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>
</table>

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 application or patent 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
11 March 2008

Date of mailing of the international search report
22 MAY 2008

Name and mailing address of the ISA/US
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<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tr>
<td>X</td>
<td>WO 2004/079014 A2 (ARCTURUS BIOSCIENCE, INC) 16 September 2004</td>
<td>1, 2, 7, 8</td>
</tr>
<tr>
<td>X</td>
<td>WO 2005/098037 A1 (ARCTURUS BIOSCIENCE, INC) 20 October 2005</td>
<td>2, 8</td>
</tr>
</tbody>
</table>
This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. These particulars are merely given for the purpose of information.

|----------------------------------------|----------------------|

END OF ANNEX
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:

See supplemental box.

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 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 to 4, 7 to 10 (completely), claims 13, 14, 16, 18 (partially, as far as they relate to BRCA1 and BRCA2).

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.
Continuation of Box No: III

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

In assessing whether there is more than one invention claimed, I have given consideration to those features which can be considered to potentially distinguish the claimed combination of features from the prior art. Where different claims have different distinguishing features they define different inventions.

This International Searching Authority has found that there are different inventions as follows:

- Claims 1, 3, 7, 9 (completely) and 13, 14, 16 and 18 (partially) are directed to methods of identifying a genetic signature (differentially expressed genes) for heterozygous carriers of a gene associated with cancer methods of detecting cancer and micro-arrays based on the genetic signature wherein the gene associated with cancer is BRCA1. It is considered that the method of identifying a genetic signature for heterozygous carriers of BRCA1 comprises a first distinguishing feature.

- Claims 2, 4, 8, 10 (completely) and 13, 14, 16 and 18 (partially) are directed to methods of identifying a genetic signature (differentially expressed genes) for heterozygous carriers of a gene associated with cancer methods of detecting cancer and micro-arrays based on the genetic signature wherein the gene associated with cancer is BRCA2. It is considered that the method of identifying a genetic signature for heterozygous carriers of BRCA2 comprises a second distinguishing feature.

- Claims 5, 11, 13 to 24 (partially) are directed to methods of identifying a genetic signature (differentially expressed genes) for heterozygous carriers of a gene associated with cancer methods of detecting cancer and micro-arrays based on the genetic signature wherein the gene associated with cancer is TSC1. It is considered that the method of identifying a genetic signature for heterozygous carriers of TSC1 comprises a third distinguishing feature.

- Claims 5, 11, 13 to 24 (partially) are directed to methods of identifying a genetic signature (differentially expressed genes) for heterozygous carriers of a gene associated with cancer methods of detecting cancer and micro-arrays based on the genetic signature wherein the gene associated with cancer is TSC2. It is considered that the method of identifying a genetic signature for heterozygous carriers of TSC2 comprises a fourth distinguishing feature.

- Claims 6, 12 (completely) and 13 to 24 (partially) are directed to methods of identifying a genetic signature (differentially expressed genes) for heterozygous carriers of a gene associated with cancer methods of detecting cancer and micro-arrays based on the genetic signature wherein the gene associated with cancer is VHL. It is considered that the method of identifying a genetic signature for heterozygous carriers of VHL comprises a fifth distinguishing feature.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

The only feature common to all of the claims is the method of identifying a genetic signature for heterozygous carriers of a gene associated with cancer, as defined by claim 13. However this concept is not novel in the light of the following document which discloses the method of identifying the genetic signature of heterozygous carriers of genes associated with cancer through examining the gene expression profile.


Continued.
Supplemental Box
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No:

This means that the common feature can not constitute a special technical feature within the meaning of PCT Rule 13.2, second sentence, since it makes no contribution over the prior art.

Because the common feature does not satisfy the requirement for being a special technical feature it follows that it cannot provide the necessary technical relationship between the identified inventions. Therefore the claims do not satisfy the requirement of unity of invention a posteriori.

The first two inventions, relating to BRCA1 and BRCA2 were searched.