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— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

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13 December 2012

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(54) Title: METHODS OF USING GENE EXPRESSION SIGNATURES TO SELECT A METHOD OF TREATMENT, PREDICT PROGNOSIS, SURVIVAL, AND/OR PREDICT RESPONSE TO TREATMENT

(57) Abstract: Methods and compositions for determining and/or predicting a response to a therapy, prognosis of a cancer subject or survival of a cancer and kits for performing the same are described herein.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/23997

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 33/48, G01N 33/53 (2012.01)
USPC - 435/6.1, 435/7.1
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)
IPC(8) - G01N 33/48, G01N 33/53 (2012.01)
USPC - 435/6.1, 435/7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/6.11, 435/6.12; 436/501, 436/86, 436/94

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT, PGPB, EPAB, JPAB); Google Scholar; Search terms: breast cancer, triple negative, predict, prognosis, diagnosis, treatment, therapy, co-regulated gene, CAPRIN2, ZWILCH, CKS2, CDKN3, FOXM1, RRM2, VRKI, TRIP13, ASPM, CEP55, TUBG 1, AURKA, SERPINE2, TNFRSF6B, CAPG, ACTNI, ACTB, DUSP4, EPHA2, FGFBPI, EIF4A1, ESR1, ODC1, TFAC, F AC, Cisplat

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 2009/158143 A1 (PEROU et al.) 30 December 2009 (30.12.2009) p 2, ln 2-27; p 6, ln 9-11; p 6, Table 1; p 7, Table 1; p 14, ln 7-12; p 20, ln 18-34; p 23, ln 14-15; p 32, ln 23-29 | 1-4 |
| Y | US 2009/0275608 A1 (OSSOVSKAYA et al.) 5 November 2009 (05.11.2009) para [0026], [0085]-[0086] | 1-4 |
| Y | US 2010/0210738 A1 (LEYLAND-JONES et al.) 19 August 2010 (19.08.2010) | 1-4 |
| Y | US 2009/0239229 A1 (WEAVER et al.) 24 September 2009 (24.09.2009) | 1-4 |

☐ 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 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 | Date of mailing of the international search report |
|---|---|
| 18 July 2012 (18.07.2012) | 26 SEP 2012 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (July 2009)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/23997

**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.: 81-88
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:
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 I: Claims 1-4, drawn to a method of predicting prognosis, selecting a treatment, or predicting survival outcome in a subject with breast cancer, wherein the method comprises replacement of at least one of a plurality of markers with a co-regulated gene.

Group II: Claims 5-31 and 34, drawn to a method for predicting a prognosis of a subject with triple negative breast cancer

Group III: Claim 32, drawn to a system for predicting prognosis of a subject with triple negative breast cancer comprising storage memory and a processor

---please see continuation on extra 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 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.:
1-4

**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.

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/US 12/23997

Continuation of Box No. III Observations where unity of invention is lacking

Group IV: Claim 33, drawn to a kit for predicting prognosis of a subject with triple negative breast cancer

Group V: Claims 35-80, drawn to a method of selecting a treatment for a subject with cancer

Group VI: Claims 89-92, drawn to a method of identifying a 3D-signature profile of a tissue

The inventions listed as Groups I-VI 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:

The shared technical feature of the inventions listed as Groups I and II is the general method steps for predicting prognosis of a subject with triple negative breast cancer. This shared technical features fails to provide a contribution over the prior art, as evidenced by WO 2009/158143 A1 to Perou et al. (published 30 December 2009; hereinafter 'Perou'). Perou discloses a method for predicting a prognosis of a subject diagnosed with triple negative breast cancer (p 2, ln 11-27 - "Methods for classifying and for evaluating prognosis and treatment of a subject with breast cancer are provided. . . Further provided are compositions and methods for predicting outcome or response to therapy of a subject diagnosed with or suspected of having breast cancer"; p 32, ln 23-29 - "Another relevant clinical distinction is the classification of "triple-negative" tumors (ER-, PgR- and HER2-)"), predicting a prognosis of a subject with breast cancer (p 2, ln 11-27), selecting a treatment for a subject with breast cancer (p 23, ln 14-15 - " choosing appropriate treatment"), or predicting a survival outcome of a subject with breast cancer (p 20 , ln 18-21 - "methods for predicting breast cancer outcome . . . In particular, the methods may be used to predict the likelihood of long-term, disease-free survival"); comprising
obtaining a dataset (p 2, ln 14-15 - "gene expression profile") associated with a sample derived from a patient diagnosed with cancer (p 14, ln 7-12 - "total RNA isolated from a biological sample, such as a tumor or tumor cell line"), wherein the dataset comprises: expression data for a plurality of markers (p 2, ln 14-15 - "The prediction model is based on the gene expression profile of the intrinsic genes listed in Table 1") selected from the group consisting of RRM2 (p 8, Table 1), CEP55 (p 7, Table 1), ESR1 (p 7, Table 1); and determining a predictive score from the dataset using an interpretation function (p 2, ln 2-16 - "The methods include prediction of breast cancer subtype using a supervised algorithm trained to stratify subjects on the basis of breast cancer intrinsic subtype. . . In some embodiments, the algorithm is a nearest centroid algorithm, similar to the Prediction Analysis of Microarray (PAM) algorithm"), wherein the predictive score is predictive of one of the following: the prognosis of a subject with triple negative breast cancer, the prognosis of a subject with breast cancer, the selection of a treatment for a subject with breast cancer, or prediction of a survival outcome of a subject with breast cancer (p 2, ln 11-27; p 23, ln 14-15; p 32, ln 23-29). In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature.

The shared technical feature of the inventions listed as Groups I-V is a dataset associated with a sample obtained from a patient diagnosed with cancer, wherein the dataset comprises expression data for a plurality of markers. As discussed above, this shared technical features fails to provide a contribution over Perou, which teaches obtaining a dataset (p 2, ln 14-15 - "gene expression profile") associated with a sample derived from a patient diagnosed with cancer (p 14, ln 7-12 - "total RNA isolated from a biological sample, such as a tumor or tumor cell line"), wherein the dataset comprises: expression data for a plurality of markers (p 2, ln 14-15 - "The prediction model is based on the gene expression profile of the intrinsic genes listed in Table 1") selected from the group consisting of RRM2 (p 8, Table 1), CEP55 (p 7, Table 1), ESR1 (p 7, Table 1). In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature.

The shared technical feature of the inventions listed as Groups I-IV is the prognosis of a subject with triple negative breast cancer. As discussed above, this shared technical features fails to provide a contribution over Perou, which teaches a method for predicting a prognosis of a subject diagnosed with triple negative breast cancer (p 2, ln 11-27 - "Methods for classifying and for evaluating prognosis and treatment of a subject with breast cancer are provided. . . Further provided are compositions and methods for predicting outcome or response to therapy of a subject diagnosed with or suspected of having breast cancer"; p 32, ln 23-29 - "Another relevant clinical distinction is the classification of "triple-negative" tumors (ER-, PgR- and HER2-), of which 65% were called Basal-like by the PAM50, with the remainder being called HER2-enriched (15%), LumA (4%), LumB (4%), and Normal-like (12%). The PAM50 classification of Basal-like appears superior to the clinical triple- negative with respect to pCR [i.e. pathological complete response] rate in that Basal-like tumors that were not scored as triple- negative had a 50% pCR compared to triple-negative tumors that were not Basal-like by PAM50 (22% pCR, Table 7)."). In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature.

The shared technical feature of the inventions listed as Groups I and V is the selection of a treatment for a subject with breast cancer. This shared technical feature fails to provide a contribution over Perou, which teaches a method for selecting a treatment for a subject with breast cancer (p 23, ln 14-15 - "The methods of the invention find particular use in choosing appropriate treatment for early-stage breast cancer patients"). In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature.

Further, the special technical feature of the inventions listed as Group I is the replacement of at least one of a plurality of markers with a co-regulated gene. This special technical feature is not shared by the inventions of Groups II-VI. The special technical feature of the inventions listed as Group II is the prediction of a prognosis for a subject with triple negative breast cancer. This special technical feature is not shared by the inventions of Groups V and VI. The special technical feature of the inventions listed as Group III is a system comprising storage memory and a processor. This special technical feature is not shared by the inventions of Groups I-II and IV-VI. The special technical feature of the inventions listed as Group IV is a kit. This special technical feature is not shared by the inventions of Groups I-III and V-VI. The special technical feature of the inventions listed as Group V is the selection of a treatment for a subject with cancer. This special technical feature is not shared by the inventions of Groups II-IV and VI. The special technical feature of the inventions listed as Group VI is a 3D-signature profile of a tissue. This special technical feature is not shared by the inventions of Groups I-V.

Unity of invention exists only when the same or corresponding technical feature is shared by the claimed inventions. Without a shared special technical feature, the inventions of Groups I-VI lack unity with one another.