(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 December 2011 (08.12.2011)

PCT

(10) International Publication Number
WO 2011/153545 A3

(51) International Patent Classification:
C12Q 1/68 (2006.01) *G06G 7/58* (2006.01)
A61K 31/33 (2006.01) *G06F 11/30* (2006.01)

(21) International Application Number:
PCT/US2011/039325

(22) International Filing Date:
6 June 2011 (06.06.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/351,385 4 June 2010 (04.06.2010) US
61/441,554 10 February 2011 (10.02.2011) US

(71) Applicant *(for all designated States except US)*: **BIOARRAY THERAPEUTICS, INC.** [US/US]; 41 Marian Road, Collegeville, PA 19426 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MARTIN, Katherine, J.** [US/US]; 61 Carleton Road, Belmont, MA 02478 (US). **MAGEE, David** [US/US]; C/o Bioarray Therapeutics, Inc., 41 Marian Road, Collegeville, PA 19426 (US). **FOURNIER, Marcia, V.** [US/US]; C/o Bioarray Therapeutics, Inc., 41 Marian Road, Collegeville, PA 19426 (US).

(74) Agent: **MILLER, Raymond, A.**; PEPPER HAMILTON LLP, 50th Floor, 500 Grant Street, Pittsburgh, PA 15219 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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

(88) Date of publication of the international search report:
26 January 2012

WO 2011/153545 A3

(54) Title: GENE EXPRESSION SIGNATURE AS A PREDICTOR OF CHEMOTHERAPEUTIC RESPONSE IN BREAST CANCER

(57) Abstract: Disclosed are methods and compositions for determining and/or predicting a response to a therapy, especially a cancer therapy, including chemotherapy. Specifically, the disclosure provides profiles of a set of marker genes in breast cancers from patients who were known to have responded or not responded to a chemotherapy for predicting response to the same therapy including different combination of chemotherapy in a patient diagnosed with breast cancer. The disclosure further provides computer complemented methods for the prediction based on genetic profiles as well as different clinical parameters. Furthermore, the disclosure provides kits for performing the method disclosed.

INTERNATIONAL SEARCH REPORT

PCT/US 11/39325

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12Q 1/68; A61K 31/33; G06G 7/58; G06F 11/30 (2011.01)
USPC - 435/6.12, 435/6.14; 514/183; 703/11; 702/183

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) - C12Q 1/68; A61K 31/33; G06G 7/58; G06F 11/30 (2011.01)
USPC - 435/6.12, 435/6.14; 514/183; 703/11; 702/183; 435/91.2; 506/16; 706/46

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - C12Q 1/68; A61K 31/33; G06G 7/58; G06F 11/30 (2011.01) - see keyword below
USPC - 435/6.12, 435/6.14; 514/183; 703/11; 702/183; 435/91.2; 506/16; 706/46 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google: FLJ10517, interpretation function, predictive model, brain, gliomas, breast, cancer, adjuvant chemotherapy, neoadjuvant chemotherapy, logistical regression, Luminal B, malignant or neoplastic, relapse-free, absent, fixed, paraffin-embedded, fresh, frozen tissue, fine needle, core, biopsy, TFAC, taxol,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FOURNIER et al. Gene Expression Signature in Organized and Growth-Arrested Mammary Acini Predicts Good Outcome in Breast Cancer, Cancer Res. 2006, Vol. 66(14), p. 7095-102. Abstract; pg 7095, col 2, para 1 and 2; pg 7096, col 2, middle para and last para; pg 7097, col 2, para 2, and Fig 2; pg 7098, col 1, last para, col 2, up para, and Table 1; pg 7099, col 1, last para, and Fig 3; and pg 7100, col 1, middle para, and col 2, last para	1-16, 24, 29-30, 33, 37-39
Y	US 2009/0093995 A1 (WOOSLEY et al.) 09 April 2009 (09.04.2009), para [0003], [0005], [0013], [0028], [0050], [0054], [0066], [0077], [0078], [0081], [0082], and [0083]	1-16, 24, 29-30, 33, 37-39
Y	US 2009/0076734 A1 (TORRES-ROCA et al.) 19 March 2009 (19.03.2009), Abstract, para [0006], [0024], [0041], [0064], [0070], [0074], [0102], [0107], [0111], [0112], [0113], [0128], [0129], [0157], [0164], and [0166]	7-8, 14, 39
Y	US 2009/0239214 A1 (DAI et al.) 24 September 2009 (24.09.2009), para [0013], [0069], [0085], and [0098]	16
Y	US 2009/0105167 A1 (Potti et al.) 23 April 2009 (23.04.2009), Abstract, para [0002], [0006], [0012], [0029], [0030], [0031], and [0083]	29-30
A	CHEN et al. AZU-1: A Candidate Breast Tumor Suppressor and Biomarker for Tumor Progression. Mol Biol Cell. 2000. Vol. 11(4), p. 1357-67. pg 1358, col 1, top para	37
A	US 2008/0256011 A1 (Rice) 16 October 2008 (16.10.2008), para [0010], and [0025]	1-16, 24, 29-30, 33, 37-39
A	US 2009/0203533 A1 (MUNNES et al.) 13 August 2009 (13.08.2009), para [0010], [0072], and [0410]	1-16, 24, 29-30, 33, 37-39

☐ 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
15 November 2011 (15.11.2011)	02 DEC 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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:
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 1-16, 24-40, drawn to a method for predicting a response to a cancer treatment in a patient diagnosed with cancer comprising obtaining a dataset associated with a sample derived from a patient diagnosed with cancer, wherein the dataset comprises: expression data for at least one marker or at least one clinical factor; and determining a predictive score from the dataset using an interpretation function, wherein the predictive score is predictive of the response to the cancer treatment. The first named invention (claims 1-16, 24, 29-30, 33, 37-39) is limited to at least one marker that is FLJ10517, wherein the patient diagnosed with cancer has an ER-positive cancer; wherein obtaining the first dataset associated with the sample comprises obtaining the sample and processing the sample to experimentally determine the dataset comprising the expression data; and wherein the cancer is predicted to respond or not respond to TFAC (combination of taxol/ fluorouracil/ anthracycline/ cyclophosphamide). Applicant is invited to elect an additional marker(s), an additional type(s) of cancer (ER-negative, Luminal B, basal-like, or triple-negative); method(s) of receiving or treating dataset (from a third party, classifying, rating the ability to respond to a specific treatment, or stored on a storage memory); or additional treatment(s) to be searched by paying additional fee for each election. **********Continued in the 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.:
1-16, 24, 29-30, 33, 37-39

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 (unity of invention is lacking)

Group II, claims 1, 17-23, drawn to a method for predicting a response to a cancer treatment in a patient diagnosed with cancer comprising obtaining a dataset associated with a sample derived from a patient diagnosed with cancer, wherein the dataset comprises: expression data for at least one marker selected from the group consisting of FLJ10517, HCAP-G, CDKN3, STK6, FOXM1, FLII0540, TNFRSF6B, HBPI7, CIQDC1, TUBGI, FLI10036, RRM2, ACTB, ACTN1, EPHA2, TRIP 13, CKS2, VRK1, DUSP4, EIF4AI, SERPINE2, and ODCI, or a at least one clinical factor; and determining a predictive score from the dataset using an interpretation function, wherein the interpretation function is based upon a predictive model.

Group III, claims 41-43, drawn to a system for predicting a response to a cancer treatment comprising a storage memory for storing a dataset associated with a sample obtained from the subject, wherein the dataset comprises expression data for at least one marker selected from the group consisting of FLJ10517, HCAP-G, CDKN3, STK6, FOXM1, FLJ10540, TNFRSF6B, HBP17, C1QDC1, TUBG1, FLJ10036, RRM2, ACTB, ACTN1, EPHA2, TRIP 13, CKS2, VRK1, DUSP4, EIF4A1, SERPINE2, and ODC1; and a processor communicatively coupled to the storage memory for determining a score with an interpretation function wherein the score is predictive of response to a cancer treatment in a subject diagnosed with cancer.

Group IV+, claims 44-50, drawn to a kit for predicting response to a cancer treatment in a subject comprising one or more reagents for determining a sample obtained from a subject expression data for at least one marker; and instructions for using the one or more reagents to determine expression data from the sample, wherein the instructions include instructions for determining a score from the dataset wherein the score is predictive of response to the cancer treatment. The first named invention (claims 44-48) is limited to at least one marker that is FLJ10517, and wherein the cancer treatment comprises a nitrogen mustard. Applicant is invited to elect an additional marker(s), or additional treatment(s) to be searched by paying additional fee for each election.

Group V, claim 51, drawn to a method for predicting a response to a cancer treatment in a patient diagnosed with cancer comprising: isolating a sample of the cancer from the patient diagnosed with cancer; obtaining a dataset associated with a sample derived from a patient diagnosed with cancer, wherein the dataset comprises expression data for at least one marker selected from the group consisting of FLJ10517, FLJ10517, HCAP-G, CDKN3, STK6, FOXM1, FLJ10540, TNFRSF6B, HBPI7, CIQDC1, TUBG1, FLJI0036, RRM2, ACTB, ACTNI, EPHA2, TRIP13, CKS2, VRKI, DUSP4, EIF4AI, SERPINE2, and ODCI and at least one clinical factor; and determining a predictive score from the dataset using an interpretation function, wherein the interpretation function is based upon a predictive model, wherein the predictive model is a logistical regression model.

The inventions listed as Groups I+-V 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:

Groups I+-III and V do not include the inventive concept of kit for predicting response to a cancer treatment in a subject comprising one or more reagents for determining from a sample obtained from a subject expression data for at least one marker; and instructions for using the one or more reagents, as required by Group IV+.

Groups I+-II and IV+-V do not include the inventive concept of a system for predicting a response to a cancer treatment comprising a storage memory for storing a dataset associated with a sample obtained from the subject, and a processor communicatively coupled to the storage memory, as required by Group III.

Groups I + and III-IV+ do not include the inventive concept of predictive model, as required by Groups II and V.

Group II does not include the inventive concept of a logistical regression model, as required by Group V. Further, Groups I+-IV+ do not include the inventive concept of isolating a sample of the cancer from the patient diagnosed with cancer, as required by Group V.

Further, between each groups of Groups I+, and IV+, each marker is structurally and functionally different from others, and each treatment or combination of treatments is different from others and will produce a different response from other treatments.

Furthermore, between Group I, a different type of cancer (claim 24 - 'ER-positive'; claim 25 - 'ER-negative'; claim 26 - 'Luminal B'; claim 27 - 'basal-like'; or claim 28 - 'triple-negative') is resulted from different pathological changes, each requires a different treatment; and different methods of receiving or treating dataset (claim 33 - 'obtaining the sample and processing the sample to experimentally determine the dataset comprising the expression data'; claim 34 - 'receiving the dataset from a third party'; claim 35 - 'classifying the first sample'; claim 36 - 'rating the ability to respond to a specific treatment'; or claim 40 - 'the dataset that is obtained is stored on a storage memory'), each is independent from others.

**********Continued in the next extra sheet**********

Continuation of:

The previous extra sheet - Box No. III (unity of invention is lacking)

The inventions of Groups I+-V share the technical feature of predicting a response to a cancer treatment in a patient diagnosed with cancer comprising obtaining a dataset associated with a sample derived from a patient diagnosed with cancer, wherein the dataset comprises: expression data for at least one marker that is FLJ10517; and determining a predictive score from the dataset, wherein the predictive score is predictive of the response to the cancer treatment. However, this shared technical feature does not represent a contribution over prior art. Specifically, an article entitled 'Gene Expression Signature in Organized and Growth-Arrested Mammary Acini Predicts Good Outcome in Breast Cancer' by FOURNIER et al. (hereinafter 'Fournier'; Cancer Res. 2006, Vol. 66(14), p. 7095-102) discloses a method for predicting a response to a cancer treatment in a patient diagnosed with cancer (Abstract - 'genes ...can be used to classify breast cancer patients into poor and good prognosis groups with high accuracy', wherein "poor and good prognosis" is resulted from not/less responsive and responsive to a cancer treatment, respectively)
---comprising obtaining a dataset associated with a sample derived from a patient diagnosed with cancer (pg 7096, col 2, middle para - 'A database consisting of the microarray profiles of 295 human breast tumors with the associated clinical data...For survival analysis of the 19 individual marker genes, the patients were stratified into quartiles for expression of each marker', which indicates "obtaining a dataset associated with a sample derived from a patient diagnosed with cancer"),
---wherein the dataset comprises: expression data for at least one marker selected from the group consisting of FLJ10517 (pg 7096, col 2, middle para pg 7096, col 2, middle para - 'A database ... profiles of 295 human breast tumors...For survival analysis of the 19 individual marker genes...for expression of each marker'; pg 7099, col 1, last para - 'The cluster analysis separated the patients into five groups, three of which had tumors that expressed comparatively lower levels of most of the 19 genes', wherein "the 19 genes" comprise "FLJ10517"; and Fig 3 - "FLJ10517"; pg 7097, Fig 2, Down late - "FLJ10517") and
---determining a predictive score from the dataset, wherein the predictive score is predictive of the response to the cancer treatment (pg 7096, col 2, middle para - 'For survival analysis of the 19 individual marker genes, the patients were stratified into quartiles for expression of each marker', wherein "quartiles" represent scores for each prediction; pg 7099, col 1, last para - 'The cluster analysis separated the patients into five groups, three of which had tumors that expressed comparatively lower levels of most of the 19 genes ... The 10-year survival rates for these five groups were 95%, 84%, 67%, 61%, and 54%, respectively', wherein "The 10-year survival rates for these five groups were 95%, 84%, 67%, 61%, and 54%" reflects "the predictive score is predictive of the response to the cancer treatment"; pg 7099, Fig 3, legend, "FLJ10517", wherein "Lower quartile" having higher survival rate; pg 7098, col 2, up para - 'the expression level of which correlated to 5-year (68%) and 10-year (53%) survival. The levels of the majority of the late down-regulated genes were higher in patients who died within 5 or 10 years .... FLJ10517'; pg 7098, Table 1 - 'Late down ...19... 13(68) ...10 (53)').
Fournier further discloses obtaining the dataset associated with the sample comprises obtaining the sample and processing the sample to experimentally determine the dataset comprising the expression data (pg 7095, col 2, para 2 - 'HMECs were obtained from reduction mammoplasty tissue ...HMT3522 S1 mammary epithelial cells were cultured'; Abstract - 'human mammary epithelial cells (HMEC)'; pg 7096, col 2, last para - 'total cellular RNA was biotin labeled and hybridized to human oligonucleotide microarrays'; pg 7097, Fig 2, Down late - "FLJ10517"; pg 7099, col 1, last para, and Fig 3 - "FLJ10517"), and a method for evaluating the response of ER-positive cancers to cancer treatment (pg 7100, col 2, last para - 'divided 83 ER-positive younger patients into ... good versus poor prognosis... a core group of ... genes ... FLJ10517...a strong contribution to stratifying tumors into good versus poor prognostic groups').

Groups I+-III and V further share the technical feature of determining a predictive score from the dataset using an interpretation function. However, this shared technical feature does not represent a contribution over prior art. Specifically, US 2009/0093995 A1 to Woosley et al. discloses a method of using interpretation function to obtain a single result from multiple variables for diagnosing diseases and predicting response to treatment (para [0013] - 'Combine the value of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a "classification," "score," "index") that is intended for use in the diagnosis of disease or ... in the cure, mitigation, treatment, ... of disease').

Groups II and V further share the technical feature of predictive model. However, this shared technical feature does not represent a contribution over prior art. Specifically, US 2008/0256011 A1 to Rice discloses applying different models including logistic regression model in predictive modeling process in different applications including medical applications (para [0010] - 'new predictive modeling process that could completely replace standard logistic regression. This Generalized RELR method works in those problems where standard logistic regression does not'; para [0025] - 'Generalized Reduced Error Logistic Regression ("Generalized RELR") that should have wide ranging applications in medicine, science').

Group IV+ further share the technical feature of a kit for predicting response to a cancer treatment in a subject comprising one or more reagents for determining a sample obtained from a subject expression data for at least one marker; and instructions for using the one or more reagents to determine expression data from the sample, wherein the instructions include instructions for determining a score from the dataset wherein the score is predictive of response to the cancer treatment. However, this shared technical feature does not represent a contribution over prior art. Specifically, US 2009/0203533 A1 to Munnes et al. discloses a kit for predicting response to a cancer treatment in a subject (para [0010] - 'kits for diagnosing, staging, prognosis, monitoring and therapy of breast cancer'), wherein the kit comprises one or more reagents for determining from a sample obtained from a subject expression data for at least one marker including FLJ10517 (para [0010] - 'kits ... comprise comparing the level of mRNA expression of a single or plurality ...of genes ... "marker genes", listed in Table 1, ...in a patient sample'; para [0072] - 'The kit comprises reagents for assessing expression of a marker gene listed within Table 1'; Table 1 - '27 ASPM hypothetical protein FLJ10517'). Furthermore US 2009/0105167 A1 to Potti et al. discloses a kit for predicting response to a cancer treatment in a subject comprising instructions for using the one or more reagents for predicting response to a cancer treatment in a subject, wherein the instructions include instructions for determining a score from the dataset wherein the score is predictive of response to the cancer treatment (Abstract - 'predicting an individual's responsitivity to cancer treatments'; para [0012] - 'a kit comprising a gene chip for predicting an individual's responsivity to a salvage therapy agent and a set of instructions for determining an individual's responsivity to salvage chemotherapy agents'; para [0002] - 'a gene predictor set ... correlated with high or low responsiveness to chemotherapeutic drugs', wherein "a gene predictor set" is a "dataset" and "high or low responsiveness" is "for determining a score from the dataset wherein the score is predictive of response to the cancer treatment"; para [0006] - 'comparing ...to a set of gene expression profiles ....from Table 1 that is capable of predicting responsiveness to other cancer therapy agents'), wherein cancer is predicted to respond or not respond to TFAC (Abstract; para [0031] - 'Prediction of patient response to neoadjuvant chemotherapy involving paclitaxel, 5-fluorouracil (5-FU), adriamycin, and cyclophosphamide (TFAC)') or nitrogen mustard (para [0083] - 'defining the value of one or more metagenes from the expression levels of the genes....with sensitivity to an anti-cancer agent ...the agent is selected from alkylating agents ... nitrogen mustards'). ***see Next extra sheet**********

Continuation of:

The previous extra sheet - Box No. III (unity of invention is lacking)

Without a shared special technical feature, the inventions lack unity with one another.

Groups I+-V therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note: 49 is assumed to be dependent upon claim 44.

In claims 30, 32, and 50, each "and" that used to connect all agents is treated as "or" so that each agent or a combination of agents is an alternative.