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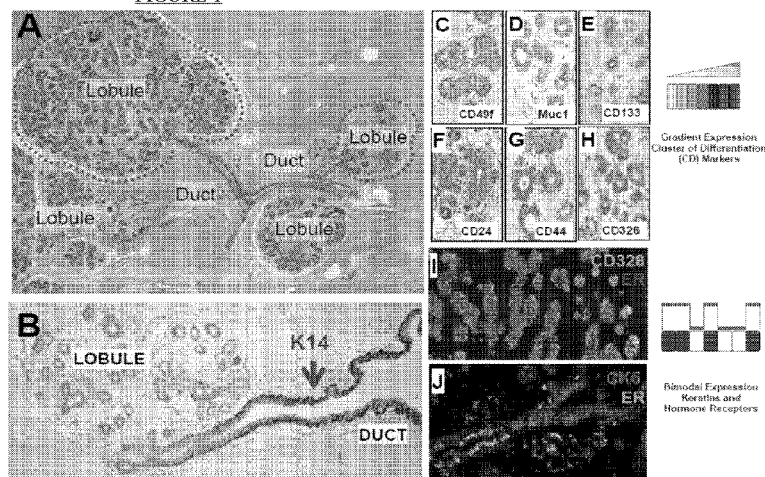
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NW 7th Avenue-Suite 110, Miami, FL 33136 (US).(72) Inventor: INCE, Tan, A.; 1800 N. Bayshore Drive,
Miami, FL 33132 (US).(74) Agents: MALLOY, Jennie S. et al.; Malloy & Malloy,
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12 March 2015(54) Title: CLASSIFICATION SYSTEM, METHODS AND KIT FOR CLASSIFYING. PREDICTING AND TREATING
BREAST CANCER

FIGURE 1



(57) **Abstract:** A novel classification system for breast cancer based on normal breast cell phenotypes and various expression levels of estrogen receptor (ER), androgen receptor (AR), and vitamin D receptor (VDR). The various categories of the classification system are associated with different survival rates and prognoses. The invention includes a method of classifying breast cancer comprising measuring the levels of ER, AR, and VDR in the cancerous tissue, and classifying the breast cancer into one of the above-noted categories according to expression levels. The invention includes a method of predicting the prognosis of breast cancer in a patient and a method of determining a treatment regimen for breast cancer depending on the category in which the breast cancer is classified. The invention includes a method of treating breast cancer according to the expression profile of ER, AR, and VDR detected in the cancerous tissue. Kits for detecting the same are also provided.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/43128

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12Q 1/68 (2014.01)

CPC - C12Q 1/6883

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 (2014.01)

CPC - C12Q 1/6883

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/6.14, 435/6.17, 435/6.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

pubWEST; Google Scholar; PatBase

search terms - androgen receptor, NR3C4, nuclear receptor subfamily 3, VDR, vitamin D, receptor, Calcitriol receptor, NR1H1, estrogen receptor, esr, esr1, er, two, three, four, mark\$, biomark\$, express\$, categor\$, subcategor\$, breast, hormone receptors, pos, positive,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2012/0157542 A1 (WIRTZ) 21 June 2012 (21.06.2012) para [0025]; [0048]; [0049]; [0059]; [0130]-[0132]; [0170]-[0190]; [0209].	1-21
Y	Krishan, Awtar, et al. "Androgen and vitamin D receptor expression in archival human breast tumors." Cytometry Part B: Clinical Cytometry 58.1 (2004): 53-60. abstract; p. 55, para 2; p. 58, last para - p. 59, para 1; Fig. 4.	1-21
Y	US 2006/0234287 A1 (ERLANDER et al.) 19 October 2006 (19.10.2006) para [0016]-[0018]; [0094]-[0096]; Tables 2-4.	10
A	US 2005/0100888 A1 (COOMBES et al.) 12 May 2005 (12.05.2005) para [0073]; [0093].	1

☐ 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

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/43128

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 defined under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-21, directed to a classification system for breast cancer.

Group II, claims 22-36, directed to a method of treating/determining a treatment regimen for a breast cancer patient.

Group III, claims 37-54, directed to an antibody staining/bioassay kit.

The groups of inventions listed above 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:

--continued on first extra sheet attached hereto--

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.:
1-21

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 14/43128

continuation of Box No III:

Special technical features

Group I has the special technical feature of a classification system for breast cancer, comprising: a first category defined by a substantial lack of estrogen receptor (ER), androgen receptor (AR), and vitamin D receptor (VDR) expression in a breast cancer tumor; a second category defined by expression of only one of ER, AR, and VDR in a breast cancer tumor; a third category defined by expression of any combination of two of ER, AR, and VDR in a breast cancer tumor; and a fourth category defined by expression of each of ER, AR, and VDR in a breast cancer tumor, that is not required by Groups II or III.

Group II has the special technical feature of a method of treating breast cancer, comprising providing a therapeutically effective amount of at least one ER antagonist to the patient when ER is detected in the breast cancer tumor, providing a therapeutically effective amount of at least one AR ligand to the patient when AR is detected in the breast cancer tumor, and providing a therapeutically effective amount of at least one VDR agonist to the patient when VDR is detected in the breast cancer tumor, that is not required by Groups I or III.

Group III has the special technical feature of an antibody staining kit comprising: a predetermined amount of primary antibody/first probe capable of binding at least one binding site of estrogen receptor (ER) protein/mRNA, capable of detecting estrogen receptor (ER) activity, a predetermined amount of primary antibody/second probe capable of binding at least one binding site of androgen receptor (AR) protein/mRNA, capable of detecting estrogen receptor (AR) activity, and a predetermined amount of primary antibody/third probe capable of binding at least one binding site of vitamin D receptor (VDR), protein/mRNA, capable of detecting estrogen receptor (VDR) activity, that is not required by Groups I or II.

Common technical features:

Groups I-III share the common technical feature of measuring the level of estrogen receptor (ER), androgen receptor (AR), and vitamin D receptor (VDR) expression or activity. Groups I and II further share the feature of a method of measuring the level of ER, AR and VDR expressed in a tumor of breast tissue of a patient, and making a determination related to said breast cancer based on the expression of each of ER, AR and VDR.

However, these shared technical features do not represent a contribution over prior art, because these shared technical features are obviated by US 2005/0100888 A1 to Coombes et al., (hereinafter Coombes).

Coombes teaches a method of measuring the level of ER, AR and VDR expression in a tumor of breast tissue of a patient and making a determination related to said breast cancer based on the expression of each of ER, AR and VDR (para [0019] 'a method for characterising the hormone dependency of a primary cancer cell or cells, comprising the steps of (1) exposing the cell or cells to a recombinant viral vector comprising a reporter gene which comprises a hormone-dependent promoter; and (2) assessing the expression of the reporter gene in the said cell or cells', [0023]-[0024] 'Preferably the hormone-dependent promoter is an estrogen-dependent promoter...the hormone-dependent promoter may be an androgen-dependent promoter...or VDR (vitamin D receptor) dependent promoter'; para [0026]-[0027] 'the cell is a primary breast cancer cell. The method of the invention may be particularly useful in relation to breast cancer because of the pattern of progression typically seen in breast cancer (in which there may be more than one change in the hormone responsiveness of the cancer), and the range of treatments available (for example, several endocrine therapy options; chemotherapy; and surgery)'). Coombes does not specifically teach measuring activity by measuring expression of ER, AR and VDR. However, since the expression of a gene is directly related to the activity of the expressed protein it encodes, it was well known in the art of molecular biology to measure expression of gene biomarkers as an indicator of the activity of said biomarkers. Therefore, it would have been obvious to one of ordinary skill in the art to have measured the expression of ER, AR and VDR in a method for characterising the hormone dependency of breast cancer cells, since the expression of these genes is directly related to the activity of the encoded proteins, and one of ordinary skill in the art would have readily appreciated measured expression as an indicator of the activity of said biomarkers.

Therefore, Groups I, II and III lack unity of invention defined under PCT Rule 13.