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(54) Title: COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF BREAST CANCER

(57) Abstract: The invention relates to nucleic acid molecules and proteins associated with breast cancer. Compositions, kits, and methods for detecting, characterizing, preventing, and treating human breast cancers are provided.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/16793

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12Q 1/68; C07H 21/02, 21/04; G01N 33/53; C07K 16/00
US CL : 435/6, 7.1; 536/23.1, 24.3; 530/387.1
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)
U.S. : 435/6, 7.1; 536/23.1, 24.3; 530/387.1

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)
WEST, GenBank, GeneSeq

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/55629 A2 (EOS BIOTECHNOLOGY, INC.), 21 September 2000 (21.09.2000); Fig. 62; page 12, lines 5,6; page13, lines 7-31; page 17, lines 5-30; page 18, lines 1-8; page 20, lines 4-13; page 22, lines 8-14; page 23, lines 7-11page 40, lines 27-30; page41, lines 1-31; page 42, lines 1,2, 9-29; page 43, lines 1-30;	1-16

☐ 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 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
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/16793

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   ☒ a sequence listing

   ☒ table(s) related to the sequence listing

   b. format of material

   ☒ on paper

   ☒ in electronic form

   c. time of filing/furnishing

   ☒ contained in the international application as filed

   ☒ filed together with the international application in electronic form

   ☐ furnished subsequently to this Authority for the purposes of search

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/16793

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.: 1-16, SEQ ID NO:1

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.

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 1-48, claim(s) 1-16, drawn to a method of assessing whether a patient is afflicted with breast cancer, the method comprising:
a) determining the level of expression of a marker in a patient sample, wherein the marker is selected from the group consisting of the markers listed in Table 1 and the markers listed in Table 2;
b) determining the level of expression of the marker in a sample from a control subject having an indolent breast tumor or no breast tumor; and
c) comparing the level of expression of the marker in the patient sample and in the sample from a control subject wherein a significant difference between the level of expression of the marker in the patient sample and the sample from a control subject is an indication that the patient is afflicted with breast cancer.

If Group 1 is elected, it corresponds to SEQ ID NO: 1, if Group 2 is elected, it corresponds to SEQ ID NO: 3, etc.

Group 49-72, claim(s) 17-21, drawn to a method of assessing whether a patient is afflicted with breast cancer, the method comprising:
a) determining the level of expression in the sample of at least two markers independently selected from the markers listed in Table 1 and Table 2;
b) determining the level of expression of each of the markers in a sample from a control subject having an indolent breast tumor or no breast tumor; and
c) comparing the level of expression of the marker in the patient sample and in the sample from the control subject; wherein a significant difference in the level of expression of more than one of the markers, relative to the corresponding control levels of expression of the markers, is an indication that the patient is afflicted with breast cancer.

If Group 49 is elected, it corresponds to SEQ ID NO: 1 and SEQ ID NO; 67, if Group 50 is elected, it corresponds to SEQ ID NO: 3 and SEQ ID NO: 69, etc.

Group 73-87, claim(s) 22, 23, drawn to a method for assessing whether a patient has breast cancer that has metastasized or is likely to metastasize, comprising:
a) determining the level of expression of a marker in a patient sample, wherein the marker is selected from the markers listed in Table 2,
b) determining the level of expression of the marker in a sample from a control subject having a non-metastasized breast tumor or no breast tumor, and
c) comparing the level of expression of the marker in the patient sample and the sample from the control subject; wherein a significantly higher level of expression in the patient sample as compared to the level in the sample from the control subject is an indication that the breast cancer bas metastasized or is likely to metastasize.

If Group 73 is elected, it corresponds to SEQ ID NO; 67, if Group 74 is elected, it corresponds to SEQ ID NO: 69, etc.

Group 88-102, claim(s) 24, drawn to a method for predicting the clinical outcome of a breast cancer patient, the method comprising:
a) determining the level of expression of a marker in a patient sample, wherein the marker is selected from the markers listed in Table 2,
b) determining the level of expression of the marker in a sample from a control subject having a good clinical outcome; and

c) comparing the level of expression of the marker in the patient sample and in the sample from the control subject; wherein a significantly higher level of expression in the patient sample as compared to the expression level in the sample from the control subject is an indication that the patient has a poor clinical outcome.

If Group 88 is elected, it corresponds to SEQ ID NO; 67, if Group 89 is elected, it corresponds to SEQ ID NO: 69, etc.

Group 103-150, claim(s) 25-29, drawn to a method for monitoring the progression of breast cancer in a patient, the method comprising:
a) determining the level of expression of a marker in a patient sample from a first point in time, wherein the marker is selected from the group consisting of the markers listed in Table l and the markers listed in Table 2,
b) determining the level of expression of the marker in a sample from the patient at a subsequent point in time; and
c) comparing the level of expression detected in steps a) and b), thereby monitoring the progression of breast cancer in the patient, wherein a change in expression of the marker is indicative of either progression or regression of breast cancer.

If Group 103 is elected, it corresponds to SEQ ID NO; 67, if Group 104 is elected, it corresponds to SEQ ID NO: 69, etc.

Group 151-198, claim(s) 30-32, drawn to a method of assessing the efficacy of a test compound for inhibiting breast cancer in a patient, the method comprising:
a) determining the expression of a marker in a first sample obtained from the patient and exposed to a test compound, wherein the marker is selected from the group consisting of the markers listed in Table 1 and the markers listed in Table 2,
b) determining the expression of the marker in a second sample obtained from the patient, wherein the sample is not exposed to the test compound,
c) comparing the expression of the marker in the sample exposed to the test compound and the sample is not exposed to the test compound; wherein a significantly lower level of expression of the marker in the sample exposed to the test compound, relative to the second sample, is an indication that the test compound is efficacious for inhibiting breast cancer in the patient..

If Group 151 is elected, it corresponds to SEQ ID NO; 1, if Group 152 is elected, it corresponds to SEQ ID NO: 3, etc.

Group 199-246, claim(s) 33, drawn to a method of assessing the efficacy of a therapy for inhibiting breast cancer in a patient, the method comprising:
a) determining the expression of a marker in a first sample obtained from the patient prior to administering at least a portion of the therapy to the patient, wherein the marker is selected from the group consisting of the markers listed in Table 1 and the markers listed in Table 2,
b) determining the expression of the marker in a second sample obtained from the patient subsequent to administering the portion of the therapy;
c) comparing the expression of the marker in the first and second samples; and
d) determining the therapy is efficacious for inhibiting breast cancer in the patient when there is a significantly lower level of expression of the marker in the second sample, relative to the first sample.

If Group 199 is elected, it corresponds to SEQ ID NO; 1, if Group 200 is elected, it corresponds to SEQ ID NO: 3, etc.

Group 247-294, claim(s) 34, drawn to a method of selecting a composition for inhibiting breast cancer in a patient, the method comprising:
a) obtaining a sample comprising cancer cells from the patient;
b) separately exposing aliquots of the sample to a plurality of test compositions;
c) comparing expression of a marker in each of the aliquots, wherein the marker is selected from the group consisting of the markers listed in Table 1 and the markers listed in Table 2; and
d) selecting at least one of the test compositions which induces a lower level of expression of the marker in the aliquot exposed to that test composition, relative to the other test compositions.

If Group 247 is elected, it corresponds to SEQ ID NO; 1, if Group 248 is elected, it corresponds to SEQ ID NO: 3, etc.

Group 295-309, claim(s) 35, drawn to a method of selecting a composition for inhibiting metastasis of breast cancer in a. patient, the method comprising:
a) obtaining a sample comprising cancer cells from the patient;
b) separately exposing aliquots of the sample to a plurality of test compositions;
c) comparing expression of a marker in each of the aliquots, wherein the marker is selected from the group consisting of the markers listed in Table 2; and
d) selecting at least one of the test compositions which induces a lower lever of expression of the marker in the aliquot exposed to that test composition, relative to the other test compositions.

If Group 295 is elected, it corresponds to SEQ ID NO; 67, if Group 296 is elected, it corresponds to SEQ ID NO: 69, etc.

Group 310-357, claim(s) 36, drawn to a method for assessing the breast cell carcinogenic potential of a test composition, the method comprising:
a) maintaining separate aliquots of breast cells in the presence and absence of a test composition; and
b) comparing expression of at least one marker selected from the markers listed in Table 1 and the markers listed in Table 2 in each of the aliquots,

c) wherein a significantly enhanced level of expression of the marker or markers in the aliquot maintained in the presence of the test composition is an indication that the test composition possesses human breast cell carcinogenic potential.

If Group 310 is elected, it corresponds to SEQ ID NO; 1, if Group 311 is elected, it corresponds to SEQ ID NO: 3, etc.

Group 358-405, claim(s) 37, 38, 40, 41, 44, drawn to a kit for assessing whether a patient is afflicted with breast cancer, the kit comprising reagents for assessing expression at least one marker selected from the group consisting of the markers listed in Table 1 and the markers listed in Table 2.

If Group 358 is elected, it corresponds to SEQ ID NO; 1, if Group 359 is elected, it corresponds to SEQ ID NO: 3, etc.

Group 406-453, claim(s) 39,43, 46, drawn to a kit for assessing the presence of breast cancer cells, the kit comprising at least one antibody, wherein the antibody or antibodies specifically bind with proteins corresponding to at least one marker selected from the group consisting of the markers listed in Table 1 and the markers listed in Table 2.

If Group 406 is elected, it corresponds to SEQ ID NO; 2, if Group 407 is elected, it corresponds to SEQ ID NO: 4, etc.

Group 454-477, claim(s) 42, 45, drawn to an isolated polypeptide comprising the amino acid sequence selected from the group consisting of: SEQ ID NO: 4, SEQ ID NO: 6, SEQ 113 NO: 8, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50. SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 64, and SEQ ID NO: 66.

If Group 454 is elected, it corresponds to SEQ ID NO; 4, if Group 455 is elected, it corresponds to SEQ ID NO: 6, etc.

The inventions listed as Groups 1-477 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: Yu et al. (U.S. patent No. 6,171,816; issued January 9, 2001) teach a sequence of SEQ ID NO: 5, 100% identical to SEQ ID NO: 1, therefore Applicants' claims do not present a contribution over prior art.