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13 January 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: GENE EXPRESSION MARKERS FOR RESPONSE TO EGFR INHIBITOR DRUGS

(57) Abstract: The present invention concerns prognostic markers associated with cancer. In particular, the invention concerns prognostic methods based on the molecular charaterization of gene expression in paraffin-embedded, fixed samples of cancer tissue, which allow a physician to predict whether a patient is likely to respond well to treatment with an EGFR inhibitor.

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INTERNATIONAL SEARCH REPORT

Interna plication No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

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 7 C12Q

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 practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HUMPHREYS R C ET AL: "Signal transducer and activator of transcription 5a influences mammary epithelial cell survival and tumorigenesis." CELL GROWTH & DIFFERENTIATION : THE MOLECULAR BIOLOGY JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. OCT 1999, vol. 10, no. 10, October 1999 (1999-10), pages 685-694, XP002286318 ISSN: 1044-9523 page 691, right-hand column - page 692, paragraph 1	1-15, 25-36, 39-52,54

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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 document 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
26 July 2004	12. 11. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Reuter, U

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2002/192652 A1 (DANENBERG KATHLEEN D) 19 December 2002 (2002-12-19) page 5, right-hand column, paragraph 3; claim 1 page 6, right-hand column, last paragraph -----	1-15, 25-36, 39-52,54
X	VEER VAN 'T L J ET AL: "Gene expression profiling predicts clinical outcome of breast cancer" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 415, no. 6871, 31 January 2002 (2002-01-31), pages 530-536, XP002259781 ISSN: 0028-0836 abstract page 532 & [Online] Retrieved from the Internet: URL:http://www.rii.com/publications/data/ArrayData_less_than_5yr.xls> STAT5A expression analysis via microarray sentence 1168 -----	25-31,54
X	HINZ MICHAEL ET AL: "Nuclear factor kappaB-dependent gene expression profiling of Hodgkin's disease tumor cells, pathogenetic significance, and link to constitutive signal transducer and activator of transcription 5a activity." THE JOURNAL OF EXPERIMENTAL MEDICINE. 2 SEP 2002, vol. 196, no. 5, 2 September 2002 (2002-09-02), pages 605-617, XP002286321 ISSN: 0022-1007 page 607, last paragraph - page 608; figure 2 page 610, left-hand column & DATABASE EMBL EMBL; ID HSU43185 13 January 1996 (1996-01-13), "Human signal transducer and activator of transcription Stat5A" Database accession no. U43185 comprises SED ID NOs 21, and 88-90 abstract -----	25-34,54

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INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/US2004/003596

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CRISTILLO ANTHONY D ET AL: "Identification of novel targets of immunosuppressive agents by cDNA-based microarray analysis." THE JOURNAL OF BIOLOGICAL CHEMISTRY. 8 FEB 2002, vol. 277, no. 6, 8 February 2002 (2002-02-08), pages 4465-4476, XP002286319 ISSN: 0021-9258 page 4466; table 1	33,34
X	WO 02/47007 A (EILS ROLAND ; PHASE IT INTELLIGENT SOLUTIONS (DE)) 13 June 2002 (2002-06-13) page 38 - page 40; sequence 26	25-31,54
X	WO 02/24867 A (HERNANDEZ JAVIER MARTIN ; MOVING HELLE OTTE (DK); UNIV AARHUS (DK); NI) 28 March 2002 (2002-03-28) page 5; claim 10 pages 37-38; claim 17 page 56	25-34,54
A	ARTEAGA C L: "THE EPIDERMAL GROWTH FACTOR RECEPTOR: FROM MUTANT ONCOGENE IN NONHUMAN CANCERS TO THERAPEUTIC TARGET IN HUMAN NEOPLASIA" JOURNAL OF CLINICAL ONCOLOGY, GRUNE AND STRATTON, NEW YORK, NY, US, vol. 19, no. 18, SUPPL, 15 September 2001 (2001-09-15), pages 32S-40S, XP008031982 ISSN: 0732-183X page 37S, left-hand column page 38S, right-hand column	1-15, 25-36, 39-52,54
A	GODFREY T E ET AL: "Quantitative mRNA expression analysis from formalin-fixed, paraffin-embedded tissues using 5' nuclease quantitative reverse transcription-polymerase chain reaction." THE JOURNAL OF MOLECULAR DIAGNOSTICS : JMD. MAY 2000, vol. 2, no. 2, May 2000 (2000-05), pages 84-91, XP002286320 ISSN: 1525-1578 page 84; table 1	1-15, 25-36, 39-52,54

INTERNATIONAL SEARCH REPORT

In...l application No.
PCT/US2004/003596

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

   [X] a sequence listing

   [X] table(s) related to the sequence listing

   b. format of material

   [X] in written format

   [X] in computer readable form

   c. time of filing/furnishing

   [X] contained in the international application as filed

   [X] filed together with the international application in computer readable form

   [ ] furnished subsequently to this Authority for the purpose 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

Int al application No.
PCT/US2004/003596

Box 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 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 additional 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 an additional fee, this Authority did not invite payment of any additional fee.

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.:

1-15, 25-36, 39-52, 54 (all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-15,25-36,39-52,54 (all partially)

A method for predicting the likelihood that a patient will respond to a treatment with an EGFR inhibitor comprising determining the expression level of STAT5A, a method of preparing a personalized genomics profile for a patient comprising determining the expression level of said gene, a method for amplification of said gene, an amplicon of said gene being defined by SEQ ID NO 21, a primer-probe set for the amplification of said amplicon defined by SEQ ID NOs 88-90, a prognostic method comprising determining the expression level of said gene, and a kit comprising reagents for performing said methods.

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2. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

A method for predicting the likelihood that a patient will respond to a treatment with an EGFR inhibitor comprising determining the expression level of STAT5B, an array comprising oligonucleotides hybridizing to said gene, a method of preparing a personalized genomics profile for a patient comprising determining the expression level of said gene, a method for amplification of said gene, an amplicon of said gene, a primer-probe set for the amplification of said amplicon, a prognostic method comprising determining the expression level of said gene, and a kit comprising reagents for performing said methods.

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3. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

A method for predicting the likelihood that a patient will respond to a treatment with an EGFR inhibitor comprising determining the expression level of WISP1, an array comprising oligonucleotides hybridizing to said gene, a method of preparing a personalized genomics profile for a patient comprising determining the expression level of said gene, a method for amplification of said gene, an amplicon of said gene, a primer-probe set for the amplification of said amplicon, a prognostic method comprising determining the expression level of said gene, and a kit comprising reagents for performing said methods.

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4. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for CKAP4

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

5. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for FGFR1
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6. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for cdc25A
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7. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for RASSF1
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8. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for G-Catenin
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9. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for H2AFZ
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10. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for NME1
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11. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for NRG1
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12. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for BC12
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13. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for TAGLN

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

14. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for YB-1
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15. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for Src
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16. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for IGF1R
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17. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for CD44
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18. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for DIABLO
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19. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for TIMP2
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20. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for AREG
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21. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for PDGFRa
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22. claims: 1-15,25-36,39-52,54 (all partially) 16,17,19-24 (all completely)

idem for CTSB
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23. claims: 1-15,25-34,37-51,53 and 54 (all partially) 16,18-24

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

(all completely)

idem for Hepsin
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24. claims: 1-15,25-34,37-51,53 and 54 (all partially) 16,18-24
(all completely)

idem for ErbB3
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25. claims: 1-15,25-34,37-51,53 and 54 (all partially) 16,18-24
(all completely)

idem for MTA1
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26. claims: 1-15,25-34,37-51,53 and 54 (all partially) 16,18-24
(all completely))

idem for Gus
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27. claims: 1-15,25-34,37-51,53 and 54 (all partially) 16,18-24
(all completely)

idem for VEGF

INTERNATIONAL SEARCH REPORT

Inter[illegible]pplication No
PCT/US2004/003596

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002192652 A1	19-12-2002	AU 2001202 A	11-06-2002
		AU 3240902 A	11-06-2002
		CA 2436910 A1	06-06-2002
		CN 1488002 T	07-04-2004
		EP 1379686 A2	14-01-2004
		WO 0244413 A2	06-06-2002
		WO 0244423 A2	06-06-2002
		US 2003211530 A1	13-11-2003
WO 0247007 A	13-06-2002	AU 2800002 A	18-06-2002
		CA 2430142 A1	13-06-2002
		WO 0247007 A2	13-06-2002
		EP 1342201 A2	10-09-2003
		JP 2004524604 T	12-08-2004
		US 2004076984 A1	22-04-2004
WO 0224867 A	28-03-2002	AU 9121701 A	02-04-2002
		WO 0224867 A2	28-03-2002
		US 2003044803 A1	06-03-2003
		US 2002164576 A1	07-11-2002
		US 2003077590 A1	24-04-2003
		US 2002115058 A1	22-08-2002
		US 2003224460 A1	04-12-2003
		WO 03006688 A2	23-01-2003
		CA 2460642 A1	23-01-2003
		WO 03006689 A2	23-01-2003
		EP 1419276 A2	19-05-2004