

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
23 December 2004 (23.12.2004)

PCT

(10) International Publication Number
WO 2004/111603 A3

(51) International Patent Classification⁷: **C12Q 1/68**

(21) International Application Number:
PCT/US2004/016553

(22) International Filing Date: 24 May 2004 (24.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/473,970 28 May 2003 (28.05.2003) US

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
21 July 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 PREDICTING RESPONSE TO CHEMOTHERAPY

(57) Abstract: The invention provides sets of genes the expression of which predicts whether cancer patients are likely to have a beneficial treatment response to chemotherapy.



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INTERNATIONAL SEARCH REPORT

International Application No
PCI/US2004/016553

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, BIOSIS, EMBASE, WPI Data, PAJ, EMBL, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DIAS SERGIO ET AL: "Vascular endothelial growth factor (VEGF)-C signaling through FLT-4 (VEGFR-3) mediates leukemic cell proliferation, survival, and resistance to chemotherapy" BLOOD, vol. 99, no. 6, 15 March 2002 (2002-03-15), pages 2179-2184, XP002318502 ISSN: 0006-4971 the whole document ----- -/--	1,2, 4-20, 23-32, 36,44, 46-51, 62-64

☒ Further documents are listed in the continuation of box C.

☒ 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
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- *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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

4 March 2005

Date of mailing of the international search report

03.06.2005

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INTERNATIONAL SEARCH REPORT

International Application No
PC1/US2004/016553

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LACROIX M ET AL: "A LOW-DENSITY DNA MICROARRAY FOR ANALYSIS OF MARKERS IN BREAST CANCER" INTERNATIONAL JOURNAL OF BIOLOGICAL MARKERS, WICHTIG EDITORE, MILAN, IT, vol. 17, no. 1, 2002, pages 5-23, XP008010290 ISSN: 0393-6155 page 6, left-hand column, paragraph 2 page 18; table 1 the whole document	1,2, 4-20, 23-32, 36,44, 46-51, 62-64
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X	ANONYMOUS: "GeneChip Human Genome U95Av2" AFFYMETRIX PRODUCT CATALOG, XX, XX, July 2002 (2002-07), pages 1-3, XP002278897 the whole document -& ANONYMOUS: "Information for probe set 1934_s_at(HG-U95Av2)" INTERNET ARTICLE, 'Online! XP002318987 Retrieved from the Internet: URL:http://genecards.weizmann.ac.il/cgi-bin/geneannot/GA_search.pl?keyword_type=probe_set_id&keyword=1934_s_at&target=genecard s> 'retrieved on 2005-02-21! -/--	32,36,44

INTERNATIONAL SEARCH REPORT

International Application No
PC1/US2004/016553

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	-& AFFYMETRIX: "GeneChip Probe Selection and Array Design" INTERNET ARTICLE, 'Online! XP002318988 Retrieved from the Internet: URL:http://www.affymetrix.com/technology/design/index.affx> 'retrieved on 2005-02-21! the whole document -----	
X	DATABASE EMBL 'Online! 10 January 1996 (1996-01-10), "Human vascular endothelial growth factor related protein VRP mRNA, complete cds." XP002318992 retrieved from EBI accession no. EM_PRO:U43142 Database accession no. U43142 See title. -----	62-64
Y	TSAI PEI-WEN ET AL: "Up-regulation of vascular endothelial growth factor C in breast cancer cells by heregulin-beta1. A critical role of p38/nuclear factor-kappaB signaling pathway." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 278, no. 8, 21 February 2003 (2003-02-21), pages 5750-5759, XP002318505 ISSN: 0021-9258 page 5757, right-hand column, paragraph 1 page 5758, left-hand column, paragraph 2 -----	1,2, 4-20, 23-32, 36,44, 46-51, 62-64
Y	NAKAMURA YASUSHI ET AL: "Clinicopathological significance of vascular endothelial growth factor-C in breast carcinoma with long-term follow-up." MODERN PATHOLOGY, vol. 16, no. 4, April 2003 (2003-04), pages 309-314, XP002318506 ISSN: 0893-3952 the whole document -----	1,2, 4-20, 23-32, 36,44, 46-51, 62-64
Y	KINOSHITA JUNKO ET AL: "Clinical significance of vascular endothelial growth factor-C (VEGF-C) in breast cancer" BREAST CANCER RESEARCH AND TREATMENT, vol. 66, no. 2, March 2001 (2001-03), pages 159-164, XP008043038 ISSN: 0167-6806 the whole document -----	1,2, 4-20, 23-32, 36,44, 46-51, 62-64
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INTERNATIONAL SEARCH REPORT

International Application No
PC 1/US2004/016553

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/46467 A (IPSOGEN; BERTUCCI, FRANCOIS; HOULGATTE, REMI; BIRNBAUM, DANIEL; NGUYEN) 13 June 2002 (2002-06-13) the whole document	1,2, 4-20, 23-32, 36,44, 46-51, 62-64
Y	SOTIRIOU CHRISTOS ET AL: "Gene expression profiles derived from fine needle aspiration correlate with response to systemic chemotherapy in breast cancer." BREAST CANCER RESEARCH : BCR. 2002, vol. 4, no. 3, 2002, pages R3-1-R3-8, XP002318508 ISSN: 1465-5411 the whole document	1,2, 4-20, 23-32, 36,44, 46-51, 62-64
Y	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 the whole document	1,2, 4-20, 23-32, 36,44, 46-51, 62-64
Y	BUCHHOLZ T A ET AL: "GLOBAL GENE EXPRESSION CHANGES DURING NEOADJUVANT CHEMOTHERAPY FOR HUMAN BREAST CANCER" CANCER JOURNAL, JONES AND BARTLETT PUBLISHERS, US, vol. 8, no. 6, November 2002 (2002-11), pages 461-468, XP009015206 ISSN: 1528-9117 the whole document	1,2, 4-20, 23-32, 36,44, 46-51, 62-64
Y	STEARNS VERED ET AL: "A prospective randomized pilot study to evaluate predictors of response in serial core biopsies to single agent neoadjuvant doxorubicin or paclitaxel for patients with locally advanced breast cancer." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. JAN 2003, vol. 9, no. 1, January 2003 (2003-01), pages 124-133, XP002318509 ISSN: 1078-0432 the whole document	1,2, 4-20, 23-32, 36,44, 46-51, 62-64

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INTERNATIONAL SEARCH REPORT

International Application No

PC I / US2004/016553

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SORLIE T ET AL: "Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 98, no. 19, 11 September 2001 (2001-09-11), pages 10869-10874, XP002215483 ISSN: 0027-8424 the whole document	1,2, 4-20, 23-32, 36,44, 46-51, 62-64
Y	MUSS HYMAN B ET AL: "C-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer" NEW ENGLAND JOURNAL OF MEDICINE, vol. 330, no. 18, 1994, pages 1260-1266, XP009040793 ISSN: 0028-4793 the whole document	1,2, 4-20, 23-32, 36,44, 46-51, 62-64
Y	SPECHT K ET AL: "Quantitative gene expression analysis in microdissected archival formalin-fixed and paraffin-embedded tumor tissue." AMERICAN JOURNAL OF PATHOLOGY. FEB 2001, vol. 158, no. 2, February 2001 (2001-02), pages 419-429, XP002318989 ISSN: 0002-9440 the whole document	1,2, 4-20, 23-32, 36,44, 46-51, 62-64
E	WO 2004/046386 A (GENOMIC HEALTH, INC; VALL D'HEBRON UNIVERSITY HOSPITAL; BAKER, JOFFRE,) 3 June 2004 (2004-06-03) See Seq.IDs 271-273 and Seq.ID 91 the whole document	1,2,4-6, 23-32, 36,44, 46-51, 62-64
E	WO 2004/074518 A (GENOMIC HEALTH, INC; SCOTT, RANDAL, W; KIEFER, MICHAEL, C; BAKER, JOFF) 2 September 2004 (2004-09-02) the whole document	1,2,4-9, 23-32, 36,44, 46-51,62
P,X	WO 03/078662 A (GENOMIC HEALTH; BAKER, JOFFRE, B; CRONIN, MAUREEN, T; KIEFER, MICHAEL,) 25 September 2003 (2003-09-25)	32,36, 44, 46-51,62
P,Y	the whole document	1,2,4-9, 23-30, 63,64

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/016553

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

national application No.
PCT/US2004/016553

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.:

1-2, 4-20, 23-32, 36, 44, 46-51, 62-64 (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.

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

Invention 1: 1-2,4-20,23-32,36,44,46-51,62-64 (all partially)

Methods for preparing a personalized genomics profile of a subject diagnosed with cancer and for predicting the response of said subject to chemotherapy wherein the method comprises determining the expression level of one gene, especially wherein the one gene is VEGFC, especially wherein the subject has been diagnosed with breast cancer; array comprising polynucleotides hybridizing to VEGFC; a PCR primer probe set consisting of primers with Seq.ID 271-273; a PCR amplicon with Seq. ID 370.

Invention 2: 1-2,4-7,46-48 (all partially)

Methods for preparing a personalized genomics profile of a subject diagnosed with cancer and for predicting the response of said subject to chemotherapy wherein the method comprises determining the expression level of one gene, wherein the one gene is VEGFC and wherein the subject has been diagnosed with ovarian cancer.

Invention 3: 1-2,4-7,46-48 (all partially)

Methods for preparing a personalized genomics profile of a subject diagnosed with cancer and for predicting the response of said subject to chemotherapy wherein the method comprises determining the expression level of one gene, wherein the one gene is VEGFC and wherein the subject has been diagnosed with gastric cancer.

Invention 4: 1-2,4-7,46-48 (all partially)

Methods for preparing a personalized genomics profile of a subject diagnosed with cancer and for predicting the response of said subject to chemotherapy wherein the method comprises determining the expression level of one gene, wherein the one gene is VEGFC and wherein the subject has been diagnosed with colorectal cancer.

Invention 5: 1-2,4-7,46-48 (all partially)

Methods for preparing a personalized genomics profile of a subject diagnosed with cancer and for predicting the response of said subject to chemotherapy wherein the method comprises determining the expression level of one gene, wherein the one gene is VEGFC and wherein the subject has been diagnosed with prostate cancer.

Invention 6: 1-2,4-7,46-48 (all partially)

Methods for preparing a personalized genomics profile of a subject diagnosed with cancer and for predicting the response of said subject to chemotherapy wherein the method comprises determining the expression level of one gene, wherein the one gene is VEGFC and wherein the subject has been diagnosed with pancreatic cancer.

Invention 7: 1-2,4-7,46-48 (all partially)

Methods for preparing a personalized genomics profile of a subject diagnosed with cancer and for predicting the response of said subject to chemotherapy wherein the method comprises determining the expression level of one gene, wherein the one gene is VEGFC and wherein the subject has been diagnosed with lung cancer.

Invention 8: 32,34,36,45 (all partially)

Array comprising polynucleotides hybridizing to VEGFC wherein at least one of said polynucleotides comprises an intron-based sequence the expression of which correlates with the expression of a corresponding exon sequence.

Inventions 9-47 : claims 1-2,4-33,36-64 (all partially)

Methods for preparing a personalized genomics profile of a subject diagnosed with cancer and for predicting the response of said subject to chemotherapy wherein the method comprises determining the expression level of one gene, wherein the one gene is B-catenin; array comprising polynucleotides hybridizing to VEGFC; array comprising polynucleotides which hybridize to B-catenin and all genes listed in claim 32; array comprising polynucleotides which hybridize to B-catenin and all genes listed in claim 36; a PCR primer probe set consisting of primers specific to B-catenin as listed in table 3 for; a PCR amplicon from B-catenin as listed in table 4.

..ibidem for inventions 10-47, each relating to a different gene selected from MMP2; MMP9; CNN; FLJ20354; TGFB3; PDGFRb; PLAUR; KRT19; ID1 ; RIZ1 ; RAD54L; RB1 ; SURV ; EIF4EL3; CYP2C8 ; STK15; ACTG2; NEK2; cMet ; TIMP2 ; C20 orf1; DR5 ; CD31; BIN1 ; COL1A2 ; HIF1A ; VIM ; CDC20; ID2 ; MCM2; CCNB1 ; MYH11 ; Chk2; G-Catenin; HER2; GSN; Ki-67; TOP2A.

Inventions 48-101: 1-4,6-35,38-61 (all partially)

Methods for preparing a personalized genomics profile of a subject diagnosed with cancer and for predicting the response of said subject to chemotherapy wherein the method comprises determining the expression level of one gene, wherein the one gene is CCND1; array comprising polynucleotides hybridizing to CCND1; array comprising polynucleotides which hybridize to CCND1 and all genes listed in claim 32; array comprising polynucleotides which hybridize to CCND1 and all genes listed in claim 36; a PCR primer probe set consisting of primers specific to CCND1 as listed in table 3 for; a PCR amplicon from CCND1 as listed in table 4.

..ibidem for inventions 49-101, each relating to a different gene selected from Estr1; KRT18 ; GATA3; cIAP2 ; KRT5 ; RAB27B ; IGF1R ; HNF3A; CA9; MCM3; STMY3; NPD009 ; BAD; BBC3 ; EGFR; CD9; AKT1 ; CD3z; KRT14 ; DKFZp564; Bcl2 ; BECN1 ; KLK10; DIABLO; MVP; VEGFB; ErbB3 ; MDM2; Bclx; CDH1; HLA-DPB1 ; PR; KRT17 ; GSTp ; IRS1 ; NFkBp65 ; IGFBP2; RPS6KB1 ; DHPS; TIMP3 ; ZNF217; KIAA1209 ; COX2; pS2; BRK; CEGP1 ; EPHX1 ; VEGF; TP53BP1 ; COL1A1 ; FGFR1 ; and CTSL2.
