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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 COLORECTAL CANCER PROGNOSIS

(57) Abstract: A method of predicting clinical outcome in a subject diagnosed with colorectal cancer comprising determining evidence of the expression of one or more predictive RNA transcripts or their expression products in a biological sample of cancer cells obtained from the subject.



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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/000995

A. CLASSIFICATION OF SUBJECT MATTER

INV. 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)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEE M O ET AL: "Differential effects of retinoic acid on growth and apoptosis in human colon cancer cell lines associated with the induction of retinoic acid receptor beta." BIOCHEMICAL PHARMACOLOGY 1 MAR 2000, vol. 59, no. 5, 1 March 2000 (2000-03-01), pages 485-496, XP002445903 ISSN: 0006-2952 abstract page 490, column 2 - page 491, column 2, paragraph 1 ----- -/--	1-8, 14-25, 30,31, 35-37

☒ 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 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

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17 October 2007

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/000995

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUN SHI-YONG: "Retinoic acid receptor beta and colon cancer." CANCER BIOLOGY & THERAPY JAN 2004, vol. 3, no. 1, January 2004 (2004-01), pages 87-88, XP002445904 ISSN: 1538-4047 abstract page 84, column 1, paragraph 2 - column 2, paragraph 1	1-8, 14-25, 30,31, 35-37
X	YOUSSEF EMILE M ET AL: "Methylation and regulation of expression of different retinoic acid receptor beta isoforms in human colon cancer." CANCER BIOLOGY & THERAPY JAN 2004, vol. 3, no. 1, January 2004 (2004-01), pages 82-86, XP002445905 ISSN: 1538-4047 the whole document	1-8, 14-25, 30,31, 35-37
A	ALAIN BARRIER ET AL: "Gene Expression Profiling of Nonneoplastic Mucosa May Predict Clinical Outcome of Colon Cancer Patients" DISEASES OF THE COLON & RECTUM, SPRINGER-VERLAG, NE, vol. 48, no. 12, 1 December 2005 (2005-12-01), pages 2238-2248, XP019368711 ISSN: 1530-0358 abstract page 2239, column 2, paragraph 3 - page 2240, column 1, paragraph 2	1-8, 14-25, 30,31, 35-37
A	SARELA A I ET AL: "EXPRESSION OF THE ANTIAPOPTOSIS GENE, SURVIVIN, PREDICTS DEATH FROM RECURRENT COLORECTAL CARCINOMA" GUT, BRITISH MEDICAL ASSOCIATION, LONDON,, GB, vol. 46, no. 5, May 2000 (2000-05), pages 645-650, XP001098316 ISSN: 0017-5749 abstract page 646, column 1, paragraph 3 page 648, column 2, paragraph 2	1-8, 14-25, 30,31, 35-37
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/000995

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROSATI GERARDO ET AL: "Thymidylate synthase expression, p53, bcl-2, Ki-67 and p27 in colorectal cancer: Relationships with tumor recurrence and survival" TUMOR BIOLOGY, KARGER, BASEL, CH, vol. 25, no. 5-6, 2004, pages 258-263, XP009087940 ISSN: 1010-4283 abstract; tables 2,3 page 259, column 2, paragraph 3 - page 260, column 1, paragraph 1 page 260, column 2, paragraph 3 - page 261, column 2	1-8, 14-25, 30,31, 35-37
A	ARANGO ET AL: "Gene-Expression Profiling Predicts Recurrence in Dukes' C Colorectal Cancer" GASTROENTEROLOGY, ELSEVIER, PHILADELPHIA, PA, US, vol. 129, no. 3, September 2005 (2005-09), pages 874-884, XP005314702 ISSN: 0016-5085 abstract page 875, column 1, paragraph 4 - column 2, paragraph 1 page 877, column 2, paragraph 4 - page 880, column 2, paragraph 1	1-8, 14-25, 30,31, 35-37
X	US 2003/148314 A1 (BERGER ALLISON [US] ET AL) 7 August 2003 (2003-08-07) paragraph [0060] paragraph [0062]	1-8, 14-39
X	WILDI S ET AL: "OVEREXPRESSION OF ACTIVIN A IN STAGE IV COLORECTAL CANCER" GUT, BRITISH MEDICAL ASSOCIATION, LONDON,, GB, vol. 49, 2001, pages 409-417, XP008075384 ISSN: 0017-5749 the whole document	1-8, 14-27, 30-38
X	WO 03/050243 A (MILLENNIUM PHARM INC [US]; BERGER ALLISON [US]; GUILLEMETTE TRACY L [U]) 19 June 2003 (2003-06-19) page 8, line 16 - line 25; table 1	1-8, 14-27, 30-38

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-8,14-39 (partially),9-13,40-44

The application relates to methods for predicting clinical outcome for a subject diagnosed with colorectal cancer following surgical resection of said cancer, based on increased expression of one or more mRNAs or their expression products in a biological sample comprising cancer cells obtained from said subject. All independent claims refer to determining the expression of "one or more" genes; claims 9-12 relate to embodiments comprising determining expression levels of at least two, three, four or five of said transcripts respectively. Insofar as they relate to more than one gene, the claims are unclear and inconcise (Art.6 PCT) in that they encompass a huge number of embodiments (the different choices of any two, three, four, five or more from the total in the group(s)) such that a meaningful search for all possible embodiments is impossible. Furthermore, no actual sets of more than one marker that can be used in the claimed methods has been disclosed in the application. Therefore, the subject-matter relating to more than one gene, i.e. claims 1-8,14-39 (in part) and claims 9-12, has not been searched.

Claim 13 relates to a purely administrative step, namely creating a report summarizing a prediction. Therefore, said claim relates to subject matter for which no search is required according to Rule 39 PCT. Given that the claim is formulated in terms of such subject matter or merely specifies commonplace features relating to its technological implementation, the search examiner could not establish any technical problem which might potentially have required an inventive step to overcome. Hence it was not possible to carry out a meaningful search into the state of the art (Art. 17(2)(a)(i) and (ii) PCT; see PCT International Search Guidelines, Chapter 9).

Claims 40-44 relate to a mere presentation of information, namely a report of a prediction of clinical outcome, for which no search is required according to Rule 39.1(v) and Art.17(2)(a)(i) PCT. It is noted that the actual technical matter to which the claims refer, namely the method of providing a prediction of clinical outcome, is covered by the scope of the remaining claims.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

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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.: 1-8, 14-39 (partially), 9-13, 40-44
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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.:
1-44 (partially)
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.:

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:

Invention 1. Claims: 1-25,30,31,35-37,40-42 (all in part)

A method for predicting clinical outcome for a subject diagnosed with colorectal cancer following surgical resection of said cancer, comprising determining the expression level of at least one RNA transcript or its expression product in a biological sample comprising cancer cells obtained from said subject, wherein said RNA is for RARB; a report therefor.

Invention 2. Claims: 1-44 (all in part)

A method for predicting clinical outcome for a subject diagnosed with colorectal cancer following surgical resection of said cancer, comprising determining the expression level of at least one RNA transcript or its expression product in a biological sample comprising cancer cells obtained from said subject, wherein said RNA is the second mentioned in Table 1A; a report therefor.

Inventions 3-750. Claims: 1-44 (all in part)

A method for predicting clinical outcome for a subject diagnosed with colorectal cancer following surgical resection of said cancer, comprising determining the expression level of at least one RNA transcript or its expression product in a biological sample comprising cancer cells obtained from said subject, wherein said RNA is respectively of each of the remaining mRNAs in Tables 1A, 1B, 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 6, 7, 1.2A, 1.2B, 2.2A, 2.2B, 3.2A, 3.2B, 4.2A, 4.2B, 5.2A, 5.2B, 6.2 and 7.2; a report therefor.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/000995

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003148314 A1	07-08-2003	NONE	
WO 03050243 A	19-06-2003	AU 2002357747 A1	23-06-2003