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Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:  
5 June 2014

(54) Title: GENE EXPRESSION SIGNATURES IN ENRICHED TUMOR CELL SAMPLES

(57) Abstract: The invention is embodied in methods for finding gene expression signatures of circulating melanoma cells, ovarian, breast, colorectal cancer cells, and circulating endothelial progenitor cells, which signatures are effective in distinguishing the circulating cancer cell from normal circulating cells and can also distinguish between different types of circulating cancer cells.



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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/10881

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12Q 1/00 (2009.01)

USPC - 435/4

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 1/00 (2009.01)

USPC - 435/4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
USPC - 435/6; 435/7.1Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
PubWest (USPT, PGPB, EPAB, JPAB), Google Patent/Scholar, PubMed. Search terms - cancer, tumor, detection, diagnosis, circulating, blood, gene expression profile, cell adhesion matrix (CAM), reference tumor sample, epithelial, comparison, normal, upregulation, downregulation.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SMIRNOV et al. Global Gene Expression Profiling of Circulating Tumor Cells. Cancer Res. June 15, 2005 (15.06.2005), Vol. 65, No. 12, pages 4993-4997 - see pg 4993, col 1, para 2 - col 2, para 1-2, 4; pg 4995, col 1, para 1-2; pg 4996, col 1, para 3.	1-3
A	US 2002/0164825 A1 (CHEN) 07 November 2002 (07.11.2002) - see entire document.	1-3

☐ 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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

08 March 2009 (08.03.2009)

Date of mailing of the international search report

25 MAR 2009

Name and mailing address of the ISA/US

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/10881

## 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:

See extra 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 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.:  
Group 1 - Claims 1-3

### 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 08/10881

Continuation of Box III - Observations where unity 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 I: Claims 1-3, directed to a method of finding a gene expression signature for a tumor cell.

Group II+: Claims 4-15 and 18-22, directed to a method of detecting an endogenous tumor cell or distinguishing a circulating tumor cell from a different type of cell, comprising comparing a tumor cell gene signature with a reference tumor cell gene signature, wherein the signature comprises at least 2 constituents from Table I, Table II, Fig. 1, Fig. 9A, Table 11, Table 14, Table 15, or Table 16. CEACAM6 and CEACAM7 from Table I will be searched without an additional search fee within Group II. The applicant is required to pay an additional search fee for each additional constituent within Group II.

Group III+: Claims 16-17, directed to a method of detecting a circulating tumor cell in a subject comprising finding a gene expression profile comprising at least one of the genes selected from KRT8, KRT16, KRT17, KRT18, KRT19, and KRT20. KRT8 will be searched without an additional search fee. The applicant is required to pay an additional search fee for each additional gene within Group III.

Group IV+: Claim 23, directed to a method of internally controlling a comparison of gene expression signatures between or among circulating tumor cells, endothelial cells, and other cells, comprising determining said gene expression signatures together with the expression of a gene selected from ITGA2, CD14, and ITGB. ITGA2 will be searched without an additional search fee. The applicant is required to pay an additional search fee for each additional gene within Group IV.

The inventions listed as Groups I-IV 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:

Each constituent or gene does not share a common utility, and/or share a substantial structural feature disclosed as being essential to that utility.

Additionally, the common technical feature is a circulating tumor cell gene expression profile or signature. However, this feature is taught by the article entitled "Global gene expression profiling of circulating tumor cells" by Smirnov et al. (Cancer. Res. 15 June 2005 (15.06.2005), Vol. 65, No. 12, pages 4993-4997), which teaches a gene expression profile for circulating tumor cells (abstract). Accordingly, this feature cannot be considered novel.

Thus, Groups I-IV do not share a special technical feature as defined by PCT Rule 13.2.