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Declarations under Rule 4.17:

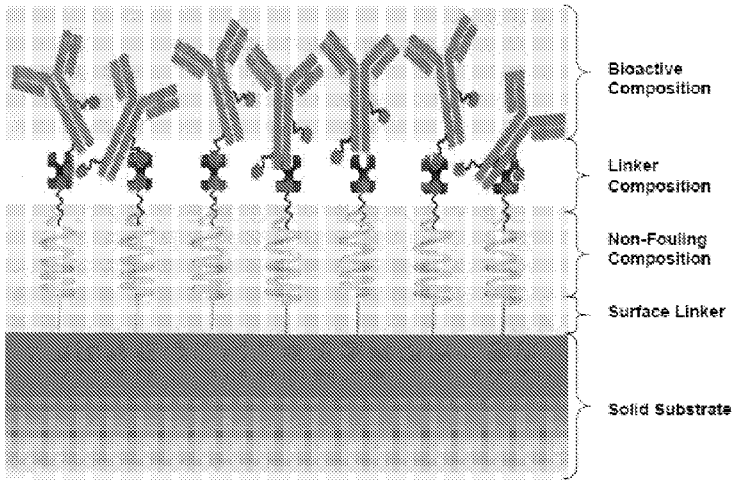
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

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

(88) Date of publication of the international search report:
14 March 2013

(54) Title: THE CAPTURE, PURIFICATION AND RELEASE OF BIOLOGICAL SUBSTANCE USING A SURFACE COATING



(57) Abstract: This invention relates to a surface coating for capture circulating rare cells, comprising a nonfouling composition to prevent the binding of non-specific cells and adsorption of serum components; a bioactive composition for binding the biological substance, such as circulating tumor cells; with or without a linker composition that binds the nonfouling and bioactive compositions. The invention also provide a surface coating for capture and purification of a biological substance, comprising a releasable composition to release the non-specific cells and other serum components; a bioactive composition for binding the biological substance, such as circulating tumor cells; with or without a linker composition that binds the releasable and bioactive compositions. The present invention also discloses a novel microfluidic chip, with specific patterned microstructures to create a flow disturbance and increase the capture rate of the biological substance.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/44701

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 33/53 (2012.01)
USPC - 436/501, 436/518, 435/7
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) - G01N 33/53 (2012.01)
USPC - 436/501, 436/518; 435/7

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)
PatBase, Google Scholar
Search terms: circulating, rare cell, circulating tumor cell, CTC, isolate, capture, purify, enrich, surface, coating, nonfouling, non-fouling, fouling, nonbiofouling, biofouling, antibody, anti-EpCAM, EpCAM, epithelial cell adhesion molecule, EpAb4-1, anti-HER2, HER2

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/124227 A2 (HONG et al.) 28 October 2010 (28.10.2010) para [0007], [0012], [0069], [0107]	1
X — Y — A	WO 2010/132795 A2 (SHAH et al.) 18 November 2010 (18.11.2010) p 3, ln 1-31; p 5, ln 20-26; p 7, ln 19-25; p 8, ln 1-30 to p 9, ln 1-2; p 10, ln 12-21; p 14, ln 14-24; p 15, ln 21-31; p 17, ln 15-24	1-7, 9, 13-18, 20-32, 34, 38-43, 45-50, 54-55 8, 10-12, 33, 35-37 19, 44, 61-63
Y	US 2003/0216534 A1 (CHAIKOF et al.) 20 November 2003 (20.11.2003) para [0014], [0031]-[0035], [0037]	8, 33
Y	US 2007/0077276 A1 (HAYNIE) 05 April 2007 (05.04.2007) para [0011], [0038], [0063], [0144], [0158]	10, 35
Y	US 2009/0259015 A1 (JIANG et al.) 15 October 2009 (15.10.2009) para [0165]	11, 36
Y	US 2008/0181861 A1 (JIANG et al.) 31 July 2008 (31.07.2008) para [0009], [0015], [0016], [0018], [0057]	12, 37
A	WO 2009/088933 A1 (TAKEUCHI) 16 July 2009 (16.07.2009) SEQ ID NO:815, SEQ ID NO: 952	19, 44, 61-63

☒ 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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2012 (20.11.2012)	10 DEC 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/44701

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/0038339 A1 (KUFER et al.) 26 February 2004 (26.02.2004) SEQ ID NO: 73	19, 44, 61-63
A	NAGRATH et al., Isolation of rare circulating tumour cells in cancer patients by microchip technology. Nature, 20 December 2007, Vol 450, No 7173, pages 1235-1239 (author manuscript p 1-11). Entire document	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/44701

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

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☒ together with the international application in electronic form

   ☐ 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 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/US 12/44701

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.: 51
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:
Claim 51 is unsearchable under PCT Article 34(4)(a)(ii) because the claim and drawing to which it refers are so unclear that no meaningful opinion can be formed on the novelty, inventive step (non-obviousness), or industrial applicability, of the claimed invention. In particular, the Figure contains features which are not otherwise elucidated in the claim, making the claimed invention for which protection is being sought unclear.

3. ☒ Claims Nos.: 52-53 and 56-60
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:
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 1-25, 54 and 55, directed to a surface coating for the capture of a circulating rare cell, said surface coating comprising: a) a non fouling composition; and b) a bioactive composition which is selective for said circulating rare cell.

Group II: claims 26-50, directed to a surface coating for the capture and purification of a biological substance, said surface coating comprising: a) a releasable composition for releasing non-specific cells and blood components; and b) a bioactive composition which is selective for said biological substance

---please 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.:

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.

Continuation of Box No III Observations where unity of invention is lacking

Group III: claim 61, directed to a method of capturing a circulating tumor cell using a biotinylated EpAb4-1 antibody, wherein said antibody comprises: (a) a heavy chain sequence, wherein said heavy chain sequence is SEQ ID NO: 1; and (b) a light chain sequence, wherein said tight chain Sequence is SEQ ID NO: 2.

The inventions listed as Groups I - III 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:

The special technical feature of the claims of Groups I-III are disclosed in the Group descriptions, above.

The only common technical element shared by the above groups is that they are related to a bioactive which is selective for a biological. Groups I and II share the common technical elements of being related to a surface coating for the capture of a biological, comprising a bioactive composition which is selective for said biological. These common technical elements do not represent an improvement over the prior art of WO 2010/124227 A2 to Hong et al., which discloses a surface coating for the capture of a circulating rare cell (para [0007] - "method of capturing a circulating tumor cell (CTC) [i.e. a circulating rare cell] in a sample comprising the step of introducing said sample into a microfluidic device under conditions that allow a CTC to bind to a cell rolling-inducing agent and a capturing agent"; para [0069] - "coating the flow modification surface with the cell-rolling inducing agent 16 and the capture agent 18"), said surface coating comprising: a) a non-fouling composition (para [0107] - "Enhanced controllability of surfaces by covalent immobilization [of the cell-rolling inducing agent P-selectin]...The chemistries described in Figure 5 were developed to achieve non-fouling surfaces"); and b) a bioactive composition which is selective for said circulating rare cell (para [0007] - "a capturing agent"; para [0012] - "the capturing agent specifically binds a moiety on a CTC cell surface").

Therefore, the inventions of Group I and Group II lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.