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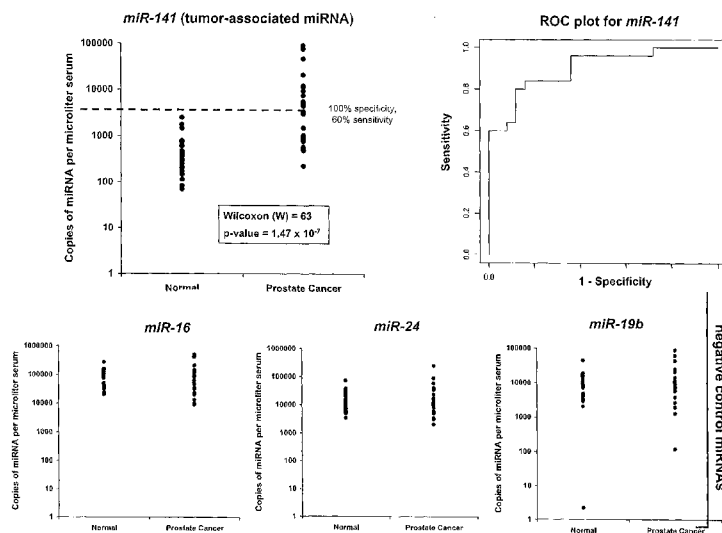
Published:

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[Continued on next page]

(54) Title: USE OF EXTRACELLULAR RNA TO MEASURE DISEASE

Figure 1



(57) Abstract: Stable, extracellular microRNAs and methods for isolating and identifying such microRNAs from a body fluid are provided. The extracellular microRNAs isolated from a bodily fluid of a subject can be used to measure disease and provide sensitive, efficient, and non invasive methods for the detection of disease, including cancer. The extracellular microRNAs can be used to develop new therapeutics for the treatment of disease, including cancer. The examples illustrate diagnosis of prostate and ovarian cancer and differential expression of miR-100, miR-135b, miR-141, miR-148a, miR-200a, miR-200c, miR-210, miR-222, miR-375, miR-425-Sp and miR-429.

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— *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))*

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/044906

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, Sequence Search, 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.
A	WANG M ET AL: "miRNA analysis in B-cell chronic lymphocytic leukaemia: proliferation centres characterized by low miR-150 and high BIC/milk-155 expression" JOURNAL OF PATHOLOGY, vol. 215, no. 1, 7 February 2008 (2008-02-07), pages 13-20, XP002545703 ISSN: 0022-3417 abstract ----- -/--	1-25, 27-40
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.		
<input checked="" type="checkbox"/> 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		
Date of the actual completion of the international search <p style="text-align: center; font-size: 1.2em;">15 September 2009</p>		Date of mailing of the international search report <p style="text-align: center; font-size: 1.2em;">11/01/2010</p>
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer <p style="text-align: center; font-size: 1.2em;">Knudsen, Henrik</p>

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/044906

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WONG THIAN-SZE ET AL: "Mature miR-184 as Potential Oncogenic microRNA of Squamous Cell Carcinoma of Tongue." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 1 MAY 2008, vol. 14, no. 9, 1 May 2008 (2008-05-01), pages 2588-2592, XP002545704 ISSN: 1078-0432	1-25, 27-31
X	abstract	32-40
A	LAWRIE CHARLES H ET AL: "Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma" BRITISH JOURNAL OF HAEMATOLOGY, vol. 141, no. 5, 3 March 2008 (2008-03-03), pages 672-675, XP002545705 ISSN: 0007-1048 page 673, left-hand column, lines 7-11; figure 1	1-25, 27-40
X	WO 2008/036765 A (ASURAGEN INC [US]; LABOURIER EMMANUEL [US]; SZAFRANSKA ANNA E [US]; DA) 27 March 2008 (2008-03-27) claims 5,8,34; example 18; table 6	1-25, 27-40
X	VARNHOLT HEIKE ET AL: "MicroRNA gene expression profile of hepatitis C virus-associated hepatocellular carcinoma." HEPATOLOGY (BALTIMORE, MD.) APR 2008, vol. 47, no. 4, April 2008 (2008-04), pages 1223-1232, XP002545744 ISSN: 1527-3350 abstract	1,18-20, 23-25, 32-40
X	YANG HUA ET AL: "MicroRNA expression profiling in human ovarian cancer: miR-214 induces cell survival and cisplatin resistance by targeting PTEN" CANCER RESEARCH, vol. 68, no. 2, January 2008 (2008-01), pages 425-433, XP002545743 ISSN: 0008-5472 figure 1	1,18-21, 23-25, 32-40
X	WO 2007/081740 A (UNIV OHIO STATE RES FOUND [US]; CROCE CARLO M [US]; CALIN GEORGE A [US]) 19 July 2007 (2007-07-19) claim 9; table 11	1,18-20
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/044906

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAM EUN JI ET AL: "MicroRNA expression profiles in serous ovarian carcinoma." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 1 MAY 2008, vol. 14, no. 9, 1 May 2008 (2008-05-01), pages 2690-2695, XP002545859 ISSN: 1078-0432 abstract; table 1	1, 18-21, 23-25
P, X	MITCHELL PATRICK S ET AL: "Circulating microRNAs as stable blood-based markers for cancer detection" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 105, no. 30, July 2008 (2008-07), pages 10513-10518, XP002545745 ISSN: 0027-8424 abstract	1-40
P, X	JP 2009 100687 A (UNIV CHIBA; UNIV KAGOSHIMA) 14 May 2009 (2009-05-14) abstract	1
P, X	-& DATABASE WPI Thomson Scientific, London, GB; AN 2009-J11442 XP002545863 & JP 2009 100687 A (UNIV CHIBA; UNIV KAGOSHIMA) 14 May 2009 (2009-05-14) abstract	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/044906

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 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 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.:

1-25, 27-40 (partially)

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.

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 1-25,27-40 (partially)

Method and kit for diagnosis in which miR-100 is determined in a biological sample and method for treatment employing miR-100 or another appropriate treatment in view of a cancer diagnosis based on the determination of miR-100 and a report on a measure of cancer based on the determination of miR-100.

Inventions 2-11: each claims 1-25,27-40 (partially)

Method and kit for diagnosis in which miR-135b (Invention 2), miR-141 (invention 3), miR-148a (Invention 4), miR-200a (invention 5), miR-200c (invention 6), miR-210 (invention 7), miR-222 (invention 8), miR-375 (invention 9), miR-425-5p (invention 10) or miR-429 (invention 11) is determined in a biological sample and method for treatment employing miR-135b (invention 2) etc. ... or another appropriate treatment in view of a cancer diagnosis based on the determination of miR-135b or ... and a report on a measure of cancer based on the determination of miR-135b etc ...

Invention 12: claim 26

Method for treating a disease or disorder characterised by underexpression of a miRNA and treatment by administration of a nucleotide sequence containing the miRNA.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2009/044906
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			US 2009131348 A1	21-05-2009
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			EP 1969147 A2	17-09-2008
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JP 2009100687	A	14-05-2009	NONE	