Title: MICRO-RNA-BASED METHODS AND COMPOSITIONS FOR THE DIAGNOSIS AND TREATMENT OF COLON CANCER-RELATED DISEASES

Abstract: The present invention provides novel methods and compositions for the diagnosis and treatment of colon cancers. The invention also provides methods of identifying inhibitors of tumorigenesis.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
   IPC: C12Q 1/68( 2006.01)
   USPC: 435/6
   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)
   U.S.: 435/6
   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)
   CAPlus, Medline, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT
   Category * Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.

Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search: 31 August 2008 (31.08.2008)

Name and mailing address of the ISA/US
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   Commissioner for Patents
   P.O. Box 1450
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Date of mailing of the international search report: 30 SEP 2008

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Form PCT/ISA/210 (second sheet) (April 2007)
INTERNATIONAL SEARCH REPORT

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:
Please See Continuation 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 any 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.

Form PCT/ISA/210 (continuation of first sheet(2)) (April 2007)
BOX III. OBSERVATIONS WHERE UNITY OF INVENTION 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 1, claim(s) 1, 2, 4-9, drawn to a method of diagnosing a colon-cancer related disease comprising measuring the level of miR20a gene product in a test sample and wherein a change in the level of the gene product in the test sample, compared to a control sample, is indicative of a cancer related disease.

Group 2, claim(s) 1-9 drawn to a method of diagnosing a colon-cancer related disease comprising measuring the level of miR-21 gene product in a test sample and wherein a change in the level of the gene product in the test sample, compared to a control sample, is indicative of a cancer related disease.

Group 3, claim(s) 1, 2, 4-9 drawn to a method of diagnosing a colon-cancer related disease comprising measuring the level of miR-106a gene product in a test sample and wherein a change in the level of the gene product in the test sample, compared to a control sample, is indicative of a cancer related disease.

Group 4, claim(s) 1, 2, 4-9 drawn to a method of diagnosing a colon-cancer related disease comprising measuring the level of miR-181b gene product in a test sample and wherein a change in the level of the gene product in the test sample, compared to a control sample, is indicative of a cancer related disease.

Group 5, claim(s) 1, 2, 4-9 drawn to a method of diagnosing a colon-cancer related disease comprising measuring the level of miR-203 gene product in a test sample and wherein a change in the level of the gene product in the test sample, compared to a control sample, is indicative of a cancer related disease.

Group 6 claim(s) 10, 12, 14, 50, 54, drawn to a method of inhibiting tumorigenesis in a subject comprising administering miR20a or an inhibitor of miR20a.

Group 7 claim(s) 10-14, 50, 51, 54, 55, drawn to a method of inhibiting tumorigenesis in a subject comprising administering miR-21 or an inhibitor of miR21.

Group 8 claim(s) 10, 12, 14, 50, 54, drawn to a method of inhibiting tumorigenesis in a subject comprising administering miR-106a or an inhibitor of miR-106a.

Group 9 claim(s) 10, 12, 14, 50, 54, drawn to a method of inhibiting tumorigenesis in a subject comprising administering miR-181b or an inhibitor of miR-181b.

Group 10 claim(s) 10, 12, 14, 50, 54, drawn to a method of inhibiting tumorigenesis in a subject comprising administering miR-203 or an inhibitor of mi-R203.

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Group 11, claim(s) 17-19, drawn to a method of identifying an inhibitor of tumorigenesis by determining if a test agent decreases the level of miR20a.

Group 12, claim(s) 17-19, drawn to a method of identifying an inhibitor of tumorigenesis by determining if a test agent decreases the level of miR-21.

Group 13, claim(s) 17-19, drawn to a method of identifying an inhibitor of tumorigenesis by determining if a test agent decreases the level of miR-106a.

Group 14, claim(s) 17-19, drawn to a method of identifying an inhibitor of tumorigenesis by determining if a test agent decreases the level of miR-181b.

Group 15, claim(s) 17-19, drawn to a method of identifying an inhibitor of tumorigenesis by determining if a test agent decreases the level of miR203.

Group 16, claim(s) 20-26, 32, 33, 35-43, 46, 52, 56, drawn to a composition comprising miR20a.

Group 17, claim(s) 20-26, 32-43, 46, 52, 53, 56, 57 drawn to a composition comprising miR-21.

Group 18, claim(s) 20-26, 32, 33, 35-43, 46, 52, 56, drawn to a composition comprising miR-106a.

Group 19, claim(s) 20-26, 32, 33, 35-43, 46, 52, 56, drawn to a composition comprising miR-181b.

Group 20, claim(s) 20-26, 32, 33, 35-43, 46, 52, 56, drawn to a composition comprising miR-203.

Group 21, claim(s) 27-31, 44, 45, drawn to a method of assessing the of a therapy to treat a colon cancer related disease by determining if a test agent alters miR20a.

Group 22, claim(s) 27-31, 44, 45, drawn to a method of assessing the of a therapy to treat a colon cancer related disease by determining if a test agent alters miR-21.

Group 23, claim(s) 27-31, 44, 45, drawn to a method of assessing the of a therapy to treat a colon cancer related disease by determining if a test agent alters miR-106a.

Group 24, claim(s) 27-31, 44, 45, drawn to a method of assessing the of a therapy to treat a colon cancer related disease by determining if a test agent alters miR-181b.

Group 25, claim(s) 27-31, 44, 45, drawn to a method of assessing the of a therapy to treat a colon cancer related disease by determining if a test agent alters miR-203.

Group 26, claim(s) 58-61, drawn to a computer readable medium.

Group 27, claim(s) 64-66, drawn to an animal model for colon cancer having an altered expression level of miR20a.

Group 28, claim(s) 64-66, drawn to an animal model for colon cancer having an altered expression level of miR-21.

Group 29, claim(s) 64-66, drawn to an animal model for colon cancer having an altered expression level of miR-106a.

Group 30, claim(s) 64-66, drawn to an animal model for colon cancer having an altered expression level of miR181b.

Group 31, claim(s) 64-66, drawn to an animal model for colon cancer having an altered expression level of miR-203.

The inventions listed as Groups 1-31 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 inventions listed as Groups 1-31 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: claim 1 does not provide a special technical feature over the prior art. PCT Rule 13.2 states "The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. (emphasis added)" Claim 1 is drawn to a method of diagnosing a colon cancer-related disease by determining if the expression of a miR gene product is altered in a sample compared to controls. The prior art recognized that miR gene products can have altered expression levels in colon cancer (e.g.,...
see Michael et al. Mol. Cancer Res. 2003, vol. 1, pp. 882-891. Therefore, claim 1 provides no special technical feature over the prior art.

Furthermore, it is noted that

37 CFR 1.475(b) states:

"An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product, or
(2) A product and process of use of said product; or
(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
(4) A process and an apparatus or means specifically designed for carrying out the said process; or
(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

37 CFR 1.475(c) states:

"If an application contains claims to more or less than one of the combination of categories of invention set forth in paragraph (b) of this section, unity of invention might not be present."

37 CFR 1.475(d) also states:

"If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and 1.476(c)."

37 CFR 1.475(e) further states:

"The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternative within a single claim."

In view of 37 CFR 1.475(b), 37 CFR 1.475(c), 37 CFR 1.475(d), and 37 CFR 1.475(e), Group 1 is considered the main invention as it is the first invention mentioned in the claims. As indicated above, since claim 1 does not define a contribution over the prior art, there is no unity of invention between the inventions. Furthermore, since Invention 1 is drawn to a process, the instant inventions do not belong to any of the acceptable categories of inventions indicated in 37 CFR 1.475(b) and there is no unity of invention.