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(71) Applicant: **MIRNA THERAPEUTICS, INC.** [US/US];
2150 Woodward Street, Suite 100, Austin, Texas 78744
(US).

(72) Inventors: **BADER, Andreas**; c/o MIRNA THERA-
PEUTICS, INC., 2150 Woodward Street, Suite 100, Aus-
tin, Texas 78744 (US). **ZHAO, Jane**; c/o MIRNA
THERAPEUTICS, INC., 2150 Woodward Street, Suite
100, Austin, Texas 78744 (US). **GUERRERO, Adriana**;
c/o MIRNA THERAPEUTICS, INC., 2150 Woodward
Street, Suite 100, Austin, Texas 78744 (US).

(74) Agent: **POULOS, Sabrina D.**; Wilson Sonsini Goodrich
& Rosati, 650 Page Mill Road, Palo Alto, California 94304
(US).

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Declarations under Rule 4.17:

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— as to the applicant's entitlement to claim the priority of the
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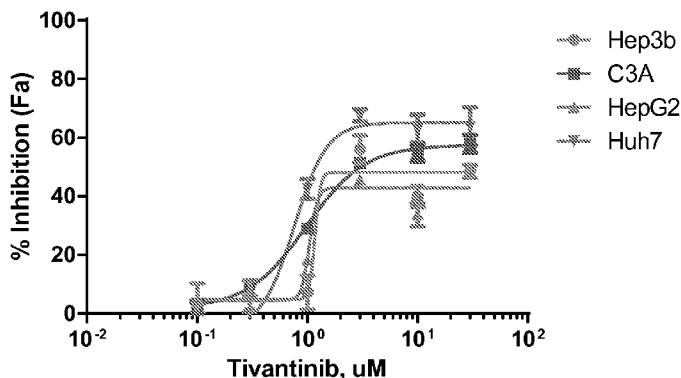
— with international search report (Art. 21(3))

— 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))

[Continued on next page]

(54) Title: COMBINATION CANCER THERAPY WITH C-MET INHIBITORS AND SYNTHETIC OLIGONUCLEOTIDES

FIG. 1A



(57) Abstract: Methods of inhibiting, and preventing the proliferation of, cancer cells, as well as treating cancer in an individual (e.g., a liver cancer, for example hepatocellular carcinoma) can include providing both a synthetic miR-34 family molecule and a c-Met inhibitor (e.g., tivantinib) to an individual in need thereof. The combination of the synthetic miRNA molecule and c-Met inhibitor can provide a desirable or superior effect, for example a more efficacious treatment than an alternative therapy, or the synthetic miRNA molecule or c-Met inhibitor alone. In some embodiments, the combinations provide a synergistic or greater than additive effect, or reduce toxicity and/or other side effects.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/61687

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 45/06; A61K 31/517, 31/713 (2016.01) CPC - A61K 31/713, 31/517 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) Classification(s): A61K 45/06; A61K 31/517, 31/713 (2016.01) CPC Classification(s): A61K 31/713, 31/517; A61K 39/39558; A61K 45/06		
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) PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google/Google Scholar; NCBI/BLAST/PubMed; EBSCO; miRNA-34, microRNA-34, cancer, tumor, c-Met, inhibitor, agent		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2014/0308274 A1 (MIRNA THERAPEUTICS, INC.) October 16, 2014; paragraphs [0006], [0011]-[0012], [0016], [0037], [0041], [0044], [0050], [0065], [0073], [0127]; SEQ ID NO: 1	1-5, 14-42, 51-59, 68-96, 105-139
Y	US 2014/0024548 A1 (NESTEC S.A.) January 23, 2014; paragraphs [0006], [0014], [0040], [0061]	1-5, 14-42, 51-59, 68-96, 105-139
Y	(BLADT, F et al.) The c-Met Inhibitor MSC2156119J Effectively Inhibits Tumor Growth in Liver Cancer Models. <i>Cancers (Basel)</i> . 19 August 2014, Vol. 6, No. 3; pages 1736-1752; page 1737, paragraph 2; DOI: 10.3390/cancers6031736	25, 54, 79, 115
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input 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 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 27 April 27 2016 (27.04.2016)		Date of mailing of the international search report 23 MAY 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/61687

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 Supplemental Page-

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.:
Groups I+, Claims 1-139; SEQ ID NO: 1 (mature miRNA sequence)

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
Information on patent family members

International application No.

PCT/US15/61687

-Continued from 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.

Groups I+, Claims 1-139 and SEQ ID NO: 1 (mature miRNA sequence) are directed toward methods of treating a cancer or reducing, inhibiting or preventing cancer cell proliferation in an individual in need thereof, comprising: administering to the individual: a. a c-Met inhibitor; and b. a synthetic miRNA molecule, comprising: i. an active strand comprising a sequence at least 80% identical to a mature miRNA; and ii. a separate complementary strand that is at least 60% complementary to the active strand; and a composition and combination therefor.

The methods, composition and combination will be searched to the extent that they encompass SEQ ID NO: 1 (first exemplary mature miRNA sequence). Applicant is invited to elect additional mature miRNA(s), with specified SEQ ID NO: for each, to be searched. Additional mature miRNA sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1-5, 14-42, 51-59, 68-96 and 105-139 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 1 (mature miRNA sequence). Applicants must specify the claims that encompass any additionally elected mature miRNA sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a mature miRNA sequence encompassing SEQ ID NO: 2 (first exemplary elected mature miRNA sequence).

No technical features are shared between the sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: a method of treating a cancer and reducing, inhibiting or preventing cancer cell proliferation in an individual in need thereof, comprising: administering to the individual: a. a c-Met inhibitor; and b. a synthetic miRNA molecule, comprising: i. an active strand comprising a sequence at least 80% identical to a mature miRNA; and ii. a separate complementary strand that is at least 60% complementary to the active strand; for use in treating a cancer.

However, these shared technical features are previously disclosed by US 2010/0227909 A1 to Cleary et al (hereinafter 'Cleary').

Cleary discloses a method of treating a cancer (a method of treating a tumor (a cancer); paragraph [0079]) and reducing, inhibiting or preventing cancer cell proliferation (reducing, inhibiting or preventing cancer cell proliferation; paragraphs [0057], [0185]) in an individual in need thereof (for a patient having cancer (in an individual in need thereof); paragraph [0079]), comprising: administering to the individual (comprising: administering to the individual; paragraphs [0079], [0084]): a. a c-Met inhibitor (an miR-34 family member that targets c-MET, and inhibits proliferation of a c-MET dependent cancer cell (a. a c-Met inhibitor; paragraphs [0080], [0185], [0258]); and b. a synthetic miRNA molecule (a synthetic miRNA molecule; paragraph [0006]), comprising: i. an active strand comprising a sequence at least 80% identical to portion of a mature miRNA (comprising a natural miR-34a guide strand (comprising: i. an active strand comprising a sequence at least 80% identical to portion of a mature miRNA); paragraph [0262]); and ii. a separate complementary strand that is at least 60% complementary to the active strand (ii. a separate complementary strand that is at least 60% complementary to the active strand; paragraphs [0006], [0050]); a composition (a composition; paragraphs [0008], [0080]) comprising: a. a c-Met inhibitor (an miR-34 family member that targets c-MET, and inhibits proliferation of a c-MET dependent cancer cell (a. a c-Met inhibitor; paragraphs [0080], [0185], [0258]); and b. a synthetic miRNA molecule (a synthetic miRNA molecule; paragraph [0006]), comprising: i. an active strand comprising a sequence at least 80% identical to portion of a mature miRNA (comprising a natural miR-34a guide strand (comprising: i. an active strand comprising a sequence at least 80% identical to portion of a mature miRNA); paragraph [0262]); and ii. a separate complementary strand that is at least 60% complementary to the active strand (ii. a separate complementary strand that is at least 60% complementary to the active strand; paragraphs [0006], [0050]); for use in treating a cancer (for use in treating a cancer; paragraph [0079]). Cleary further discloses wherein the expression of two or more genes is regulated by the miRNA (wherein the expression of two or more genes is regulated by the miRNA; paragraph [0140]), as well as wherein more than one miR-34 family member may be used (wherein more than one miR-34 family member may be used).

Cleary does not disclose a composition comprising a combination of: a. a c-Met inhibitor; and b. a synthetic miRNA molecule.

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Cleary to have provided a composition comprising a combination of a c-Met targeted specific miR-34 family member, as well as a second synthetic miRNA comprising an additional miR-34 member in order to effect the down regulation of two or more genes disclosed by Cleary, in order to provide a more effective treatment for a target cancer.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Cleary reference, unity of invention is lacking.