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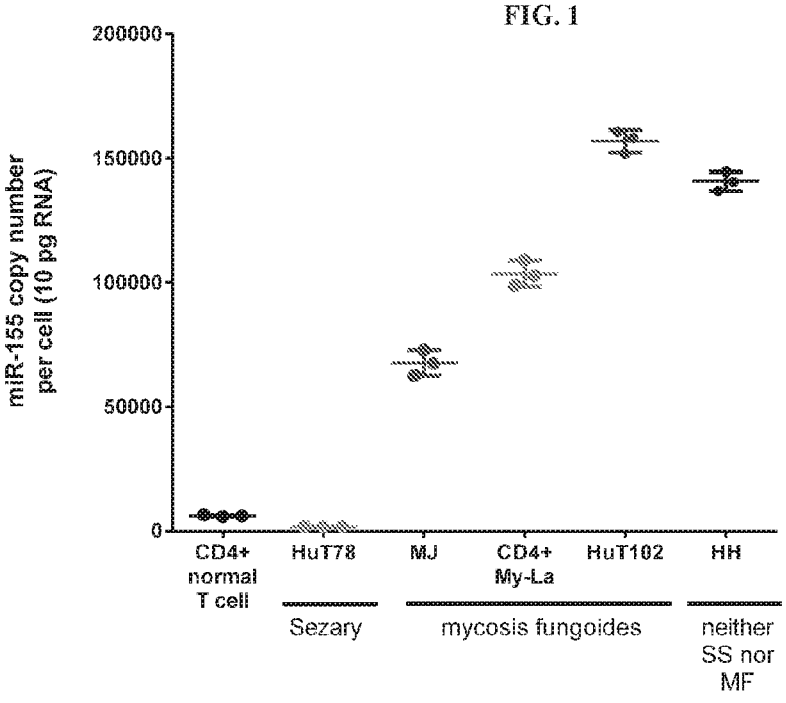
[Continued on next page]

(54) Title: MIR-155 INHIBITORS FOR TREATING CUTANEOUS T CELL LYMPHOMA (CTCL)

FIG. 1



(57) Abstract: The present invention provides oligonucleotide inhibitors of miR-155 and compositions thereof. The invention further provides methods for treating cancer such as a T cell lymphoma in a subject by administering to the subject an oligonucleotide inhibitor of miR- 155. The invention also provides methods for reducing or inhibiting the proliferation of malignant T cells by administering an oligonucleotide inhibitor of miR-155.

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LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
9 February 2017

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/35865

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 15/113, A61P 35/00, A61K 31/7088 (2016.01)
CPC - C12N 15/113, C12N 2310/141
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): C12N 15/113, A61P 35/00, A61K 31/7088 (2016.01)
CPC: C12N 15/113, C12N 2310/141

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 536/23.1, 536/24.5

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar, Google Web, search terms: oligonucleotide inhibitor, miRNA, miR-155, antimir, antisense, fully complementary, therapeutic agent, cancer, modified nucleotides, RNAseH resistant, DNA nucleotide, LNA, locked nucleotide, ethylene-bridged nucleotides, 2'-C-bridged bicyclic nucleotides, phosphorothioate backbone

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0077288 A1 (KAUPPINEN et al.) 31 March 2011 (31.03.2011) para [0010], [0012], [0017], [0039], [0052], [0054]-[0059], [0062]-[0064], [0068], [0072], [0104], [0111], [0112], [0225], Tables 1, 3, SEQ ID NOs: 164, 165, 194-199	1-10, 17-29
A	US 2010/0298410 A1 (OBAD et al.) 25 November 2010 (25.11.2010) entire document	1-10, 17-29
A	US 2010/0286234 A1 (ELMEN et al.) 11 November 2010 (11.11.2010) entire document	1-10, 17-29

☐ 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
16 November 2016	15DEC 2016
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. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/35865

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.: 11-16, 34-36, 41-48, 55-57, 62-68
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.:
1-10 and 17-29

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 16/35865

Continuation of Box No. 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 I: Claims 1-10 and 17-29, directed to a composition comprising an oligonucleotide inhibitor of miR-155.

Group II: Claims 30-33, 37-40, 49-54, 58-61 and 69-70, directed to a method for treating cancer in a subject.

Group III: Claim 71, directed to a method for selecting a subject for treatment of cutaneous T cell lymphoma (CTCL).

The inventions listed as Groups I through 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:

Special Technical Features
Groups II and III do not require a composition comprising an isolated oligonucleotide inhibitor of miR-l55, as required by group I.

Groups I and III do not require a method of treating cancer in a subject by inhibiting malignant T-cells, as required by group II.

Group I and II do not require a method for selecting a subject for cancer treatment by measuring biomarker levels, as required by group III.

Common Technical Features
The common technical feature shared by Groups I and II is an oligonudeotide inhibitor of miR-155 comprising a sequence of 11 to 14 nucleotides, wherein said oligonudeotide inhibitor is fully complementary to a mature sequence of miR- 155 and has a full phosphorothioate backbone, wherein at least the first three nucleotides from the 3' end of said oligonudeotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide, wherein modified nucleotides comprise locked nucleotides. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is anticipated by US 2011/0077288 A1 to Kauppinen et al. (hereinafter 'Kauppinen'). Kauppinen teaches said oligonudeotide inhibitor of miR-155 (Table 3 shows SEQ ID NOs: 195 and 196, 12 and 14 oligonucleotides targeting miR-155, para [0039] "'mixmer' refers to oligomers which comprise both naturally and non-naturally occurring nucleotides", para [0063] "the mixmer has the following substitution pattern, which is repeated from nucleotide eleven, counting from the 3' end, to the 5' end: XXXxXXXx ... wherein "X" denotes an LNA [locked nucleotide] unit and "x" denotes a non-LNA unit", para [0064] "In a preferred embodiment, the mixmer contains 12 nucleotides and the substitution pattern for positions 11 to 12, counting from the 3' end [e.g. positions 1 and 2 from the 5'-end of a 12 mer], is selected from the group consisting of xX and Xx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit."", para [0062] " "x" is ... most preferably DNA.", Thus, Kauppinen's mixmer oligonucleotides comprise xX or xX at positions 1 and 2 counting from the 5'-end, thus comprise mixmers having a DNA nucleotide at the second nucleotide from the 5' end., Kauppinen's SEQ ID NO: 195 has the claimed sequence of SEQ ID NOs: 22, 23 and 25, Kauppinen's SEQ ID NO: 196 has the sequence of the claimed SEQ ID NO: 39.).

A common technical feature shared by Groups II and III is treatment of malignant T cells. Kauppinen teaches treatment of malignant T cells (TABLE 1 "Examples of some diseases where specific microRNAs have been indicated. ... miR-155 lymphoma, pancreatic tumor development, breast and lung cancer", Table 3 shows said oligonudeotide inhibitors of miR-155.).

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Groups I through III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.