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- with international search report (Art. 21(3))
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- (88) **Date of publication of the international search report:**
10 March 2016

(54) **Title:** TERMINAL MODIFICATIONS OF POLYNUCLEOTIDES

(57) **Abstract:** The present invention relates to compositions and methods for the preparation, manufacture and therapeutic use of polynucleotides comprising at least one terminal modification.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/40835

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12N 15/11; C07H 21/02; A61K 31/7088 (2015.01)

CPC - C12N 2310/141; C12N 2310/10; C12N 15/113

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 15/11; C07H 21/02; A61K 31/7088 (2015.01)

CPC - C12N 2310/141; C12N 2310/10; C12N 15/113

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CPC: C12N 2310/141; C12N 2310/10; C12N 15/113 (text search)

USPC: 514/4/44R; 514/44A; 536/23.1; 536/24.1 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Electronic data bases: PatBase; Google Patents; Google Scholar

Search terms: Synthetic mRNA, heterologous untranslated region, chimeric, heterologous 5'UTR or 3'UTR; miRNA in 5'UTR or 3'UTR, flanking regions, miR-142-3p, miR-122

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/0147454 A1 (CHAKRABORTY et al.) 29 May 2014 (29.05.2014). Especially [0013], [0014], [0044], [0051], [0052], [0053], [0116], [0119], [0199], [0238], [0246], [0439], [0464], [1012], [1014], [1015], [1058], [1060], sheet 1 fig 1.	1-12, 22, 23B, (24,25,28)/(1-12,22,23B), (26,27)/(22, 23B)
X,P	WO 2014/164253 A1 (Moderna Therapeutics Inc.) 09 October 2014 (09.10.2014). Especially para [0009]-[0013], [0112], [0113]	1-12, 22, 23B, (24,25,28)/(1-12,22,23B), (26,27)/(22, 23B)

☐ 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

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/40835

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:

- a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
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 forming part of 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 15/40835

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:
-----Go to Extra Sheet for continuation-----

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.:
Claims 1-28, limited to the first named miRNA; miR-142-3p (claim 11) and the specifically elected miRNA, miR-122 (claim 11)(Claims 1-12, 22, 23B, (24-28) (in part))
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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/40835

-----continuation of Box III (Lack of Unity of Invention)-----

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 1-22, 23A, 23B, 24-28, drawn to a polynucleotide composition or a method of making or using the polynucleotide composition.

The polynucleotide composition or method of making or using it will be searched to the extent that the second terminal region comprises the first named miRNA, miR-142-3p (claim 11). It is believed that claims 1-12, 22, 23B, (24-28) (in part) read on this first named invention and thus these claims will be searched without fee to the extent that they encompass miR-142-3p. [NOTE, claims 20-21 are excluded from the first invention because central nervous system specific miRs is selected from miR-132, miR-125 and miR-124]. Additional miRs in the second terminal region will be searched upon payment of additional fees. Applicant must specify the claims that encompass any additional elected miR(s). Applicants must further indicate, if applicable, the claims which read on 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: miR-21 (claims 1-12, 16, 22, 23B, (24-28) (in part)).

The inventions listed as Group I+ 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:

Among the inventions listed as Groups I+ are the specific microRNAs (miRNAs) recited therein. The inventions do not share a special technical feature, because no significant structural similarities can readily be ascertained among miRNAs.

Common Technical Feature:

The common technical feature of Group I+ is claim 1: A polynucleotide comprising

- (a) a first region of linked nucleosides encoding a polypeptide of interest;
 - (b) a first terminal region located 5' relative to said first region comprising a 5' untranslated region;
 - (c) a second terminal region located 3' relative to said first region; and
 - (d) a tailing region,
- wherein the 5' untranslated region is a synthetic 5' untranslated region having a length of 3 - 13 nucleotides.

However, said common technical feature does not represent a contribution over the prior art, and is anticipated by US 2014/0147454 A1 to Chakraborty et al. (hereinafter "Chakraborty") [published 29 May 2014].

Chakraborty teaches claim 1: A polynucleotide comprising

- (a) a first region of linked nucleosides encoding a polypeptide of interest (para [0014]; "In one embodiment, provided herein are terminally optimized mRNA comprising first region of linked nucleosides encoding a polypeptide of interest which is located 5' relative to the first region, a second terminal region located 3' relative to the first terminal region and a 3' tailing region of linked nucleosides and at least one chain terminating nucleoside located 3' relative to the terminally optimized mRNA"; para [0044] and sheet 1 fig 1);
- (b) a first terminal region located 5' relative to said first region comprising a 5' untranslated region (para [0014]; para [0044] and sheet 1 fig 1);
- (c) a second terminal region located 3' relative to said first region (para [0014]; para [0044] and sheet 1 fig 1); and
- (d) a tailing region (para [0014]; para [0044] and sheet 1 fig 1), wherein the 5' untranslated region is a synthetic 5' untranslated region having a length of 3 - 13 nucleotides (para [0044] and sheet 1 fig 1; "The flanking region 104 may comprise a region of linked nucleotides comprising one or more complete or incomplete 5' UTRs sequences. The flanking region 104 may also comprise a 5' terminal cap 108"; para [0053]; According to the present invention, the capping region may comprise a single cap or a series of nucleotides forming the cap. In this embodiment the capping region may be from 1 to 10, e.g. 2-9, 3-8, 4-7, 1-5, 5-10, or at least 2, or 10 or fewer nucleotides in length"; para [0246].- Cap analogs, which herein are also referred to as synthetic cap analogs, chemical caps, chemical cap analogs, or structural or functional cap analogs, differ from natural (i.e. endogenous, wild-type or physiological) 5'-caps in their chemical structure").

As the common technical feature was known in the art at the time of the invention, this cannot be considered a common special technical feature that would otherwise unify the groups. The inventions lack unity with one another.

Therefore, Group I+ lacks unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note concerning claim 23: The instant application contains 2 claim 23s. For the purposes of the international search report, the first claim 23 is assigned as claim 23A and depends from claim 22, and the second claim 23 is assigned as claim 23B, and depends from claim 1.