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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:
18 July 2019 (18.07.2019)

(54) Title: GLP-1 RECEPTOR LIGAND MOIETY CONJUGATED OLIGONUCLEOTIDES AND USES THEREOF

(57) Abstract: The present embodiments provide compounds and methods for targeting cells expressing GLP-1 receptor.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB18/58752

A. CLASSIFICATION OF SUBJECT MATTER
IPC - C07K 14/535; C12N 15/10, 15/64 (2019.01)
CPC - C07K 14/535; C12N 15/10, 15/64

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2017/0204422 A1 (MODERNA THERAPEUTICS, INC.) 20 July 2017; paragraphs [0056]-[0061], [0066], [0070], [1076], [1121]	8, 13/8, 14/8, 15/8, 16/8 --- 1, 13/1, 14/1, 15/1, 16/1
Y	US 2017/0189441 A1 (COLLETTI, SL et al.) 06 July 2017; paragraphs [0069]-[0073], [0132], [0226]	1, 13/1, 14/1, 15/1, 16/1
A	US 2017/0202979 A1 (MODERNATX, INC.) 20 July 2017; entire document	1, 8, 13/1, 13/8, 14/1, 14/8, 15/1, 15/8, 16/1, 16/8

☐ Further documents are listed in the continuation of Box C. ☐ 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	Date of mailing of the international search report
30 January 2019 (30.01.2019)	17 MAY 2019
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

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB18/58752

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.: 17-66
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:

-***-Continued Within the Next Supplemental Box-***-

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.:
1, 8, 13/1, 13/8, 14/1, 14/8, 15/1, 15/8, 16/1, 16/8

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.

-***-Continued from 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.

Groups I+, Claims 1-16 (in-part); an oligonucleotide linked to a GLP-1 receptor ligand conjugate moiety by a conjugate linker, wherein the compound is as shown in claim 1 wherein N-N=N represents an azido group of the GLP-1 receptor ligand conjugate moiety and X directly attaches to the remainder of the GLP-1 receptor ligand conjugate moiety; n and o are each 2; and Y directly attaches to the oligonucleotide (first exemplary compound structure).

The compound will be searched to the extent the compound encompasses an oligonucleotide linked to a GLP-1 receptor ligand conjugate moiety by a conjugate linker, wherein the compound is as shown in claim 1 wherein N-N=N represents an azido group of the GLP-1 receptor ligand conjugate moiety and X directly attaches to the remainder of the GLP-1 receptor ligand conjugate moiety; n and o are each 2; and Y directly attaches to the oligonucleotide (first exemplary compound structure). Applicant is invited to elect additional compound(s), with fully specified structure (e.g. no optional or variable atoms or substituents) for each, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part) and 13-16 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass an oligonucleotide linked to a GLP-1 receptor ligand conjugate moiety by a conjugate linker, wherein the compound is as shown in claim 1 wherein N-N=N represents an azido group of the GLP-1 receptor ligand conjugate moiety and X directly attaches to the remainder of the GLP-1 receptor ligand conjugate moiety; n and o are each 2; and Y directly attaches to the oligonucleotide (first exemplary compound structure). Applicants must specify the claims that encompass any additionally elected compound structure(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 an oligonucleotide linked to a GLP-1 receptor ligand conjugate moiety by a conjugate linker, wherein the compound is as shown in claim 1 wherein N-N=N represents an azido group of the GLP-1 receptor ligand conjugate moiety and X directly attaches to the remainder of the GLP-1 receptor ligand conjugate moiety; n and o are each 3; and Y directly attaches to the oligonucleotide (first exemplary elected compound structure).

Groups I+ share the technical features including: an oligonucleotide linked to a GLP-1 receptor ligand conjugate moiety by a conjugate linker, wherein the compound is as shown in claim 1 wherein N-N=N represents an azido group of the GLP-1 receptor ligand conjugate moiety and X directly attaches to the remainder of the GLP-1 receptor ligand conjugate moiety; n and o are each 2; and Y directly attaches to the oligonucleotide.

However, these shared technical features are previously disclosed by US 2017/0204422 A1 (MODERNA THERAPEUTICS, INC.) (*hereinafter 'Moderna') in view of US 2017/0189441 A1 to Colletti, et al. (hereinafter 'Colletti')*.

Moderna discloses an oligonucleotide linked to a GLP-1 receptor ligand conjugate moiety by a conjugate linker, wherein the compound is similar to: the compound as shown, wherein N-N=N represents an azido group of the GLP-1 receptor ligand conjugate moiety and X directly attaches to the remainder of the GLP-1 receptor ligand conjugate moiety; n and o are each 2; and Y directly attaches to the oligonucleotide (compound of formula II wherein o is between 10-1000 (oligonucleotide linked) and L1 has the structure of formula III, R4 is the second shown moiety in paragraph [00080] (N-N=N is azido group of GLP-1 receptor ligand conjugate moiety), at least one of a-c is 1 (X directly attaches to remainder of GLP-1 receptor ligand), d is 1, R5 is C6 heteroalkyl wherein two carbon atoms are replaced with oxygen atoms and one carbon is substituted by oxo, e is 1, R6 is phosphoryl, f is 0, [Bo] is formula IV wherein X4 is O (Y directly attached to oligonucleotide); paragraphs [0056]-[0061], [0066], [0070], [1076], [1121]). Moderna does not disclose wherein the compound comprises a –NHCH2CH2SS- linker moiety. However, Colletti discloses wherein a compound comprises a –NHCH2CH2SS- linker moiety (oligonucleotide conjugate of the formula shown in paragraph [0042] wherein d is 1 and L is second linker as shown in table 3a on page 76; paragraphs [0069]-[0073], [0132], [0226]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by Moderna, in order to have provided wherein a compound comprises a –NHCH2CH2SS- linker moiety, as previously disclosed by Colletti, for providing oligonucleotide conjugate compounds designed to enhance the delivery of therapeutic agents to target cells (Moderna paragraph [0009]; Colletti; paragraphs [0018]-[0019]).

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 Moderna and Colletti references, unity of invention is lacking.