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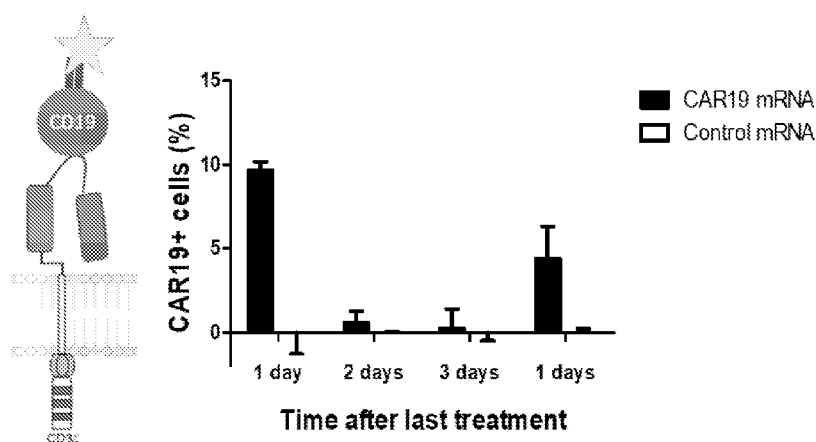
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(54) Title: HYBRID IMMOLATIVE CELL-PENETRATING COMPLEXES FOR NUCLEIC ACID DELIVERY

FIG. 29



(57) Abstract: There are provided herein, *inter alia*, complexes, compositions and methods for the delivery of nucleic acid into a cell *in vivo*. The complexes, compositions and methods may facilitate complexation, protection, delivery and release of oligonucleotides and polyanionic cargos into target cells, tissues, and organs both *in vitro* and *in vivo*.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/60807

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 48/00; C12N 15/85; A61K 47/69 (2020.01)

CPC - A61K 48/0041; C12N 15/115; C12N 15/85; A61K 47/6883

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	US 2018/0028688 A1 (The Board of Trustees of the Leland Stanford Junior University) 01 February 2018 (01.02.2018); Figure 7B, para [0005], [0007], [0009], [0011], [0117], [0121], [0126], [0131], [0135], [0152], [0198], [0207], [0209]-[0210], [0217]-[0218], [0223], [0229], [0267], [0273]-[0274], [0317], [0325], [0631]-[0634], [0719]	1-27, 29-33, 43-46, 89-114
Y		----- 28, 34-42
Y	Inoo et al. "Immunological quality and performance of tumor vessel-targeting CAR-T cells prepared by mRNA-EP for clinical research" Molecular Therapy - Oncolytics. 11 January 2017 (11.01.2017) vol 3, pg. 1-13; pg. 1, abstract	28, 34-42
A	US 2016/0348073 A1 (President and Fellows of Harvard College) 01 December 2016 (01.12.2016); entire document	1-46, 89-114
A	WO 2014/099671 A1 (BLUEBIRD BIO, INC.) 26 June 2014 (26.06.2014); entire document	1-46, 89-114

☐ 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

"D" document cited by the applicant in the international application

"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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Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/60807

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:
(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.:
1-46 and 89-114

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/US 19/60807

--continued from Box No. III--

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 searched, the appropriate additional search fees must be paid.

Group I: Claims 1-46 and 89-114, directed to a cell-penetrating complex of claim 1 comprising a nucleic acid non-covalently bound to a cationic amphipathic polymer, said cationic amphipathic polymer comprising a pH-sensitive immolation domain and a lipophilic polymer domain, wherein said cationic amphipathic polymer has the formula: $R1A-[L1-[(LP1)z1-(LP2)z3-(IM)z2]z4-L2-R2A]z5$.

Group II: Claims 47-88 and 115-130, directed to a method of transfecting a nucleic acid encoding a receptor protein/chimeric antigen receptor (CAR) / cell receptor (TCR) into a cell, the method comprising contacting a cell with a cell-penetrating complex comprising a nucleic acid encoding said receptor bound to a compound wherein said compound degrades upon delivery into said cell, thereby transfecting a nucleic acid encoding a said receptor into a cell in a subject.

The group of inventions listed above 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:

Group I includes the technical feature of a cell-penetrating complex comprising a nucleic acid non-covalently bound to a cationic amphipathic polymer, wherein said cationic amphipathic polymer has the formula: $R1A-[L1-[(LP1)z1-(LP2)z3-(IM)z2]z4-L2-R2A]z5$, which is not required by any other invention of Group II.

Group II includes the technical feature of a method of transfecting a nucleic acid encoding a receptor protein/chimeric antigen receptor (CAR) / cell receptor (TCR) into a cell in a subject, which is not required by any other invention of Group I.

Common technical features:

The inventions of Groups I and II share the technical feature of a cell-penetrating complex comprising a nucleic acid non-covalently bound to a cationic amphipathic polymer, said cationic amphipathic polymer comprising a pH-sensitive immolation domain and a lipophilic polymer domain.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by US 2018/0028688 A1 to The Board of Trustees of the Leland Stanford Junior University (hereinafter Stanford). Stanford discloses a cell-penetrating complex comprising a nucleic acid non-covalently bound to a cationic amphipathic polymer (para [0131]: a cell - penetrating complex including a nucleic acid non - covalently bound to a cationic amphipathic polymer , the cationic amphipathic polymer including a pH - sensitive immolation domain), said cationic amphipathic polymer comprising a pH-sensitive immolation domain (para [0131]: pH - sensitive immolation domain) and a lipophilic polymer domain (para [0007]: wherein at least one of LP1 or LP2 is a lipophilic polymer domain).

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I or II. The inventions of Group I or II thus lack unity under PCT Rule 13.