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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))

(88) Date of publication of the international search report:

14 December 2017 (14.12.2017)

(54) Title: AMPHIPHILIC NANOPARTICLES FOR DELIVERY OF CRISPR BASED THERAPY

(57) Abstract: Disclosed are copolymer micelles for simultaneous delivery of Cas9 mRNA and guide RNA for Cas9 CRISPR gene editing. Also disclosed are copolymer micelles for simultaneous delivery of a therapeutic or diagnostic nucleic acid and a cross-linking or alkylating anticancer agent.



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/030541

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 additional 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 an 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.:

1-78

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/US2017/030541

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/60
ADD.

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)
A61K

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)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/008300 A2 (ECOLE POLYTECH [CH]; SEGURA TATIANA [CH]; HUBBELL JEFFREY A [CH]) 18 January 2007 (2007-01-18)	1-78
Y	claims 1, 3, 6, 19, 20	1-78
Y	RUOGU QI ET AL: "Biodegradable copolymers with identical cationic segments and their performance in siRNA delivery", JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 159, no. 2, 13 January 2012 (2012-01-13), pages 251-260, XP028484312, ISSN: 0168-3659, DOI: 10.1016/J.JCONREL.2012.01.015 [retrieved on 2012-01-21] abstract	1-78



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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/030541

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PEIFENG LIU ET AL: "A mPEG-PLGA--PLL copolymer carrier for adriamycin and siRNA delivery", BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 33, no. 17, 23 February 2012 (2012-02-23), pages 4403-4412, XP028478185, ISSN: 0142-9612, DOI: 10.1016/J.BIOMATERIALS.2012.02.041 [retrieved on 2012-02-29] page 4403, right column, first complete paragraph abstract -----	1-78
Y	WO 2011/110694 A2 (DSM IP ASSETS BV [NL]; LEBOUILLE JEROME GEORGE JOZEPH LOUIS [BE]; KOCK) 15 September 2011 (2011-09-15) claims 1, 6, 9 page 8, line 15 page 6, line 4 -----	1-78
Y	WO 2016/037165 A1 (SELECTA BIOSCIENCES INC [US]) 10 March 2016 (2016-03-10) examples 29-31 -----	1-78
Y	LING LI ET AL: "Challenges in CRISPR/CAS9 Delivery: Potential Roles of Nonviral Vectors", HUMAN GENE THERAPY, vol. 26, no. 7, 1 July 2015 (2015-07-01), pages 452-462, XP055263140, US ISSN: 1043-0342, DOI: 10.1089/hum.2015.069 abstract page 456-457, item "poly L-lysine" -----	1-78
Y	JOHN A ZURIS ET AL: "Cationic lipid-mediated delivery of proteins enables efficient protein-based genome editing in vitro and in vivo", NATURE BIOTECHNOLOGY, vol. 33, no. 1, 30 October 2014 (2014-10-30), pages 73-80, XP055246826, US ISSN: 1087-0156, DOI: 10.1038/nbt.3081 abstract figure 4 -----	1-78

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/030541

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-78

a composition comprising certain nucleases or the corresponding nucleic acids encoding these nucleases; and a tri-block copolymer having a hydrophilic block, a hydrophobic block, and a block wherein the monomers carry positive charges at about neutral ph

2. claims: 79-99

a tri-block copolymer with a hydrophilic first block comprising certain specific monomers, a hydrophobic block comprising side chain protected lysine monomers, and a third block comprising certain amino acid monomers with a basic side chain

3. claims: 100-140

a composition comprising (a) a tri-block copolymer having a hydrophilic block, a hydrophobic block, and a block wherein the monomers carry positive charges at about neutral ph, and (b) a second block copolymer wherein the first block comprises monomers with a certain pKa
