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CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM,
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RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ,
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SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a
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Published:

— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the
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(88) Date of publication of the international search report:

12 September 2024 (12.09.2024)

(54) Title: COMPOSITIONS AND METHODS FOR DELIVERY OF NUCLEIC ACID EDITORS

(57) Abstract: Disclosed herein, in aspects, are compositions, methods, kits, and systems relating to delivery of molecules (e.g., a prime editor and a recombinase) for targeted integration of nucleic acid molecules into cells, for instance, for in vivo delivery via lipid delivery particles.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/085507

A. CLASSIFICATION OF SUBJECT MATTERIPC: **C12N 15/113** (2024.01); C12N 15/55 (2024.01); C12N 15/62 (2024.01); C12N 15/63 (2024.01); C12N 15/90 (2024.01); C12N 5/10 (2024.01); C12N 9/16 (2024.01); C12N 9/22 (2024.01)CPC: **C12N 15/113**; C12N 15/62; C12N 15/63; C12N 15/90; C12N 5/10; C12N 9/16; C12N 9/22

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.
A	WO 2021/226558 A1 (THE BROAD INSTITUTE INC. et al.) 11 November 2021 (11.11.2021) entire document	1-20, 22, 23, 25-30, 32-39, 43-45, 47-50, 52, 53, 55-59, 61-78, 80, 81, 83-88, 90-92, 94-97, 99, 100, 102- 105, 107-124, 126, 127, 129-134, 136-143, 147-149, 151-154, 156- 163, 165-168, 171-176



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

11 June 2024 (11.06.2024)

Date of mailing of the international search report

09 August 2024 (09.08.2024)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/085507

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.
 - b. ☒ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☒ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/085507

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.: **40-42, 144-146, 169, 170**
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:

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 need to be paid.

Group I+: claims 1-39, 43-143, 147-168, and 171-176 are drawn to lipid particles and compositions and systems comprising the same.

The first invention of Group I+ is restricted to a lipid delivery particle comprising a lipid containing a template RNA which encodes a donor nucleic acid molecule, where the template RNA is selected to be SEQ ID NO:345, and compositions and systems comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the template RNA sequences (LTR) listed in instant claim 17. It is believed that claims 1-20, 22, 23, 25-30, 32-39, 43-45, 47-50, 52, 53, 55-59, 61-78, 80, 81, 83-88, 90-92, 94-97, 99, 100, 102-105, 107-124, 126, 127, 129-134, 136-143, 147-149, 151-154, 156-163, 165-168, and 171-176 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NO:345.

Applicant is invited to elect additional LTR, viral envelopes, plasma membrane recruitment elements, retroviral envelope proteins, nucleic acid polypeptides, reverse transcriptases, and/or target nucleic acids, and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be to a lipid delivery particle comprising a lipid containing a template RNA which encodes a donor nucleic acid molecule, where the template RNA is selected to be SEQ ID NO:346, and compositions and systems comprising the same. Additional LTR, viral envelopes, plasma membrane recruitment elements, retroviral envelope proteins, nucleic acid polypeptides, reverse transcriptases, and/or target nucleic acids, and their respective, corresponding, SEQ ID NOs will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. 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.

The inventions listed in Groups 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:

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

The Groups I+ formulas do not share a significant structural element responsible for delivery of molecules for targeted integration into cells, requiring the selection of alternative LTR where “the LTR sequence comprises a nucleic acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98 %, or 100% sequence identity to any one of the sequences set forth in SEQ ID NOs: 345-352,” viral envelopes where “the viral envelope protein comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% sequence identity to any one of the sequences set forth in SEQ ID NOs: 83-104,” plasma membrane recruitment elements where “the plasma membrane recruitment element comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% sequence identity to any one of the sequences set forth in SEQ ID NOs: 1-48,” retroviral envelope proteins where “the human endogenous retroviral envelope protein comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% sequence identity to any one of the sequences set forth in SEQ ID NOs: 49-82,” nucleic acid guided polypeptides where “the nucleic acid-guided polypeptide comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% sequence identity to any one of the sequences set forth in SEQ ID NOs: 318-338,” reverse transcriptases where “the reverse transcriptase comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% sequence identity to any one of the sequences set forth in SEQ ID NOs: 339-344,” and/or target nucleic acids where “the recombinase recognizes a nucleic acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% sequence identity to any one of the sequences set forth in SEQ ID NOs: 105-317 or 515-538.”

Additionally, even if Groups I+ were considered to share the technical features of a lipid delivery particle, comprising: (d) a lipid containing membrane; (e) a recombinase; and (f) a ribonucleoprotein complex that comprises: (iii) a prime editor comprising a nucleic acid-guided polypeptide coupled to a nucleic acid polymerase; and (iv) a guide nucleic acid molecule, wherein the recombinase and the ribonucleoprotein complex are within an inside cavity encapsulated by the lipid containing membrane; a lipid delivery particle, comprising: (d) a recombinase or a nucleic acid sequence encoding the recombinase; (e) (i) a ribonucleoprotein complex comprising: (1) a prime editor comprising a nucleic acid-guided polypeptide coupled to a nucleic acid polymerase; and (2) a guide nucleic acid molecule, or (ii) (1) a nucleic acid sequence encoding the prime editor; and (2) the guide nucleic acid molecule or a nucleic acid sequence encoding the guide nucleic acid molecule; and (f) a template RNA that encodes a donor nucleic acid molecule, wherein the donor nucleic acid molecule comprises a donor nucleic acid sequence and a second recombinase recognition sequence, and wherein the recombinase mediates recombination between a first recombinase recognition sequence and the second recombinase recognition sequence; a lipid delivery particle comprising: a first nucleic acid sequence encoding a prime editor, wherein the prime editor comprises a nucleic acid-guided polypeptide coupled to a nucleic acid polymerase; a guide nucleic acid molecule or a second nucleic acid sequence encoding the guide nucleic acid molecule; a third nucleic acid sequence encoding a recombinase; and a donor nucleic acid sequence that comprises a second recombinase recognition sequence, or a template RNA encoding the donor nucleic acid sequence, and wherein the recombinase mediates recombination between a first recombinase recognition sequence and the second recombinase recognition sequence; a composition comprising: a first nucleic acid sequence encoding a first chimeric protein comprising a first plasma membrane recruitment element coupled to a prime editor, wherein the prime editor comprises a nucleic acid-guided polypeptide coupled to a nucleic acid polymerase; a guide nucleic acid molecule or a second nucleic acid sequence encoding the guide nucleic acid molecule; and a third nucleic acid sequence encoding a second chimeric protein comprising a second plasma membrane recruitment element coupled to a recombinase; a composition comprising: a first nucleic acid sequence encoding a prime editor, wherein the prime editor comprises a nucleic acid-guided polypeptide coupled to a nucleic acid polymerase; a guide nucleic acid molecule or a second nucleic acid sequence encoding the guide nucleic acid molecule; a third nucleic acid sequence encoding a recombinase; a donor nucleic acid sequence that comprises a second recombinase recognition sequence, or a template RNA encoding the donor nucleic acid sequence; and a nucleic acid sequence encoding an envelope protein; wherein the recombinase mediates recombination between a first recombinase recognition sequence and the second recombinase recognition sequence; a system, comprising: (1) a lipid delivery particle comprising (c) a lipid containing membrane; and (d) a ribonucleoprotein complex comprising: (A) a prime editor comprising a nucleic acid-guided polypeptide coupled to a nucleic acid polymerase; and (B) a guide nucleic acid molecule, wherein the ribonucleoprotein complex is within an inside cavity encapsulated by the lipid containing membrane; and (2) a recombinase or a nucleic acid sequence encoding the recombinase. a system, comprising: (1) a lipid delivery particle comprising (c) a lipid containing membrane; and (d) a recombinase, wherein the recombinase is within an inside cavity encapsulated by the lipid containing membrane; and (2) (i) a ribonucleoprotein

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

complex comprising: (A) a prime editor comprising a nucleic acid- guided polypeptide coupled to a nucleic acid polymerase; and (B) a guide nucleic acid molecule, or (ii) (A) a nucleic acid sequence encoding the prime editor; and (B) the guide nucleic acid molecule or a nucleic acid sequence encoding the guide nucleic acid molecule . However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2022/0340889 A1 to The Regents Of The University Of California discloses a lipid delivery particle (a delivery particle comprising lipid, Para. [0317]), comprising: (d) a lipid containing membrane (biodegradable core-shell structured nanoparticle with a poly (beta -amino ester) (PBAE) core enveloped by a phospholipid bilayer shell can be used, Para. [0318]); (e) a recombinase (a fusion Cas12J protein includes a heterologous polypeptide that has enzymatic activity ...recombinase activity, Para. [0162]); and (f) a ribonucleoprotein complex that comprises: and (iv) a guide nucleic acid molecule (present disclosure provides ribonucleoprotein complexes comprising: a Cas12J polypeptide of the present disclosure; and a guide RNA, Para. [0095]), wherein the recombinase and the ribonucleoprotein complex are within an inside cavity encapsulated by the lipid containing membrane (Cas12J system of the present disclosure, or a component thereof, may be delivered encapsulated in PLGA microspheres, Para. [0333]; biodegradable core-shell structured nanoparticle with a poly (beta -amino ester) (PBAE) core enveloped by a phospholipid bilayer shell can be used, Para. [0318]; a fusion Cas12J protein includes a heterologous polypeptide that has enzymatic activity ...recombinase activity, Para. [0162]); a lipid delivery particle (a delivery particle comprising lipid, Para. [0317]), comprising: (d) a recombinase or a nucleic acid sequence encoding the recombinase (a fusion Cas12J protein includes a heterologous polypeptide that has enzymatic activity ...recombinase activity, Para. [0162]); (e) (i) a ribonucleoprotein complex comprising: (2) a guide nucleic acid Molecule (present disclosure provides ribonucleoprotein complexes comprising: a Cas12J polypeptide of the present disclosure; and a guide RNA, Para. [0095]),

a lipid delivery particle (a delivery particle comprising lipid, Para. [0317]) comprising: a first nucleic acid sequence encoding a prime editor (a fusion Cas12J protein includes a heterologous polypeptide that has enzymatic activity ...recombinase activity, Para. [0162]); a composition (compositions, Para. [0004]) comprising: a composition (compositions, Para. [0004]) comprising: a system ([t]he present disclosure provides a Cas12J system, Para. [0241]), comprising: (1) a lipid delivery particle comprising (c) a lipid containing membrane (biodegradable core-shell structured nanoparticle with a poly (beta -amino ester) (PBAE) core enveloped by a phospholipid bilayer shell can be used, Para. [0318]); and (d) a recombinase (a fusion Cas12J protein includes a heterologous polypeptide that has enzymatic activity ...recombinase activity, Para. [0162]), wherein the recombinase is within an inside cavity encapsulated by the lipid containing membrane (Cas12J system of the present disclosure, or a component thereof, may be delivered encapsulated in PLGA microspheres, Para. [0333]; biodegradable core-shell structured nanoparticle with a poly (beta -amino ester) (PBAE) core enveloped by a phospholipid bilayer shell can be used, Para. [0318]; a fusion Cas12J protein includes a heterologous polypeptide that has enzymatic activity ...recombinase activity, Para. [0162]); and (2) (i) a ribonucleoprotein complex comprising: (B) a guide nucleic acid molecule, or (ii) (A) a nucleic acid sequence encoding the prime editor; and (B) the guide nucleic acid molecule or a nucleic acid sequence encoding the guide nucleic acid molecule (present disclosure provides ribonucleoprotein complexes comprising: a Cas12J polypeptide of the present disclosure; and a guide RNA, Para. [0095]).

Further, WO 2021/226558 A1 to The Broad Institute, Inc et al. teaches (iii) a prime editor comprising a nucleic acid-guided polypeptide coupled to a nucleic acid polymerase (fusion protein comprising a reverse transcriptase fused to a Cas9 protein in complex with an extended guide RNA molecule, Para. [0096]); (f) a template RNA that encodes a donor nucleic acid molecule, wherein the donor nucleic acid

molecule comprises a donor nucleic acid sequence and a second recombinase recognition sequence, and wherein the recombinase mediates recombination between a first recombinase recognition sequence and the second recombinase recognition sequence (system comprising a first prime editor/pegRNA complex capable of installing a first 3' nucleic acid flap at a first nick site on a first strand of a target site and a second prime editor/pegRNA complex capable of installing a second 3' nucleic acid flap at a second nick site on a second strand of a target site, wherein the first 3' nucleic acid flap and the second 3' nucleic acid flap are reverse complement sequences that form a duplex, and wherein the duplex comprises a first recombinase site, and wherein the cell installs the duplex comprising the first recombinase site at the target site in place of an endogenous duplex positioned between the first and second nick sites; (ii) contacting the first recombinase site with a donor nucleic acid comprising a second recombinase site; and (iii) contacting the genome with a recombinase capable recombination between the first and second recombinase sites, thereby integrating the donor nucleic

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

acid at the target site in the genome, Para. [0954]); a guide nucleic acid molecule or a second nucleic acid sequence encoding the guide nucleic acid molecule; a third nucleic acid sequence encoding a recombinase; and a donor nucleic acid sequence that comprises a second recombinase recognition sequence, or a template RNA encoding the donor nucleic acid sequence, and wherein the recombinase mediates recombination between a first recombinase recognition sequence and the second recombinase recognition sequence (system comprising a first prime editor/pegRNA complex capable of installing a first 3' nucleic acid flap at a first nick site on a first strand of a target site and a second prime editor/pegRNA complex capable of installing a second 3' nucleic acid flap at a second nick site on a second strand of a target site, wherein the first 3' nucleic acid flap and the second 3' nucleic acid flap are reverse complement sequences that form a duplex, and wherein the duplex comprises a first recombinase site, and wherein the cell installs the duplex comprising the first recombinase site at the target site in place of an endogenous duplex positioned between the first and second nick sites; (ii) contacting the first recombinase site with a donor nucleic acid comprising a second recombinase site; and (iii) contacting the genome with a recombinase capable recombination between the first and second recombinase sites, thereby integrating the donor nucleic acid at the target site in the genome, Para. [0954]); a first nucleic acid sequence encoding a prime editor, wherein the prime editor comprises a nucleic acid-guided polypeptide coupled to a nucleic acid polymerase; a guide nucleic acid molecule or a second nucleic acid sequence encoding the guide nucleic acid molecule; a third nucleic acid sequence encoding a recombinase; a donor nucleic acid sequence that comprises a second recombinase recognition sequence, or a template RNA encoding the donor nucleic acid sequence; and a nucleic acid sequence encoding an envelope protein; wherein the recombinase mediates recombination between a first recombinase recognition sequence and the second recombinase recognition sequence (system comprising a first prime editor/pegRNA complex capable of installing a first 3' nucleic acid flap at a first nick site on a first strand of a target site and a second prime editor/pegRNA complex capable of installing a second 3' nucleic acid flap at a second nick site on a second strand of a target site, wherein the first 3' nucleic acid flap and the second 3' nucleic acid flap are reverse complement sequences that form a duplex, and wherein the duplex comprises a first recombinase site, and wherein the cell installs the duplex comprising the first recombinase site at the target site in place of an endogenous duplex positioned between the first and second nick sites; (ii) contacting the first recombinase site with a donor nucleic acid comprising a second recombinase site; and (iii) contacting the genome with a recombinase capable recombination between the first and second recombinase sites, thereby integrating the donor nucleic acid at the target site in the genome, Para. [0954]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

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.: **1-20, 22, 23, 25-30, 32-39, 43-45, 47-50, 52, 53, 55-59, 61-78, 80, 81, 83-88, 90-92, 94-97, 99, 100, 102-105, 107-124, 126, 127, 129-134, 136-143, 147-149, 151-154, 156-163, 165-168, 171-176**

- 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/US2023/085507

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2022/0340889 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 27 October 2022 (27.10.2022) entire document	1-20, 22, 23, 25-30, 32-39, 43-45, 47-50, 52, 53, 55-59, 61-78, 80, 81, 83-88, 90-92, 94-97, 99, 100, 102- 105, 107-124, 126, 127, 129-134, 136-143, 147-149, 151-154, 156- 163, 165-168, 171-176
A	US 2019/0345490 A1 (EDITAS MEDICINE INC.) 14 November 2019 (14.11.2019) entire document	1-20, 22, 23, 25-30, 32-39, 43-45, 47-50, 52, 53, 55-59, 61-78, 80, 81, 83-88, 90-92, 94-97, 99, 100, 102- 105, 107-124, 126, 127, 129-134, 136-143, 147-149, 151-154, 156- 163, 165-168, 171-176
A	US 2018/0245065 A1 (NOVARTIS AG) 30 August 2018 (30.08.2018) entire document	1-20, 22, 23, 25-30, 32-39, 43-45, 47-50, 52, 53, 55-59, 61-78, 80, 81, 83-88, 90-92, 94-97, 99, 100, 102- 105, 107-124, 126, 127, 129-134, 136-143, 147-149, 151-154, 156- 163, 165-168, 171-176