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[Continued on next page]

(54) Title: PROCESSES AND COMPOSITIONS FOR LIPOSOMAL AND EFFICIENT DELIVERY OF GENE SILENCING THERAPEUTICS

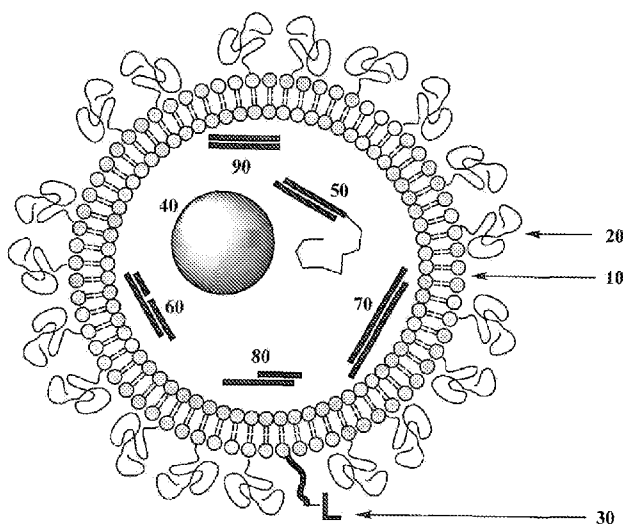


Fig. 1

(57) Abstract: Processes and compositions for liposomal delivery of therapeutics prepared by contacting an aqueous solution of an active agent with a solution of liposome-forming components containing one or more DILA2 amino acid compounds or lipids in organic solvent to form an impinging stream. A protocol including flow rates, pH, and an incubation period are used to control formation of liposomal components for therapeutic applications. The impinging stream may be collected and incubated to prepare a liposomal formulation which encapsulates the active agent. The composition can be quenched with buffer and filtered by tangential flow and diafiltration and other means for finishing as a pharmaceutical composition. An efficiency for delivering a drug cargo is provided. Compositions can include a liposome containing one or more carrier particles, each carrier particle having an active agent and a peptide, wherein the ratio of the mass of the peptide plus the mass of the liposome to the mass of the active agent is less than about 15.



TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

— 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))

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

— with sequence listing part of description (Rule 5.2(a))

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

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INTERNATIONAL SEARCH REPORT

International application No

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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/127 A61K48/00 C12N15/11 C12N15/88

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 practical, search terms used)

EPO-Internal, BIOSIS, INSPEC, BEILSTEIN Data, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GABIZON AA ET AL.: "Pros and cons of the liposome platform in cancer drug targeting" JOURNAL OF LIPOSOME RESEARCH, vol. 16, no. 3, 2006, pages 175-183, XP002591241 ISSN: 0898-2104 the whole document ----- -/--	1-34



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 document 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

9 July 2010

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/060930

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MAINARDES R M ET AL: "Liposomes and micro/nanoparticles as colloidal carriers for nasal drug delivery" CURRENT DRUG DELIVERY, vol. 3, no. 3, 1 January 2006 (2006-01-01), pages 275-285, XP009095996 BENTHAM SCIENCE PUBLISHERS, HILVERSUM, NL ISSN: 1567-2018 DOI: 10.2174/156720106777731019 the whole document -----	1-34
Y	SHARMA A ET AL: "LIPOSOMES IN DRUG DELIVERY: PROGRESS AND LIMITATIONS" INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 154, no. 2, 1 January 1997 (1997-01-01), pages 123-140, XP008047948 ELSEVIER BV, NL ISSN: 0378-5173 DOI: 10.1016/S0378-5173(97)00135-X the whole document -----	1-34
Y	MINGHUI FAN ET AL: "Preparation of salidroside nano-liposomes by ethanol injection method and in vitro release study" EUROPEAN FOOD RESEARCH AND TECHNOLOGY, vol. 227, no. 1, 25 July 2007 (2007-07-25), pages 167-174, XP019621668 ZEITSCHRIFT FÜR LEBENSMITTELUNTERSUCHUNG UND -FORSCHUNG A, SPRINGER, BERLIN, DE ISSN: 1438-2385 the whole document page 168, column 2, paragraph 2 -----	1-34
Y	MAITANI Y ET AL: "MODIFIED ETHANOL INJECTION METHOD FOR LIPOSOMES CONTAINING beta-SITOSTEROL beta-D-GLUCOSIDE." JOURNAL OF LIPOSOME RESEARCH, vol. 11, no. 1, 2001, pages 115-125, XP002591242 ISSN: 1532-2394 the whole document page 117; figures 2,3; table 1 ----- -/--	1-34

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/060930

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PONS M ET AL: "Liposomes obtained by the ethanol injection method" INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 95, no. 1-3, 30 June 1993 (1993-06-30), pages 51-56, XP023831858 ELSEVIER BV, NL ISSN: 0378-5173 DOI: 10.1016/0378-5173(93)90389-W [retrieved on 1993-06-30] the whole document page 52	1-34
Y	SKALKO NATASA ET AL: "Liposomes with nifedipine and nifedipine-cyclodextrin complex: Calorimetical and plasma stability comparison" EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 4, no. 6, 1996, pages 359-366, XP002591243 ISSN: 0928-0987 the whole document paragraph [02.3]	1-34
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A,P	WO 2009/046220 A2 (MDRNA INC [US]; ADAMI ROGER C [US]; HOUSTON MICHAEL E [US]; JOHNS RACH) 9 April 2009 (2009-04-09)	1-34
A	FREDERIKSEN LENE ET AL: "Preparation of liposomes encapsulating water-soluble compounds using supercritical carbon dioxide" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 86, no. 8, 1997, pages 921-928, XP002591244 ISSN: 0022-3549	1-34
A	MAITANI ET AL: "Cationic liposome (DC-Chol/DOPE=1:2) and a modified ethanol injection method to prepare liposomes, increased gene expression" INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 342, no. 1-2, 17 August 2007 (2007-08-17), pages 33-39, XP022206304 ELSEVIER BV, NL ISSN: 0378-5173 DOI: 10.1016/J.IJPHARM.2007.04.035	1-34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/060930

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.:

1-34

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-34

A process according to claim 1 for making a composition comprising an active agent. A composition made by said process. Methods for:

- delivering a nucleic acid,
 - inhibiting the expression of a gene, and
 - treating a disease in human,
- using a composition made by said process.
-

2. claims: 35-61

A composition according to claim 35. Methods for:

- delivering a nucleic acid,
 - inhibiting the expression of a gene, and
 - treating a disease in human,
- using said composition.
-

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/060930

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
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			CN	101674853	A	17-03-2010
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			US	2008317839	A1	25-12-2008
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