Title: LIPOSOMES, LIPOID COMPOSITIONS, AND METHODS OF USING THEM

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(54) Title: LIPOSOMES, LIPOID COMPOSITIONS, AND METHODS OF USING THEM

(1) R1, R2, N

(XI) Z

(57) Abstract: Disclosed are formulation and optimization protocols for delivery of therapeutically effective amounts of biologically active agents to liver, tumors, and/or other cells or tissues. Also provided are compositions and uses for cationic lipid compounds of formula (I). The invention also relates to compositions and uses for stealth lipids of formula (XI). Also provided are processes for making such compounds, compositions, and formulations, plus methods and uses of such compounds, compositions, and formulations to deliver biologically active agents to cells and/or tissues.

[Continued on next page]

Declarations under Rule 4.17:

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

Published:

— with international search report (Art. 21(3))
INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2010/070412

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. [x] 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.:

2, 3 (completely) ; 1, 5-22 (partially)

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.
A. CLASSIFICATION OF SUBJECT MATTER

INV. A61P35/00 A61P1/16 A61P43/00 A61K9/127 A61K9/14

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P C07D

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, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
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[X] Further documents are listed in the continuation of Box C.  
[X] See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

3 May 2011

Date of mailing of the international search report

12/09/2011

Name and mailing address of the ISA/

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Lemarchand, Aude

Form PCT/ISA/210 (second sheet) (April 2005)
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<td>WO 2008/103276 A2 (MERCK &amp; CO INC [US]; JADHAV VASANT [US]; VARGEESE CHANDRA [US]; SHAW L) 28 August 2008 (2008-08-28) C01M structure; page 275 C01eyl -2MeIm; ClNi-Im; ClNi-2MeI; pages 276-277 L149; page 278 L237-L240; page 280</td>
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Form PCT/ISA/210 (continuation of second sheet) (April 2008)
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<td>wo 2011/022460 AI (MERCK SHARP &amp; DOHME [US]; CAMERON MARK [US]; DAVIS JENNI FER R [US]; GE) 24 February 2011 (2011-02-24) page 22; compound 10a page 15; compound 10 claims 1-4 page 1, line 35 - page 2, line 2; compound A</td>
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<td>SIMPLE S C ET AL: &quot;Rational design of cationic lipids for siRNA delivery&quot;, NATURE BIOTECHNOLOGY, vol. 28, no. 2, February 2010 (2010-02), pages 172-176+METHOD, XP002633693, NATURE PUBLISHING GROUP USA ISSN: 1087-0156, DOI: 10.1038/NBT.1602 page 174, last paragraph - page 175, paragraph first; table 1</td>
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<td>SIMPLE&lt;a&gt; S C ET AL: &quot;Efficient encapsulation of anti-sense oligonucleotides in lipid vesicles using cationic nanolipids: formation of novel small unilamellar vesicle structures&quot;, BIOCHIMICA ET BIOPHYSICA ACTA, BIOMEMBRANES, AMSTERDAM, NL, vol. 1510, no. 1-2, 9 February 2001 (2001-02-09), pages 152-166, XP004248775, ISSN: 0005-2736, DOI: DOI: 10.1016/50005-2736(00)00343-6 page 158, left-hand column, last paragraph - page 159, right-hand column, paragraph first</td>
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WO 2011022460 A1 24-02-2011 NONE
1. claims: 2, 3 (completely) ; 1, 5-22 (partially)

a composition comprising a catonic lipid, one helper lipid
and one stealth lipid for delivery of a biologically active
agent, wherein the biologically active agent is for delivery
to a tissue or cell selected from: a) a liver or liver
cells, wherein the composition has a catonic lipid with a
pKa of from about 6.2 or above; b) a tumor or tumor cell,
wherein the composition has a catonic lipid with a pKa of
from about 6.2 or below; c) a liver or liver cells, wherein
the composition has a catonic lipid with a pKa of from
about 5.1 to about 7.4; and
d) a tumor or tumor cell, wherein the composition has a
catonic lipid with a pKa of from about 5.0 to about 6.7,
wherein the catonic lipid is a compound of formula (I) as
defined in claim 2;
a compound of formula (I) as defined in claim 2.

2. claims: 4 (completely) ; 1, 5-22 (partially)

a "stealth lipid" of formula (XI) as defined in claim 4 and
a composition comprising said stealth lipid, a catonic
lipid, one helper lipid for use in the delivery of a
biologically active agent, wherein the biologically active
agent is for delivery to a tissue or cell selected from:
a) a liver or liver cells, wherein the composition has a
catonic lipid with a pKa of from about 6.2 or above; b) a
tumor or tumor cell, wherein the composition has a catonic
lipid with a pKa of from about 6.2 or below; c) a liver or
liver cells, wherein the composition has a catonic lipid
with a pKa of from about 5.1 to about 7.4; and d) a tumor or
tumor cell, wherein the composition has a catonic lipid
with a pKa of from about 5.0 to about 6.7.

3. claims: 1, 6-9, 12-22 (all partially)

1. A composition comprising at least one catonic lipid, at
least one helper lipid and at least one stealth lipid for
delivery of a biologically active agent, wherein the
biologically active agent is for delivery to a tissue or
cell selected from:
a) a liver or liver cells, wherein the composition has a
catonic lipid with a pKa of from about 6.2 or above;
b) a tumor or tumor cell, wherein the composition has a
catonic lipid with a pKa of from about 6.2 or below;
c) a liver or liver cells, wherein the composition has a
catonic lipid with a pKa of from about 5.1 to about 7.4;
and
d) a tumor or tumor cell, wherein the composition has a
catonic lipid with a pKa of from about 5.0 to about 6.7
wherein 1) the cationic agent is not a compound of formula (I) as defined in claim 2 and 2) the steal thlpid is not a compound of formula (XI) as defined in claim 4.