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Published:

— *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:
27 September 2012

(54) Title: GALACTOSE CLUSTER-PHARMACOKINETIC MODULATOR TARGETING MOIETY FOR SIRNA

(57) Abstract: The present invention is directed compositions for targeted delivery of RNA interference (RNAi) polynucleotides to cell in vivo. The pharmacokinetic modulator improve in vivo targeting compared to the targeting ligand alone. Targeting ligand-pharmacokinetic modulator targeting moiety targeted RNAi polynucleotides can be administered in vivo alone or together with co- targeted delivery polymers.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 15/11; C07H 21/04 (2012.01)
USPC - 514/44A, 536/24.5
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)
USPC- 514/44A, 536/24.5

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)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google Patents; Google Scholar: silencing, interference, dsDNA, shRNA, RNAi, siRNA, miRNA, covalent, link, hydrophobic, palmitoyl, hexadec-8-enoyl, oleyl, (9E,12E)-octadeca-9,12-dienoyl, dioctanoyl, C16-C20, cholesterol, lipophilic, galactose, galactosamine, Roche Madison Inc, Arrowhead Research Corporation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	Wolfrum, et al. Mechanisms and optimization of in vivo delivery of lipophilic siRNAs. Nat Biotechnol. 2007, 25(10):1149-1157; pg 1152, col 1, pg 1153, col 1 to col 2, pg 1150, Fig 1 and its legend	1, 3-5, 15 ---------- 2
X -- Y	WO 2009/126933 A2 (Manoharan, et al.) 15 October 2009 (15.10.2009) Abstract, claim 1, 9, 34, pg 10, ln 1 to pg 11, ln 8; pg 40, ln 1 to pg 43, ln 15; pg 45, ln 1 to pg 47, ln 2; pg 59, ln 13-15; pg 65, ln 10-18	16-20 ---------- 2
X, P	US 2011/0207799 A1 (Rozema, et al.) 25 August 2011 (25.08.2011) Abstract	1-5, 15-20
A	Hean, et al. Inhibition of hepatitis B virus replication in vivo using lipoplexes containing altritol-modified antiviral siRNAs. Artif DNA PNA XNA July 2010, 1(1):17-26; pg 19, Fig 2A	1-5, 15-20
A	US 2010/0015218 A1 (Jadhav, et al.) 21 January 2010 (21.01.2010) para [0177], [0284]	1-5, 15-20
A	US 2010/0144831 A1 (Fakhral, et al.) 10 June 2010 (10.06.2010) para [0145], [0176]	1-5, 15-20
A	US 2008/0281074 A1 (Rozema, et al.) 13 November 2008 (13.11.2008) Abstract, para [0009], [0010], [0092], [0093], [0098], [0134], [0177], [0179]-[0184], [0207], [0208], Table 5	1-5, 15-20
A	US 2009/0264636 A1 (Vargeese, et al.) 22 October 2009 (22.10.2009) Abstract, para [0006], [0073]-[0084]	1-5, 15-20

☐ Further documents are listed in the continuation of Box C. ☐

* 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	Date of mailing of the international search report
18 July 2012 (18.07.2012)	03 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
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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:
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.

Group I+: claims 1-15, drawn to a composition for delivering an oligonucleotide to a cell in vivo comprising: an RNA interference polynucleotide covalently linked to a targeting ligand-pharmacokinetic modulator targeting moiety. The first invention (claims 1-5, 15) is restricted to the palmitoyl pharmacokinetic modulator targeting moiety. Should an additional fee(s) be paid, Applicant is invited to elect an additional pharmacokinetic modulator(s) to be searched.

Group II: claims 16-20, drawn to a composition for delivering an polynucleotide to a liver cell in vivo comprising: said polynucleotide covalently linked to an ASGPr targeting moiety-pharmacokinetic modulator targeting moiety.

********** See Supplemental Sheet to continue **********

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.:
1-5, 15, restricted to the palmitoyl, and 16-20

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.:

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.

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********** Supplemental Sheet **********

In Continuation of Box III. Observations where unity of invention is lacking:

The inventions listed as Groups I+ and II 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:

The inventions of Group I+ do not include the inventive concept of a composition for delivering an polynulceotide to a liver cell in vivo comprising: said polynucleotide covalently linked to an ASGPr targeting moiety-pharmacokinetic modulator targeting moiety , as required by Group II.

The inventions of Group I+ share the technical feature of a composition of claim 1. However, this shared technical feature does not represent a contribution over prior art as being anticipated by an article titled "Mechanisms and optimization of in vivo delivery of lipophilic siRNAs" by Wolfrum, et al. (Nat Biotechnol. 2007, 25(10):1149-57) that discloses a composition (pg 1153, col 1 to col 2, "Purified HDL and LDL particles were saturated with cholesterol-siRNA-apoB1 and injected into Syrian hamsters") for delivering an oligonucleotide to a cell in vivo (pg 1152, col 1, "To determine whether the binding affinity of cholesterol-siRNA to HDL, LDL and albumin in vitro reflects their relative affinity in vivo, we determined the plasma distribution of 32P-cholesterolsiRNA complexed with purified hamster LDL, HDL and albumin in hamsters at 1, 2, 3 and 4 h after systemic administration") comprising: an RNA interference polynucleotide covalently (pg 1150, Fig 1 and its legend, "(a) Structure of lipid conjugated siRNAs. The desired lipophile (L) is conjugated to the 3'-end of the sense strand of the apoB siRNA4 (siRNAapoB1) via a trans-4-hydroxyprolinol linker") linked to a targeting ligand-pharmacokinetic modulator targeting moiety (pg 1152, col 1, 32P-cholesterolsiRNA"). As said composition was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Group I+ is the specific targeting ligand-pharmacokinetic modulator recited therein. The inventions do not share a special technical feature, because Wolfrum discloses the claimed palmitoyl and oleyl modulators (pg 1150, Fig 1b and its legend, palmitoyl (C16) and Oleoyl (C18,w-9)). Without a shared special technical feature, the inventions lack unity with one another.

Groups I+ and II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.