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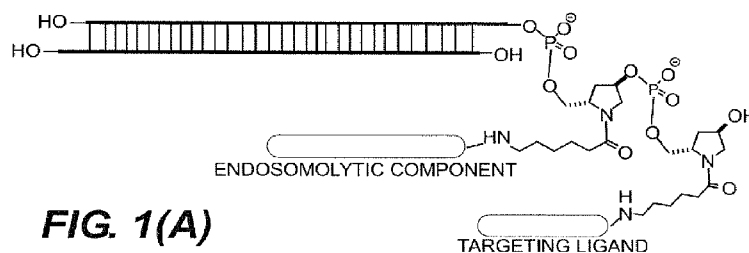


FIG. 1(A)

(57) Abstract: The invention relates to compositions and methods for site-specific delivery of nucleic acids by combining them with targeting ligands and endosomolytic components.



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## INTERNATIONAL SEARCH REPORT

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## A. CLASSIFICATION OF SUBJECT MATTER

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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)

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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, 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	WO 2008/022309 A2 (MIRUS BIO CORP [US]; ROZEMA DAVID B [US]; WAKEFIELD DARREN H [US]; WOL) 21 February 2008 (2008-02-21) cited in the application the whole document	1-41
Y	WO 2006/078278 A2 (ALNYLAM PHARMACEUTICALS [US]; MANOHARAN MUTHIAH [US]; RAJEEV KALLANTHO) 27 July 2006 (2006-07-27) cited in the application the whole document	1-41
A	WO 2006/052649 A2 (EXPRESSION GENETICS INC [US]; SLOBODKIN GREGORY [US]; MATAR MAJED [US]) 18 May 2006 (2006-05-18) cited in the application the whole document	1-41
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MANOHARAN MUTHIAH: "Oligonucleotide conjugates as potential antisense drugs with improved uptake, biodistribution, targeted delivery, and mechanisms of action"  ANTISENSE AND NUCLEIC ACID DRUG DEVELOPMENT,  vol. 12, no. 2, April 2002 (2002-04),  pages 103-128, XP002557015  ISSN: 1087-2906  the whole document</p>	1-41
A	<p>TURK M J ET AL: "Characterization of a novel pH-sensitive peptide that enhances drug release from folate-targeted liposomes at endosomal pHs"  BIOCHIMICA ET BIOPHYSICA ACTA. BIOMEMBRANES,  vol. 1559, no. 1,  10 February 2002 (2002-02-10), pages 56-68, XP004334733  ISSN: 0005-2736  cited in the application  the whole document</p>	1-41
E	<p>WO 2009/082606 A2 (ALNYLAM PHARMACEUTICALS INC [US]; MANOHARAN MUTHIAH [US]; RAJEEV KALLA) 2 July 2009 (2009-07-02)  the whole document</p>	1-41
E	<p>WO 2009/073809 A2 (ALNYLAM PHARMACEUTICALS INC [US]; MANOHARAN MUTHIAH [US]; RAJEEV KALLA) 11 June 2009 (2009-06-11)  cited in the application  the whole document</p>	1-41

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/040274

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2008022309	A2	21-02-2008	AU 2007285782 A1	21-02-2008
			CA 2660842 A1	21-02-2008
			EP 2061443 A2	27-05-2009
			KR 20090042918 A	04-05-2009
			US 2009023890 A1	22-01-2009
			US 2008281044 A1	13-11-2008
			US 2008269450 A1	30-10-2008
			US 2008152661 A1	26-06-2008
WO 2006078278	A2	27-07-2006	AU 2005325262 A1	27-07-2006
			CA 2562685 A1	27-07-2006
			EP 1768998 A2	04-04-2007
			JP 2008501319 T	24-01-2008
WO 2006052649	A2	18-05-2006	CA 2585974 A1	18-05-2006
			CN 101094652 A	26-12-2007
			EP 1807054 A2	18-07-2007
			JP 2008519128 T	05-06-2008
			KR 20070085500 A	27-08-2007
			US 2006093674 A1	04-05-2006
WO 2009082606	A2	02-07-2009	US 2009247614 A1	01-10-2009
WO 2009073809	A2	11-06-2009	US 2009239814 A1	24-09-2009
			US 2009247608 A1	01-10-2009
			WO 2009082607 A2	02-07-2009