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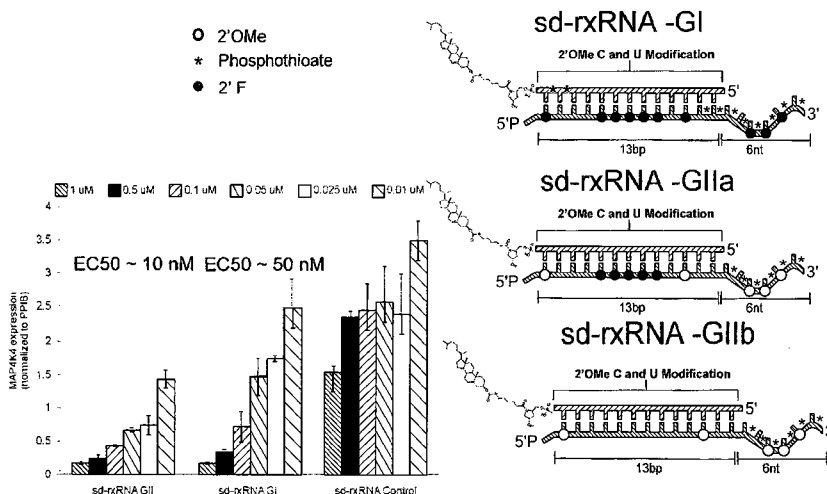
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[Continued on next page]

(54) Title: REDUCED SIZE SELF-DELIVERING RNAI COMPOUNDS

Figure 61



(57) Abstract: The present invention relates to RNAi constructs with minimal double-stranded regions, and their use in gene silencing. RNAi constructs associated with the invention include a double stranded region of 8-14 nucleotides and a variety of chemical modifications, and are highly effective in gene silencing.

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- *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:**  
3 June 2010
- *with sequence listing part of description (Rule 5.2(a))*

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2009/005247

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. C12N15/113 A61K31/713

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)  
 C12N 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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/079533 A (UNIVERSITY OF MASSACHUSETTS [US]; RANA TARIQ M [US]) 1 September 2005 (2005-09-01)	37-40
Y	page 35  the whole document	41, 42, 51, 52, 54
Y	WO 2008/036825 A (DHARMACON INC [US]; YAMADA CHRISTINA [US]; KHVOROVA ANASTASIA [US]; KA) 27 March 2008 (2008-03-27) page 115; figure 11; example 55 the whole document	41, 42, 51, 52, 54
A	US 2008/020990 A1 (NIPPON SHINYAKU CO., LTD [JP]) 24 January 2008 (2008-01-24) page 22; example 4 the whole document	
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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
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Date of the actual completion of the international search  <b>18 January 2010</b>	Date of mailing of the international search report  <b>16/04/2010</b>
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  <b>Macchia, Giovanni</b>
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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/005247

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FEDOROV Y. ET AL.: "Off-target effects by siRNA can induce toxic phenotype" RNA,, vol. 12, no. 7, 1 July 2006 (2006-07-01), pages 1188-1196, XP002547706 page 1191 - page 1192; figure 3k the whole document	
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A	ELBASHIR S.M. ET AL.: "Functional anatomy of siRNAs for mediating efficient RNAi in Drosophila melanogaster embryo lysate" EMBO JOURNAL, vol. 20, no. 23, 3 December 2001 (2001-12-03), pages 6877-6888, XP002225998 ISSN: 0261-4189 the whole document	
A	ELBASHIR S.M. ET AL.: "Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells" NATURE, vol. 411, no. 6836, 24 May 2001 (2001-05-24), pages 494-498, XP002206451 ISSN: 0028-0836 the whole document	
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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/005247

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>KUBO TAKANORI ET AL.: "Modified 27-nt dsRNAs with dramatically enhanced stability in serum and long-term RNAi activity"            OLIGONUCLEOTIDES,            vol. 17, no. 4,            1 December 2007 (2007-12-01), pages            445-464, XP002537984            ISSN: 1545-4576            the whole document</p>	
A	<p>JACKSON A.L. ET AL.: "Position-specific chemical modification of siRNAs reduces off-target transcript silencing"            RNA,            vol. 12, 1 January 2006 (2006-01-01),            pages 1197-1205, XP002558507            the whole document</p>	
A	<p>WO 2005/097992 A (DHARMAON, INC. [US];            LEAKE; FEDOROV; REYNOLDS; KHVOROVA;            MARSHALL) 20 October 2005 (2005-10-20)            page 28            claims            figure 1            the whole document            page 62 - page 63            page 88; figure 14K</p>	1-3
A	<p>WO 2006/113679 A (TEXAS UNIVERSITY [US])            26 October 2006 (2006-10-26)            page 15, line 28 - line 32            page 25, line 3 - line 4            page 29 - page 30            the whole document</p>	
A	<p>DEBART F. ET AL.: "Chemical modifications to improve the cellular uptake of oligonucleotides"            CURRENT TOPICS IN MEDICINAL CHEMISTRY,            vol. 7, 2007, pages 727-737, XP002562043            page 729 - page 730            the whole document</p>	
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2009/005247

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DYKXHOORN D.M. ET AL.: "The silent treatment: siRNAs as small molecule drugs" GENE THERAPY, vol. 13, 2006, pages 541-552, XP002562042 the whole document	
Y	WO 2006/019430 A (NASTECH PHARMACEUTICAL COMPANY, INC. [US]; AHMADIAN; CUI; CHEN; HOUSTO) 23 February 2006 (2006-02-23) the whole document	42
Y	WO 2006/039656 A (CHIRON CORPORATION [US]; HAN JANG; HOUGHTON MICHAEL) 13 April 2006 (2006-04-13) page 27, paragraph 131 the whole document	42
A	BROWN K. AND SAMARSKY D.: "RNAi off-targeting: Light at the end of the tunnel." JOURNAL OF RNAI AND GENE SILENCING, vol. 2, no. 2, 2006, pages 175-177, XP002563015 ISSN: 1747-0854 the whole document	
A	LEE HUI SUN ET AL.: "Contributions of 3'-overhang to the dissociation of small interfering RNAs from the PAZ domain: Molecular dynamics simulation study" JOURNAL OF MOLECULAR GRAPHICS AND MODELLING, vol. 25, no. 6, 9 February 2007 (2007-02-09), pages 784-793, XP005881341 ISSN: 1093-3263 the whole document	

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2009/005247

## 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.:

see annex

### 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: 1-9,11-16,20,21,24-26,37-42,51-54,58-64,91 in toto;  
17-19,22,23,27-36,45-50,66,68-90 in part

Isolated nucleic acid molecules comprising a passenger strand of 8-16 or less nucleotides, as claimed in claims 1-9, 42. Isolated double stranded nucleic acid molecules wherein the region of the molecule that is double stranded is 8-14 nucleotides long, as claimed in claims 11-16, 37-41, 51-54. Isolated nucleic acid molecules comprising a passenger strand of 10-17 nucleotides, as claimed in claim 91. Compositions and methods related thereto

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2. claims: 10 totally; 17-19, 22, 23, 27-36, 45-50, 70, 77, 80-90  
all partially

An isolated double stranded nucleic acid molecule as claimed in claim 10. Compositions and methods related thereto.

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3. claims: 43 totally; 45-50, 80-90 all partially

Duplex polynucleotides as claimed in claim 43. Compositions and methods related thereto.

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4. claims: 44 totally; 45-50, 80-90 all partially

Duplex polynucleotides as claimed in claim 44. Compositions and methods related thereto.

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5. claims: 55-57, 65, 67 all totally; 66, 68, 69, 71-90 all  
partially

An isolated hydrophobic modified polynucleotide as claimed in claims 55-57. Compositions and methods related thereto.

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/005247

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