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AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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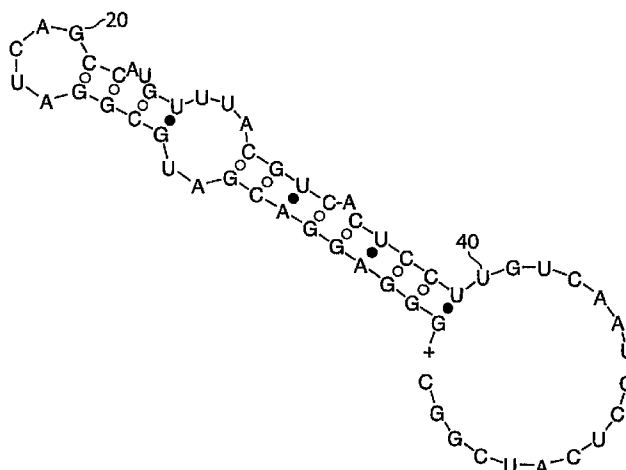
Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

[Continued on next page]

(54) Title: INHIBITOR NUCLEIC ACIDS

The predicted secondary structure for the xPSM-A10-3 aptamer.



dG = -12.4 [initially -12.4] 04Dec06-16-58-56

(57) Abstract: The present invention provides methods and compositions for attenuating expression of a target gene in vivo. In general, the method includes administering RNAi constructs (such as small-interfering RNAs (i.e., siRNAs) that are targeted to particular mRNA sequences, or nucleic acid material that can produce siRNAs in a cell), in an amount sufficient to attenuate expression of a target gene by an RNA interference mechanism. In particular, the RNAi constructs may include one or more modifications to improve serum stability, cellular uptake and/or to avoid non-specific effect. In certain embodiments, the RNAi constructs contain an aptamer portion. The aptamer may bind to human serum albumin to improve serum half life. The aptamer may also bind to a cell surface protein that improves uptake of the construct.

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**(88) Date of publication of the international search report:**

26 April 2007

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2006/003193

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. C12N15/11 C07H21/02 A61K31/713 A61K31/7125 A61K48/00

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 C07H 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, Sequence Search, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/008617 A1 (CHEN JIANZHU ET AL) 13 January 2005 (2005-01-13)	19-26
Y	paragraphs [0108] - [0133]; claims 72-75,91-95; figures 1-8	1-18,27
Y	HICKE B J ET AL: "Escort aptamers: A delivery service for diagnosis and therapy" JOURNAL OF CLINICAL INVESTIGATION, NEW YORK, NY, US, vol. 106, no. 8, October 2000 (2000-10), pages 923-928, XP002280743 ISSN: 0021-9738 cited in the application the whole document	1-18,27
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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

Date of the actual completion of the international search

19 February 2007

Date of mailing of the international search report

01/03/2007

Name and mailing address of the ISA/

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Authorized officer

Romano, Alper

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2006/003193

## Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
  - a. type of material
    - a sequence listing
    - table(s) related to the sequence listing
  - b. format of material
    - on paper
    - in electronic form
  - c. time of filing/furnishing
    - contained in the international application as filed
    - filed together with the international application in electronic form
    - furnished subsequently to this Authority for the purpose of search
2.  In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2006/003193

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 2005/250106 A1 (EPSTEIN DAVID ET AL) 10 November 2005 (2005-11-10) page 2,; claim 15; figure 7 -----	1-23,27
A	US 2002/119473 A1 (LUPOLD SHAWN E ET AL) 29 August 2002 (2002-08-29) the whole document paragraph [0070] -----	1-18,27
A	FAROKHZAD O C ET AL: "Nanoparticle-aptamer bioconjugates: a new approach for targeting prostate cancer cells" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 64, no. 21, 1 November 2004 (2004-11-01), pages 7668-7672, XP002325935 ISSN: 0008-5472 cited in the application the whole document -----	1-18,27
A	SCHIFFELERS RAYMOND M ET AL: "Cancer siRNA therapy by tumor selective delivery with ligand-targeted sterically stabilized nanoparticle." NUCLEIC ACIDS RESEARCH. 2004, vol. 32, no. 19, 2004, page e149, XP002397466 ISSN: 1362-4962 the whole document -----	1-18,27
E	WO 2006/045590 A (DEVGEN N.V; BOGAERT, THIERRY, ANDRE, OLIVIER, EDDY; FELDMANN, PASCALE;) 4 May 2006 (2006-05-04)  pages 35,36; claims 1,2; figures 1,2 -----	1,9,10, 13-17, 19,23, 24,27
E	WO 2006/042112 A (CALIFORNIA INSTITUTE OF TECHNOLOGY; SMOLKE, CHRISTINA, D; BAYER, TRAVI) 20 April 2006 (2006-04-20) figure 21 -----	1-3,15, 16,19, 20,23,27
T	MCNAMARA JAMES O 2ND ET AL: "Cell type-specific delivery of siRNAs with aptamer-siRNA chimeras." NATURE BIOTECHNOLOGY. AUG 2006, vol. 24, no. 8, August 2006 (2006-08), pages 1005-1015, XP002397468 ISSN: 1087-0156 the whole document -----	1-18,27

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2006/003193

## Box 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 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 fee, this Authority did not invite payment of any additional fee.
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.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

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

1. claims: 1-18, 27

A double stranded nucleic acid comprising a sense strand, an antisense strand which can inhibit expression of a target gene and an aptamer

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2. claims: 19-23

A double stranded nucleic acid comprising a sense strand and an antisense strand which can inhibit expression of a target gene

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3. claims: 24-26

A double stranded nucleic acid comprising a sense strand, an antisense strand which can inhibit expression of a target gene and a polypeptide

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/003193

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005008617 A1	13-01-2005	NONE	
US 2005250106 A1	10-11-2005	NONE	
US 2002119473 A1	29-08-2002	US 2005158780 A1	21-07-2005
WO 2006045590 A	04-05-2006	NONE	
WO 2006042112 A	20-04-2006	NONE	