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(54) **RNA INTERFERENCE AGENTS FOR GST-PI GENE MODULATION**

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A61B 5/00 (2006.01)
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C07D 311/30 (2006.01)
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C12N 15/113 (2010.01)
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 CPC **A61B 5/0071** (2013.01); **A61K 49/0021** (2013.01); **C07D 311/30** (2013.01); **C07F 9/6533** (2013.01); **C12N 15/113** (2013.01); **C12N 15/1135** (2013.01); **C12N 15/1137** (2013.01); **C12Q 1/02** (2013.01); **G01N 33/582** (2013.01); **H05K 999/99** (2013.01); **A61K 31/713** (2013.01); **C12N 2310/14** (2013.01); **C12N 2310/322** (2013.01); **C12N 2310/344** (2013.01); **C12N 2310/3515** (2013.01); **C12N 2310/531** (2013.01); **C12N 2320/30** (2013.01); **C12N 2320/32** (2013.01); **C12N 2320/35** (2013.01); **C12N 2320/53** (2013.01)

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 CPC . C07F 9/6533; C12N 15/1135; C12N 15/113; C12N 2310/14; G01N 33/582; C07D 311/30; A61B 5/0071; A61K 49/0021
 See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,968,737 A	10/1999	Ali-Osman	
8,067,390 B2	11/2011	Merritt	
8,227,188 B2	7/2012	De Fougerolles et al.	
8,367,628 B2	2/2013	Goodwin	
8,603,995 B2	12/2013	Labow et al.	
8,664,376 B2	3/2014	Niitsu	
8,686,052 B2	4/2014	Niitsu	
8,710,209 B2	4/2014	Jin	
8,741,867 B2	6/2014	Niitsu	
8,895,717 B2	11/2014	Sood	
9,151,758 B2	10/2015	Zetter	
9,206,424 B2	12/2015	Jin	
9,771,582 B2	9/2017	Niitsu et al.	
9,914,983 B2	3/2018	Niitsu et al.	
10,047,110 B2	8/2018	Minomi et al.	
10,047,111 B2	8/2018	Minomi et al.	
10,358,647 B2 *	7/2019	Minomi	C12N 15/1137
10,792,299 B2 *	10/2020	Minomi	A61K 31/7105
RE48,887 E *	1/2022	Niitsu	C12N 15/1137

(Continued)

FOREIGN PATENT DOCUMENTS

CN	103619355 A	3/2014
CN	103695421 A	4/2014
EP	2724729 A1	4/2014
EP	2937099 A1	10/2015
JP	2009-513151 A	4/2009
JP	2009-536827 A	10/2009
JP	2013-212113 A	10/2013
JP	2018-512373 A	5/2018
JP	2018-513669 A	5/2018
RU	2448974	4/2012

(Continued)

OTHER PUBLICATIONS

AC114115, Gen Bank Accession No. AC114115, *Rattus norvegicus* clone CH230-2808, Working Draft Sequence, 6 unordered pieces, May 13, 2003 [online]. [Retrieved on Apr. 30, 2016]. Retrieved from the internet <URL: <http://www.ncbi.nlm.nih.gov/nuccore/AC114115>>.

(Continued)

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(57) **ABSTRACT**

This invention provides compounds, compositions and methods for modulating the expression of human GST- π using RNA interference. The RNA interference molecules can be used in methods for preventing or treating diseases such as malignant tumor. Provided are a range of siRNA structures, having one or more of nucleotides being modified or chemically-modified. Advantageous structures include siRNAs with 2'-deoxy nucleotides located in the seed region, as well as other nucleotide modifications.

23 Claims, 14 Drawing Sheets

Specification includes a Sequence Listing.

(56)

References Cited

U.S. PATENT DOCUMENTS

2003/0099974	A1	5/2003	Lillie et al.
2004/0029275	A1	2/2004	Brown et al.
2004/0219600	A1	11/2004	Williams
2005/0142596	A1	6/2005	Krolewski et al.
2005/0233998	A1	10/2005	Jadhav et al.
2005/0245475	A1	11/2005	Khvorova et al.
2005/0255487	A1	11/2005	Khvorova
2007/0083334	A1	4/2007	Mintz
2007/0083945	A1	4/2007	Byrum
2011/0269819	A1	11/2011	Jones et al.
2012/0276209	A1	11/2012	Cullis et al.
2013/0017249	A1	1/2013	Niitsu et al.
2013/0028885	A1	1/2013	Zetter
2013/0052160	A1	2/2013	Zitvogel
2013/0053270	A1	2/2013	Gill
2013/0196434	A1	8/2013	Maier et al.
2013/0267581	A1	10/2013	Niitsu
2014/0005134	A1	1/2014	Saus et al.
2014/0134158	A1	5/2014	Bardelli
2014/0294934	A1	10/2014	Niitsu et al.
2014/0303237	A1	10/2014	Shapiro et al.
2014/0315975	A1	10/2014	Niitsu
2014/0315976	A1	10/2014	Brahmbhatt et al.
2016/0187319	A1	6/2016	Tanaka

FOREIGN PATENT DOCUMENTS

WO	WO 1998/021359	A1	5/1998
WO	WO 2004/094636	A1	11/2004
WO	WO 2007/051303		5/2007
WO	WO 2007/061922	A2	5/2007
WO	WO 2007/072220		6/2007
WO	WO 2007/134161		11/2007
WO	WO 2009/029688		3/2009
WO	WO 2009/033284		3/2009
WO	WO 2012/170952		12/2012
WO	WO 2012/176282	A1	12/2012
WO	WO 2013/075140		5/2013
WO	WO 2013/192364	A1	12/2013
WO	WO 2014/022739		2/2014
WO	WO 2014/098210	A1	6/2014
WO	WO 2016/106404		6/2016
WO	WO 2016/106406		6/2016
WO	WO 2017/106111		6/2017

OTHER PUBLICATIONS

Birkeland, Kras gene amplification and overexpression but not mutation associates with aggressive and metastatic endometrial cancer, 2012, British Journal of Cancer, vol. 107, pp. 1997-2004. G0761423, GenBank Accession No. G0761423, 0010260TNA004657HT OTNA Ovis aries cDNA 5-, mRNA sequence, May 8, 2009 [online], [Retrieved on Apr. 30, 2016]. Retrieved from the internet <URL: <http://www.ncbi.nlm.nih.gov/nuccore/G0761423>>.

G0786145, GenBank Accession No. G0786145, 0009200TNA002813HT OTNA Ovis aries cDNA 5-, mRNA sequence, May 8, 2009 [online]. [Retrieved on Apr. 30, 2016]. Retrieved from the internet <URL: <http://www.ncbi.nlm.nih.gov/nuccore/G0786145>>.

Hida, Serum Glutathione S-Transferase-Pi Level as a Tumor Marker for Non-Small Cell Lung Cancer, Cancer, Mar. 1, 1994, vol. 73, No. 5, pp. 1377-1382.

JU528663, GenBank Accession No. JU528663, TSA: Ctenomys sociabilis 330326.Ctso mRNA sequence, Oct. 10, 2012 [online]. [Retrieved on Apr. 30, 2016]. Retrieved from the internet <URL: <http://www.ncbi.nlm.nih.gov/nuccore/JU528663>>.

Love, Lipid-like materials for low-dose, in vivo gene silencing, Proc Natl Acad Sci U S A., 2010, vol. 107(5), pp. 1864-1869.

Wagner, In Situ Evidence of KRAS Amplification and Association With Increased p21 Levels in Non-Small Cell Lung Carcinoma, 2009, Am J Clin Pathol, vol. 132, pp. 500-505.

Yin et al., Cancer Res. 2000 60, 4053-4057, Glutathione S-Transferase p Elicits Protection against H₂O₂-induced Cell Death via Coordinated Regulation of Stress Kinases.

Birkeland et al., British J. of Cancer, 2012, 107, 1997-2004. §.

Chen et al., Sensitization of mesothelioma cells to platinum-based chemotherapy by GST Pi knockdown. Biochem Biophys Res Commun. 2014, 447(1):77-82.

Chiu, Ya-Lin and Tariq M. Rana, "siRNA function in RNAi: A chemical modification analysis", RNA, Cold Spring Harbor Laboratory Press, vol. 9, Jan. 1, 2003 (Jan. 1, 2003), pp. 1034-1048.

Morrow et al., Structure of the human genomic glutathione S-transferase-pi gene. Gene, 1989, 75(1): 3-11.

Nagaprashantha et al., "2'-Hydroxyflavone inhibits proliferation, tumor vascularization and promotes normal differentiation in VHL-mutant renal cell carcinoma, 2011, Carcinogenesis", vol. 32, No. 4, pp. 568-575.

Noguchi et al., "PI3K-AKT Network Roles in Infectious Diseases, Kansenshogaku zasshi." The Journal of the Japanese Association for Infectious Diseases, 2008, vol. 82, No. 3, pp. 161-167.

Patel et al., Rescue of paclitaxel sensitivity by repression of Prohibitin 1 in drug-resistant cancer cells. PNAS U.S.A. Feb. 9, 2010; 107(6): 2503-2508.

Tripathi et al., "Reactive nitrogen species regulate autophagy through ATM-AMPK-TSC2-mediated suppression of mTORC1", Proceedings of the National Academy of Sciences, 2013, vol. 110, No. 32, pp. E2950-E2957.

Japanese Office Action dated Apr. 2, 2019 for Application No. 2018-134405 (w English Machine Translation) in 7 pages.

Japanese Office Action dated Oct. 23, 2018 for Application No. 2018-134405 in 7 pages.

Office Action issued in CN patent application No. 201580071191.3, dated May 24, 2019.

Office Action issued in JP patent application No. 2015-247725, dated Oct. 15, 2019.

Office Action issued in JP Patent Application No. 2018-134405, dated Apr. 2, 2019.

Office Action issued in Taiwanese Application No. 105120007 dated May 6, 2020.

Russian Office Action dated Jun. 5, 2019 for Application No. 2017126613/10 (w English Translation) in 9 pages.

Search Report issued in European Patent Application No. 20156350.9 dated May 26, 2020.

Elbashir et al., "Functional anatomy of siRNAs for mediating efficient RNAi in *Drosophila melanogaster* embryo lysate", The EMBO Journal, vol. 20(23), pp. 6877-6888, 2001.

Hokaiwado et al., "Glutathione S-transferase Pi mediates proliferation of androgen-independent prostate cancer cells", Carcinogenesis, vol. (29)6, p. 1134-1138, 2008.

Liu et al., "Biocompatible Flavone-Based Fluorogenic Probes for Quick Wash-Free Mitochondrial Imaging in Living Cells", ACS Appl. Mater. Interfaces, vol. 6(23), pp. 21638-21644, 2014.

Xia et al., BMC, 2011, 11, 1-9.

Ui-Tei et al., "Functional dissection of siRNA sequence by systematic DNA substitution: modified siRNA with a DNA seed arm is a powerful tool for mammalian gene silencing with significantly reduced off-target effect", Nucleic Acids Research, vol. 36(7), pp. 2136-2215, 2008.

Valtorta et al., "KRAS gene amplification in colorectal cancer and impact on response to EGFR-targeted therapy", Int. J. Cancer, vol. 133(5), pp. 1259-1265, 2013.

Wagner et al., "In Situ Evidence of KRAS Amplification and Association With Increased p21 Levels in Non-Small Cell Lung Carcinoma", Am. J. Clin. Pathol., vol. 132, pp. 500-505, 2009.

Zhang et al., "Reversal of multidrug resistance by small interfering double-stranded RNAs in ovarian cancer cells", Gynecologic Oncology, 2005, vol. 97, pp. 501-507, 2005.

Brazilian Office Action received in Brazilian Application No. BR112017013597 dated Oct. 16, 2020 in 6 pages.

Fletcher et al., "Influence of glutathione-S-transferase (GST) inhibition on lung epithelial cell injury: role of oxidative stress and metabolism", Am J Physiol Lung Cell Mol Physiol 308: L1274-L1285, 2015.

(56)

References Cited

OTHER PUBLICATIONS

Schnekenburger, et. al., "Regulation of epigenetic traits of the glutathione S-transferase P1 gene: from detoxification toward cancer prevention and diagnosis", *Frontiers in Pharmacology*, Article 170, vol. 5, pp. 1-7, Jul. 16, 2014.

Exam Report issued in IN application No. 201717026030, dated Apr. 8, 2021.

Office Action issued in JP Application No. 2017-534297, dated Oct. 23, 2018.

Office Action issued in AU Application No. 2015369592, dated May 11, 2020.

Office Action issued in CA Application No. 2971881, dated Nov. 1, 2021.

Office Action issued in CN Application No. 201580071191.3, dated May 24, 2019.

Office Action issued in EP Application No. 15874361.7, dated Mar. 6, 2019.

Office Action issued in RU Application No. 2017126613, dated Nov. 1, 2019.

Office Action issued in corresponding KR application No. 10-2017-7020898, dated May 24, 2022.

AC230665, GenBank Accession No. AC230665, *Bos taurus* clone CH240-502B15, Jul. 10, 2008 [online]. [Retrieved on May 1, 2016]. Retrieved from the internet <URL: <http://www.ncbi.nlm.nih.gov/nucleotide/AC230665>>.

AC230574, GenBank Accession No. AC230574, *Bos taurus* clone CH240-504M17, Jul. 10, 2008 [online]. [Retrieved on May 1, 2016]. Retrieved from the internet <URL: <http://www.ncbi.nlm.nih.gov/nucleotide/AC230574>>.

BV207757, GenBank Accession No. BV207757, sqnm2244B3 Human DNA (Sequenom) *Homo sapiens* STS genomic, Oct. 17, 2009 [online]. [Retrieved on May 1, 2016]. Retrieved from the internet <URL: <http://www.ncbi.nlm.nih.gov/nucleotide/BV207757>>.

AW374759, GenBank Accession No. AW374759, MR1-CT005B-291199-003-a05 CT0058 *Homo sapiens* cDNA. mRNA sequence, Jan. 9, 2011 [online]. (Retrieved on May 1, 2016). Retrieved from the internet <URL: <http://www.ncbi.nlm.nih.gov/nucest/6B79413/>>.

Xue, Small RNA combination therapy for lung cancer, *Proc Natl Acad Sci U S A*, 2014, vol. 111(34), pp. E3553-E3561.

Xu, Enhancing tumor cell response to chemotherapy through nanoparticle-mediated codelivery of siRNA and cisplatin prodrug, *Proc Natl Acad Sci U S A*, 2013, vol. 110, No. 46, pp. 18638-18643.

Ui-Tei, Functional dissection of siRNA sequence by systematic DNA substitution: modified siRNA with a DNA seed arm is a powerful tool for mammalian gene silencing with significantly reduced off-target effect, *Nucleic Acids Res.*, 2008, vol. 36(7), pp. 2136-2151.

Niitsu, Serum Glutathione-S-Transferase-rr as a Tumor Marker for Gastrointestinal Malignancies, *Cancer*, Jan. 15, 1989, vol. 63, pp. 317-323.

Hirata, Significance of Glutathione S-Transferase-Pi as a Tumor Marker in Patients with Oral Cancer, *Cancer*, Nov. 15, 1992, vol. 70, No. 10, pp. 2381-2387.

Ban, Transfection of Glutathione S-Transferase (GST)-Pi Antisense Complementary DNA Increases the Sensitivity of a Colon Cancer Cell Line to Adriamycin, Cisplatin, Melphalan, and Etoposide, *Cancer Research*, Aug. 1, 1996, vol. 56, 3577-3582.

Morgan, Tumor Efficacy and Bone Marrow-sparing Properties of TER286, a Cytotoxin Activated by Glutathione S-Transferase, *Cancer Research*, Jun. 15, 1998, vol. 58, pp. 2568-2575.

Niitsu, A proof of glutathione S-transferase-pi-related multidrug resistance by transfer of antisense gene to cancer cells and sense gene to bone marrow stem cell, *Chemico-Biological Interactions*, 1998, vol. 111-112, pp. 325-332.

Miyanishi, Glutathione S-Transferase-pi Overexpression is Closely Associated With K-ras Mutation During Human Colon Carcinogenesis, *Gastroenterology*, 2001, vol. 121, pp. 865-874.

Matsunaga, C(H)OP refractory chronic lymphocytic Leukemia patients in whom salvage chemotherapy chosen by evaluating multiple chemotherapeutic drug-resistant factors was remarkably effective, *Int J Clin Oncol*, 2003, vol. 8, pp. 326-331.

Hayashi, Suppressive effect of sulindac on branch duct-intraductal papillary mucinous neoplasms, *J Gastroenterol*, 2009, vol. 44, pp. 964-975.

Morse, The role of glutathione S-transferase P1-1 in colorectal cancer: friend or foe?, *Gastroenterology*, 2001, vol. 121(4), pp. 1010-1013.

Steckel, Determination of synthetic lethal interactions in KRAS oncogene-dependent cancer cells reveals novel therapeutic targeting strategies, *Cell Res.*, 2012, vol. 22(8), pp. 1227-1245.

Collins, KRAS as a key oncogene and therapeutic target in pancreatic cancer, *Front Physiol.*, 2013, vol. 4, Article 407, pp. 1-8. <https://cansar.icr.ac.uk/cansar/cell-lines/A549/mutations/> retrieved from the web on Jun. 20, 2016.

Valtorta, KRAS gene amplification in colorectal cancer and impact on response to EGFR-targeted therapy, 2013, *Int. J. Cancer*, vol. 133, pp. 1259-1266.

Ruan, Analysis of EGFR signaling pathway in nasopharyngeal carcinoma cells by quantitative phosphoproteomics, *Proteome Science*, Jun 28, 2011, vol. 9, pp. 1-11.

Singhal, 1,3-Bis(3,5-dichlorophenyl) urea compound 'COH-SR4' inhibits proliferation and activates apoptosis in melanoma, *Biochemical Pharmacology*, Dec. 1, 2012, vol. 84, Iss. 11, pp. 1419-1427.

Hokaiwado, Glutathione S-transferase Pi mediates proliferation of androgen-independent prostate cancer cells, *Carcinogenesis*, Apr. 15, 2008, vol. 29, pp. 1134-1138.

Futreal, A Census of Human Cancer Genes, *Nature Reviews Cancer* 2004, vol. 4, pp. 177-183.

Takahashi et al., *Gan To Kagaku Ryoho*. 1994; 21 (7): 945-51, English summary p. 951.

Ban et al., *Cancer Res*. 1996; 56 (15): 3577-82, Transfection of Glutathione S-Transferase (GST)-n' Antisense complementary DNA Increases the Sensitivity of a Colon Cancer Cell Line to Adriamycin, Cisplatin, Melphalan, and Etoposide.

Nakajima et al., *J Pharmacol Exp Ther*. 2003; 306 (3): 861-9, Reversal of Multiple Drug Resistance in Cholangiocarcinoma by the Glutathione S-Transferase-Pi-Specific Inhibitor O1-Hexadecyl-gamma-glutamyl-S-benzylcysteinyl-D-phenylglycine Ethylester.

Hokaiwado et al., *Carcinogenesis*. 2008; 29 (6): 1134-8, Glutathione S-transferase Pi mediates proliferation of androgen-independent prostate cancer cells.

Adler et al., *EMBO J*. 1999, 18, 1321-1334, Regulation of JNK signaling by GSTp.

Townsend, et. al., *J. Biol. Chem*. 2009, 284, 436-445, Novel Role for Glutathione S-Transferase Pi Regulator of Protein S-Glutathionylation Following Oxidative and Nitrosative Stress.

Nishita et al., AACR 102nd Annual Meeting, Abstract No. 1065, 2011, Regulation of autophagy and MAPK signaling by glutathione S-transferase Pi in KRAS mutated cancer cells.

Jackson, Expression profiling reveals off-target gene regulation by RNAi, 2003, *Nature Biotechnology*, vol. 21, pp. 635-637.

Muller, Thiazolides inhibit growth and induce glutathione-S-transferase Pi (GSTP1)-dependent cell death in human colon cancer cells, 2008, *Int. J. Cancer*, vol. 123, pp. 1797-1806.

Sawyers, Glutathione S-transferase Pi (GSTP1) directly influences platinum drug chemosensitivity in ovarian tumour cell lines, *British Journal of Cancer*, 2014, vol. 111, pp. 1150-1158.

* cited by examiner

FIG. 1

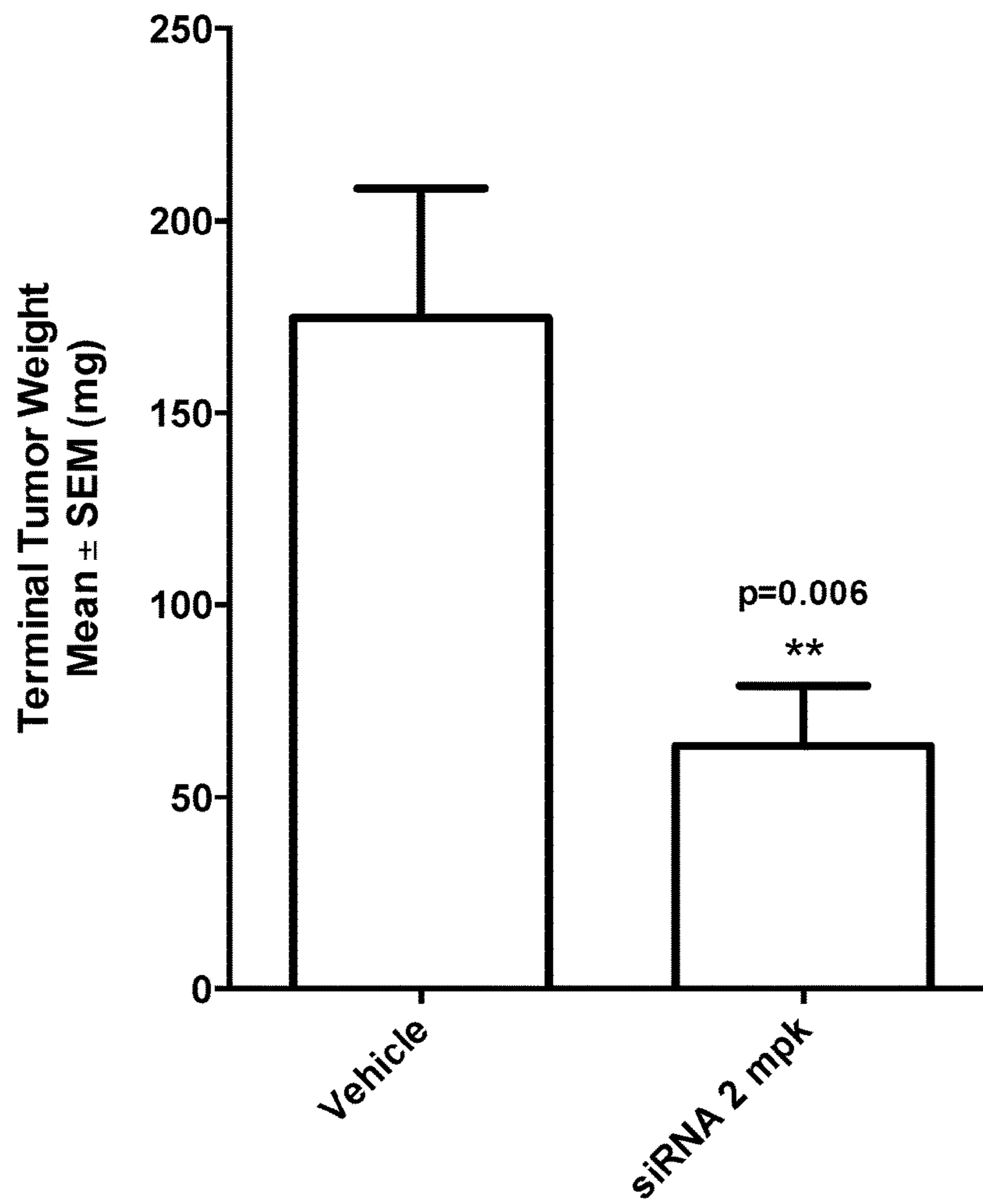


FIG. 2

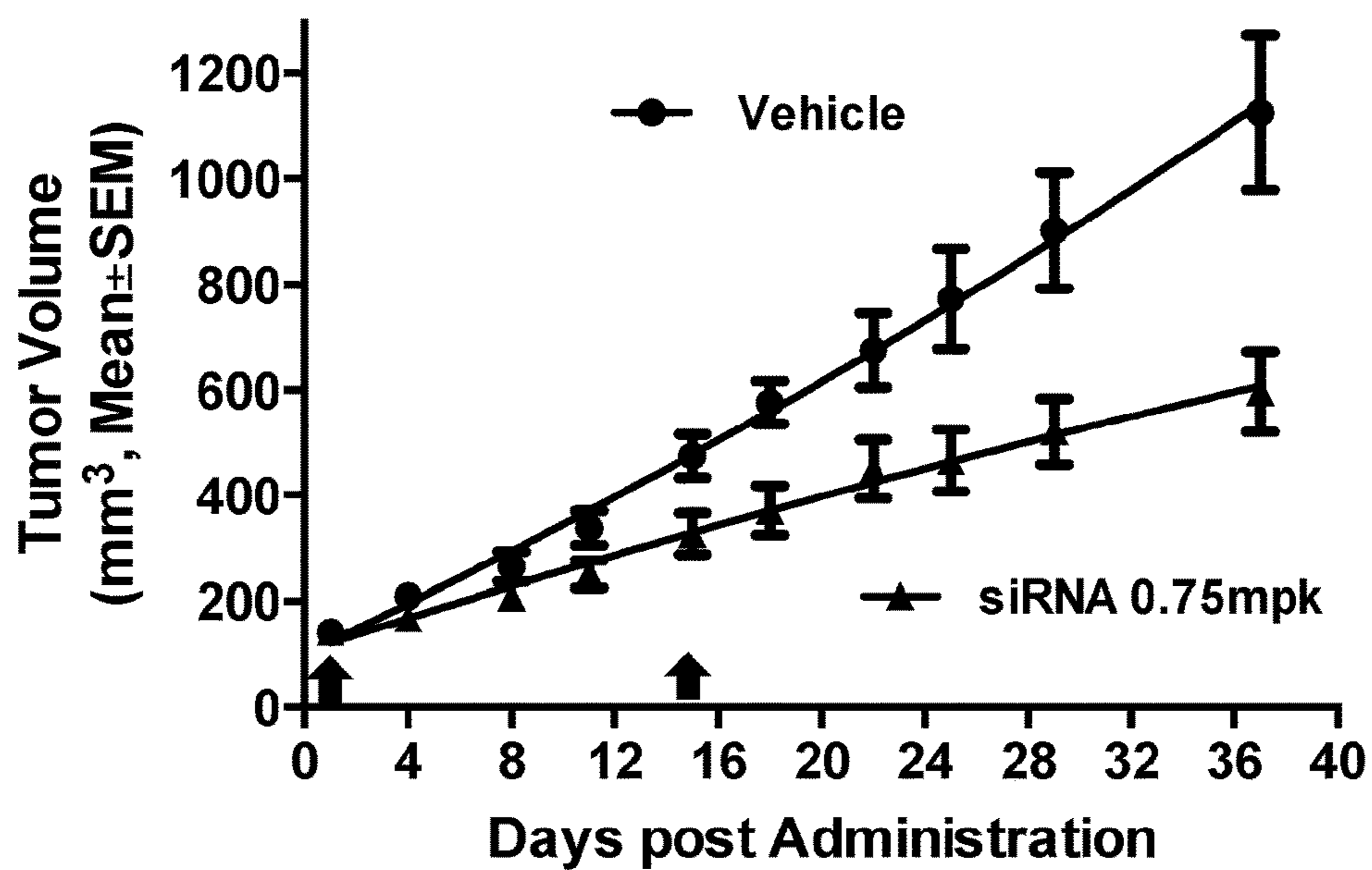


FIG. 3

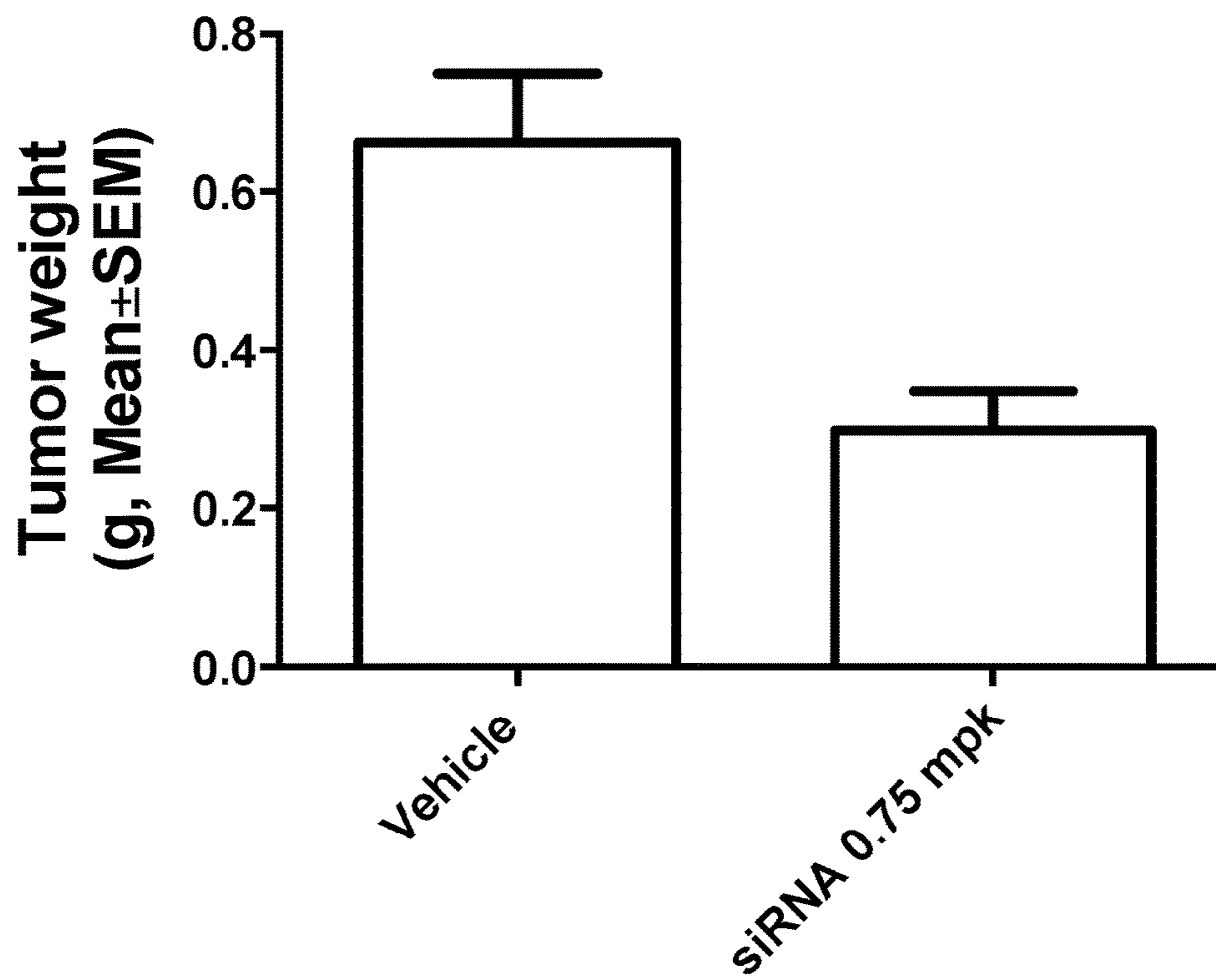


FIG. 4

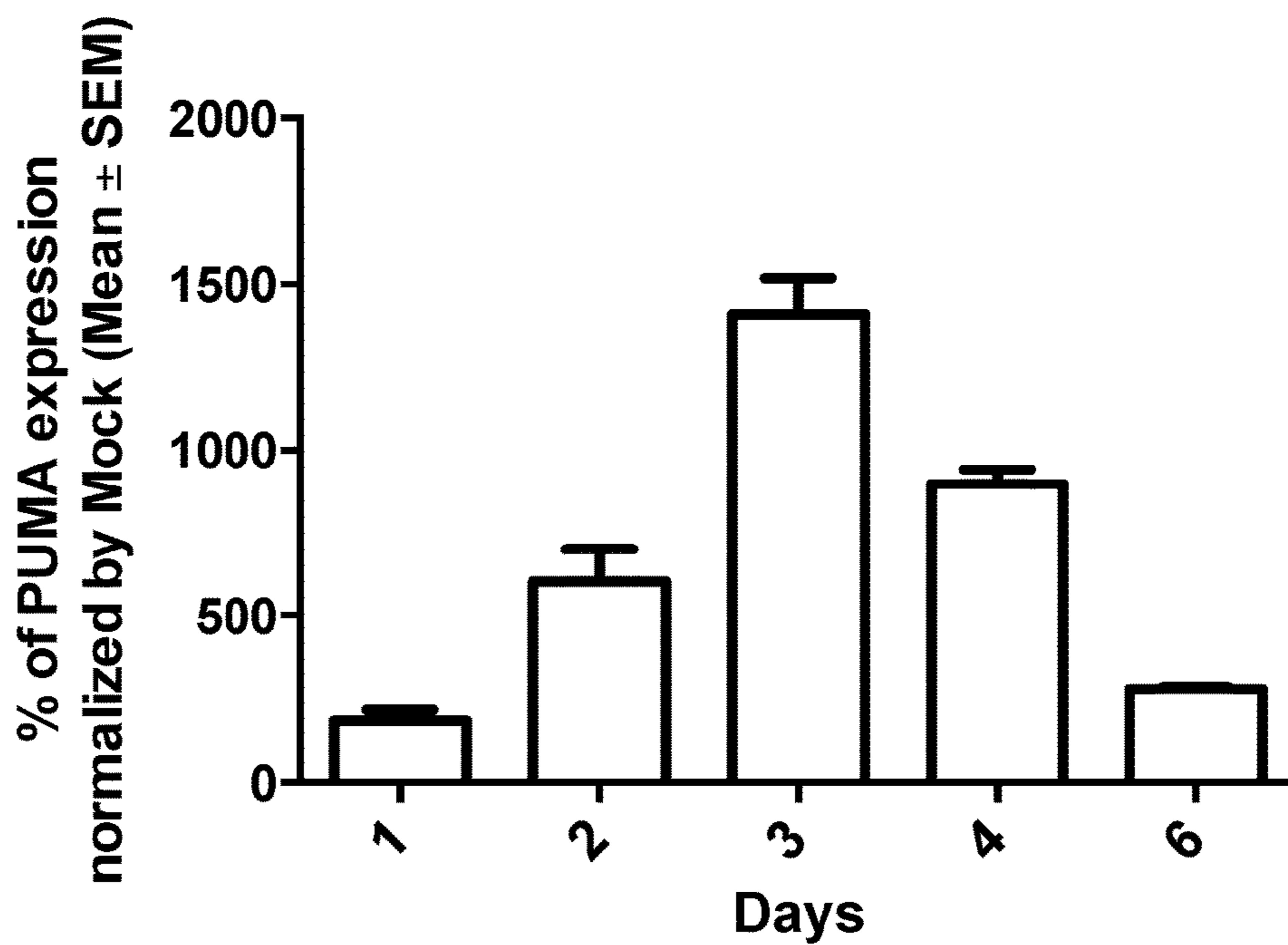


FIG. 5

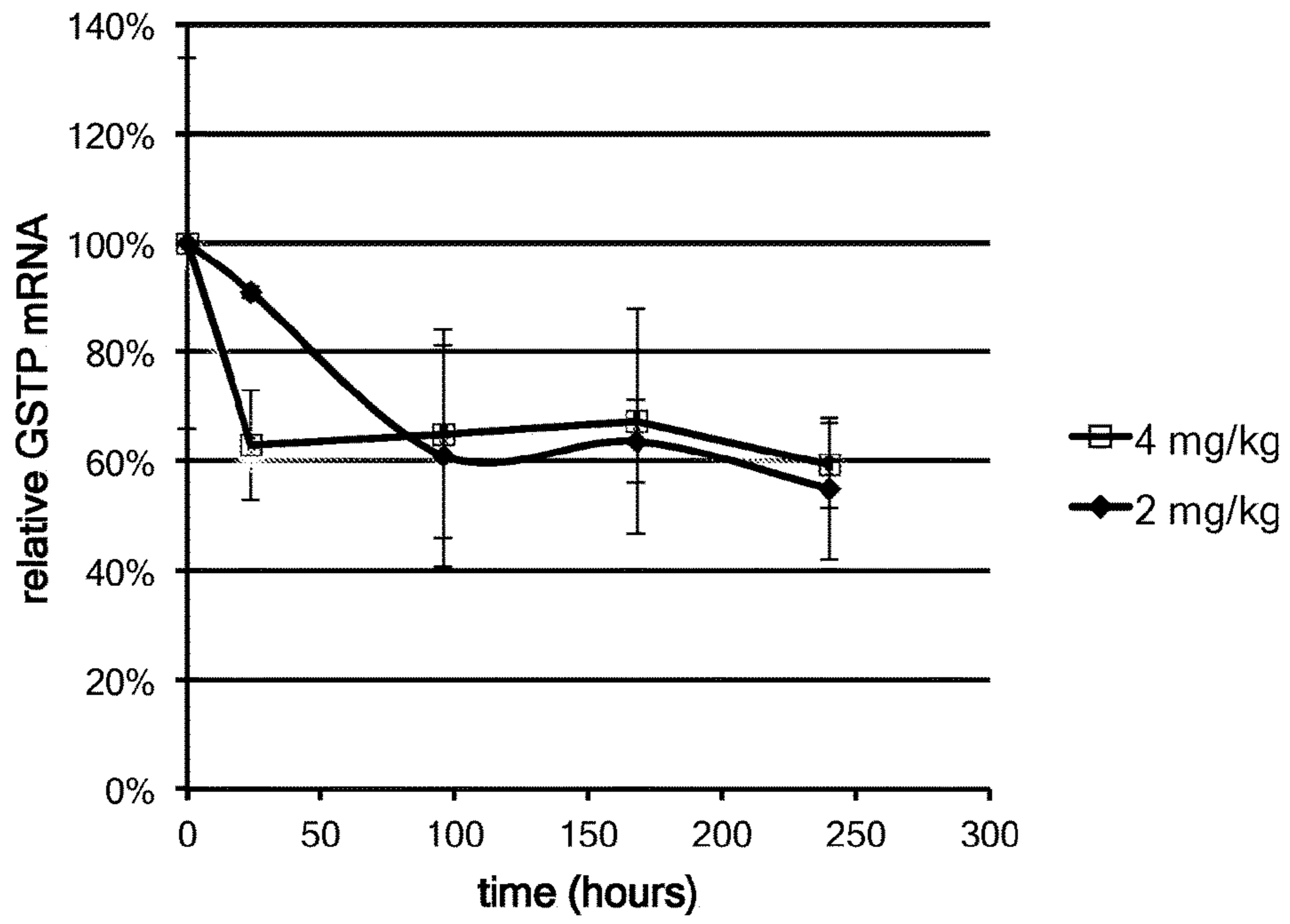


FIG. 6

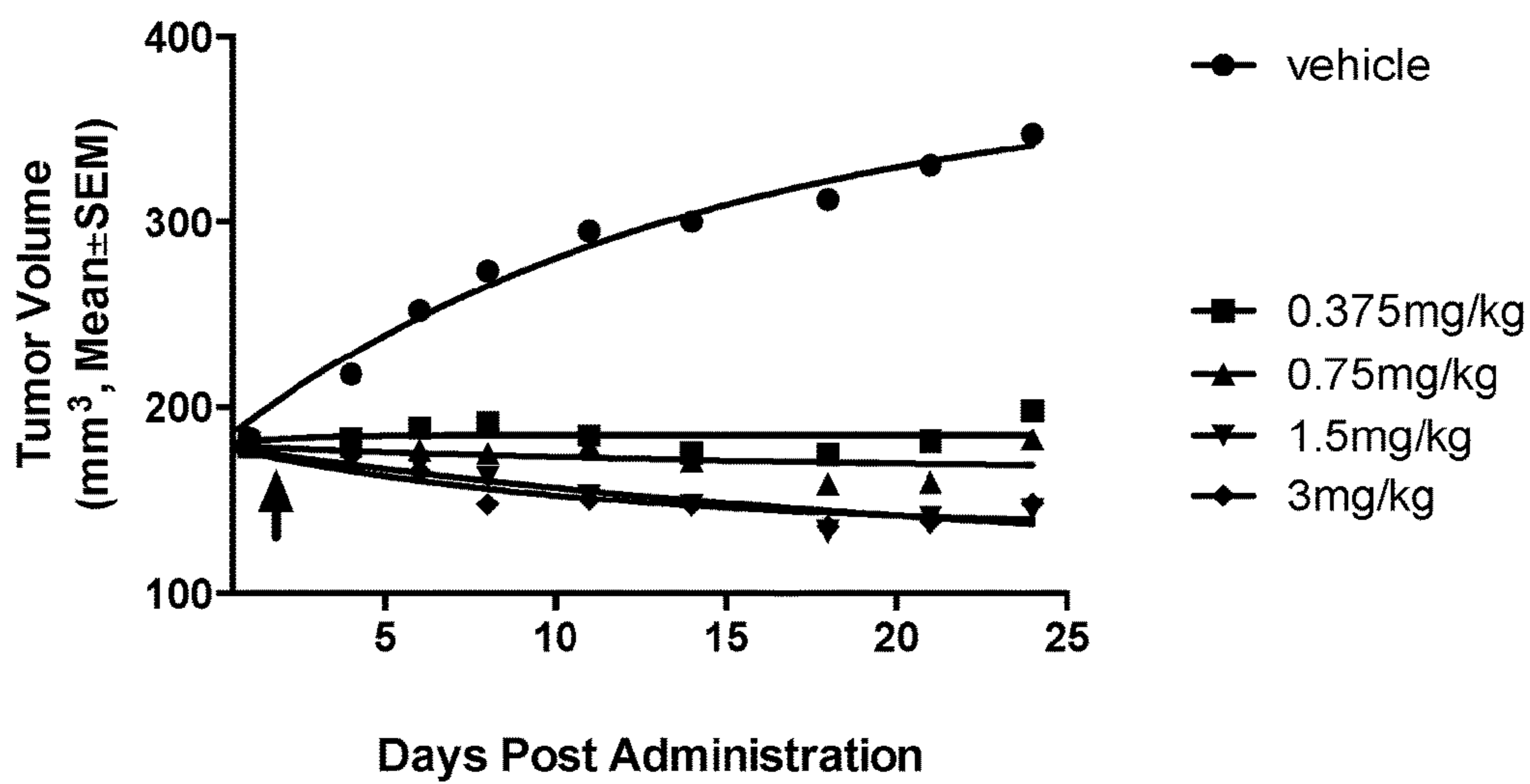


FIG. 7

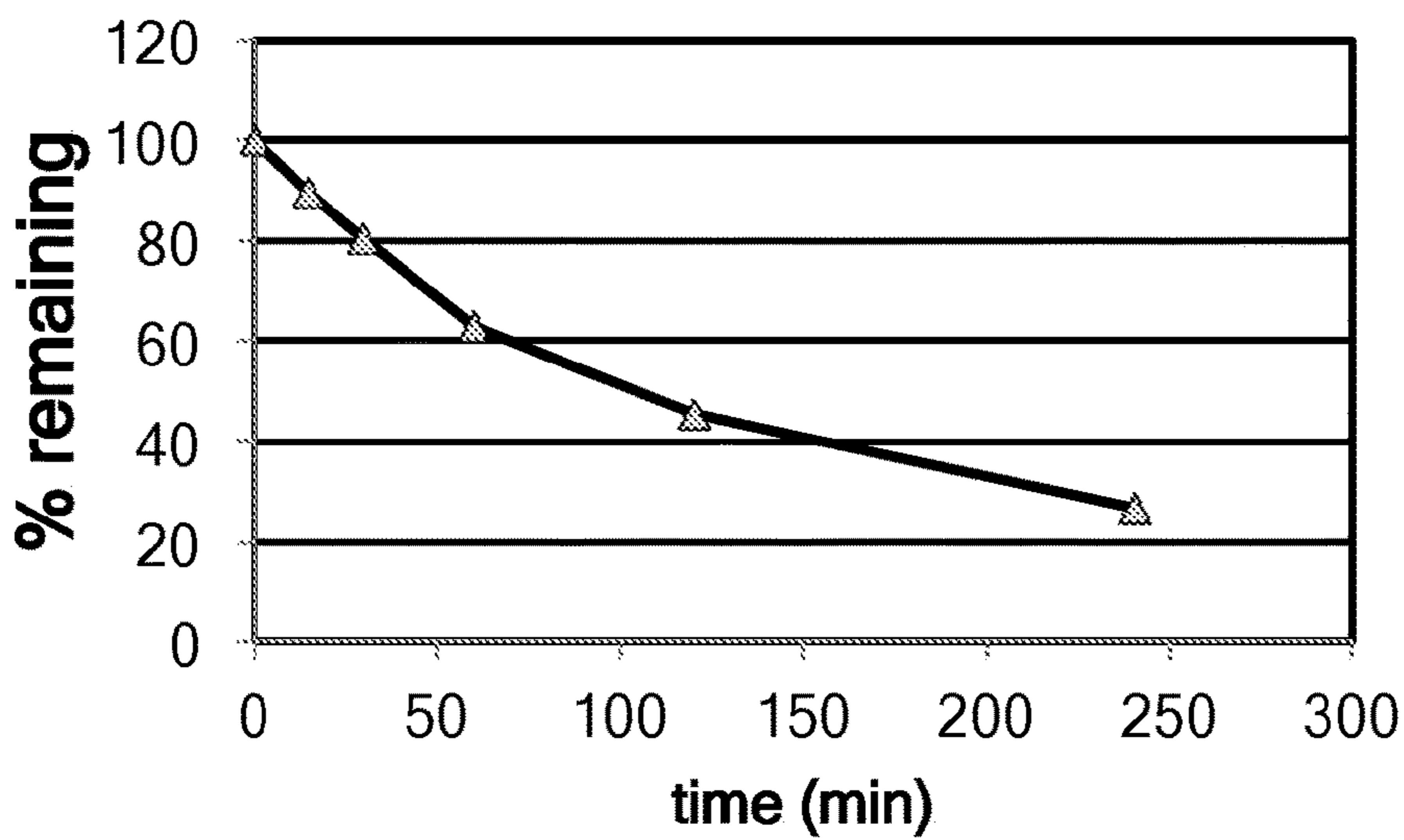
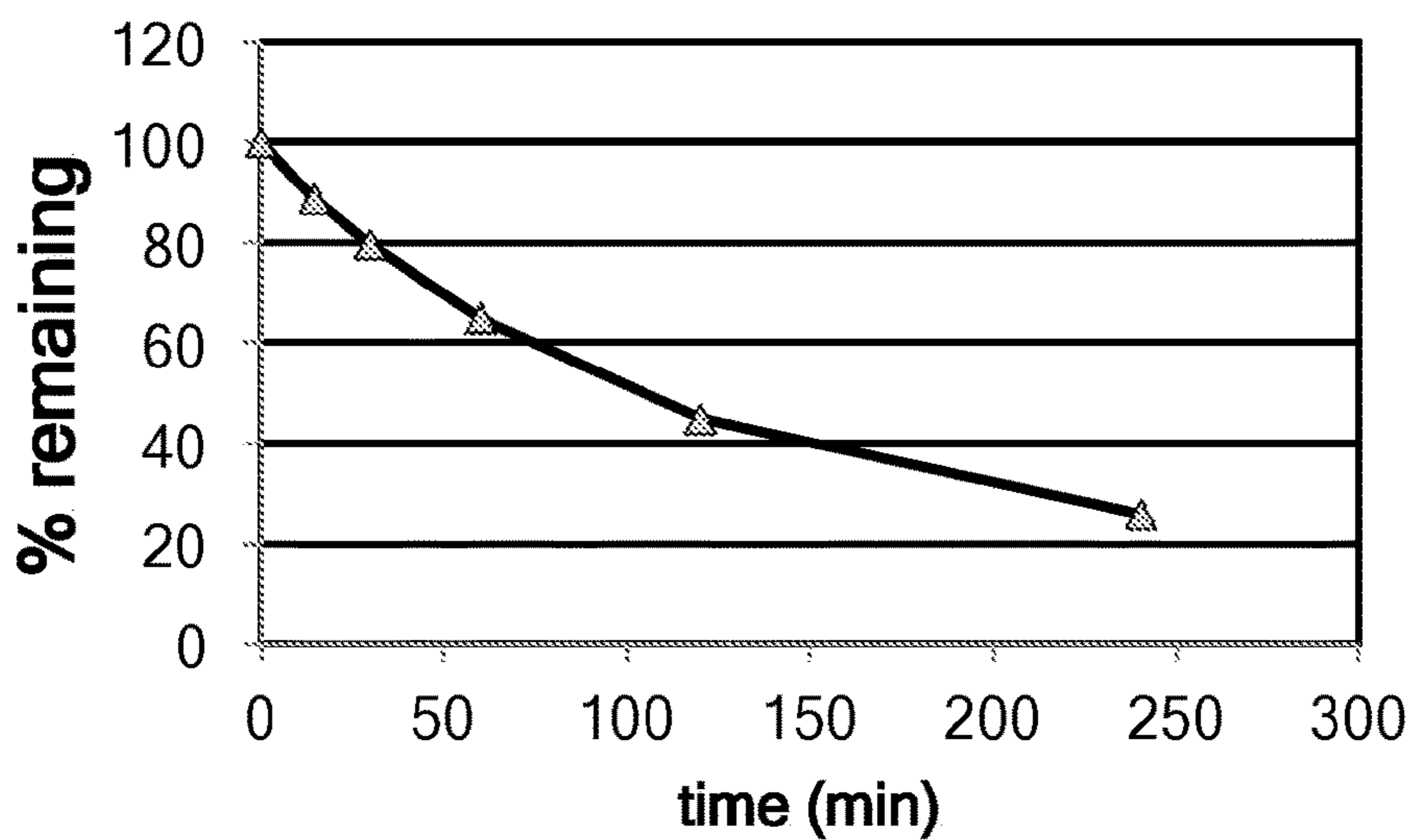


FIG. 8

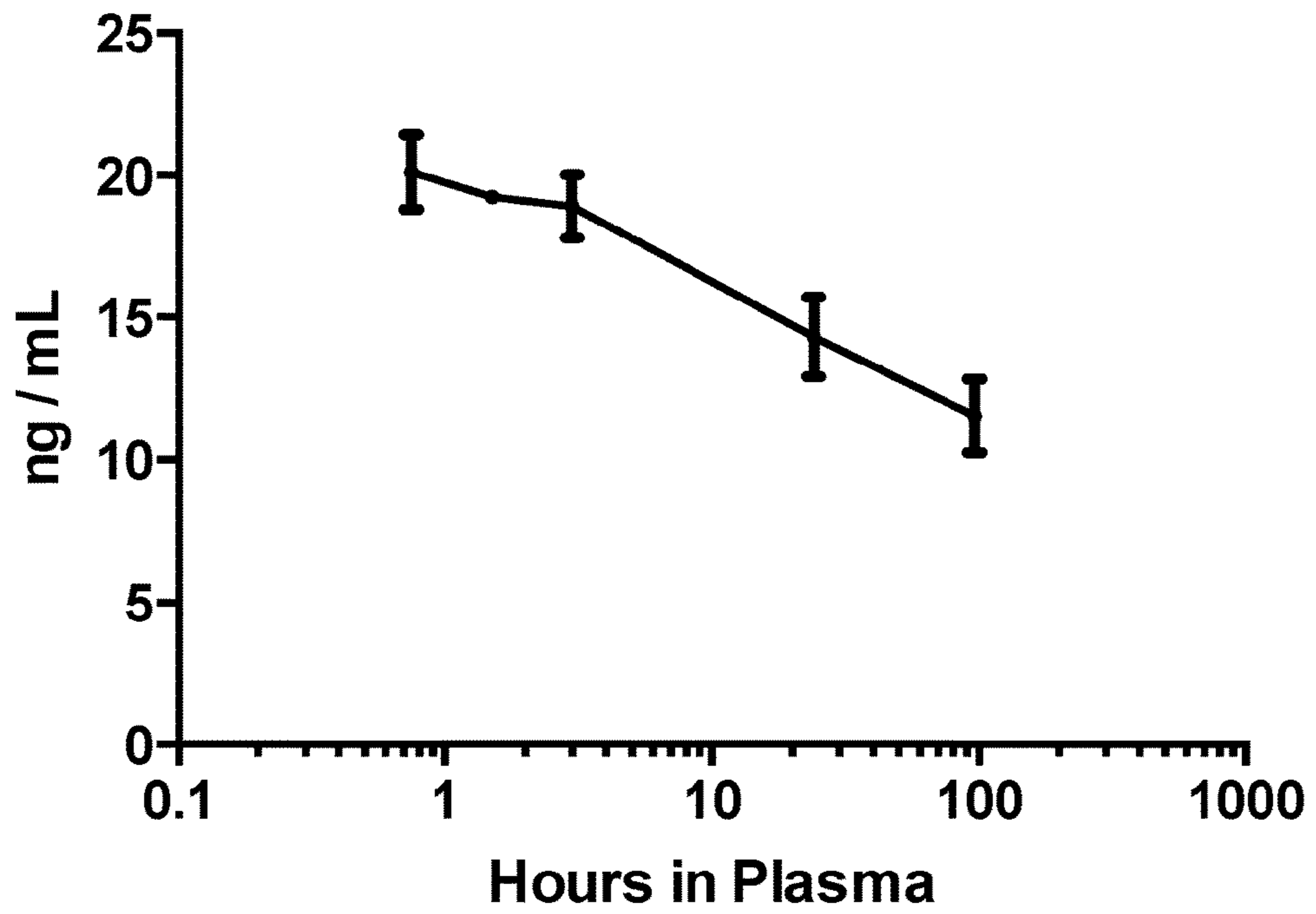


FIG. 9

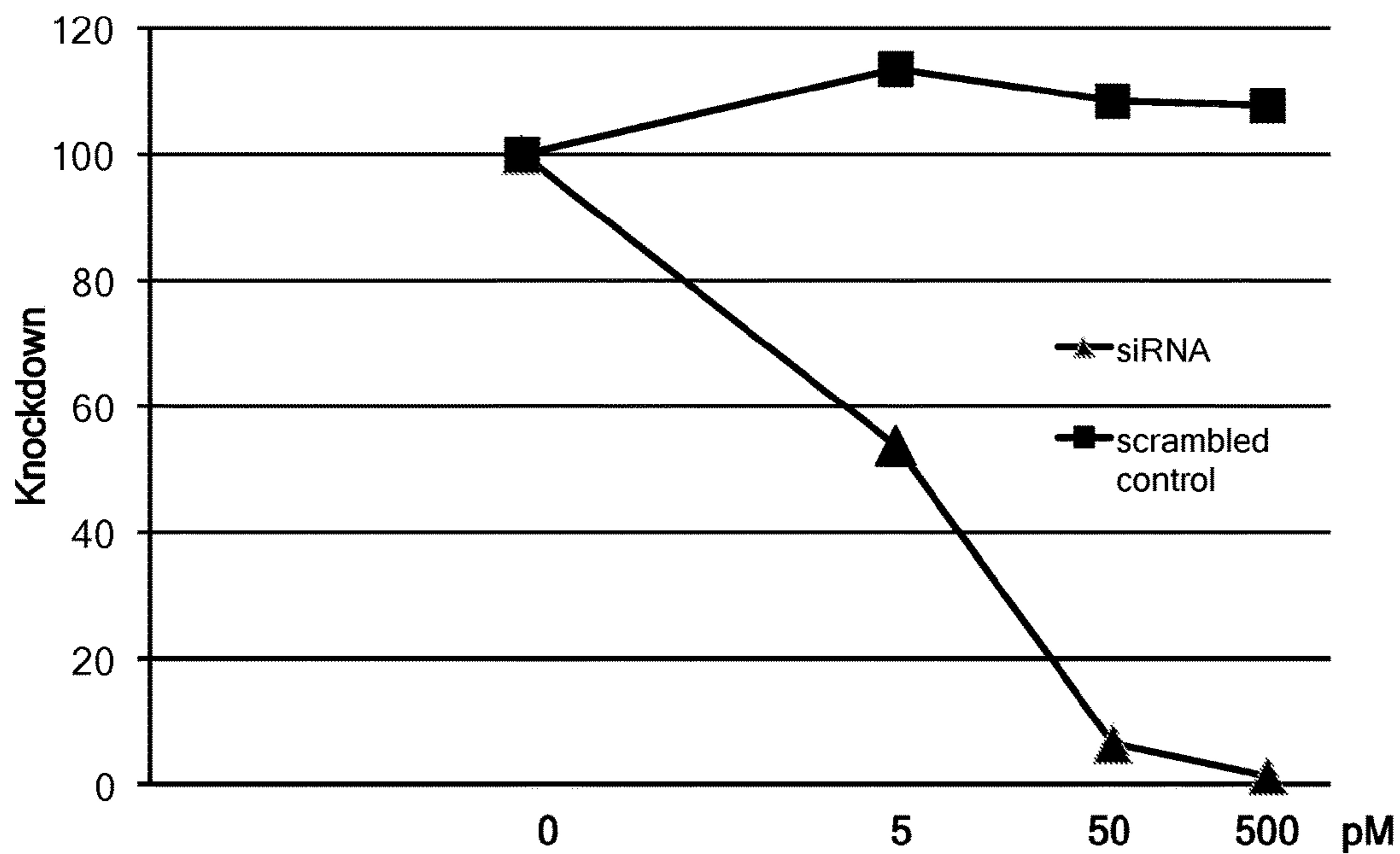


FIG. 10

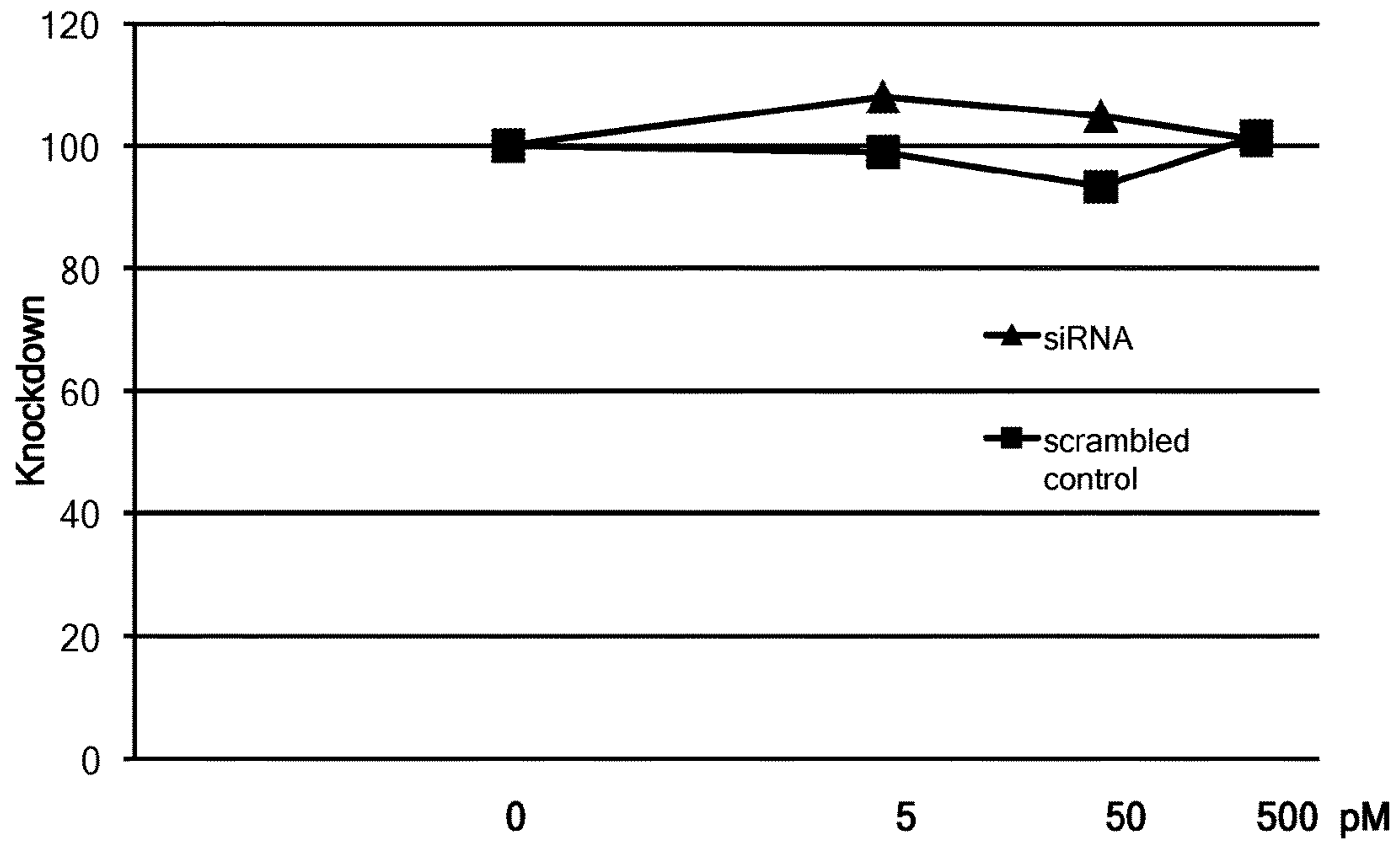


FIG. 11

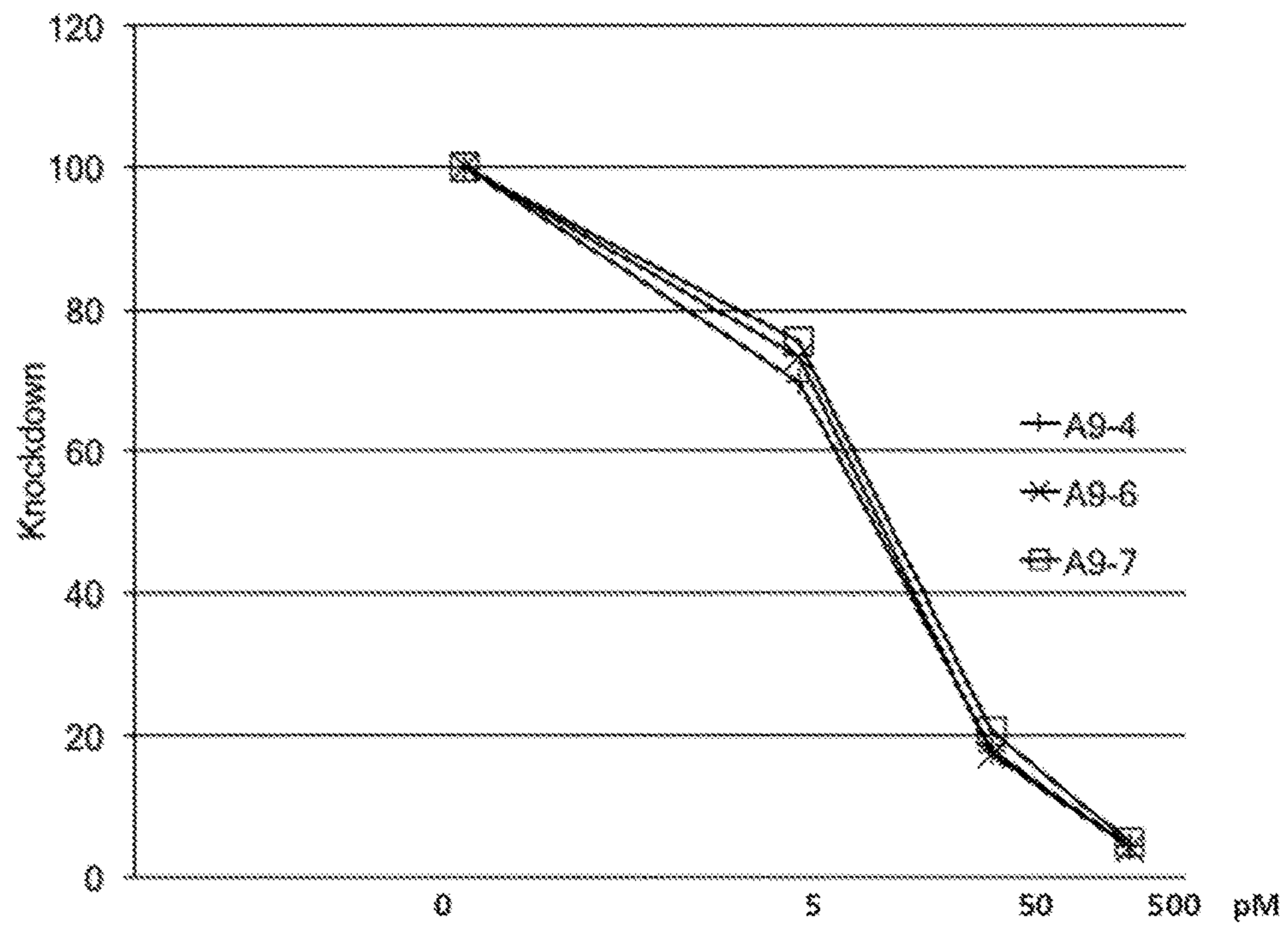


FIG. 12

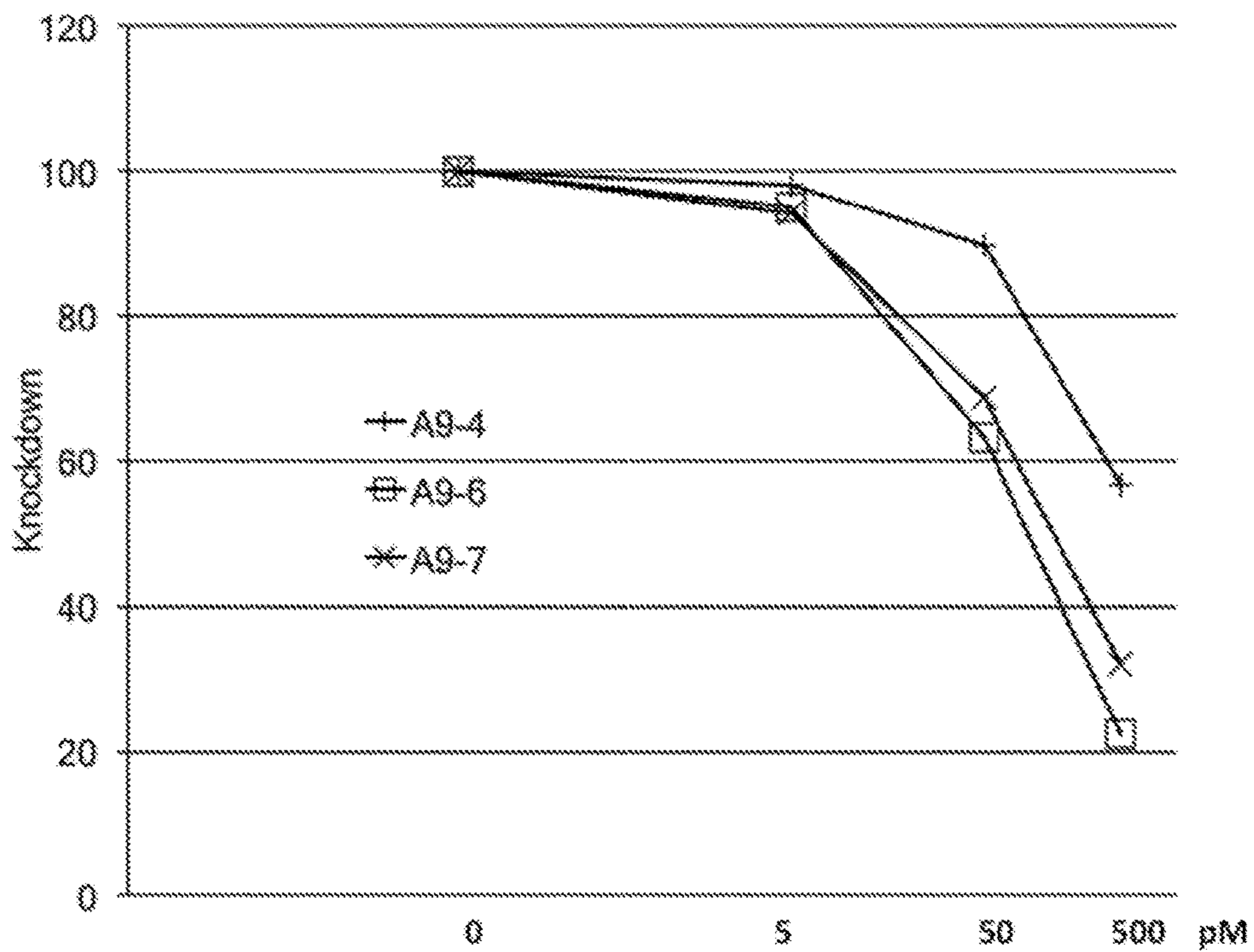


FIG. 13

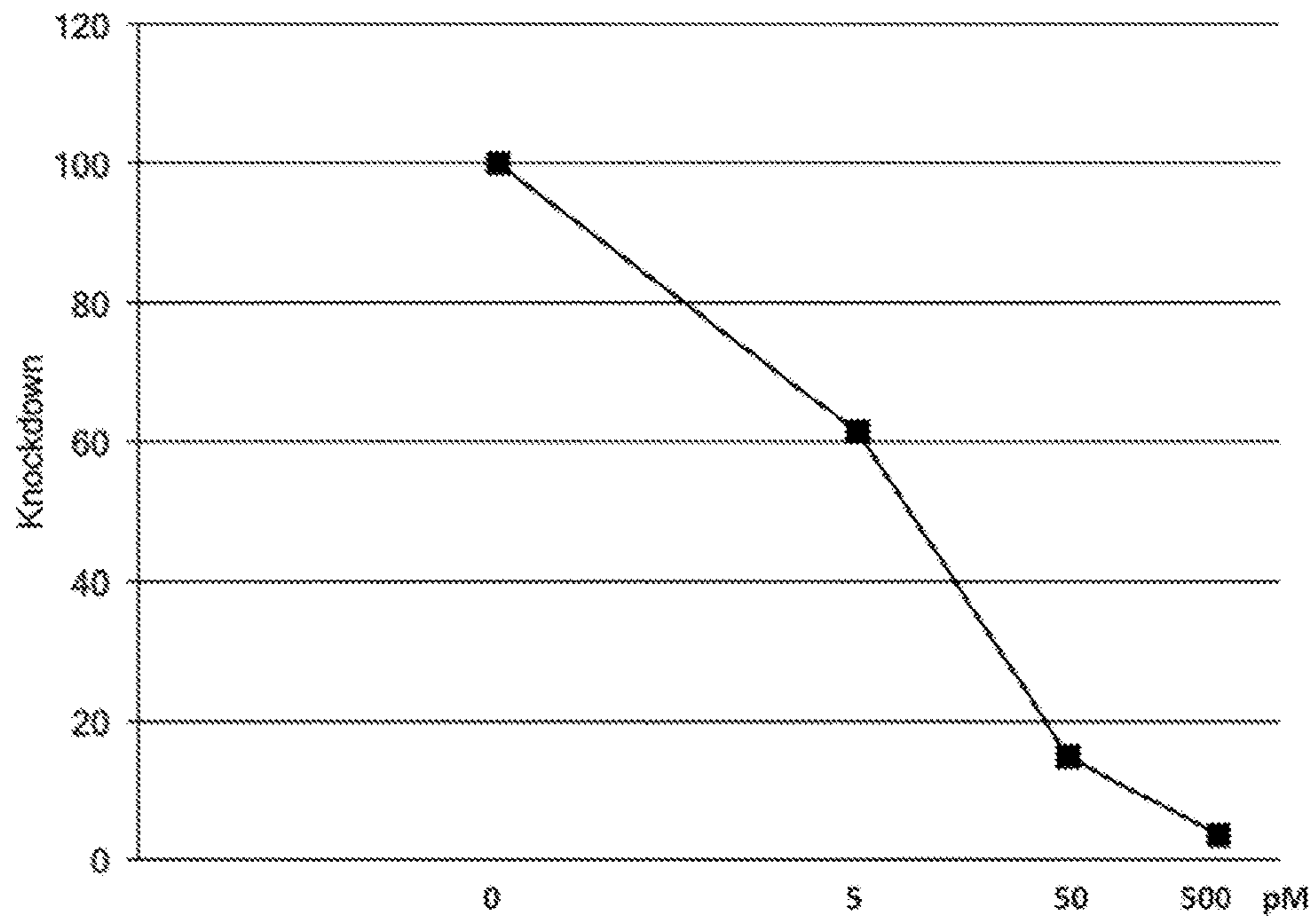
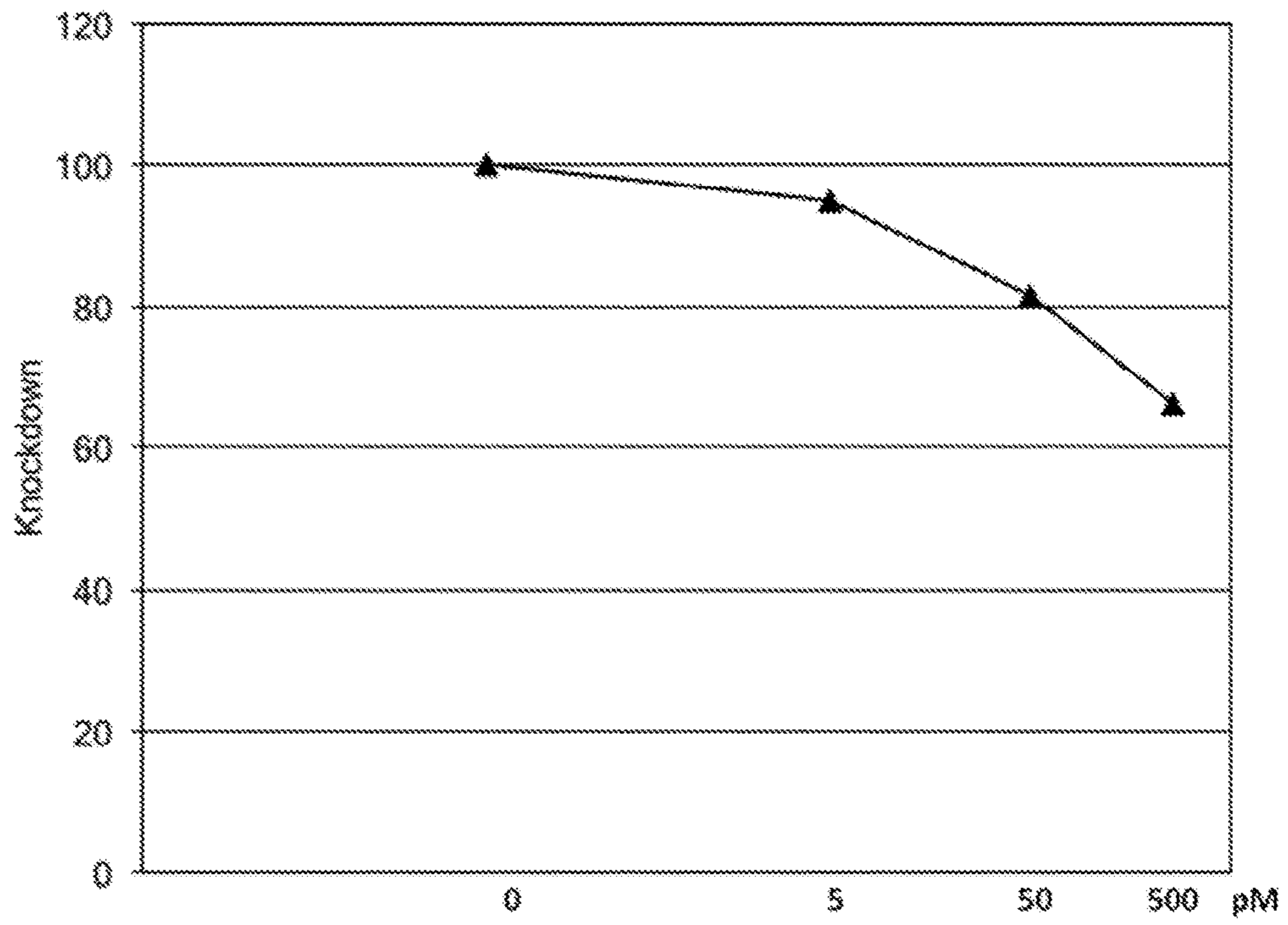


FIG. 14



RNA INTERFERENCE AGENTS FOR GST-PI GENE MODULATION

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.

SEQUENCE LISTING

This application includes a Sequence Listing submitted electronically as an ASCII file created on Jan. 2, 2016, named ND5123385US_SL.txt, which is 112,822 bytes in size, and is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Various human cancer tissues have been found to correlate with the appearance of mutated KRAS gene. In some cases, the tissues also present an elevated level of Glutathione S-Transferase Pi (GST- π) expression. (Miyaniishi et al., *Gastroenterology*, 2001, Vol. 121:865-874, Abstract) For example, elevated serum GST- π levels were observed in patients with various gastrointestinal malignancies. (Niitsu et al., *Cancer*, 1989, Vol. 63, No. 2, pp. 317-323, Abstract)

GST- π is a member of a GST family of enzymes that play a role in detoxification by catalyzing the conjugation of hydrophobic and electrophilic compounds with reduced glutathione. GST- π expression can be reduced in vitro with a siRNA. (Niitsu et al., US 2014/0315975 A1). However, there are many drawbacks of existing siRNA agents, such as insufficient activity, off target effects, lack of serum stability, and lack of in vivo potency or efficacy.

There is an urgent need for compositions and methods for modulating the expression of genes associated with cancer. In particular, therapeutics based on inhibition of GST- π expression will require highly potent and stable siRNA sequences and structures, which can reduce off target effects.

What is needed are siRNA sequences, compounds and structures for modulating GST- π expression, with uses for treating disease, such as malignant tumors.

BRIEF SUMMARY

This invention relates to the fields of biopharmaceuticals and therapeutics composed of nucleic acid based molecules. More particularly, this invention relates to compounds and compositions utilizing RNA interference (RNAi) for modulating the expression of human GST- π , and uses thereof.

This invention relates to compounds, compositions and methods for modulating the expression of human GST- π using RNA interference.

In some embodiments, this invention provides molecules for RNA interference gene silencing of GST- π .

In further embodiments, the structures, molecules and compositions of this invention can be used in methods for preventing or treating diseases, or ameliorating symptoms of conditions or disorders associated with GST- π , including malignant tumor.

Embodiments of this invention include the following:

A nucleic acid molecule for inhibiting expression of GST- π comprising a sense strand and an antisense strand, wherein the strands form a duplex region. The nucleic acid molecules can be siRNA molecules for inhibiting expression

of GST- π , and may contain one or more nucleotides that are modified or chemically-modified.

In some embodiments, the nucleic acid siRNA molecules for inhibiting expression of GST- π may include 2'-deoxy nucleotides, 2'-O-alkyl substituted nucleotides, 2'-deoxy-2'-fluoro substituted nucleotides, or any combination thereof. In certain embodiments, the 2'-deoxy nucleotides may be in the seed region of the siRNA molecules. In certain aspects, the siRNA molecules for inhibiting expression of GST- π may have deoxynucleotides in a plurality of positions in the antisense strand.

The nucleic acid molecules of this invention may advantageously inhibit expression of GST- π mRNA with an IC₅₀ of less than 300 pM. In certain embodiments, the nucleic acid molecules may inhibit expression of GST- π mRNA levels by at least 25% in vivo, upon a single administration of the molecules. In some embodiments, the nucleic acid molecules may have passenger strand off target activity reduced, or reduced by at least 50-fold, or at least 100-fold.

Embodiments of this invention further provide pharmaceutical compositions containing the siRNA molecules and a pharmaceutically acceptable carrier. In some embodiments, the carrier may be a lipid molecule, or liposome. This invention includes vectors or cells comprising the nucleic acid molecules.

Also contemplated in this invention are methods for treating a disease associated with GST- π expression, by administering to a subject in need a composition containing an siRNA, where the disease is malignant tumor, cancer, cancer caused by cells expressing mutated KRAS, sarcoma, or carcinoma.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the profound reduction of orthotopic lung cancer tumors in vivo by a siRNA of this invention targeted to GST- π . The GST- π siRNA was administered in a liposomal formulation at a dose of 2 mg/kg to athymic nude mice presenting A549 orthotopic lung cancer tumors. Final primary tumor weights were measured at necropsy for the treatment group and a vehicle control group. The GST- π siRNA showed significant efficacy for inhibition of lung cancer tumors in this six-week study. As shown in FIG. 1, after 43 days, the GST- π siRNA showed markedly advantageous tumor inhibition, with final primary tumor average weights significantly reduced by 2.8-fold, as compared to control.

FIG. 2 shows tumor inhibition efficacy in vivo for a GST- π siRNA. A cancer xenograft model using A549 cells was utilized with a relatively low dose of siRNA at 0.75 mg/kg. The GST- π siRNA showed advantageous tumor inhibition within a few days. After 36 days, the GST- π siRNA showed markedly advantageous tumor inhibition, with final tumor average volumes significantly reduced by about 2-fold, as compared to control.

FIG. 3 shows tumor inhibition efficacy in vivo for a GST- π siRNA at the endpoint of FIG. 2. The GST- π siRNA showed advantageous tumor inhibition with average tumor weights reduced by more than 2-fold.

FIG. 4 shows that a GST- π siRNA of this invention greatly increased cancer cell death by apoptosis in vitro. The GST- π siRNA caused upregulation of PUMA, a biomarker for apoptosis, which is associated with loss in cell viability. In FIG. 4, the expression of PUMA was greatly increased from 2-6 days after transfection of the GST- π siRNA.

FIG. 5 shows that a GST- π siRNA of this invention provided knockdown efficacy for A549 xenograft tumors in

vivo. Dose dependent knockdown of GST- π mRNA was observed in athymic nude (nu/nu) female mice (Charles River) with the siRNA targeted to GST- π . As shown in FIG. 5, at a dose of 4 mg/kg, significant reduction of about 40% in GST- π mRNA was detected 24 hours after injection.

FIG. 6 shows that a GST- π siRNA of this invention inhibited pancreatic cancer xenograft tumors in vivo. The GST- π siRNA provided gene silencing potency in vivo when administered in a liposomal formulation to pancreatic cancer xenograft tumors in athymic nude female mice, 6 to 8 weeks old. As shown in FIG. 6, a dose response was obtained with doses ranging from 0.375 mg/kg to 3 mg/kg of siRNA targeted to GST- π . The GST- π siRNA showed advantageous tumor inhibition within a few days after administration, the tumor volume being reduced by about 2-fold at the endpoint.

FIG. 7 shows that a GST- π siRNA of this invention exhibited increased serum stability. As shown in FIG. 7, the half-life ($t_{1/2}$) in serum for both the sense strand (FIG. 7, top) and antisense strand (FIG. 7, bottom) of a GST- π siRNA was about 100 minutes.

FIG. 8 shows that a GST- π siRNA of this invention exhibited enhanced stability in formulation in plasma. FIG. 8 shows incubation of a liposomal formulation of a GST- π siRNA in 50% human serum in PBS, and detection of remaining siRNA at various time points. As shown in FIG. 8, the half-life ($t_{1/2}$) in plasma of the formulation of the GST- π siRNA was significantly longer than 100 hours.

FIG. 9 shows in vitro knockdown for the guide strand of a GST- π siRNA. As shown in FIG. 9, the guide strand knockdown of the GST- π siRNA was approximately exponential, as compared to a control with scrambled sequence that exhibited no effect.

FIG. 10 shows in vitro knockdown for the passenger strand of the GST- π siRNA of FIG. 9. As shown in FIG. 10, the passenger strand off target knockdown for the GST- π siRNA was greatly reduced, with essentially no effect.

FIG. 11 shows in vitro knockdown for the guide strands of several highly active GST- π siRNAs. As shown in FIG. 11, the guide strand knockdown activities of the GST- π siRNAs were approximately exponential.

FIG. 12 shows in vitro knockdown for the passenger strand of the GST- π siRNAs of FIG. 11. As shown in FIG. 12, the passenger strand off target knockdown activities for the GST- π siRNAs were significantly reduced below about 500 pM.

FIG. 13 shows in vitro knockdown for the guide strand of a highly active GST- π siRNA. As shown in FIG. 13, the guide strand knockdown activity of the GST- π siRNA was approximately exponential.

FIG. 14 shows in vitro knockdown for the passenger strand of the GST- π siRNA of FIG. 13. As shown in FIG. 14, the passenger strand off target knockdown activity for the GST- π siRNA was significantly reduced.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds, compositions and methods for nucleic acid based therapeutics for modulating expression of GST- π .

In some embodiments, this invention provides molecules active in RNA interference, as well as structures and compositions that can silence expression of GST- π .

The structures and compositions of this disclosure can be used in preventing or treating various diseases such as malignant tumor.

In further embodiments, this invention provides compositions for delivery and uptake of one or more therapeutic RNAi molecules of this invention, as well as methods of use thereof. The RNA-based compositions of this invention can be used in methods for preventing or treating malignant tumors, such as cancers.

Therapeutic compositions of this invention include nucleic acid molecules that are active in RNA interference. The therapeutic nucleic acid molecules can be targeted to GSTP1 (GST- π) for gene silencing.

In various embodiments, this invention provides a range of molecules that can be active as a small interfering RNA (siRNA), and can regulate or silence GST- π gene expression.

The siRNAs of this invention can be used for preventing or treating malignant tumors.

Embodiments of this invention further provide a vehicle, formulation, or lipid nanoparticle formulation for delivery of the inventive siRNAs to subjects in need of preventing or treating a malignant tumor. This invention further contemplates methods for administering siRNAs as therapeutics to mammals.

The therapeutic molecules and compositions of this invention can be used for RNA interference directed to preventing or treating a GST- π associated disease, by administering a compound or composition to a subject in need.

The methods of this invention can utilize the inventive compounds for preventing or treating malignant tumor.

In some aspects, the malignant tumor can be presented in various diseases, for example, cancers that highly expressing GST- π , cancers caused by cells expressing mutated KRAS, sarcomas, fibrosarcoma, malignant fibrous histiocytoma, liposarcoma, rhabdomyosarcoma, leiomyosarcoma, angiosarcoma, Kaposi's sarcoma, lymphangiosarcoma, synovial sarcoma, chondrosarcoma, osteosarcoma, and carcinomas.

In certain aspects, methods of this invention can utilize the inventive compounds for preventing or treating malignant tumors and cancers in any organ or tissue, including, for example, brain tumor, head and neck cancer, breast cancer, lung cancer, esophageal cancer, stomach cancer, duodenal cancer, colorectal cancer, liver cancer, pancreatic cancer, gallbladder cancer, bile duct cancer, kidney cancer, urethral cancer, bladder cancer, prostate cancer, testicular cancer, uterine cancer, ovary cancer, skin cancer, leukemia, malignant lymphoma, epithelial malignant tumors, and non-epithelial malignant tumors.

In certain embodiments, a combination of therapeutic molecules of this invention can be used for silencing or inhibiting GST- π gene expression.

This invention provides a range of RNAi molecules, where each molecule has a polynucleotide sense strand and a polynucleotide antisense strand; each strand of the molecule is from 15 to 30 nucleotides in length; a contiguous region of from 15 to 30 nucleotides of the antisense strand is complementary to a sequence of an mRNA encoding GST- π ; and at least a portion of the sense strand is complementary to at least a portion of the antisense strand, and the molecule has a duplex region of from 15 to 30 nucleotides in length.

A RNAi molecule of this invention can have a contiguous region of from 15 to 30 nucleotides of the antisense strand that is complementary to a sequence of an mRNA encoding GST- π , which is located in the duplex region of the molecule.

In some embodiments, a RNAi molecule can have a contiguous region of from 15 to 30 nucleotides of the antisense strand that is complementary to a sequence of an mRNA encoding GST- π .

Embodiments of this invention may further provide methods for preventing, treating or ameliorating one or more symptoms of malignant tumor, or reducing the risk of developing malignant tumor, or delaying the onset of malignant tumor in a mammal in need thereof.

GST- π and RNAi Molecules

The nucleic acid sequence of an example target human glutathione S-transferase pi (human GST- π) mRNA is disclosed in GenBank accession number NM_000852.3 (hGSTP1), and is 986 nucleotides in length.

One of ordinary skill in the art would understand that a reported sequence may change over time and to incorporate any changes needed in the nucleic acid molecules herein accordingly.

Embodiments of this invention can provide compositions and methods for gene silencing of GST- π expression using small nucleic acid molecules. Examples of nucleic acid molecules include molecules active in RNA interference (RNAi molecules), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules, as well as DNA-directed RNAs (ddRNA), Piwi-interacting RNAs (piRNA), and repeat associated siRNAs (rasiRNA). Such molecules are capable of mediating RNA interference against GST- π gene expression.

The composition and methods disclosed herein can also be used in treating various kinds of malignant tumors in a subject.

The nucleic acid molecules and methods of this invention may be used to down regulate the expression of genes that encode GST- π .

The compositions and methods of this invention can include one or more nucleic acid molecules, which, independently or in combination, can modulate or regulate the expression of GST- π protein and/or genes encoding GST- π proteins, proteins and/or genes encoding GST- π associated with the maintenance and/or development of diseases, conditions or disorders associated with GST- π , such as malignant tumor.

The compositions and methods of this invention are described with reference to exemplary sequences of GST- π . A person of ordinary skill in the art would understand that various aspects and embodiments of the invention are directed to any related GST- π genes, sequences, or variants, such as homolog genes and transcript variants, and polymorphisms, including single nucleotide polymorphism (SNP) associated with any GST- π genes.

In some embodiments, the compositions and methods of this invention can provide a double-stranded short interfering nucleic acid (siRNA) molecule that downregulates the expression of a GST- π gene, for example human GST- π .

A RNAi molecule of this invention can be targeted to GST- π and any homologous sequences, for example, using complementary sequences or by incorporating non-canonical base pairs, for example, mismatches and/or wobble base pairs, that can provide additional target sequences.

In instances where mismatches are identified, non-canonical base pairs, for example, mismatches and/or wobble bases can be used to generate nucleic acid molecules that target more than one gene sequence.

For example, non-canonical base pairs such as UU and CC base pairs can be used to generate nucleic acid molecules that are capable of targeting sequences for differing GST- π

targets that share sequence homology. Thus, a RNAi molecule can be targeted to a nucleotide sequence that is conserved between homologous genes, and a single RNAi molecule can be used to inhibit expression of more than one gene.

In some aspects, the compositions and methods of this invention include RNAi molecules that are active against GST- π mRNA, where the RNAi molecule includes a sequence complementary to any mRNA encoding a GST- π sequence.

In some embodiments, a RNAi molecule of this disclosure can have activity against GST- π RNA, where the RNAi molecule includes a sequence complementary to an RNA having a variant GST- π encoding sequence, for example, a mutant GST- π gene known in the art to be associated with malignant tumor.

In further embodiments, a RNAi molecule of this invention can include a nucleotide sequence that can interact with a nucleotide sequence of a GST- π gene and mediate silencing of GST- π gene expression.

The nucleic acid molecules for inhibiting expression of GST- π may have a sense strand and an antisense strand, wherein the strands form a duplex region. The nucleic acid molecules may have one or more of the nucleotides in the duplex region being modified or chemically-modified, including such modifications as are known in the art. Any nucleotide in an overhang of the siRNA may also be modified or chemically-modified.

In some embodiments, the preferred modified or chemically-modified nucleotides are 2'-deoxy nucleotides. In additional embodiments, the modified or chemically-modified nucleotides can include 2'-O-alkyl substituted nucleotides, 2'-deoxy-2'-fluoro substituted nucleotides, phosphorothioate nucleotides, locked nucleotides, or any combination thereof.

In certain embodiments, a preferred structure can have an antisense strand containing deoxynucleotides in a plurality of positions, the plurality of positions being one of the following: each of positions 4, 6 and 8, from the 5' end of the antisense strand; each of positions 3, 5 and 7, from the 5' end of the antisense strand; each of positions 1, 3, 5 and 7, from the 5' end of the antisense strand; each of positions 3-8, from the 5' end of the antisense strand; and each of positions 5-8, from the 5' end of the antisense strand. Any of these structures can be combined with one or more 2'-deoxy-2'-fluoro substituted nucleotides in the duplex region.

The nucleic acid molecules of this invention can inhibit expression of GST- π mRNA with an advantageous IC₅₀ of less than about 300 pM, or less than about 200 pM, or less than about 100 pM, or less than about 50 pM.

Further, the nucleic acid molecules can inhibit expression of GST- π mRNA levels by at least 25% in vivo, upon a single administration.

Pharmaceutical compositions are contemplated in this invention, which can contain one or more siRNAs as described herein, in combination with a pharmaceutically acceptable carrier. Any suitable carrier may be used, including those known in the art, as well as lipid molecules, nanoparticles, or liposomes, any of which may encapsulate the siRNA molecules.

This invention discloses methods for treating a disease associated with GST- π expression, which methods include administering to a subject in need a composition containing one or more of the siRNAs. Diseases to be treated may include malignant tumor, cancer, cancer caused by cells expressing mutated KRAS, sarcoma, and carcinoma, among others.

Examples of RNAi molecules of this invention targeted to GST- π mRNA are shown in Table 1.

TABLE 1

RNAi molecule sequences for GST- π					
ID	Ref Pos	SEQ ID NO	SENSE STRAND	SEQ	ANTISENSE STRAND
			(5'→3')	ID	(5'→3')
			SEQ ID NOS: 1 to 65	ID NO	SEQ ID NOS: 66 to 130
A1	652	1	UCCCAGAACCAGGGAGGCAt t	66	UGCCUCCCUGGUUCUGGGAc a
A10	635	2	CUUUUGAGACCCUGCUGUCt t	67	GACAGCAGGGUCUCAAAAGgc
A11	649	3	CUGUCCCAGAACCAGGGAGt t	68	CUCCCUGGUUCUGGGACAGc a
A12	650	4	UGUCCCAGAACCAGGGAGGt t	69	CCUCCCUGGUUCUGGGACAgc
A13	631	5	AAGCCUUUUGAGACCCUGCt t	70	GCAGGGUCUCAAAAGGCUUc a
A14	638	6	UUGAGACCCUGCUGUCCAt t	71	UGGGACAGCAGGGUCUCAAAa
A15	636	7	UUUUGAGACCCUGCUGUCt t	72	GGACAGCAGGGUCUCAAAAgg
A16	640	8	GAGACCCUGCUGUCCAGAt t	73	UCUGGGACAGCAGGGUCUCaa
A17	332	9	GCUGGAAGGAGGAGGUGUt t	74	ACCACCUCUCCUCCAGCt c
A18	333	10	CUGGAAGGAGGAGGUGUGt t	75	CACCACCUCUCCUCCAGc t
A19	321	11	UCAGGGCCAGAGCUGGAAGt t	76	CUUCCAGCUCUGGCCUGAt c
A2	639	12	UGAGACCCUGCUGUCCAGt t	77	CUGGGACAGCAGGGUCUCAaa
A20	323	13	AGGGCCAGAGCUGGAAGGAt t	78	UCCUCCAGCUCUGGCCUg a
A21	331	14	AGCUGGAAGGAGGAGGUGt t	79	CCACCUCUCCUCCAGCUc t
A22	641	15	AGACCCUGCUGUCCAGAAt t	80	UUCUGGGACAGCAGGGUCUc a
A23	330	16	GAGCUGGAAGGAGGAGGUGt t	81	CACCUCUCCUCCAGCUCt g
A25	647	17	UGCUGUCCCAGAACCAGGGt t	82	CCCUGGUUCUGGGACAGCAgg
A26	653	18	CCCAGAACCAGGGAGGCAAt t	83	UUGCCUCCUGGUUCUGGGac
A3	654	19	CCAGAACCAGGGAGGCAAGt t	84	CUUGCCUCCUGGUUCUGGg a
A4	637	20	UUUGAGACCCUGCUGUCCt t	85	GGGACAGCAGGGUCUCAAAag
AS	642	21	GACCCUGCUGUCCAGAAc t	86	GUUCUGGGACAGCAGGGUCt c
A6	319	22	GAUCAGGGCCAGAGCUGGAt t	87	UCCAGCUCUGGCCUGAUc t g
A7	632	23	AGCCUUUUGAGACCCUGCUt t	88	AGCAGGGUCUCAAAAGGCUt c
A8	633	24	GCCUUUUGAGACCCUGCUGt t	89	CAGCAGGGUCUCAAAAGGc t t
A9	634	25	CCUUUUGAGACCCUGCUGUt t	90	ACAGCAGGGUCUCAAAAGGc t
AG7	632	26	CGCCUUUUGAGACCCUGCAt t	91	UGCAGGGUCUCAAAAGGCGt c
AK1	257	27	CCUACACCGUGGUCUAUUUt t	92	AAAUAGACCACGGUGUAGGgc
AK10	681	28	UGUGGGAGACCAGAUCUCc t	93	GGAGAUCUGGUCUCCACAat
AK11	901	29	GCGGGAGGCAGAGUUUGCt t	94	GGCAAACUCUGCCUCCCGc t c
AK12	922	30	CCUUUCUCCAGGACCAAUAt t	95	UAUUGGUCCUGGAGAAAGGaa
AK13/ A24	643	31	ACCCUGCUGUCCAGAACc t	96	GGUUCUGGGACAGCAGGGUc t

TABLE 1-continued

RNAi molecule sequences for GST- π					
ID	Ref Pos	SEQ ID NO	SENSE STRAND	SEQ	ANTISENSE STRAND
			(5'→3')	ID	(5'→3')
			SEQ ID NOS: 1 to 65	ID NO	SEQ ID NOS: 66 to 130
AK2	267	32	GGUCUAUUUCCAGUUCGAtt	97	UCGAACUGGGAAAUAGACCac
AK3	512	33	CCCUGGUGGACAUGGUGAAtt	98	UUCACCAUGUCCACCAGGGct
AK4	560	34	ACAUCUCCCUCAUCUACACTt	99	GUGUAGAUGAGGGAGAUGUat
AK5	593	35	GCAAGGAUGACUAUGUGAAtt	100	UUCACAUAUGUCAUCCUUGCcc
AK6	698	36	CCUUCGCUGACUACAACCUtt	101	AGGUUGUAGUCAGCGAAGGag
AK7	313	37	CUGGCAGAU CAGGGCCAGAtt	102	UCUGGCCUGAUCUGCCAGca
AK8	421	38	GACGGAGACCU CACCCUGUtt	103	ACAGGGUGAGGUCUCCGUCct
AK9	590	39	CGGGCAAGGAUGACUAUGUtt	104	ACAUAGUCAUCCUUGCCCGcc
AU10	635	40	CUUUUGAGACCCUGCUGUAtt	105	UACAGCAGGGUCUAAAAGgc
AU23	330	41	GAGCUGGAAGGAGGAGGUAtt	106	UACCUCCUCCUCCAGCUCtg
AU24	643	42	ACCCUGCUGUCCAGAACAAtt	107	UGUUCUGGGACAGCAGGGUct
AU25	648	43	UGCUGUCCAGAACCAGGAtt	108	UCCUGGUUCUGGGACAGCAgg
AU7	632	44	AGCCUUUUGAGACCCUGCAAtt	109	UGCAGGGUCUAAAAGGCUt c
AU9	634	45	CCUUUUGAGACCCUGCUGAtt	110	UCAGCAGGGUCUAAAAGGct
B1	629	46	UGAAGCCUUUUGAGACCCUtt	111	AGGGUCUAAAAGGCUUCAg t
B10	627	47	ACUGAAGCCUUUUGAGACctt	112	GGUCUAAAAGGCUUCAGUt g
B11	596	48	AGGAUGACUAUGUGAAGGctt	113	GCCUUCACAUAGUCAUCCUt g
B12	597	49	GGAUGACUAUGUGAAGGCAAtt	114	UGCCUUCACAUAGUCAUCctt
B13	598	50	GAUGACUAUGUGAAGGCActt	115	GUGCCUUCACAUAGUCAUCctt
B14	564	51	CUCCUCAUCUACACCAACTt	116	GUUGGUGUAGAUGAGGGAGat
B2	630	52	GAAGCCUUUUGAGACCCUGtt	117	CAGGGUCUAAAAGGCUUCag
B3	563	53	UCUCCUCAUCUACACCAAtt	118	UUGGUGUAGAUGAGGGAGAt g
B4	567	54	CCUCAUCUACACCAACUAUtt	119	AUAGUUGGUGUAGAUGAGGgja
B5	566	55	CCCUCAUCUACACCAACUAAtt	120	UAGUUGGUGUAGAUGAGGGag
B6	625	56	CAACUGAAGCCUUUUGAGAtt	121	UCUAAAAGGCUUCAGUUGcc
B7	626	57	AACUGAAGCCUUUUGAGActt	122	GUCUAAAAGGCUUCAGUUGgc
B8	628	58	CUGAAGCCUUUUGAGACCCctt	123	GGGUCUAAAAGGCUUCAGtt
B9	565	59	UCCUCAUCUACACCAACUtt	124	AGUUGGUGUAGAUGAGGGaja
BG3	563	60	GCUCCUCAUCUACACCAAtt	125	UUGGUGUAGAUGAGGGAGctg
BU2	630	61	GAAGCCUUUUGAGACCCUAAtt	126	UAGGGUCUAAAAGGCUUCag
BU10	627	62	ACUGAAGCCUUUUGAGACAtt	127	UGUCUAAAAGGCUUCAGUt g
BU14	565	63	CUCCUCAUCUACACCAAAtt	128	UUUGGUGUAGAUGAGGGAGat
BU4	567	64	CCUCAUCUACACCAACUAAtt	129	UUAGUUGGUGUAGAUGAGGgja
C1- 934	934	65	ACCAAUAAAAUUUCUAAGAtt	130	UCUUAGAAAAUUUAUUGGUcc

Key for Table 1: Upper case A, G, C and U refer to ribo-A, ribo-G, ribo-C and ribo-U, respectively. The lower case letters a, u, g, c, t refer to 2'-deoxy-A, 2'-deoxy-U, 2'-deoxy-G, 2'-deoxy-C, and deoxythymidine respectively.

Examples of RNAi molecules of this invention targeted to GST- π mRNA are shown in Table 2.

TABLE 2

RNAi molecule sequences for GST- π						
ID	SEQ ID NO	SENSE STRAND (5'→3')		SEQ ID NO	ANTISENSE STRAND (5'→3')	
		SEQ	ID NOS: 131 to 156		SEQ	ID NOS: 157 to 182
BU2'	131	GAAGCCUUUUGAGACCCUANN		157	UAGGGUCUCAAAAAGGCUUCNN	
14	132	GAAGCCUUUUGAGACCCUAUU		158	UAGGGUCUCAAAAAGGCUUCUU	
15	133	GAAGCCUUUUGAGACCCUAUU		159	uagggucuCAAAAAGGCUUCUU	
16	134	GAAGCCUUUUGAGACCCUAUU		160	UagggucuCAAAAAGGCUUCUU	
17	135	GAAGCCUUUUGAGACCCUAUU		161	UAgggucuCAAAAAGGCUUCUU	
18	136	GAAGCCUUUUGAGACCCUAUU		162	UAGggucuCAAAAAGGCUUCUU	
19	137	GAAGCCUUUUGAGACCCUAUU		163	UAGGgucuCAAAAAGGCUUCUU	
20	138	GAAGCCUUUUGAGACCCUAUU		164	uAgGgUcUCAAAAAGGCUUCUU	
21	139	GAAGCCUUUUGAGACCCUAUU		165	UAgGgUcUCAAAAAGGCUUCUU	
22	140	GAAGCCUUUUGAGACCCUAUU		166	UaGgGuCuCAAAAAGGCUUCUU	
23	141	GAAGCCUUUUGAGACCCUAUU		167	UAGgGuCuCAAAAAGGCUUCUU	
24	142	GAAGCCUUUUGAGACCCUAtt		168	UagggucuCAAAAAGGCUUCUU	
25	143	GAAGCCUUUUGAGACCCUAUU		169	<u>U</u> AGGGUCUCAAAAAGGCUUCUU	
26	144	GAAGCCUUUUGAGACCCUAUU		170	fUAGGGUCUCAAAAAGGCUUCUU	
27	145	GAAGCCUUUUGAGACCCUAUU		171	uAGGGUCUCAAAAAGGCUUCUU	
28	146	GAAGCCUUUUGAGACCCUAUU		172	UsAGGGUCUCAAAAAGGCUUCUU	
29	147	GAAGCCUUUUGAGACCCUfAUU		173	fUAGGGUCUfCAAAAAGGcfUUCUU	
30	148	GAAGCCUUUUGAGfACCCUfAUU		174	fUAGGGUCUfCAfafaAAGGcfUUCUU	
31	149	GAAGCCUUUUGAGACCCUAUU		175	<u>U</u> AGGGUCU <u>C</u> AAAAGGCUUCUU	
31'	150	GAAGCCUUUUGAGACCCUAUU		176	fUAGGGUCU <u>C</u> AAAAGGCUUCUU	
32	151	<u>GA</u> AGCCUUUUGAGACCCUAUU		177	UAGGGUCUCAAAAAGGCUUCUU	
39	152	<u>GA</u> AGCCU <u>U</u> UUGAGACCCUAUU		178	UAGgGuCuCAAAAAGGCUUCUU	
45	153	<u>GA</u> AGCCU <u>U</u> UUGAGACCCUAUU		179	<u>U</u> AGgGuCu <u>C</u> AAAAGGCUUCUU	
46	154	<u>GA</u> AGCCU <u>U</u> UUGAGACCCUAUU		180	<u>U</u> AGgGuCu <u>C</u> AAAAGGCUUCUU	
47	155	<u>GA</u> AGCCU <u>U</u> UUGAGACCCUAUU		181	<u>U</u> AGgGuCu <u>C</u> AAAAGGCUUCUU	
48	156	<u>GA</u> AGCCU <u>U</u> UUGAGACCCUAUU		182	fUAGgGuCu <u>C</u> AAAAGGCUUCUU	

Key for Table 2: Upper case A, G, C and U refer to ribo-A, ribo-G, ribo-C and ribo-U, respectively. The lower case letters a, u, g, c, t refer to 2'-deoxy-A, 2'-deoxy-U, 2'-deoxy-G, 2'-deoxy-C, and deoxythymidine (dT=T=t) respectively. Underlining refers to 2'-OMe-substituted, e.g., U. The lower

case letter f refers to 2'-deoxy-2'-fluoro substitution, e.g. fU is 2'-deoxy-2'-fluoro-U. N is A, C, G, U, U, a, c, g, u, t, or a modified, inverted, or chemically modified nucleotide. An "s" character represents a phosphorothioate linkage.

Examples of RNAi molecules of this invention targeted to GST- π mRNA are shown in Table 3.

TABLE 3

RNAi molecule sequences for GST- π				
ID	SEQ ID NO	SENSE STRAND	SEQ ID NO	ANTISENSE STRAND
		(5'→3') SEQ ID NOS: 207 to 221		(5'→3') SEQ ID NOS: 222 to 236
A9'	183	CCUUUUGAGACCCUGCUGUNN	195	ACAGCAGGGUCUCAAAGGNN
1	184	CCUCAUCUACACCAACUAUUU	196	AUAGUUGGUGUAGAUGAGGUU
2	185	CCUCAUCUACACCAACUAUUU	197	auaguuggUGUAGAUGAGGUU
3	186	CCUCAUCUACACCAACUAUUU	198	AuaguuggUGUAGAUGAGGUU
4	187	CCUCAUCUACACCAACUAUUU	199	AUaguuggUGUAGAUGAGGUU
5	188	CCUCAUCUACACCAACUAUUU	200	AUAguggUGUAGAUGAGGUU
6	189	CCUCAUCUACACCAACUAUUU	201	AUAGuuggUGUAGAUGAGGUU
7	190	CCUCAUCUACACCAACUAUUU	202	aUaGuUgGUGUAGAUGAGGUU
8	191	CCUCAUCUACACCAACUAUUU	203	AUaGuUgGUGUAGAUGAGGUU
9	192	CCUCAUCUACACCAACUAUUU	204	AuAgUuGgUGUAGAUGAGGUU
10	193	CCUCAUCUACACCAACUAUUU	205	AUAgUuGgUGUAGAUGAGGUU
11	194	<u>CCUCAUCUACACCAACUAUUU</u>	206	AuaguuggUGUAG <u>UAGAGGUU</u>

Key for Table 3: Upper case A, G, C and U refer to ribo-A, ribo-G, ribo-C and ribo-U, respectively. The lower case letters a, u, g, c, t refer to 2'-deoxy-A, 2'-deoxy-U, 2'-deoxy-G, 2'-deoxy-C, and deoxythymidine (dT=T=t) respectively. Underlining refers to 2'-OMe-substituted, e.g., U. The lower

case letter f refers to 2'-deoxy-2'-fluoro substitution, e.g. fU is 2'-deoxy-2'-fluoro-U. N is A, C, G, U, U, a, c, g, u, t, or a modified, inverted, or chemically modified nucleotide.

Examples of RNAi molecules of this invention targeted to GST- π mRNA are shown in Table 4.

TABLE 4

RNAi molecule sequences for GST- π				
ID	SEQ ID NO	SENSE STRAND	SEQ ID NO	ANTISENSE STRAND
		(5'→3') SEQ ID NOS: 207 to 221		(5'→3') SEQ ID NOS: 222 to 236
B13'	207	GAUGACUAUGUGAAGGCACNN	222	GUGCCUUCACAUAGUCAUCNN
4	208	GGAUGACUAUGUGAAGGCAUU	223	UGCCUUCACAUAGUCAUCCUU
5	209	GGAUGACUAUGUGAAGGCAUU	224	ugccuucacAUAGUCAUCCUU
6	210	GGAUGACUAUGUGAAGGCAUU	225	UgccuucacAUAGUCAUCCUU
7	211	GGAUGACUAUGUGAAGGCAUU	226	UGccuucacAUAGUCAUCCUU
8	212	GGAUGACUAUGUGAAGGCAUU	227	UGCcuucacAUAGUCAUCCUU
9	213	GGAUGACUAUGUGAAGGCAUU	228	UGCCuucacAUAGUCAUCCUU
10	214	GGAUGACUAUGUGAAGGCAUU	229	uGcCuUcACAUAGUCAUCCUU
11	215	GGAUGACUAUGUGAAGGCAUU	230	UGcCuUcACAUAGUCAUCCUU
12	216	GGAUGACUAUGUGAAGGCAUU	231	UgCcUuCaCAUAGUCAUCCUU
13	217	GGAUGACUAUGUGAAGGCAUU	232	UGCcUuCaCAUAGUCAUCCUU
14	218	<u>GGAUGACUAUGUGAAGGCAUU</u>	233	UgccuucacAUAG <u>UCAUCCUU</u>
15	219	GGAUGACUAufGUfGAAGGCAUU	234	UGcfCUUCACAUAGUCAUCCUU

TABLE 4-continued

RNAi molecule sequences for GST- π				
ID	SEQ ID NO	SENSE STRAND	SEQ ID NO	ANTISENSE STRAND
		(5'→3') SEQ ID NOS: 207 to 221		(5'→3') SEQ ID NOS: 222 to 236
17	220	<u>GGAUGACUAUGUGAAGGCAUU</u>	235	UGCCUUCACAUAGUCAUCCUU
18	221	<u>GGAUGACUAUGUGAAGGCAUU</u>	236	UGCCUUCACAUAGUCAUCCUU

Key for Table 4: Upper case A, G, C and U refer to ribo-A, ribo-G, ribo-C and ribo-U, respectively. The lower case letters a, u, g, c, t refer to 2'-deoxy-A, 2'-deoxy-U, 2'-deoxy-G, 2'-deoxy-C, and deoxythymidine (dT=T=t) respectively. Underlining refers to 2'-OMe-substituted, e.g., U. The lower case letter f refers to 2'-deoxy-2'-fluoro substitution, e.g. fU is 2'-deoxy-2'-fluoro-U. N is A, C, G, U, U, a, c, g, u, t, or a modified, inverted, or chemically modified nucleotide.

Examples of RNAi molecules of this invention targeted to GST- π mRNA are shown in Table 5.

TABLE 5

RNAi molecule sequences for GST- π				
ID	SEQ ID NO	SENSE STRAND	SEQ ID NO	ANTISENSE STRAND
		(5'→3') SEQ ID NOS: 237 to 248		(5'→3') SEQ ID NOS: 249 to 260
B2'	237	GAAGCCUUUUGAGACCCUGNN	249	CAGGGUCUCAAAGGCUUCNN
1	238	GAAGCCUUUUGAGACCCUGUU	250	CAGGGUCUCAAAGGCUUCUU
2	239	GAAGCCUUUUGAGACCCUGUU	251	cagggucuCAAAGGCUUCUU
3	240	GAAGCCUUUUGAGACCCUGUU	252	CagggucuCAAAGGCUUCUU
4	241	GAAGCCUUUUGAGACCCUGUU	253	CAgggucuCAAAGGCUUCUU
5	242	GAAGCCUUUUGAGACCCUGUU	254	CAGggucuCAAAGGCUUCUU
6	243	GAAGCCUUUUGAGACCCUGUU	255	CAGGgucuCAAAGGCUUCUU
7	244	GAAGCCUUUUGAGACCCUGUU	256	cAgGgUcUCAAAGGCUUCUU
8	245	GAAGCCUUUUGAGACCCUGUU	257	CAgGgUcUCAAAGGCUUCUU
9	246	GAAGCCUUUUGAGACCCUGUU	258	CaGgGuCuCAAAGGCUUCUU
10	247	GAAGCCUUUUGAGACCCUGUU	259	CAGgGuCuCAAAGGCUUCUU
11	248	<u>GAAGCCUUUUGAGACCCUGUU</u>	260	CagggucuCAAAGGCUUCUU

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Key for Table 5: Upper case A, G, C and U refer to ribo-A, ribo-G, ribo-C and ribo-U, respectively. The lower case letters a, u, g, c, t refer to 2'-deoxy-A, 2'-deoxy-U, 2'-deoxy-G, 2'-deoxy-C, and deoxythymidine (dT=T=t) respectively. Underlining refers to 2'-OMe-substituted, e.g., U. The lower

case letter f refers to 2'-deoxy-2'-fluoro substitution, e.g. fU is 2'-deoxy-2'-fluoro-U. N is A, C, G, U, U, a, c, g, u, t, or a modified, inverted, or chemically modified nucleotide.

Examples of RNAi molecules of this invention targeted to GST- π mRNA are shown in Table 6.

TABLE 6

RNAi molecule sequences for GST- π				
ID	SEQ ID NO	SENSE STRAND	SEQ ID NO	ANTISENSE STRAND
		(5'→3') SEQ ID NOS: 261 to 272		(5'→3') SEQ ID NOS: 273 to 284
B4'	261	CCUCAUCUACACCAACUAUNN	273	AUAGUUGGUGUAGAUGAGGNN
1	262	CCUCAUCUACACCAACUAUUU	274	AUAGUUGGUGUAGAUGAGGUU

TABLE 6-continued

RNAi molecule sequences for GST- π				
ID	SEQ ID NO	SENSE STRAND	SEQ ID NO	ANTISENSE STRAND
		(5'→3') SEQ ID NOS: 261 to 272		(5'→3') SEQ ID NOS: 273 to 284
2	263	CCUCAUCUACACCAACUAUUU	275	auaguuggUGUAGAUGAGGUU
3	264	CCUCAUCUACACCAACUAUUU	276	AuaguuggUGUAGAUGAGGUU
4	265	CCUCAUCUACACCAACUAUUU	277	AUaguuggUGUAGAUGAGGUU
5	266	CCUCAUCUACACCAACUAUUU	278	AUAGuuggUGUAGAUGAGGUU
6	267	CCUCAUCUACACCAACUAUUU	279	AUAGuuggUGUAGAUGAGGUU
7	268	CCUCAUCUACACCAACUAUUU	280	aUaGuUgGUGUAGAUGAGGUU
8	269	CCUCAUCUACACCAACUAUUU	281	AUaGuUgGUGUAGAUGAGGUU
9	270	CCUCAUCUACACCAACUAUUU	282	AuAgUuGgUGUAGAUGAGGUU
10	271	CCUCAUCUACACCAACUAUUU	283	AUAgUuGgUGUAGAUGAGGUU
11	272	CCUCAUCUACACCAACUAUUU	284	AuaguuggUGUAGAUGAGGUU

Key for Table 6: Upper case A, G, C and U refer to ribo-A, ribo-G, ribo-C and ribo-U, respectively. The lower case letters a, u, g, c, t refer to 2'-deoxy-A, 2'-deoxy-U, 2'-deoxy-G, 2'-deoxy-C, and deoxythymidine (dT=T=t) respectively. Underlining refers to 2'-OMe-substituted, e.g., U. The lower case letter f refers to 2'-deoxy-2'-fluoro substitution, e.g. fU is 2'-deoxy-2'-fluoro-U. N is A, C, G, U, U, a, c, g, u, t, or a modified, inverted, or chemically modified nucleotide.

In some embodiments, this invention provides a range of nucleic acid molecules, wherein: a) the molecule has a polynucleotide sense strand and a polynucleotide antisense strand; b) each strand of the molecule is from 15 to 30 nucleotides in length; c) a contiguous region of from 15 to 30 nucleotides of the antisense strand is complementary to a sequence of an mRNA encoding GST- π ; d) at least a portion of the sense strand is complementary to at least a portion of the antisense strand, and the molecule has a duplex region of from 15 to 30 nucleotides in length.

In some embodiments, the nucleic acid molecule can have a contiguous region of from 15 to 30 nucleotides of the antisense strand that is complementary to a sequence of an mRNA encoding GST- π is located in the duplex region of the molecule.

In additional embodiments, the nucleic acid molecule can have a contiguous region of from 15 to 30 nucleotides of the antisense strand that is complementary to a sequence of an mRNA encoding GST- π .

In certain embodiments, each strand of the nucleic acid molecule can be from 18 to 22 nucleotides in length. The duplex region of the nucleic acid molecule can be 19 nucleotides in length.

In alternative forms, the nucleic acid molecule can have a polynucleotide sense strand and a polynucleotide antisense strand that are connected as a single strand, and form a duplex region connected at one end by a loop.

Some embodiments of a nucleic acid molecule of this disclosure can have a blunt end. In certain embodiments, a nucleic acid molecule can have one or more 3' overhangs.

This invention provides a range of nucleic acid molecules that are RNAi molecules active for gene silencing. The inventive nucleic acid molecules can be a dsRNA, a siRNA, a micro-RNA, or a shRNA active for gene silencing, as well

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as a DNA-directed RNA (ddRNA), Piwi-interacting RNA (piRNA), or a repeat associated siRNA (rasiRNA). The nucleic acid molecules can be active for inhibiting expression of GST- π .

Embodiments of this invention further provide nucleic acid molecules having an IC₅₀ for knockdown of GST- π of less than 100 pM.

Additional embodiments of this invention provide nucleic acid molecules having an IC₅₀ for knockdown of GST- π of less than 50 pM.

This invention further contemplates compositions containing one or more of the inventive nucleic acid molecules, along with a pharmaceutically acceptable carrier. In certain embodiments, the carrier can be a lipid molecule or liposome.

The compounds and compositions of this invention are useful in methods for preventing or treating a GST- π associated disease, by administering a compound or composition to a subject in need.

The methods of this invention can utilize the inventive compounds for preventing or treating malignant tumor. The malignant tumor can be presented in various diseases, for example, cancers associated with GST- π expression, cancers caused by cells expressing mutated KRAS, sarcomas, fibrosarcoma, malignant fibrous histiocytoma, liposarcoma, rhabdomyosarcoma, leiomyosarcoma, angiosarcoma, Kaposi's sarcoma, lymphangiosarcoma, synovial sarcoma, chondrosarcoma, osteosarcoma, carcinomas, brain tumor, head and neck cancer, breast cancer, lung cancer, esophageal cancer, stomach cancer, duodenal cancer, appendix cancer, colorectal cancer, rectal cancer, liver cancer, pancreatic cancer, gallbladder cancer, bile duct cancer, anus cancer, kidney cancer, urethral cancer, urinary bladder cancer, prostate cancer, testicular cancer, uterine cancer, ovary cancer, skin cancer, leukemia, malignant lymphoma, epithelial malignant tumors, and non-epithelial malignant tumors.

Modified and Chemically-Modified siRNAs

Embodiments of this invention encompass siRNA molecules that are modified or chemically-modified to provide enhanced properties for therapeutic use, such as increased activity and potency for gene silencing. This invention provides modified or chemically-modified siRNA molecules

that can have increased serum stability, as well as reduced off target effects, without loss of activity and potency of the siRNA molecules for gene modulation and gene silencing. In some aspects, this invention provides siRNAs having modifications or chemical modifications in various combinations, which enhance the stability and efficacy of the siRNA.

In some embodiments, the siRNA molecules of this invention can have passenger strand off target activity reduced by at least 10-fold, or at least 20-fold, or at least 30-fold, or at least 50-fold, or at least 100-fold.

As used herein, the terms modified and chemically-modified refer to changes made in the structure of a naturally-occurring nucleotide or nuclei acid structure of an siRNA, which encompasses siRNAs having one or more nucleotide analogs, altered nucleotides, non-standard nucleotides, non-naturally occurring nucleotides, and combinations thereof.

In some embodiments, the number of modified or chemically-modified structures in an siRNA can include all of the structural components, and/or all of the nucleotides of the siRNA molecule.

Examples of modified and chemically-modified siRNAs include siRNAs having modification of the sugar group of a nucleotide, modification of a nucleobase of a nucleotide, modification of a nucleic acid backbone or linkage, modification of the structure of a nucleotide or nucleotides at the terminus of a siRNA strand, and combinations thereof.

Examples of modified and chemically-modified siRNAs include siRNAs having modification of the substituent at the 2' carbon of the sugar.

Examples of modified and chemically-modified siRNAs include siRNAs having modification at the 5' end, the 3' end, or at both ends of a strand.

Examples of modified and chemically-modified siRNAs include siRNAs having modifications that produce complementarity mismatches between the strands.

Examples of modified and chemically-modified siRNAs include siRNAs having a 5'-propylamine end, a 5'-phosphorylated end, a 3'-puromycin end, or a 3'-biotin end group.

Examples of modified and chemically-modified siRNAs include siRNAs having a 2'-fluoro substituted ribonucleotide, a 2'-OMe substituted ribonucleotide, a 2'-deoxy ribonucleotide, a 2'-amino substituted ribonucleotide, a 2'-thio substituted ribonucleotide.

Examples of modified and chemically-modified siRNAs include siRNAs having one or more 5-halouridines, 5-halocytidines, 5-methylcytidines, ribothymidines, 2-aminopurines, 2,6-diaminopurines, 4-thiouridines, or 5-aminoallyluridines.

Examples of modified and chemically-modified siRNAs include siRNAs having one or more phosphorothioate groups.

Examples of modified and chemically-modified siRNAs include siRNAs having one or more 2'-fluoro substituted ribonucleotides, 2'-fluorouridines, 2'-fluorocytidines, 2'-deoxyribonucleotides, 2'-deoxyadenosines, or 2'-deoxyguanosines.

Examples of modified and chemically-modified siRNAs include siRNAs having one or more phosphorothioate linkages.

Examples of modified and chemically-modified siRNAs include siRNAs having one or more alkylene diol linkages, oxy-alkylthio linkages, or oxycarbonyloxy linkages.

Examples of modified and chemically-modified siRNAs include siRNAs having one or more deoxyabasic groups,

inosines, N3-methyl-uridines, N6,N6-dimethyl-adenosines, pseudouridines, purine ribonucleosides, and ribavirins.

Examples of modified and chemically-modified siRNAs include siRNAs having one or more 3' or 5' inverted terminal groups.

Examples of modified and chemically-modified siRNAs include siRNAs having one or more 5-(2-amino)propyluridines, 5-bromouridines, adenosines, 8-bromo guanosines, 7-deaza-adenosines, or N6-methyl adenosine.

Methods for Modulating GST- π and Treating Malignant Tumor

Embodiments of this invention can provide RNAi molecules that can be used to down regulate or inhibit the expression of GST- π and/or GST- π proteins.

In some embodiments, a RNAi molecule of this invention can be used to down regulate or inhibit the expression of GST- π and/or GST- π proteins arising from GST- π haplotype polymorphisms that may be associated with a disease or condition such as malignant tumor.

Monitoring of GST- π protein or mRNA levels can be used to characterize gene silencing, and to determine the efficacy of compounds and compositions of this invention.

The RNAi molecules of this disclosure can be used individually, or in combination with other siRNAs for modulating the expression of one or more genes.

The RNAi molecules of this disclosure can be used individually, or in combination, or in conjunction with other known drugs for preventing or treating diseases, or ameliorating symptoms of conditions or disorders associated with GST- π , including malignant tumor.

The RNAi molecules of this invention can be used to modulate or inhibit the expression of GST- π in a sequence-specific manner.

The RNAi molecules of this disclosure can include a guide strand for which a series of contiguous nucleotides are at least partially complementary to a GST- π mRNA.

In certain aspects, malignant tumor may be treated by RNA interference using a RNAi molecule of this invention.

Treatment of malignant tumor may be characterized in suitable cell-based models, as well as ex vivo or in vivo animal models.

Treatment of malignant tumor may be characterized by determining the level of GST- π mRNA or the level of GST- π protein in cells of affected tissue.

Treatment of malignant tumor may be characterized by non-invasive medical scanning of an affected organ or tissue.

Embodiments of this invention may include methods for preventing, treating, or ameliorating the symptoms of a GST- π associated disease or condition in a subject in need thereof.

In some embodiments, methods for preventing, treating, or ameliorating the symptoms of malignant tumor in a subject can include administering to the subject a RNAi molecule of this invention to modulate the expression of a GST- π gene in the subject or organism.

In some embodiments, this invention contemplates methods for down regulating the expression of a GST- π gene in a cell or organism, by contacting the cell or organism with a RNAi molecule of this invention.

Embodiments of this invention encompass siRNA molecules of Tables 1-6 that are modified or chemically-modified according to the examples above.

RNA Interference

RNA interference (RNAi) refers to sequence-specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs). See, e.g., Zamore et al.,

Cell, 2000, Vol. 101, pp. 25-33; Fire et al., Nature, 1998, Vol. 391, pp. 806811; Sharp, Genes & Development, 1999, Vol. 13, pp. 139-141.

An RNAi response in cells can be triggered by a double stranded RNA (dsRNA), although the mechanism is not yet fully understood. Certain dsRNAs in cells can undergo the action of Dicer enzyme, a ribonuclease III enzyme. See, e.g., Zamore et al., Cell, 2000, Vol. 101, pp. 25-33; Hammond et al., Nature, 2000, Vol. 404, pp. 293-296. Dicer can process the dsRNA into shorter pieces of dsRNA, which are siRNAs.

In general, siRNAs can be from about 21 to about 23 nucleotides in length and include a base pair duplex region about 19 nucleotides in length.

RNAi involves an endonuclease complex known as the RNA induced silencing complex (RISC). An siRNA has an antisense or guide strand which enters the RISC complex and mediates cleavage of a single stranded RNA target having a sequence complementary to the antisense strand of the siRNA duplex. The other strand of the siRNA is the passenger strand. Cleavage of the target RNA takes place in the middle of the region complementary to the antisense strand of the siRNA duplex See, e.g., Elbashir et al., Genes & Development, 2001, Vol. 15, pp. 188-200.

As used herein, the term "sense strand" refers to a nucleotide sequence of a siRNA molecule that is partially or fully complementary to at least a portion of a corresponding antisense strand of the siRNA molecule. The sense strand of a siRNA molecule can include a nucleic acid sequence having homology with a target nucleic acid sequence.

As used herein, the term "antisense strand" refers to a nucleotide sequence of a siRNA molecule that is partially or fully complementary to at least a portion of a target nucleic acid sequence. The antisense strand of a siRNA molecule can include a nucleic acid sequence that is complementary to at least a portion of a corresponding sense strand of the siRNA molecule.

RNAi molecules can down regulate or knock down gene expression by mediating RNA interference in a sequence-specific manner. See, e.g., Zamore et al., Cell, 2000, Vol. 101, pp. 25-33; Elbashir et al., Nature, 2001, Vol. 411, pp. 494-498; Kreutzer et al., WO2000/044895; Zernicka-Goetz et al., WO2001/36646; Fire et al., WO1999/032619; Plaetinck et al., WO2000/01846; Mello et al., WO2001/029058.

As used herein, the terms "inhibit," "down-regulate," or "reduce" with respect to gene expression means that the expression of the gene, or the level of mRNA molecules encoding one or more proteins, or the activity of one or more of the encoded proteins is reduced below that observed in the absence of a RNAi molecule or siRNA of this invention. For example, the level of expression, level of mRNA, or level of encoded protein activity may be reduced by at least 1%, or at least 10%, or at least 20%, or at least 50%, or at least 90%, or more from that observed in the absence of a RNAi molecule or siRNA of this invention.

RNAi molecules can also be used to knock down viral gene expression, and therefore affect viral replication.

RNAi molecules can be made from separate polynucleotide strands: a sense strand or passenger strand, and an antisense strand or guide strand. The guide and passenger strands are at least partially complementary. The guide strand and passenger strand can form a duplex region having from about 15 to about 49 base pairs.

In some embodiments, the duplex region of a siRNA can have 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or 49 base pairs.

In certain embodiments, a RNAi molecule can be active in a RISC complex, with a length of duplex region active for RISC.

In additional embodiments, a RNAi molecule can be active as a Dicer substrate, to be converted to a RNAi molecule that can be active in a RISC complex.

In some aspects, a RNAi molecule can have complementary guide and passenger sequence portions at opposing ends of a long molecule, so that the molecule can form a duplex region with the complementary sequence portions, and the strands are linked at one end of the duplex region by either nucleotide or non-nucleotide linkers. For example, a hairpin arrangement, or a stem and loop arrangement. The linker interactions with the strands can be covalent bonds or non-covalent interactions.

A RNAi molecule of this disclosure may include a nucleotide, non-nucleotide, or mixed nucleotide/non-nucleotide linker that joins the sense region of the nucleic acid to the antisense region of the nucleic acid. A nucleotide linker can be a linker of 2 nucleotides in length, for example about 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length. The nucleotide linker can be a nucleic acid aptamer. By "aptamer" or "nucleic acid aptamer" as used herein refers to a nucleic acid molecule that binds specifically to a target molecule wherein the nucleic acid molecule has sequence that includes a sequence recognized by the target molecule in its natural setting. Alternately, an aptamer can be a nucleic acid molecule that binds to a target molecule, where the target molecule does not naturally bind to a nucleic acid. For example, the aptamer can be used to bind to a ligand-binding domain of a protein, thereby preventing interaction of the naturally occurring ligand with the protein. See, e.g., Gold et al., Annu Rev Biochem, 1995, Vol. 64, pp. 763-797; Brody et al., J. Biotechnol., 2000, Vol. 74, pp. 5-13; Hermann et al., Science, 2000, Vol. 287, pp. 820-825.

Examples of a non-nucleotide linker include an abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, polyhydrocarbon, or other polymeric compounds, for example polyethylene glycols such as those having from 2 to 100 ethylene glycol units. Some examples are described in Seela et al., Nucleic Acids Research, 1987, Vol. 15, pp. 3113-3129; Cload et al., J. Am. Chem. Soc., 1991, Vol. 113, pp. 6324-6326; Jaeschke et al., Tetrahedron Lett., 1993, Vol. 34, pp. 301; Arnold et al., WO1989/002439; Usman et al., WO1995/006731; Dudycz et al., WO1995/011910, and Ferentz et al., J. Am. Chem. Soc., 1991, Vol. 113, pp. 4000-4002.

A RNAi molecule can have one or more overhangs from the duplex region. The overhangs, which are non-base-paired, single strand regions, can be from one to eight nucleotides in length, or longer. An overhang can be a 3'-end overhang, wherein the 3'-end of a strand has a single strand region of from one to eight nucleotides. An overhang can be a 5'-end overhang, wherein the 5'-end of a strand has a single strand region of from one to eight nucleotides.

The overhangs of a RNAi molecule can have the same length, or can be different lengths.

A RNAi molecule can have one or more blunt ends, in which the duplex region ends with no overhang, and the strands are base paired to the end of the duplex region.

A RNAi molecule of this disclosure can have one or more blunt ends, or can have one or more overhangs, or can have a combination of a blunt end and an overhang end.

A 5'-end of a strand of a RNAi molecule may be in a blunt end, or can be in an overhang. A 3'-end of a strand of a RNAi molecule may be in a blunt end, or can be in an overhang.

A 5'-end of a strand of a RNAi molecule may be in a blunt end, while the 3'-end is in an overhang. A 3'-end of a strand of a RNAi molecule may be in a blunt end, while the 5'-end is in an overhang.

In some embodiments, both ends of a RNAi molecule are blunt ends.

In additional embodiments, both ends of a RNAi molecule have an overhang.

The overhangs at the 5'- and 3'-ends may be of different lengths.

In certain embodiments, a RNAi molecule may have a blunt end where the 5'-end of the antisense strand and the 3'-end of the sense strand do not have any overhanging nucleotides.

In further embodiments, a RNAi molecule may have a blunt end where the 3'-end of the antisense strand and the 5'-end of the sense strand do not have any overhanging nucleotides.

A RNAi molecule may have mismatches in base pairing in the duplex region.

Any nucleotide in an overhang of a RNAi molecule can be a deoxyribonucleotide, or a ribonucleotide.

One or more deoxyribonucleotides may be at the 5'-end, where the 3'-end of the other strand of the RNAi molecule may not have an overhang, or may not have a deoxyribonucleotide overhang.

One or more deoxyribonucleotides may be at the 3'-end, where the 5'-end of the other strand of the RNAi molecule may not have an overhang, or may not have a deoxyribonucleotide overhang.

In some embodiments, one or more, or all of the overhang nucleotides of a RNAi molecule may be 2'-deoxyribonucleotides.

Dicer Substrate RNAi Molecules

In some aspects, a RNAi molecule can be of a length suitable as a Dicer substrate, which can be processed to produce a RISC active RNAi molecule. See, e.g., Rossi et al., US2005/0244858.

A double stranded RNA (dsRNA) that is a Dicer substrate can be of a length sufficient such that it is processed by Dicer to produce an active RNAi molecule, and may further include one or more of the following properties: (i) the Dicer substrate dsRNA can be asymmetric, for example, having a 3' overhang on the antisense strand, and (ii) the Dicer substrate dsRNA can have a modified 3' end on the sense strand to direct orientation of Dicer binding and processing of the dsRNA to an active RNAi molecule.

In certain embodiments, the longest strand in a Dicer substrate dsRNA may be 24-30 nucleotides in length.

A Dicer substrate dsRNA can be symmetric or asymmetric.

In some embodiments, a Dicer substrate dsRNA can have a sense strand of 22-28 nucleotides and an antisense strand of 24-30 nucleotides.

In certain embodiments, a Dicer substrate dsRNA may have an overhang on the 3' end of the antisense strand.

In further embodiments, a Dicer substrate dsRNA may have a sense strand 25 nucleotides in length, and an antisense strand 27 nucleotides in length, with a 2 base 3'-overhang. The overhang may be 1, 2 or 3 nucleotides in length. The sense strand may also have a 5' phosphate.

An asymmetric Dicer substrate dsRNA may have two deoxyribonucleotides at the 3'-end of the sense strand in place of two of the ribonucleotides.

The sense strand of a Dicer substrate dsRNA may be from about 22 to about 30, or from about 22 to about 28; or from about 24 to about 30; or from about 25 to about 30; or from

about 26 to about 30; or from about 26 and 29; or from about 27 to about 28 nucleotides in length.

The sense strand of a Dicer substrate dsRNA may be 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length.

In certain embodiments, a Dicer substrate dsRNA may have sense and antisense strands that are at least about 25 nucleotides in length, and no longer than about 30 nucleotides in length.

In certain embodiments, a Dicer substrate dsRNA may have sense and antisense strands that are 26 to 29 nucleotides in length.

In certain embodiments, a Dicer substrate dsRNA may have sense and antisense strands that are 27 nucleotides in length.

The sense and antisense strands of a Dicer substrate dsRNA may be the same length as in being blunt ended, or different lengths as in having overhangs, or may have a blunt end and an overhang.

A Dicer substrate dsRNA may have a duplex region of 19, 20, 21, 22, 23, 24, 25, 26 or 27 nucleotides in length.

The antisense strand of a Dicer substrate dsRNA may have any sequence that anneals to at least a portion of the sequence of the sense strand under biological conditions, such as within the cytoplasm of a eukaryotic cell.

A Dicer substrate with a sense and an antisense strand can be linked by a third structure, such as a linker group or a linker oligonucleotide. The linker connects the two strands of the dsRNA, for example, so that a hairpin is formed upon annealing.

The sense and antisense strands of a Dicer substrate are in general complementary, but may have mismatches in base pairing.

In some embodiments, a Dicer substrate dsRNA can be asymmetric such that the sense strand has 22-28 nucleotides and the antisense strand has 24-30 nucleotides.

A region of one of the strands, particularly the antisense strand, of the Dicer substrate dsRNA may have a sequence length of at least 19 nucleotides, wherein these nucleotides are in the 21-nucleotide region adjacent to the 3' end of the antisense strand and are sufficiently complementary to a nucleotide sequence of the RNA produced from the target gene.

An antisense strand of a Dicer substrate dsRNA can have from 1 to 9 ribonucleotides on the 5'-end, to give a length of 22-28 nucleotides. When the antisense strand has a length of 21 nucleotides, then 1-7 ribonucleotides, or 2-5 ribonucleotides, or 4 ribonucleotides may be added on the 3'-end. The added ribonucleotides may have any sequence.

A sense strand of a Dicer substrate dsRNA may have 24-30 nucleotides. The sense strand may be substantially complementary with the antisense strand to anneal to the antisense strand under biological conditions.

Methods for Using RNAi Molecules

The nucleic acid molecules and RNAi molecules of this invention may be delivered to a cell or tissue by direct application of the molecules, or with the molecules combined with a carrier or a diluent.

The nucleic acid molecules and RNAi molecules of this invention can be delivered or administered to a cell, tissue, organ, or subject by direct application of the molecules with a carrier or diluent, or any other delivery vehicle that acts to assist, promote or facilitate entry into a cell, for example, viral sequences, viral material, or lipid or liposome formulations.

The nucleic acid molecules and RNAi molecules of this invention can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or

tissues. The nucleic acid or nucleic acid complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through direct dermal application, transdermal application, or injection.

Delivery systems may include, for example, aqueous and nonaqueous gels, creams, emulsions, microemulsions, liposomes, ointments, aqueous and nonaqueous solutions, lotions, aerosols, hydrocarbon bases and powders, and can contain excipients such as solubilizers and permeation enhancers.

Compositions and methods of this disclosure can include an expression vector that includes a nucleic acid sequence encoding at least one RNAi molecule of this invention in a manner that allows expression of the nucleic acid molecule.

The nucleic acid molecules and RNAi molecules of this invention can be expressed from transcription units inserted into DNA or RNA vectors. Recombinant vectors can be DNA plasmids or viral vectors. Viral vectors can be used that provide for transient expression of nucleic acid molecules.

For example, the vector may contain sequences encoding both strands of a RNAi molecule of a duplex, or a single nucleic acid molecule that is self-complementary and thus forms a RNAi molecule. An expression vector may include a nucleic acid sequence encoding two or more nucleic acid molecules.

A nucleic acid molecule may be expressed within cells from eukaryotic promoters. Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector.

In some aspects, a viral construct can be used to introduce an expression construct into a cell, for transcription of a dsRNA construct encoded by the expression construct.

Lipid formulations can be administered to animals by intravenous, intramuscular, or intraperitoneal injection, or orally or by inhalation or other methods as are known in the art.

Pharmaceutically acceptable formulations for administering oligonucleotides are known and can be used.

Example Protocol for In Vitro Knockdown

One day before the transfection, cells were plated in a 96-well plate at 2×10^3 cells per well with 100 μ l of DMEM (HyClone Cat. #SH30243.01) containing 10% FBS and culture in a 37° C. incubator containing a humidified atmosphere of 5% CO₂ in air. Before transfection, medium was changed to 90 μ l of Opti-MEM I Reduced Serum Medium (Life Technologies Cat. #31985-070) containing 2% FBS. Then, 0.2 μ l of Lipofectamine RNAiMax (Life Technologies Cat. #13778-100) was mixed with 4.8 μ l of Opti-MEM I for 5 minutes at room temperature. Next, 1 μ l of siRNA was mixed with 4 μ l of Opti-MEM I and combined with the LF2000 solution, and mixed gently, without vortex. After 5 minutes at room temperature, the mixture was incubated for an additional 10 minutes at room temperature to allow the RNA-RNAiMax complexes to form. Further, the 10 μ l of RNA-RNAiMax complexes was added to a well, and the plate was shaken gently by hand. The cells were incubated in a 37° C. incubator containing a humidified atmosphere of 5% CO₂ in air for 2 hours. The medium was changed to fresh Opti-MEM I Reduced Serum Medium containing 2% FBS. 24 hours after transfection, the cells were washed with ice-cold PBS once. The cells were lysed with 50 μ l of Cell-to-Ct Lysis Buffer (Life Technologies Cat. #4391851 C) for 5-30 minutes at room temperature. 5 μ l of Stop Solution was added, and it was incubated for 2 minutes at room temperature. The mRNA level was measured by RT-qPCR with TAQMAN immediately. Samples could be frozen at -80° C. and assayed at a later time.

Example Protocol for Serum Stability

0.2 mg/ml siRNA was incubated with 10% human serum at 37° C. At certain time points (0, 5, 15 and 30 min), 200

μ l of sample was aliquoted and extracted with 200 μ l extraction solvent (Chloroform:phenol:Isoamyl alcohol=24:25:1). The sample was vortexed and centrifuged at 13,000 rpm for 10 min at RT, then the top layer solution was transferred and filtered it with 0.45 μ m filter. The filtrate was transferred into a 300 μ l HPLC injection vial. For LCMS, the Mobile phase was MPA: 100 mM HFIP+7 mM TEA in H₂O, MPB: 50% Methanol+50% Acetonitrile. The Column: Waters Acquity OST 2.1 \times 50 mm, 1.7 μ m.

EXAMPLES

Example 1

siRNAs of this invention targeted to GST- π were found to be active for gene silencing *in vitro*. The dose-dependent activities of GST- π siRNAs for gene knockdown were found to exhibit an IC₅₀ below about 250 picomolar (pM), and as low as 1 pM.

In vitro transfection was performed in an A549 cell line to determine siRNA knockdown efficacy. Dose dependent knockdown for GST- π mRNA was observed with siRNAs of Table 1, as shown in Table 7.

TABLE 7

Dose dependent knockdown for GST- π mRNA in an A549 cell line	
siRNA structure	IC ₅₀ (pM)
A9 (SEQ ID NOs: 25 and 90)	24
B2 (SEQ ID NOs: 52 and 117)	121
B3 (SEQ ID NOs: 53 and 118)	235
B4 (SEQ ID NOs: 54 and 119)	229
B13 (SEQ ID NOs: 50 and 115)	17
BU2 (SEQ ID NOs: 61 and 126)	31

As shown in Table 7, the activities of GST- π siRNAs of Table 1 were in the range 17-235 pM, which is suitable for many uses, including as a drug agent to be used *in vivo*.

Example 2

The structure of GST- π siRNAs of this invention having deoxynucleotides located in the seed region of the antisense strand of the siRNA provided unexpectedly and advantageously increased gene knockdown activity *in vitro*.

In vitro transfection was performed in an A549 cell line to determine knockdown efficacy for GST- π siRNAs based on structure BU2' (SEQ ID NOs:131 and 157). Dose dependent knockdown of GST- π mRNA was observed with GST- π siRNAs based on structure BU2' as shown in Table 8.

TABLE 8

Dose dependent knockdown of GST- π mRNA in an A549 cell line for GST- π siRNAs based on structure BU2'	
GST- π siRNA structure	IC ₅₀ (pM)
BU2 with no deoxynucleotides in the duplex region (SEQ ID NOs: 61 and 126)	31
BU2 with deoxynucleotides in positions 3, 5, and 7 of the seed region antisense strand (SEQ ID NOs: 139 and 165)	5
BU2 with deoxynucleotides in positions 4, 6, and 8 of the seed region antisense strand (SEQ ID NOs: 141 and 167)	8
BU2 with deoxynucleotides in positions 4, 6, and 8 of the seed region antisense strand (SEQ ID NOs: 156 and 182)	5

As shown in Table 8, the activities of GST- π siRNAs based on structure BU2' having three deoxynucleotides in the seed region of the antisense strand were surprisingly and unexpectedly increased by up to 6-fold, as compared to a GST- π siRNA without deoxynucleotides in the duplex region.

These data show that GST- π siRNAs having a structure with three deoxynucleotides located at positions 3, 5 and 7, or at positions 4, 6 and 8 in the seed region of the antisense strand provided surprisingly increased gene knockdown activity as compared to a GST- π siRNA without deoxynucleotides in the duplex region.

The activities shown in Table 8 for GST- π siRNAs having three deoxynucleotides in the seed region of the antisense strand were in the range 5 to 8 pM, which is exceptionally suitable for many uses, including as a drug agent to be used in vivo.

Example 3

The structure of GST- π siRNAs of this invention having deoxynucleotides located in the seed region of the antisense strand of the siRNA provided unexpectedly and advantageously increased gene knockdown activity in vitro.

In vitro transfection was performed in an A549 cell line to determine knockdown efficacy for GST- π siRNAs based on structure A9' (SEQ ID NOs:183 and 195). Dose dependent knockdown of GST- π mRNA was observed with the GST- π siRNAs based on structure A9', as shown in Table 9.

TABLE 9

Dose dependent knockdown of GST- π mRNA in an A549 cell line for GST- π siRNAs based on structure structure A9'	
GST- π siRNA structure	IC50 (pM)
A9 with no deoxynucleotides in the duplex region (SEQ ID NOs: 25 and 90)	24
A9 with deoxynucleotides in positions 4, 6, and 8 of the seed region antisense strand (SEQ ID NOs: 193 and 205)	1
A9 with deoxynucleotides in positions 1, 3, 5, and 7 of the seed region antisense strand (SEQ ID NOs: 190 and 202)	5
A9 with deoxynucleotides in positions 3-8 of the seed region antisense strand (SEQ ID NOs: 187 and 199)	6
A9 with deoxynucleotides in positions 5-8 of the seed region antisense strand (SEQ ID NOs: 189 and 201)	7
A9 with deoxynucleotides in positions 3, 5, and 7 of the seed region antisense strand (SEQ ID NOs: 191 and 203)	15

As shown in Table 9, the activities of GST- π siRNAs based on structure A9' having three to six deoxynucleotides in the seed region of the antisense strand were surprisingly increased by up to 24-fold, as compared to a GST- π siRNA without deoxynucleotides in the duplex region.

These data show that GST- π siRNAs having a structure with three to six deoxynucleotides located at positions 4, 6 and 8, or at positions 1, 3, 5 and 7, or at positions 3-8, or at positions 5-8, or at positions 3, 5 and 7 in the seed region of the antisense strand provided unexpectedly increased gene knockdown activity as compared to a GST- π siRNA without deoxynucleotides in the duplex region.

The activity shown in Table 9 for GST- π siRNAs having three to six deoxynucleotides in the seed region of the antisense strand was in the range 1 to 15 pM, which is exceptionally suitable for many uses, including as a drug agent to be used in vivo.

Example 4

The structure of GST- π siRNAs having deoxynucleotides located in the seed region of the antisense strand of the siRNA provided unexpectedly and advantageously increased gene knockdown activity in vitro.

In vitro transfection was performed in an A549 cell line to determine knockdown efficacy for GST- π siRNAs based on structure B13' (SEQ ID NOs:207 and 222). Dose dependent knockdown of GST- π mRNA was observed with the GST- π siRNAs based on structure B13', as shown in Table 10.

TABLE 10

Dose dependent knockdown of GST- π mRNA in an A549 cell line for GST- π siRNAs based on structure B13'	
GST- π siRNA structure	IC50 (pM)
B13 with no deoxynucleotides in the duplex region (SEQ ID NOs: 50 and 115)	17
B13 with deoxynucleotides in positions 4, 6, and 8 of the seed region antisense strand (SEQ ID NOs: 217 and 232)	11

As shown in Table 10, the activity of a GST- π siRNA based on structure B13' having three deoxynucleotides in the seed region of the antisense strand was unexpectedly increased, as compared to a GST- π siRNA without deoxynucleotides in the duplex region.

These data show that GST- π siRNAs having a structure with three deoxynucleotides located at positions 4, 6 and 8 in the seed region of the antisense strand provided unexpectedly increased gene knockdown activity as compared to a GST- π siRNA without deoxynucleotides in the duplex region.

The activity shown in Table 10 for GST- π siRNAs having three deoxynucleotides in the seed region of the antisense strand was in the picomolar range at 11 pM, which is exceptionally suitable for many uses, including as a drug agent to be used in vivo.

Example 5

The structure of GST- π siRNAs having deoxynucleotides located in the seed region of the antisense strand of the siRNA provided unexpectedly and advantageously increased gene knockdown activity in vitro.

In vitro transfection was performed in an A549 cell line to determine knockdown efficacy for GST- π siRNAs based on structure B4' (SEQ ID NOs:261 and 273). Dose dependent knockdown of GST- π mRNA was observed with the GST- π siRNAs based on structure B4', as shown in Table 11.

TABLE 11

Dose dependent knockdown of GST- π mRNA in an A549 cell line for GST- π siRNAs based on structure B4'	
GST- π siRNA structure	IC50 (pM)
B4 with no deoxynucleotides in the duplex region (SEQ ID NOs: 54 and 119)	229
B4 with deoxynucleotides in positions 3-8 of the seed region antisense strand (SEQ ID NOs: 265 and 277)	113

As shown in Table 11, the activities of GST- π siRNAs based on structure B4' having six deoxynucleotides in the seed region of the antisense strand were unexpectedly

increased by more than two-fold, as compared to a GST- π siRNA without deoxynucleotides in the duplex region.

These data show that GST- π siRNAs having a structure with six deoxynucleotides located at positions 3-8 in the seed region of the antisense strand provided surprisingly increased gene knockdown activity as compared to a GST- π siRNA without deoxynucleotides in the duplex region.

The activity shown in Table 11 for a GST- π siRNA having six deoxynucleotides in the seed region of the antisense strand was in the picomolar range at 113 pM, which is exceptionally suitable for many uses, including as a drug agent to be used in vivo.

Example 6

The structure of GST- π siRNAs having deoxynucleotides located in the seed region of the antisense strand of the siRNA provided unexpectedly and advantageously increased gene knockdown activity in vitro.

In vitro transfection was performed in an A549 cell line to determine knockdown efficacy for GST- π siRNAs based on structure B2' (SEQ ID NOs:237 and 249). Dose dependent knockdown of GST- π mRNA was observed with the GST- π siRNAs based on structure B2', as shown in Table 12.

TABLE 12

Dose dependent knockdown of GST- π mRNA in an A549 cell line for GST- π siRNAs based on structure B2'	
GST- π siRNA structure	IC50 (pM)
B2 with no deoxynucleotides in the duplex region (SEQ ID NOs: 52 and 117)	121
B2 with deoxynucleotides in positions 5-8 of the seed region antisense strand (SEQ ID NOs: 243 and 255)	30
B2 with deoxynucleotides in positions 1, 3, 5, and 7 of the seed region antisense strand (SEQ ID NOs: 244 and 256)	50
B2 with deoxynucleotides in positions 3, 5, and 7 of the seed region antisense strand (SEQ ID NOs: 245 and 257)	100

As shown in Table 12, the activities of GST- π siRNAs based on structure B2' having three to four deoxynucleotides in the seed region of the antisense strand were surprisingly increased by up to 4-fold, as compared to a GST- π siRNA without deoxynucleotides in the duplex region.

These data show that GST- π siRNAs having a structure with three to four deoxynucleotides located at positions 5-8, or at positions 1, 3, 5 and 7, or at positions 3, 5 and 7 in the seed region of the antisense strand provided unexpectedly increased gene knockdown activity as compared to a GST- π siRNA without deoxynucleotides in the duplex region.

The activities shown in Table 12 for GST- π siRNAs having three to four deoxynucleotides in the seed region of the antisense strand were in the range 30-100 pM, which is exceptionally suitable for many uses, including as a drug agent to be used in vivo.

Example 7

The structure of GST- π siRNAs containing one or more 2'-deoxy-2'-fluoro substituted nucleotides provided unexpectedly increased gene knockdown activity in vitro.

In vitro transfection was performed in an A549 cell line to determine knockdown efficacy for GST- π siRNAs based on structure BU2' (SEQ ID NOs:131 and 157). Dose dependent knockdown of GST- π mRNA was observed with the GST- π siRNAs based on structure BU2', as shown in Table 13.

TABLE 13

Dose dependent knockdown of GST- π mRNA in an A549 cell line for GST- π siRNAs based on structure BU2'	
GST- π siRNA structure	IC50 (pM)
BU2 with no 2'-F deoxynucleotides (SEQ ID NOs: 61 and 126)	31
BU2 with seven 2'-F deoxynucleotides, one in position 1 at the 3' end of the antisense strand (SEQ ID NOs: 148 and 174)	3
BU2 with four 2'-F deoxynucleotides, one in position 1 at the 3' end of the antisense strand (SEQ ID NOs: 147 and 173)	11
BU2 with one 2'-F deoxynucleotide in position 1 at the 3' end of the antisense strand (SEQ ID NOs: 144 and 170)	13

As shown in Table 13, the activities of GST- π siRNAs based on structure BU2' having one or more 2'-F deoxynucleotides were surprisingly increased by up to 10-fold, as compared to a GST- π siRNA without 2'-F deoxynucleotides.

These data show that GST- π siRNAs having a structure with one or more 2'-F deoxynucleotides provided unexpectedly increased gene knockdown activity as compared to a GST- π siRNA without a 2'-F deoxynucleotide.

The activities shown in Table 13 for GST- π siRNAs having one or more 2'-F deoxynucleotides were in the range 3 to 13 pM, which is exceptionally suitable for many uses, including as a drug agent to be used in vivo.

Example 8

The structure of GST- π siRNAs containing one or more 2'-deoxy-2'-fluoro substituted nucleotides provided unexpectedly increased gene knockdown activity in vitro.

In vitro transfection was performed in an A549 cell line to determine knockdown efficacy for GST- π siRNAs based on structure B13' (SEQ ID NOs:207 and 222). Dose dependent knockdown of GST- π mRNA was observed with the GST- π siRNAs based on structure B 13', as shown in Table 14.

TABLE 14

Dose dependent knockdown of GST- π mRNA in an A549 cell line for GST- π siRNAs based on structure B13'	
GST- π siRNA structure	IC50 (pM)
B13 with no 2'-F deoxynucleotides (SEQ ID NOs: 50 and 115)	17
B13 with three 2'-F deoxynucleotides located in non-overhang positions (SEQ ID NOs: 219 and 234)	6

As shown in Table 14, the activity of a GST- π siRNA based on structure B13' having three 2'-F deoxynucleotides located in non-overhang positions was surprisingly increased by about 3-fold, as compared to a GST- π siRNA without 2'-F deoxynucleotides.

These data show that GST- π siRNAs having a structure with one or more 2'-F deoxynucleotides provided unexpectedly increased gene knockdown activity as compared to a GST- π siRNA without a 2'-F deoxynucleotide.

The activity shown in Table 14 for GST- π siRNAs having one or more 2'-F deoxynucleotides was in the picomolar range at 6 pM, which is exceptionally suitable for many uses, including as a drug agent to be used in vivo.

Example 9: Orthotopic A549 Lung Cancer Mouse Model

The GST- π siRNAs of this invention can exhibit profound reduction of orthotopic lung cancer tumors in vivo. In this

example, a GST- π siRNA provided gene knockdown potency in vivo when administered in a liposomal formulation to the orthotopic lung cancer tumors in athymic nude mice.

In general, an orthotopic tumor model can exhibit direct clinical relevance for drug efficacy and potency, as well as improved predictive ability. In the orthotopic tumor model, tumor cells are implanted directly into the same kind of organ from which the cells originated.

The anti-tumor efficacy of the siRNA formulation against human lung cancer A549 was evaluated by comparing the final primary tumor weights measured at necropsy for the treatment group and the vehicle control group.

FIG. 1 shows orthotopic lung cancer tumor inhibition in vivo for a GST- π siRNA based on structure BU2 (SEQ ID NOs:61 and 126). An orthotopic A549 lung cancer mouse model was utilized with a relatively low dose at 2 mg/kg of the siRNA targeted to GST- π .

The GST- π siRNA showed significant and unexpectedly advantageous lung tumor inhibition efficacy in this six-week study. As shown in FIG. 1, after 43 days, the GST- π siRNA showed markedly advantageous tumor inhibition efficacy, with final tumor average weights significantly reduced by 2.8-fold as compared to control.

For this study, male NCr nu/nu mice, 5-6 weeks old, were used. The experimental animals were maintained in a HEPA filtered environment during the experimental period. The siRNA formulations were stored at 4° C. before use, and warmed to room temperature 10 minutes prior to injection in mouse.

For this A549 human lung cancer orthotopic model, on the day of surgical orthotopic implantation (SOI), the stock tumors were harvested from the subcutaneous site of animals bearing A549 tumor xenograft and placed in RPMI-1640 medium. Necrotic tissues were removed and viable tissues were cut into 1.5-2 mm³ pieces. The animals were anesthetized with isoflurane inhalation and the surgical area was sterilized with iodine and alcohol. A transverse incision approximately 1.5 cm long was made in the left chest wall of the mouse using a pair of surgical scissors. An intercostal incision was made between the third and the fourth rib and the left lung was exposed. One A549 tumor fragment was transplanted to the surface of the lung with an 8-0 surgical suture (nylon). The chest wall was closed with a 6-0 surgical suture (silk). The lung was re-inflated by intrathoracic puncture using a 3 cc syringe with a 25 G \times 1½ needle to draw out the remaining air in the chest cavity. The chest wall was closed with a 6-0 surgical silk suture. All procedures of the operation described above were performed with a 7 \times magnification microscope under HEPA filtered laminar flow hoods.

Three days after tumor implantation, the model tumor-bearing mice were randomly divided into groups of ten mice per group. For the group of interest, treatment of the ten mice was initiated three days after tumor implantation.

For the group of interest, the formulation was (Ionizable lipid:cholesterol:DOPE:DOPC:DPPE-PEG-2K:D SPE-PEG-2K), a liposomal composition. The liposomes encapsulated the GST- π siRNA.

For the study endpoint, the experimental mice were sacrificed forty-two days after treatment initiation. Primary tumors were excised and weighed on an electronic balance for subsequent analysis.

For an estimation of compound toxicity, the mean body weight of the mice in the treated and control groups was

maintained within the normal range during the entire experimental period. Other symptoms of toxicity were not observed in the mice.

Example 10

The GST- π siRNAs of this invention exhibited profound reduction of cancer xenograft tumors in vivo. The GST- π siRNAs provided gene knockdown potency in vivo when administered in a liposomal formulation to the cancer xenograft tumors.

FIG. 2 shows tumor inhibition efficacy for a GST- π siRNA (SEQ ID Nos:156 and 182). A cancer xenograft model was utilized with a relatively low dose at 0.75 mg/kg of siRNA targeted to GST- π .

The GST- π siRNA showed significant and unexpectedly advantageous tumor inhibition efficacy within a few days after administration. After 36 days, the GST- π siRNA showed markedly advantageous tumor inhibition efficacy, with tumor volume reduced by 2-fold as compared to control.

As shown in FIG. 3, the GST- π siRNA demonstrated significant and unexpectedly advantageous tumor inhibition efficacy at the endpoint day. In particular, tumor weight was reduced by more than 2-fold.

The GST- π siRNA was administered in two injections (day 1 and 15) of a liposomal formulation having the composition (Ionizable lipid:Cholesterol:DOPE:DOPC:DPPE-PEG-2K) (25:30:20:20:5).

For the cancer xenograft model, an A549 cell line was obtained from ATCC. The cells were maintained in culture medium supplemented with 10% Fetal Bovine Serum and 100 U/ml penicillin and 100 μ g/ml streptomycin. Cells were split 48 hrs before inoculation so that cells were in log phase growth when harvested. Cells were lightly trypsinized with trypsin-EDTA and harvested from tissue culture. The number of viable cells was counted and determined in a hemocytometer in the presence of trypan blue (only viable cells are counted). The cells were resuspended to a concentration of 5 \times 10⁷/ml in media without serum. Then the cell suspension was mixed well with ice thawed BD matrigel at 1:1 ratio for injection.

Mice were Charles River Laboratory Athymic Nude (nu/nu) Female Mice, immuno-compromised, 6-8 weeks old, 7-8 mice per group.

For tumor model preparation, each mouse was inoculated subcutaneously in the right flank with 0.1 ml an inoculum of 2.5 \times 10⁶ of A549 cells using a 25 G needle and syringe, one inoculum per mouse. Mice were not anesthetized for inoculation.

For tumor volume measurements and randomization, tumor size was measured to the nearest 0.1 mm. Tumor volumes were calculated using the formula: Tumor volume=length \times width²/2. Once the established tumors reached approximately 120-175 mm³, average tumor volume was about 150 mm³, the mice were assigned into the various vehicle control and treatment groups such that the mean tumor volumes in the treated groups were within 10% of the mean tumor volume in the vehicle control group, ideally, the CV % of tumor volume was less than 25%. On the same day, test articles and control vehicle were administered according to the dosing regimen. Tumor volumes were monitored three times for week 1, twice for the rest of weeks, including the day of study termination.

For dosage administration, on the dosing day, the test articles were taken out from -80° C. freezer and thawed on ice. Before applied to syringes, the bottle containing formu-

lation was reverted by hands for a few times. All test articles were dosed at 0.75 mg/kg by IV, q2w×2, at 10 ml/kg.

For body weight, mice were weighed to the nearest 0.1 g. Body weights were monitored and recorded daily within 7 days post dosing for first dose. Body weights were monitored and recorded twice for weeks, for the rest of weeks, including the day of study termination.

For tumors collection, on 28 days post first dosing, tumor volume was measured, and tumor was dissected for weight measurement, and stored for PD biomarker study. Tumor weight was recorded.

Example 11

The GST- π siRNAs of this invention demonstrated increased cancer cell death by apoptosis of cancer cells in vitro. The GST- π siRNAs provided GST- π knockdown, which resulted in upregulation of PUMA, a biomarker for apoptosis and associated with loss in cell viability.

GST- π siRNA SEQ ID NOs:156 and 182, which contained a combination of deoxynucleotides in the seed region, a 2'-F substituted deoxynucleotide, and 2'-OMe substituted ribonucleotides, provided unexpectedly increased apoptosis of cancer cells.

The level of expression of PUMA for GST- π siRNA SEQ ID NOs:156 and 182 was measured as shown in FIG. 4. In FIG. 4, the expression of PUMA was greatly increased from 2-4 days after transfection of the GST- π siRNA.

These data show that the structure of GST- π siRNAs containing a combination of deoxynucleotides in the seed region, a 2'-F substituted deoxynucleotide, and 2'-OMe substituted ribonucleotides provided unexpectedly increased apoptosis of cancer cells.

The protocol for the PUMA biomarker was as follows. One day before transfection, cells were plated in a 96-well plate at 2×10^3 cells per well with 100 μ l of DMEM (HyClone Cat. #SH30243.01) containing 10% FBS and cultured in a 37° C. incubator containing a humidified atmosphere of 5% CO₂ in air. Next day, before transfection the medium was replaced with 90 μ l of Opti-MEM I Reduced Serum Medium (Life Technologies Cat. #31985-070) containing 2% FBS. Then, 0.2 μ l of Lipofectamine RNAiMAX (Life Technologies Cat. #13778-100) were mixed with 4.8 μ l of Opti-MEM I for 5 minutes at room temperature. 1 μ l of the GST- π siRNA (stock conc. 1 μ M) was mixed with 4 μ l of Opti-MEM I and combined with the RNAiMAX solution and then mixed gently. The mixture was incubated for 10 minutes at room temperature to allow the RNA-RNAiMAX complexes to form. 10 μ l of RNA-RNAiMAX complexes were added per well, to final concentration of the siRNA 10 nM. The cells were incubated for 2 hours and medium changed to fresh Opti-MEM I Reduced Serum Medium containing 2% FBS. For 1, 2, 3, 4, and 6 days post transfection, the cells were washed with ice-cold PBS once and then lysed with 50 μ l of Cell-to-Ct Lysis Buffer (Life Technologies Cat. #4391851 C) for 5-30 minutes at room temperature. 5 μ l of Stop Solution was added and incubated for 2 minutes at room temperature. PUMA (BBC3, Cat#Hs00248075, Life Technologies) mRNA levels were measured by qPCR with TAQMAN.

Example 12

The GST- π siRNAs of this invention can exhibit profound reduction of cancer xenograft tumors in vivo. The GST- π

siRNAs can provide gene knockdown potency in vivo when administered in a liposomal formulation to the cancer xenograft tumors.

FIG. 5 shows tumor inhibition efficacy for a GST- π siRNA (SEQ ID NOs:61 and 126). Dose dependent knockdown of GST- π mRNA was observed in vivo with the siRNA targeted to GST- π . A cancer xenograft model was utilized with a siRNA targeted to GST- π .

The GST- π siRNA showed significant and unexpectedly advantageous tumor inhibition efficacy within a few days after administration. As shown in FIG. 5, treatment with a GST- π siRNA resulted in significant reduction of GST- π mRNA expression 4 days after injection in a lipid formulation. At the higher dose of 4 mg/kg, significant reduction of about 40% was detected 24 hours after injection.

The GST- π siRNA was administered in a single injection of 10 mL/kg of a liposomal formulation having the composition (Ionizable lipid:Cholesterol:DOPE:DOPC:DPPE-PEG-2K) (25:30:20:20:5).

For the cancer xenograft model, an A549 cell line was obtained from ATCC. The cells were maintained in RPMI-1640 supplemented with 10% Fetal Bovine Serum and 100 U/ml penicillin and 100 μ g/ml streptomycin. Cells were split 48 hrs before inoculation so that cells were in log phase growth when harvested. Cells were lightly trypsinized with trypsin-EDTA and harvested from tissue culture. The number of viable cells was counted and determined in a hemocytometer in the presence of trypan blue (only viable cells are counted). The cells were resuspended to a concentration of 4×10^7 /ml in RPMI media without serum. Then the cell suspension was mixed well with ice thawed BD matrigel at 1:1 ratio for injection.

Mice were Charles River Laboratory Athymic Nude (nu/nu) Female Mice, immuno-compromised, 6-8 weeks old, 3 mice per group.

For tumor model preparation, each mouse was inoculated subcutaneously in the right flank with 0.1 ml an inoculum of 2×10^6 of A549 cells using a 25 G needle and syringe, one inoculum per mouse. Mice were not anesthetized for inoculation.

For tumor volume measurements and randomization, tumor size was measured to the nearest 0.1 mm. Tumor volumes were calculated using the formula: Tumor volume=length×width²/2. Tumor volumes were monitored twice a week. Once the established tumors reached approximately 350-600 mm³, the mice were assigned into groups with varied time points. On the same day, test articles were administered according to the dosing regimen.

For dosage administration, on the day when the established tumors reached approximately 350-600 mm³, the test articles were taken out from 4° C. fridge. Before being applied to syringes, the bottle containing formulation was reverted by hand for a few times to make a homogeneous solution.

For body weight, mice were weighed to the nearest 0.1 g. Body weights were monitored and recorded twice for weeks, for the rest of weeks, including the day of study termination.

For tumors collection, animals were sacrificed by overdosed CO₂ and tumors were dissected at 0, 24, 48, 72, 96(optional), and 168 hours following the dosing. Tumors were first wet weighted, and then separated into three parts for KD, distribution and biomarker analysis. The samples were snap frozen in liquid nitrogen and stored at -80° C. until ready to be processed.

Example 13

The GST- π siRNAs of this invention inhibited pancreatic cancer xenograft tumors in vivo. The GST- π siRNAs pro-

vided gene knockdown potency in vivo when administered in a liposomal formulation to the pancreatic cancer xenograft tumors.

In this xenograft model, each mouse was inoculated subcutaneously in the right flank with 0.1 ml an inoculum of 2.5×10^6 of PANC-1 cells. Athymic nude female mice, 6 to 8 weeks, Charles River, were used. Tumor size was measured to the nearest 0.1 mm. Once the established tumors reached approximately 150-250 mm³ (average tumor volume at about 200 mm³), the mice were assigned into the various vehicle control and treatment groups such that the mean tumor volumes in the treated groups were within 10% of the mean tumor volume in the vehicle control group. On the same day, test articles and control vehicle were administered according to the dosing regimen. Tumor volumes were monitored three times for week 1, twice for the rest of weeks, including the day of study termination.

FIG. 6 shows tumor inhibition efficacy for a GST- π siRNA (SEQ ID Nos:61 and 126). As shown in FIG. 6, a dose response was obtained with doses ranging from 0.375 mg/kg to 3 mg/kg of siRNA targeted to GST- π . The GST- π siRNA showed significant and unexpectedly advantageous tumor inhibition efficacy within a few days after administration. Thus, the GST- π siRNA demonstrated significant and unexpectedly advantageous tumor inhibition efficacy at the endpoint.

The GST- π siRNAs were administered in a liposomal formulation having the composition (Ionizable lipid:cholesterol:DOPE:DOPC:DPPE-PEG-2K) (25:30:20:20:5).

Example 14

The GST- π siRNAs of this invention exhibited increased serum stability.

FIG. 7 shows incubation in human serum and detection of remaining siRNA at various time points by HPLS/LCMS. As shown in FIG. 7, the half-life ($t_{1/2}$) in serum for both the sense strand (FIG. 7, top) and antisense strand (FIG. 7, bottom) of a GST- π siRNA (SEQ ID Nos:61 and 126) was about 100 minutes.

Example 15

The GST- π siRNAs of this invention exhibited enhanced stability in formulation in plasma.

FIG. 8 shows incubation of formulation in plasma and detection of remaining siRNA at various time points. As shown in FIG. 8, the half-life ($t_{1/2}$) in plasma of a formulation of GST- π siRNA (SEQ ID Nos:61 and 126) was significantly longer than 100 hours.

The GST- π siRNA was prepared in a liposomal formulation having the composition (Ionizing lipid:cholesterol:DOPE:DOPC:DPPE-PEG-2K) (25:30:20:20:5). The z-average size for the liposomal nanoparticles was 40.0 nm, and the siRNA was 91% encapsulated.

The formulation was incubated in 50% human serum in PBS for 40 min, 1.5 h, 3 h, 24 h, and 96 h. The amount of the GST- π siRNA was determined by an ELISA-based assay.

Example 16

The GST- π siRNAs of this invention exhibited reduced off target effects by the passenger strand.

For the GST- π siRNA (SEQ ID Nos:156 and 182), FIG. 9 shows that in vitro knockdown for the guide strand was approximately exponential, as compared to a control with

scrambled sequence that exhibited no effect. The IC₅₀ of this siRNA was measured at 5 pM. FIG. 10 shows in vitro knockdown for the passenger strand of the same GST- π siRNA. As shown in FIG. 10, the passenger strand off target knockdown for the GST- π siRNA was greatly reduced, by more than 100-fold.

For the GST- π siRNAs (SEQ ID Nos:187 and 199), (SEQ ID Nos:189 and 201), and (SEQ ID Nos:190 and 202), FIG. 11 shows that the in vitro knockdowns for the guide strands were approximately exponential. The IC₅₀s of these siRNAs were measured at 6, 7, and 5 pM, respectively. As shown in FIG. 12, the in vitro knockdowns for the passenger strands of these GST- π siRNAs were significantly reduced by at least 10-fold. All of these GST- π siRNAs had deoxynucleotides in the seed region of the duplex region, with no other modifications in the duplex region.

For the GST- π siRNAs (SEQ ID Nos:217 and 232), FIG. 13 shows that the in vitro knockdown for the guide strand of this highly active GST- π siRNA was approximately exponential. The IC₅₀ of this siRNA was measured at 11 pM. As shown in FIG. 14, the in vitro knockdown for the passenger strand of this GST- π siRNA was significantly reduced by more than 100-fold. This GST- π siRNA had deoxynucleotides in the seed region of the duplex region, with no other modifications in the duplex region.

Off-target effects were determined using the expression reporter plasmid psiCHECK-2, which encodes the Renilla luciferase gene. (Dual-Luciferase Reporter Assay System, Promega, Cat#:E1960). The siRNA concentration was typically 50 pM. Protocol: Day 1, HeLa cell seeded at 5 to 7.5 \times 10³/100 ul/well. Day 2, co-transfection with cell confluence about 80%. Day 3, cells harvested for luciferase activity measurement. Luciferase activity was measured using Promega's Luciferase Assay System (E4550), according to manufacturer's protocol.

The psiCHECK-2 vector enabled monitoring of changes in expression of a target gene fused to the reporter gene of Renilla luciferase. The siRNA constructs were cloned into the multiple cloning region, and the vector was cotransfected with the siRNA into HeLa cells. If a specific siRNA binds to the target mRNA and initiates the RNAi process, the fused Renilla luciferase: construct mRNA will be cleaved and subsequently degraded, decreasing the Renilla luciferase signal.

For example, the plasmid inserts for siRNAs with the BU2' structure were as follows:

```

PsiCHECK-2 (F) plasmid insert:
                                     SEQ ID NO.: 285
ctcgag gggcaacTGAAGCCTTTGAGACCTGcTgTcccag
gcggccgc

PsiCHECK-2 (R) plasmid insert:
                                     SEQ ID NO.: 286
ctcgag cTgggacagCAGGGTCTCAAAGGCTTCagTTgccc
gcggccgc

```

Example 17

The GST- π siRNAs of this invention exhibited advantageously reduced miRNA-like off target effects, which are seed-dependent unintended off-target gene silencing.

For the GST- π siRNAs (SEQ ID Nos:156 and 182), (SEQ ID Nos:187 and 199), (SEQ ID Nos:189 and 201), (SEQ ID Nos:190 and 202), and (SEQ ID Nos:217 and 232), off target activity mimicking miRNA was found to be essentially negligible. The seed-dependent unintended off-target gene

silencing for these GST- π siRNAs was at least 10-fold to 100-fold less than the on-target activity of the guide strand.

For testing miRNA-related off target effects, one to four repeats of seed-matched target sequences complementary to the entire seed-containing region, positions 1-8 of the 5' end of the antisense strand, but not to the remaining non-seed region, positions 9-21, were introduced into the region corresponding to the 3'UTR of the luciferase mRNA, to determine the efficiency of the seed-dependent unintended off-target effects. Plasmid inserts were used to mimic a miRNA with complete matching in the seed region and mismatches (bulges) in the non-seed region.

For example, the plasmid inserts for siRNAs with the BU2' structure were as follows:

PsiCHECK-2 (Fmi1) plasmid insert:
SEQ ID NO.: 287
ctcgag gggcaacTCTACGCAAAACAGACCCTGcTgTcccag
gcggccgc

PsiCHECK-2 (Fmi2) plasmid insert:
SEQ ID NO.: 288
ctcgag gggcaacTCTACGCAAAACAGACCCTGcT
CTACGCAAAACAGACCCTGcT gTcccag gcggccgc

PsiCHECK-2 (Fmi3) plasmid insert:
SEQ ID NO.: 289
ctcgag gggcaacTCTACGCAAAACAGACCCTGcT
CTACGCAAAACAGACCCTGcT CTACGCAAAACAGACCCTGcT
gTcccag gcggccgc

PsiCHECK-2 (Fmi4) plasmid insert:
SEQ ID NO.: 290
ctcgag gggcaacTCTACGCAAAACAGACCCTGcT
CTACGCAAAACAGACCCTGcT CTACGCAAAACAGACCCTGcT
CTACGCAAAACAGACCCTGcT gTcccag gcggccgc

The embodiments described herein are not limiting and one skilled in the art can readily appreciate that specific combinations of the modifications described herein can be tested without undue experimentation toward identifying nucleic acid molecules with improved RNAi activity.

All publications, patents and literature specifically mentioned herein are incorporated by reference in their entirety for all purposes.

It is understood that this invention is not limited to the particular methodology, protocols, materials, and reagents described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention. It will be readily apparent to one skilled in the art that varying substitutions and modifications can be made to the description disclosed herein without departing from the scope and spirit of the description, and that those embodiments are within the scope of this description and the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. As well, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprises," "comprising," "containing," "including", and "having" can be used interchangeably, and shall be read expansively and without limitation.

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. For Markush groups, those skilled in the art will recognize that this description includes the individual members, as well as subgroups of the members of the Markush group.

Without further elaboration, it is believed that one skilled in the art can, based on the above description, utilize the present invention to its fullest extent. The following specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose.

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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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 <400> SEQUENCE: 53

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<210> SEQ ID NO 54
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
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 <400> SEQUENCE: 54

 ccucaucua accaacuaut t 21

<210> SEQ ID NO 55
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 <220> FEATURE:
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 <400> SEQUENCE: 55

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<210> SEQ ID NO 56
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 <220> FEATURE:
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 Synthetic oligonucleotide

 <400> SEQUENCE: 56

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<400> SEQUENCE: 57

aacugaagcc uuuugagact t 21

<210> SEQ ID NO 58
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<400> SEQUENCE: 58

cugaagccuu uugagaccct t 21

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<400> SEQUENCE: 59

uccucaucu acaccaacut t 21

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<400> SEQUENCE: 60

gcucccuc au cuacaccaat t 21

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<400> SEQUENCE: 61

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oligonucleotide
<220> FEATURE:
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Synthetic oligonucleotide

<400> SEQUENCE: 62

acugaagccu uuugagacat t 21

<210> SEQ ID NO 63
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<400> SEQUENCE: 63

cucccucauc uacaccaa t 21

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<400> SEQUENCE: 64

ccucaucac accaacuaat t 21

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<400> SEQUENCE: 65

accaaiaaaa uuucuaagat t 21

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<400> SEQUENCE: 66

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 <400> SEQUENCE: 67

 gacagcaggg ucucaaaagg c 21

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 <220> FEATURE:
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 <400> SEQUENCE: 68

 cuccucgguu cugggacagc a 21

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 <220> FEATURE:
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 <400> SEQUENCE: 69

 ccuuccuggu ucugggacag c 21

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 <220> FEATURE:
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 <400> SEQUENCE: 70

 gcagggucuc aaaagguuc a 21

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 <220> FEATURE:
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 <400> SEQUENCE: 71

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<400> SEQUENCE: 72
ggacagcagg gucucaaaag g 21

<210> SEQ ID NO 73
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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 73
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<210> SEQ ID NO 74
<211> LENGTH: 21
<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
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<400> SEQUENCE: 74
accaccuccu ccuuccagct c 21

<210> SEQ ID NO 75
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<400> SEQUENCE: 75
caccaccucc uccuuccagc t 21

<210> SEQ ID NO 76
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<220> FEATURE:
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<400> SEQUENCE: 76
cuuccagcuc uggcccugat c 21

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<210> SEQ ID NO 77
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<220> FEATURE:
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<400> SEQUENCE: 77

cugggacagc agggucucuaa a 21

<210> SEQ ID NO 78
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<400> SEQUENCE: 78

uccuuccagc ucuggcccug a 21

<210> SEQ ID NO 79
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
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<400> SEQUENCE: 79

ccaccuccuc cuuccagcuc t 21

<210> SEQ ID NO 80
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
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<400> SEQUENCE: 80

uucugggaca gcaggucuc a 21

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<400> SEQUENCE: 81

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<400> SEQUENCE: 82
cccugguucu gggacagcag g 21

<210> SEQ ID NO 83
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<400> SEQUENCE: 83
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<210> SEQ ID NO 84
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<220> FEATURE:
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<220> FEATURE:
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<400> SEQUENCE: 84
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<210> SEQ ID NO 85
<211> LENGTH: 21
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<400> SEQUENCE: 85
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<210> SEQ ID NO 86
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
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<400> SEQUENCE: 86
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<210> SEQ ID NO 87
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
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<400> SEQUENCE: 87

uccagcucug gcccgauct g 21

<210> SEQ ID NO 88
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<400> SEQUENCE: 88

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<210> SEQ ID NO 89
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
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<400> SEQUENCE: 89

cagcaggguc ucaaaaggct t 21

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<400> SEQUENCE: 90

acagcaggggu cucaaaaggc t 21

<210> SEQ ID NO 91
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<400> SEQUENCE: 91

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<400> SEQUENCE: 92

aaauagacca cgguguaggg c 21

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<400> SEQUENCE: 93

ggagaucugg ucuccacaa t 21

<210> SEQ ID NO 94
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<212> TYPE: DNA
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<400> SEQUENCE: 94

ggcaaacucu gccuccgct c 21

<210> SEQ ID NO 95
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 95

uauugguccu ggagaaagga a 21

<210> SEQ ID NO 96
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<400> SEQUENCE: 96

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<210> SEQ ID NO 97
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 97

ucgaacuggg aaauagacca c 21

<210> SEQ ID NO 98
<211> LENGTH: 21
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<400> SEQUENCE: 98

uucaccaugu ccaccagggc t 21

<210> SEQ ID NO 99
<211> LENGTH: 21
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<220> FEATURE:
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<400> SEQUENCE: 99

guguagauga gggagaugua t 21

<210> SEQ ID NO 100
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<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 100

uucacauagu cauccuugcc c 21

<210> SEQ ID NO 101
<211> LENGTH: 21
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 101

agguuguagu cagcgaagga g 21

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<210> SEQ ID NO 102
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 102

ucuggcccug aucugccagc a 21

<210> SEQ ID NO 103
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<220> FEATURE:
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<400> SEQUENCE: 103

acagggugag gucuccgucc t 21

<210> SEQ ID NO 104
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<220> FEATURE:
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<400> SEQUENCE: 104

acauagucan ccuugcccgc c 21

<210> SEQ ID NO 105
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<212> TYPE: DNA
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<400> SEQUENCE: 105

uacagcaggg ucucaaaagg c 21

<210> SEQ ID NO 106
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 106

uaccuccucc uaccagcuct g 21

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 <220> FEATURE:
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 <400> SEQUENCE: 107

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<210> SEQ ID NO 108
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 <220> FEATURE:
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 <400> SEQUENCE: 108

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<210> SEQ ID NO 109
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 <220> FEATURE:
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 <400> SEQUENCE: 109

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<210> SEQ ID NO 110
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 <220> FEATURE:
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 <400> SEQUENCE: 110

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<210> SEQ ID NO 111
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 <220> FEATURE:
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 <400> SEQUENCE: 111

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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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 <400> SEQUENCE: 112

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 <210> SEQ ID NO 113
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
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 <400> SEQUENCE: 113

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 <210> SEQ ID NO 114
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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 <400> SEQUENCE: 114

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 <210> SEQ ID NO 115
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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 <400> SEQUENCE: 115

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 <210> SEQ ID NO 116
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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 <400> SEQUENCE: 116

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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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 <400> SEQUENCE: 117

 caggguuca aaagguuca g 21

 <210> SEQ ID NO 118
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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 <400> SEQUENCE: 118

 uugguguaga ugaggagat g 21

 <210> SEQ ID NO 119
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
 Synthetic oligonucleotide

 <400> SEQUENCE: 119

 auaguuggug uaugagagg a 21

 <210> SEQ ID NO 120
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 <400> SEQUENCE: 120

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 <220> FEATURE:
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<400> SEQUENCE: 122

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<400> SEQUENCE: 123

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<400> SEQUENCE: 124

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 <400> SEQUENCE: 127

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 <223> OTHER INFORMATION: a, c, t, g, u, unknown or other

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<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<212> TYPE: RNA

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<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<212> TYPE: RNA

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 138

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<212> TYPE: RNA
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<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<400> SEQUENCE: 140

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 141

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 142

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<210> SEQ ID NO 143
<211> LENGTH: 21
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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 143

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<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 144

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<221> NAME/KEY: modified_base

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<223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 147

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<211> LENGTH: 21

<212> TYPE: RNA

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<223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide

<220> FEATURE:

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<222> LOCATION: (19)..(19)

<223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 148

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<211> LENGTH: 21

<212> TYPE: RNA

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<220> FEATURE:

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<220> FEATURE:

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<222> LOCATION: (19)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (19)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 150

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<212> TYPE: RNA

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<220> FEATURE:

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<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 151

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<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (1)..(3)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<220> FEATURE:

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<220> FEATURE:

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<222> LOCATION: (10)..(10)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<221> NAME/KEY: modified_base

<222> LOCATION: (18)..(18)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 152

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<210> SEQ ID NO 153
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

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<210> SEQ ID NO 154
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 154

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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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<400> SEQUENCE: 155

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<210> SEQ ID NO 156

<211> LENGTH: 21

<212> TYPE: RNA

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<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (1)..(3)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<221> NAME/KEY: modified_base

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<220> FEATURE:

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<222> LOCATION: (18)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: a, c, t, g, u, unknown or other

<400> SEQUENCE: 157

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<210> SEQ ID NO 158

<211> LENGTH: 21

<212> TYPE: RNA

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<220> FEATURE:

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<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
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 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

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 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 165

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<210> SEQ ID NO 166
 <211> LENGTH: 21
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
 <220> FEATURE:
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 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 166

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<210> SEQ ID NO 167
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 167

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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 168

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<210> SEQ ID NO 169
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 169

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<210> SEQ ID NO 170
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 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
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 <220> FEATURE:
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 <222> LOCATION: (1)..(1)
 <223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

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<400> SEQUENCE: 170

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<210> SEQ ID NO 171

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<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<220> FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

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<222> LOCATION: (1)..(1)

<223> OTHER INFORMATION: 2'-deoxy-nucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 171

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<210> SEQ ID NO 172

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<220> FEATURE:

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<223> OTHER INFORMATION: Phosphorothioate linkage

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 172

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21

<210> SEQ ID NO 173

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<223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide

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<223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (17)..(17)

<223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 173

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21

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<223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide
<220> FEATURE:
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<223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide
<220> FEATURE:
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<223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide
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<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<400> SEQUENCE: 174

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<223> OTHER INFORMATION: 2'-OMe-nucleotide
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<223> OTHER INFORMATION: 2'-OMe-nucleotide
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<223> OTHER INFORMATION: 2'-OMe-nucleotide
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<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 176

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 177

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<210> SEQ ID NO 178
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<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
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<223> OTHER INFORMATION: 2'-deoxy-nucleotide
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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 178

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<223> OTHER INFORMATION: 2'-deoxy-nucleotide

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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 179

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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 180

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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 181

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<210> SEQ ID NO 182
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 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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 <222> LOCATION: (1)..(1)
 <223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide
 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (4)..(4)
 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

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<220> FEATURE:
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 182

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 <210> SEQ ID NO 183
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: a, c, t, g, u, unknown or other

 <400> SEQUENCE: 183

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 <210> SEQ ID NO 184
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 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 184

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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 185

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 <210> SEQ ID NO 186
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 <212> TYPE: RNA
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

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<400> SEQUENCE: 186

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<210> SEQ ID NO 187

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 187

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21

<210> SEQ ID NO 188

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<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 188

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<211> LENGTH: 21

<212> TYPE: RNA

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 189

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<211> LENGTH: 21

<212> TYPE: RNA

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<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 190

ccucaucuac accaacuauu u

21

<210> SEQ ID NO 191

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 191

ccucaucuaac accaacuauu u                               21

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<212> TYPE: RNA
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<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 192

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<210> SEQ ID NO 193
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<212> TYPE: RNA
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<222> LOCATION: (20)..(21)
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<400> SEQUENCE: 193

ccucaucuaac accaacuauu u                               21

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<223> OTHER INFORMATION: 2'-OMe-nucleotide
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<221> NAME/KEY: modified_base
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: 2'-OMe-nucleotide
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<223> OTHER INFORMATION: 2'-OMe-nucleotide
<220> FEATURE:
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<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: 2'-OMe-nucleotide
<220> FEATURE:
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<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<400> SEQUENCE: 194

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21

<210> SEQ ID NO 195

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: a, c, t, g, u, unknown or other

<400> SEQUENCE: 195

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<210> SEQ ID NO 196

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<212> TYPE: RNA

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 196

auaguuggug uagaugaggu u

21

<210> SEQ ID NO 197

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

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<220> FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (2)..(2)

<223> OTHER INFORMATION: 2'-deoxy-nucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (5)..(6)

<223> OTHER INFORMATION: 2'-deoxy-nucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 197

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21

<210> SEQ ID NO 198

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
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 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 198

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 <210> SEQ ID NO 199
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 <222> LOCATION: (5)..(6)
 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
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 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 199

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 <210> SEQ ID NO 200
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 <213> ORGANISM: Artificial Sequence
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 <220> FEATURE:
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 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 200

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 <210> SEQ ID NO 201
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 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
 Synthetic oligonucleotide

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<220> FEATURE:
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 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
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 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 201

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 <212> TYPE: DNA
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 <220> FEATURE:
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 <221> NAME/KEY: modified_base
 <222> LOCATION: (5)..(5)
 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
 <220> FEATURE:
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 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 202

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 <210> SEQ ID NO 203
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 <220> FEATURE:
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 <222> LOCATION: (5)..(5)
 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 203

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 <210> SEQ ID NO 204
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 <212> TYPE: DNA
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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 <222> LOCATION: (2)..(2)
 <223> OTHER INFORMATION: 2'-deoxy-nucleotide

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<220> FEATURE:
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<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 204

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<210> SEQ ID NO 205
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 205

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<210> SEQ ID NO 206
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
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Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5)..(6)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: 2'-OMe-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: 2'-OMe-nucleotide
<220> FEATURE:
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<223> OTHER INFORMATION: 2'-OMe-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 206

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<210> SEQ ID NO 207
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: a, c, t, g, u, unknown or other

 <400> SEQUENCE: 207

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 <210> SEQ ID NO 208
 <211> LENGTH: 21
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 208

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 <210> SEQ ID NO 209
 <211> LENGTH: 21
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 209

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 <210> SEQ ID NO 210
 <211> LENGTH: 21
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 210

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 <210> SEQ ID NO 211
 <211> LENGTH: 21
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 oligonucleotide

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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 211

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<210> SEQ ID NO 212
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 212

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<210> SEQ ID NO 213
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 213

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<210> SEQ ID NO 214
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 214

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<210> SEQ ID NO 215
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 215

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<210> SEQ ID NO 216
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 216

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<210> SEQ ID NO 217
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 217

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<210> SEQ ID NO 218
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: 2'-OMe-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 2'-OMe-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: 2'-OMe-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: 2'-OMe-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 218

ggaugacuau gugaaggcau u 21

<210> SEQ ID NO 219
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide

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<220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (13)..(13)
 <223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide
 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 219

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<210> SEQ ID NO 220
 <211> LENGTH: 21
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (1)..(2)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide
 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 220

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<210> SEQ ID NO 221
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 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (1)..(2)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide
 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

 <400> SEQUENCE: 221

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<210> SEQ ID NO 222
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 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 oligonucleotide
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: a, c, t, g, u, unknown or other

 <400> SEQUENCE: 222

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<210> SEQ ID NO 223
 <211> LENGTH: 21
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 223

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<210> SEQ ID NO 224
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
 Synthetic oligonucleotide
 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (1)..(1)
 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (5)..(6)
 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 224

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<210> SEQ ID NO 225
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 oligonucleotide
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
 Synthetic oligonucleotide
 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (5)..(6)
 <223> OTHER INFORMATION: 2'-deoxy-nucleotide
 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 225

ugccuucaca uagucauccu u 21

<210> SEQ ID NO 226
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
 Synthetic oligonucleotide

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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5)..(6)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 226

ugccuucaca uagucauccu u                                21

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<210> SEQ ID NO 227
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5)..(6)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 227

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<210> SEQ ID NO 228
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5)..(6)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 228

ugccuucaca uagucauccu u                                21

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<210> SEQ ID NO 229
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide

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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 229

ugccuucaca uagucauccu u 21

<210> SEQ ID NO 230
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 230

ugccuucaca uagucauccu u 21

<210> SEQ ID NO 231
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 231

ugccuucaca uagucauccu u 21

<210> SEQ ID NO 232
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide

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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 232

ugccuucaca uagucauccu u 21

<210> SEQ ID NO 233
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5)..(6)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: 2'-OMe-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: 2'-OMe-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: 2'-OMe-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 233

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<210> SEQ ID NO 234
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: 2'-deoxy-2'-fluoro-nucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 234

ugccuucaca uagucauccu u 21

<210> SEQ ID NO 235
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<212> TYPE: RNA
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 236

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 <223> OTHER INFORMATION: a, c, t, g, u, unknown or other

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 238

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<210> SEQ ID NO 242
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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 243

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 244

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<212> TYPE: RNA

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 245

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<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 246

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21

<210> SEQ ID NO 247

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 247

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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
 <220> FEATURE:
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 <222> LOCATION: (3)..(3)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <223> OTHER INFORMATION: 2'-OMe-nucleotide
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 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 248

gaagccuuuu gagaccugu u 21

<210> SEQ ID NO 249
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 <220> FEATURE:
 <221> NAME/KEY: modified_base
 <222> LOCATION: (20)..(21)
 <223> OTHER INFORMATION: a, c, t, g, u, unknown or other

<400> SEQUENCE: 249

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<210> SEQ ID NO 250
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 <212> TYPE: RNA
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 250

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<210> SEQ ID NO 251
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<212> TYPE: DNA
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<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide

<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide

<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 251

cagggucuca aaagguucu u 21

<210> SEQ ID NO 252
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<223> OTHER INFORMATION: 2'-deoxy-nucleotide

<220> FEATURE:
<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: 2'-deoxy-nucleotide

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<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 252

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<210> SEQ ID NO 253
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<220> FEATURE:
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<223> OTHER INFORMATION: 2'-deoxy-nucleotide
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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 253

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<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: 2'-deoxy-nucleotide
<220> FEATURE:
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<223> OTHER INFORMATION: 2'-deoxy-nucleotide
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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 254

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 255

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 <223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 256

caggguuca aaagguuca u 21

<210> SEQ ID NO 257
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<400> SEQUENCE: 257

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<210> SEQ ID NO 258
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<400> SEQUENCE: 258

caggguuca aaagguuca u 21

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 <223> OTHER INFORMATION: 2'-deoxy-nucleotide

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 <400> SEQUENCE: 260

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 <210> SEQ ID NO 261
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 <221> NAME/KEY: modified_base
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 <223> OTHER INFORMATION: a, c, t, g, u, unknown or other

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 <210> SEQ ID NO 262
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<220> FEATURE:
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<400> SEQUENCE: 262

ccucaucuaac accaacuauu u 21

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<220> FEATURE:
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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 263

ccucaucuaac accaacuauu u 21

<210> SEQ ID NO 264
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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 264

ccucaucuaac accaacuauu u 21

<210> SEQ ID NO 265
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<212> TYPE: RNA
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<400> SEQUENCE: 265

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<210> SEQ ID NO 266
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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 266

ccucaucuaac accaacuauu u 21

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 267

ccucaucuaac accaacuaau u 21

<210> SEQ ID NO 268
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oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 268

ccucaucuaac accaacuaau u 21

<210> SEQ ID NO 269
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<212> TYPE: RNA
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oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 269

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<210> SEQ ID NO 270
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<212> TYPE: RNA
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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 270

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<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<400> SEQUENCE: 271

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21

<210> SEQ ID NO 272

<211> LENGTH: 21

<212> TYPE: RNA

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<221> NAME/KEY: modified_base

<222> LOCATION: (1)..(1)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<220> FEATURE:

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<222> LOCATION: (3)..(3)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<220> FEATURE:

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<222> LOCATION: (5)..(5)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

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<222> LOCATION: (7)..(7)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (9)..(9)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 272

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<210> SEQ ID NO 273

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (20)..(21)

<223> OTHER INFORMATION: a, c, t, g, u, unknown or other

<400> SEQUENCE: 273

auaguuggug uagaugagn n

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<210> SEQ ID NO 274

<211> LENGTH: 21

<212> TYPE: RNA

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<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<221> NAME/KEY: modified_base

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<223> OTHER INFORMATION: 2'-OMe-nucleotide

<400> SEQUENCE: 274

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21

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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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 <220> FEATURE:
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 <220> FEATURE:
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<223> OTHER INFORMATION: 2'-OMe-nucleotide
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<223> OTHER INFORMATION: 2'-OMe-nucleotide
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<400> SEQUENCE: 284

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ctcgaggggc aactctacgc aaaacagacc ctgctgtccc aggcggccgc      50

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gcaaaacaga ccctgctgtc ccaggcggcc gc                                       92

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<400> SEQUENCE: 290

ctcgaggggc aactctacgc aaaacagacc ctgctctacg caaacagac cctgctctac      60
gcaaaacaga ccctgctcta cgcaaaacag acctgctgt cccaggcggc cgc                113

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What is claimed is:

1. A nucleic acid molecule for inhibiting expression of GST- π comprising a sense strand and an antisense strand, wherein the strands form a duplex region, and wherein the antisense strand is UAGGGUCUAAAAGGCUUCNN SEQ ID NO:157 and the sense strand is GAAGCC-UUUUGAGACCCUANN SEQ ID NO:131, wherein N is selected from the group of A, C, G, U, 2'-OMe-U, a, c, g, u, t, an inverted nucleotide, and a chemically modified nucleotide.

2. The nucleic acid molecule of claim 1, wherein one or more of the nucleotides in the duplex region is chemically-modified.

3. The nucleic acid molecule of claim 2, wherein the chemically-modified nucleotides are selected from 2'-deoxy nucleotides, 2'-O-alkyl substituted nucleotides, 2'-deoxy-2'-fluoro substituted nucleotides, phosphorothioate nucleotides, locked nucleotides, and any combination thereof.

4. The nucleic acid molecule of claim 2, wherein the antisense strand has deoxynucleotides in a plurality of positions, the plurality of positions being one of the following:

each of positions 4, 6 and 8, from the 5' end of the antisense strand;
 each of positions 3, 5 and 7, from the 5' end of the antisense strand;
 each of positions 1, 3, 5 and 7, from the 5' end of the antisense strand;
 each of positions 3-8, from the 5' end of the antisense strand; or
 each of positions 5-8, from the 5' end of the antisense strand.

5. The nucleic acid molecule of claim 4, wherein the molecule has one or more 2'-deoxy-2'-fluoro substituted nucleotides in the duplex region.

6. The nucleic acid molecule of claim 2, wherein the antisense strand is SEQ ID NO:182 and the sense strand is SEQ ID NO:156.

7. The nucleic acid molecule of claim 2, wherein the antisense strand is SEQ ID NO:180 and the sense strand is SEQ ID NO:154.

8. The nucleic acid molecule of claim 2, wherein the antisense strand is SEQ ID NO:181 and the sense strand is SEQ ID NO:155.

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9. The nucleic acid molecule of claim 1, wherein the molecule inhibits expression of GST- π mRNA in A549 cells with an IC50 of less than 50 pM.

10. A pharmaceutical composition comprising the nucleic acid molecule of claim 1 and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, wherein the carrier comprises a lipid molecule or liposome.

12. A vector or cell comprising the nucleic acid molecule of claim 1.

13. A method for treating pancreatic cancer or lung cancer, the method comprising administering to a subject in need a composition of claim 10.

14. A nucleic acid molecule for inhibiting expression of GST- π comprising a sense strand and an antisense strand, wherein the strands form a duplex region, and wherein the antisense strand is ACAGCAGGGUCUCAAAGGNN SEQ ID NO:195 and the sense strand is CCUUUGA-GACCCUGCUGUNN SEQ ID NO:183, wherein N is selected from the group of A, C, G, U, 2'-OMe-U, a, c, g, u, t, an inverted nucleotide, and a chemically modified nucleotide.

15. The nucleic acid molecule of claim 14, wherein one or more of the nucleotides in the duplex region is chemically-modified.

16. The nucleic acid molecule of claim 15, wherein the chemically-modified nucleotides are selected from 2'-deoxy nucleotides, 2'-O-alkyl substituted nucleotides, 2'-deoxy-2'-fluoro substituted nucleotides, phosphorothioate nucleotides, locked nucleotides, and any combination thereof.

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17. The nucleic acid molecule of claim 15, wherein the antisense strand has deoxynucleotides in a plurality of positions, which plurality of positions are one of the following:

each of positions 4, 6 and 8, from the 5' end of the antisense strand;

each of positions 3, 5 and 7, from the 5' end of the antisense strand;

each of positions 1, 3, 5 and 7, from the 5' end of the antisense strand;

each of positions 3-8, from the 5' end of the antisense strand; or

each of positions 5-8, from the 5' end of the antisense strand.

18. The nucleic acid molecule of claim 17, wherein the molecule has one or more 2'-deoxy-2'-fluoro substituted nucleotides in the duplex region.

19. The nucleic acid molecule of claim 14, wherein the molecule inhibits expression of GST- π mRNA in A549 cells with an IC50 of less than 50 pM.

20. A pharmaceutical composition comprising the nucleic acid molecule of claim 14 and a pharmaceutically acceptable carrier.

21. The pharmaceutical composition of claim 20, wherein the carrier is a lipid molecule or liposome.

22. A vector or cell comprising the nucleic acid molecule of claim 14.

23. A method for treating pancreatic cancer or lung cancer, the method comprising administering to a subject in need a composition of claim 20.

* * * * *