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(54) Titre : AGENTS A BASE D'ARN UTILISABLES EN VUE DE LA MODULATION DU GENE GST-PI
(54) Title: RNA AGENTS FOR GST-PI GENE MODULATION

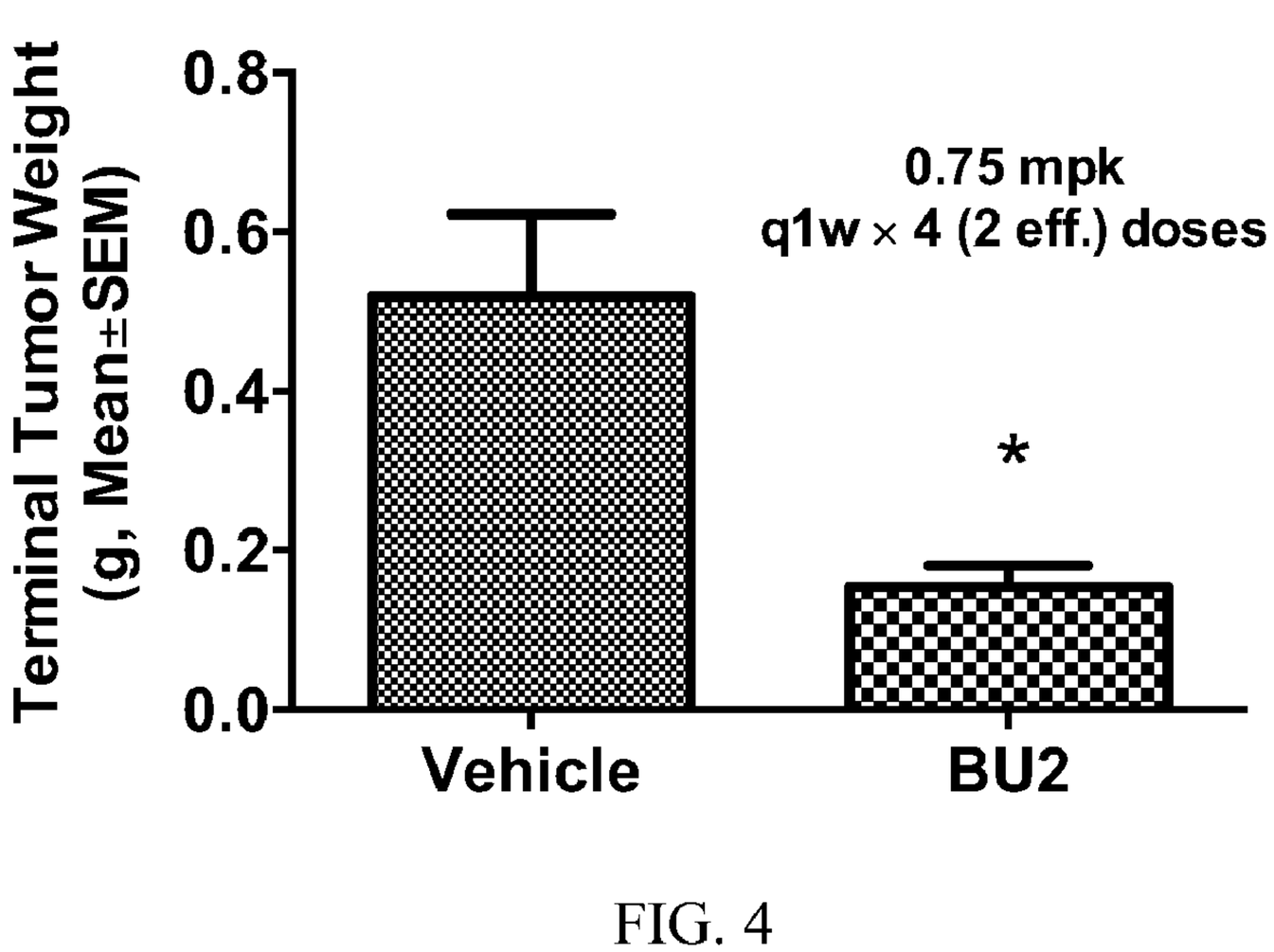

FIG. 4

(57) Abrégé/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

CA 2972265 A1 2016/06/30

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(57) Abrégé(suite)/Abstract(continued):
tumor. A nucleic acid molecule can have a) a polynucleotide sense strand and a polynucleotide antisense strand; b) each strand of the molecule being from 15 to 30 nucleotides in length; c) a contiguous region of from 15 to 30 nucleotides of the antisense strand being complementary to a sequence of an mRNA encoding GST-π; and d) at least a portion of the sense strand can be 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.

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(54) Title: RNA AGENTS FOR GST-PI GENE MODULATION

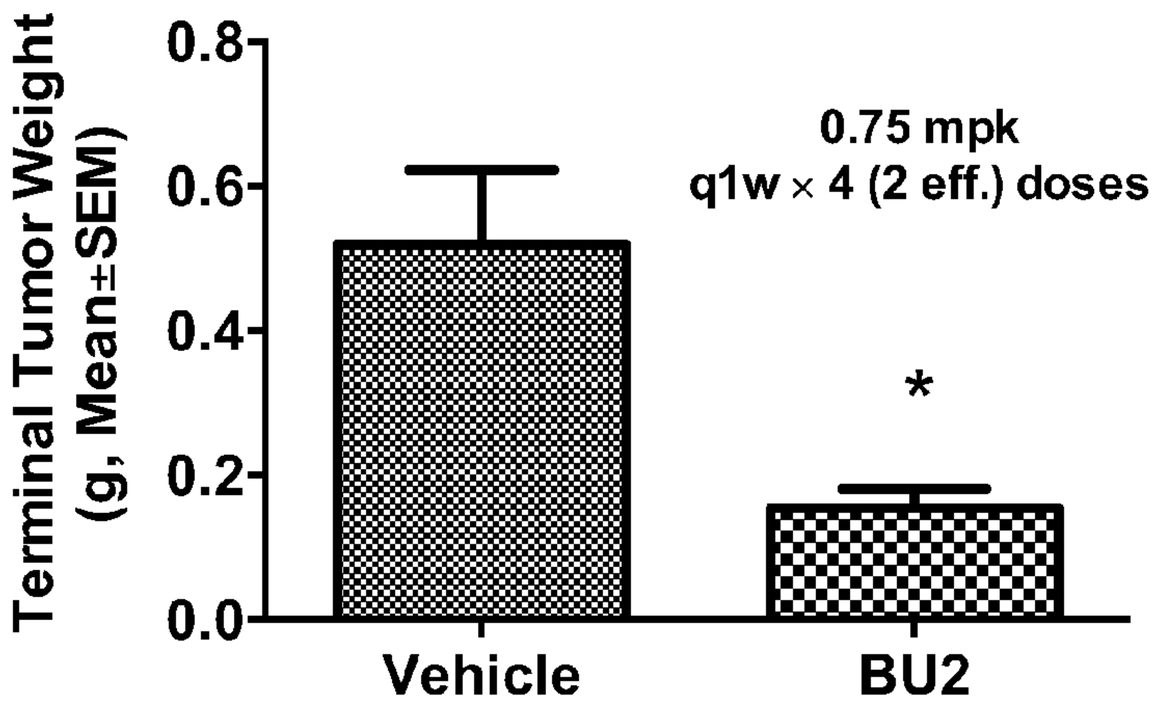

FIG. 4

(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. A nucleic acid molecule can have a) a polynucleotide sense strand and a polynucleotide antisense strand; b) each strand of the molecule being from 15 to 30 nucleotides in length; c) a contiguous region of from 15 to 30 nucleotides of the antisense strand being complementary to a sequence of an mRNA encoding GST-π; and d) at least a portion of the sense strand can be 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.

WO 2016/106406 A3

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RNA AGENTS FOR GST-PI GENE MODULATION

TECHNICAL FIELD OF THE INVENTION

[0001] 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.

SEQUENCE LISTING

[0002] This application includes a Sequence Listing submitted electronically as an ASCII file created on December 23, 2015, named ND5123202WO_SL.txt, which is 442,955 bytes in size, and is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0003] 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-Tranferase Pi (GST-π) expression. (Miyanishi 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)

[0004] 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)

[0005] Therapeutics for inhibition of GST-π expression will require highly potent siRNA sequences and structures.

[0006] What is needed are siRNA sequences, compounds and structures for inhibition of GST-π expression.

BRIEF SUMMARY

[0007] This invention relates to compounds, compositions and methods for modulating the expression of human GST-π using RNA interference.

[0008] In some embodiments, this invention provides molecules for RNA interference gene silencing of GST-π.

[0009] 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.

[0010] Embodiments of this invention include the following:

[0011] A nucleic acid molecule, 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.

[0012] In some embodiments, the nucleic acid molecule can have 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.

[0013] 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.

[0014] Compounds of this invention can have a sequence of an mRNA encoding GST-π that is selected from the group consisting of 5'UTR positions 1 to 249 of SEQ ID NO:1, CDS positions 250 to 882 of SEQ ID NO:1, and 3'UTR positions 883 to 986 of SEQ ID NO:1.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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 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.

[0019] Embodiments of this invention further provide nucleic acid molecules having an IC50 for knockdown of GST-π of less than 100 pM.

[0020] 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.

[0021] 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.

[0022] 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. 1: Fig. 1 shows SEQ ID NO: 1, which is the nucleic acid sequence of target human glutathione S -transferase pi (human GST-π) mRNA, disclosed in GenBank accession number NM_000852.3 (hGSTP1), which is 986 nucleotides in length.

[0024] FIG. 2: Fig. 2 shows in vivo knockdown efficacy for GST-π siRNA. Dose dependent knockdown of GST-π mRNA was observed in vivo with siRNA targeted to GST-π, as shown in Fig. 2.

[0025] FIG. 3: Fig. 3 shows inhibition of proliferation by GST-π siRNA. Dose-dependent inhibition of proliferation was observed in an A549 cell line in vitro with siRNA targeted to GST-π, as shown in Fig. 3.

[0026] FIG. 4: Fig. 4 shows tumor inhibition efficacy for GST-π siRNA. A pancreatic 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 demonstrated significant tumor inhibition efficacy.

DETAILED DESCRIPTION OF THE INVENTION

[0027] This invention relates to compounds, compositions and methods for nucleic acid based therapeutics for modulating expression of GST-π.

[0028] In some embodiments, this invention provides molecules active in RNA interference, as well as structures and compositions that can silence expression of GST-π.

[0029] The structures and compositions of this disclosure can be used in preventing or treating various diseases such as malignant tumor.

[0030] 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.

[0031] 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.

[0032] 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.

[0033] The siRNAs of this invention can be used for preventing or treating malignant tumors.

[0034] 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.

[0035] 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.

[0036] 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 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, carcinomas, 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.

[0037] In certain embodiments, a combination of therapeutic molecules of this invention can be used for silencing or inhibiting GST-π gene expression.

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] <u>GST-π and RNAi molecules</u>

[0043] Fig. 1 shows the nucleic acid sequence of an example target human glutathione S-transferase pi (human GST-π) mRNA, which is disclosed in GenBank accession number NM_000852.3 (hGSTP1), and is 986 nucleotides in length (SEQ ID NO: 1).

[0044] 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.

[0045] 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.

[0046] The composition and methods disclosed herein can also be used in treating various kinds of malignant tumors in a subject.

[0047] The nucleic acid molecules and methods of this invention may be used to down regulate the expression of genes that encode GST-π.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] Examples of RNAi molecules of this invention targeted to GST-π mRNA are shown in Tables 1 and 2.

Table 1: RNAi molecule sequences for GST-π

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
232	2	GCCGCAGUCUUCGCCACCAtt	609	UGGUGGCGAAGACUGCGGCgg
233	3	CCGCAGUCUUCGCCACCAUtt	610	AUGGUGGCGAAGACUGCGGcg
234	4	CGCAGUCUUCGCCACCAUGtt	611	CAUGGUGGCGAAGACUGCGgc
235	5	GCAGUCUUCGCCACCAUGCtt	612	GCAUGGUGGCGAAGACUGCgg
236	6	CAGUCUUCGCCACCAUGCCtt	613	GGCAUGGUGGCGAAGACUGcg

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
237	7	AGUCUUCGCCACCAUGCCGtt	614	CGGCAUGGUGGCGAAGACUgc
238	8	GUCUUCGCCACCAUGCCGCtt	615	GCGGCAUGGUGGCGAAGACtg
239	9	UCUUCGCCACCAUGCCGCCtt	616	GGCGGCAUGGUGGCGAAGAct
240	10	CUUCGCCACCAUGCCGCCCtt	617	GGGCGGCAUGGUGGCGAAGac
241	11	UUCGCCACCAUGCCGCCCUtt	618	AGGGCGGCAUGGUGGCGAAga
242	12	UCGCCACCAUGCCGCCCUAtt	619	UAGGGCGGCAUGGUGGCGAag
243	13	CGCCACCAUGCCGCCCUACtt	620	GUAGGGCGGCAUGGUGGCGaa
244	14	GCCACCAUGCCGCCCUACAtt	621	UGUAGGGCGGCAUGGUGGCga
245	15	CCACCAUGCCGCCCUACACtt	622	GUGUAGGGCGGCAUGGUGGcg
246	16	CACCAUGCCGCCCUACACCtt	623	GGUGUAGGGCGGCAUGGUGgc
247	17	ACCAUGCCGCCCUACACCGtt	624	CGGUGUAGGGCGGCAUGGUgg
248	18	CCAUGCCGCCCUACACCGUtt	625	ACGGUGUAGGGCGGCAUGGtg
249	19	CAUGCCGCCCUACACCGUGtt	626	CACGGUGUAGGGCGGCAUGgt
250	20	AUGCCGCCCUACACCGUGGtt	627	CCACGGUGUAGGGCGGCAUgg
251	21	UGCCGCCCUACACCGUGGUtt	628	ACCACGGUGUAGGGCGGCAtg
252	22	GCCGCCCUACACCGUGGUCtt	629	GACCACGGUGUAGGGCGGCat
253	23	CCGCCCUACACCGUGGUCUtt	630	AGACCACGGUGUAGGGCGGca
254	24	CGCCCUACACCGUGGUCUAtt	631	UAGACCACGGUGUAGGGCGgc
255	25	GCCCUACACCGUGGUCUAUtt	632	AUAGACCACGGUGUAGGGCgg
256	26	CCCUACACCGUGGUCUAUUtt	633	AAUAGACCACGGUGUAGGGcg
257	27	CCUACACCGUGGUCUAUUUtt	634	AAAUAGACCACGGUGUAGGgc
258	28	CUACACCGUGGUCUAUUUCtt	635	GAAAUAGACCACGGUGUAGgg
259	29	UACACCGUGGUCUAUUUCCtt	636	GGAAAUAGACCACGGUGUAgg
260	30	ACACCGUGGUCUAUUUCCCtt	637	GGGAAAUAGACCACGGUGUag
261	31	CACCGUGGUCUAUUUCCCAtt	638	UGGGAAAUAGACCACGGUGta
262	32	ACCGUGGUCUAUUUCCCAGtt	639	CUGGGAAAUAGACCACGGUgt
263	33	CCGUGGUCUAUUUCCCAGUtt	640	ACUGGGAAAUAGACCACGGtg
264	34	CGUGGUCUAUUUCCCAGUUtt	641	AACUGGGAAAUAGACCACGgt
265	35	GUGGUCUAUUUCCCAGUUCtt	642	GAACUGGGAAAUAGACCACgg

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
266	36	UGGUCUAUUUCCCAGUUCGtt	643	CGAACUGGGAAAUAGACCAcg
267	37	GGUCUAUUUCCCAGUUCGAtt	644	UCGAACUGGGAAAUAGACCac
268	38	GUCUAUUUCCCAGUUCGAGtt	645	CUCGAACUGGGAAAUAGACCa
269	39	UCUAUUUCCCAGUUCGAGGtt	646	CCUCGAACUGGGAAAUAGAcc
270	40	CUAUUUCCCAGUUCGAGGCtt	647	GCCUCGAACUGGGAAAUAGac
271	41	UAUUUCCCAGUUCGAGGCCtt	648	GGCCUCGAACUGGGAAAUAga
272	42	AUUUCCCAGUUCGAGGCCGtt	649	CGGCCUCGAACUGGGAAAUag
273	43	UUUCCCAGUUCGAGGCCGCtt	650	GCGGCCUCGAACUGGGAAAta
274	44	UUCCCAGUUCGAGGCCGCUtt	651	AGCGGCCUCGAACUGGGAAat
275	45	UCCCAGUUCGAGGCCGCUGtt	652	CAGCGGCCUCGAACUGGGAaa
276	46	CCCAGUUCGAGGCCGCUGCtt	653	GCAGCGGCCUCGAACUGGGaa
277	47	CCAGUUCGAGGCCGCUGCGtt	654	CGCAGCGGCCUCGAACUGGga
278	48	CAGUUCGAGGCCGCUGCGCtt	655	GCGCAGCGGCCUCGAACUGgg
279	49	AGUUCGAGGCCGCUGCGCGtt	656	CGCGCAGCGGCCUCGAACUgg
280	50	GUUCGAGGCCGCUGCGCGGtt	657	CCGCGCAGCGGCCUCGAACtg
281	51	UUCGAGGCCGCUGCGCGGCtt	658	GCCGCGCAGCGGCCUCGAAct
282	52	UCGAGGCCGCUGCGCGGCCtt	659	GGCCGCGCAGCGGCCUCGAac
283	53	CGAGGCCGCUGCGCGGCCCtt	660	GGGCCGCGCAGCGGCCUCGaa
284	54	GAGGCCGCUGCGCGGCCCUtt	661	AGGGCCGCGCAGCGGCCUCga
285	55	AGGCCGCUGCGCGGCCCUGtt	662	CAGGGCCGCGCAGCGGCCUcg
286	56	GGCCGCUGCGCGGCCCUGCtt	663	GCAGGGCCGCGCAGCGGCCtc
287	57	GCCGCUGCGCGGCCCUGCGtt	664	CGCAGGGCCGCGCAGCGGCct
288	58	CCGCUGCGCGGCCCUGCGCtt	665	GCGCAGGGCCGCGCAGCGGcc
289	59	CGCUGCGCGGCCCUGCGCAtt	666	UGCGCAGGGCCGCGCAGCGgc
290	60	GCUGCGCGGCCCUGCGCAUtt	667	AUGCGCAGGGCCGCGCAGCgg
291	61	CUGCGCGGCCCUGCGCAUGtt	668	CAUGCGCAGGGCCGCGCAGcg
292	62	UGCGCGGCCCUGCGCAUGCtt	669	GCAUGCGCAGGGCCGCGCAgc
293	63	GCGCGGCCCUGCGCAUGCUtt	670	AGCAUGCGCAGGGCCGCGCag
294	64	CGCGGCCCUGCGCAUGCUGtt	671	CAGCAUGCGCAGGGCCGCGca

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
295	65	GCGGCCCUGCGCAUGCUGCtt	672	GCAGCAUGCGCAGGGCCGCgc
296	66	CGGCCCUGCGCAUGCUGCUtt	673	AGCAGCAUGCGCAGGGCCGcg
297	67	GGCCCUGCGCAUGCUGCUGtt	674	CAGCAGCAUGCGCAGGGCCgc
298	68	GCCCUGCGCAUGCUGCUGGtt	675	CCAGCAGCAUGCGCAGGGCcg
299	69	CCCUGCGCAUGCUGCUGGCtt	676	GCCAGCAGCAUGCGCAGGGcc
300	70	CCUGCGCAUGCUGCUGGCAtt	677	UGCCAGCAGCAUGCGCAGGgc
301	71	CUGCGCAUGCUGCUGGCAGtt	678	CUGCCAGCAGCAUGCGCAGgg
302	72	UGCGCAUGCUGCUGGCAGAtt	679	UCUGCCAGCAGCAUGCGCAgg
303	73	GCGCAUGCUGCUGGCAGAUtt	680	AUCUGCCAGCAGCAUGCGCag
304	74	CGCAUGCUGCUGGCAGAUCtt	681	GAUCUGCCAGCAGCAUGCGca
305	75	GCAUGCUGCUGGCAGAUCAtt	682	UGAUCUGCCAGCAGCAUGCgc
306	76	CAUGCUGCUGGCAGAUCAGtt	683	CUGAUCUGCCAGCAGCAUGcg
307	77	AUGCUGCUGGCAGAUCAGGtt	684	CCUGAUCUGCCAGCAGCAUgc
308	78	UGCUGCUGGCAGAUCAGGGtt	685	CCCUGAUCUGCCAGCAGCAtg
309	79	GCUGCUGGCAGAUCAGGGCtt	686	GCCCUGAUCUGCCAGCAGCat
310	80	CUGCUGGCAGAUCAGGGCCtt	687	GGCCCUGAUCUGCCAGCAGca
311	81	UGCUGGCAGAUCAGGGCCAtt	688	UGGCCCUGAUCUGCCAGCAgc
312	82	GCUGGCAGAUCAGGGCCAGtt	689	CUGGCCCUGAUCUGCCAGCag
313	83	CUGGCAGAUCAGGGCCAGAtt	690	UCUGGCCCUGAUCUGCCAGca
314	84	UGGCAGAUCAGGGCCAGAGtt	691	CUCUGGCCCUGAUCUGCCAgc
315	85	GGCAGAUCAGGGCCAGAGCtt	692	GCUCUGGCCCUGAUCUGCCag
316	86	GCAGAUCAGGGCCAGAGCUtt	693	AGCUCUGGCCCUGAUCUGCca
317	87	CAGAUCAGGGCCAGAGCUGtt	694	CAGCUCUGGCCCUGAUCUGcc
318	88	AGAUCAGGGCCAGAGCUGGtt	695	CCAGCUCUGGCCCUGAUCUgc
319	89	GAUCAGGGCCAGAGCUGGAtt	696	UCCAGCUCUGGCCCUGAUCtg
320	90	AUCAGGGCCAGAGCUGGAAtt	697	UUCCAGCUCUGGCCCUGAUct
321	91	UCAGGGCCAGAGCUGGAAGtt	698	CUUCCAGCUCUGGCCCUGAtc
322	92	CAGGGCCAGAGCUGGAAGGtt	699	CCUUCCAGCUCUGGCCCUGat
323	93	AGGGCCAGAGCUGGAAGGAtt	700	UCCUUCCAGCUCUGGCCCUga

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
324	94	GGGCCAGAGCUGGAAGGAGtt	701	CUCCUUCCAGCUCUGGCCCtg
325	95	GGCCAGAGCUGGAAGGAGGtt	702	CCUCCUUCCAGCUCUGGCCct
326	96	GCCAGAGCUGGAAGGAGGAtt	703	UCCUCCUUCCAGCUCUGGCcc
327	97	CCAGAGCUGGAAGGAGGAGtt	704	CUCCUCCUUCCAGCUCUGGcc
328	98	CAGAGCUGGAAGGAGGAGGtt	705	CCUCCUCCUUCCAGCUCUGgc
329	99	AGAGCUGGAAGGAGGAGGUtt	706	ACCUCCUCCUUCCAGCUCUgg
330	100	GAGCUGGAAGGAGGAGGUGtt	707	CACCUCCUCCUUCCAGCUCtg
330	101	GAGCUGGAAGGAGGAGGUAtt	708	UACCUCCUCCUUCCAGCUCtg
331	102	AGCUGGAAGGAGGAGGUGGtt	709	CCACCUCCUCCUUCCAGCUct
332	103	GCUGGAAGGAGGAGGUGGUtt	710	ACCACCUCCUCCUUCCAGCtc
333	104	CUGGAAGGAGGAGGUGGUGtt	711	CACCACCUCCUCCUUCCAGct
334	105	UGGAAGGAGGAGGUGGUGAtt	712	UCACCACCUCCUCCUUCCAgc
335	106	GGAAGGAGGAGGUGGUGACtt	713	GUCACCACCUCCUCCUUCCag
336	107	GAAGGAGGAGGUGGUGACCtt	714	GGUCACCACCUCCUCCUUCca
337	108	AAGGAGGAGGUGGUGACCGtt	715	CGGUCACCACCUCCUCCUUcc
338	109	AGGAGGAGGUGGUGACCGUtt	716	ACGGUCACCACCUCCUCCUtc
339	110	GGAGGAGGUGGUGACCGUGtt	717	CACGGUCACCACCUCCUCCtt
340	111	GAGGAGGUGGUGACCGUGGtt	718	CCACGGUCACCACCUCCUCct
341	112	AGGAGGUGGUGACCGUGGAtt	719	UCCACGGUCACCACCUCCUcc
342	113	GGAGGUGGUGACCGUGGAGtt	720	CUCCACGGUCACCACCUCCtc
343	114	GAGGUGGUGACCGUGGAGAtt	721	UCUCCACGGUCACCACCUCct
344	115	AGGUGGUGACCGUGGAGACtt	722	GUCUCCACGGUCACCACCUcc
345	116	GGUGGUGACCGUGGAGACGtt	723	CGUCUCCACGGUCACCACCtc
346	117	GUGGUGACCGUGGAGACGUtt	724	ACGUCUCCACGGUCACCACct
347	118	UGGUGACCGUGGAGACGUGtt	725	CACGUCUCCACGGUCACCAcc
348	119	GGUGACCGUGGAGACGUGGtt	726	CCACGUCUCCACGGUCACCac
349	120	GUGACCGUGGAGACGUGGCtt	727	GCCACGUCUCCACGGUCACca
350	121	UGACCGUGGAGACGUGGCAtt	728	UGCCACGUCUCCACGGUCAcc
351	122	GACCGUGGAGACGUGGCAGtt	729	CUGCCACGUCUCCACGGUCac

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
352	123	ACCGUGGAGACGUGGCAGGtt	730	CCUGCCACGUCUCCACGGUca
353	124	CCGUGGAGACGUGGCAGGAtt	731	UCCUGCCACGUCUCCACGGtc
354	125	CGUGGAGACGUGGCAGGAGtt	732	CUCCUGCCACGUCUCCACGgt
355	126	GUGGAGACGUGGCAGGAGGtt	733	CCUCCUGCCACGUCUCCACgg
356	127	UGGAGACGUGGCAGGAGGGtt	734	CCCUCCUGCCACGUCUCCAcg
357	128	GGAGACGUGGCAGGAGGGCtt	735	GCCCUCCUGCCACGUCUCCac
358	129	GAGACGUGGCAGGAGGGCUtt	736	AGCCCUCCUGCCACGUCUCCa
359	130	AGACGUGGCAGGAGGGCUCtt	737	GAGCCCUCCUGCCACGUCUCc
360	131	GACGUGGCAGGAGGGCUCAtt	738	UGAGCCCUCCUGCCACGUCtc
361	132	ACGUGGCAGGAGGGCUCACtt	739	GUGAGCCCUCCUGCCACGUct
362	133	CGUGGCAGGAGGGCUCACUtt	740	AGUGAGCCCUCCUGCCACGtc
363	134	GUGGCAGGAGGGCUCACUCtt	741	GAGUGAGCCCUCCUGCCACgt
364	135	UGGCAGGAGGGCUCACUCAtt	742	UGAGUGAGCCCUCCUGCCAcg
365	136	GGCAGGAGGGCUCACUCAAtt	743	UUGAGUGAGCCCUCCUGCCac
366	137	GCAGGAGGGCUCACUCAAAtt	744	UUUGAGUGAGCCCUCCUGCca
367	138	CAGGAGGGCUCACUCAAAGtt	745	CUUUGAGUGAGCCCUCCUGcc
368	139	AGGAGGGCUCACUCAAAGCtt	746	GCUUUGAGUGAGCCCUCCUgc
369	140	GGAGGGCUCACUCAAAGCCtt	747	GGCUUUGAGUGAGCCCUCCtg
370	141	GAGGGCUCACUCAAAGCCUtt	748	AGGCUUUGAGUGAGCCCUCct
371	142	AGGGCUCACUCAAAGCCUCtt	749	GAGGCUUUGAGUGAGCCCUcc
372	143	GGGCUCACUCAAAGCCUCCtt	750	GGAGGCUUUGAGUGAGCCCtc
373	144	GGCUCACUCAAAGCCUCCUtt	751	AGGAGGCUUUGAGUGAGCCct
374	145	GCUCACUCAAAGCCUCCUGtt	752	CAGGAGGCUUUGAGUGAGCcc
375	146	CUCACUCAAAGCCUCCUGCtt	753	GCAGGAGGCUUUGAGUGAGcc
376	147	UCACUCAAAGCCUCCUGCCtt	754	GGCAGGAGGCUUUGAGUGAgc
377	148	CACUCAAAGCCUCCUGCCUtt	755	AGGCAGGAGGCUUUGAGUGag
378	149	ACUCAAAGCCUCCUGCCUAtt	756	UAGGCAGGAGGCUUUGAGUga
379	150	CUCAAAGCCUCCUGCCUAUtt	757	AUAGGCAGGAGGCUUUGAGtg
380	151	UCAAAGCCUCCUGCCUAUAtt	758	UAUAGGCAGGAGGCUUUGAgt

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
381	152	CAAAGCCUCCUGCCUAUACtt	759	GUAUAGGCAGGAGGCUUUGag
382	153	AAAGCCUCCUGCCUAUACGtt	760	CGUAUAGGCAGGAGGCUUUga
383	154	AAGCCUCCUGCCUAUACGGtt	761	CCGUAUAGGCAGGAGGCUUtg
384	155	AGCCUCCUGCCUAUACGGGtt	762	CCCGUAUAGGCAGGAGGCUtt
385	156	GCCUCCUGCCUAUACGGGCtt	763	GCCCGUAUAGGCAGGAGGCtt
386	157	CCUCCUGCCUAUACGGGCAtt	764	UGCCCGUAUAGGCAGGAGGct
387	158	CUCCUGCCUAUACGGGCAGtt	765	CUGCCCGUAUAGGCAGGAGgc
388	159	UCCUGCCUAUACGGGCAGCtt	766	GCUGCCCGUAUAGGCAGGAgg
389	160	CCUGCCUAUACGGGCAGCUtt	767	AGCUGCCCGUAUAGGCAGGag
390	161	CUGCCUAUACGGGCAGCUCtt	768	GAGCUGCCCGUAUAGGCAGga
391	162	UGCCUAUACGGGCAGCUCCtt	769	GGAGCUGCCCGUAUAGGCAgg
392	163	GCCUAUACGGGCAGCUCCCtt	770	GGGAGCUGCCCGUAUAGGCag
409	164	CCCAAGUUCCAGGACGGAGtt	771	CUCCGUCCUGGAACUUGGGga
410	165	CCAAGUUCCAGGACGGAGAtt	772	UCUCCGUCCUGGAACUUGGgg
411	166	CAAGUUCCAGGACGGAGACtt	773	GUCUCCGUCCUGGAACUUGgg
412	167	AAGUUCCAGGACGGAGACCtt	774	GGUCUCCGUCCUGGAACUUgg
413	168	AGUUCCAGGACGGAGACCUtt	775	AGGUCUCCGUCCUGGAACUtg
414	169	GUUCCAGGACGGAGACCUCtt	776	GAGGUCUCCGUCCUGGAACtt
415	170	UUCCAGGACGGAGACCUCAtt	777	UGAGGUCUCCGUCCUGGAAct
416	171	UCCAGGACGGAGACCUCACtt	778	GUGAGGUCUCCGUCCUGGAac
417	172	CCAGGACGGAGACCUCACCtt	779	GGUGAGGUCUCCGUCCUGGaa
418	173	CAGGACGGAGACCUCACCCtt	780	GGGUGAGGUCUCCGUCCUGga
419	174	AGGACGGAGACCUCACCCUtt	781	AGGGUGAGGUCUCCGUCCUgg
420	175	GGACGGAGACCUCACCCUGtt	782	CAGGGUGAGGUCUCCGUCCtg
421	176	GACGGAGACCUCACCCUGUtt	783	ACAGGGUGAGGUCUCCGUCct
422	177	ACGGAGACCUCACCCUGUAtt	784	UACAGGGUGAGGUCUCCGUcc
423	178	CGGAGACCUCACCCUGUACtt	785	GUACAGGGUGAGGUCUCCGtc
424	179	GGAGACCUCACCCUGUACCtt	786	GGUACAGGGUGAGGUCUCCgt
425	180	GAGACCUCACCCUGUACCAtt	787	UGGUACAGGGUGAGGUCUCcg

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
426	181	AGACCUCACCCUGUACCAGtt	788	CUGGUACAGGGUGAGGUCUcc
427	182	GACCUCACCCUGUACCAGUtt	789	ACUGGUACAGGGUGAGGUCtc
428	183	ACCUCACCCUGUACCAGUCtt	790	GACUGGUACAGGGUGAGGUct
429	184	CCUCACCCUGUACCAGUCCtt	791	GGACUGGUACAGGGUGAGGtc
430	185	CUCACCCUGUACCAGUCCAtt	792	UGGACUGGUACAGGGUGAGgt
431	186	UCACCCUGUACCAGUCCAAtt	793	UUGGACUGGUACAGGGUGAgg
432	187	CACCCUGUACCAGUCCAAUtt	794	AUUGGACUGGUACAGGGUGag
433	188	ACCCUGUACCAGUCCAAUAtt	795	UAUUGGACUGGUACAGGGUga
434	189	CCCUGUACCAGUCCAAUACtt	796	GUAUUGGACUGGUACAGGGtg
435	190	CCUGUACCAGUCCAAUACCtt	797	GGUAUUGGACUGGUACAGGgt
436	191	CUGUACCAGUCCAAUACCAtt	798	UGGUAUUGGACUGGUACAGgg
437	192	UGUACCAGUCCAAUACCAUtt	799	AUGGUAUUGGACUGGUACAgg
438	193	GUACCAGUCCAAUACCAUCtt	800	GAUGGUAUUGGACUGGUACag
439	194	UACCAGUCCAAUACCAUCCtt	801	GGAUGGUAUUGGACUGGUAca
440	195	ACCAGUCCAAUACCAUCCUtt	802	AGGAUGGUAUUGGACUGGUac
441	196	CCAGUCCAAUACCAUCCUGtt	803	CAGGAUGGUAUUGGACUGGta
442	197	CAGUCCAAUACCAUCCUGCtt	804	GCAGGAUGGUAUUGGACUGgt
443	198	AGUCCAAUACCAUCCUGCGtt	805	CGCAGGAUGGUAUUGGACUgg
444	199	GUCCAAUACCAUCCUGCGUtt	806	ACGCAGGAUGGUAUUGGACtg
445	200	UCCAAUACCAUCCUGCGUCtt	807	GACGCAGGAUGGUAUUGGAct
446	201	CCAAUACCAUCCUGCGUCAtt	808	UGACGCAGGAUGGUAUUGGac
447	202	CAAUACCAUCCUGCGUCACtt	809	GUGACGCAGGAUGGUAUUGga
448	203	AAUACCAUCCUGCGUCACCtt	810	GGUGACGCAGGAUGGUAUUgg
449	204	AUACCAUCCUGCGUCACCUtt	811	AGGUGACGCAGGAUGGUAUtg
450	205	UACCAUCCUGCGUCACCUGtt	812	CAGGUGACGCAGGAUGGUAtt
451	206	ACCAUCCUGCGUCACCUGGtt	813	CCAGGUGACGCAGGAUGGUat
452	207	CCAUCCUGCGUCACCUGGGtt	814	CCCAGGUGACGCAGGAUGGta
453	208	CAUCCUGCGUCACCUGGGCtt	815	GCCCAGGUGACGCAGGAUGgt
454	209	AUCCUGCGUCACCUGGGCCtt	816	GGCCCAGGUGACGCAGGAUgg

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
455	210	UCCUGCGUCACCUGGGCCGtt	817	CGGCCCAGGUGACGCAGGAtg
456	211	CCUGCGUCACCUGGGCCGCtt	818	GCGGCCCAGGUGACGCAGGat
457	212	CUGCGUCACCUGGGCCGCAtt	819	UGCGGCCCAGGUGACGCAGga
458	213	UGCGUCACCUGGGCCGCACtt	820	GUGCGGCCCAGGUGACGCAgg
459	214	GCGUCACCUGGGCCGCACCtt	821	GGUGCGGCCCAGGUGACGCag
460	215	CGUCACCUGGGCCGCACCCtt	822	GGGUGCGGCCCAGGUGACGca
461	216	GUCACCUGGGCCGCACCCUtt	823	AGGGUGCGGCCCAGGUGACgc
462	217	UCACCUGGGCCGCACCCUUtt	824	AAGGGUGCGGCCCAGGUGAcg
463	218	CACCUGGGCCGCACCCUUGtt	825	CAAGGGUGCGGCCCAGGUGac
464	219	ACCUGGGCCGCACCCUUGGtt	826	CCAAGGGUGCGGCCCAGGUga
465	220	CCUGGGCCGCACCCUUGGGtt	827	CCCAAGGGUGCGGCCCAGGtg
466	221	CUGGGCCGCACCCUUGGGCtt	828	GCCCAAGGGUGCGGCCCAGgt
467	222	UGGGCCGCACCCUUGGGCUtt	829	AGCCCAAGGGUGCGGCCCAgg
468	223	GGGCCGCACCCUUGGGCUCtt	830	GAGCCCAAGGGUGCGGCCCag
469	224	GGCCGCACCCUUGGGCUCUtt	831	AGAGCCCAAGGGUGCGGCCca
470	225	GCCGCACCCUUGGGCUCUAtt	832	UAGAGCCCAAGGGUGCGGCcc
471	226	CCGCACCCUUGGGCUCUAUtt	833	AUAGAGCCCAAGGGUGCGGcc
472	227	CGCACCCUUGGGCUCUAUGtt	834	CAUAGAGCCCAAGGGUGCGgc
473	228	GCACCCUUGGGCUCUAUGGtt	835	CCAUAGAGCCCAAGGGUGCgg
474	229	CACCCUUGGGCUCUAUGGGtt	836	CCCAUAGAGCCCAAGGGUGcg
475	230	ACCCUUGGGCUCUAUGGGAtt	837	UCCCAUAGAGCCCAAGGGUgc
476	231	CCCUUGGGCUCUAUGGGAAtt	838	UUCCCAUAGAGCCCAAGGGtg
477	232	CCUUGGGCUCUAUGGGAAGtt	839	CUUCCCAUAGAGCCCAAGGgt
478	233	CUUGGGCUCUAUGGGAAGGtt	840	CCUUCCCAUAGAGCCCAAGgg
479	234	UUGGGCUCUAUGGGAAGGAtt	841	UCCUUCCCAUAGAGCCCAAgg
480	235	UGGGCUCUAUGGGAAGGACtt	842	GUCCUUCCCAUAGAGCCCAag
481	236	GGGCUCUAUGGGAAGGACCtt	843	GGUCCUUCCCAUAGAGCCCaa
482	237	GGCUCUAUGGGAAGGACCAtt	844	UGGUCCUUCCCAUAGAGCCca
483	238	GCUCUAUGGGAAGGACCAGtt	845	CUGGUCCUUCCCAUAGAGCcc

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484	239	CUCUAUGGGAAGGACCAGCtt	846	GCUGGUCCUUCCCAUAGAGcc
485	240	UCUAUGGGAAGGACCAGCAtt	847	UGCUGGUCCUUCCCAUAGAgc
486	241	CUAUGGGAAGGACCAGCAGtt	848	CUGCUGGUCCUUCCCAUAGag
487	242	UAUGGGAAGGACCAGCAGGtt	849	CCUGCUGGUCCUUCCCAUAga
488	243	AUGGGAAGGACCAGCAGGAtt	850	UCCUGCUGGUCCUUCCCAUag
489	244	UGGGAAGGACCAGCAGGAGtt	851	CUCCUGCUGGUCCUUCCCAta
490	245	GGGAAGGACCAGCAGGAGGtt	852	CCUCCUGCUGGUCCUUCCCat
491	246	GGAAGGACCAGCAGGAGGCtt	853	GCCUCCUGCUGGUCCUUCCca
492	247	GAAGGACCAGCAGGAGGCAtt	854	UGCCUCCUGCUGGUCCUUCcc
493	248	AAGGACCAGCAGGAGGCAGtt	855	CUGCCUCCUGCUGGUCCUUcc
494	249	AGGACCAGCAGGAGGCAGCtt	856	GCUGCCUCCUGCUGGUCCUtc
495	250	GGACCAGCAGGAGGCAGCCtt	857	GGCUGCCUCCUGCUGGUCCtt
496	251	GACCAGCAGGAGGCAGCCCtt	858	GGGCUGCCUCCUGCUGGUCct
497	252	ACCAGCAGGAGGCAGCCCUtt	859	AGGGCUGCCUCCUGCUGGUcc
498	253	CCAGCAGGAGGCAGCCCUGtt	860	CAGGGCUGCCUCCUGCUGGtc
499	254	CAGCAGGAGGCAGCCCUGGtt	861	CCAGGGCUGCCUCCUGCUGgt
500	255	AGCAGGAGGCAGCCCUGGUtt	862	ACCAGGGCUGCCUCCUGCUgg
501	256	GCAGGAGGCAGCCCUGGUGtt	863	CACCAGGGCUGCCUCCUGCtg
502	257	CAGGAGGCAGCCCUGGUGGtt	864	CCACCAGGGCUGCCUCCUGct
503	258	AGGAGGCAGCCCUGGUGGAtt	865	UCCACCAGGGCUGCCUCCUgc
504	259	GGAGGCAGCCCUGGUGGACtt	866	GUCCACCAGGGCUGCCUCCtg
505	260	GAGGCAGCCCUGGUGGACAtt	867	UGUCCACCAGGGCUGCCUCct
506	261	AGGCAGCCCUGGUGGACAUtt	868	AUGUCCACCAGGGCUGCCUcc
507	262	GGCAGCCCUGGUGGACAUGtt	869	CAUGUCCACCAGGGCUGCCtc
508	263	GCAGCCCUGGUGGACAUGGtt	870	CCAUGUCCACCAGGGCUGCct
509	264	CAGCCCUGGUGGACAUGGUtt	871	ACCAUGUCCACCAGGGCUGcc
510	265	AGCCCUGGUGGACAUGGUGtt	872	CACCAUGUCCACCAGGGCUgc
511	266	GCCCUGGUGGACAUGGUGAtt	873	UCACCAUGUCCACCAGGGCtg
512	267	CCCUGGUGGACAUGGUGAAtt	874	UUCACCAUGUCCACCAGGGct

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513	268	CCUGGUGGACAUGGUGAAUtt	875	AUUCACCAUGUCCACCAGGgc
514	269	CUGGUGGACAUGGUGAAUGtt	876	CAUUCACCAUGUCCACCAGgg
515	270	UGGUGGACAUGGUGAAUGAtt	877	UCAUUCACCAUGUCCACCAgg
516	271	GGUGGACAUGGUGAAUGACtt	878	GUCAUUCACCAUGUCCACCag
517	272	GUGGACAUGGUGAAUGACGtt	879	CGUCAUUCACCAUGUCCACca
518	273	UGGACAUGGUGAAUGACGGtt	880	CCGUCAUUCACCAUGUCCAcc
519	274	GGACAUGGUGAAUGACGGCtt	881	GCCGUCAUUCACCAUGUCCac
520	275	GACAUGGUGAAUGACGGCGtt	882	CGCCGUCAUUCACCAUGUCca
521	276	ACAUGGUGAAUGACGGCGUtt	883	ACGCCGUCAUUCACCAUGUcc
522	277	CAUGGUGAAUGACGGCGUGtt	884	CACGCCGUCAUUCACCAUGtc
523	278	AUGGUGAAUGACGGCGUGGtt	885	CCACGCCGUCAUUCACCAUgt
524	279	UGGUGAAUGACGGCGUGGAtt	886	UCCACGCCGUCAUUCACCAtg
525	280	GGUGAAUGACGGCGUGGAGtt	887	CUCCACGCCGUCAUUCACCat
526	281	GUGAAUGACGGCGUGGAGGtt	888	CCUCCACGCCGUCAUUCACca
527	282	UGAAUGACGGCGUGGAGGAtt	889	UCCUCCACGCCGUCAUUCAcc
528	283	GAAUGACGGCGUGGAGGACtt	890	GUCCUCCACGCCGUCAUUCac
529	284	AAUGACGGCGUGGAGGACCtt	891	GGUCCUCCACGCCGUCAUUca
530	285	AUGACGGCGUGGAGGACCUtt	892	AGGUCCUCCACGCCGUCAUtc
531	286	UGACGGCGUGGAGGACCUCtt	893	GAGGUCCUCCACGCCGUCAtt
532	287	GACGGCGUGGAGGACCUCCtt	894	GGAGGUCCUCCACGCCGUCat
533	288	ACGGCGUGGAGGACCUCCGtt	895	CGGAGGUCCUCCACGCCGUca
534	289	CGGCGUGGAGGACCUCCGCtt	896	GCGGAGGUCCUCCACGCCGtc
535	290	GGCGUGGAGGACCUCCGCUtt	897	AGCGGAGGUCCUCCACGCCgt
536	291	GCGUGGAGGACCUCCGCUGtt	898	CAGCGGAGGUCCUCCACGCcg
537	292	CGUGGAGGACCUCCGCUGCtt	899	GCAGCGGAGGUCCUCCACGcc
538	293	GUGGAGGACCUCCGCUGCAtt	900	UGCAGCGGAGGUCCUCCACgc
539	294	UGGAGGACCUCCGCUGCAAtt	901	UUGCAGCGGAGGUCCUCCAcg
540	295	GGAGGACCUCCGCUGCAAAtt	902	UUUGCAGCGGAGGUCCUCCac
541	296	GAGGACCUCCGCUGCAAAUtt	903	AUUUGCAGCGGAGGUCCUCca

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
542	297	AGGACCUCCGCUGCAAAUAtt	904	UAUUUGCAGCGGAGGUCCUcc
543	298	GGACCUCCGCUGCAAAUACtt	905	GUAUUUGCAGCGGAGGUCCtc
544	299	GACCUCCGCUGCAAAUACAtt	906	UGUAUUUGCAGCGGAGGUCct
545	300	ACCUCCGCUGCAAAUACAUtt	907	AUGUAUUUGCAGCGGAGGUcc
546	301	CCUCCGCUGCAAAUACAUCtt	908	GAUGUAUUUGCAGCGGAGGtc
547	302	CUCCGCUGCAAAUACAUCUtt	909	AGAUGUAUUUGCAGCGGAGgt
548	303	UCCGCUGCAAAUACAUCUCtt	910	GAGAUGUAUUUGCAGCGGAgg
549	304	CCGCUGCAAAUACAUCUCCtt	911	GGAGAUGUAUUUGCAGCGGag
550	305	CGCUGCAAAUACAUCUCCCtt	912	GGGAGAUGUAUUUGCAGCGga
551	306	GCUGCAAAUACAUCUCCCUtt	913	AGGGAGAUGUAUUUGCAGCgg
552	307	CUGCAAAUACAUCUCCCUCtt	914	GAGGGAGAUGUAUUUGCAGcg
553	308	UGCAAAUACAUCUCCCUCAtt	915	UGAGGGAGAUGUAUUUGCAgc
554	309	GCAAAUACAUCUCCCUCAUtt	916	AUGAGGGAGAUGUAUUUGCag
555	310	CAAAUACAUCUCCCUCAUCtt	917	GAUGAGGGAGAUGUAUUUGca
556	311	AAAUACAUCUCCCUCAUCUtt	918	AGAUGAGGGAGAUGUAUUUgc
557	312	AAUACAUCUCCCUCAUCUAtt	919	UAGAUGAGGGAGAUGUAUUtg
558	313	AUACAUCUCCCUCAUCUACtt	920	GUAGAUGAGGGAGAUGUAUtt
559	314	UACAUCUCCCUCAUCUACAtt	921	UGUAGAUGAGGGAGAUGUAtt
560	315	ACAUCUCCCUCAUCUACACtt	922	GUGUAGAUGAGGGAGAUGUat
561	316	CAUCUCCCUCAUCUACACCtt	923	GGUGUAGAUGAGGGAGAUGta
562	317	AUCUCCCUCAUCUACACCAtt	924	UGGUGUAGAUGAGGGAGAUgt
563	318	UCUCCCUCAUCUACACCAAtt	925	UUGGUGUAGAUGAGGGAGAtg
563	319	GCUCCCUCAUCUACACCAAtt	926	UUGGUGUAGAUGAGGGAGCtg
564	320	CUCCCUCAUCUACACCAACtt	927	GUUGGUGUAGAUGAGGGAGat
565	321	UCCCUCAUCUACACCAACUtt	928	AGUUGGUGUAGAUGAGGGAga
565	322	CUCCCUCAUCUACACCAAAtt	929	UUUGGUGUAGAUGAGGGAGat
566	323	CCCUCAUCUACACCAACUAtt	930	UAGUUGGUGUAGAUGAGGGag
567	324	CCUCAUCUACACCAACUAUtt	931	AUAGUUGGUGUAGAUGAGGga
567	325	CCUCAUCUACACCAACUAAtt	932	UUAGUUGGUGUAGAUGAGGga

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
568	326	CUCAUCUACACCAACUAUGtt	933	CAUAGUUGGUGUAGAUGAGgg
569	327	UCAUCUACACCAACUAUGAtt	934	UCAUAGUUGGUGUAGAUGAgg
570	328	CAUCUACACCAACUAUGAGtt	935	CUCAUAGUUGGUGUAGAUGag
571	329	AUCUACACCAACUAUGAGGtt	936	CCUCAUAGUUGGUGUAGAUga
572	330	UCUACACCAACUAUGAGGCtt	937	GCCUCAUAGUUGGUGUAGAtg
573	331	CUACACCAACUAUGAGGCGtt	938	CGCCUCAUAGUUGGUGUAGat
574	332	UACACCAACUAUGAGGCGGtt	939	CCGCCUCAUAGUUGGUGUAga
575	333	ACACCAACUAUGAGGCGGGtt	940	CCCGCCUCAUAGUUGGUGUag
576	334	CACCAACUAUGAGGCGGGCtt	941	GCCCGCCUCAUAGUUGGUGta
577	335	ACCAACUAUGAGGCGGGCAtt	942	UGCCCGCCUCAUAGUUGGUgt
578	336	CCAACUAUGAGGCGGGCAAtt	943	UUGCCCGCCUCAUAGUUGGtg
579	337	CAACUAUGAGGCGGGCAAGtt	944	CUUGCCCGCCUCAUAGUUGgt
580	338	AACUAUGAGGCGGGCAAGGtt	945	CCUUGCCCGCCUCAUAGUUgg
581	339	ACUAUGAGGCGGGCAAGGAtt	946	UCCUUGCCCGCCUCAUAGUtg
582	340	CUAUGAGGCGGGCAAGGAUtt	947	AUCCUUGCCCGCCUCAUAGtt
583	341	UAUGAGGCGGGCAAGGAUGtt	948	CAUCCUUGCCCGCCUCAUAgt
584	342	AUGAGGCGGGCAAGGAUGAtt	949	UCAUCCUUGCCCGCCUCAUag
585	343	UGAGGCGGGCAAGGAUGACtt	950	GUCAUCCUUGCCCGCCUCAta
586	344	GAGGCGGGCAAGGAUGACUtt	951	AGUCAUCCUUGCCCGCCUCat
587	345	AGGCGGGCAAGGAUGACUAtt	952	UAGUCAUCCUUGCCCGCCUca
588	346	GGCGGGCAAGGAUGACUAUtt	953	AUAGUCAUCCUUGCCCGCCtc
589	347	GCGGGCAAGGAUGACUAUGtt	954	CAUAGUCAUCCUUGCCCGCct
590	348	CGGGCAAGGAUGACUAUGUtt	955	ACAUAGUCAUCCUUGCCCGcc
591	349	GGGCAAGGAUGACUAUGUGtt	956	CACAUAGUCAUCCUUGCCCgc
592	350	GGCAAGGAUGACUAUGUGAtt	957	UCACAUAGUCAUCCUUGCCcg
593	351	GCAAGGAUGACUAUGUGAAtt	958	UUCACAUAGUCAUCCUUGCcc
594	352	CAAGGAUGACUAUGUGAAGtt	959	CUUCACAUAGUCAUCCUUGcc
595	353	AAGGAUGACUAUGUGAAGGtt	960	CCUUCACAUAGUCAUCCUUgc
596	354	AGGAUGACUAUGUGAAGGCtt	961	GCCUUCACAUAGUCAUCCUtg

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
597	355	GGAUGACUAUGUGAAGGCAtt	962	UGCCUUCACAUAGUCAUCCtt
598	356	GAUGACUAUGUGAAGGCACtt	963	GUGCCUUCACAUAGUCAUCct
599	357	AUGACUAUGUGAAGGCACUtt	964	AGUGCCUUCACAUAGUCAUcc
600	358	UGACUAUGUGAAGGCACUGtt	965	CAGUGCCUUCACAUAGUCAtc
601	359	GACUAUGUGAAGGCACUGCtt	966	GCAGUGCCUUCACAUAGUCat
602	360	ACUAUGUGAAGGCACUGCCtt	967	GGCAGUGCCUUCACAUAGUca
603	361	CUAUGUGAAGGCACUGCCCtt	968	GGGCAGUGCCUUCACAUAGtc
604	362	UAUGUGAAGGCACUGCCCGtt	969	CGGGCAGUGCCUUCACAUAgt
605	363	AUGUGAAGGCACUGCCCGGtt	970	CCGGGCAGUGCCUUCACAUag
606	364	UGUGAAGGCACUGCCCGGGtt	971	CCCGGGCAGUGCCUUCACAta
607	365	GUGAAGGCACUGCCCGGGCtt	972	GCCCGGGCAGUGCCUUCACat
608	366	UGAAGGCACUGCCCGGGCAtt	973	UGCCCGGGCAGUGCCUUCAca
609	367	GAAGGCACUGCCCGGGCAAtt	974	UUGCCCGGGCAGUGCCUUCac
610	368	AAGGCACUGCCCGGGCAACtt	975	GUUGCCCGGGCAGUGCCUUca
611	369	AGGCACUGCCCGGGCAACUtt	976	AGUUGCCCGGGCAGUGCCUtc
612	370	GGCACUGCCCGGGCAACUGtt	977	CAGUUGCCCGGGCAGUGCCtt
613	371	GCACUGCCCGGGCAACUGAtt	978	UCAGUUGCCCGGGCAGUGCct
614	372	CACUGCCCGGGCAACUGAAtt	979	UUCAGUUGCCCGGGCAGUGcc
615	373	ACUGCCCGGGCAACUGAAGtt	980	CUUCAGUUGCCCGGGCAGUgc
616	374	CUGCCCGGGCAACUGAAGCtt	981	GCUUCAGUUGCCCGGGCAGtg
617	375	UGCCCGGGCAACUGAAGCCtt	982	GGCUUCAGUUGCCCGGGCAgt
618	376	GCCCGGGCAACUGAAGCCUtt	983	AGGCUUCAGUUGCCCGGGCag
619	377	CCCGGGCAACUGAAGCCUUtt	984	AAGGCUUCAGUUGCCCGGGca
620	378	CCGGGCAACUGAAGCCUUUtt	985	AAAGGCUUCAGUUGCCCGGgc
621	379	CGGGCAACUGAAGCCUUUUtt	986	AAAAGGCUUCAGUUGCCCGgg
622	380	GGGCAACUGAAGCCUUUUGtt	987	CAAAAGGCUUCAGUUGCCCgg
623	381	GGCAACUGAAGCCUUUUGAtt	988	UCAAAAGGCUUCAGUUGCCcg
624	382	GCAACUGAAGCCUUUUGAGtt	989	CUCAAAAGGCUUCAGUUGCcc
625	383	CAACUGAAGCCUUUUGAGAtt	990	UCUCAAAAGGCUUCAGUUGcc

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
626	384	AACUGAAGCCUUUUGAGACtt	991	GUCUCAAAAGGCUUCAGUUgc
627	385	ACUGAAGCCUUUUGAGACCtt	992	GGUCUCAAAAGGCUUCAGUtg
627	386	ACUGAAGCCUUUUGAGACAtt	993	UGUCUCAAAAGGCUUCAGUtg
628	387	CUGAAGCCUUUUGAGACCCtt	994	GGGUCUCAAAAGGCUUCAGtt
629	388	UGAAGCCUUUUGAGACCCUtt	995	AGGGUCUCAAAAGGCUUCAgt
630	389	GAAGCCUUUUGAGACCCUGtt	996	CAGGGUCUCAAAAGGCUUCag
631	390	AAGCCUUUUGAGACCCUGCtt	997	GCAGGGUCUCAAAAGGCUUca
631	391	GAAGCCUUUUGAGACCCUAtt	998	UAGGGUCUCAAAAGGCUUCag
632	392	AGCCUUUUGAGACCCUGCUtt	999	AGCAGGGUCUCAAAAGGCUtc
632	393	CGCCUUUUGAGACCCUGCAtt	1000	UGCAGGGUCUCAAAAGGCGtc
632	394	AGCCUUUUGAGACCCUGCAtt	1001	UGCAGGGUCUCAAAAGGCUtc
633	395	GCCUUUUGAGACCCUGCUGtt	1002	CAGCAGGGUCUCAAAAGGCtt
634	396	CCUUUUGAGACCCUGCUGUtt	1003	ACAGCAGGGUCUCAAAAGGct
634	397	CCUUUUGAGACCCUGCUGAtt	1004	UCAGCAGGGUCUCAAAAGGct
635	398	CUUUUGAGACCCUGCUGUCtt	1005	GACAGCAGGGUCUCAAAAGgc
635	399	CUUUUGAGACCCUGCUGUAtt	1006	UACAGCAGGGUCUCAAAAGgc
636	400	UUUUGAGACCCUGCUGUCCtt	1007	GGACAGCAGGGUCUCAAAAgg
637	401	UUUGAGACCCUGCUGUCCCtt	1008	GGGACAGCAGGGUCUCAAAag
638	402	UUGAGACCCUGCUGUCCCAtt	1009	UGGGACAGCAGGGUCUCAAaa
639	403	UGAGACCCUGCUGUCCCAGtt	1010	CUGGGACAGCAGGGUCUCAaa
640	404	GAGACCCUGCUGUCCCAGAtt	1011	UCUGGGACAGCAGGGUCUCaa
641	405	AGACCCUGCUGUCCCAGAAtt	1012	UUCUGGGACAGCAGGGUCUca
642	406	GACCCUGCUGUCCCAGAACtt	1013	GUUCUGGGACAGCAGGGUCtc
643	407	ACCCUGCUGUCCCAGAACCtt	1014	GGUUCUGGGACAGCAGGGUct
643	408	ACCCUGCUGUCCCAGAACAtt	1015	UGUUCUGGGACAGCAGGGUct
644	409	CCCUGCUGUCCCAGAACCAtt	1016	UGGUUCUGGGACAGCAGGGtc
645	410	CCUGCUGUCCCAGAACCAGtt	1017	CUGGUUCUGGGACAGCAGGgt
646	411	CUGCUGUCCCAGAACCAGGtt	1018	CCUGGUUCUGGGACAGCAGgg
647	412	UGCUGUCCCAGAACCAGGGtt	1019	CCCUGGUUCUGGGACAGCAgg

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
648	413	UGCUGUCCCAGAACCAGGAtt	1020	UCCUGGUUCUGGGACAGCAgg
648	414	GCUGUCCCAGAACCAGGGAtt	1021	UCCCUGGUUCUGGGACAGCag
649	415	CUGUCCCAGAACCAGGGAGtt	1022	CUCCCUGGUUCUGGGACAGca
650	416	UGUCCCAGAACCAGGGAGGtt	1023	CCUCCCUGGUUCUGGGACAgc
651	417	GUCCCAGAACCAGGGAGGCtt	1024	GCCUCCCUGGUUCUGGGACag
652	418	UCCCAGAACCAGGGAGGCAtt	1025	UGCCUCCCUGGUUCUGGGAca
653	419	CCCAGAACCAGGGAGGCAAtt	1026	UUGCCUCCCUGGUUCUGGGac
654	420	CCAGAACCAGGGAGGCAAGtt	1027	CUUGCCUCCCUGGUUCUGGga
655	421	CAGAACCAGGGAGGCAAGAtt	1028	UCUUGCCUCCCUGGUUCUGgg
656	422	AGAACCAGGGAGGCAAGACtt	1029	GUCUUGCCUCCCUGGUUCUgg
657	423	GAACCAGGGAGGCAAGACCtt	1030	GGUCUUGCCUCCCUGGUUCtg
658	424	AACCAGGGAGGCAAGACCUtt	1031	AGGUCUUGCCUCCCUGGUUct
659	425	ACCAGGGAGGCAAGACCUUtt	1032	AAGGUCUUGCCUCCCUGGUtc
660	426	CCAGGGAGGCAAGACCUUCtt	1033	GAAGGUCUUGCCUCCCUGGtt
661	427	CAGGGAGGCAAGACCUUCAtt	1034	UGAAGGUCUUGCCUCCCUGgt
662	428	AGGGAGGCAAGACCUUCAUtt	1035	AUGAAGGUCUUGCCUCCCUgg
663	429	GGGAGGCAAGACCUUCAUUtt	1036	AAUGAAGGUCUUGCCUCCCtg
664	430	GGAGGCAAGACCUUCAUUGtt	1037	CAAUGAAGGUCUUGCCUCCct
665	431	GAGGCAAGACCUUCAUUGUtt	1038	ACAAUGAAGGUCUUGCCUCcc
666	432	AGGCAAGACCUUCAUUGUGtt	1039	CACAAUGAAGGUCUUGCCUcc
667	433	GGCAAGACCUUCAUUGUGGtt	1040	CCACAAUGAAGGUCUUGCCtc
668	434	GCAAGACCUUCAUUGUGGGtt	1041	CCCACAAUGAAGGUCUUGCct
669	435	CAAGACCUUCAUUGUGGGAtt	1042	UCCCACAAUGAAGGUCUUGcc
670	436	AAGACCUUCAUUGUGGGAGtt	1043	CUCCCACAAUGAAGGUCUUgc
671	437	AGACCUUCAUUGUGGGAGAtt	1044	UCUCCCACAAUGAAGGUCUtg
672	438	GACCUUCAUUGUGGGAGACtt	1045	GUCUCCCACAAUGAAGGUCtt
673	439	ACCUUCAUUGUGGGAGACCtt	1046	GGUCUCCCACAAUGAAGGUct
674	440	CCUUCAUUGUGGGAGACCAtt	1047	UGGUCUCCCACAAUGAAGGtc
675	441	CUUCAUUGUGGGAGACCAGtt	1048	CUGGUCUCCCACAAUGAAGgt

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
676	442	UUCAUUGUGGGAGACCAGAtt	1049	UCUGGUCUCCCACAAUGAAgg
677	443	UCAUUGUGGGAGACCAGAUtt	1050	AUCUGGUCUCCCACAAUGAag
678	444	CAUUGUGGGAGACCAGAUCtt	1051	GAUCUGGUCUCCCACAAUGaa
679	445	AUUGUGGGAGACCAGAUCUtt	1052	AGAUCUGGUCUCCCACAAUga
680	446	UUGUGGGAGACCAGAUCUCtt	1053	GAGAUCUGGUCUCCCACAAtg
681	447	UGUGGGAGACCAGAUCUCCtt	1054	GGAGAUCUGGUCUCCCACAat
682	448	GUGGGAGACCAGAUCUCCUtt	1055	AGGAGAUCUGGUCUCCCACaa
683	449	UGGGAGACCAGAUCUCCUUtt	1056	AAGGAGAUCUGGUCUCCCAca
684	450	GGGAGACCAGAUCUCCUUCtt	1057	GAAGGAGAUCUGGUCUCCCac
685	451	GGAGACCAGAUCUCCUUCGtt	1058	CGAAGGAGAUCUGGUCUCCca
686	452	GAGACCAGAUCUCCUUCGCtt	1059	GCGAAGGAGAUCUGGUCUCcc
687	453	AGACCAGAUCUCCUUCGCUtt	1060	AGCGAAGGAGAUCUGGUCUcc
688	454	GACCAGAUCUCCUUCGCUGtt	1061	CAGCGAAGGAGAUCUGGUCtc
689	455	ACCAGAUCUCCUUCGCUGAtt	1062	UCAGCGAAGGAGAUCUGGUct
690	456	CCAGAUCUCCUUCGCUGACtt	1063	GUCAGCGAAGGAGAUCUGGtc
691	457	CAGAUCUCCUUCGCUGACUtt	1064	AGUCAGCGAAGGAGAUCUGgt
692	458	AGAUCUCCUUCGCUGACUAtt	1065	UAGUCAGCGAAGGAGAUCUgg
693	459	GAUCUCCUUCGCUGACUACtt	1066	GUAGUCAGCGAAGGAGAUCtg
694	460	AUCUCCUUCGCUGACUACAtt	1067	UGUAGUCAGCGAAGGAGAUct
695	461	UCUCCUUCGCUGACUACAAtt	1068	UUGUAGUCAGCGAAGGAGAtc
696	462	CUCCUUCGCUGACUACAACtt	1069	GUUGUAGUCAGCGAAGGAGat
697	463	UCCUUCGCUGACUACAACCtt	1070	GGUUGUAGUCAGCGAAGGAga
698	464	CCUUCGCUGACUACAACCUtt	1071	AGGUUGUAGUCAGCGAAGGag
699	465	CUUCGCUGACUACAACCUGtt	1072	CAGGUUGUAGUCAGCGAAGga
700	466	UUCGCUGACUACAACCUGCtt	1073	GCAGGUUGUAGUCAGCGAAgg
701	467	UCGCUGACUACAACCUGCUtt	1074	AGCAGGUUGUAGUCAGCGAag
702	468	CGCUGACUACAACCUGCUGtt	1075	CAGCAGGUUGUAGUCAGCGaa
703	469	GCUGACUACAACCUGCUGGtt	1076	CCAGCAGGUUGUAGUCAGCga
704	470	CUGACUACAACCUGCUGGAtt	1077	UCCAGCAGGUUGUAGUCAGcg

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
705	471	UGACUACAACCUGCUGGACtt	1078	GUCCAGCAGGUUGUAGUCAgc
706	472	GACUACAACCUGCUGGACUtt	1079	AGUCCAGCAGGUUGUAGUCag
707	473	ACUACAACCUGCUGGACUUtt	1080	AAGUCCAGCAGGUUGUAGUca
708	474	CUACAACCUGCUGGACUUGtt	1081	CAAGUCCAGCAGGUUGUAGtc
709	475	UACAACCUGCUGGACUUGCtt	1082	GCAAGUCCAGCAGGUUGUAgt
710	476	ACAACCUGCUGGACUUGCUtt	1083	AGCAAGUCCAGCAGGUUGUag
711	477	CAACCUGCUGGACUUGCUGtt	1084	CAGCAAGUCCAGCAGGUUGta
712	478	AACCUGCUGGACUUGCUGCtt	1085	GCAGCAAGUCCAGCAGGUUgt
713	479	ACCUGCUGGACUUGCUGCUtt	1086	AGCAGCAAGUCCAGCAGGUtg
714	480	CCUGCUGGACUUGCUGCUGtt	1087	CAGCAGCAAGUCCAGCAGGtt
715	481	CUGCUGGACUUGCUGCUGAtt	1088	UCAGCAGCAAGUCCAGCAGgt
716	482	UGCUGGACUUGCUGCUGAUtt	1089	AUCAGCAGCAAGUCCAGCAgg
717	483	GCUGGACUUGCUGCUGAUCtt	1090	GAUCAGCAGCAAGUCCAGCag
718	484	CUGGACUUGCUGCUGAUCCtt	1091	GGAUCAGCAGCAAGUCCAGca
719	485	UGGACUUGCUGCUGAUCCAtt	1092	UGGAUCAGCAGCAAGUCCAgc
720	486	GGACUUGCUGCUGAUCCAUtt	1093	AUGGAUCAGCAGCAAGUCCag
721	487	GACUUGCUGCUGAUCCAUGtt	1094	CAUGGAUCAGCAGCAAGUCca
722	488	ACUUGCUGCUGAUCCAUGAtt	1095	UCAUGGAUCAGCAGCAAGUcc
723	489	CUUGCUGCUGAUCCAUGAGtt	1096	CUCAUGGAUCAGCAGCAAGtc
724	490	UUGCUGCUGAUCCAUGAGGtt	1097	CCUCAUGGAUCAGCAGCAAgt
725	491	UGCUGCUGAUCCAUGAGGUtt	1098	ACCUCAUGGAUCAGCAGCAag
726	492	GCUGCUGAUCCAUGAGGUCtt	1099	GACCUCAUGGAUCAGCAGCaa
727	493	CUGCUGAUCCAUGAGGUCCtt	1100	GGACCUCAUGGAUCAGCAGca
728	494	UGCUGAUCCAUGAGGUCCUtt	1101	AGGACCUCAUGGAUCAGCAgc
729	495	GCUGAUCCAUGAGGUCCUAtt	1102	UAGGACCUCAUGGAUCAGCag
730	496	CUGAUCCAUGAGGUCCUAGtt	1103	CUAGGACCUCAUGGAUCAGca
731	497	UGAUCCAUGAGGUCCUAGCtt	1104	GCUAGGACCUCAUGGAUCAgc
732	498	GAUCCAUGAGGUCCUAGCCtt	1105	GGCUAGGACCUCAUGGAUCag
733	499	AUCCAUGAGGUCCUAGCCCtt	1106	GGGCUAGGACCUCAUGGAUca

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
750	500	CCCUGGCUGCCUGGAUGCGtt	1107	CGCAUCCAGGCAGCCAGGGgc
751	501	CCUGGCUGCCUGGAUGCGUtt	1108	ACGCAUCCAGGCAGCCAGGgg
752	502	CUGGCUGCCUGGAUGCGUUtt	1109	AACGCAUCCAGGCAGCCAGgg
753	503	UGGCUGCCUGGAUGCGUUCtt	1110	GAACGCAUCCAGGCAGCCAgg
754	504	GGCUGCCUGGAUGCGUUCCtt	1111	GGAACGCAUCCAGGCAGCCag
755	505	GCUGCCUGGAUGCGUUCCCtt	1112	GGGAACGCAUCCAGGCAGCca
773	506	CCCUGCUCUCAGCAUAUGUtt	1113	ACAUAUGCUGAGAGCAGGGgg
774	507	CCUGCUCUCAGCAUAUGUGtt	1114	CACAUAUGCUGAGAGCAGGgg
775	508	CUGCUCUCAGCAUAUGUGGtt	1115	CCACAUAUGCUGAGAGCAGgg
776	509	UGCUCUCAGCAUAUGUGGGtt	1116	CCCACAUAUGCUGAGAGCAgg
793	510	GGGCGCCUCAGUGCCCGGCtt	1117	GCCGGGCACUGAGGCGCCCca
794	511	GGCGCCUCAGUGCCCGGCCtt	1118	GGCCGGGCACUGAGGCGCCcc
795	512	GCGCCUCAGUGCCCGGCCCtt	1119	GGGCCGGGCACUGAGGCGCcc
796	513	CGCCUCAGUGCCCGGCCCAtt	1120	UGGGCCGGGCACUGAGGCGcc
797	514	GCCUCAGUGCCCGGCCCAAtt	1121	UUGGGCCGGGCACUGAGGCgc
798	515	CCUCAGUGCCCGGCCCAAGtt	1122	CUUGGGCCGGGCACUGAGGcg
799	516	CUCAGUGCCCGGCCCAAGCtt	1123	GCUUGGGCCGGGCACUGAGgc
800	517	UCAGUGCCCGGCCCAAGCUtt	1124	AGCUUGGGCCGGGCACUGAgg
801	518	CAGUGCCCGGCCCAAGCUCtt	1125	GAGCUUGGGCCGGGCACUGag
802	519	AGUGCCCGGCCCAAGCUCAtt	1126	UGAGCUUGGGCCGGGCACUga
803	520	GUGCCCGGCCCAAGCUCAAtt	1127	UUGAGCUUGGGCCGGGCACtg
804	521	UGCCCGGCCCAAGCUCAAGtt	1128	CUUGAGCUUGGGCCGGGCAct
805	522	GCCCGGCCCAAGCUCAAGGtt	1129	CCUUGAGCUUGGGCCGGGCac
806	523	CCCGGCCCAAGCUCAAGGCtt	1130	GCCUUGAGCUUGGGCCGGGca
807	524	CCGGCCCAAGCUCAAGGCCtt	1131	GGCCUUGAGCUUGGGCCGGgc
808	525	CGGCCCAAGCUCAAGGCCUtt	1132	AGGCCUUGAGCUUGGGCCGgg
809	526	GGCCCAAGCUCAAGGCCUUtt	1133	AAGGCCUUGAGCUUGGGCCgg
810	527	GCCCAAGCUCAAGGCCUUCtt	1134	GAAGGCCUUGAGCUUGGGCcg
811	528	CCCAAGCUCAAGGCCUUCCtt	1135	GGAAGGCCUUGAGCUUGGGcc

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
812	529	CCAAGCUCAAGGCCUUCCUtt	1136	AGGAAGGCCUUGAGCUUGGgc
813	530	CAAGCUCAAGGCCUUCCUGtt	1137	CAGGAAGGCCUUGAGCUUGgg
814	531	AAGCUCAAGGCCUUCCUGGtt	1138	CCAGGAAGGCCUUGAGCUUgg
815	532	AGCUCAAGGCCUUCCUGGCtt	1139	GCCAGGAAGGCCUUGAGCUtg
816	533	GCUCAAGGCCUUCCUGGCCtt	1140	GGCCAGGAAGGCCUUGAGCtt
817	534	CUCAAGGCCUUCCUGGCCUtt	1141	AGGCCAGGAAGGCCUUGAGct
818	535	UCAAGGCCUUCCUGGCCUCtt	1142	GAGGCCAGGAAGGCCUUGAgc
819	536	CAAGGCCUUCCUGGCCUCCtt	1143	GGAGGCCAGGAAGGCCUUGag
820	537	AAGGCCUUCCUGGCCUCCCtt	1144	GGGAGGCCAGGAAGGCCUUga
837	538	CCCUGAGUACGUGAACCUCtt	1145	GAGGUUCACGUACUCAGGGga
838	539	CCUGAGUACGUGAACCUCCtt	1146	GGAGGUUCACGUACUCAGGgg
839	540	CUGAGUACGUGAACCUCCCtt	1147	GGGAGGUUCACGUACUCAGgg
856	541	CCCAUCAAUGGCAACGGGAtt	1148	UCCCGUUGCCAUUGAUGGGga
857	542	CCAUCAAUGGCAACGGGAAtt	1149	UUCCCGUUGCCAUUGAUGGgg
858	543	CAUCAAUGGCAACGGGAAAtt	1150	UUUCCCGUUGCCAUUGAUGgg
859	544	AUCAAUGGCAACGGGAAACtt	1151	GUUUCCCGUUGCCAUUGAUgg
860	545	UCAAUGGCAACGGGAAACAtt	1152	UGUUUCCCGUUGCCAUUGAtg
861	546	CAAUGGCAACGGGAAACAGtt	1153	CUGUUUCCCGUUGCCAUUGat
862	547	AAUGGCAACGGGAAACAGUtt	1154	ACUGUUUCCCGUUGCCAUUga
863	548	AUGGCAACGGGAAACAGUGtt	1155	CACUGUUUCCCGUUGCCAUtg
864	549	UGGCAACGGGAAACAGUGAtt	1156	UCACUGUUUCCCGUUGCCAtt
865	550	GGCAACGGGAAACAGUGAGtt	1157	CUCACUGUUUCCCGUUGCCat
866	551	GCAACGGGAAACAGUGAGGtt	1158	CCUCACUGUUUCCCGUUGCca
867	552	CAACGGGAAACAGUGAGGGtt	1159	CCCUCACUGUUUCCCGUUGcc
868	553	AACGGGAAACAGUGAGGGUtt	1160	ACCCUCACUGUUUCCCGUUgc
869	554	ACGGGAAACAGUGAGGGUUtt	1161	AACCCUCACUGUUUCCCGUtg
870	555	CGGGAAACAGUGAGGGUUGtt	1162	CAACCCUCACUGUUUCCCGtt
871	556	GGGAAACAGUGAGGGUUGGtt	1163	CCAACCCUCACUGUUUCCCgt
872	557	GGAAACAGUGAGGGUUGGGtt	1164	CCCAACCCUCACUGUUUCCcg

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
891	558	GGGACUCUGAGCGGGAGGCtt	1165	GCCUCCCGCUCAGAGUCCCcc
892	559	GGACUCUGAGCGGGAGGCAtt	1166	UGCCUCCCGCUCAGAGUCCcc
894	560	ACUCUGAGCGGGAGGCAGAtt	1167	UCUGCCUCCCGCUCAGAGUcc
896	561	UCUGAGCGGGAGGCAGAGUtt	1168	ACUCUGCCUCCCGCUCAGAgt
897	562	CUGAGCGGGAGGCAGAGUUtt	1169	AACUCUGCCUCCCGCUCAGag
898	563	UGAGCGGGAGGCAGAGUUUtt	1170	AAACUCUGCCUCCCGCUCAga
899	564	GAGCGGGAGGCAGAGUUUGtt	1171	CAAACUCUGCCUCCCGCUCag
900	565	AGCGGGAGGCAGAGUUUGCtt	1172	GCAAACUCUGCCUCCCGCUca
901	566	GCGGGAGGCAGAGUUUGCCtt	1173	GGCAAACUCUGCCUCCCGCtc
902	567	CGGGAGGCAGAGUUUGCCUtt	1174	AGGCAAACUCUGCCUCCCGct
903	568	GGGAGGCAGAGUUUGCCUUtt	1175	AAGGCAAACUCUGCCUCCCgc
904	569	GGAGGCAGAGUUUGCCUUCtt	1176	GAAGGCAAACUCUGCCUCCcg
905	570	GAGGCAGAGUUUGCCUUCCtt	1177	GGAAGGCAAACUCUGCCUCcc
906	571	AGGCAGAGUUUGCCUUCCUtt	1178	AGGAAGGCAAACUCUGCCUcc
907	572	GGCAGAGUUUGCCUUCCUUtt	1179	AAGGAAGGCAAACUCUGCCtc
908	573	GCAGAGUUUGCCUUCCUUUtt	1180	AAAGGAAGGCAAACUCUGCct
909	574	CAGAGUUUGCCUUCCUUUCtt	1181	GAAAGGAAGGCAAACUCUGcc
910	575	AGAGUUUGCCUUCCUUUCUtt	1182	AGAAAGGAAGGCAAACUCUgc
911	576	GAGUUUGCCUUCCUUUCUCtt	1183	GAGAAAGGAAGGCAAACUCtg
912	577	AGUUUGCCUUCCUUUCUCCtt	1184	GGAGAAAGGAAGGCAAACUct
913	578	GUUUGCCUUCCUUUCUCCAtt	1185	UGGAGAAAGGAAGGCAAACtc
914	579	UUUGCCUUCCUUUCUCCAGtt	1186	CUGGAGAAAGGAAGGCAAAct
915	580	UUGCCUUCCUUUCUCCAGGtt	1187	CCUGGAGAAAGGAAGGCAAac
916	581	UGCCUUCCUUUCUCCAGGAtt	1188	UCCUGGAGAAAGGAAGGCAaa
917	582	GCCUUCCUUUCUCCAGGACtt	1189	GUCCUGGAGAAAGGAAGGCaa
918	583	CCUUCCUUUCUCCAGGACCtt	1190	GGUCCUGGAGAAAGGAAGGca
919	584	CUUCCUUUCUCCAGGACCAtt	1191	UGGUCCUGGAGAAAGGAAGgc
920	585	UUCCUUUCUCCAGGACCAAtt	1192	UUGGUCCUGGAGAAAGGAAgg
921	586	UCCUUUCUCCAGGACCAAUtt	1193	AUUGGUCCUGGAGAAAGGAag

Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:2 to 608	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:609 to 1215
922	587	CCUUUCUCCAGGACCAAUAtt	1194	UAUUGGUCCUGGAGAAAGGaa
923	588	CUUUCUCCAGGACCAAUAAtt	1195	UUAUUGGUCCUGGAGAAAGga
924	589	UUUCUCCAGGACCAAUAAAtt	1196	UUUAUUGGUCCUGGAGAAAgg
925	590	UUCUCCAGGACCAAUAAAAtt	1197	UUUUAUUGGUCCUGGAGAAag
926	591	UCUCCAGGACCAAUAAAAUtt	1198	AUUUUAUUGGUCCUGGAGAaa
927	592	CUCCAGGACCAAUAAAAUUtt	1199	AAUUUUAUUGGUCCUGGAGaa
928	593	UCCAGGACCAAUAAAAUUUtt	1200	AAAUUUUAUUGGUCCUGGAga
929	594	CCAGGACCAAUAAAAUUUCtt	1201	GAAAUUUUAUUGGUCCUGGag
930	595	CAGGACCAAUAAAAUUUCUtt	1202	AGAAAUUUUAUUGGUCCUGga
931	596	AGGACCAAUAAAAUUUCUAtt	1203	UAGAAAUUUUAUUGGUCCUgg
932	597	GGACCAAUAAAAUUUCUAAtt	1204	UUAGAAAUUUUAUUGGUCCtg
933	598	GACCAAUAAAAUUUCUAAGtt	1205	CUUAGAAAUUUUAUUGGUCct
934	599	ACCAAUAAAAUUUCUAAGAtt	1206	UCUUAGAAAUUUUAUUGGUcc
935	600	CCAAUAAAAUUUCUAAGAGtt	1207	CUCUUAGAAAUUUUAUUGGtc
936	601	CAAUAAAAUUUCUAAGAGAtt	1208	UCUCUUAGAAAUUUUAUUGgt
937	602	AAUAAAAUUUCUAAGAGAGtt	1209	CUCUCUUAGAAAUUUUAUUgg
938	603	AUAAAAUUUCUAAGAGAGCtt	1210	GCUCUCUUAGAAAUUUUAUtg
939	604	UAAAAUUUCUAAGAGAGCUtt	1211	AGCUCUCUUAGAAAUUUUAtt
940	605	AAAAUUUCUAAGAGAGCUAtt	1212	UAGCUCUCUUAGAAAUUUUat
941	606	AAAUUUCUAAGAGAGCUAAtt	1213	UUAGCUCUCUUAGAAAUUUta
942	607	AAUUUCUAAGAGAGCUAAAtt	1214	UUUAGCUCUCUUAGAAAUUtt
943	608	AUUUCUAAGAGAGCUAAAAtt	1215	UUUUAGCUCUCUUAGAAAUtt

[0058] Key for Table 1: Upper case A, G, C and U referred to for ribo-A, ribo-G, ribo-C and ribo-U respectively. The lower case letters a, g, c, t represent 2'-deoxy-A, 2'-deoxy-G, 2'-deoxy-C and thymidine respectively.

Table 2: RNAi molecule sequences for GST-π

ID	Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:1216 to 1280	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:1281 to 1345
A1	652	1216	UCCCAGAACCAGGGAGGCAtt	1281	UGCCUCCCUGGUUCUGGGAca
A10	635	1217	CUUUUGAGACCCUGCUGUCtt	1282	GACAGCAGGGUCUCAAAAGgc
A11	649	1218	CUGUCCCAGAACCAGGGAGtt	1283	CUCCCUGGUUCUGGGACAGca
A12	650	1219	UGUCCCAGAACCAGGGAGGtt	1284	CCUCCCUGGUUCUGGGACAgc
A13	631	1220	AAGCCUUUUGAGACCCUGCtt	1285	GCAGGGUCUCAAAAGGCUUca
A14	638	1221	UUGAGACCCUGCUGUCCCAtt	1286	UGGGACAGCAGGGUCUCAAaa
A15	636	1222	UUUUGAGACCCUGCUGUCCtt	1287	GGACAGCAGGGUCUCAAAAgg
A16	640	1223	GAGACCCUGCUGUCCCAGAtt	1288	UCUGGGACAGCAGGGUCUCaa
A17	332	1224	GCUGGAAGGAGGAGGUGGUtt	1289	ACCACCUCCUCCUUCCAGCtc
A18	333	1225	CUGGAAGGAGGAGGUGGUGtt	1290	CACCACCUCCUCCUUCCAGct
A19	321	1226	UCAGGGCCAGAGCUGGAAGtt	1291	CUUCCAGCUCUGGCCCUGAtc
A2	639	1227	UGAGACCCUGCUGUCCCAGtt	1292	CUGGGACAGCAGGGUCUCAaa
A20	323	1228	AGGGCCAGAGCUGGAAGGAtt	1293	UCCUUCCAGCUCUGGCCCUga
A21	331	1229	AGCUGGAAGGAGGAGGUGGtt	1294	CCACCUCCUCCUUCCAGCUct
A22	641	1230	AGACCCUGCUGUCCCAGAAtt	1295	UUCUGGGACAGCAGGGUCUca
A23	330	1231	GAGCUGGAAGGAGGAGGUGtt	1296	CACCUCCUCCUUCCAGCUCtg
A25	647	1232	UGCUGUCCCAGAACCAGGGtt	1297	CCCUGGUUCUGGGACAGCAgg
A26	653	1233	CCCAGAACCAGGGAGGCAAtt	1298	UUGCCUCCCUGGUUCUGGGac
A3	654	1234	CCAGAACCAGGGAGGCAAGtt	1299	CUUGCCUCCCUGGUUCUGGga
A4	637	1235	UUUGAGACCCUGCUGUCCCtt	1300	GGGACAGCAGGGUCUCAAAag
A5	642	1236	GACCCUGCUGUCCCAGAACtt	1301	GUUCUGGGACAGCAGGGUCtc
A6	319	1237	GAUCAGGGCCAGAGCUGGAtt	1302	UCCAGCUCUGGCCCUGAUCtg
A7	632	1238	AGCCUUUUGAGACCCUGCUtt	1303	AGCAGGGUCUCAAAAGGCUtc
A8	633	1239	GCCUUUUGAGACCCUGCUGtt	1304	CAGCAGGGUCUCAAAAGGCtt
A9	634	1240	CCUUUUGAGACCCUGCUGUtt	1305	ACAGCAGGGUCUCAAAAGGct
AG7	632	1241	CGCCUUUUGAGACCCUGCAtt	1306	UGCAGGGUCUCAAAAGGCGtc

ID	Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:1216 to 1280	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:1281 to 1345
AK1	257	1242	CCUACACCGUGGUCUAUUUtt	1307	AAAUAGACCACGGUGUAGGgc
AK10	681	1243	UGUGGGAGACCAGAUCUCCtt	1308	GGAGAUCUGGUCUCCCACAat
AK11	901	1244	GCGGGAGGCAGAGUUUGCCtt	1309	GGCAAACUCUGCCUCCCGCtc
AK12	922	1245	CCUUUCUCCAGGACCAAUAtt	1310	UAUUGGUCCUGGAGAAAGGaa
AK13 /A24	643	1246	ACCCUGCUGUCCCAGAACCtt	1311	GGUUCUGGGACAGCAGGGUct
AK2	267	1247	GGUCUAUUUCCCAGUUCGAtt	1312	UCGAACUGGGAAAUAGACCac
AK3	512	1248	CCCUGGUGGACAUGGUGAAtt	1313	UUCACCAUGUCCACCAGGGct
AK4	560	1249	ACAUCUCCCUCAUCUACACtt	1314	GUGUAGAUGAGGGAGAUGUat
AK5	593	1250	GCAAGGAUGACUAUGUGAAtt	1315	UUCACAUAGUCAUCCUUGCcc
AK6	698	1251	CCUUCGCUGACUACAACCUtt	1316	AGGUUGUAGUCAGCGAAGGag
AK7	313	1252	CUGGCAGAUCAGGGCCAGAtt	1317	UCUGGCCCUGAUCUGCCAGca
AK8	421	1253	GACGGAGACCUCACCCUGUtt	1318	ACAGGGUGAGGUCUCCGUCct
AK9	590	1254	CGGGCAAGGAUGACUAUGUtt	1319	ACAUAGUCAUCCUUGCCCGcc
AU10	635	1255	CUUUUGAGACCCUGCUGUAtt	1320	UACAGCAGGGUCUCAAAAGgc
AU23	330	1256	GAGCUGGAAGGAGGAGGUAtt	1321	UACCUCCUCCUUCCAGCUCtg
AU24	643	1257	ACCCUGCUGUCCCAGAACAtt	1322	UGUUCUGGGACAGCAGGGUct
AU25	648	1258	UGCUGUCCCAGAACCAGGAtt	1323	UCCUGGUUCUGGGACAGCAgg
AU7	632	1259	AGCCUUUUGAGACCCUGCAtt	1324	UGCAGGGUCUCAAAAGGCUtc
AU9	634	1260	CCUUUUGAGACCCUGCUGAtt	1325	UCAGCAGGGUCUCAAAAGGct
B1	629	1261	UGAAGCCUUUUGAGACCCUtt	1326	AGGGUCUCAAAAGGCUUCAgt
B10	627	1262	ACUGAAGCCUUUUGAGACCtt	1327	GGUCUCAAAAGGCUUCAGUtg
B11	596	1263	AGGAUGACUAUGUGAAGGCtt	1328	GCCUUCACAUAGUCAUCCUtg
B12	597	1264	GGAUGACUAUGUGAAGGCAtt	1329	UGCCUUCACAUAGUCAUCCtt
B13	598	1265	GAUGACUAUGUGAAGGCACtt	1330	GUGCCUUCACAUAGUCAUCct
B14	564	1266	CUCCCUCAUCUACACCAACtt	1331	GUUGGUGUAGAUGAGGGAGat
B2	630	1267	GAAGCCUUUUGAGACCCUGtt	1332	CAGGGUCUCAAAAGGCUUCag
B3	563	1268	UCUCCCUCAUCUACACCAAtt	1333	UUGGUGUAGAUGAGGGAGAtg
B4	567	1269	CCUCAUCUACACCAACUAUtt	1334	AUAGUUGGUGUAGAUGAGGga
B5	566	1270	CCCUCAUCUACACCAACUAtt	1335	UAGUUGGUGUAGAUGAGGGag

ID	Ref Pos	SEQ ID NO	SENSE STRAND (5'-->3') SEQ ID NOS:1216 to 1280	SEQ ID NO	ANTISENSE STRAND (5'-->3') SEQ ID NOS:1281 to 1345
B6	625	1271	CAACUGAAGCCUUUUGAGAtt	1336	UCUCAAAAGGCUUCAGUUGcc
B7	626	1272	AACUGAAGCCUUUUGAGACtt	1337	GUCUCAAAAGGCUUCAGUUgc
B8	628	1273	CUGAAGCCUUUUGAGACCCtt	1338	GGGUCUCAAAAGGCUUCAGtt
B9	565	1274	UCCCUCAUCUACACCAACUtt	1339	AGUUGGUGUAGAUGAGGGAga
BG3	563	1275	GCUCCCUCAUCUACACCAAtt	1340	UUGGUGUAGAUGAGGGAGCtg
BU02	631	1276	GAAGCCUUUUGAGACCCUAtt	1341	UAGGGUCUCAAAAGGCUUCag
BU10	627	1277	ACUGAAGCCUUUUGAGACAtt	1342	UGUCUCAAAAGGCUUCAGUtg
BU14	565	1278	CUCCCUCAUCUACACCAAAtt	1343	UUUGGUGUAGAUGAGGGAGat
BU4	567	1279	CCUCAUCUACACCAACUAAtt	1344	UUAGUUGGUGUAGAUGAGGga
C1-934	934	1280	ACCAAUAAAAUUUCUAAGAtt	1345	UCUUAGAAAUUUUAUUGGUcc

[0059] Key for Table 2: Upper case A, G, C and U referred to for ribo-A, ribo-G, ribo-C and ribo-U respectively. The lower case letters a, g, c, t represent 2'-deoxy-A, 2'-deoxy-G, 2'-deoxy-C and thymidine respectively.

[0060] For example, a siRNA of this invention may have an antisense strand which is SEQ ID NO:1341, and a sense strand which is SEQ ID NO:1276, or chemically modified strands thereof.

[0061] For example, a siRNA of this invention may have an antisense strand which is SEQ ID NO:1305, and a sense strand which is SEQ ID NO:1240, or chemically modified strands thereof.

[0062] Chemical modifications may comprise a 2'-OMe substituent group on any nucleotide in any position in a strand, as well as other modifications known in the art.

[0063] Methods for modulating GST-π and treating malignant tumor

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] The RNAi molecules of this invention can be used to modulate or inhibit the expression of GST-π in a sequence-specific manner.

[0070] 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.

[0071] In certain aspects, malignant tumor may be treated by RNA interference using a RNAi molecule of this invention.

[0072] Treatment of malignant tumor may be characterized in suitable cell-based models, as well as ex vivo or in vivo animal models.

[0073] 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.

[0074] Treatment of malignant tumor may be characterized by non-invasive medical scanning of an affected organ or tissue.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] RNA Interference

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] RNAi molecules can also be used to knock down viral gene expression, and therefore affect viral replication.

[0088] 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.

[0089] 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.

[0090] In certain embodiments, a RNAi molecule can be active in a RISC complex, with a length of duplex region active for RISC.

[0091] 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.

[0092] 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.

[0093] 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 $\geqq$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.

[0094] 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.

[0095] 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.

[0096] The overhangs of a RNAi molecule can have the same length, or can be different lengths.

[0097] 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.

[0098] 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.

[0099] 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.

[00100] 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.

[00101] In some embodiments, both ends of a RNAi molecule are blunt ends.

[00102] In additional embodiments, both ends of a RNAi molecule have an overhang.

[00103] The overhangs at the 5′- and 3′-ends may be of different lengths.

[00104] 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.

[00105] 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.

[00106] A RNAi molecule may have mismatches in base pairing in the duplex region.

[00107] Any nucleotide in an overhang of a RNAi molecule can be a deoxyribonucleotide, or a ribonucleotide.

[00108] 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.

[00109] 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.

[00110] In some embodiments, one or more, or all of the overhang nucleotides of a RNAi molecule may be 2′-deoxyribonucleotides.

[00111] Dicer Substrate RNAi Molecules

[00112] 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.

[00113] 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.

[00114] In certain embodiments, the longest strand in a Dicer substrate dsRNA may be 24-30 nucleotides in length.

[00115] A Dicer substrate dsRNA can be symmetric or asymmetric.

[00116] In some embodiments, a Dicer substrate dsRNA can have a sense strand of 22-28 nucleotides and an antisense strand of 24-30 nucleotides.

[00117] In certain embodiments, a Dicer substrate dsRNA may have an overhang on the 3′ end of the antisense strand.

[00118] 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.

[00119] An asymmetric Dicer substrate dsRNA may have two deoxyribonucleotides at the 3′-end of the sense strand in place of two of the ribonucleotides.

[00120] 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.

[00121] The sense strand of a Dicer substrate dsRNA may be 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length.

[00122] 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.

[00123] In certain embodiments, a Dicer substrate dsRNA may have sense and antisense strands that are 26 to 29 nucleotides in length.

[00124] In certain embodiments, a Dicer substrate dsRNA may have sense and antisense strands that are 27 nucleotides in length.

[00125] 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.

[00126] A Dicer substrate dsRNA may have a duplex region of 19, 20, 21, 22, 23, 24, 25, 26 or 27 nucleotides in length.

[00127] 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.

[00128] 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.

[00129] The sense and antisense strands of a Dicer substrate are in general complementary, but may have mismatches in base pairing.

[00130] 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.

[00131] 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.

[00132] 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.

[00133] 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.

[00134] Methods of use of RNAi molecules

[00135] 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.

[00136] 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.

[00137] 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.

[00138] 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.

[00139] 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.

[00140] 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.

[00141] 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.

[00142] 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.

[00143] 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.

[00144] 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.

[00145] Pharmaceutically acceptable formulations for administering oligonucleotides are known and can be used.

[00146] EXAMPLES

[00147] **Example 1:** 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 as shown in Table 3.

Table 3: Dose dependent knockdown for GST-π mRNA in an A549 cell line

siRNA	IC50 (pM)
A9	27, 29
B2	121
B3	235
B4	229
B13	23, 34
BU02	21, 25, 34

[00148] **Example 2:** Protocol for in vitro knockdown.

[00149] One day before the transfection, plate the cells in a 96-well plate at 2 x 103 cells per well with 100 µl 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, change medium to 90 µl of Opti-MEM I Reduced Serum Medium (Life Technologies Cat. # 31985-070) containing 2% FBS. Mix 0.2 µl of Lipofectamine RNAiMax (Life Technologies Cat. # 13778-100) with 4.8 µl of Opti-MEM I for 5 minutes at room temperature. Mix 1 µl of siRNA with 4 µl of Opti-MEM I and combine with the LF2000 solution and then mix gently, without vortex. Wait for 5 minutes at room temperature. Incubate the mixture for 10 minutes at room temperature to allow the RNA-RNAiMax complexes to form. Add the 10 µl of RNA-RNAiMax complexes to a well and shake the plate gently by hand. Incubate the cells in a 37˚C incubator containing a humidified atmosphere of 5% CO2 in air for 2 hours. Change medium to fresh -MEM I Reduced Serum Medium (Life Technologies Cat. # 31985-070) containing 2% FBS. 24 hours after transfection, wash the cells with ice-cold PBS once. Lyse the cells with 50 µl of Cell-to-Ct Lysis Buffer (Life Technologies Cat. # 4391851 C) for 5-30 minutes at room temperature. Add 5 µl of Stop Solution and incubate for 2 minutes at room temperature. Measure mRNA level by RT-qPCR with TAQMAN immediately. Alternatively, the samples can be frozen at -80 °C and assayed at a later time.

[00150] **Example 3:** Fig. 2 shows in vivo knockdown efficacy for GST-π siRNA. Dose dependent knockdown of GST-π mRNA was observed in vivo with BU02 siRNA targeted to GST-π, as shown in Fig. 2.

[00151] **Example 4:** Fig. 3 shows inhibition of cell proliferation by GST-π targeted siRNA. Dose-dependent inhibition of proliferation was observed in an A549 cell line in vitro with siRNA targeted to GST-π, as shown in Fig. 3.

[00152] **Example 5:** Fig. 4 shows tumor inhibition efficacy for GST-π siRNA (BU02). A pancreatic 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 demonstrated significant and unexpectedly advantageous tumor inhibition efficacy at day 28.

[00153] In this experiment, A549 and PANC-1 cell lines were obtained from ATCC. The cell suspension was mixed well with ice thawed BD matrigel at 1:1 ratio for injection. Each mouse, athymic nude female mice, 6 to 8 weeks, Charles River, was inoculated subcutaneously in the right flank with 0.1 ml of an inoculum of 2×10^6 (A549) or 2.5×10^6 (PANC-1) cells using a 25 G needle and syringe (1 inoculum per mouse). Mice were anesthetized for inoculation. On the day when the established tumors reached approximately 250 - 350 mm^3 (A549) or 150 - 250 mm^3 (PANC-1) animals were subjected to bolus injection through tail vein. Animals were sacrificed by overdosed CO_2 and tumors dissected at different time points following the dosing. Tumors were first wet weighted, and then separated into three parts for measurement of GST-π knockdown, biodistribution of siRNA, and biomarker analysis. The samples were snap frozen in liquid nitrogen and stored at -80°C until ready to be processed for bioanalysis.

[00154] **Example 6: 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.

[00155] 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.

[00156] 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.

[00157] Orthotopic lung cancer tumor inhibition was observed in vivo for a GST-π siRNA based on structure BU2 (SEQ ID NOs:1276 and 1341). 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.

[00158] The GST-π siRNA showed significant and unexpectedly advantageous lung tumor inhibition efficacy in this six-week study. 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.

[00159] 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 4^0 C before use, and warmed to room temperature 10 minutes prior to injection in mouse.

[00160] 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 mm^3 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 X 1 ½ 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 x magnification microscope under HEPA filtered laminar flow hoods.

[00161] 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.

[00162] For the group of interest, the formulation was (Ionizable lipid:cholesterol:DOPE:DOPC:DPPE-PEG-2K:DSPE-PEG-2K), a liposomal composition. The liposomes encapsulated the GST-π siRNA.

[00163] 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.

[00164] 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.

[00165] **Example 7:** Effect of small interfering RNA (siRNA) targeting GST-π on A549 cell growth in nude mice and angiogenesis on chorioallantoic membrane (CAM) assay. Three pairs of GST-π siRNA-plasmid and non-silencing-plasmid are constructed, and transfected into A549 cells through LIPOFECTAMINE 2000, respectively. The most effective pair of GST-π siRNA-plasmid is selected by ELISA and real-time RT-PCR. A549 cells are transfected with selected GST-π siRNA- plasmid, A549 cells are transfected with non-silencing-plasmid, and A549 cells without transfection are inoculated into nude mice, respectively. Chick embryos are randomly divided into four groups and CAM is treated by different solutions for 48 h: culture media DMEM as negative control group, un-transfected A549 cell culture supernatants as positive control group, GST-π siRNA A549 cell culture supernatants as GST-π siRNA group and non-silencing siRNA A549 cell culture supernatants as non-silencing siRNA group. The CAMs were harvested on day 12 for microscopic assays.

[00166] Compared with control group, GST-π siRNA-plasmid induces reduction in GST-π secretion by A549 cells accompanied by reduction in GST-π mRNA. Compared with non-silencing siRNA group, the mean tumor volume of murine xenograft is reduced in GST-π siRNA group; time for xenografts growing to 50 mm^3 is delayed. GST-π contents in xenograft are reduced. In CAM assays, GST-π content is zero in negative group, and in GST-π siRNA group is reduced by 20-70% compared to non-silencing siRNA group or positive group; vessels branch points of CAM in GST-π siRNA group or non-silencing siRNA group or positive group are increased compared with negative group; total vessel length of CAM in GST-π siRNA group is increased compared with negative group, while in non-silencing siRNA group or positive group it is increased. Compared with negative control group, the proliferation of microvessels is increased when cell culture supernatant with GST-π is added in GST-π siRNA group, significant proliferated vessels are observed in non-silencing siRNA group or positive group.

[00167] **Example 8:** Cell culture. The human non-small cell lung carcinoma cell line, A549 is cultured in F-12K medium (ATCC) supplemented with 10% FBS (FBS, Invitrogen) at 37 °C in a humidified atmosphere with 5% CO_2. The cells stably expressing control, or GSTπ siRNAs are generated by transducing A549TR cells with the respective lentiviral transduction particles as per manufacturer's instructions (Sigma-Aldrich). Resistant clones are selected in 2.5 μg/mL puromycin (Invivogen) for 12 d, isolated using cloning cylinders, and subsequently expanded and maintained in puromycin-containing medium.

[00168] **Example 9:** GST-π targeted siRNA results in profound regression of tumor volume in vivo.

[00169] A lipid formulation is used to encapsulate and deliver siRNA in nanoparticles to xenografts of human A549 lung cancer cells in scid mice. The xenografts are tested to identify the presence of KRAS mutations or aberrant levels of expression compared to normal cells. When tumors became established (>100 mm^3), mice are treated with either GST-π targeted siRNA or Control (non-specific) siRNA every 2 days for 2 weeks. The trial is halted when the control group has to be euthanized.

[00170] Results: Treatment with GST-π targeted siRNA prevents tumor expansion and results in dramatic tumor volume reduction.

[00171] The tumors that are recovered are sectioned and visualized by TUNEL staining. GST-π targeted siRNA-treated tumors display significantly higher levels of apoptosis. RNA is extracted from the tumors, and real-time PCR is performed to examine specific knockdown of GST-π.

[00172] Results: Treatment with GST-π targeted siRNA dramatically reduces expression of GST-π in vivo.

[00173] **Example 10:** The GST-π siRNAs of this invention exhibited increased serum stability.

[00174] A GST-π siRNA was incubated in human serum and detection of remaining siRNA at various time points was done by HPLS/LCMS. The half-life ($t_{1/2}$) in

serum for both the sense strand and antisense strand of the GST-π siRNA (SEQ ID Nos:1276 and 1341) was about 100 minutes.

[00175] **Example 11:** The GST-π siRNAs of this invention exhibited enhanced stability in formulation in plasma.

[00176] A GST-π siRNA was incubated in a formulation in plasma and detection of remaining siRNA was done at various time points. The half-life ($t_{1/2}$) in plasma of a formulation of GST-π siRNA (SEQ ID Nos:1276 and 1341) was significantly longer than 100 hours.

[00177] 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 nanparticles was 40.0 nm, and the siRNA was 91% encapsulated.

[00178] The formulation was incubated in 50% human serum in PBS for 40min, 1.5h, 3h, 24h, and 96h. The amount of the GST-π siRNA was determined by an ELISA-based assay.

[00179] **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.

[00180] Tumor inhibition efficacy was observed for a GST-π siRNA (SEQ ID NOs:1276 and 1341). 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.

[00181] The GST-π siRNA showed significant and unexpectedly advantageous tumor inhibition efficacy within a few days after administration. 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 4mg/kg, significant reduction of about 40% was detected 24 hours after injection.

[00182] 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).

[00183] 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 µg/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.

[00184] Mice were Charles River Laboratory Athymic Nude (nu/nu) Female Mice, immuno-compromised, 6-8 weeks old, 3 mice per group.

[00185] 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.

[00186] 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 x width^2/2. Tumor volumes were monitored twice a week. Once the established tumors reached approximately 350 - 600 mm^3, the mice were assigned into groups with varied time points. On the same day, test articles were administered according to the dosing regimen.

[00187] For dosage administration, on the day when the established tumors reached approximately 350 - 600 mm^3, 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.

[00188] 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.

[00189] For tumors collection, animals were sacrificed by overdosed CO_2 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.

[00190] 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.

[00191] All publications, patents and literature specifically mentioned herein are incorporated by reference in their entirety for all purposes.

[00192] 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.

[00193] 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.

[00194] 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.

[00195] 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.

[00196] 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.

WHAT IS CLAIMED IS:

1. A nucleic acid molecule, 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.

2. The nucleic acid molecule of claim 1, wherein the antisense strand is SEQ ID NO:1341, and the sense strand is SEQ ID NO:1276, or chemically modified strands thereof.

3. The nucleic acid molecule of claim 1, wherein the antisense strand is SEQ ID NO:1305, and the sense strand is SEQ ID NO:1240, or chemically modified strands thereof.

4. The nucleic acid molecule of claim 1, wherein the 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.

5. The nucleic acid molecule of claim 1, wherein the 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 selected from a sequence of human GSTP1, wherein human GSTP1 mRNA is SEQ ID NO:1.

6. The nucleic acid molecule of claim 1, wherein the sequence of an mRNA encoding GST-π is selected from the group consisting of 5'UTR positions 1 to 249 of SEQ ID NO:1, CDS positions 250 to 882 of SEQ ID NO:1, and 3'UTR positions 883 to 986 of SEQ ID NO:1.

7. The nucleic acid molecule of claim 1, wherein the antisense strand contains a sequence selected from any one of SEQ ID NOs:609-1215.

8. The nucleic acid molecule of claim 1, wherein the antisense strand contains a sequence selected from any one of SEQ ID NOs:1281-1345.

9. The nucleic acid molecule of claim 1, wherein the molecule is composed of an antisense and sense strand pair selected from the group consisting of SEQ ID NO:1240 and 1305, SEQ ID NO:1265 and 1330, SEQ ID NO:1267 and 1332, SEQ ID NO:1269 and 1334, and SEQ ID NO:1276 and 1341.

10. The nucleic acid molecule of claim 1, wherein each strand of the molecule is from 18 to 22 nucleotides in length.

11. The nucleic acid molecule of claim 1, wherein the duplex region is 19 nucleotides in length.

12. The nucleic acid molecule of claim 1, wherein the polynucleotide sense strand and the polynucleotide antisense strand are connected as a single strand, and form a duplex region connected at one end by a loop.

13. The nucleic acid molecule of claim 1, wherein the molecule has a blunt end.

14. The nucleic acid molecule of claim 1, wherein the molecule has one or more 3' overhangs.

15. The nucleic acid molecule of claim 1, wherein the molecule is an RNAi molecule active for gene silencing.

16. The nucleic acid molecule of claim 1, wherein the molecule is a dsRNA, a siRNA, a micro-RNA, or a shRNA active for gene silencing.

17. The nucleic acid molecule of claim 1, wherein the molecule is active for inhibiting expression of GST-π.

18. The nucleic acid molecule of claim 1, wherein the molecule has an IC50 for knockdown of GST-π of less than 100 pM.

19. A composition comprising one or more nucleic acid molecules of any one of claims 1-18 and a pharmaceutically acceptable carrier.

20. The composition of claim 19, wherein the carrier is a lipid molecule or liposome.

21. A method for treating a disease associated with GST-π expression, the method comprising administering to a subject in need a composition of claim 19.

22. The method of claim 21, wherein the disease is malignant tumor.

23. The method of claim 22, wherein the malignant tumor is presented in a disease selected from the group consisting of 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, colorectal cancer, colon cancer, liver cancer, pancreatic cancer, gallbladder cancer, bile duct cancer, kidney cancer, urethral cancer, bladder cancer, prostate cancer, testicular cancer, penile cancer, uterine cancer, ovarian cancer, skin cancer, bone cancer, leukemia, malignant lymphoma, epithelial malignant tumors, and non-epithelial malignant tumors.

SEQ ID NO:1

TGGGAAAGAGGGAAAGGCTTCCCCGGCCAGCTGCGCGGCGACTCCGGGGACTCCAGGGCGCCCCTCTGCG
GCCGACGCCCCGGGGTGCAGCGGCCGCCGGGGCTGGGGCCGGCGGGAGTCCGCGGGACCCTCCAGAAGAGC
GGCCGGCGCCGTGACTCAGCACTGGGGCGGAGCGGGGCGGGACCACCCTTATAAGGCTCGGAGGCCGCGA
GGCCTTCGCTGGAGTTTCGCCGCCGCAGTCTTCGCCACCATGCCGCCCTACACCGTGGTCTATTTCCCAG
TTCGAGGCCGCTGCGCGGCCCTGCGCATGCTGCTGGCAGATCAGGGCCAGAGCTGGAAGGAGGAGGTGGT
GACCGTGGAGACGTGGCAGGAGGGCTCACTCAAAGCCTCCTGCCTATACGGGCAGCTCCCCAAGTTCCAG
GACGGAGACCTCACCCTGTACCAGTCCAATACCATCCTGCGTCACCTGGGCCGCACCCTTGGGCTCTATG
GGAAGGACCAGCAGGAGGCAGCCCTGGTGGACATGGTGAATGACGGCGTGGAGGACCTCCGCTGCAAATA
CATCTCCCTCATCTACACCAACTATGAGGCGGGCAAGGATGACTATGTGAAGGCACTGCCCGGGCAACTG
AAGCCTTTTGAGACCCTGCTGTCCCAGAACCAGGGAGGCAAGACCTTCATTGTGGGAGACCAGATCTCCT
TCGCTGACTACAACCTGCTGGACTTGCTGCTGATCCATGAGGTCCTAGCCCCTGGCTGCCTGGATGCGTT
CCCCCTGCTCTCAGCATATGTGGGGCGCCTCAGTGCCCGGCCCAAGCTCAAGGCCTTCCTGGCCTCCCCT
GAGTACGTGAACCTCCCCATCAATGGCAACGGGAAACAGTGAGGGTTGGGGGGACTCTGAGCGGGAGGCA
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AAAAAA

FIG. 1

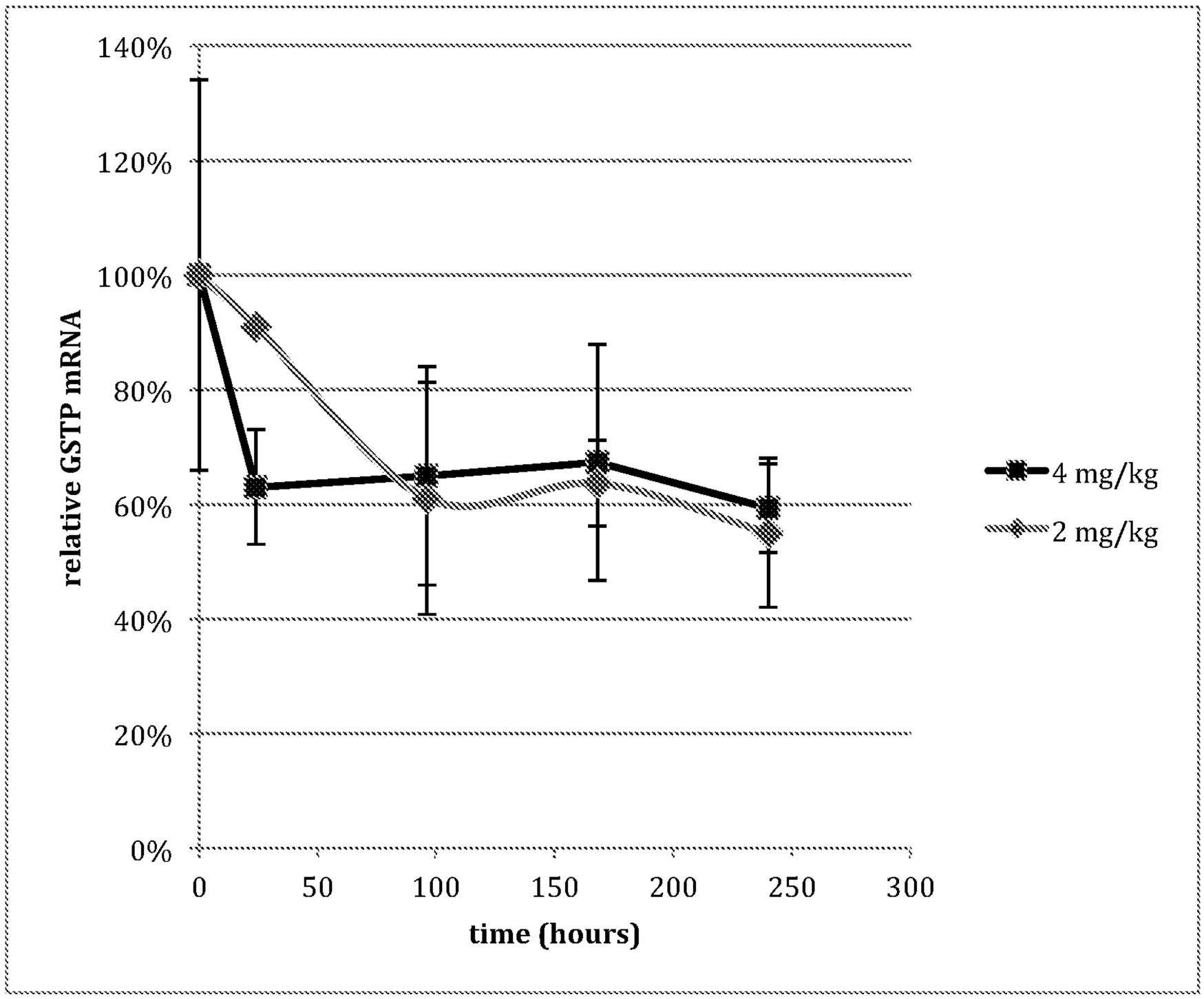
140%
120%
100%
80%
60%
40%
20%
0%
relative GSTP mRNA
0
50
100
150
200
250
300
time (hours)
4 mg/kg
2 mg/kg

FIG. 2

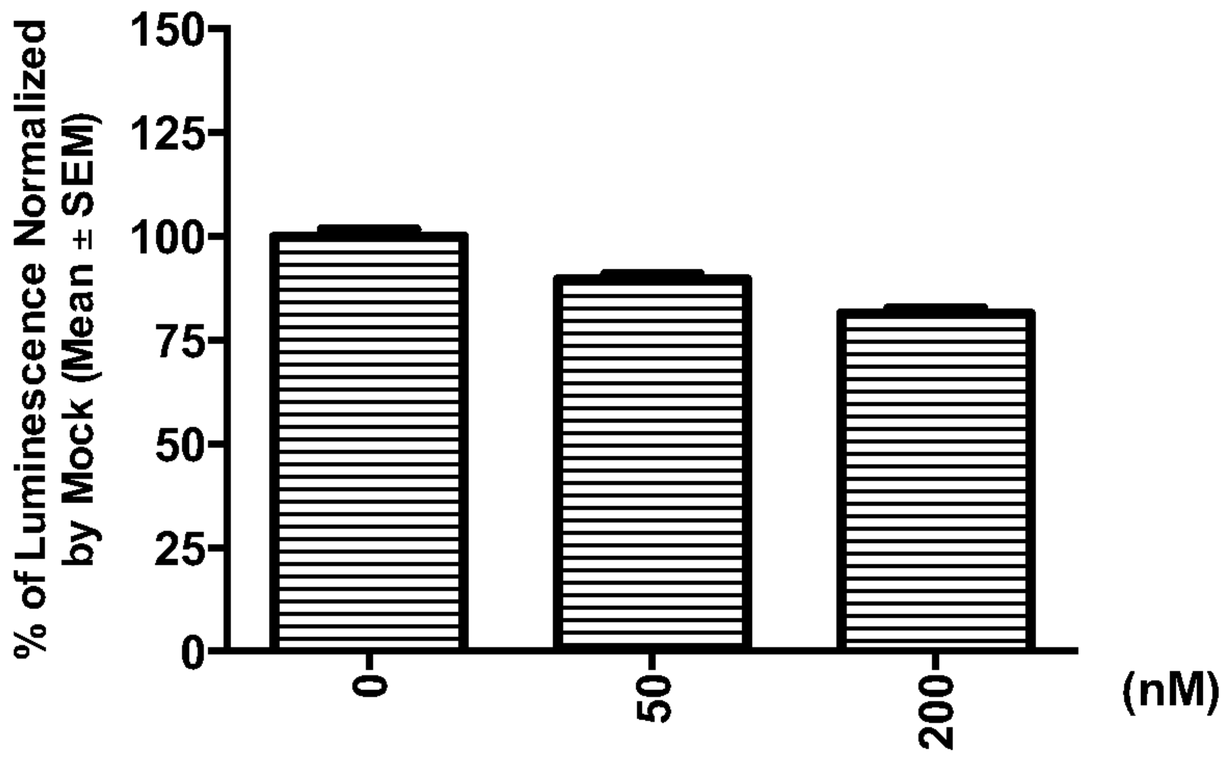
% of Luminescence Normalized by Mock (Mean ± SEM)
150
125
100
75
50
25
0
0
50
200
(nM)

FIG. 3

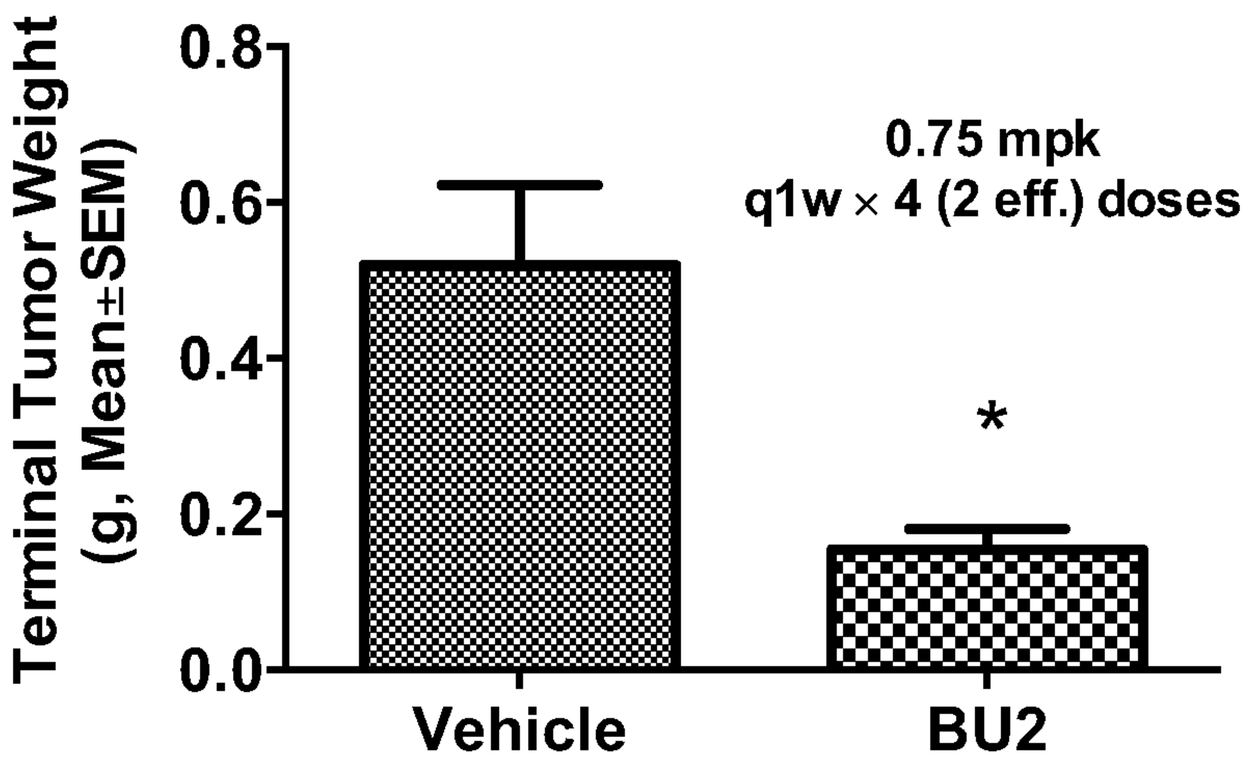
Terminal Tumor Weight
(g, Mean±SEM)
0.8
0.6
0.4
0.2
0.0
0.75 mpk
q1w × 4 (2 eff.) doses
*
Vehicle
BU2

FIG. 4

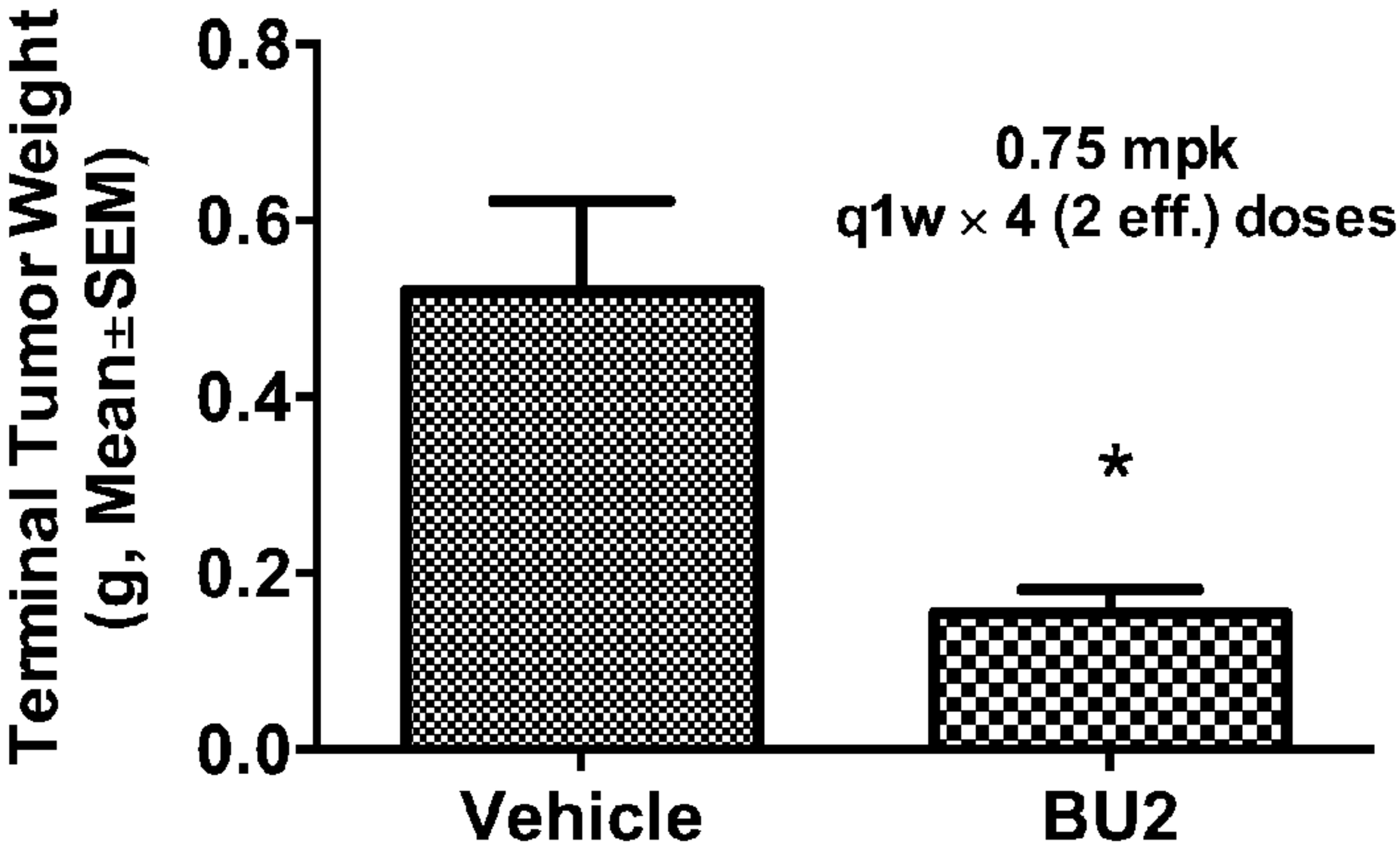
Terminal Tumor Weight
(g, Mean±SEM)
0.8
0.6
0.4
0.2
0.0
0.75 mpk
q1w × 4 (2 eff.) doses
*
Vehicle
BU2

FIG. 4