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(54) **Titre :** COMPOSITIONS D'ARNI ET METHODES D'INACTIVATION DE L'ANGIOTENSINOGENE (AGT)
(54) **Title:** IRNA COMPOSITIONS AND METHODS FOR SILENCING ANGIOTENSINOGEN (AGT)

(57) **Abrégé/Abstract:**

The present invention relates to RNAi agents, e.g., double stranded RNA (dsRNA) agents, targeting an angiotensinogen (AGT) gene. The invention also relates to methods of using such RNAi agents to inhibit expression of an AGT gene and to methods of preventing and treating an AGT- associated disorder, e.g., hypertension.



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(54) Title: iRNA COMPOSITIONS AND METHODS FOR SILENCING ANGIOTENSINOGEN (AGT)

(57) Abstract: The present invention relates to RNAi agents, e.g., double stranded RNA (dsRNA) agents, targeting an angiotensinogen

(AGT) gene. The invention also relates to methods of using such RNAi agents to inhibit expression of an AGT gene and to methods

of preventing and treating an AGT- associated disorder, e.g., hypertension.

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CECI EST LE TOME 1 DE 2
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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
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siRNA COMPOSITIONS AND METHODS FOR SILENCING ANGIOTENSINOGEN (AGT)**RELATED APPLICATIONS**

This application claims the benefit of priority to U.S. Provisional Application No. 63/229085, filed on August 4, 2021 and U.S. Provisional Application No. 63/272769, filed on October 28, 2021. The entire contents of each of the foregoing application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

The renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the regulation of blood pressure. The RAAS cascade begins with the release of angiotensinogen from the liver, and renin by the juxtaglomerular cells of the kidney into the circulation. Renin secretion is stimulated by several factors, including Na⁺ load in the distal tubule, β -sympathetic stimulation, or reduced renal perfusion. Active renin in the plasma cleaves angiotensinogen (produced by the liver) to angiotensin I, which is then converted by circulating and locally expressed angiotensin-converting enzyme (ACE) to angiotensin II. Most of the effects of angiotensin II on the RAAS are exerted by its binding to angiotensin II type 1 receptors (AT₁R), leading to arterial vasoconstriction, tubular and glomerular effects, such as enhanced Na⁺ reabsorption or modulation of glomerular filtration rate. In addition, together with other stimuli such as adrenocorticotropin, anti-diuretic hormone, catecholamines, endothelin, serotonin, and levels of Mg²⁺ and K⁺, AT₁R stimulation leads to aldosterone release which, in turn, promotes Na⁺ and K⁺ excretion in the renal distal convoluted tubule.

Dysregulation of the RAAS leading to, for example, excessive angiotensin II production or AT₁R stimulation results in hypertension which can lead to, *e.g.*, increased oxidative stress, promotion of inflammation, hypertrophy, and fibrosis in the heart, kidneys, and arteries, and result in, *e.g.*, left ventricular fibrosis, arterial remodeling, and glomerulosclerosis.

Hypertension is the most prevalent, controllable disease in developed countries, affecting 20–50% of adult populations. Hypertension is a major risk factor for various diseases, disorders and conditions such as, shortened life expectancy, chronic kidney disease, stroke, myocardial infarction, heart failure, aneurysms (*e.g.* aortic aneurysm), peripheral artery disease, heart damage (*e.g.*, heart enlargement or hypertrophy) and other cardiovascular related diseases, disorders, or conditions. In addition, hypertension has been shown to be an important risk factor for cardiovascular morbidity and mortality accounting for, or contributing to, 62% of all strokes and 49% of all cases of heart disease. In 2017, changes in the guidelines for diagnosis, prevention, and treatment of hypertension were developed providing goals for even lower blood pressure to further decrease risk of development of diseases and disorders associated with hypertension (see, *e.g.*, Reboussin *et al.* Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American

College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2017 Nov 7. pii: S0735-1097(17)41517-8. doi: 10.1016/j.jacc.2017.11.004; and Whelton *et al.* (2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2017 Nov 7. pii: S0735-1097(17)41519-1. doi: 10.1016/j.jacc.2017.11.006).

Despite the number of anti-hypertensive drugs available for treating hypertension, more than two-thirds of subjects are not controlled with one anti-hypertensive agent and require two or more anti-hypertensive agents selected from different drug classes. This further reduces the number of subjects with controlled blood pressure as adherence is reduced and side-effects are increased with increasing numbers of medications.

SUMMARY OF THE INVENTION

The present invention provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding angiotensinogen (AGT). The AGT gene may be within a cell, *e.g.*, a cell within a subject, such as a human subject. The present invention also provides methods of using the iRNA compositions of the invention for inhibiting the expression of an AGT gene and/or for treating a subject who would benefit from inhibiting or reducing the expression of an AGT gene, *e.g.*, a subject suffering or prone to suffering from an AGT-associated disorder, *e.g.*, hypertension.

Accordingly, in an aspect, the invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of angiotensinogen (AGT) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, or 20, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:3 and the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, or 20, contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the corresponding portion of the nucleotide sequence of SEQ ID NO:2 or SEQ ID NO:4.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) for inhibiting expression of angiotensinogen (AGT) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding AGT, and wherein the region of complementarity comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, or 20, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-7.

In one embodiment, the dsRNA agent comprises a sense strand comprising at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

In one embodiment, the dsRNA agent comprises a sense strand comprising at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

In one embodiment, the dsRNA agent comprises a sense strand comprising at least 15 contiguous nucleotides differing by no more than one nucleotide from any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than one nucleotide from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

In one embodiment, the dsRNA agent comprises a sense strand comprising or consisting of a nucleotide sequence selected from the group consisting of any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising or consisting of a nucleotide sequence selected from the group consisting of any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

In one embodiment, the dsRNA agent comprises at least one modified nucleotide.

In one embodiment, substantially all of the nucleotides of the sense strand are modified nucleotides; substantially all of the nucleotides of the antisense strand are modified nucleotides; or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, all of the nucleotides of the sense strand are modified nucleotides; all of the nucleotides of the antisense strand are modified nucleotides; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythymidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a

phosphorothioate group, a nucleotide comprising a methylphosphonate group, a vinyl phosphonate nucleotide, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), a nucleotide comprising a 2' phosphate, and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

5 In one embodiment, at least one of the modified nucleotides is selected from the group consisting of LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C-allyl, 2'-fluoro, 2'-deoxy, 2'-hydroxyl, and glycol; and combinations thereof.

In one embodiment, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, 10 a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), *e.g.*, Ggn, Cgn, Tgn, or Agn, a nucleotide with a 2' phosphate, *e.g.*, G2p, C2p, A2p or U2p, and a nucleotide comprising a phosphorothioate group, and combinations thereof.

In another embodiment, at least one of the modified nucleotides is a nucleotide with a thermally destabilizing nucleotide modification.

15 In one embodiment, the thermally destabilizing nucleotide modification is selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; a destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an unlocked nucleic acid (UNA), and a glycerol nucleic acid (GNA).

In some embodiments, the modified nucleotide comprises a short sequence of 3'-terminal 20 deoxythymidine nucleotides (dT).

In some embodiments, the dsRNA agent further comprises at least one phosphorothioate internucleotide linkage. In some embodiments, the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages. In one embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand. Optionally, the strand is the antisense 25 strand. In another embodiment, the strand is the sense strand. In a related embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand. Optionally, the strand is the antisense strand. In another embodiment, the strand is the sense strand. In another embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand. Optionally, the strand is the antisense strand. In another 30 embodiment, the strand is the sense strand.

The double stranded region may be 19-30 nucleotide pairs in length; 19-25 nucleotide pairs in length; 19-23 nucleotide pairs in length; 23-27 nucleotide pairs in length; or 21-23 nucleotide pairs in length.

In one embodiment, each strand is independently no more than 30 nucleotides in length.

35 In one embodiment, the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.

The region of complementarity may be at least 17 nucleotides in length; between 19 and 23 nucleotides in length; or 19 nucleotides in length.

In one embodiment, at least one strand comprises a 3' overhang of at least 1 nucleotide. In another embodiment, at least one strand comprises a 3' overhang of at least 2 nucleotides.

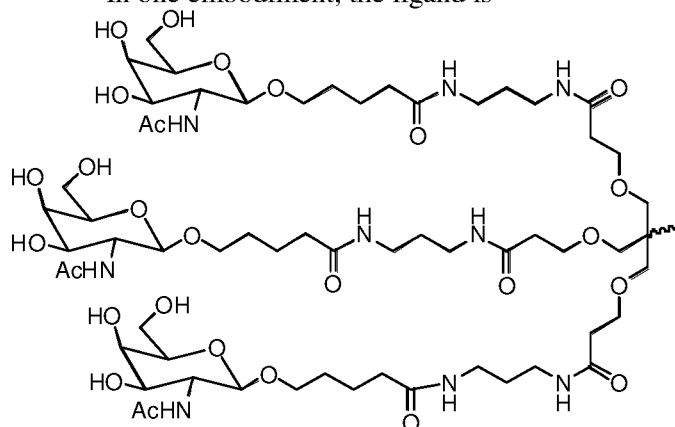
5 In one embodiment, the dsRNA agent further comprises a ligand.

In one embodiment, the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

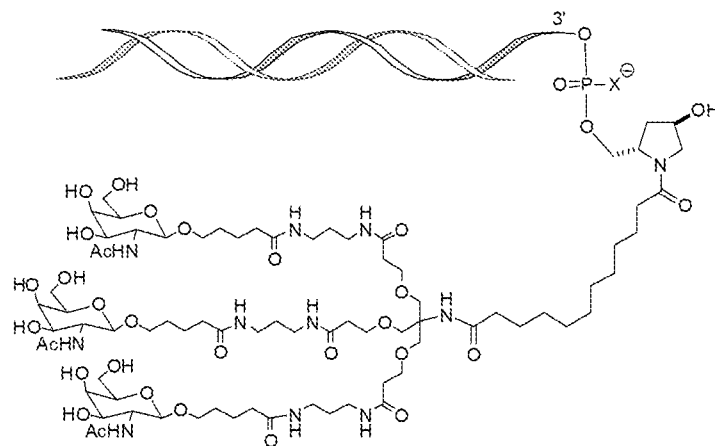
In one embodiment, the ligand is an N-acetylgalactosamine (GalNAc) derivative.

10 In one embodiment, the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In one embodiment, the ligand is



In one embodiment, the dsRNA agent is conjugated to the ligand as shown in the following schematic



15 and, wherein X is O or S.

In one embodiment, the X is O.

In one embodiment, the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

20 In one embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand, *e.g.*, the antisense strand or the sense strand.

In another embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand, *e.g.*, the antisense strand or the sense strand.

In one embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand. In one embodiment, the strand is the antisense strand.

5 In one embodiment, the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair.

The present invention also provides cells containing any of the dsRNA agents of the invention and pharmaceutical compositions comprising any of the dsRNA agents of the invention.

10 The pharmaceutical composition of the invention may include dsRNA agent in an unbuffered solution, *e.g.*, saline or water, or the pharmaceutical composition of the invention may include the dsRNA agent is in a buffer solution, *e.g.*, a buffer solution comprising acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof; or phosphate buffered saline (PBS).

15 In one aspect, the present invention provides a method of inhibiting expression of an angiotensinogen (AGT) gene in a cell. The method includes contacting the cell with any of the dsRNAs of the invention or any of the pharmaceutical compositions of the invention, thereby inhibiting expression of the AGT gene in the cell.

In one embodiment, the cell is within a subject, *e.g.*, a human subject, *e.g.*, a subject having a angiotensinogen (AGT)-associated disorder, such as high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension isolated systolic or diastolic
20 hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy,
25 diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR) , fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2
30 diabetes (non-insulin dependent diabetes), and metabolic syndrome.

In certain embodiments, the subject has a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 80 mm Hg. In certain embodiments, the subject has a systolic blood pressure of at least 140 mm Hg and a diastolic blood pressure of at least 80 mm Hg. In certain
35 embodiments, the subject is part of a group susceptible to salt sensitivity, is overweight, is obese, or is pregnant.

In certain embodiments, contacting the cell with the dsRNA agent inhibits the expression of AGT by at least 50%, 60%, 70%, 80%, 90%, 95% (*e.g.*, as compared to the level of expression of

AGT prior to first contacting the cell with the dsRNA agent; *e.g.*, prior to administration of a first dose of the dsRNA agent to the subject). In certain embodiments, inhibiting expression of AGT decreases an AGT protein level in a subject serum sample(s) by at least 50%, 60%, 70%, 80%, 90%, or 95%, *e.g.*, as compared to the level of expression of AGT prior to first contacting the cell with the dsRNA agent.

In one aspect, the present invention provides a method of treating a subject having a disorder that would benefit from reduction in angiotensinogen (AGT) expression. The method includes administering to the subject a therapeutically effective amount of any of the dsRNAs of the invention or any of the pharmaceutical compositions of the invention, thereby treating the subject having the disorder that would benefit from reduction in AGT expression.

In another aspect, the present invention provides a method of preventing at least one symptom in a subject having a disorder that would benefit from reduction in angiotensinogen (AGT) expression. The method includes administering to the subject a prophylactically effective amount of any of the dsRNAs of the invention or any of the pharmaceutical compositions of the invention, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in AGT expression.

In certain embodiments, the disorder is an angiotensinogen (AGT)-associated disorder.

In certain embodiments, the subject has a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 80 mm Hg. In certain embodiments, the subject has a systolic blood pressure of at least 140 mm Hg and diastolic blood pressure of at least 80 mm Hg. In certain embodiments, the subject is human. In certain embodiments, subject is part of a group susceptible to salt sensitivity, is overweight, is obese, or is pregnant.

In some embodiments, the AGT-associated disorder is selected from the group consisting of high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension, isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR), fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome.

In a further aspect, the present invention also provides methods of inhibiting the expression of angiotensinogen (AGT) in a subject. The methods include administering to the subject a

therapeutically effective amount of any of the dsRNAs provided herein, thereby inhibiting the expression of AGT in the subject.

In one embodiment, the subject is human.

In one embodiment, administration of the dsRNA agent to the subject causes a decrease in
5 AGT protein accumulation in the subject.

In one embodiment, the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

In one embodiment, the dsRNA agent is administered to the subject subcutaneously.

In one embodiment, the methods of the invention further include determining the level of
10 AGT in the subject sample(s) is an AGT protein level in a blood or a serum or a urine or a liver tissue sample(s).

In some embodiments, the methods of the invention further include determining the level of bradykinin; prekallikrein, or blood pressure in the subject.

In certain embodiments, the methods of the invention further comprise administering to the
15 subject an additional therapeutic agent.

In certain embodiments, the additional therapeutic agent is selected from the group consisting of of a diuretic, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a beta-blocker, a vasodialator, a calcium channel blocker, an aldosterone antagonist, an alpha2-agonist, a renin inhibitor, an alpha-blocker, a peripheral acting adrenergic agent, a selective D1
20 receptor partial agonist, a nonselective alpha-adrenergic antagonist, a synthetic, and steroidal antimineralocorticoid agent; or a combination of any of the foregoing, and a hypertension therapeutic agent formulated as a combination of agents. In certain embodiments, the additional therapeutic agent comprises an angiotensin II receptor antagonist, *e.g.*, losartan, valsartan, olmesartan, eprosartan, and azilsartan. In certain embodiments, the additional therapeutic agent is an angiotensin receptor-
25 neprilysin inhibitor (ARNi), *e.g.*, Entresto®, sacubitril/valsartan; or an endothelin receptor antagonist (ERA), *e.g.*, sitaxentan, ambrisentan, atrasentan, BQ-123, zibotentan, bosentan, macitentan, and tezosentan.

The present invention also provides kits comprising any of the dsRNAs of the invention or any of the pharmaceutical compositions of the invention, and optionally, instructions for use. In one
30 embodiment, the invention provides a kit for performing a method of inhibiting expression of an AGT gene in a cell by contacting a cell with a double stranded RNAi agent of the invention in an amount effective to inhibit expression of the AGT in the cell. The kit comprises an RNAi agent and instructions for use and, optionally, means for administering the RNAi agent to a subject.

The present invention also provides vials comprising the dsRNA agent of the invention or the
35 pharmaceutical composition of the invention. The present invention further provides syringes comprising the dsRNA agent of the invention or the pharmaceutical composition of the invention.

The present invention further provides an RNA-induced silencing complex (RISC) comprising an antisense strand of any of the dsRNA agents of the invention.

In one embodiment, the RNAi agent is a pharmaceutically acceptable salt thereof.

“Pharmaceutically acceptable salts” of each of RNAi agents herein include, but are not limited to, a sodium salt, a calcium salt, a lithium salt, a potassium salt, an ammonium salt, a magnesium salt, an mixtures thereof. One skilled in the art will appreciate that the RNAi agent, when provided as a polycationic salt having one cation per free acid group of the optionally modified phosphodiester backbone and/or any other acidic modifications (*e.g.*, 5'-terminal phosphonate groups). For example, an oligonucleotide of “n” nucleotides in length contains n-1 optionally modified phosphodiester, so that an oligonucleotide of 21 nt in length may be provided as a salt having up to 20 cations (*e.g.*, 20 sodium cations). Similarly, an RNAi agent having a sense strand of 21 nt in length and an antisense strand of 23 nt in length may be provided as a salt having up to 42 cations (*e.g.*, 42 sodium cations). In the preceding example, where the RNAi agent also includes a 5'-terminal phosphate or a 5'-terminal vinylphosphonate group, the RNAi agent may be provided as a salt having up to 44 cations (*e.g.*, 44 sodium cations).

The present invention is further illustrated by the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an angiotensinogen (AGT) gene. The gene may be within a cell, *e.g.*, a cell within a subject, such as a human. The use of these iRNAs enables the targeted degradation of mRNAs of the corresponding gene (AGT) in mammals.

The iRNAs of the invention have been designed to target the human angiotensinogen (AGT) gene, including portions of the gene that are conserved in the AGT orthologs of other mammalian species. Without intending to be limited by theory, it is believed that a combination or sub-combination of the foregoing properties and the specific target sites or the specific modifications in these iRNAs confer to the iRNAs of the invention improved efficacy, stability, potency, durability, and safety.

Accordingly, the present invention provides methods for treating and preventing an angiotensinogen (AGT)-associated disorder, *e.g.*, high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy,

diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR), fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome, using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an AGT gene.

The iRNAs of the invention include an RNA strand (the antisense strand) having a region which is up to about 30 nucleotides or less in length, *e.g.*, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of an AGT gene.

In certain embodiments, one or both of the strands of the double stranded RNAi agents of the invention is up to 66 nucleotides in length, *e.g.*, 36-66, 26-36, 25-36, 31-60, 22-43, 27-53 nucleotides in length, with a region of at least 19 contiguous nucleotides that is substantially complementary to at least a part of an mRNA transcript of an AGT gene. In some embodiments, such iRNA agents having longer length antisense strands may, for example, include a second RNA strand (the sense strand) of 20-60 nucleotides in length wherein the sense and antisense strands form a duplex of 18-30 contiguous nucleotides.

The use of iRNAs of the invention enables the targeted degradation of mRNAs of the corresponding gene (AGT gene) in mammals. Using *in vitro* assays, the present inventors have demonstrated that iRNAs targeting an AGT gene can potently mediate RNAi, resulting in significant inhibition of expression of an AGT gene. Thus, methods and compositions including these iRNAs are useful for treating a subject having an AGT-associated disorder, *e.g.*, high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, hypertension associated with low plasma renin activity or plasma renin concentration, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR), fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic

Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome.

Accordingly, the present invention provides methods and combination therapies for treating a subject having a disorder that would benefit from inhibiting or reducing the expression of an AGT gene, *e.g.*, an angiotensinogenI (AGT)-associated disorder, such as high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR) , fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome, using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an AGT gene.

The present invention also provides methods for preventing at least one symptom in a subject having a disorder that would benefit from inhibiting or reducing the expression of an AGT gene, *e.g.*, an angiotensinogen (AGT)-associated disorder, such as high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR) , fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome.

The following detailed description discloses how to make and use compositions containing iRNAs to inhibit the expression of an AGT gene as well as compositions, uses, and methods for

treating subjects that would benefit from inhibition and/or reduction of the expression of an AGT gene, *e.g.*, subjects susceptible to or diagnosed with an AGT-associated disorder.

I. Definitions

In order that the present invention may be more readily understood, certain terms are first defined. In addition, it should be noted that whenever a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also intended to be part of this invention.

The articles “a” and “an” are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element, *e.g.*, a plurality of elements.

The term “including” is used herein to mean, and is used interchangeably with, the phrase “including but not limited to”.

The term “or” is used herein to mean, and is used interchangeably with, the term “and/or,” unless context clearly indicates otherwise. For example, “sense strand or antisense strand” is understood as “sense strand or antisense strand or sense strand and antisense strand.”

The term “about” is used herein to mean within the typical ranges of tolerances in the art. For example, “about” can be understood as about 2 standard deviations from the mean. In certain embodiments, about means $\pm 10\%$. In certain embodiments, about means $\pm 5\%$. When about is present before a series of numbers or a range, it is understood that “about” can modify each of the numbers in the series or range.

The term “at least”, “no less than”, or “or more” prior to a number or series of numbers is understood to include the number adjacent to the term “at least”, and all subsequent numbers or integers that could logically be included, as clear from context. For example, the number of nucleotides in a nucleic acid molecule must be an integer. For example, “at least 19 nucleotides of a 21 nucleotide nucleic acid molecule” means that 19, 20, or 21 nucleotides have the indicated property. When at least is present before a series of numbers or a range, it is understood that “at least” can modify each of the numbers in the series or range.

As used herein, “no more than” or “or less” is understood as the value adjacent to the phrase and logical lower values or integers, as logical from context, to zero. For example, a duplex with an overhang of “no more than 2 nucleotides” has a 2, 1, or 0 nucleotide overhang. When “no more than” is present before a series of numbers or a range, it is understood that “no more than” can modify each of the numbers in the series or range. As used herein, ranges include both the upper and lower limit.

As used herein, methods of detection can include determination that the amount of analyte present is below the level of detection of the method.

In the event of a conflict between an indicated target site and the nucleotide sequence for a sense or antisense strand, the indicated sequence takes precedence.

In the event of a conflict between a sequence and its indicated site on a transcript or other sequence, the nucleotide sequence recited in the specification takes precedence.

As used herein, “angiotensinogen,” used interchangeably with the term “AGT” refers to the well-known gene and polypeptide, also known in the art as Serpin Peptidase Inhibitor, Clade A, Member 8; Alpha-1 Antiproteinase; Antitrypsin; SERPINA8; Angiotensin I; Serpin A8; Angiotensin II; Alpha-1 Antiproteinase angiotensinogen; antitrypsin; pre-angiotensinogen2; ANHU; Serine Proteinase Inhibitor; and Cysteine Proteinase Inhibitor.

The sequence of a human AGT mRNA transcript can be found at, for example, GenBank Accession No. GI: 1813757520 (NM_000505.4; SEQ ID NO:1; reverse complement, SEQ ID NO: 2) and NM_001384479.1 (SEQ ID NO:3; reverse complement, SEQ ID NO:4). The sequence of *Macaca fascicularis* AGT mRNA can be found at, for example, GenBank Accession No. GI: 90075391 (NM_000029.1; SEQ ID NO:5; reverse complement, SEQ ID NO:6). The sequence of mouse AGT mRNA can be found at, for example, GenBank Accession No. GI: 113461997 (NM_007428.3; SEQ ID NO:7; reverse complement, SEQ ID NO:8). The sequence of rat AGT mRNA can be found at, for example, GenBank Accession No. GI: 51036672 (NM_134432.2; SEQ ID NO:9; reverse complement, SEQ ID NO: 10). The sequence of *Macaca mulatta* AGT mRNA can be found at, for example, GenBank XM_015126038 (SEQ ID NO:11; reverse complement, SEQ ID NO:12).

Additional examples of AGT mRNA sequences are readily available through publicly available databases, *e.g.*, GenBank, UniProt, OMIM, and the *Macaca* genome project web site.

Further information on AGT can be found, for example, at www.ncbi.nlm.nih.gov/gene/?term=AGT.

The entire contents of each of the foregoing GenBank Accession numbers and the Gene database numbers are incorporated herein by reference as of the date of filing this application.

The term “AGT,” as used herein, also refers to naturally occurring DNA sequence variations of the AGT gene, such as a single nucleotide polymorphism (SNP) in the AGT gene. Exemplary SNPs may be found in the dbSNP database available at www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?geneId=183. Non-limiting examples of sequence variations within the AGT gene include, for example, those described in U.S. Patent No. 5,589,584, the entire contents of which are incorporated herein by reference. For example, sequence variations within the AGT gene may include as a C→T at position -532 (relative to the transcription start site); a G→A at position -386; a G→A at position -218; a C→T at position -18; a G→A and a A→C at position -6 and -10; a C→T at position +10 (untanslated); a C→T at position +521 (T174M); a T→C at position +597 (P199P); a T→C at position +704 (M235T; also see, *e.g.*, Reference SNP (refSNP) Cluster Report: rs699, available at www.ncbi.nlm.nih.gov/SNP); a A→G at position +743 (Y248C); a C→T at position +813 (N271N); a G→A at position +1017 (L339L); a C→A at position +1075 (L359M); and/or a G→A at position +1162 (V388M).

As used herein, “target sequence” refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of an AGT gene, including mRNA that is a product of RNA processing of a primary transcription product. In one embodiment, the target portion of the sequence will be at least long enough to serve as a substrate for iRNA-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during the transcription of an AGT gene.

The target sequence may be from about 19-36 nucleotides in length, *e.g.*, about 19-30 nucleotides in length. For example, the target sequence can be about 19-30 nucleotides, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length. In certain embodiments, the target sequence is 19-23 nucleotides in length, optionally 21-23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

As used herein, the term “strand comprising a sequence” refers to an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature.

“G,” “C,” “A,” “T,” and “U” each generally stand for a nucleotide that contains guanine, cytosine, adenine, thymidine, and uracil as a base, respectively. However, it will be understood that the term “ribonucleotide” or “nucleotide” can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety (see, *e.g.*, Table 1). The skilled person is well aware that guanine, cytosine, adenine, and uracil can be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base can base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine can be replaced in the nucleotide sequences of dsRNA featured in the invention by a nucleotide containing, for example, inosine. In another example, adenine and cytosine anywhere in the oligonucleotide can be replaced with guanine and uracil, respectively to form G-U Wobble base pairing with the target mRNA. Sequences containing such replacement moieties are suitable for the compositions and methods featured in the invention.

The terms “iRNA”, “RNAi agent,” “iRNA agent,” “RNA interference agent” as used interchangeably herein, refer to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript *via* an RNA-induced silencing complex (RISC) pathway. iRNA directs the sequence-specific degradation of mRNA through a process known as RNA interference (RNAi). The iRNA modulates, *e.g.*, inhibits, the expression of an AGT gene in a cell, *e.g.*, a liver cell within a subject, such as a mammalian subject.

In one embodiment, an RNAi agent of the invention includes a single stranded RNA that interacts with a target RNA sequence, *e.g.*, an AGT target mRNA sequence, to direct the cleavage of

the target RNA. Without wishing to be bound by theory it is believed that long double stranded RNA introduced into cells is broken down into siRNA by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) *Genes Dev.* 15:485). Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409:363). The siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, *et al.*, (2001) *Cell* 107:309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleave the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15:188). Thus, in one aspect the invention relates to a single stranded RNA (siRNA) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.*, an AGT gene. Accordingly, the term “siRNA” is also used herein to refer to an iRNA as described above.

In certain embodiments, the RNAi agent may be a single-stranded siRNA (ssRNAi) that is introduced into a cell or organism to inhibit a target mRNA. Single-stranded RNAi agents bind to the RISC endonuclease, Argonaute 2, which then cleaves the target mRNA. The single-stranded siRNAs are generally 15-30 nucleotides and are chemically modified. The design and testing of single-stranded siRNAs are described in U.S. Patent No. 8,101,348 and in Lima *et al.*, (2012) *Cell* 150:883-894, the entire contents of each of which are hereby incorporated herein by reference. Any of the antisense nucleotide sequences described herein may be used as a single-stranded siRNA as described herein or as chemically modified by the methods described in Lima *et al.*, (2012) *Cell* 150:883-894.

In certain embodiments, an “iRNA” for use in the compositions, uses, and methods of the invention is a double stranded RNA and is referred to herein as a “double stranded RNA agent,” “double stranded RNA (dsRNA) molecule,” “dsRNA agent,” or “dsRNA”. The term “dsRNA”, refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary nucleic acid strands, referred to as having “sense” and “antisense” orientations with respect to a target RNA, *i.e.*, an AGT gene. In some embodiments of the invention, a double stranded RNA (dsRNA) triggers the degradation of a target RNA, *e.g.*, an mRNA, through a post-transcriptional gene-silencing mechanism referred to herein as RNA interference or RNAi.

In general, the majority of nucleotides of each strand of a dsRNA molecule are ribonucleotides, but as described in detail herein, each or both strands can also include one or more non-ribonucleotides, *e.g.*, a deoxyribonucleotide or a modified nucleotide. In addition, as used in this specification, an “iRNA” may include ribonucleotides with chemical modifications; an iRNA may include substantial modifications at multiple nucleotides. As used herein, the term “modified nucleotide” refers to a nucleotide having, independently, a modified sugar moiety, a modified internucleotide linkage, or modified nucleobase, or any combination thereof. Thus, the term modified nucleotide encompasses substitutions, additions or removal of, *e.g.*, a functional group or atom, to internucleoside linkages, sugar moieties, or nucleobases. The modifications suitable for use in the

agents of the invention include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a siRNA type molecule, are encompassed by “iRNA” or “RNAi agent” for the purposes of this specification and claims.

In certain embodiments of the instant disclosure, inclusion of a deoxy-nucleotide if present within an RNAi agent can be considered to constitute a modified nucleotide.

The duplex region may be of any length that permits specific degradation of a desired target RNA through a RISC pathway, and may range from about 19 to 36 base pairs in length, *e.g.*, about 19-30 base pairs in length, for example, about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 base pairs in length, such as about 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In certain embodiments, the duplex region is 19-21 base pairs in length, *e.g.*, 21 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

The two strands forming the duplex structure may be different portions of one larger RNA molecule, or they may be separate RNA molecules. Where the two strands are part of one larger molecule, and therefore are connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting RNA chain is referred to as a “hairpin loop.” A hairpin loop can comprise at least one unpaired nucleotide. In some embodiments, the hairpin loop can comprise at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 23 or more unpaired nucleotides. In some embodiments, the hairpin loop can be 10 or fewer nucleotides. In some embodiments, the hairpin loop can be 8 or fewer unpaired nucleotides. In some embodiments, the hairpin loop can be 4-10 unpaired nucleotides. In some embodiments, the hairpin loop can be 4-8 nucleotides.

Where the two substantially complementary strands of a dsRNA are comprised by separate RNA molecules, those molecules need not be, but can be covalently connected. Where the two strands are connected covalently by means other than an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting structure is referred to as a “linker.” The RNA strands may have the same or a different number of nucleotides. The maximum number of base pairs is the number of nucleotides in the shortest strand of the dsRNA minus any overhangs that are present in the duplex. In addition to the duplex structure, an RNAi may comprise one or more nucleotide overhangs. In one embodiment of the RNAi agent, at least one strand comprises a 3' overhang of at least 1 nucleotide. In another embodiment, at least one strand comprises a 3' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In other embodiments, at least one strand of the RNAi agent comprises a 5' overhang of at least 1 nucleotide. In certain embodiments, at least one strand comprises a 5' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15

nucleotides. In still other embodiments, both the 3' and the 5' end of one strand of the RNAi agent comprise an overhang of at least 1 nucleotide.

In certain embodiments, an iRNA agent of the invention is a dsRNA, each strand of which comprises 19-23 nucleotides, that interacts with a target RNA sequence, *e.g.*, an AGT gene, to direct
5 cleavage of the target RNA.

In some embodiments, an iRNA of the invention is a dsRNA of 24-30 nucleotides that interacts with a target RNA sequence, *e.g.*, an AGT target mRNA sequence, to direct the cleavage of the target RNA.

As used herein, the term “nucleotide overhang” refers to at least one unpaired nucleotide that
10 protrudes from the duplex structure of a double stranded iRNA. For example, when a 3'-end of one strand of a dsRNA extends beyond the 5'-end of the other strand, or *vice versa*, there is a nucleotide overhang. A dsRNA can comprise an overhang of at least one nucleotide; alternatively the overhang can comprise at least two nucleotides, at least three nucleotides, at least four nucleotides, at least five
15 nucleotides or more. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can be on the sense strand, the antisense strand, or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5'-end, 3'-end, or both ends of either an antisense or sense strand of a dsRNA.

In one embodiment, the antisense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In one embodiment, the sense
20 strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

In certain embodiments, the antisense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, 0-3, 1-3, 2-4, 2-5, 4-10, 5-10, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-
25 end. In one embodiment, the sense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

In certain embodiments, the antisense strand of a dsRNA has a 1-10 nucleotides, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In certain embodiments, the
30 overhang on the sense strand or the antisense strand, or both, can include extended lengths longer than 10 nucleotides, *e.g.*, 1-30 nucleotides, 2-30 nucleotides, 10-30 nucleotides, 10-25 nucleotides, 10-20 nucleotides, or 10-15 nucleotides in length. In certain embodiments, an extended overhang is on the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 3' end of the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 5' end
35 of the sense strand of the duplex. In certain embodiments, an extended overhang is on the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 3' end of the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 5' end

of the antisense strand of the duplex. In certain embodiments, one or more of the nucleotides in the extended overhang is replaced with a nucleoside thiophosphate. In certain embodiments, the overhang includes a self-complementary portion such that the overhang is capable of forming a hairpin structure that is stable under physiological conditions.

5 “Blunt” or “blunt end” means that there are no unpaired nucleotides at that end of the double stranded RNA agent, *i.e.*, no nucleotide overhang. A “blunt ended” double stranded RNA agent is double stranded over its entire length, *i.e.*, no nucleotide overhang at either end of the molecule. The RNAi agents of the invention include RNAi agents with no nucleotide overhang at one end (*i.e.*, agents with one overhang and one blunt end) or with no nucleotide overhangs at either end. Most
10 often such a molecule will be double-stranded over its entire length.

The term “antisense strand” or “guide strand” refers to the strand of an iRNA, *e.g.*, a dsRNA, which includes a region that is substantially complementary to a target sequence, *e.g.*, an AGT mRNA.

As used herein, the term “region of complementarity” refers to the region on the antisense
15 strand that is substantially complementary to a sequence, for example a target sequence, *e.g.*, an AGT nucleotide sequence, as defined herein. Where the region of complementarity is not fully complementary to the target sequence, the mismatches can be in the internal or terminal regions of the molecule. Generally, the most tolerated mismatches are in the terminal regions, *e.g.*, within 5, 4, or 3 nucleotides of the 5’- or 3’-end of the iRNA. In some embodiments, a double stranded RNA agent of
20 the invention includes a nucleotide mismatch in the antisense strand. In some embodiments, the antisense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the target mRNA, *e.g.*, the antisense strand includes 4, 3, 2, 1, or 0 mismatches with the target mRNA. In some embodiments, the antisense strand double stranded RNA agent of the invention includes no more than 4 mismatches with the sense strand, *e.g.*, the antisense strand
25 includes 4, 3, 2, 1, or 0 mismatches with the sense strand. In some embodiments, a double stranded RNA agent of the invention includes a nucleotide mismatch in the sense strand. In some embodiments, the sense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the antisense strand, *e.g.*, the sense strand includes 4, 3, 2, 1, or 0 mismatches with the antisense strand. In some embodiments, the nucleotide mismatch is, for example, within 5, 4,
30 3 nucleotides from the 3’-end of the iRNA. In another embodiment, the nucleotide mismatch is, for example, in the 3’-terminal nucleotide of the iRNA agent. In some embodiments, the mismatch(s) is not in the seed region.

Thus, an RNAi agent as described herein can contain one or more mismatches to the target sequence. In one embodiment, an RNAi agent as described herein contains no more than 3
35 mismatches (*i.e.*, 3, 2, 1, or 0 mismatches). In one embodiment, an RNAi agent as described herein contains no more than 2 mismatches. In one embodiment, an RNAi agent as described herein contains no more than 1 mismatch. In one embodiment, an RNAi agent as described herein contains 0

mismatches. In certain embodiments, if the antisense strand of the RNAi agent contains mismatches to the target sequence, the mismatch can optionally be restricted to be within the last 5 nucleotides from either the 5'- or 3'-end of the region of complementarity. For example, in such embodiments, for a 23 nucleotide RNAi agent, the strand which is complementary to a region of an AGT gene,

generally does not contain any mismatch within the central 13 nucleotides. The methods described herein or methods known in the art can be used to determine whether an RNAi agent containing a mismatch to a target sequence is effective in inhibiting the expression of an AGT gene. Consideration of the efficacy of RNAi agents with mismatches in inhibiting expression of an AGT gene is important, especially if the particular region of complementarity in an AGT gene is known to have polymorphic sequence variation within the population.

The term "sense strand" or "passenger strand" as used herein, refers to the strand of an iRNA that includes a region that is substantially complementary to a region of the antisense strand as that term is defined herein.

As used herein, "substantially all of the nucleotides are modified" are largely but not wholly modified and can include not more than 5, 4, 3, 2, or 1 unmodified nucleotides.

As used herein, the term "cleavage region" refers to a region that is located immediately adjacent to the cleavage site. The cleavage site is the site on the target at which cleavage occurs. In some embodiments, the cleavage region comprises three bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage region comprises two bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage site specifically occurs at the site bound by nucleotides 10 and 11 of the antisense strand, and the cleavage region comprises nucleotides 11, 12 and 13.

As used herein, and unless otherwise indicated, the term "complementary," when used to describe a first nucleotide sequence in relation to a second nucleotide sequence, refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize and form a duplex structure under certain conditions with an oligonucleotide or polynucleotide comprising the second nucleotide sequence, as will be understood by the skilled person. Such conditions can, for example, be stringent conditions, where stringent conditions can include: 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50°C or 70°C for 12-16 hours followed by washing (see, *e.g.*, "Molecular Cloning: A Laboratory Manual, Sambrook, *et al.* (1989) Cold Spring Harbor Laboratory Press). Other conditions, such as physiologically relevant conditions as can be encountered inside an organism, can apply. The skilled person will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides.

Complementary sequences within an iRNA, *e.g.*, within a dsRNA as described herein, include base-pairing of the oligonucleotide or polynucleotide comprising a first nucleotide sequence to an oligonucleotide or polynucleotide comprising a second nucleotide sequence over the entire length of

one or both nucleotide sequences. Such sequences can be referred to as “fully complementary” with respect to each other herein. However, where a first sequence is referred to as “substantially complementary” with respect to a second sequence herein, the two sequences can be fully complementary, or they can form one or more, but generally not more than 5, 4, 3, or 2 mismatched base pairs upon hybridization for a duplex up to 30 base pairs, while retaining the ability to hybridize under the conditions most relevant to their ultimate application, *e.g.*, inhibition of gene expression, *in vitro* or *in vivo*. However, where two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a dsRNA comprising one oligonucleotide 21 nucleotides in length and another oligonucleotide 23 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 21 nucleotides that is fully complementary to the shorter oligonucleotide, can yet be referred to as “fully complementary” for the purposes described herein.

“Complementary” sequences, as used herein, can also include, or be formed entirely from, non-Watson-Crick base pairs or base pairs formed from non-natural and modified nucleotides, in so far as the above requirements with respect to their ability to hybridize are fulfilled. Such non-Watson-Crick base pairs include, but are not limited to, G:U Wobble or Hoogsteen base pairing.

The terms “complementary,” “fully complementary” and “substantially complementary” herein can be used with respect to the base matching between the sense strand and the antisense strand of a dsRNA, or between two oligonucleotides or polynucleotides, such as the antisense strand of a double stranded RNA agent and a target sequence, as will be understood from the context of their use.

As used herein, a polynucleotide that is “substantially complementary to at least part of” a messenger RNA (mRNA) refers to a polynucleotide that is substantially complementary to a contiguous portion of the mRNA of interest (*e.g.*, an mRNA encoding an AGT gene). For example, a polynucleotide is complementary to at least a part of an AGT mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding an AGT gene.

Accordingly, in some embodiments, the antisense polynucleotides disclosed herein are fully complementary to the target AGT sequence. In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target AGT sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to the equivalent region of the nucleotide sequence of any one of SEQ ID NOs:1, 3, 5, 7, 9, or 11, or a fragment of any one of SEQ ID NOs:1, 3, 5, 7, 9, or 11, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target AGT sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the sense strand nucleotide sequences in any one of any one of Tables 2-7, or a fragment of any one of the sense strand nucleotide

sequences in any one of Tables 2-7, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary.

In one embodiment, an RNAi agent of the disclosure includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is the same as a target AGT sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs: 2, 4, 6, 8, 10, or 12, or a fragment of any one of SEQ ID NOs: 2, 4, 6, 8, 10, or 12, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary.

In some embodiments, an iRNA of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target AGT sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the antisense strand nucleotide sequences in any one of any one of Tables 2-7, or a fragment of any one of the antisense strand nucleotide sequences in any one of Tables 2-7, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary.

In general, an “iRNA” includes ribonucleotides with chemical modifications. Such modifications may include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a dsRNA molecule, are encompassed by “iRNA” for the purposes of this specification and claims.

In certain embodiments of the instant disclosure, inclusion of a deoxy-nucleotide if present within an RNAi agent can be considered to constitute a modified nucleotide.

In an aspect of the invention, an agent for use in the methods and compositions of the invention is a single-stranded antisense oligonucleotide molecule that inhibits a target mRNA *via* an antisense inhibition mechanism. The single-stranded antisense oligonucleotide molecule is complementary to a sequence within the target mRNA. The single-stranded antisense oligonucleotides can inhibit translation in a stoichiometric manner by base pairing to the mRNA and physically obstructing the translation machinery, see Dias, N. *et al.*, (2002) *Mol Cancer Ther* 1:347-355. The single-stranded antisense oligonucleotide molecule may be about 14 to about 30 nucleotides in length and have a sequence that is complementary to a target sequence. For example, the single-stranded antisense oligonucleotide molecule may comprise a sequence that is at least about 14, 15, 16, 17, 18, 19, 20, or more contiguous nucleotides from any one of the antisense sequences described herein.

The phrase “contacting a cell with an iRNA,” such as a dsRNA, as used herein, includes contacting a cell by any possible means. Contacting a cell with an iRNA includes contacting a cell *in*

vitro with the iRNA or contacting a cell *in vivo* with the iRNA. The contacting may be done directly or indirectly. Thus, for example, the iRNA may be put into physical contact with the cell by the individual performing the method, or alternatively, the iRNA may be put into a situation that will permit or cause it to subsequently come into contact with the cell.

5 Contacting a cell *in vitro* may be done, for example, by incubating the cell with the iRNA. Contacting a cell *in vivo* may be done, for example, by injecting the iRNA into or near the tissue where the cell is located, or by injecting the iRNA into another area, *e.g.*, the bloodstream or the subcutaneous space, such that the agent will subsequently reach the tissue where the cell to be contacted is located. For example, the iRNA may contain or be coupled to a ligand, *e.g.*, GalNAc,
10 that directs the iRNA to a site of interest, *e.g.*, the liver. Combinations of *in vitro* and *in vivo* methods of contacting are also possible. For example, a cell may also be contacted *in vitro* with an iRNA and subsequently transplanted into a subject.

 In certain embodiments, contacting a cell with an iRNA includes “introducing” or “delivering the iRNA into the cell” by facilitating or effecting uptake or absorption into the cell. Absorption or
15 uptake of an iRNA can occur through unaided diffusion or active cellular processes, or by auxiliary agents or devices. Introducing an iRNA into a cell may be *in vitro* or *in vivo*. For example, for *in vivo* introduction, iRNA can be injected into a tissue site or administered systemically. *In vitro* introduction into a cell includes methods known in the art such as electroporation and lipofection. Further approaches are described herein below or are known in the art.

20 The term “lipid nanoparticle” or “LNP” is a vesicle comprising a lipid layer encapsulating a pharmaceutically active molecule, such as a nucleic acid molecule, *e.g.*, an iRNA or a plasmid from which an iRNA is transcribed. LNPs are described in, for example, U.S. Patent Nos. 6,858,225, 6,815,432, 8,158,601, and 8,058,069, the entire contents of which are hereby incorporated herein by reference.

25 As used herein, a “subject” is an animal, such as a mammal, including a primate (such as a human, a non-human primate, *e.g.*, a monkey, and a chimpanzee), a non-primate (such as a cow, a pig, a horse, a goat, a rabbit, a sheep, a hamster, a guinea pig, a cat, a dog, a rat, or a mouse), or a bird that expresses the target gene, either endogenously or heterologously. In an embodiment, the subject is a human, such as a human being treated or assessed for a disease or disorder that would benefit
30 from reduction in AGT expression; a human at risk for a disease or disorder that would benefit from reduction in AGT expression; a human having a disease or disorder that would benefit from reduction in AGT expression; or human being treated for a disease or disorder that would benefit from reduction in AGT expression as described herein. The diagnostic criteria for an AGT-associated disorder, *e.g.*, hypertension, are provided below. In some embodiments, the subject is a female human. In other
35 embodiments, the subject is a male human. In certain embodiments, the subject is part of a group susceptible to salt sensitivity, *e.g.*, black or an older adult (> 65 years of age). In certain embodiments, the subject is overweight or obese, *e.g.*, a subject that suffers from central obesity. In

certain embodiments, the subject is sedentary. In certain embodiments, the subject is pregnant. In another embodiment, the subject is a pediatric subject.

As used herein, the terms “treating” or “treatment” refer to a beneficial or desired result, such as reducing at least one sign or symptom of an AGT-associated disorder in a subject. Treatment also includes a reduction of one or more sign or symptoms associated with unwanted AGT expression; diminishing the extent of unwanted AGT activation or stabilization; amelioration or palliation of unwanted AGT activation or stabilization. Treatment also includes a reduction of one or more sign or symptoms associated with unwanted AGT expression, *e.g.*, angiotensin II type 1 receptor activation (AT1R) (*e.g.*, hypertension, chronic kidney disease, stroke, myocardial infarction, heart failure, aneurysms, peripheral artery disease, heart disease, increased oxidative stress, *e.g.*, increased superoxide formation, inflammation, vasoconstriction, sodium and water retention, potassium and magnesium loss, renin suppression, myocyte and smooth muscle hypertrophy, increased collagen synthesis, stimulation of vascular, myocardial and renal fibrosis, increased rate and force of cardiac contractions, altered heart rate, *e.g.*, increased arrhythmia, stimulation of plasminogen activator inhibitor 1 (PAI1), activation of the sympathetic nervous system, and increased endothelin secretion), symptoms of pregnancy-associated hypertension (*e.g.*, preeclampsia, and eclampsia), including, but not limited to intrauterine growth restriction (IUGR) or fetal growth restriction, symptoms associated with malignant hypertension, symptoms associated with hyperaldosteronism; diminishing the extent of unwanted AT1R activation; stabilization (*i.e.*, not worsening) of the state of chronic AT1R activation; amelioration or palliation of unwanted AT1R activation (*e.g.*, hypertension, chronic kidney disease, stroke, myocardial infarction, heart failure, aneurysms, peripheral artery disease, heart disease, increased oxidative stress, *e.g.*, increased superoxide formation, inflammation, vasoconstriction, sodium and water retention, potassium and magnesium loss, renin suppression, myocyte and smooth muscle hypertrophy, increased collagen synthesis, stimulation of vascular, myocardial and renal fibrosis, increased rate and force of cardiac contractions, altered heart rate, *e.g.*, increased arrhythmia, stimulation of plasminogen activator inhibitor 1 (PAI1), activation of the sympathetic nervous system, and increased endothelin secretion) whether detectable or undetectable. AGT-associated disorders can also include obesity, liver steatosis/ fatty liver, *e.g.*, non-alcoholic Steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD), glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome. In certain embodiments, hypertension includes hypertension associated with low plasma renin activity or plasma renin concentration. “Treatment” can also mean prolonging survival as compared to expected survival in the absence of treatment.

The term “lower” in the context of the level of AGT in a subject or a disease marker or symptom refers to a statistically significant decrease in such level. The decrease can be, for example, at least 10%, 15%, 20%, 25%, 30%, %, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more. In certain embodiments, a decrease is at least 20%. In certain embodiments, the

decrease is at least 50% in a disease marker, *e.g.*, protein or gene expression level. “Lower” in the context of the level of AGT in a subject is a decrease to a level accepted as within the range of normal for an individual without such disorder. In certain embodiments, “lower” is the decrease in the difference between the level of a marker or symptom for a subject suffering from a disease and a level accepted within the range of normal for an individual. The term “lower” can also be used in association with normalizing a symptom of a disease or condition, *i.e.* decreasing the difference between a level in a subject suffering from an AGT-associated disorder towards or to a level in a normal subject not suffering from an AGT-associated disorder. As used herein, if a disease is associated with an elevated value for a symptom, “normal” is considered to be the upper limit of normal. If a disease is associated with a decreased value for a symptom, “normal” is considered to be the lower limit of normal.

As used herein, “prevention” or “preventing,” when used in reference to a disease or disorder, that would benefit from a reduction in expression of an AGT gene or production of agt protein, *e.g.*, in a subject susceptible to an AGT-associated disorder due to, *e.g.*, aging, genetic factors, hormone changes, diet, and a sedentary lifestyle. In certain embodiments, the disease or disorder is *e.g.*, a symptom of unwanted AT1R activation, such as a hypertension, chronic kidney disease, stroke, myocardial infarction, heart failure, aneurysms, peripheral artery disease, heart disease, increased oxidative stress, *e.g.*, increased superoxide formation, inflammation, vasoconstriction, sodium and water retention, potassium and magnesium loss, renin suppression, myocyte and smooth muscle hypertrophy, increased collagen synthesis, stimulation of vascular, myocardial and renal fibrosis, increased rate and force of cardiac contractions, altered heart rate, *e.g.*, increased arrhythmia, stimulation of plasminogen activator inhibitor 1 (PAI1), activation of the sympathetic nervous system, and increased endothelin secretion. AGT-associated disorders can also include obesity, liver steatosis/ fatty liver, *e.g.*, non-alcoholic Steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD), glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome. In certain embodiments, hypertension includes hypertension associated with low plasma renin activity or plasma renin concentration. The likelihood of developing, *e.g.*, hypertension, is reduced, for example, when an individual having one or more risk factors for a hypertension either fails to develop hypertension or develops hypertension with less severity relative to a population having the same risk factors and not receiving treatment as described herein. The failure to develop an AGT-associated disorder, *e.g.*, hypertension or a delay in the time to develop hypertension by months or years is considered effective prevention. Prevention may require administration of more than one dose if the iRNA agent.

As used herein, the term “angiotensinogen-associated disease” or “AGT-associated disease,” is a disease or disorder that is caused by, or associated with renin-angiotensin-aldosterone system (RAAS) activation, or a disease or disorder the symptoms of which or progression of which responds to RAAS inactivation. The term “angiotensinogen-associated disease” includes a disease, disorder or

condition that would benefit from reduction in AGT expression. Such diseases are typically associated with high blood pressure. Non-limiting examples of angiotensinogen-associated diseases include hypertension, *e.g.*, borderline hypertension (also known as prehypertension), primary hypertension (also known as essential hypertension or idiopathic hypertension), secondary hypertension (also known as inessential hypertension), isolated systolic or diastolic hypertension, pregnancy-associated hypertension (*e.g.*, preeclampsia, eclampsia, and post-partum preeclampsia), diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension (also known as renal hypertension), Goldblatt hypertension, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy (including peripheral vascular disease), diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, sleep apnea, heart failure (*e.g.*, left ventricular systolic dysfunction), myocardial infarction, angina, stroke, renal disease *e.g.*, chronic kidney disease or diabetic nephropathy optionally in the context of pregnancy, renal failure, *e.g.*, chronic renal failure, and systemic sclerosis (*e.g.*, scleroderma renal crisis). In certain embodiments, AGT- associated disease includes intrauterine growth restriction (IUGR) or fetal growth restriction. In certain embodiments, AGT-associated disorders also include obesity, liver steatosis/ fatty liver, *e.g.*, non-alcoholic Steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD), glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome. In certain embodiments, hypertension includes hypertension associated with low plasma renin activity or plasma renin concentration.

Thresholds for high blood pressure and stages of hypertension are discussed in detail below.

In one embodiment, an angiotensinogen-associated disease is primary hypertension. “Primary hypertension” is a result of environmental or genetic causes (*e.g.*, a result of no obvious underlying medical cause).

In one embodiment, an angiotensinogen-associated disease is secondary hypertension. “Secondary hypertension” has an identifiable underlying disorder which can be of multiple etiologies, including renal, vascular, and endocrine causes, *e.g.*, renal parenchymal disease (*e.g.*, polycystic kidneys, glomerular or interstitial disease), renal vascular disease (*e.g.*, renal artery stenosis, fibromuscular dysplasia), endocrine disorders (*e.g.*, adrenocorticosteroid or mineralocorticoid excess, pheochromocytoma, hyperthyroidism or hypothyroidism, growth hormone excess, hyperparathyroidism), coarctation of the aorta, or oral contraceptive use.

In one embodiment, an angiotensinogen-associated disease is pregnancy-associated hypertension, *e.g.*, chronic hypertension of pregnancy, gestational hypertension, preeclampsia, eclampsia, preeclampsia superimposed on chronic hypertension, HELLP syndrome, and gestational hypertension (also known as transient hypertension of pregnancy, chronic hypertension identified in

the latter half of pregnancy, and pregnancy-induced hypertension (PIH)). Diagnostic criteria for pregnancy-associated hypertension are provided below.

In one embodiment, an angiotensinogen-associated disease is resistant hypertension.

“Resistant hypertension” is blood pressure that remains above goal (*e.g.*, above 130 mm Hg systolic or above 90 diastolic) in spite of concurrent use of three antihypertensive agents of different classes, one of which is a thiazide diuretic. Subjects whose blood pressure is controlled with four or more medications are also considered to have resistant hypertension.

“Therapeutically effective amount,” as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having an AGT-associated disorder, is sufficient to effect treatment of the disease (*e.g.*, by diminishing, ameliorating, or maintaining the existing disease or one or more symptoms of disease). The “therapeutically effective amount” may vary depending on the RNAi agent, how the agent is administered, the disease and its severity and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the subject to be treated.

“Prophylactically effective amount,” as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having an AGT-associated disorder, is sufficient to prevent or ameliorate the disorder or one or more symptoms of the disorder. Ameliorating the disease includes slowing the course of the disease or reducing the severity of later-developing disease. The “prophylactically effective amount” may vary depending on the RNAi agent, how the agent is administered, the degree of risk of disease, and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the patient to be treated.

A “therapeutically-effective amount” or “prophylactically effective amount” also includes an amount of an RNAi agent that produces some desired effect at a reasonable benefit/risk ratio applicable to any treatment. The iRNA employed in the methods of the present invention may be administered in a sufficient amount to produce a reasonable benefit/risk ratio applicable to such treatment.

The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials (including salts), compositions, or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human subjects and animal subjects without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase “pharmaceutically-acceptable carrier” as used herein means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (*e.g.*, lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the

sense of being compatible with the other ingredients of the formulation and not injurious to the subject being treated. Such carriers are known in the art. Pharmaceutically acceptable carriers include carriers for administration by injection.

The term “sample,” as used herein, includes a collection of similar fluids, cells, or tissues isolated from a subject, as well as fluids, cells, or tissues present within a subject. Examples of biological fluids include blood, serum and serosal fluids, plasma, cerebrospinal fluid, ocular fluids, lymph, urine, saliva, and the like. Tissue samples may include samples from tissues, organs, or localized regions. For example, samples may be derived from particular organs, parts of organs, or fluids or cells within those organs. In certain embodiments, samples may be derived from the liver (*e.g.*, whole liver or certain segments of liver or certain types of cells in the liver, such as, *e.g.*, hepatocytes). In some embodiments, a “sample derived from a subject” refers to urine obtained from the subject. A “sample derived from a subject” can refer to blood or blood derived serum or plasma from the subject.

II. iRNAs of the Invention

The present invention provides iRNAs which inhibit the expression of an AGT gene. In certain embodiments, the iRNA includes double stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of an AGT gene in a cell, such as a cell within a subject, *e.g.*, a mammal, such as a human susceptible to developing an AGT-associated disorder, *e.g.*, hypertension. The dsRNAi agent includes an antisense strand having a region of complementarity which is complementary to at least a part of an mRNA formed in the expression of an AGT gene. The region of complementarity is about 19-30 nucleotides in length (*e.g.*, about 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, or 19 nucleotides in length).

Upon contact with a cell expressing the AGT gene, the iRNA inhibits the expression of the AGT gene (*e.g.*, a human, a primate, a non-primate, or a rat AGT gene) by at least about 50% as assayed by, for example, a PCR or branched DNA (bDNA)-based method, or by a protein-based method, such as by immunofluorescence analysis, using, for example, western blotting or flow cytometric techniques. In certain embodiments, inhibition of expression is determined by the qPCR method provided in the examples herein with the siRNA at, *e.g.*, a 10 nM concentration, in an appropriate organism cell line provided therein. In certain embodiments, inhibition of expression *in vivo* is determined by knockdown of the human gene in a rodent expressing the human gene, *e.g.*, a mouse or an AAV-infected mouse expressing the human target gene, *e.g.*, when administered as single dose, *e.g.*, at 3 mg/kg at the nadir of RNA expression.

A dsRNA includes two RNA strands that are complementary and hybridize to form a duplex structure under conditions in which the dsRNA will be used. One strand of a dsRNA (the antisense strand) includes a region of complementarity that is substantially complementary, and generally fully complementary, to a target sequence. The target sequence can be derived from the sequence of an

mRNA formed during the expression of an AGT gene. The other strand (the sense strand) includes a region that is complementary to the antisense strand, such that the two strands hybridize and form a duplex structure when combined under suitable conditions. As described elsewhere herein and as known in the art, the complementary sequences of a dsRNA can also be contained as self-complementary regions of a single nucleic acid molecule, as opposed to being on separate oligonucleotides.

Generally, the duplex structure is 15 to 30 base pairs in length, *e.g.*, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In certain embodiments, the duplex structure is 18 to 25 base pairs in length, *e.g.*, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-25, 20-24, 20-23, 20-22, 20-21, 21-25, 21-24, 21-23, 21-22, 22-25, 22-24, 22-23, 23-25, 23-24 or 24-25 base pairs in length, for example, 19-21 basepairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

Similarly, the region of complementarity to the target sequence is 15 to 30 nucleotides in length, *e.g.*, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length, for example 19-23 nucleotides in length or 21-23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

In some embodiments, the duplex structure is 19 to 30 base pairs in length. Similarly, the region of complementarity to the target sequence is 19 to 30 nucleotides in length.

In some embodiments, the dsRNA is about 19 to about 23 nucleotides in length, or about 25 to about 30 nucleotides in length. In general, the dsRNA is long enough to serve as a substrate for the Dicer enzyme. For example, it is well-known in the art that dsRNAs longer than about 21-23 nucleotides in length may serve as substrates for Dicer. As the ordinarily skilled person will also recognize, the region of an RNA targeted for cleavage will most often be part of a larger RNA molecule, often an mRNA molecule. Where relevant, a “part” of an mRNA target is a contiguous sequence of an mRNA target of sufficient length to allow it to be a substrate for RNAi-directed cleavage (*i.e.*, cleavage through a RISC pathway).

One of skill in the art will also recognize that the duplex region is a primary functional portion of a dsRNA, *e.g.*, a duplex region of about 19 to about 30 base pairs, *e.g.*, about 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base

pairs. Thus, in one embodiment, to the extent that it becomes processed to a functional duplex, of *e.g.*, 15-30 base pairs, that targets a desired RNA for cleavage, an RNA molecule or complex of RNA molecules having a duplex region greater than 30 base pairs is a dsRNA. Thus, an ordinarily skilled artisan will recognize that in one embodiment, a miRNA is a dsRNA. In another embodiment, a dsRNA is not a naturally occurring miRNA. In another embodiment, an iRNA agent useful to target AGT gene expression is not generated in the target cell by cleavage of a larger dsRNA.

A dsRNA as described herein can further include one or more single-stranded nucleotide overhangs, *e.g.*, 1-4, 2-4, 1-3, 2-3, 1, 2, 3, or 4 nucleotides. dsRNAs having at least one nucleotide overhang can have superior inhibitory properties relative to their blunt-ended counterparts. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can be on the sense strand, the antisense strand, or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5'-end, 3'-end, or both ends of an antisense or sense strand of a dsRNA.

A dsRNA can be synthesized by standard methods known in the art. Double stranded RNAi compounds of the invention may be prepared using a two-step procedure. First, the individual strands of the double stranded RNA molecule are prepared separately. Then, the component strands are annealed. The individual strands of the siRNA compound can be prepared using solution-phase or solid-phase organic synthesis or both. Organic synthesis offers the advantage that the oligonucleotide strands comprising unnatural or modified nucleotides can be easily prepared. Similarly, single-stranded oligonucleotides of the invention can be prepared using solution-phase or solid-phase organic synthesis or both.

In an aspect, a dsRNA of the invention includes at least two nucleotide sequences, a sense sequence and an anti-sense sequence. The sense strand is selected from the group of sequences provided in any one of Tables 2-7, and the corresponding antisense strand of the sense strand is selected from the group of sequences of any one of Tables 2-7. In this aspect, one of the two sequences is complementary to the other of the two sequences, with one of the sequences being substantially complementary to a sequence of an mRNA generated in the expression of an AGT gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand in any one of Tables 2-7, and the second oligonucleotide is described as the corresponding antisense strand of the sense strand in any one of Tables 2-7.

In certain embodiments, the substantially complementary sequences of the dsRNA are contained on separate oligonucleotides. In other embodiments, the substantially complementary sequences of the dsRNA are contained on a single oligonucleotide.

It will be understood that, although the sequences in, for example, Table 2, are not described as modified or conjugated sequences, the RNA of the iRNA of the invention *e.g.*, a dsRNA of the invention, may comprise any one of the sequences set forth in any one of Tables 2-7 that is unmodified, un-conjugated, or modified or conjugated differently than described therein. In other

words, the invention encompasses dsRNA of Tables 2-7 which are un-modified, un-conjugated, modified, or conjugated, as described herein.

The skilled person is well aware that dsRNAs having a duplex structure of about 20 to 23 base pairs, *e.g.*, 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir *et al.*, *EMBO* 2001, 20:6877-6888). However, others have found that shorter or longer RNA duplex structures can also be effective (Chu and Rana (2007) *RNA* 14:1714-1719; Kim *et al.* (2005) *Nat Biotech* 23:222-226). In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided in any one of Tables 2-7. dsRNAs described herein can include at least one strand of a length of minimally 21 nucleotides. It can be reasonably expected that shorter duplexes having any one of the sequences in any one of Tables 2-7 minus only a few nucleotides on one or both ends can be similarly effective as compared to the dsRNAs described above. Hence, dsRNAs having a sequence of at least 19, 20, or more contiguous nucleotides derived from any one of the sequences of any one of Tables 2-7, and differing in their ability to inhibit the expression of an AGT gene by not more than about 5, 10, 15, 20, 25, or 30 % inhibition from a dsRNA comprising the full sequence, are contemplated to be within the scope of the present invention.

In addition, the RNAs provided in Tables 2-7 identify a site(s) in an AGT transcript that is susceptible to RISC-mediated cleavage. As such, the present invention further features iRNAs that target within one of these sites. As used herein, an iRNA is said to target within a particular site of an RNA transcript if the iRNA promotes cleavage of the transcript anywhere within that particular site. Such an iRNA will generally include at least about 19 contiguous nucleotides from any one of the sequences provided in any one of Tables 2-7 coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in an AGT gene.

III. Modified iRNAs of the Invention

In certain embodiments, the RNA of the iRNA of the invention *e.g.*, a dsRNA, is un-modified, and does not comprise, *e.g.*, chemical modifications or conjugations known in the art and described herein. In other embodiments, the RNA of an iRNA of the invention, *e.g.*, a dsRNA, is chemically modified to enhance stability or other beneficial characteristics. In certain embodiments of the invention, substantially all of the nucleotides of an iRNA of the invention are modified. In other embodiments of the invention, all of the nucleotides of an iRNA or substantially all of the nucleotides of an iRNA are modified, *i.e.*, not more than 5, 4, 3, 2, or 1 unmodified nucleotides are present in a strand of the iRNA.

The nucleic acids featured in the invention can be synthesized or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S.L. *et al.* (Edrs.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference. Modifications include, for example, end modifications, *e.g.*, 5'-end modifications (phosphorylation, conjugation, inverted linkages) or 3'-end modifications (conjugation,

DNA nucleotides, inverted linkages, *etc.*); base modifications, *e.g.*, replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases; sugar modifications (*e.g.*, at the 2'-position or 4'-position) or replacement of the sugar; or backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of iRNA compounds useful in the embodiments described herein include, but are not limited to RNAs containing modified backbones or no natural internucleoside linkages. RNAs having modified backbones include, among others, those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In some embodiments, a modified iRNA will have a phosphorus atom in its internucleoside backbone.

Modified RNA backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5'-linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included. In some embodiments of the invention, the dsRNA agents of the invention are in a free acid form. In other embodiments of the invention, the dsRNA agents of the invention are in a salt form. In one embodiment, the dsRNA agents of the invention are in a sodium salt form. In certain embodiments, when the dsRNA agents of the invention are in the sodium salt form, sodium ions are present in the agent as counterions for substantially all of the phosphodiester and/or phosphorothioate groups present in the agent. Agents in which substantially all of the phosphodiester and/or phosphorothioate linkages have a sodium counterion include not more than 5, 4, 3, 2, or 1 phosphodiester and/or phosphorothioate linkages without a sodium counterion. In some embodiments, when the dsRNA agents of the invention are in the sodium salt form, sodium ions are present in the agent as counterions for all of the phosphodiester and/or phosphorothioate groups present in the agent.

Representative U.S. Patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Patent Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,625,050; 6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6,239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and U.S. Pat RE39464, the entire contents of each of which are hereby incorporated herein by reference.

Modified RNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S, and CH₂ component parts.

Representative U.S. Patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Patent Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439, the entire contents of each of which are hereby incorporated herein by reference.

Suitable RNA mimetics are contemplated for use in iRNAs provided herein, in which both the sugar and the internucleoside linkage, *i.e.*, the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound in which an RNA mimetic that has been shown to have excellent hybridization properties is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an RNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative US patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262, the entire contents of each of which are hereby incorporated herein by reference. Additional PNA compounds suitable for use in the iRNAs of the invention are described in, for example, in Nielsen *et al.*, *Science*, 1991, 254, 1497-1500.

Some embodiments featured in the invention include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular --CH₂--NH--CH₂--, --CH₂--N(CH₃)--O--CH₂--[known as a methylene (methylimino) or MMI backbone], --CH₂--O--N(CH₃)--CH₂--, --CH₂--N(CH₃)--N(CH₃)--CH₂-- and --N(CH₃)--CH₂--CH₂-- of the above-referenced U.S. Patent No. 5,489,677, and the amide backbones of the above-referenced U.S. Patent No. 5,602,240. In some embodiments, the RNAs featured herein have morpholino backbone structures of the above-referenced U.S. Patent No. 5,034,506. The native phosphodiester backbone can be represented as O-P(O)(OH)-OCH₂--.

Modified RNAs can also contain one or more substituted sugar moieties. The iRNAs, *e.g.*, dsRNAs, featured herein can include one of the following at the 2'-position: OH; F; O-, S-, or N-alkyl;

O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Exemplary suitable modifications include O[(CH₂)_nO]_mCH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10. In other

embodiments, dsRNAs include one of the following at the 2' position: C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an iRNA, or a group for

improving the pharmacodynamic properties of an iRNA, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminoethoxy, *i.e.*, a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE, as described in

examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH₂--O--CH₂--N(CH₃)₂. Further exemplary modifications include : 5'-Me-2'-F nucleotides, 5'-Me-2'-OMe nucleotides, 5'-Me-2'-deoxynucleotides, (both R and S isomers in these three families); 2'-alkoxyalkyl; and 2'-NMA (N-methylacetamide).

Other modifications include 2'-methoxy (2'-OCH₃), 2'-aminopropoxy (2'-OCH₂CH₂CH₂NH₂) and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of an iRNA, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. iRNAs can also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative US patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Patent Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application,. The entire contents of each of the foregoing are hereby incorporated herein by reference.

An iRNA can also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as deoxythymidine (dT), 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil

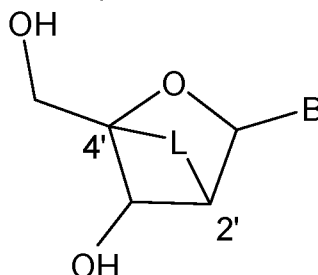
(pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*, Herdewijn, P. ed. Wiley-VCH, 2008; those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, pages 858-859, Kroschwitz, J. L., ed. John Wiley & Sons, 1990, those disclosed by Englisch *et al.*, *Angewandte Chemie*, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y. S., Chapter 15, *dsRNA Research and Applications*, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds featured in the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., *dsRNA Research and Applications*, CRC Press, Boca Raton, 1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Representative U.S. Patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Patent Nos. 3,687,808, 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; 5,750,692; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, the entire contents of each of which are hereby incorporated herein by reference.

In some embodiments, an RNAi agent of the disclosure can also be modified to include one or more bicyclic sugar moieties. A "bicyclic sugar" is a furanosyl ring modified by a ring formed by the bridging of two carbons, whether adjacent or non-adjacent. A "bicyclic nucleoside" ("BNA") is a nucleoside having a sugar moiety comprising a ring formed by bridging two carbons, whether adjacent or non-adjacent, of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4'-carbon and the 2'-carbon of the sugar ring, optionally, via the 2'-acyclic oxygen atom. Thus, in some embodiments an agent of the invention may include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. In other words, an LNA is a nucleotide comprising a bicyclic sugar moiety comprising a 4'-CH₂-O-2' bridge. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook,

OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193). Examples of bicyclic nucleosides for use in the polynucleotides of the invention include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, the antisense polynucleotide agents of the invention include one or more bicyclic nucleosides comprising a 4' to 2' bridge.

A locked nucleoside can be represented by the structure (omitting stereochemistry),



wherein B is a nucleobase or modified nucleobase and L is the linking group that joins the 2'-carbon to the 4'-carbon of the ribose ring. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to 4'-(CH₂)—O-2' (LNA); 4'-(CH₂)—S-2'; 4'-(CH₂)₂—O-2' (ENA); 4'-CH(CH₃)—O-2' (also referred to as "constrained ethyl" or "cEt") and 4'-CH(CH₂OCH₃)—O-2' (and analogs thereof; see, *e.g.*, U.S. Patent No. 7,399,845); 4'-C(CH₃)(CH₃)—O-2' (and analogs thereof; see *e.g.*, U.S. Patent No. 8,278,283); 4'-CH₂—N(OCH₃)-2' (and analogs thereof; see *e.g.*, U.S. Patent No. 8,278,425); 4'-CH₂—O—N(CH₃)-2' (see, *e.g.*, U.S. Patent Publication No. 2004/0171570); 4'-CH₂—N(R)—O-2', wherein R is H, C1-C12 alkyl, or a nitrogen protecting group (see, *e.g.*, U.S. Patent No. 7,427,672); 4'-CH₂—C(H)(CH₃)-2' (see, *e.g.*, Chattopadhyaya *et al.*, *J. Org. Chem.*, 2009, 74, 118-134); and 4'-CH₂—C(=CH₂)-2' (and analogs thereof; see, *e.g.*, U.S. Patent No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein by reference.

Additional representative U.S. Patents and U.S. Patent Publications that teach the preparation of locked nucleic acid nucleotides include, but are not limited to, the following: U.S. Patent Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 6,998,484; 7,053,207; 7,034,133; 7,084,125; 7,399,845; 7,427,672; 7,569,686; 7,741,457; 8,022,193; 8,030,467; 8,278,425; 8,278,426; 8,278,283; US 2008/0039618; and US 2009/0012281, the entire contents of each of which are hereby incorporated herein by reference.

Any of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α-L-ribofuranose and β-D-ribofuranose (see WO 99/14226).

The RNA of an iRNA can also be modified to include one or more constrained ethyl nucleotides. As used herein, a "constrained ethyl nucleotide" or "cEt" is a locked nucleic acid comprising a bicyclic sugar moiety comprising a 4'-CH(CH₃)-O-2' bridge (*i.e.*, L in the preceding

structure). In one embodiment, a constrained ethyl nucleotide is in the S conformation referred to herein as "S-cEt."

An iRNA of the invention may also include one or more "conformationally restricted nucleotides" ("CRN"). CRN are nucleotide analogs with a linker connecting the C2' and C4' carbons of ribose or the C3 and -C5' carbons of ribose. CRN lock the ribose ring into a stable conformation and increase the hybridization affinity to mRNA. The linker is of sufficient length to place the oxygen in an optimal position for stability and affinity resulting in less ribose ring puckering.

Representative publications that teach the preparation of certain of the above noted CRN include, but are not limited to, U.S. Patent Publication No. 2013/0190383; and PCT publication WO 2013/036868, the entire contents of each of which are hereby incorporated herein by reference.

In some embodiments, an iRNA of the invention comprises one or more monomers that are UNA (unlocked nucleic acid) nucleotides. UNA is unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked "sugar" residue. In one example, UNA also encompasses monomer with bonds between C1'-C4' have been removed (*i.e.* the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (*i.e.* the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar has been removed (see *Nuc. Acids Symp. Series*, 52, 133-134 (2008) and Fluiter *et al.*, *Mol. Biosyst.*, 2009, 10, 1039 hereby incorporated by reference).

Representative U.S. publications that teach the preparation of UNA include, but are not limited to, U.S. Patent No. 8,314,227; and U.S. Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.

Potentially stabilizing modifications to the ends of RNA molecules can include N-(acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-O-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3'-phosphate, inverted 2'-deoxy-modified ribonucleotide, such as inverted dT(idT), inverted dA (idA), and inverted abasic 2'-deoxyribonucleotide (iAb) and others. Disclosure of this modification can be found in WO 2011/005861.

In one example, the 3' or 5' terminal end of an oligonucleotide is linked to an inverted 2'-deoxy-modified ribonucleotide, such as inverted dT(idT), inverted dA (idA), or an inverted abasic 2'-deoxyribonucleotide (iAb). In one particular example, the inverted 2'-deoxy-modified ribonucleotide is linked to the 3'-end of an oligonucleotide, such as the 3'-end of a sense strand described herein, where the linking is via a 3'-3' phosphodiester linkage or a 3'-3'-phosphorothioate linkage.

In another example, the 3'-end of a sense strand is linked via a 3'-3'-phosphorothioate linkage to an inverted abasic ribonucleotide (iAb). In another example, the 3'-end of a sense strand is linked via a 3'-3'-phosphorothioate linkage to an inverted dA (idA).

In one particular example, the inverted 2'-deoxy-modified ribonucleotide is linked to the 3'-end of an oligonucleotide, such as the 3'-end of a sense strand described herein, where the linking is via a 3'-3' phosphodiester linkage or a 3'-3'-phosphorothioate linkage.

In another example, the 3'-terminal nucleotides of a sense strand is an inverted dA (idA) and is linked to the preceding nucleotide via a 3'-3'- linkage (*e.g.*, 3'-3'-phosphorothioate linkage).

Other modifications of the nucleotides of an iRNA of the invention include a 5' phosphate or 5' phosphate mimic, *e.g.*, a 5'-terminal phosphate or phosphate mimic on the antisense strand of an iRNA. Suitable phosphate mimics are disclosed in, for example U.S. Patent Publication No. 2012/0157511, the entire contents of which are incorporated herein by reference.

A. Modified iRNAs Comprising Motifs of the Invention

In certain aspects of the invention, the double stranded RNA agents of the invention include agents with chemical modifications as disclosed, for example, in PCT Application No. PCT/US2021/057016, entitled "Modified Double Stranded Oligonucleotides", filed on October 28, 2021 (Attorney Docket No. ALN-384WO), the entire contents of which are incorporated herein by reference.

In certain aspects of the invention, the double stranded RNA agents of the invention include agents with chemical modifications as disclosed, for example, in WO2013/075035, the entire contents of each of which are incorporated herein by reference. As shown herein and in WO2013/075035, one or more motifs of three identical modifications on three consecutive nucleotides may be introduced into a sense strand or antisense strand of a dsRNAi agent, particularly at or near the cleavage site. In some embodiments, the sense strand and antisense strand of the dsRNAi agent may otherwise be completely modified. The introduction of these motifs interrupts the modification pattern, if present, of the sense or antisense strand. The dsRNAi agent may be optionally conjugated with a GalNAc derivative ligand, for instance on the sense strand.

More specifically, when the sense strand and antisense strand of the double stranded RNA agent are completely modified to have one or more motifs of three identical modifications on three consecutive nucleotides at or near the cleavage site of at least one strand of a dsRNAi agent, the gene silencing activity of the dsRNAi agent was observed.

Accordingly, the invention provides double stranded RNA agents capable of inhibiting the expression of a target gene (*i.e.*, AGT gene) *in vivo*. The RNAi agent comprises a sense strand and an antisense strand. Each strand of the RNAi agent may be, for example, 17-30 nucleotides in length, 25-30 nucleotides in length, 27-30 nucleotides in length, 19-25 nucleotides in length, 19-23 nucleotides in length, 19-21 nucleotides in length, 21-25 nucleotides in length, or 21-23 nucleotides in length.

The sense strand and antisense strand typically form a duplex double stranded RNA ("dsRNA"), also referred to herein as "dsRNAi agent." The duplex region of a dsRNAi agent may be,

for example, the duplex region can be 27-30 nucleotide pairs in length, 19-25 nucleotide pairs in length, 19-23 nucleotide pairs in length, 19- 21 nucleotide pairs in length, 21-25 nucleotide pairs in length, or 21-23 nucleotide pairs in length. In another example, the duplex region is selected from 19, 20, 21, 22, 23, 24, 25, 26, and 27 nucleotides in length.

5 In certain embodiments, the dsRNAi agent may contain one or more overhang regions or capping groups at the 3'-end, 5'-end, or both ends of one or both strands. The overhang can be, independently, 1-6 nucleotides in length, for instance 2-6 nucleotides in length, 1-5 nucleotides in length, 2-5 nucleotides in length, 1-4 nucleotides in length, 2-4 nucleotides in length, 1-3 nucleotides in length, 2-3 nucleotides in length, or 1-2 nucleotides in length. In certain embodiments, the
10 overhang regions can include extended overhang regions as provided above. The overhangs can be the result of one strand being longer than the other, or the result of two strands of the same length being staggered. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence. The first and second strands can also be joined, *e.g.*, by additional bases to form a hairpin, or by other non-base
15 linkers.

In certain embodiments, the nucleotides in the overhang region of the dsRNAi agent can each independently be a modified or unmodified nucleotide including, but not limited to 2'-sugar modified, such as, 2'-F, 2'-O-methyl, thymidine (T), 2'-O-methoxyethyl-5-methyluridine (Teo), 2'-O-methoxyethyladenosine (Aeo), 2'-O-methoxyethyl-5-methylcytidine (m5Ceo), and any combinations
20 thereof.

For example, TT can be an overhang sequence for either end on either strand. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence.

The 5'- or 3'- overhangs at the sense strand, antisense strand, or both strands of the dsRNAi
25 agent may be phosphorylated. In some embodiments, the overhang region(s) contains two nucleotides having a phosphorothioate between the two nucleotides, where the two nucleotides can be the same or different. In some embodiments, the overhang is present at the 3'-end of the sense strand, antisense strand, or both strands. In some embodiments, this 3'-overhang is present in the antisense strand. In some embodiments, this 3'-overhang is present in the sense strand.

30 The dsRNAi agent may contain only a single overhang, which can strengthen the interference activity of the RNAi, without affecting its overall stability. For example, the single-stranded overhang may be located at the 3'- end of the sense strand or, alternatively, at the 3'-end of the antisense strand. The RNAi may also have a blunt end, located at the 5'-end of the antisense strand (*i.e.*, the 3'-end of the sense strand) or *vice versa*. Generally, the antisense strand of the dsRNAi agent
35 has a nucleotide overhang at the 3'-end, and the 5'-end is blunt. While not wishing to be bound by theory, the asymmetric blunt end at the 5'-end of the antisense strand and 3'-end overhang of the antisense strand favor the guide strand loading into RISC process.

In certain embodiments, the dsRNAi agent is a double blunt-ended of 19 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 7, 8, 9 from the 5' end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, and 13 from the 5' end.

In other embodiments, the dsRNAi agent is a double blunt-ended of 20 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 8, 9, and 10 from the 5' end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, and 13 from the 5' end.

In yet other embodiments, the dsRNAi agent is a double blunt-ended of 21 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9, 10, and 11 from the 5' end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, and 13 from the 5' end.

In certain embodiments, the dsRNAi agent comprises a 21 nucleotide sense strand and a 23 nucleotide antisense strand, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9, 10, and 11 from the 5' end; the antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, and 13 from the 5' end, wherein one end of the RNAi agent is blunt, while the other end comprises a 2 nucleotide overhang. In one embodiment, the 2 nucleotide overhang is at the 3'-end of the antisense strand.

When the 2 nucleotide overhang is at the 3'-end of the antisense strand, there may be two phosphorothioate internucleotide linkages between the terminal three nucleotides, wherein two of the three nucleotides are the overhang nucleotides, and the third nucleotide is a paired nucleotide next to the overhang nucleotide. In one embodiment, the RNAi agent additionally has two phosphorothioate internucleotide linkages between the terminal three nucleotides at both the 5'-end of the sense strand and at the 5'-end of the antisense strand. In certain embodiments, every nucleotide in the sense strand and the antisense strand of the dsRNAi agent, including the nucleotides that are part of the motifs are modified nucleotides. In certain embodiments each residue is independently modified with a 2'-O-methyl or 3'-fluoro, *e.g.*, in an alternating motif. Optionally, the dsRNAi agent further comprises a ligand (such as, GalNAc₃).

In certain embodiments, the dsRNAi agent comprises a sense and an antisense strand, wherein the sense strand is 25-30 nucleotide residues in length, wherein starting from the 5' terminal nucleotide (position 1) positions 1 to 23 of the first strand comprise at least 8 ribonucleotides; the antisense strand is 36-66 nucleotide residues in length and, starting from the 3' terminal nucleotide, comprises at least 8 ribonucleotides in the positions paired with positions 1- 23 of sense strand to form

a duplex; wherein at least the 3' terminal nucleotide of antisense strand is unpaired with sense strand, and up to 6 consecutive 3' terminal nucleotides are unpaired with sense strand, thereby forming a 3' single stranded overhang of 1-6 nucleotides; wherein the 5' terminus of antisense strand comprises from 10-30 consecutive nucleotides which are unpaired with sense strand, thereby forming a 10-30 nucleotide single stranded 5' overhang; wherein at least the sense strand 5' terminal and 3' terminal nucleotides are base paired with nucleotides of antisense strand when sense and antisense strands are aligned for maximum complementarity, thereby forming a substantially duplexed region between sense and antisense strands; and antisense strand is sufficiently complementary to a target RNA along at least 19 ribonucleotides of antisense strand length to reduce target gene expression when the double stranded nucleic acid is introduced into a mammalian cell; and wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at or near the cleavage site.

In certain embodiments, the dsRNAi agent comprises sense and antisense strands, wherein the dsRNAi agent comprises a first strand having a length which is at least 25 and at most 29 nucleotides and a second strand having a length which is at most 30 nucleotides with at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at position 11, 12, 13 from the 5' end; wherein the 3' end of the first strand and the 5' end of the second strand form a blunt end and the second strand is 1-4 nucleotides longer at its 3' end than the first strand, wherein the duplex region which is at least 25 nucleotides in length, and the second strand is sufficiently complementary to a target mRNA along at least 19 nucleotide of the second strand length to reduce target gene expression when the RNAi agent is introduced into a mammalian cell, and wherein Dicer cleavage of the dsRNAi agent results in an siRNA comprising the 3'-end of the second strand, thereby reducing expression of the target gene in the mammal. Optionally, the dsRNAi agent further comprises a ligand.

In certain embodiments, the sense strand of the dsRNAi agent contains at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at the cleavage site in the sense strand.

In certain embodiments, the antisense strand of the dsRNAi agent can also contain at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at or near the cleavage site in the antisense strand.

For a dsRNAi agent having a duplex region of 19-23 nucleotides in length, the cleavage site of the antisense strand is typically around the 10, 11, and 12 positions from the 5'-end. Thus the motifs of three identical modifications may occur at the 9, 10, 11 positions; the 10, 11, 12 positions; the 11, 12, 13 positions; the 12, 13, 14 positions; or the 13, 14, 15 positions of the antisense strand, the count starting from the first nucleotide from the 5'-end of the antisense strand, or, the count starting from the first paired nucleotide within the duplex region from the 5'-end of the antisense strand. The

cleavage site in the antisense strand may also change according to the length of the duplex region of the dsRNAi agent from the 5'-end.

The sense strand of the dsRNAi agent may contain at least one motif of three identical modifications on three consecutive nucleotides at the cleavage site of the strand; and the antisense strand may have at least one motif of three identical modifications on three consecutive nucleotides at or near the cleavage site of the strand. When the sense strand and the antisense strand form a dsRNA duplex, the sense strand and the antisense strand can be so aligned that one motif of the three nucleotides on the sense strand and one motif of the three nucleotides on the antisense strand have at least one nucleotide overlap, *i.e.*, at least one of the three nucleotides of the motif in the sense strand forms a base pair with at least one of the three nucleotides of the motif in the antisense strand. Alternatively, at least two nucleotides may overlap, or all three nucleotides may overlap.

In some embodiments, the sense strand of the dsRNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides. The first motif may occur at or near the cleavage site of the strand and the other motifs may be a wing modification. The term "wing modification" herein refers to a motif occurring at another portion of the strand that is separated from the motif at or near the cleavage site of the same strand. The wing modification is either adjacent to the first motif or is separated by at least one or more nucleotides. When the motifs are immediately adjacent to each other then the chemistries of the motifs are distinct from each other, and when the motifs are separated by one or more nucleotide then the chemistries can be the same or different. Two or more wing modifications may be present. For instance, when two wing modifications are present, each wing modification may occur at one end relative to the first motif which is at or near cleavage site or on either side of the lead motif.

Like the sense strand, the antisense strand of the dsRNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides, with at least one of the motifs occurring at or near the cleavage site of the strand. This antisense strand may also contain one or more wing modifications in an alignment similar to the wing modifications that may be present on the sense strand.

In some embodiments, the wing modification on the sense strand or antisense strand of the dsRNAi agent typically does not include the first one or two terminal nucleotides at the 3'-end, 5'-end, or both ends of the strand.

In other embodiments, the wing modification on the sense strand or antisense strand of the dsRNAi agent typically does not include the first one or two paired nucleotides within the duplex region at the 3'-end, 5'-end, or both ends of the strand.

When the sense strand and the antisense strand of the dsRNAi agent each contain at least one wing modification, the wing modifications may fall on the same end of the duplex region, and have an overlap of one, two, or three nucleotides.

When the sense strand and the antisense strand of the dsRNAi agent each contain at least two wing modifications, the sense strand and the antisense strand can be so aligned that two modifications each from one strand fall on one end of the duplex region, having an overlap of one, two, or three nucleotides; two modifications each from one strand fall on the other end of the duplex region, having an overlap of one, two or three nucleotides; two modifications one strand fall on each side of the lead motif, having an overlap of one, two or three nucleotides in the duplex region.

In some embodiments, every nucleotide in the sense strand and antisense strand of the dsRNAi agent, including the nucleotides that are part of the motifs, may be modified. Each nucleotide may be modified with the same or different modification which can include one or more alteration of one or both of the non-linking phosphate oxygens or of one or more of the linking phosphate oxygens; alteration of a constituent of the ribose sugar, *e.g.*, of the 2'-hydroxyl on the ribose sugar; wholesale replacement of the phosphate moiety with "dephospho" linkers; modification or replacement of a naturally occurring base; and replacement or modification of the ribose-phosphate backbone.

As nucleic acids are polymers of subunits, many of the modifications occur at a position which is repeated within a nucleic acid, *e.g.*, a modification of a base, or a phosphate moiety, or a non-linking O of a phosphate moiety. In some cases the modification will occur at all of the subject positions in the nucleic acid but in many cases it will not. By way of example, a modification may only occur at a 3'- or 5' terminal position, may only occur in a terminal region, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand. A modification may occur in a double strand region, a single strand region, or in both. A modification may occur only in the double strand region of an RNA or may only occur in a single strand region of a RNA. For example, a phosphorothioate modification at a non-linking O position may only occur at one or both termini, may only occur in a terminal region, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand, or may occur in double strand and single strand regions, particularly at termini. The 5'-end or ends can be phosphorylated.

It may be possible, *e.g.*, to enhance stability, to include particular bases in overhangs, or to include modified nucleotides or nucleotide surrogates, in single strand overhangs, *e.g.*, in a 5'- or 3'-overhang, or in both. For example, it can be desirable to include purine nucleotides in overhangs. In some embodiments all or some of the bases in a 3'- or 5'-overhang may be modified, *e.g.*, with a modification described herein. Modifications can include, *e.g.*, the use of modifications at the 2' position of the ribose sugar with modifications that are known in the art, *e.g.*, the use of deoxyribonucleotides, 2'-deoxy-2'-fluoro (2'-F) or 2'-O-methyl modified instead of the ribosugar of the nucleobase, and modifications in the phosphate group, *e.g.*, phosphorothioate modifications. Overhangs need not be homologous with the target sequence.

In some embodiments, each residue of the sense strand and antisense strand is independently modified with LNA, CRN, cET, UNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-methyl, 2'-O-allyl, 2'-

C- allyl, 2'-deoxy, 2'-hydroxyl, or 2'-fluoro. The strands can contain more than one modification. In one embodiment, each residue of the sense strand and antisense strand is independently modified with 2'-O-methyl or 2'-fluoro.

At least two different modifications are typically present on the sense strand and antisense strand. Those two modifications may be the 2'-O-methyl or 2'-fluoro modifications, or others.

In certain embodiments, the N_a or N_b comprise modifications of an alternating pattern. The term "alternating motif" as used herein refers to a motif having one or more modifications, each modification occurring on alternating nucleotides of one strand. The alternating nucleotide may refer to one per every other nucleotide or one per every three nucleotides, or a similar pattern. For example, if A, B and C each represent one type of modification to the nucleotide, the alternating motif can be "ABABABABABAB...", "AABBAABBAABB...", "AABAABAABAAB...", "AAABAAABAAB...", "AAABBBAAABBB...", or "ABCABCABCABC...", *etc.*

The type of modifications contained in the alternating motif may be the same or different. For example, if A, B, C, D each represent one type of modification on the nucleotide, the alternating pattern, *i.e.*, modifications on every other nucleotide, may be the same, but each of the sense strand or antisense strand can be selected from several possibilities of modifications within the alternating motif such as "ABABAB...", "ACACAC..." "BDBDBD..." or "CDCDCD...", *etc.*

In some embodiments, the dsRNAi agent of the invention comprises the modification pattern for the alternating motif on the sense strand relative to the modification pattern for the alternating motif on the antisense strand is shifted. The shift may be such that the modified group of nucleotides of the sense strand corresponds to a differently modified group of nucleotides of the antisense strand and *vice versa*. For example, the sense strand when paired with the antisense strand in the dsRNA duplex, the alternating motif in the sense strand may start with "ABABAB" from 5' to 3' of the strand and the alternating motif in the antisense strand may start with "BABABA" from 5' to 3' of the strand within the duplex region. As another example, the alternating motif in the sense strand may start with "AABBAABB" from 5' to 3' of the strand and the alternating motif in the antisense strand may start with "BBAABBAA" from 5' to 3' of the strand within the duplex region, so that there is a complete or partial shift of the modification patterns between the sense strand and the antisense strand.

In one particular example, the alternating motif in the sense strand is "ABABAB" from 5' to 3' of the strand, where each A is an unmodified ribonucleotide and each B is a 2'-O-methyl modified nucleotide.

In one particular example, the alternating motif in the sense strand is "ABABAB" from 5' to 3' of the strand, where each A is a 2'-deoxy-2'-fluoro modified nucleotide and each B is a 2'-O-methyl modified nucleotide.

In another particular example, the alternating motif in the antisense strand is "BABABA" from 3'-5' of the strand, where each A is a 2'-deoxy-2'-fluoro modified nucleotide and each B is a 2'-O-methyl modified nucleotide.

In one particular example, the alternating motif in the sense strand is “ABABAB” sfrom 5’ 3’ of the strand and the alternating motif in the antisense strand is “BABABA” from 3’-5’ of the strand, where each A is an unmodified ribonucleotide and each B is a 2’-O-methyl modified nucleotide.

In one particular example, the alternating motif in the sense strand is “ABABAB” sfrom 5’ 3’ of the strand and the alternating motif in the antisense strand is “BABABA” from 3’-5’ of the strand, where each A is a 2’-deoxy-2’-fluoro modified nucleotide and each B is a 2’-O-methyl modified nucleotide.

In some embodiments, the dsRNAi agent comprises the pattern of the alternating motif of 2’-O-methyl modification and 2’-F modification on the sense strand initially has a shift relative to the pattern of the alternating motif of 2’-O-methyl modification and 2’-F modification on the antisense strand initially, *i.e.*, the 2’-O-methyl modified nucleotide on the sense strand base pairs with a 2’-F modified nucleotide on the antisense strand and vice versa. The 1 position of the sense strand may start with the 2’-F modification, and the 1 position of the antisense strand may start with the 2’-O-methyl modification.

The introduction of one or more motifs of three identical modifications on three consecutive nucleotides to the sense strand or antisense strand interrupts the initial modification pattern present in the sense strand or antisense strand. This interruption of the modification pattern of the sense or antisense strand by introducing one or more motifs of three identical modifications on three consecutive nucleotides to the sense or antisense strand may enhance the gene silencing activity against the target gene.

In some embodiments, when the motif of three identical modifications on three consecutive nucleotides is introduced to any of the strands, the modification of the nucleotide next to the motif is a different modification than the modification of the motif. For example, the portion of the sequence containing the motif is “...N_aYYYN_b...,” where “Y” represents the modification of the motif of three identical modifications on three consecutive nucleotide, and “N_a” and “N_b” represent a modification to the nucleotide next to the motif “YYY” that is different than the modification of Y, and where N_a and N_b can be the same or different modifications. Alternatively, N_a or N_b may be present or absent when there is a wing modification present.

The iRNA may further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage. The phosphorothioate or methylphosphonate internucleotide linkage modification may occur on any nucleotide of the sense strand, antisense strand, or both strands in any position of the strand. For instance, the internucleotide linkage modification may occur on every nucleotide on the sense strand or antisense strand; each internucleotide linkage modification may occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand may contain both internucleotide linkage modifications in an alternating pattern. The alternating pattern of the internucleotide linkage modification on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the internucleotide linkage

modification on the sense strand may have a shift relative to the alternating pattern of the internucleotide linkage modification on the antisense strand. In one embodiment, a double-stranded RNAi agent comprises 6-8 phosphorothioate internucleotide linkages. In some embodiments, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-end and two phosphorothioate internucleotide linkages at the 3'-end, and the sense strand comprises at least two phosphorothioate internucleotide linkages at either the 5'-end or the 3'-end.

In some embodiments, the dsRNAi agent comprises a phosphorothioate or methylphosphonate internucleotide linkage modification in the overhang region. For example, the overhang region may contain two nucleotides having a phosphorothioate or methylphosphonate internucleotide linkage between the two nucleotides. Internucleotide linkage modifications also may be made to link the overhang nucleotides with the terminal paired nucleotides within the duplex region. For example, at least 2, 3, 4, or all the overhang nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage, and optionally, there may be additional phosphorothioate or methylphosphonate internucleotide linkages linking the overhang nucleotide with a paired nucleotide that is next to the overhang nucleotide. For instance, there may be at least two phosphorothioate internucleotide linkages between the terminal three nucleotides, in which two of the three nucleotides are overhang nucleotides, and the third is a paired nucleotide next to the overhang nucleotide. These terminal three nucleotides may be at the 3'-end of the antisense strand, the 3'-end of the sense strand, the 5'-end of the antisense strand, or the 5'-end of the antisense strand.

In some embodiments, the 2-nucleotide overhang is at the 3'-end of the antisense strand, and there are two phosphorothioate internucleotide linkages between the terminal three nucleotides, wherein two of the three nucleotides are the overhang nucleotides, and the third nucleotide is a paired nucleotide next to the overhang nucleotide. Optionally, the dsRNAi agent may additionally have two phosphorothioate internucleotide linkages between the terminal three nucleotides at both the 5'-end of the sense strand and at the 5'-end of the antisense strand.

In one embodiment, the dsRNAi agent comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mismatch may occur in the overhang region or the duplex region. The base pair may be ranked on the basis of their propensity to promote dissociation or melting (*e.g.*, on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis can also be used). In terms of promoting dissociation: A:U is preferred over G:C; G:U is preferred over G:C; and I:C is preferred over G:C (I=inosine). Mismatches, *e.g.*, non-canonical or other than canonical pairings (as described elsewhere herein) are preferred over canonical (A:T, A:U, G:C) pairings; and pairings which include a universal base are preferred over canonical pairings.

In certain embodiments, the dsRNAi agent comprises at least one of the first 1, 2, 3, 4, or 5 base pairs within the duplex regions from the 5'-end of the antisense strand independently selected

from the group of: A:U, G:U, I:C, and mismatched pairs, *e.g.*, non-canonical or other than canonical pairings or pairings which include a universal base, to promote the dissociation of the antisense strand at the 5'-end of the duplex.

In certain embodiments, the nucleotide at the 1 position within the duplex region from the 5'-end in the antisense strand is selected from A, dA, dU, U, and dT. Alternatively, at least one of the first 1, 2, or 3 base pair within the duplex region from the 5'-end of the antisense strand is an AU base pair. For example, the first base pair within the duplex region from the 5'-end of the antisense strand is an AU base pair.

In other embodiments, the nucleotide at the 3'-end of the sense strand is deoxythymidine (dT) or the nucleotide at the 3'-end of the antisense strand is deoxythymidine (dT). For example, there is a short sequence of deoxythymidine nucleotides, for example, two dT nucleotides on the 3'-end of the sense, antisense strand, or both strands.

In certain embodiments, the sense strand sequence may be represented by formula (I):



wherein:

i and j are each independently 0 or 1;

p and q are each independently 0-6;

each N_a independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

each n_p and n_q independently represent an overhang nucleotide;

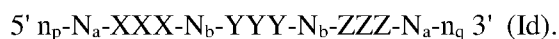
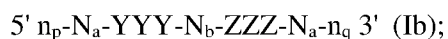
wherein N_b and Y do not have the same modification; and

XXX, YYY, and ZZZ each independently represent one motif of three identical modifications on three consecutive nucleotides. In one embodiment, YYY is all 2'-F modified nucleotides.

In some embodiments, the N_a or N_b comprises modifications of alternating pattern.

In some embodiments, the YYY motif occurs at or near the cleavage site of the sense strand. For example, when the dsRNAi agent has a duplex region of 17-23 nucleotides in length, the YYY motif can occur at or the vicinity of the cleavage site (*e.g.*: can occur at positions 6, 7, 8; 7, 8, 9; 8, 9, 10; 9, 10, 11; 10, 11, 12; or 11, 12, 13) of the sense strand, the count starting from the first nucleotide, from the 5'-end; or optionally, the count starting at the first paired nucleotide within the duplex region, from the 5'-end.

In one embodiment, i is 1 and j is 0, or i is 0 and j is 1, or both i and j are 1. The sense strand can therefore be represented by the following formulas:



When the sense strand is represented by formula (Ib), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2, or 0 modified nucleotides. Each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the sense strand is represented as formula (Ic), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2, or 0 modified nucleotides. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the sense strand is represented as formula (Id), each N_b independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2, or 0 modified nucleotides. In one embodiment, N_b is 0, 1, 2, 3, 4, 5, or 6. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

Each of X, Y and Z may be the same or different from each other.

In other embodiments, i is 0 and j is 0, and the sense strand may be represented by the formula:

5' n_p - N_a -YYY- N_a - n_q 3' (Ia).

When the sense strand is represented by formula (Ia), each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

In one embodiment, the antisense strand sequence of the RNAi may be represented by formula (II):

5' $n_{q'}$ - $N_{a'}$ -(Z'Z'Z')_k- $N_{b'}$ -Y'Y'Y'- $N_{b'}$ -(X'X'X')_l- $N_{a'}$ - $n_{p'}$ 3' (II)

wherein:

k and l are each independently 0 or 1;

p' and q' are each independently 0-6;

each $N_{a'}$ independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each $N_{b'}$ independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

each $n_{p'}$ and $n_{q'}$ independently represent an overhang nucleotide;

wherein $N_{b'}$ and Y' do not have the same modification; and

X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides.

In some embodiments, the $N_{a'}$ or $N_{b'}$ comprises modifications of alternating pattern.

The Y'Y'Y' motif occurs at or near the cleavage site of the antisense strand. For example, when the dsRNAi agent has a duplex region of 17-23 nucleotides in length, the Y'Y'Y' motif can occur at positions 9, 10, 11; 10, 11, 12; 11, 12, 13; 12, 13, 14; or 13, 14, 15 of the antisense strand, with the count starting from the first nucleotide, from the 5'-end; or optionally, the count starting at

the first paired nucleotide within the duplex region, from the 5'-end. In one embodiment, the Y'Y'Y' motif occurs at positions 11, 12, 13.

In certain embodiments, Y'Y'Y' motif is all 2'-OMe modified nucleotides.

In certain embodiments, k is 1 and l is 0, or k is 0 and l is 1, or both k and l are 1.

5 The antisense strand can therefore be represented by the following formulas:

5' n_q'-N_a'-Z'Z'Z'-N_b'-Y'Y'Y'-N_a'-n_p' 3' (IIb);

5' n_q'-N_a'-Y'Y'Y'-N_b'-X'X'X'-n_p' 3' (IIc); or

5' n_q'-N_a'-Z'Z'Z'-N_b'-Y'Y'Y'-N_b'-X'X'X'-N_a'-n_p' 3' (IId).

10 When the antisense strand is represented by formula (IIb), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2, or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

15 When the antisense strand is represented as formula (IIc), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2, or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

20 When the antisense strand is represented as formula (IId), each N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2, or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. In one embodiment, N_b is 0, 1, 2, 3, 4, 5, or 6.

In other embodiments, k is 0 and l is 0 and the antisense strand may be represented by the formula:

5' n_p'-N_a'-Y'Y'Y'-N_a'-n_q' 3' (Ia).

25 When the antisense strand is represented as formula (IIa), each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Each of X', Y' and Z' may be the same or different from each other.

30 Each nucleotide of the sense strand and antisense strand may be independently modified with LNA, CRN, UNA, cEt, HNA, CeNA, 2'-methoxyethyl, 2'-O-methyl, 2'-O-allyl, 2'-C-allyl, 2'-hydroxyl, or 2'-fluoro. For example, each nucleotide of the sense strand and antisense strand is independently modified with 2'-O-methyl or 2'-fluoro. Each X, Y, Z, X', Y', and Z', in particular, may represent a 2'-O-methyl modification or a 2'-fluoro modification.

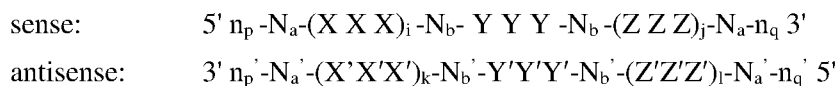
35 In some embodiments, the sense strand of the dsRNAi agent may contain YYY motif occurring at 9, 10, and 11 positions of the strand when the duplex region is 21 nt, the count starting from the first nucleotide from the 5'-end, or optionally, the count starting at the first paired nucleotide within the duplex region, from the 5'-end; and Y represents 2'-F modification. The sense strand may additionally contain XXX motif or ZZZ motifs as wing modifications at the opposite end of the

duplex region; and XXX and ZZZ each independently represents a 2'-OMe modification or 2'-F modification.

In some embodiments the antisense strand may contain Y'Y'Y' motif occurring at positions 11, 12, 13 of the strand, the count starting from the first nucleotide from the 5'-end, or optionally, the count starting at the first paired nucleotide within the duplex region, from the 5' - end; and Y' represents 2'-O-methyl modification. The antisense strand may additionally contain X'X'X' motif or Z'Z'Z' motifs as wing modifications at the opposite end of the duplex region; and X'X'X' and Z'Z'Z' each independently represents a 2'-OMe modification or 2'-F modification.

The sense strand represented by any one of the above formulas (Ia), (Ib), (Ic), and (Id) forms a duplex with an antisense strand being represented by any one of formulas (IIa), (IIb), (IIc), and (IId), respectively.

Accordingly, the dsRNAi agents for use in the methods of the invention may comprise a sense strand and an antisense strand, each strand having 14 to 30 nucleotides, the iRNA duplex represented by formula (III):



(III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q' are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

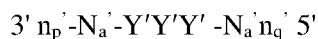
each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

wherein each n_p' , n_p , n_q' , and n_q , each of which may or may not be present, independently represents an overhang nucleotide; and

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides.

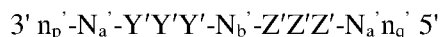
In one embodiment, i is 0 and j is 0; or i is 1 and j is 0; or i is 0 and j is 1; or both i and j are 0; or both i and j are 1. In another embodiment, k is 0 and l is 0; or k is 1 and l is 0; k is 0 and l is 1; or both k and l are 0; or both k and l are 1.

Exemplary combinations of the sense strand and antisense strand forming an iRNA duplex include the formulas below:

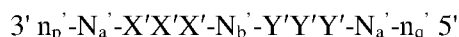
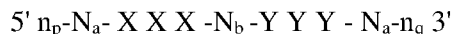


(IIIa)





(IIIb)



(IIIc)



(IIId)

When the dsRNAi agent is represented by formula (IIIa), each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the dsRNAi agent is represented by formula (IIIb), each N_b independently represents an oligonucleotide sequence comprising 1-10, 1-7, 1-5, or 1-4 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the dsRNAi agent is represented as formula (IIIc), each N_b , N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2, or 0 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the dsRNAi agent is represented as formula (IIId), each N_b , N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2, or 0 modified nucleotides. Each N_a , N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Each of N_a , N_a' , N_b , and N_b' independently comprises modifications of alternating pattern.

Each of X, Y, and Z in formulas (III), (IIIa), (IIIb), (IIIc), and (IIId) may be the same or different from each other.

When the dsRNAi agent is represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), at least one of the Y nucleotides may form a base pair with one of the Y' nucleotides. Alternatively, at least two of the Y nucleotides form base pairs with the corresponding Y' nucleotides; or all three of the Y nucleotides all form base pairs with the corresponding Y' nucleotides.

When the dsRNAi agent is represented by formula (IIIb) or (IIId), at least one of the Z nucleotides may form a base pair with one of the Z' nucleotides. Alternatively, at least two of the Z nucleotides form base pairs with the corresponding Z' nucleotides; or all three of the Z nucleotides all form base pairs with the corresponding Z' nucleotides.

When the dsRNAi agent is represented as formula (IIIc) or (IIId), at least one of the X nucleotides may form a base pair with one of the X' nucleotides. Alternatively, at least two of the X nucleotides form base pairs with the corresponding X' nucleotides; or all three of the X nucleotides all form base pairs with the corresponding X' nucleotides.

In certain embodiments, the modification on the Y nucleotide is different than the modification on the Y' nucleotide, the modification on the Z nucleotide is different than the modification on the Z' nucleotide, or the modification on the X nucleotide is different than the modification on the X' nucleotide.

5 In certain embodiments, when the dsRNAi agent is represented by formula (IIIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications. In other embodiments, when the RNAi agent is represented by formula (IIIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications and n_p' > 0 and at least one n_p' is linked to a neighboring nucleotide *via* phosphorothioate linkage. In yet other embodiments, when the RNAi agent is represented by formula (IIIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, n_p' > 0 and at least one n_p' is linked to a neighboring
10 nucleotide *via* phosphorothioate linkage, and the sense strand is conjugated to one or more GalNAc derivatives attached through a bivalent or trivalent branched linker (described below). In other embodiments, when the RNAi agent is represented by formula (IIIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, n_p' > 0 and at least one n_p' is linked to a neighboring nucleotide *via*
15 phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In some embodiments, when the dsRNAi agent is represented by formula (IIIa), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, n_p' > 0 and at least one n_p' is linked to a
20 neighboring nucleotide *via* phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In some embodiments, the dsRNAi agent is a multimer containing at least two duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a
25 linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

In some embodiments, the dsRNAi agent is a multimer containing three, four, five, six, or more duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are
30 connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

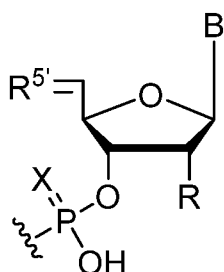
In one embodiment, two dsRNAi agents represented by at least one of formulas (III), (IIIa), (IIIb), (IIIc), and (IIId) are linked to each other at the 5' end, and one or both of the 3' ends, and are
35 optionally conjugated to a ligand. Each of the agents can target the same gene or two different genes; or each of the agents can target same gene at two different target sites.

In certain embodiments, an RNAi agent of the invention may contain a low number of nucleotides containing a 2'-fluoro modification, *e.g.*, 10 or fewer nucleotides with 2'-fluoro modification. For example, the RNAi agent may contain 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0 nucleotides with a 2'-fluoro modification. In a specific embodiment, the RNAi agent of the invention contains 10 nucleotides with a 2'-fluoro modification, *e.g.*, 4 nucleotides with a 2'-fluoro modification in the sense strand and 6 nucleotides with a 2'-fluoro modification in the antisense strand. In another specific embodiment, the RNAi agent of the invention contains 6 nucleotides with a 2'-fluoro modification, *e.g.*, 4 nucleotides with a 2'-fluoro modification in the sense strand and 2 nucleotides with a 2'-fluoro modification in the antisense strand.

In other embodiments, an RNAi agent of the invention may contain an ultra low number of nucleotides containing a 2'-fluoro modification, *e.g.*, 2 or fewer nucleotides containing a 2'-fluoro modification. For example, the RNAi agent may contain 2, 1 or 0 nucleotides with a 2'-fluoro modification. In a specific embodiment, the RNAi agent may contain 2 nucleotides with a 2'-fluoro modification, *e.g.*, 0 nucleotides with a 2'-fluoro modification in the sense strand and 2 nucleotides with a 2'-fluoro modification in the antisense strand.

Various publications describe multimeric iRNAs that can be used in the methods of the invention. Such publications include WO2007/091269, U.S. Patent No. 7,858,769, WO2010/141511, WO2007/117686, WO2009/014887, and WO2011/031520 the entire contents of each of which are hereby incorporated herein by reference.

In certain embodiments, the compositions and methods of the disclosure include a vinyl phosphonate (VP) modification of an RNAi agent as described herein. In exemplary embodiments, a 5' vinyl phosphonate modified nucleotide of the disclosure has the structure:



wherein X is O or S;

R is hydrogen, hydroxy, fluoro, or C_{1-20} alkoxy (*e.g.*, methoxy or n-hexadecyloxy);

$R^{5'}$ is $=C(H)-P(O)(OH)_2$ and the double bond between the C5' carbon and $R^{5'}$ is in the *E* or *Z* orientation (*e.g.*, *E* orientation); and

B is a nucleobase or a modified nucleobase, optionally where B is adenine, guanine, cytosine, thymine, or uracil.

In one embodiment, $R^{5'}$ is $=C(H)-P(O)(OH)_2$ and the double bond between the C5' carbon and $R^{5'}$ is in the *E* orientation. In another embodiment, R is methoxy and $R^{5'}$ is $=C(H)-P(O)(OH)_2$

and the double bond between the C5' carbon and R5' is in the E orientation. In another embodiment, X is S, R is methoxy, and R5' is $=C(H)-P(O)(OH)_2$ and the double bond between the C5' carbon and R5' is in the E orientation.

A vinyl phosphonate of the instant disclosure may be attached to either the antisense or the sense strand of a dsRNA of the disclosure. In certain embodiments, a vinyl phosphonate of the instant disclosure is attached to the antisense strand of a dsRNA, optionally at the 5' end of the antisense strand of the dsRNA.

Vinyl phosphonate modifications are also contemplated for the compositions and methods of the instant disclosure. An exemplary vinyl phosphonate structure includes the preceding structure, where R5' is $=C(H)-OP(O)(OH)_2$ and the double bond between the C5' carbon and R5' is in the E or Z orientation (*e.g.*, E orientation).

As described in more detail below, the iRNA that contains conjugations of one or more carbohydrate moieties to an iRNA can optimize one or more properties of the iRNA. In many cases, the carbohydrate moiety will be attached to a modified subunit of the iRNA. For example, the ribose sugar of one or more ribonucleotide subunits of a iRNA can be replaced with another moiety, *e.g.*, a non-carbohydrate (such as, cyclic) carrier to which is attached a carbohydrate ligand. A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS). A cyclic carrier may be a carbocyclic ring system, *i.e.*, all ring atoms are carbon atoms, or a heterocyclic ring system, *i.e.*, one or more ring atoms may be a heteroatom, *e.g.*, nitrogen, oxygen, sulfur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, *e.g.* fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds.

The ligand may be attached to the polynucleotide *via* a carrier. The carriers include (i) at least one "backbone attachment point," such as, two "backbone attachment points" and (ii) at least one "tethering attachment point." A "backbone attachment point" as used herein refers to a functional group, *e.g.* a hydroxyl group, or generally, a bond available for, and that is suitable for incorporation of the carrier into the backbone, *e.g.*, the phosphate, or modified phosphate, *e.g.*, sulfur containing, backbone, of a ribonucleic acid. A "tethering attachment point" (TAP) in some embodiments refers to a constituent ring atom of the cyclic carrier, *e.g.*, a carbon atom or a heteroatom (distinct from an atom which provides a backbone attachment point), that connects a selected moiety. The moiety can be, *e.g.*, a carbohydrate, *e.g.* monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, or polysaccharide. Optionally, the selected moiety is connected by an intervening tether to the cyclic carrier. Thus, the cyclic carrier will often include a functional group, *e.g.*, an amino group, or generally, provide a bond, that is suitable for incorporation or tethering of another chemical entity, *e.g.*, a ligand to the constituent ring.

The iRNA may be conjugated to a ligand *via* a carrier, wherein the carrier can be cyclic group or acyclic group. In one embodiment, the cyclic group is selected from pyrrolidinyl, pyrazolinyl,

pyrazolidinyl, imidazoliny, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholiny, thiazolidinyl, isothiazolidinyl, quinoxaliny, pyridazinonyl, tetrahydrofuryl, and decalin. In one embodiment, the acyclic group is a serinol backbone or diethanolamine backbone.

5

i. Thermally Destabilizing Modifications

In certain embodiments, a dsRNA molecule can be optimized for RNA interference by incorporating thermally destabilizing modifications in the seed region of the antisense strand. As used herein “seed region” means at positions 2-9 of the 5'-end of the referenced strand or at positions 2-8

10 of the 5'-end of the referenced strand. For example, thermally destabilizing modifications can be incorporated in the seed region of the antisense strand to reduce or inhibit off-target gene silencing.

The term “thermally destabilizing modification(s)” includes modification(s) that would result with a dsRNA with a lower overall melting temperature (T_m) than the T_m of the dsRNA without having such modification(s). For example, the thermally destabilizing modification(s) can decrease

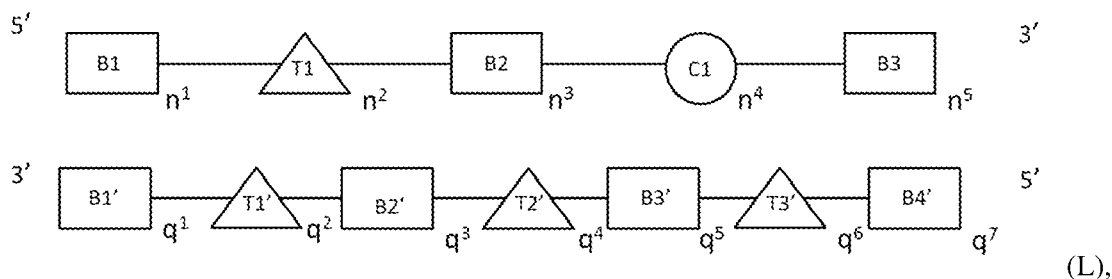
15 the T_m of the dsRNA by 1 – 4 °C, such as one, two, three or four degrees Celcius. And, the term “thermally destabilizing nucleotide” refers to a nucleotide containing one or more thermally destabilizing modifications.

It has been discovered that dsRNAs with an antisense strand comprising at least one thermally destabilizing modification of the duplex within the first 9 nucleotide positions, counting from the 5'

20 end, of the antisense strand have reduced off-target gene silencing activity. Accordingly, in some embodiments, the antisense strand comprises at least one (*e.g.*, one, two, three, four, five or more) thermally destabilizing modification of the duplex within the first 9 nucleotide positions of the 5' region of the antisense strand. In some embodiments, one or more thermally destabilizing

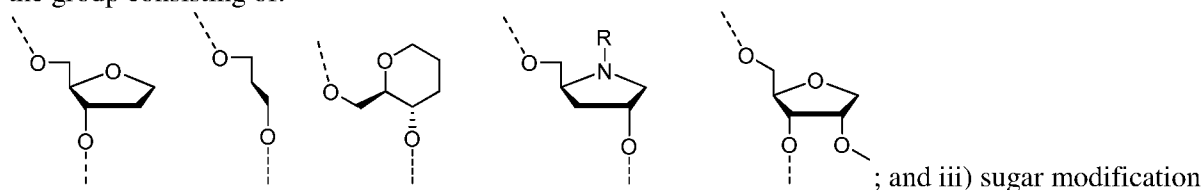
25 modification(s) of the duplex is/are located in positions 2-9, such as, positions 4-8, from the 5'-end of the antisense strand. In some further embodiments, the thermally destabilizing modification(s) of the duplex is/are located at position 6, 7 or 8 from the 5'-end of the antisense strand. In still some further embodiments, the thermally destabilizing modification of the duplex is located at position 7 from the 5'-end of the antisense strand. In some embodiments, the thermally destabilizing modification of the duplex is located at position 2, 3, 4, 5 or 9 from the 5'-end of the antisense strand.

30 An iRNA agent comprises a sense strand and an antisense strand, each strand having 14 to 40 nucleotides. The RNAi agent may be represented by formula (L):

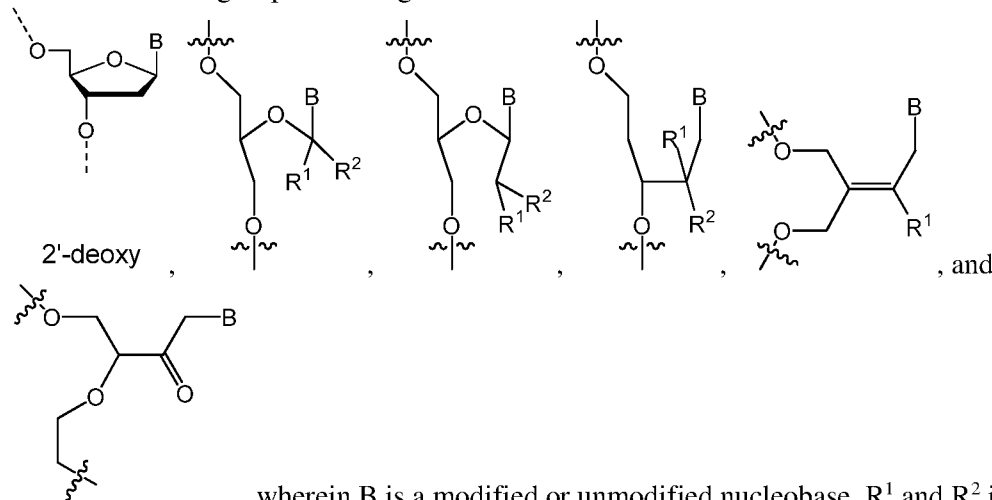


In formula (L), B1, B2, B3, B1', B2', B3', and B4' each are independently a nucleotide containing a modification selected from the group consisting of 2'-O-alkyl, 2'-substituted alkoxy, 2'-substituted alkyl, 2'-halo, ENA, and BNA/LNA. In one embodiment, B1, B2, B3, B1', B2', B3', and B4' each contain 2'-OMe modifications. In one embodiment, B1, B2, B3, B1', B2', B3', and B4' each contain 2'-OMe or 2'-F modifications. In one embodiment, at least one of B1, B2, B3, B1', B2', B3', and B4' contain 2'-O-N-methylacetamido (2'-O-NMA, 2'-O-CH₂C(O)N(Me)H) modification.

C1 is a thermally destabilizing nucleotide placed at a site opposite to the seed region of the antisense strand (*i.e.*, at positions 2-8 of the 5'-end of the antisense strand or at positions 2-9 of the 5'-end of the antisense strand). For example, C1 is at a position of the sense strand that pairs with a nucleotide at positions 2-8 of the 5'-end of the antisense strand. In one example, C1 is at position 15 from the 5'-end of the sense strand. C1 nucleotide bears the thermally destabilizing modification which can include abasic modification; mismatch with the opposing nucleotide in the duplex; and sugar modification such as 2'-deoxy modification or acyclic nucleotide *e.g.*, unlocked nucleic acids (UNA), glycerol nucleic acid (GNA), or 2'-5'-linked ribonucleotides ("3'-RNA"). In one embodiment, C1 has thermally destabilizing modification selected from the group consisting of: i) mismatch with the opposing nucleotide in the antisense strand; ii) abasic modification selected from the group consisting of:

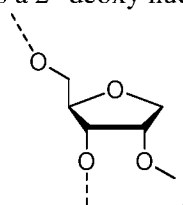


selected from the group consisting of:



H, halogen, OR₃, or alkyl; and R₃ is H, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar. In one embodiment, the thermally destabilizing modification in C1 is a mismatch selected from the group consisting of G:G, G:A, G:U, G:T, A:A, A:C, C:C, C:U, C:T, U:U, T:T, and U:T; and optionally, at

least one nucleobase in the mismatch pair is a 2'-deoxy nucleobase. In one example, the thermally



destabilizing modification in C1 is GNA or

T1, T1', T2', and T3' each independently represent a nucleotide comprising a modification providing the nucleotide a steric bulk that is less or equal to the steric bulk of a 2'-OMe modification. A steric bulk refers to the sum of steric effects of a modification. Methods for determining steric effects of a modification of a nucleotide are known to one skilled in the art. The modification can be at the 2' position of a ribose sugar of the nucleotide, or a modification to a non-ribose nucleotide, acyclic nucleotide, or the backbone of the nucleotide that is similar or equivalent to the 2' position of the ribose sugar, and provides the nucleotide a steric bulk that is less than or equal to the steric bulk of a 2'-OMe modification. For example, T1, T1', T2', and T3' are each independently selected from DNA, RNA, LNA, 2'-F, and 2'-F-5'-methyl. In one embodiment, T1 is DNA. In one embodiment, T1' is DNA, RNA or LNA. In one embodiment, T2' is DNA or RNA. In one embodiment, T3' is DNA or RNA.

n^1 , n^3 , and q^1 are independently 4 to 15 nucleotides in length.

n^5 , q^3 , and q^7 are independently 1-6 nucleotide(s) in length.

n^4 , q^2 , and q^6 are independently 1-3 nucleotide(s) in length; alternatively, n^4 is 0.

q^5 is independently 0-10 nucleotide(s) in length.

n^2 and q^4 are independently 0-3 nucleotide(s) in length.

Alternatively, n^4 is 0-3 nucleotide(s) in length.

In one embodiment, n^4 can be 0. In one example, n^4 is 0, and q^2 and q^6 are 1. In another example, n^4 is 0, and q^2 and q^6 are 1, with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand).

In one embodiment, n^4 , q^2 , and q^6 are each 1.

In one embodiment, n^2 , n^4 , q^2 , q^4 , and q^6 are each 1.

In one embodiment, C1 is at position 14-17 of the 5'-end of the sense strand, when the sense strand is 19-22 nucleotides in length, and n^4 is 1. In one embodiment, C1 is at position 15 of the 5'-end of the sense strand

In one embodiment, T3' starts at position 2 from the 5' end of the antisense strand. In one example, T3' is at position 2 from the 5' end of the antisense strand and q^6 is equal to 1.

In one embodiment, T1' starts at position 14 from the 5' end of the antisense strand. In one example, T1' is at position 14 from the 5' end of the antisense strand and q^2 is equal to 1.

In an exemplary embodiment, T3' starts from position 2 from the 5' end of the antisense strand and T1' starts from position 14 from the 5' end of the antisense strand. In one example, T3' starts from position 2 from the 5' end of the antisense strand and q^6 is equal to 1 and T1' starts from position 14 from the 5' end of the antisense strand and q^2 is equal to 1.

In one embodiment, T1' and T3' are separated by 11 nucleotides in length (*i.e.* not counting the T1' and T3' nucleotides).

In one embodiment, T1' is at position 14 from the 5' end of the antisense strand. In one example, T1' is at position 14 from the 5' end of the antisense strand and q^2 is equal to 1, and the modification at the 2' position or positions in a non-ribose, acyclic or backbone that provide less steric bulk than a 2'-OMe ribose.

In one embodiment, T3' is at position 2 from the 5' end of the antisense strand. In one example, T3' is at position 2 from the 5' end of the antisense strand and q^6 is equal to 1, and the modification at the 2' position or positions in a non-ribose, acyclic or backbone that provide less than or equal to steric bulk than a 2'-OMe ribose.

In one embodiment, T1 is at the cleavage site of the sense strand. In one example, T1 is at position 11 from the 5' end of the sense strand, when the sense strand is 19-22 nucleotides in length, and n^2 is 1. In an exemplary embodiment, T1 is at the cleavage site of the sense strand at position 11 from the 5' end of the sense strand, when the sense strand is 19-22 nucleotides in length, and n^2 is 1,

In one embodiment, T2' starts at position 6 from the 5' end of the antisense strand. In one example, T2' is at positions 6-10 from the 5' end of the antisense strand, and q^4 is 1.

In an exemplary embodiment, T1 is at the cleavage site of the sense strand, for instance, at position 11 from the 5' end of the sense strand, when the sense strand is 19-22 nucleotides in length, and n^2 is 1; T1' is at position 14 from the 5' end of the antisense strand, and q^2 is equal to 1, and the modification to T1' is at the 2' position of a ribose sugar or at positions in a non-ribose, acyclic or backbone that provide less steric bulk than a 2'-OMe ribose; T2' is at positions 6-10 from the 5' end of the antisense strand, and q^4 is 1; and T3' is at position 2 from the 5' end of the antisense strand, and q^6 is equal to 1, and the modification to T3' is at the 2' position or at positions in a non-ribose, acyclic or backbone that provide less than or equal to steric bulk than a 2'-OMe ribose.

In one embodiment, T2' starts at position 8 from the 5' end of the antisense strand. In one example, T2' starts at position 8 from the 5' end of the antisense strand, and q^4 is 2.

In one embodiment, T2' starts at position 9 from the 5' end of the antisense strand. In one example, T2' is at position 9 from the 5' end of the antisense strand, and q^4 is 1.

In one embodiment, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 1, B3' is 2'-OMe or 2'-F, q^5 is 6, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense

strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand).

In one embodiment, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 1, B3' is 2'-OMe or 2'-F, q^5 is 6, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand).

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand).

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 6, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 7, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 6, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 7, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand).

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F,

q^3 is 4, $T2'$ is 2'-F, q^4 is 1, $B3'$ is 2'-OMe or 2'-F, q^5 is 6, $T3'$ is 2'-F, q^6 is 1, $B4'$ is 2'-OMe, and q^7 is 1.

In one embodiment, $B1$ is 2'-OMe or 2'-F, n^1 is 8, $T1$ is 2'-F, n^2 is 3, $B2$ is 2'-OMe, n^3 is 7, n^4 is 0, $B3$ is 2'-OMe, n^5 is 3, $B1'$ is 2'-OMe or 2'-F, q^1 is 9, $T1'$ is 2'-F, q^2 is 1, $B2'$ is 2'-OMe or 2'-F, q^3 is 4, $T2'$ is 2'-F, q^4 is 1, $B3'$ is 2'-OMe or 2'-F, q^5 is 6, $T3'$ is 2'-F, q^6 is 1, $B4'$ is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand).

In one embodiment, $B1$ is 2'-OMe or 2'-F, n^1 is 8, $T1$ is 2'-F, n^2 is 3, $B2$ is 2'-OMe, n^3 is 7, n^4 is 0, $B3$ is 2'-OMe, n^5 is 3, $B1'$ is 2'-OMe or 2'-F, q^1 is 9, $T1'$ is 2'-F, q^2 is 1, $B2'$ is 2'-OMe or 2'-F, q^3 is 5, $T2'$ is 2'-F, q^4 is 1, $B3'$ is 2'-OMe or 2'-F, q^5 is 5, $T3'$ is 2'-F, q^6 is 1, $B4'$ is 2'-OMe, and q^7 is 1; optionally with at least 2 additional TT at the 3'-end of the antisense strand.

In one embodiment, $B1$ is 2'-OMe or 2'-F, n^1 is 8, $T1$ is 2'-F, n^2 is 3, $B2$ is 2'-OMe, n^3 is 7, n^4 is 0, $B3$ is 2'-OMe, n^5 is 3, $B1'$ is 2'-OMe or 2'-F, q^1 is 9, $T1'$ is 2'-F, q^2 is 1, $B2'$ is 2'-OMe or 2'-F, q^3 is 5, $T2'$ is 2'-F, q^4 is 1, $B3'$ is 2'-OMe or 2'-F, q^5 is 5, $T3'$ is 2'-F, q^6 is 1, $B4'$ is 2'-OMe, and q^7 is 1; optionally with at least 2 additional TT at the 3'-end of the antisense strand; with two phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand).

In one embodiment, $B1$ is 2'-OMe or 2'-F, n^1 is 8, $T1$ is 2'-F, n^2 is 3, $B2$ is 2'-OMe, n^3 is 7, n^4 is 0, $B3$ is 2'-OMe, n^5 is 3, $B1'$ is 2'-OMe or 2'-F, q^1 is 9, $T1'$ is 2'-F, q^2 is 1, $B2'$ is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, $B3'$ is 2'-OMe or 2'-F, q^5 is 7, $T3'$ is 2'-F, q^6 is 1, $B4'$ is 2'-OMe, and q^7 is 1.

In one embodiment, $B1$ is 2'-OMe or 2'-F, n^1 is 8, $T1$ is 2'-F, n^2 is 3, $B2$ is 2'-OMe, n^3 is 7, n^4 is 0, $B3$ is 2'-OMe, n^5 is 3, $B1'$ is 2'-OMe or 2'-F, q^1 is 9, $T1'$ is 2'-F, q^2 is 1, $B2'$ is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, $B3'$ is 2'-OMe or 2'-F, q^5 is 7, $T3'$ is 2'-F, q^6 is 1, $B4'$ is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

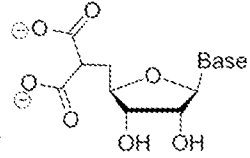
In one embodiment, $B1$ is 2'-OMe or 2'-F, n^1 is 8, $T1$ is 2'-F, n^2 is 3, $B2$ is 2'-OMe, n^3 is 7, n^4 is 0, $B3$ is 2'-OMe, n^5 is 3, $B1'$ is 2'-OMe or 2'-F, q^1 is 9, $T1'$ is 2'-F, q^2 is 1, $B2'$ is 2'-OMe or 2'-F, q^3 is 4, $T2'$ is 2'-F, q^4 is 2, $B3'$ is 2'-OMe or 2'-F, q^5 is 5, $T3'$ is 2'-F, q^6 is 1, $B4'$ is 2'-F, and q^7 is 1. In one embodiment, $B1$ is 2'-OMe or 2'-F, n^1 is 8, $T1$ is 2'-F, n^2 is 3, $B2$ is 2'-OMe, n^3 is 7, n^4 is 0, $B3$ is 2'-OMe, n^5 is 3, $B1'$ is 2'-OMe or 2'-F, q^1 is 9, $T1'$ is 2'-F, q^2 is 1, $B2'$ is 2'-OMe or 2'-F, q^3 is 4,

T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1; with two phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand).

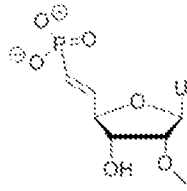
In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, q⁴ is 0, B3' is 2'-OMe or 2'-F, q⁵ is 7, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, q⁴ is 0, B3' is 2'-OMe or 2'-F, q⁵ is 7, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1; with two phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand).

The RNAi agent can comprise a phosphorus-containing group at the 5'-end of the sense strand or antisense strand. The 5'-end phosphorus-containing group can be 5'-end phosphate (5'-P), 5'-end phosphorothioate (5'-PS), 5'-end phosphorodithioate (5'-PS₂), 5'-end vinylphosphonate (5'-

VP), 5'-end methylphosphonate (MePhos), or 5'-deoxy-5'-C-malonyl (). When the 5'-end phosphorus-containing group is 5'-end vinylphosphonate (5'-VP), the 5'-VP can be either

5'-E-VP isomer (*i.e.*, *trans*-vinylphosphonate,



5'-Z-VP isomer (*i.e.*, *cis*-

vinylphosphonate,), or mixtures thereof.

In one embodiment, the RNAi agent comprises a phosphorus-containing group at the 5'-end of the sense strand. In one embodiment, the RNAi agent comprises a phosphorus-containing group at the 5'-end of the antisense strand.

In one embodiment, the RNAi agent comprises a 5'-P. In one embodiment, the RNAi agent comprises a 5'-P in the antisense strand.

In one embodiment, the RNAi agent comprises a 5'-PS. In one embodiment, the RNAi agent comprises a 5'-PS in the antisense strand.

In one embodiment, the RNAi agent comprises a 5'-VP. In one embodiment, the RNAi agent comprises a 5'-VP in the antisense strand. In one embodiment, the RNAi agent comprises a 5'-E-VP in the antisense strand. In one embodiment, the RNAi agent comprises a 5'-Z-VP in the antisense strand.

5 In one embodiment, the RNAi agent comprises a 5'-PS₂. In one embodiment, the RNAi agent comprises a 5'-PS₂ in the antisense strand.

In one embodiment, the RNAi agent comprises a 5'-PS₂. In one embodiment, the RNAi agent comprises a 5'-deoxy-5'-C-malonyl in the antisense strand.

10 In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-OMe, and q⁷ is 1. The RNAi agent also comprises a 5'-PS.

15 In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-OMe, and q⁷ is 1. The RNAi agent also comprises a 5'-P.

20 In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-OMe, and q⁷ is 1. The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-E-VP, 5'-Z-VP, or combination thereof.

25 In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-OMe, and q⁷ is 1. The RNAi agent also comprises a 5'-PS₂.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-OMe, and q⁷ is 1. The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl.

30 In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-OMe, and q⁷ is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide
35 linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-P.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-E-VP, 5'-Z-VP, or combination thereof.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS₂.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'-P.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The dsRNA agent also comprises a 5'-PS.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-E-VP, 5'-Z-VP, or combination thereof.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'-PS₂.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-P.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-PS.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-

23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-E-VP, 5'-Z-VP, or combination thereof.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-PS₂.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'-P.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'-PS.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-E-VP, 5'-Z-VP, or combination thereof.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The dsRNAi RNA agent also comprises a 5'-PS₂.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F,

q^3 is 4, $T2'$ is 2'-F, q^4 is 2, $B3'$ is 2'-OMe or 2'-F, q^5 is 5, $T3'$ is 2'-F, q^6 is 1, $B4'$ is 2'-F, and q^7 is 1. The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl.

In one embodiment, $B1$ is 2'-OMe or 2'-F, n^1 is 8, $T1$ is 2'-F, n^2 is 3, $B2$ is 2'-OMe, n^3 is 7, n^4 is 0, $B3$ is 2'-OMe, n^5 is 3, $B1'$ is 2'-OMe or 2'-F, q^1 is 9, $T1'$ is 2'-F, q^2 is 1, $B2'$ is 2'-OMe or 2'-F, q^3 is 4, $T2'$ is 2'-F, q^4 is 2, $B3'$ is 2'-OMe or 2'-F, q^5 is 5, $T3'$ is 2'-F, q^6 is 1, $B4'$ is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-P.

In one embodiment, $B1$ is 2'-OMe or 2'-F, n^1 is 8, $T1$ is 2'-F, n^2 is 3, $B2$ is 2'-OMe, n^3 is 7, n^4 is 0, $B3$ is 2'-OMe, n^5 is 3, $B1'$ is 2'-OMe or 2'-F, q^1 is 9, $T1'$ is 2'-F, q^2 is 1, $B2'$ is 2'-OMe or 2'-F, q^3 is 4, $T2'$ is 2'-F, q^4 is 2, $B3'$ is 2'-OMe or 2'-F, q^5 is 5, $T3'$ is 2'-F, q^6 is 1, $B4'$ is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS.

In one embodiment, $B1$ is 2'-OMe or 2'-F, n^1 is 8, $T1$ is 2'-F, n^2 is 3, $B2$ is 2'-OMe, n^3 is 7, n^4 is 0, $B3$ is 2'-OMe, n^5 is 3, $B1'$ is 2'-OMe or 2'-F, q^1 is 9, $T1'$ is 2'-F, q^2 is 1, $B2'$ is 2'-OMe or 2'-F, q^3 is 4, $T2'$ is 2'-F, q^4 is 2, $B3'$ is 2'-OMe or 2'-F, q^5 is 5, $T3'$ is 2'-F, q^6 is 1, $B4'$ is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-E-VP, 5'-Z-VP, or combination thereof.

In one embodiment, $B1$ is 2'-OMe or 2'-F, n^1 is 8, $T1$ is 2'-F, n^2 is 3, $B2$ is 2'-OMe, n^3 is 7, n^4 is 0, $B3$ is 2'-OMe, n^5 is 3, $B1'$ is 2'-OMe or 2'-F, q^1 is 9, $T1'$ is 2'-F, q^2 is 1, $B2'$ is 2'-OMe or 2'-F, q^3 is 4, $T2'$ is 2'-F, q^4 is 2, $B3'$ is 2'-OMe or 2'-F, q^5 is 5, $T3'$ is 2'-F, q^6 is 1, $B4'$ is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS₂.

In one embodiment, $B1$ is 2'-OMe or 2'-F, n^1 is 8, $T1$ is 2'-F, n^2 is 3, $B2$ is 2'-OMe, n^3 is 7, n^4 is 0, $B3$ is 2'-OMe, n^5 is 3, $B1'$ is 2'-OMe or 2'-F, q^1 is 9, $T1'$ is 2'-F, q^2 is 1, $B2'$ is 2'-OMe or 2'-F,

q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, q⁴ is 0, B3' is 2'-OMe or 2'-F, q⁵ is 7, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1. The RNAi agent also comprises a 5' - P.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, q⁴ is 0, B3' is 2'-OMe or 2'-F, q⁵ is 7, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1. The RNAi agent also comprises a 5' - PS.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, q⁴ is 0, B3' is 2'-OMe or 2'-F, q⁵ is 7, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1. The RNAi agent also comprises a 5' - VP. The 5'-VP may be 5'-E-VP, 5'-Z-VP, or combination thereof.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, q⁴ is 0, B3' is 2'-OMe or 2'-F, q⁵ is 7, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1. The RNAi agent also comprises a 5' - PS₂.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, q⁴ is 0, B3' is 2'-OMe or 2'-F, q⁵ is 7, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1. The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, q⁴ is 0, B3' is 2'-OMe or 2'-F, q⁵ is 7, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5' - P.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, q⁴ is 0, B3' is 2'-OMe or 2'-F, q⁵ is 7, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1; with two

phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-E-VP, 5'-Z-VP, or combination thereof.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS₂.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense

strand). The RNAi agent also comprises a 5'-P and a targeting ligand. In one embodiment, the 5'-P is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS and a targeting ligand. In one embodiment, the 5'-PS is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-VP (e.g., a 5'-E-VP, 5'-Z-VP, or combination thereof), and a targeting ligand.

In one embodiment, the 5'-VP is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS₂ and a targeting ligand. In one embodiment, the 5'-PS₂ is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage

modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl and a targeting ligand. In one embodiment, the 5'-deoxy-5'-C-malonyl is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-P and a targeting ligand. In one embodiment, the 5'-P is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-PS and a targeting ligand. In one embodiment, the 5'-PS is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-VP (*e.g.*, a 5'-E-VP, 5'-Z-VP, or combination thereof) and a targeting ligand. In one embodiment, the 5'-VP is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-

23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-PS₂ and a targeting ligand. In one embodiment, the 5'-PS₂ is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, q⁴ is 0, B3' is 2'-OMe or 2'-F, q⁵ is 7, T3' is 2'-F, q⁶ is 1, B4' is 2'-OMe, and q⁷ is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl and a targeting ligand. In one embodiment, the 5'-deoxy-5'-C-malonyl is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-P and a targeting ligand. In one embodiment, the 5'-P is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS and a targeting ligand. In one embodiment, the 5'-PS is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand).

strand). The RNAi agent also comprises a 5'-VP (*e.g.*, a 5'-E-VP, 5'-Z-VP, or combination thereof) and a targeting ligand. In one embodiment, the 5'-VP is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS₂ and a targeting ligand. In one embodiment, the 5'-PS₂ is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl and a targeting ligand. In one embodiment, the 5'-deoxy-5'-C-malonyl is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-P and a targeting ligand. In one embodiment, the 5'-P is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications

within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS and a targeting ligand. In one embodiment, the 5'-PS is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-VP (*e.g.*, a 5'-E-VP, 5'-Z-VP, or combination thereof) and a targeting ligand. In one embodiment, the 5'-VP is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS₂ and a targeting ligand. In one embodiment, the 5'-PS₂ is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl and a targeting ligand. In one embodiment, the 5'-deoxy-5'-C-malonyl is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In a particular embodiment, an RNAi agent of the present invention comprises:

- (a) a sense strand having:
 - (i) a length of 21 nucleotides;
 - (ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker; and

(iii) 2'-F modifications at positions 1, 3, 5, 7, 9 to 11, 13, 17, 19, and 21, and 2'-OMe modifications at positions 2, 4, 6, 8, 12, 14 to 16, 18, and 20 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) 2'-OMe modifications at positions 1, 3, 5, 9, 11 to 13, 15, 17, 19, 21, and 23, and 2'-F modifications at positions 2, 4, 6 to 8, 10, 14, 16, 18, 20, and 22 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 21 and 22,

and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the dsRNA agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, an RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;

(iii) 2'-F modifications at positions 1, 3, 5, 7, 9 to 11, 13, 15, 17, 19, and 21, and 2'-OMe modifications at positions 2, 4, 6, 8, 12, 14, 16, 18, and 20 (counting from the 5' end);

and

(iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) 2'-OMe modifications at positions 1, 3, 5, 7, 9, 11 to 13, 15, 17, 19, and 21 to 23, and 2'-F modifications at positions 2, 4, 6, 8, 10, 14, 16, 18, and 20 (counting from the 5' end);

and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the RNAi agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, a RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

- (ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;
- (iii) 2'-OMe modifications at positions 1 to 6, 8, 10, and 12 to 21, 2'-F modifications at positions 7, and 9, and a deoxy-nucleotide (*e.g.* dT) at position 11 (counting from the 5' end); and
- (iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

- (b) an antisense strand having:

- (i) a length of 23 nucleotides;
- (ii) 2'-OMe modifications at positions 1, 3, 7, 9, 11, 13, 15, 17, and 19 to 23, and 2'-F modifications at positions 2, 4 to 6, 8, 10, 12, 14, 16, and 18 (counting from the 5' end); and
- (iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the RNAi agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, a RNAi agent of the present invention comprises:

- (a) a sense strand having:
 - (i) a length of 21 nucleotides;
 - (ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;
 - (iii) 2'-OMe modifications at positions 1 to 6, 8, 10, 12, 14, and 16 to 21, and 2'-F modifications at positions 7, 9, 11, 13, and 15; and
 - (iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

- (b) an antisense strand having:

- (i) a length of 23 nucleotides;
- (ii) 2'-OMe modifications at positions 1, 5, 7, 9, 11, 13, 15, 17, 19, and 21 to 23, and 2'-F modifications at positions 2 to 4, 6, 8, 10, 12, 14, 16, 18, and 20 (counting from the 5' end); and
- (iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the RNAi agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, a RNAi agent of the present invention comprises:

(a) a sense strand having:

- 5 (i) a length of 21 nucleotides;
- (ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;
- (iii) 2'-OMe modifications at positions 1 to 9, and 12 to 21, and 2'-F modifications at positions 10, and 11; and
- 10 (iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

- (i) a length of 23 nucleotides;
- 15 (ii) 2'-OMe modifications at positions 1, 3, 5, 7, 9, 11 to 13, 15, 17, 19, and 21 to 23, and 2'-F modifications at positions 2, 4, 6, 8, 10, 14, 16, 18, and 20 (counting from the 5' end); and
- (iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between
- 20 nucleotide positions 22 and 23 (counting from the 5' end);

wherein the RNAi agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, a RNAi agent of the present invention comprises:

(a) a sense strand having:

- 25 (i) a length of 21 nucleotides;
- (ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;
- (iii) 2'-F modifications at positions 1, 3, 5, 7, 9 to 11, and 13, and 2'-OMe modifications at positions 2, 4, 6, 8, 12, and 14 to 21; and
- 30 (iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

- (i) a length of 23 nucleotides;
- 35 (ii) 2'-OMe modifications at positions 1, 3, 5 to 7, 9, 11 to 13, 15, 17 to 19, and 21 to 23, and 2'-F modifications at positions 2, 4, 8, 10, 14, 16, and 20 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the RNAi agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, a RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;

(iii) 2'-OMe modifications at positions 1, 2, 4, 6, 8, 12, 14, 15, 17, and 19 to 21, and 2'-F modifications at positions 3, 5, 7, 9 to 11, 13, 16, and 18; and

(iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 25 nucleotides;

(ii) 2'-OMe modifications at positions 1, 4, 6, 7, 9, 11 to 13, 15, 17, and 19 to 23, 2'-F modifications at positions 2, 3, 5, 8, 10, 14, 16, and 18, and deoxy-nucleotides (*e.g.* dT) at positions 24 and 25 (counting from the 5' end); and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the RNAi agents have a four nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, a RNAi agent of the present invention comprises:

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;

(iii) 2'-OMe modifications at positions 1 to 6, 8, and 12 to 21, and 2'-F modifications at positions 7, and 9 to 11; and

(iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

- (ii) 2'-OMe modifications at positions 1, 3 to 5, 7, 8, 10 to 13, 15, and 17 to 23, and 2'-F modifications at positions 2, 6, 9, 14, and 16 (counting from the 5' end); and
- (iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the RNAi agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, a RNAi agent of the present invention comprises:

- (a) a sense strand having:
 - (i) a length of 21 nucleotides;
 - (ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;
 - (iii) 2'-OMe modifications at positions 1 to 6, 8, and 12 to 21, and 2'-F modifications at positions 7, and 9 to 11; and
 - (iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

- (b) an antisense strand having:
 - (i) a length of 23 nucleotides;
 - (ii) 2'-OMe modifications at positions 1, 3 to 5, 7, 10 to 13, 15, and 17 to 23, and 2'-F modifications at positions 2, 6, 8, 9, 14, and 16 (counting from the 5' end); and
 - (iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 (counting from the 5' end);

wherein the RNAi agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In another particular embodiment, a RNAi agent of the present invention comprises:

- (a) a sense strand having:
 - (i) a length of 19 nucleotides;
 - (ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;
 - (iii) 2'-OMe modifications at positions 1 to 4, 6, and 10 to 19, and 2'-F modifications at positions 5, and 7 to 9; and
 - (iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

- (b) an antisense strand having:

- (i) a length of 21 nucleotides;
- (ii) 2'-OMe modifications at positions 1, 3 to 5, 7, 10 to 13, 15, and 17 to 21, and 2'-F modifications at positions 2, 6, 8, 9, 14, and 16 (counting from the 5' end); and
- (iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 19 and 20, and between nucleotide positions 20 and 21 (counting from the 5' end);

wherein the RNAi agents have a two nucleotide overhang at the 3'-end of the antisense strand, and a blunt end at the 5'-end of the antisense strand.

In certain embodiments, the iRNA for use in the methods of the invention is an agent selected from agents listed in any one of Tables 2-7. These agents may further comprise a ligand.

III. iRNAs Conjugated to Ligands

Another modification of the RNA of an iRNA of the invention involves chemically linking to the iRNA one or more ligands, moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the iRNA *e.g.*, into a cell. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 1989, 86: 6553-6556). In other embodiments, the ligand is cholic acid (Manoharan *et al.*, *Biorg. Med. Chem. Lett.*, 1994, 4:1053-1060), a thioether, *e.g.*, beryl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660:306-309; Manoharan *et al.*, *Biorg. Med. Chem. Lett.*, 1993, 3:2765-2770), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, 20:533-538), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J*, 1991, 10:1111-1118; Kabanov *et al.*, *FEBS Lett.*, 1990, 259:327-330; Svinarchuk *et al.*, *Biochimie*, 1993, 75:49-54), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651-3654; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18:3777-3783), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995, 14:969-973), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651-3654), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, 1264:229-237), or an octadecylamine or hexylamino-carboxyloxycholesterol moiety (Crooke *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, 277:923-937).

In certain embodiments, a ligand alters the distribution, targeting, or lifetime of an iRNA agent into which it is incorporated. In some embodiments a ligand provides an enhanced affinity for a selected target, *e.g.*, molecule, cell or cell type, compartment, *e.g.*, a cellular or organ compartment, tissue, organ or region of the body, as, *e.g.*, compared to a species absent such a ligand. In some embodiments, ligands do not take part in duplex pairing in a duplexed nucleic acid.

Ligands can include a naturally occurring substance, such as a protein (*e.g.*, human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (*e.g.*, a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin, N-acetylglucosamine, N-acetylgalactosamine, or hyaluronic

acid); or a lipid. The ligand can also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.*, a synthetic polyamino acid. Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolide) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

Ligands can also include targeting groups, *e.g.*, a cell or tissue targeting agent, *e.g.*, a lectin, glycoprotein, lipid or protein, *e.g.*, an antibody, that binds to a specified cell type such as a kidney cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, vitamin A, biotin, or an RGD peptide or RGD peptide mimetic. In certain embodiments, the ligand is a multivalent galactose, *e.g.*, an N-acetyl-galactosamine.

Other examples of ligands include dyes, intercalating agents (*e.g.* acridines), cross-linkers (*e.g.* psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial endonucleases (*e.g.* EDTA), lipophilic molecules, *e.g.*, cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine) and peptide conjugates (*e.g.*, antennapedia peptide, Tat peptide), alkylating agents, phosphate, amino, mercapto, PEG (*e.g.*, PEG-40K), MPEG, [MPEG]₂, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (*e.g.* biotin), transport/absorption facilitators (*e.g.*, aspirin, vitamin E, folic acid), synthetic ribonucleases (*e.g.*, imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu³⁺ complexes of tetraazamacrocycles), dinitrophenyl, HRP, or AP.

Ligands can be proteins, *e.g.*, glycoproteins, or peptides, *e.g.*, molecules having a specific affinity for a co-ligand, or antibodies *e.g.*, an antibody, that binds to a specified cell type such as a hepatic cell. Ligands can also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, or multivalent fucose. The ligand can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an activator of NF- κ B.

The ligand can be a substance, *e.g.*, a drug, which can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.*, by disrupting the cell's microtubules, microfilaments, or intermediate filaments. The drug can be, for example, taxol, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin.

In some embodiments, a ligand attached to an iRNA as described herein acts as a pharmacokinetic modulator (PK modulator). PK modulators include lipophiles, bile acids, steroids, phospholipid analogues, peptides, protein binding agents, PEG, vitamins, *etc.* Exemplary PK modulators include, but are not limited to, cholesterol, fatty acids, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, phospholipids, sphingolipids, naproxen, ibuprofen, vitamin E, biotin. Oligonucleotides that comprise a number of phosphorothioate linkages are also known to bind to serum protein, thus short oligonucleotides, *e.g.*, oligonucleotides of about 5 bases, 10 bases, 15 bases, or 20 bases, comprising multiple of phosphorothioate linkages in the backbone are also amenable to the present invention as ligands (*e.g.* as PK modulating ligands). In addition, aptamers that bind serum components (*e.g.* serum proteins) are also suitable for use as PK modulating ligands in the embodiments described herein.

Ligand-conjugated iRNAs of the invention may be synthesized by the use of an oligonucleotide that bears a pendant reactive functionality, such as that derived from the attachment of a linking molecule onto the oligonucleotide (described below). This reactive oligonucleotide may be reacted directly with commercially-available ligands, ligands that are synthesized bearing any of a variety of protecting groups, or ligands that have a linking moiety attached thereto.

The oligonucleotides used in the conjugates of the present invention may be conveniently and routinely made through the well-known technique of solid-phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems® (Foster City, Calif.). Any other methods for such synthesis known in the art may additionally or alternatively be employed. It is also known to use similar techniques to prepare other oligonucleotides, such as the phosphorothioates and alkylated derivatives.

In the ligand-conjugated iRNAs and ligand-molecule bearing sequence-specific linked nucleosides of the present invention, the oligonucleotides and oligonucleosides may be assembled on a suitable DNA synthesizer utilizing standard nucleotide or nucleoside precursors, or nucleotide or nucleoside conjugate precursors that already bear the linking moiety, ligand-nucleotide or nucleoside-conjugate precursors that already bear the ligand molecule, or non-nucleoside ligand-bearing building blocks.

When using nucleotide-conjugate precursors that already bear a linking moiety, the synthesis of the sequence-specific linked nucleosides is typically completed, and the ligand molecule is then reacted with the linking moiety to form the ligand-conjugated oligonucleotide. In some embodiments, the oligonucleotides or linked nucleosides of the present invention are synthesized by an automated

synthesizer using phosphoramidites derived from ligand-nucleoside conjugates in addition to the standard phosphoramidites and non-standard phosphoramidites that are commercially available and routinely used in oligonucleotide synthesis.

A. *Lipid Conjugates*

In certain embodiments, the ligand or conjugate is a lipid or lipid-based molecule. In one embodiment, such a lipid or lipid-based molecule binds a serum protein, *e.g.*, human serum albumin (HSA). An HSA binding ligand allows for distribution of the conjugate to a target tissue, *e.g.*, a non-kidney target tissue of the body. For example, the target tissue can be the liver, including parenchymal cells of the liver. Other molecules that can bind HSA can also be used as ligands. For example, naproxen or aspirin can be used. A lipid or lipid-based ligand can (a) increase resistance to degradation of the conjugate, (b) increase targeting or transport into a target cell or cell membrane, or (c) can be used to adjust binding to a serum protein, *e.g.*, HSA.

A lipid based ligand can be used to inhibit, *e.g.*, control the binding of the conjugate to a target tissue. For example, a lipid or lipid-based ligand that binds to HSA more strongly will be less likely to be targeted to the kidney and therefore less likely to be cleared from the body. A lipid or lipid-based ligand that binds to HSA less strongly can be used to target the conjugate to the kidney.

In certain embodiments, the lipid based ligand binds HSA. In one embodiment, it binds HSA with a sufficient affinity such that the conjugate will be distributed to a non-kidney tissue. However, it is preferred that the affinity not be so strong that the HSA-ligand binding cannot be reversed.

In other embodiments, the lipid based ligand binds HSA weakly or not at all. In one embodiment, the conjugate will be distributed to the kidney. Other moieties that target to kidney cells can also be used in place of, or in addition to, the lipid based ligand.

In another aspect, the ligand is a moiety, *e.g.*, a vitamin, which is taken up by a target cell, *e.g.*, a proliferating cell. These are particularly useful for treating disorders characterized by unwanted cell proliferation, *e.g.*, of the malignant or non-malignant type, *e.g.*, cancer cells. Exemplary vitamins include vitamin A, E, and K. Other exemplary vitamins include are B vitamin, *e.g.*, folic acid, B12, riboflavin, biotin, pyridoxal or other vitamins or nutrients taken up by target cells such as liver cells. Also included are HSA and low density lipoprotein (LDL).

B. *Cell Permeation Agents*

In another aspect, the ligand is a cell-permeation agent, such as, a helical cell-permeation agent. In one embodiment, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopodia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. In one embodiment, the helical agent is an alpha-helical agent, which has a lipophilic and a lipophobic phase.

The ligand can be a peptide or peptidomimetic. A peptidomimetic (also referred to herein as an oligopeptidomimetic) is a molecule capable of folding into a defined three-dimensional structure

similar to a natural peptide. The attachment of peptide and peptidomimetics to iRNA agents can affect pharmacokinetic distribution of the iRNA, such as by enhancing cellular recognition and absorption. The peptide or peptidomimetic moiety can be about 5-50 amino acids long, *e.g.*, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

5 A peptide or peptidomimetic can be, for example, a cell permeation peptide, cationic peptide, amphipathic peptide, or hydrophobic peptide (*e.g.*, consisting primarily of Tyr, Trp, or Phe). The peptide moiety can be a dendrimer peptide, constrained peptide or crosslinked peptide. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). An exemplary hydrophobic MTS-containing peptide is RFGF having the amino acid sequence
10 AAVALLPAVLLALLAP (SEQ ID NO: 14). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO:15) containing a hydrophobic MTS can also be a targeting moiety. The peptide moiety can be a “delivery” peptide, which can carry large polar molecules including peptides, oligonucleotides, and protein across cell membranes. For example, sequences from the HIV
15 Tat protein (GRKKRRQRRRPPQ (SEQ ID NO:16) and the Drosophila Antennapedia protein (RQIKIWFQNRRMKWKK (SEQ ID NO:17) have been found to be capable of functioning as delivery peptides. A peptide or peptidomimetic can be encoded by a random sequence of DNA, such as a peptide identified from a phage-display library, or one-bead-one-compound (OBOC) combinatorial library (Lam *et al.*, Nature, 354:82-84, 1991). Examples of a peptide or peptidomimetic tethered to a dsRNA agent *via* an incorporated monomer unit for cell targeting
20 purposes is an arginine-glycine-aspartic acid (RGD)-peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.

 An RGD peptide for use in the compositions and methods of the invention may be linear or
25 cyclic, and may be modified, *e.g.*, glycosylated or methylated, to facilitate targeting to a specific tissue(s). RGD-containing peptides and peptidomimemtics may include D-amino acids, as well as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the integrin ligand, *e.g.*, PECAM-1 or VEGF.

 A “cell permeation peptide” is capable of permeating a cell, *e.g.*, a microbial cell, such as a
30 bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, an α -helical linear peptide (*e.g.*, LL-37 or Ceropin P1), a disulfide bond-containing peptide (*e.g.*, α -defensin, β -defensin or bactenecin), or a peptide containing only one or two dominating amino acids (*e.g.*, PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite
35 amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni *et al.*, Nucl. Acids Res. 31:2717-2724, 2003).

C. Carbohydrate Conjugates

In some embodiments of the compositions and methods of the invention, an iRNA further comprises a carbohydrate. The carbohydrate conjugated iRNA is advantageous for the *in vivo* delivery of nucleic acids, as well as compositions suitable for *in vivo* therapeutic use, as described herein. As used herein, “carbohydrate” refers to a compound which is either a carbohydrate *per se* made up of one or more monosaccharide units having at least 6 carbon atoms (which can be linear, branched or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom; or a compound having as a part thereof a carbohydrate moiety made up of one or more monosaccharide units each having at least six carbon atoms (which can be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Representative carbohydrates include the sugars (mono-, di-, tri-, and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9 monosaccharide units), and polysaccharides such as starches, glycogen, cellulose and polysaccharide gums. Specific monosaccharides include C5 and above (*e.g.*, C5, C6, C7, or C8) sugars; di- and trisaccharides include sugars having two or three monosaccharide units (*e.g.*, C5, C6, C7, or C8).

In certain embodiments, a carbohydrate conjugate for use in the compositions and methods of the invention is a monosaccharide.

In certain embodiments, the monosaccharide is an N-acetylgalactosamine (GalNAc). GalNAc conjugates, which comprise one or more N-acetylgalactosamine (GalNAc) derivatives, are described, for example, in US 8,106,022, the entire content of which is hereby incorporated herein by reference.

In some embodiments, the GalNAc conjugate serves as a ligand that targets the iRNA to particular cells. In some embodiments, the GalNAc conjugate targets the iRNA to liver cells, *e.g.*, by serving as a ligand for the asialoglycoprotein receptor of liver cells (*e.g.*, hepatocytes).

In some embodiments, the carbohydrate conjugate comprises one or more GalNAc derivatives. The GalNAc derivatives may be attached *via* a linker, *e.g.*, a bivalent or trivalent branched linker. In some embodiments the GalNAc conjugate is conjugated to the 3' end of the sense strand. In some embodiments, the GalNAc conjugate is conjugated to the iRNA agent (*e.g.*, to the 3' end of the sense strand) *via* a linker, *e.g.*, a linker as described herein. In some embodiments the GalNAc conjugate is conjugated to the 5' end of the sense strand. In some embodiments, the GalNAc conjugate is conjugated to the iRNA agent (*e.g.*, to the 5' end of the sense strand) *via* a linker, *e.g.*, a linker as described herein.

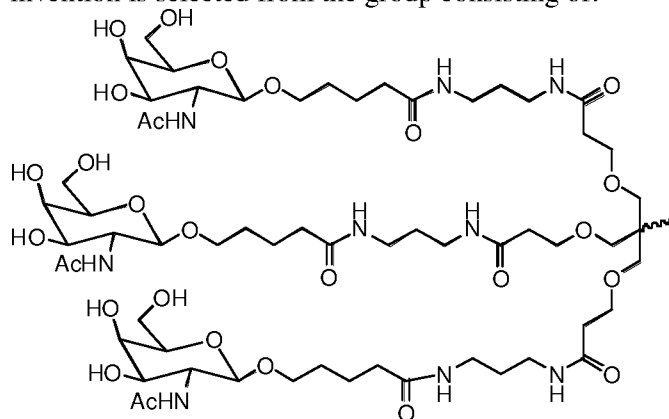
In certain embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a bivalent linker. In yet other embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a trivalent linker. In other embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a tetravalent linker.

In certain embodiments, the double stranded RNAi agents of the invention comprise one GalNAc or GalNAc derivative attached to the iRNA agent. In certain embodiments, the double stranded RNAi agents of the invention comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently attached to a plurality of nucleotides of the double stranded RNAi agent through a plurality of monovalent linkers.

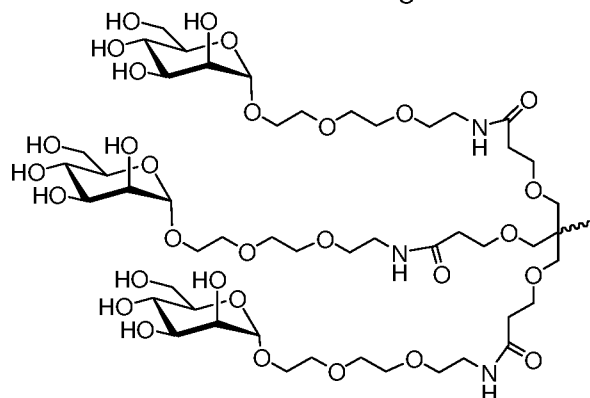
In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker. The hairpin loop may also be formed by an extended overhang in one strand of the duplex.

In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker. The hairpin loop may also be formed by an extended overhang in one strand of the duplex.

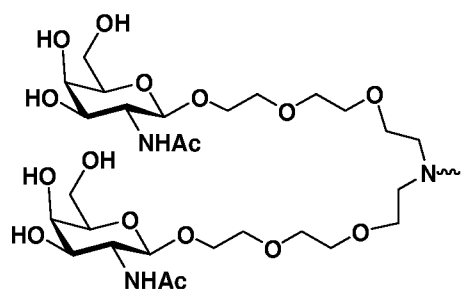
In one embodiment, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



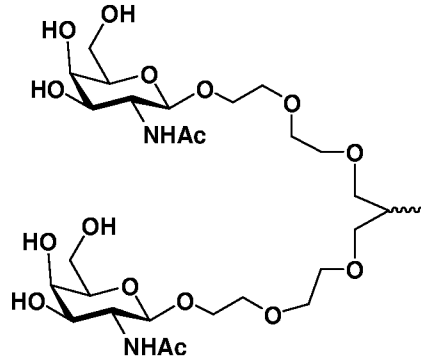
Formula II,



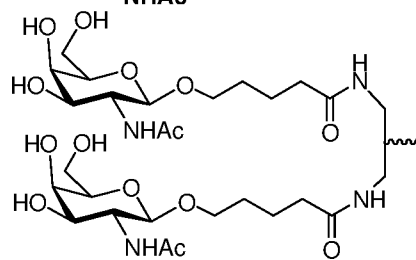
Formula III,



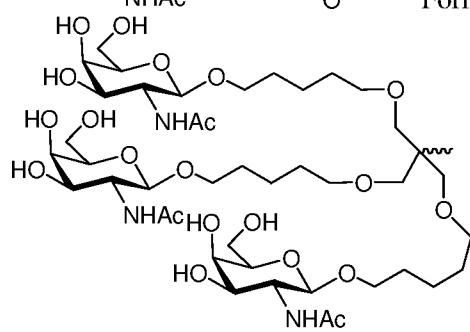
Formula IV,



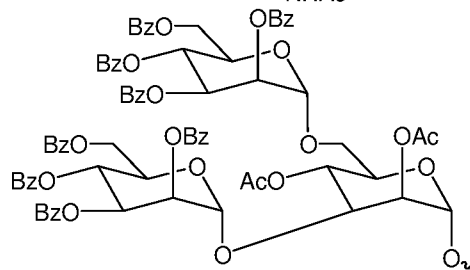
Formula V,



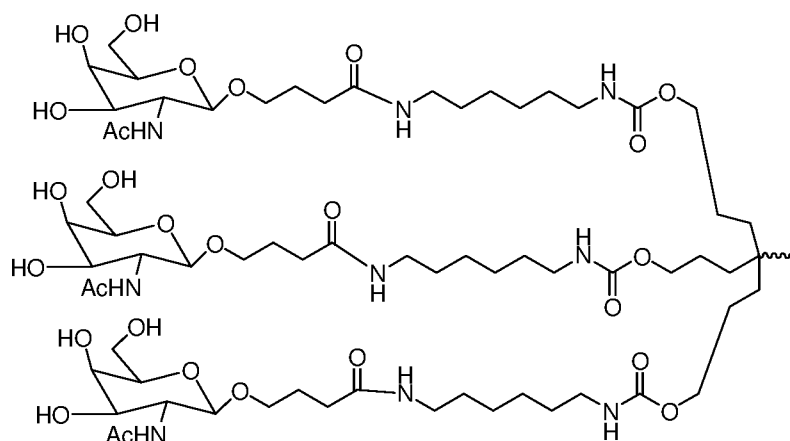
Formula VI,



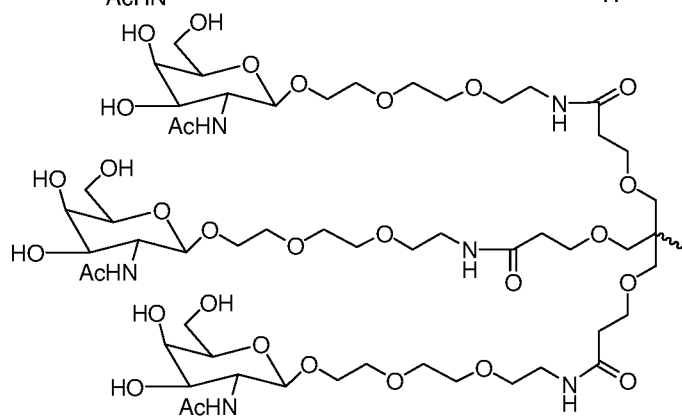
Formula VII,



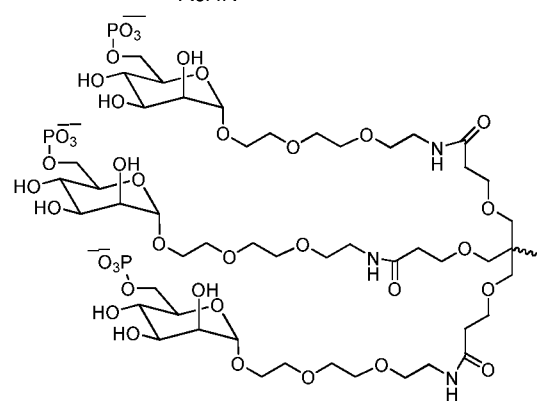
Formula VIII,



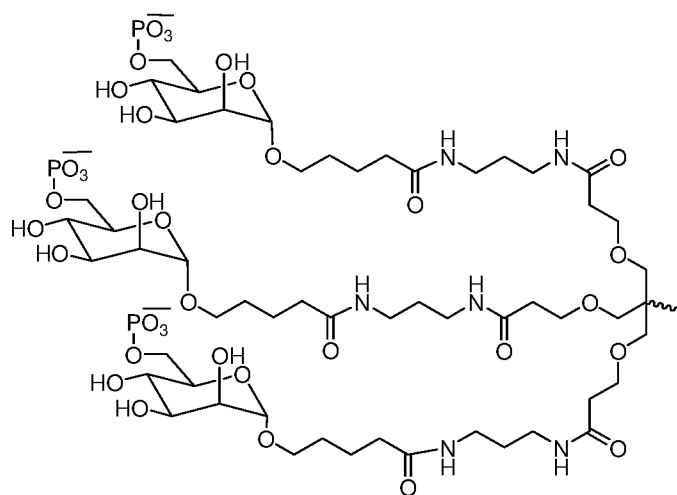
Formula IX,



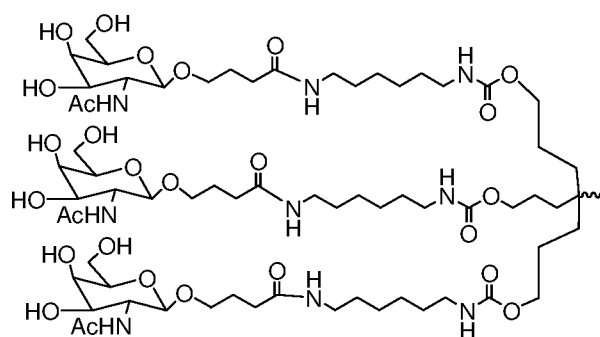
Formula X,



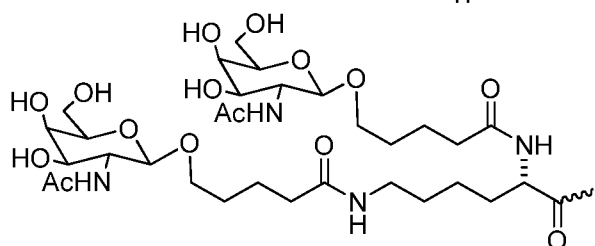
Formula XI,



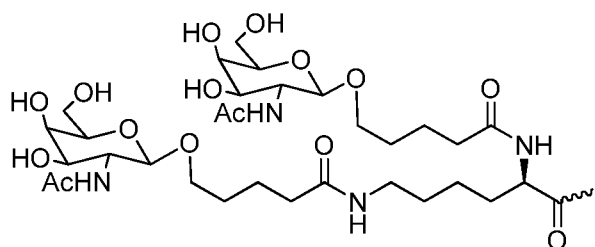
Formula XII,



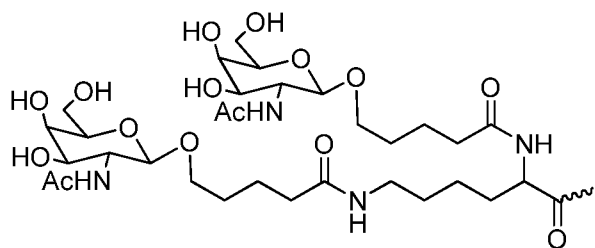
Formula XIII,



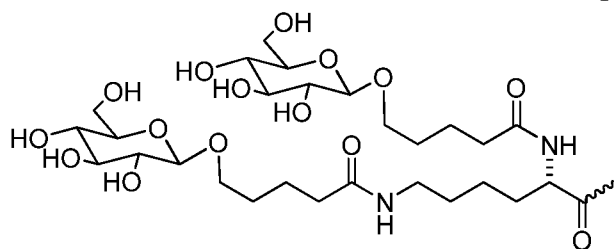
Formula XIV,



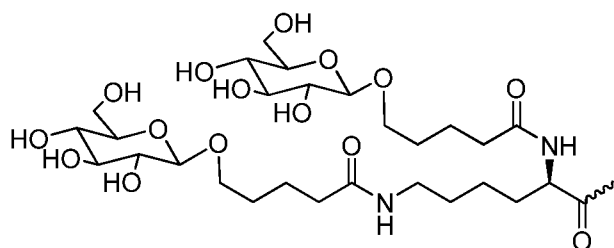
Formula XV,



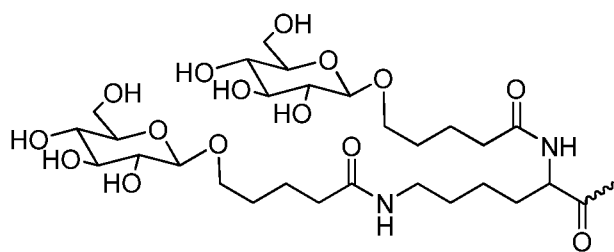
Formula XVI,



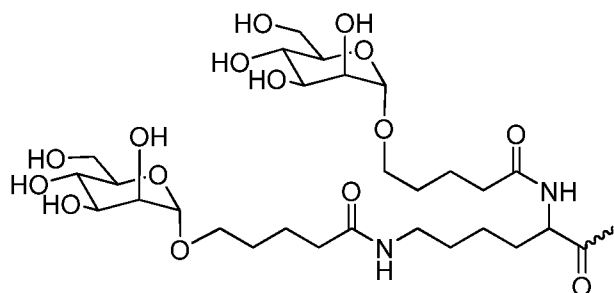
Formula XVII,



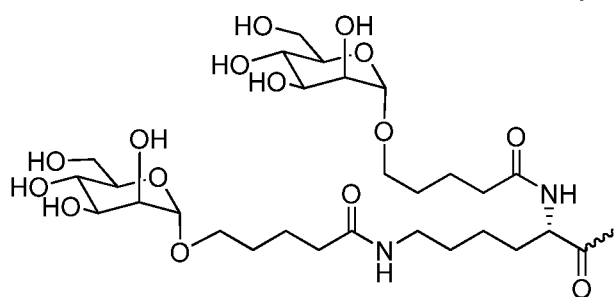
Formula XVIII,



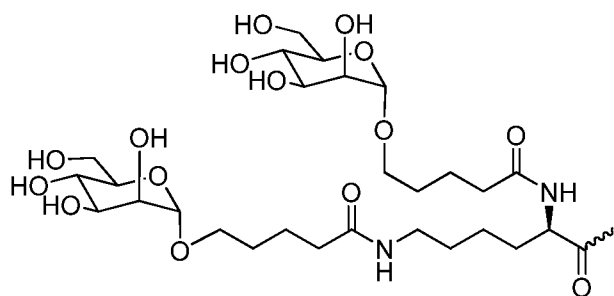
Formula XIX,



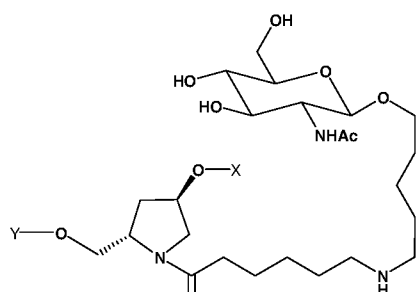
Formula XX,



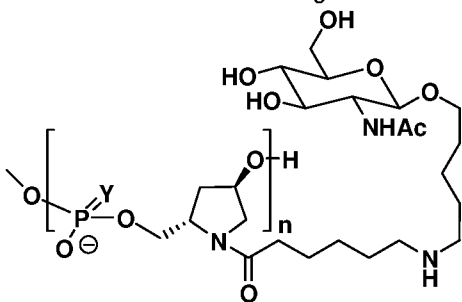
Formula XXI,



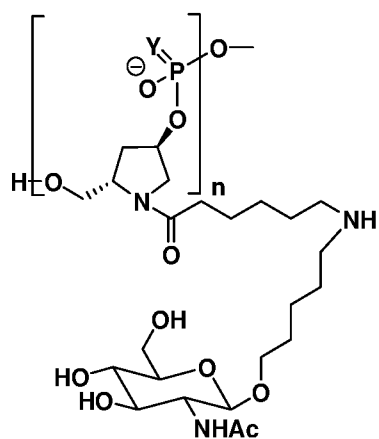
Formula XXII,



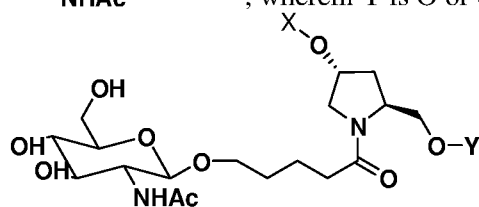
Formula XXIII;



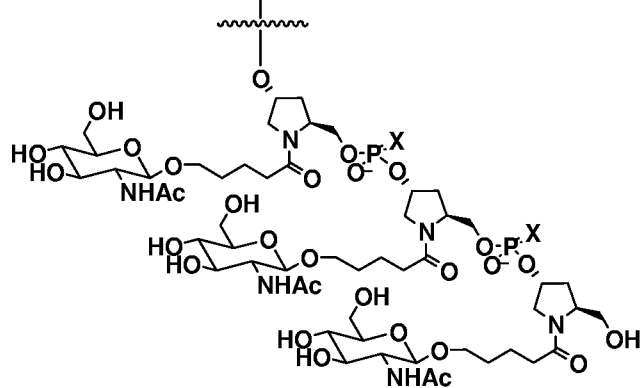
, wherein Y is O or S and n is 3 -6 (Formula XXIV);



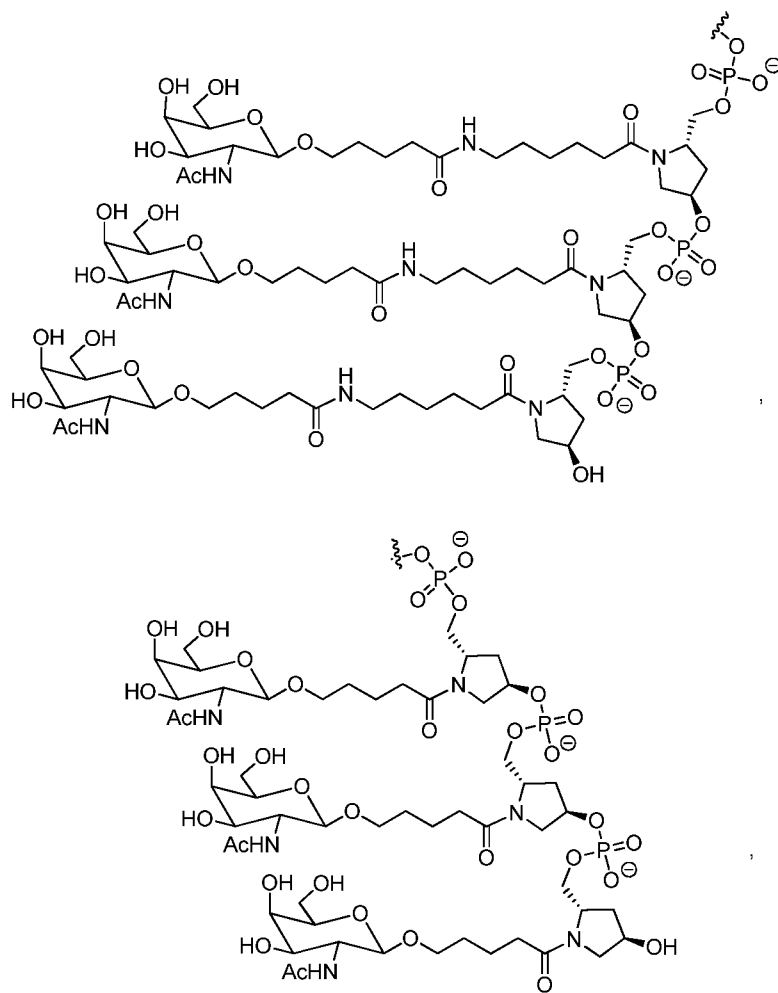
, wherein Y is O or S and n is 3-6 (Formula XXV);



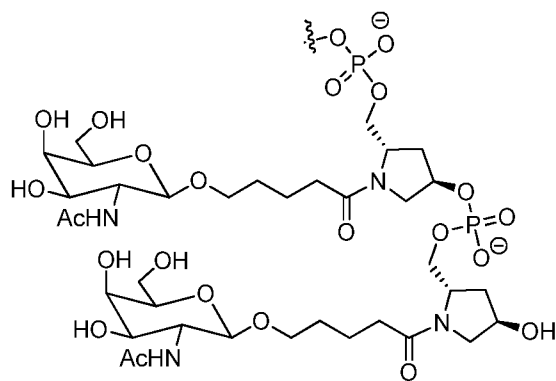
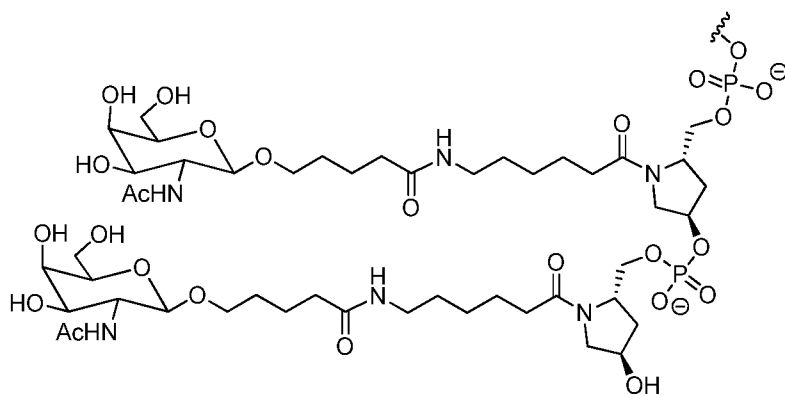
Formula XXVI;



, wherein X is O or S (Formula XXVII);

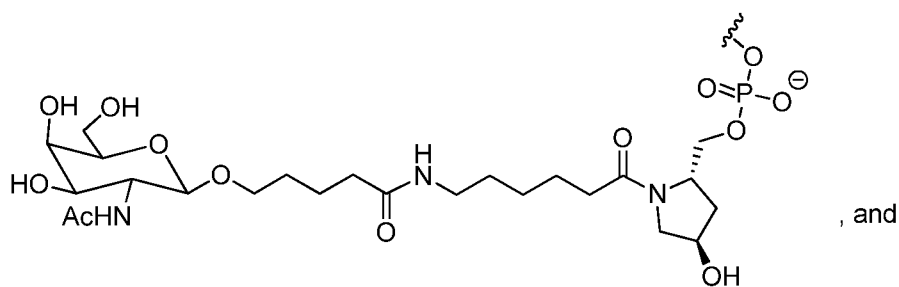


Formula XXVII; Formula XXIX;

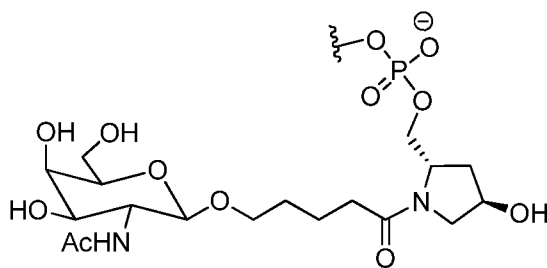


Formula XXX;

Formula XXXI;

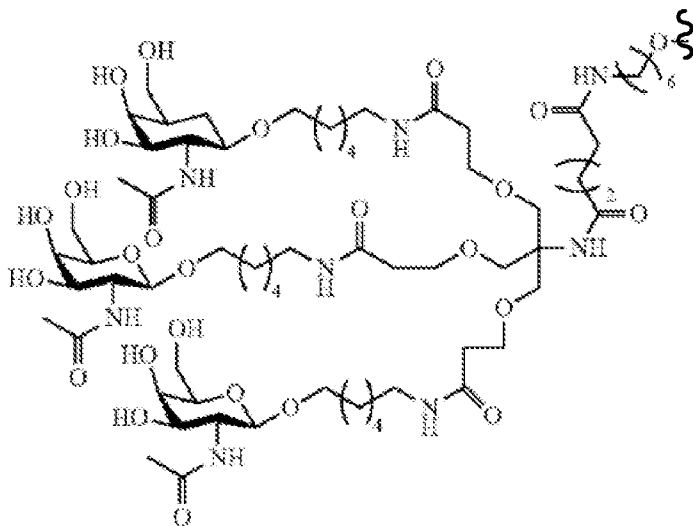


, and



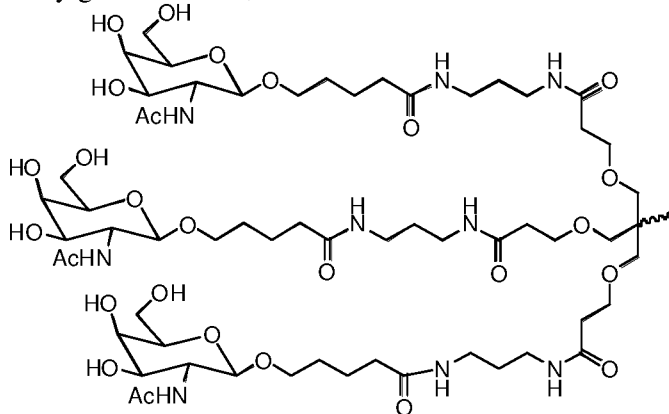
Formula XXXII;

5 Formula XXXIII.



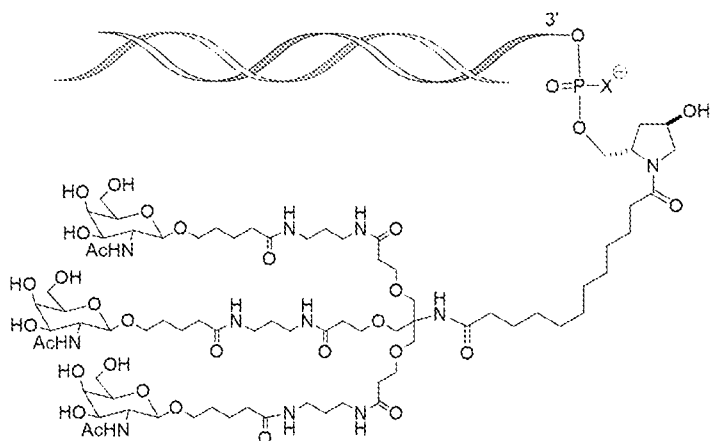
Formula XXXIV.

In another embodiment, a carbohydrate conjugate for use in the compositions and methods of the invention is a monosaccharide. In one embodiment, the monosaccharide is an N-acetylgalactosamine, such as

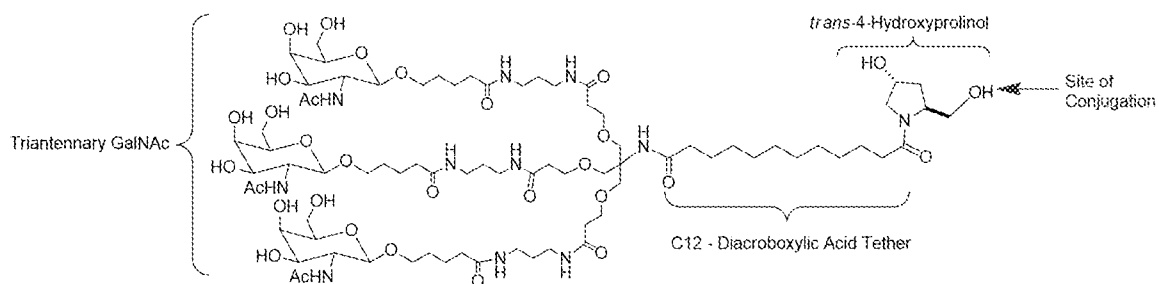


Formula II.

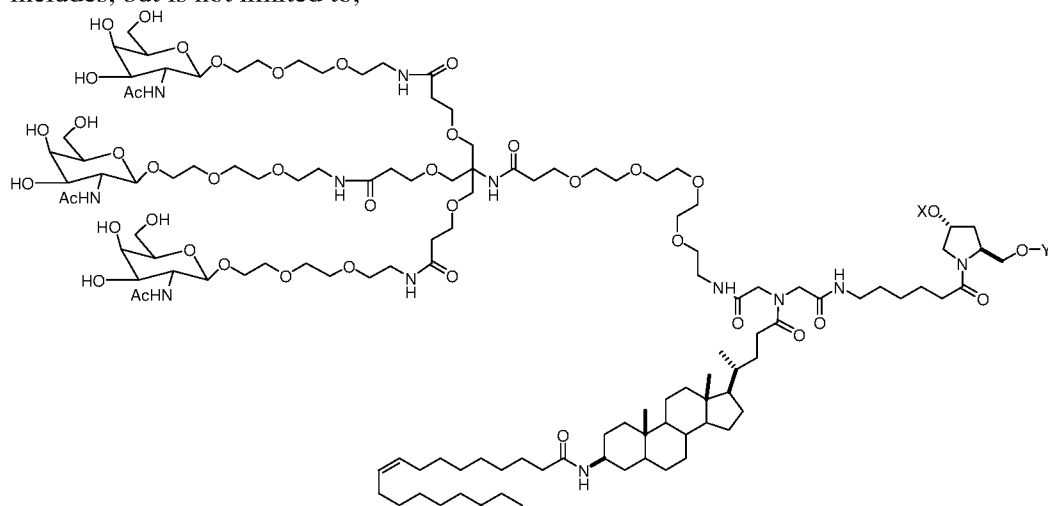
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate *via* a linker as shown in the following schematic, wherein X is O or S.



In some embodiments, the RNAi agent is conjugated to L96 as defined in Table 1 and shown below:

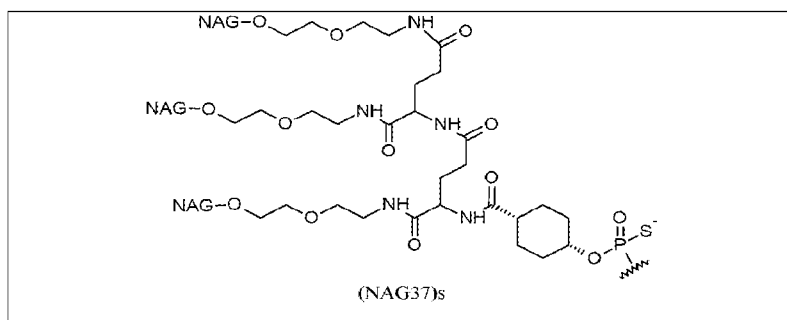


5 Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,



(Formula XXXVI), when one of X or Y is an oligonucleotide, the other is a hydrogen.

10 In some embodiments, a suitable ligand is a ligand disclosed in WO 2019/055633, the entire contents of which are incorporated herein by reference. In one embodiment the ligand comprises the structure below:



In certain embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a bivalent linker. In yet other

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embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a trivalent linker.

In one embodiment, the double stranded RNAi agents of the invention comprise one or more GalNAc or GalNAc derivative attached to the iRNA agent. The GalNAc may be attached to any nucleotide *via* a linker on the sense strand or antisense strand. The GalNAc may be attached to the

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5'-end of the sense strand, the 3' end of the sense strand, the 5'-end of the antisense strand, or the 3' – end of the antisense strand. In one embodiment, the GalNAc is attached to the 3' end of the sense strand, *e.g.*, *via* a trivalent linker.

In other embodiments, the double stranded RNAi agents of the invention comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently attached to a plurality of

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nucleotides of the double stranded RNAi agent through a plurality of linkers, *e.g.*, monovalent linkers.

In some embodiments, for example, when the two strands of an iRNA agent of the invention is part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently

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comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker.

In some embodiments, the carbohydrate conjugate further comprises one or more additional ligands as described above, such as, but not limited to, a PK modulator or a cell permeation peptide.

Additional carbohydrate conjugates and linkers suitable for use in the present invention include those described in PCT Publication Nos. WO 2014/179620 and WO 2014/179627, the entire

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contents of each of which are incorporated herein by reference.

D. Linkers

In some embodiments, the conjugate or ligand described herein can be attached to an iRNA oligonucleotide with various linkers that can be cleavable or non-cleavable.

The term "linker" or "linking group" means an organic moiety that connects two parts of a compound, *e.g.*, covalently attaches two parts of a compound. Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR₈, C(O), C(O)NH, SO, SO₂, SO₂NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, aryl, heteroaryl, heterocycl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclalkyl, alkylheterocyclalkenyl, alkylheterocyclalkynyl, alkenylheterocyclalkyl, alkenylheterocyclalkenyl, alkenylheterocyclalkynyl, alkynylheterocyclalkyl, alkynylheterocyclalkenyl, alkynylheterocyclalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylheteroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO₂, N(R₈), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclic; where R₈ is hydrogen, acyl, aliphatic, or substituted aliphatic. In one embodiment, the linker is about 1-24 atoms, 2-24, 3-24, 4-24, 5-24, 6-24, 6-18, 7-18, 8-18, 7-17, 8-17, 6-16, 7-17, or 8-16 atoms.

A cleavable linking group is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In an exemplary embodiment, the cleavable linking group is cleaved at least about 10 times, 20, times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, or more, or at least 100 times faster in a target cell or under a first reference condition (which can, *e.g.*, be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, *e.g.*, be selected to mimic or represent conditions found in the blood or serum).

Cleavable linking groups are susceptible to cleavage agents, *e.g.*, pH, redox potential, or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, *e.g.*, oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linking group by reduction; esterases; endosomes or agents that can create an acidic environment, *e.g.*, those that result in a pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable linking group by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

A cleavable linkage group, such as a disulfide bond can be susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic pH at around 5.0. Some linkers will have a cleavable linking group that is cleaved at a selected pH, thereby releasing a cationic lipid from the ligand inside the cell, or into the desired compartment of the cell.

A linker can include a cleavable linking group that is cleavable by a particular enzyme. The type of cleavable linking group incorporated into a linker can depend on the cell to be targeted. For example, a liver-targeting ligand can be linked to a cationic lipid through a linker that includes an ester group. Liver cells are rich in esterases, and therefore the linker will be cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Other cell-types rich in esterases include cells of the lung, renal cortex, and testis.

Linkers that contain peptide bonds can be used when targeting cell types rich in peptidases, such as liver cells and synoviocytes.

In general, the suitability of a candidate cleavable linking group can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate linking group. It will also be desirable to also test the candidate cleavable linking group for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus, one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, *e.g.*, blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. It can be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in whole animals. In certain embodiments, useful candidate compounds are cleaved at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

i. Redox cleavable linking groups

In certain embodiments, a cleavable linking group is a redox cleavable linking group that is cleaved upon reduction or oxidation. An example of reductively cleavable linking group is a disulphide linking group (-S-S-). To determine if a candidate cleavable linking group is a suitable “reductively cleavable linking group,” or for example is suitable for use with a particular iRNA moiety and particular targeting agent one can look to methods described herein. For example, a candidate can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent using reagents known in the art, which mimic the rate of cleavage which would be observed in a cell, *e.g.*, a target cell. The candidates can also be evaluated under conditions which are selected to mimic blood

or serum conditions. In one, candidate compounds are cleaved by at most about 10% in the blood. In other embodiments, useful candidate compounds are degraded at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood (or under *in vitro* conditions selected to mimic extracellular conditions). The rate of cleavage of candidate compounds can be determined using standard enzyme kinetics assays under conditions chosen to mimic intracellular media and compared to conditions chosen to mimic extracellular media.

ii. Phosphate-based cleavable linking groups

In other embodiments, a cleavable linker comprises a phosphate-based cleavable linking group. A phosphate-based cleavable linking group is cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that cleaves phosphate groups in cells are enzymes such as phosphatases in cells. Examples of phosphate-based linking groups are -O-P(O)(ORk)-O-, -O-P(S)(ORk)-O-, -O-P(S)(SRk)-O-, -S-P(O)(ORk)-O-, -O-P(O)(ORk)-S-, -S-P(O)(ORk)-S-, -O-P(S)(ORk)-S-, -S-P(S)(ORk)-O-, -O-P(O)(Rk)-O-, -O-P(S)(Rk)-O-, -S-P(O)(Rk)-O-, -S-P(S)(Rk)-O-, -S-P(O)(Rk)-S-, -O-P(S)(Rk)-S-, wherein Rk at each occurrence can be, independently, C1-C20 alkyl, C1-C20 haloalkyl, C6-C10 aryl, or C7-C12 aralkyl. Exemplary embodiments include -O-P(O)(OH)-O-, -O-P(S)(OH)-O-, -O-P(S)(SH)-O-, -S-P(O)(OH)-O-, -O-P(O)(OH)-S-, -S-P(O)(OH)-S-, -O-P(S)(OH)-S-, -S-P(S)(OH)-O-, -O-P(O)(H)-O-, -O-P(S)(H)-O-, -S-P(O)(H)-O-, -S-P(S)(H)-O-, -S-P(O)(H)-S-, and -O-P(S)(H)-S-. In certain embodiments a phosphate-based linking group is -O-P(O)(OH)-O-. These candidates can be evaluated using methods analogous to those described above.

iii. Acid cleavable linking groups

In other embodiments, a cleavable linker comprises an acid cleavable linking group. An acid cleavable linking group is a linking group that is cleaved under acidic conditions. In certain embodiments acid cleavable linking groups are cleaved in an acidic environment with a pH of about 6.5 or lower (*e.g.*, about 6.0, 5.5, 5.0, or lower), or by agents such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes can provide a cleaving environment for acid cleavable linking groups. Examples of acid cleavable linking groups include but are not limited to hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula -C=NN-, C(O)O, or -OC(O). An exemplary embodiment is when the carbon attached to the oxygen of the ester (the alkoxy group) is an aryl group, substituted alkyl group, or tertiary alkyl group such as dimethyl pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

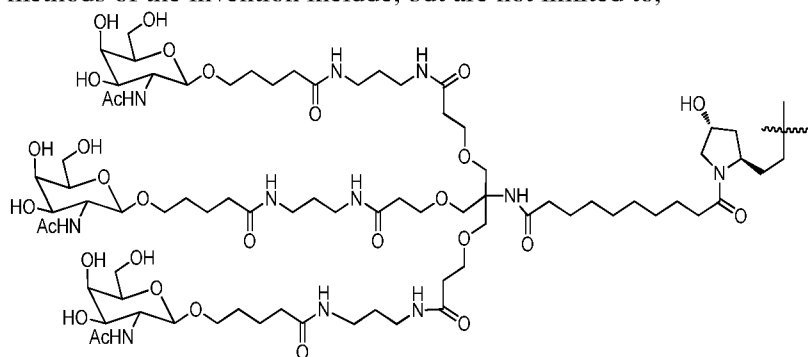
iv. Ester-based linking groups

In other embodiments, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include, but are not limited to, esters of alkylene, alkenylene and alkynylene groups. Ester cleavable linking groups have the general formula $-C(O)O-$, or $-OC(O)-$. These candidates can be evaluated using methods analogous to those described above.

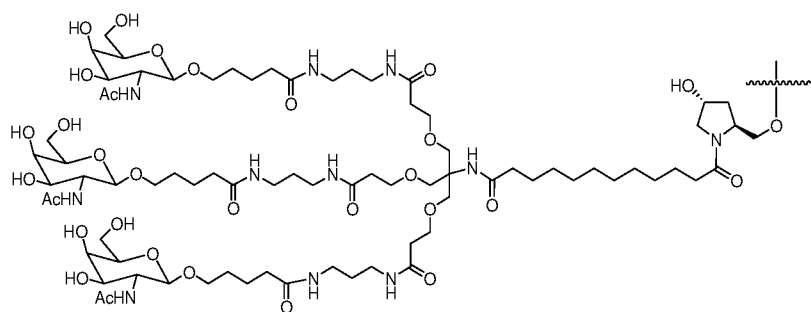
v. Peptide-based cleaving groups

In yet other embodiments, a cleavable linker comprises a peptide-based cleavable linking group. A peptide-based cleavable linking group is cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (*e.g.*, dipeptides, tripeptides *etc.*) and polypeptides. Peptide-based cleavable groups do not include the amide group $(-C(O)NH-)$. The amide group can be formed between any alkylene, alkenylene or alkynylene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide based cleavage group is generally limited to the peptide bond (*i.e.*, the amide bond) formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula $-NHCHRAC(O)NHCHRBC(O)-$, where RA and RB are the R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

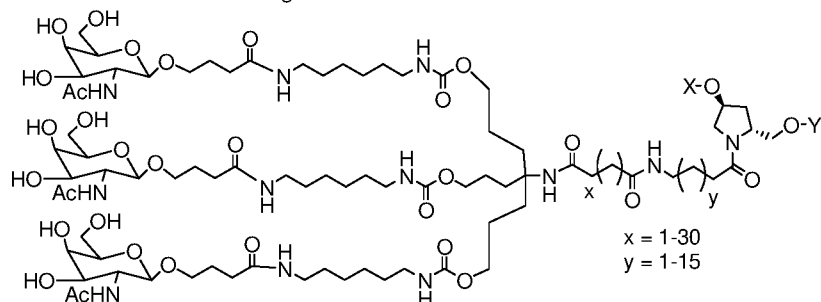
In some embodiments, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



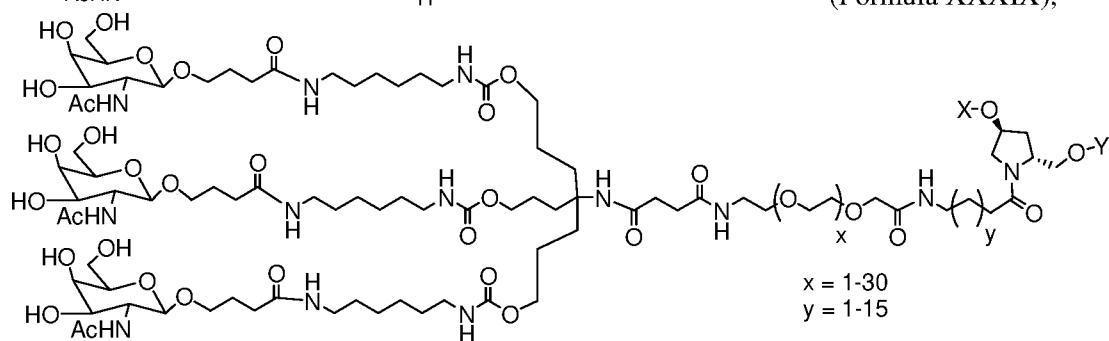
(Formula XXXVII),



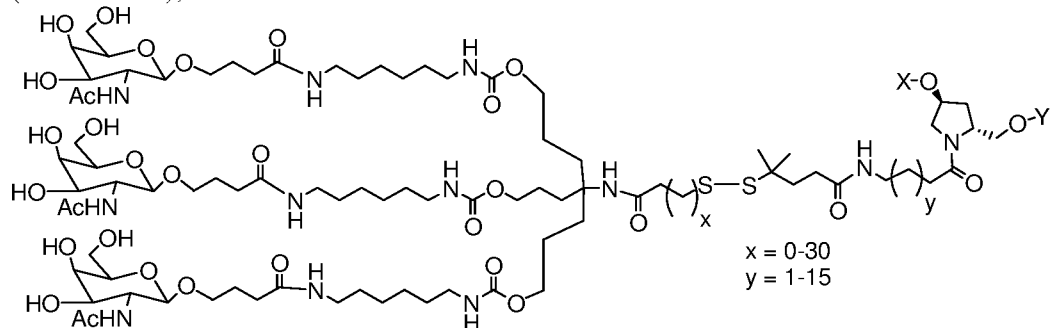
(Formula XXXVIII),



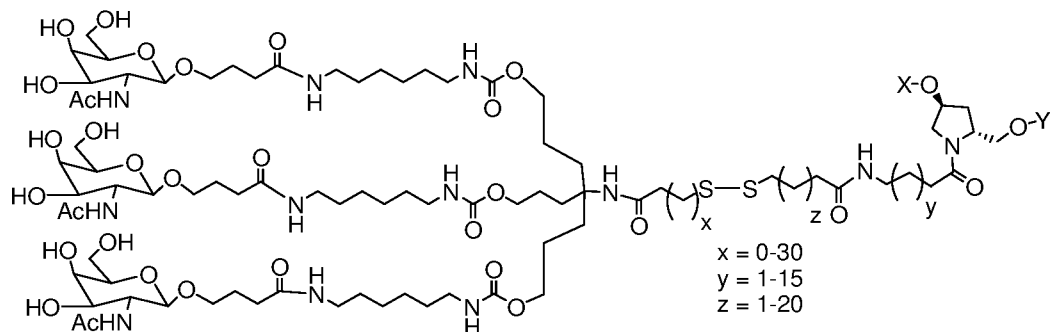
(Formula XXXIX),



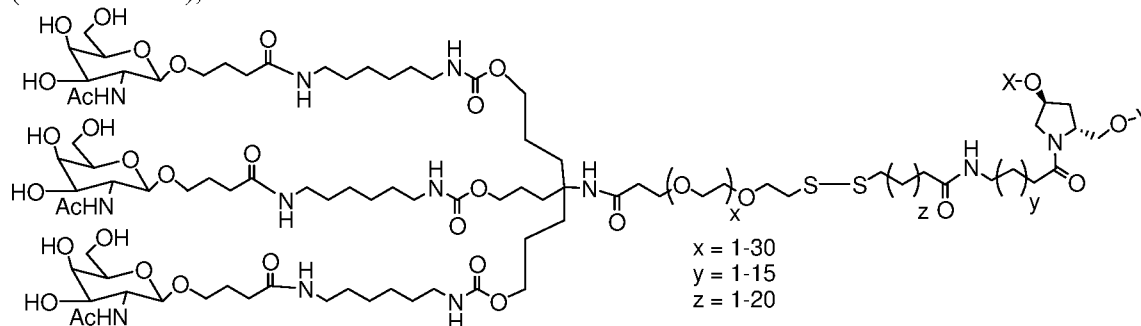
(Formula XL),



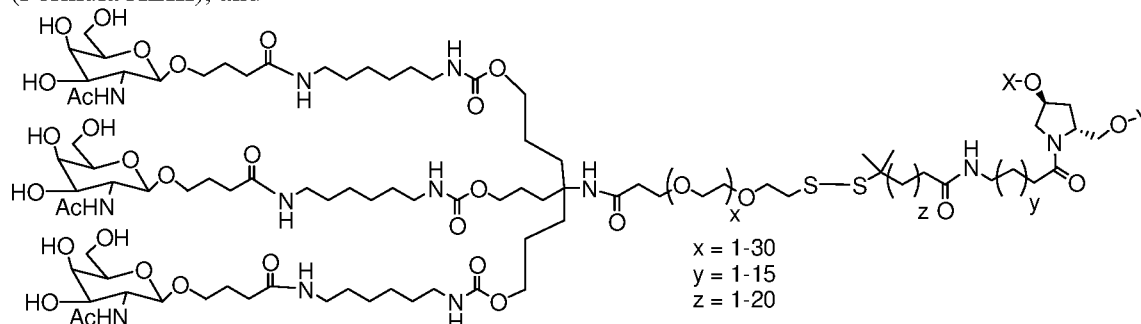
(Formula XLI),



(Formula XLII),



(Formula XLIII), and

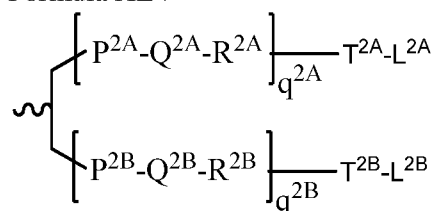


- 5 (Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

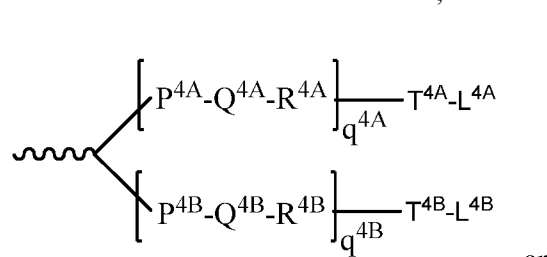
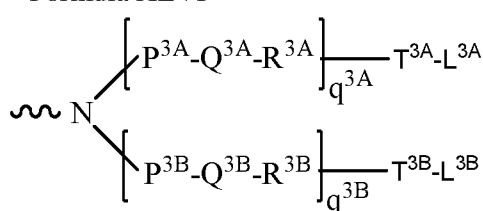
In certain embodiments of the compositions and methods of the invention, a ligand is one or more “GalNAc” (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

- 10 In one embodiment, a dsRNA of the invention is conjugated to a bivalent or trivalent branched linker selected from the group of structures shown in any of formula (XLV) – (XLVIII):

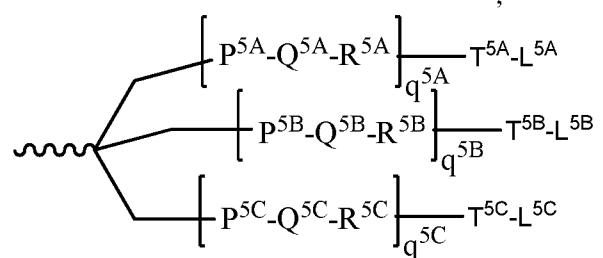
Formula XLV



Formula XLVI



Formula XLVII



Formula XLVIII

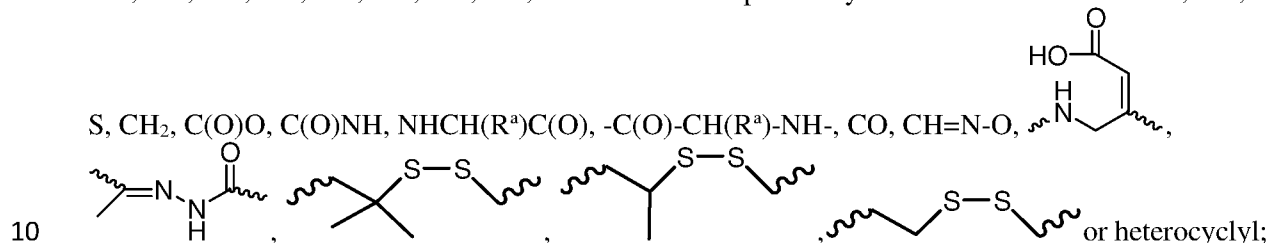
- 15 wherein:

q2A, q2B, q3A, q3B, q4A, q4B, q5A, q5B and q5C represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different;

p^{2A}, p^{2B}, p^{3A}, p^{3B}, p^{4A}, p^{4B}, p^{5A}, p^{5B}, p^{5C}, t^{2A}, t^{2B}, t^{3A}, t^{3B}, t^{4A}, t^{4B}, t^{4A}, t^{5B}, t^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH₂, CH₂NH or CH₂O;

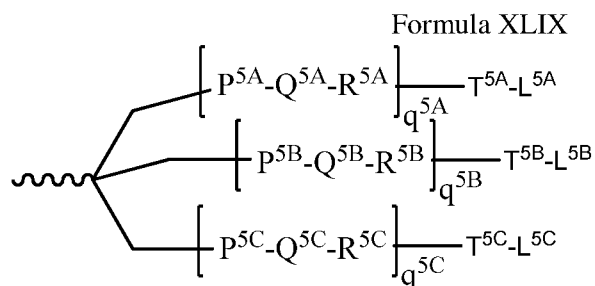
5 Q^{2A}, Q^{2B}, Q^{3A}, Q^{3B}, Q^{4A}, Q^{4B}, Q^{5A}, Q^{5B}, Q^{5C} are independently for each occurrence absent, alkylene, substituted alkylene wherein one or more methylenes can be interrupted or terminated by one or more of O, S, S(O), SO₂, N(R^N), C(R')=C(R''), C≡C or C(O);

R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{5C} are each independently for each occurrence absent, NH, O,



L^{2A}, L^{2B}, L^{3A}, L^{3B}, L^{4A}, L^{4B}, L^{5A}, L^{5B} and L^{5C} represent the ligand; *i.e.* each independently for each occurrence a monosaccharide (such as GalNAc), disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, or polysaccharide; and R^a is H or amino acid side chain. Trivalent conjugating GalNAc derivatives are particularly useful for use with RNAi agents for inhibiting the expression of a target gene, such as those of formula (XLIX):

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wherein L^{5A}, L^{5B} and L^{5C} represent a monosaccharide, such as GalNAc derivative.

20 Examples of suitable bivalent and trivalent branched linker groups conjugating GalNAc derivatives include, but are not limited to, the structures recited above as formulas II, VII, XI, X, and XIII.

Representative U.S. Patents that teach the preparation of RNA conjugates include, but are not limited to, U.S. Patent Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241; 5,391,723; 5,416,203; 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928; 5,688,941; 6,294,664; 6,320,017;

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6,576,752; 6,783,931; 6,900,297; 7,037,646; and 8,106,022, the entire contents of each of which are hereby incorporated herein by reference.

It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications can be incorporated in a single compound or even at a single nucleoside within an iRNA. The present invention also includes iRNA compounds that are chimeric compounds.

“Chimeric” iRNA compounds or “chimeras,” in the context of this invention, are iRNA compounds, such as, dsRNAi agents, that contain two or more chemically distinct regions, each made up of at least one monomer unit, *i.e.*, a nucleotide in the case of a dsRNA compound. These iRNAs typically contain at least one region wherein the RNA is modified so as to confer upon the iRNA increased resistance to nuclease degradation, increased cellular uptake, or increased binding affinity for the target nucleic acid. An additional region of the iRNA can serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of iRNA inhibition of gene expression. Consequently, comparable results can often be obtained with shorter iRNAs when chimeric dsRNAs are used, compared to phosphorothioate deoxy dsRNAs hybridizing to the same target region. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

In certain instances, the RNA of an iRNA can be modified by a non-ligand group. A number of non-ligand molecules have been conjugated to iRNAs in order to enhance the activity, cellular distribution or cellular uptake of the iRNA, and procedures for performing such conjugations are available in the scientific literature. Such non-ligand moieties have included lipid moieties, such as cholesterol (Kubo, T. *et al.*, *Biochem. Biophys. Res. Comm.*, 2007, 365(1):54-61; Letsinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 1989, 86:6553), cholic acid (Manoharan *et al.*, *Bioorg. Med. Chem. Lett.*, 1994, 4:1053), a thioether, *e.g.*, hexyl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660:306; Manoharan *et al.*, *Bioorg. Med. Chem. Lett.*, 1993, 3:2765), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, 20:533), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J.*, 1991, 10:111; Kabanov *et al.*, *FEBS Lett.*, 1990, 259:327; Svinarchuk *et al.*, *Biochimie*, 1993, 75:49), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18:3777), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995, 14:969), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, 1264:229), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, 277:923). Representative United States patents that teach the preparation of such RNA conjugates have been listed above. Typical conjugation protocols involve

the synthesis of RNAs bearing an aminolinker at one or more positions of the sequence. The amino group is then reacted with the molecule being conjugated using appropriate coupling or activating reagents. The conjugation reaction can be performed either with the RNA still bound to the solid support or following cleavage of the RNA, in solution phase. Purification of the RNA conjugate by HPLC typically affords the pure conjugate.

IV. Delivery of an iRNA of the Invention

The delivery of an iRNA of the invention to a cell *e.g.*, a cell within a subject, such as a human subject (*e.g.*, a subject in need thereof, such as a subject susceptible to or diagnosed with an AGT-associated disorder, *e.g.*, hypertension, can be achieved in a number of different ways. For example, delivery may be performed by contacting a cell with an iRNA of the invention either *in vitro* or *in vivo*. *In vivo* delivery may also be performed directly by administering a composition comprising an iRNA, *e.g.*, a dsRNA, to a subject. Alternatively, *in vivo* delivery may be performed indirectly by administering one or more vectors that encode and direct the expression of the iRNA. These alternatives are discussed further below.

In general, any method of delivering a nucleic acid molecule (*in vitro* or *in vivo*) can be adapted for use with an iRNA of the invention (see *e.g.*, Akhtar S. and Julian RL. (1992) *Trends Cell Biol.* 2(5):139-144 and WO94/02595, which are incorporated herein by reference in their entireties). For *in vivo* delivery, factors to consider in order to deliver an iRNA molecule include, for example, biological stability of the delivered molecule, prevention of non-specific effects, and accumulation of the delivered molecule in the target tissue. RNA interference has also shown success with local delivery to the CNS by direct injection (Dorn, G., *et al.* (2004) *Nucleic Acids* 32:e49; Tan, PH., *et al* (2005) *Gene Ther.* 12:59-66; Makimura, H., *et al* (2002) *BMC Neurosci.* 3:18; Shishkina, GT., *et al* (2004) *Neuroscience* 129:521-528; Thakker, ER., *et al* (2004) *Proc. Natl. Acad. Sci. U.S.A.* 101:17270-17275; Akaneya, Y., *et al* (2005) *J. Neurophysiol.* 93:594-602). Modification of the RNA or the pharmaceutical carrier can also permit targeting of the iRNA to the target tissue and avoid undesirable off-target effects. iRNA molecules can be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For example, an iRNA directed against ApoB conjugated to a lipophilic cholesterol moiety was injected systemically into mice and resulted in knockdown of apoB mRNA in both the liver and jejunum (Soutschek, J., *et al* (2004) *Nature* 432:173-178).

In an alternative embodiment, the iRNA can be delivered using drug delivery systems such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery systems facilitate binding of an iRNA molecule (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an iRNA by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an iRNA, or induced to form a vesicle or micelle (see *e.g.*, Kim SH, *et al* (2008) *Journal of Controlled Release* 129(2):107-

116) that encases an iRNA. The formation of vesicles or micelles further prevents degradation of the iRNA when administered systemically. Methods for making and administering cationic- iRNA complexes are well within the abilities of one skilled in the art (see *e.g.*, Sorensen, DR, *et al* (2003) *J. Mol. Biol* 327:761-766; Verma, UN, *et al* (2003) *Clin. Cancer Res.* 9:1291-1300; Arnold, AS *et al* (2007) *J. Hypertens.* 25:197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of iRNAs include DOTAP (Sorensen, DR., *et al* (2003), *supra*; Verma, UN, *et al* (2003), *supra*), "solid nucleic acid lipid particles" (Zimmermann, TS, *et al* (2006) *Nature* 441:111-114), cardiolipin (Chien, PY, *et al* (2005) *Cancer Gene Ther.* 12:321-328; Pal, A, *et al* (2005) *Int J. Oncol.* 26:1087-1091), polyethyleneimine (Bonnet ME, *et al* (2008) *Pharm. Res.* Aug 16 Epub ahead of print; Aigner, A. (2006) *J. Biomed. Biotechnol.* 71659), Arg-Gly-Asp (RGD) peptides (Liu, S. (2006) *Mol. Pharm.* 3:472-487), and polyamidoamines (Tomalia, DA, *et al* (2007) *Biochem. Soc. Trans.* 35:61-67; Yoo, H., *et al* (1999) *Pharm. Res.* 16:1799-1804). In some embodiments, an iRNA forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of iRNAs and cyclodextrins can be found in U.S. Patent No. 7,427,605, which is herein incorporated by reference in its entirety. Certain aspects of the instant disclosure relate to a method of reducing the expression of an AGT gene in a cell, comprising contacting said cell with the double-stranded RNAi agent of the disclosure. In one embodiment, the cell is a hepatic cell, optionally a hepatocyte. In one embodiment, the cell is an extrahepatic cell.

A. Vector encoded iRNAs of the Invention

iRNA targeting the AGT gene can be expressed from transcription units inserted into DNA or RNA vectors (see, *e.g.*, Couture, A, *et al.*, *TIG.* (1996), 12:5-10; Skillern, A, *et al.*, International PCT Publication No. WO 00/22113, Conrad, International PCT Publication No. WO 00/22114, and Conrad, U.S. Patent No. 6,054,299). Expression can be transient (on the order of hours to weeks) or sustained (weeks to months or longer), depending upon the specific construct used and the target tissue or cell type. These transgenes can be introduced as a linear construct, a circular plasmid, or a viral vector, which can be an integrating or non-integrating vector. The transgene can also be constructed to permit it to be inherited as an extrachromosomal plasmid (Gassmann, *et al.*, *Proc. Natl. Acad. Sci. USA* (1995) 92:1292).

Viral vector systems which can be utilized with the methods and compositions described herein include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but not limited to lentiviral vectors, moloney murine leukemia virus, *etc.*; (c) adeno- associated virus vectors; (d) herpes simplex virus vectors; (e) SV 40 vectors; (f) polyoma virus vectors; (g) papilloma virus vectors; (h) picornavirus vectors; (i) pox virus vectors such as an orthopox, *e.g.*, vaccinia virus vectors or avipox, *e.g.* canary pox or fowl pox; and (j) a helper-dependent or gutless adenovirus. Replication-defective viruses can also be advantageous. Different vectors will or will not become incorporated

into the cells' genome. The constructs can include viral sequences for transfection, if desired. Alternatively, the construct can be incorporated into vectors capable of episomal replication, *e.g.* EPV and EBV vectors. Constructs for the recombinant expression of an iRNA will generally require regulatory elements, *e.g.*, promoters, enhancers, *etc.*, to ensure the expression of the iRNA in target cells. Other aspects to consider for vectors and constructs are known in the art.

V. Pharmaceutical Compositions of the Invention

The present invention also includes pharmaceutical compositions and formulations which include the iRNAs of the invention. In one embodiment, provided herein are pharmaceutical compositions containing an iRNA, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the iRNA are useful for preventing or treating an AGT-associated disorder, *e.g.*, hypertension.

Such pharmaceutical compositions are formulated based on the mode of delivery. One example is compositions that are formulated for systemic administration *via* parenteral delivery, *e.g.*, by subcutaneous (SC), intramuscular (IM), or intravenous (IV) delivery. The pharmaceutical compositions of the invention may be administered in dosages sufficient to inhibit expression of an AGT gene.

In some embodiments, the pharmaceutical compositions of the invention are sterile. In another embodiment, the pharmaceutical compositions of the invention are pyrogen free.

The pharmaceutical compositions of the invention may be administered in dosages sufficient to inhibit expression of an AGT gene. In general, a suitable dose of an iRNA of the invention will be in the range of about 0.001 to about 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of about 1 to 50 mg per kilogram body weight per day. Typically, a suitable dose of an iRNA of the invention will be in the range of about 0.1 mg/kg to about 5.0 mg/kg, such as, about 0.3 mg/kg and about 3.0 mg/kg. A repeat-dose regimen may include administration of a therapeutic amount of iRNA on a regular basis, such as every month, once every 3-6 months, or once a year. In certain embodiments, the iRNA is administered about once per month to about once per six months.

After an initial treatment regimen, the treatments can be administered on a less frequent basis. Duration of treatment can be determined based on the severity of disease.

In other embodiments, a single dose of the pharmaceutical compositions can be long lasting, such that doses are administered at not more than 1, 2, 3, or 4 month intervals. In some embodiments of the invention, a single dose of the pharmaceutical compositions of the invention is administered about once per month. In other embodiments of the invention, a single dose of the pharmaceutical compositions of the invention is administered quarterly (*i.e.*, about every three months). In other embodiments of the invention, a single dose of the pharmaceutical compositions of the invention is administered twice per year (*i.e.*, about once every six months).

The skilled artisan will appreciate that certain factors can influence the dosage and timing required to effectively treat a subject, including but not limited to mutations present in the subject, previous treatments, the general health or age of the subject, and other diseases present. Moreover, treatment of a subject with a prophylactically or therapeutically effective amount, as appropriate, of a composition can include a single treatment or a series of treatments.

The pharmaceutical compositions of the present disclosure can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic, vaginal, rectal, intranasal, transdermal), oral, or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal, *e.g.*, via an implanted device; or intracranial, *e.g.*, by intraparenchymal, intrathecal or intraventricular, administration.

The iRNA can be delivered in a manner to target a particular tissue, such as the liver.

Pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like can be necessary or desirable. Coated condoms, gloves and the like can also be useful. Suitable topical formulations include those in which the RNAi agents featured in the disclosure are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Suitable lipids and liposomes include neutral (*e.g.*, dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearoylphosphatidyl choline) negative (*e.g.*, dimyristoylphosphatidyl glycerol DMPG) and cationic (*e.g.*, dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). RNAi agents featured in the disclosure can be encapsulated within liposomes or can form complexes thereto, in particular to cationic liposomes. Alternatively, RNAi agents can be complexed to lipids, in particular to cationic lipids. Suitable fatty acids and esters include but are not limited to arachidonic acid, oleic acid, eicosanoic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprinate, tricaprinate, monoolein, dilaurin, glyceryl 1-monocaprinate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C1-20 alkyl ester (*e.g.*, isopropylmyristate IPM), monoglyceride, diglyceride or pharmaceutically acceptable salt thereof. Topical formulations are described in detail in US 6,747,014, which is incorporated herein by reference.

In one embodiment, the siRNAs, double stranded RNA agents of the invention, are administered to a cell in a pharmaceutical composition by a topical route of administration.

In one embodiment, the pharmaceutical composition may include an siRNA compound mixed with a topical delivery agent. The topical delivery agent can be a plurality of microscopic vesicles. The microscopic vesicles can be liposomes. In some embodiments the liposomes are cationic liposomes.

In another embodiment, the dsRNA agent is admixed with a topical penetration enhancer. In one embodiment, the topical penetration enhancer is a fatty acid. The fatty acid can be arachidonic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C1-10 alkyl ester, monoglyceride, diglyceride or pharmaceutically acceptable salt thereof.

In another embodiment, the topical penetration enhancer is a bile salt. The bile salt can be cholic acid, dehydrocholic acid, deoxycholic acid, glucolic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, chenodeoxycholic acid, ursodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate, sodium glycodihydrofusidate, polyoxyethylene-9-lauryl ether or a pharmaceutically acceptable salt thereof.

In another embodiment, the penetration enhancer is a chelating agent. The chelating agent can be EDTA, citric acid, a salicylate, a N-acyl derivative of collagen, laureth-9, an N-amino acyl derivative of a beta-diketone or a mixture thereof.

In another embodiment, the penetration enhancer is a surfactant, *e.g.*, an ionic or nonionic surfactant. The surfactant can be sodium lauryl sulfate, polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether, a perfluorchemical emulsion or mixture thereof.

In another embodiment, the penetration enhancer can be selected from a group consisting of unsaturated cyclic ureas, 1-alkyl-alkones, 1-alkenylazacyclo-alkanones, steroidal anti-inflammatory agents and mixtures thereof. In yet another embodiment the penetration enhancer can be a glycol, a pyrrol, an azone, or a terpenes.

In one aspect, the invention features a pharmaceutical composition including an siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, (*e.g.*, a precursor, *e.g.*, a larger siRNA compound which can be processed into a ssiRNA compound, or a DNA which encodes an siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, or precursor thereof) in an injectable dosage form. In one embodiment, the injectable dosage form of the pharmaceutical composition includes sterile aqueous solutions or dispersions and sterile powders. In some embodiments the sterile solution can include a diluent such as water; saline solution; fixed oils, polyethylene glycols, glycerin, or propylene glycol.

The iRNA molecules of the invention can be incorporated into pharmaceutical compositions. Such compositions typically include one or more species of iRNA and a pharmaceutically acceptable carrier. As used herein the language “pharmaceutically acceptable carrier” is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration to a cell, *e.g.*, a liver cell. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound,

use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Pharmaceutical compositions of the present invention include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions can be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids, and self-emulsifying semisolids. Formulations include those that target the liver.

The pharmaceutical formulations of the present invention, which can conveniently be presented in unit dosage form, can be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers.

A. Additional Formulations

i. Emulsions

The compositions of the present invention can be prepared and formulated as emulsions. Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1 μm in diameter (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi *et al.*, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 301). Emulsions are often biphasic systems comprising two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions can be of either the water-in-oil (w/o) or the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase, the resulting composition is called a water-in-oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase, the resulting composition is called an oil-in-water (o/w) emulsion. Emulsions can contain additional components in addition to the dispersed phases, and the active drug which can be present as a solution either in the aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants can also be present in emulsions as needed. Pharmaceutical emulsions can also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o) and water-in-oil-in-water (w/o/w) emulsions. Such complex formulations often provide certain advantages that simple binary emulsions

do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion. Likewise a system of oil droplets enclosed in globules of water stabilized in an oily continuous phase provides an o/w/o emulsion.

Emulsions are characterized by little or no thermodynamic stability. Often, the dispersed or discontinuous phase of the emulsion is well dispersed into the external or continuous phase and maintained in this form through the means of emulsifiers or the viscosity of the formulation. Other means of stabilizing emulsions entail the use of emulsifiers that can be incorporated into either phase of the emulsion. Emulsifiers can broadly be classified into four categories: synthetic surfactants, naturally occurring emulsifiers, absorption bases, and finely dispersed solids (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Synthetic surfactants, also known as surface active agents, have found wide applicability in the formulation of emulsions and have been reviewed in the literature (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rieger, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), Marcel Dekker, Inc., New York, N.Y., 1988, volume 1, p. 199). Surfactants are typically amphiphilic and comprise a hydrophilic and a hydrophobic portion. The ratio of the hydrophilic to the hydrophobic nature of the surfactant has been termed the hydrophile/lipophile balance (HLB) and is a valuable tool in categorizing and selecting surfactants in the preparation of formulations. Surfactants can be classified into different classes based on the nature of the hydrophilic group: nonionic, anionic, cationic, and amphoteric (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rieger, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285).

A large variety of non-emulsifying materials are also included in emulsion formulations and contribute to the properties of emulsions. These include fats, oils, waxes, fatty acids, fatty alcohols, fatty esters, humectants, hydrophilic colloids, preservatives, and antioxidants (Block, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

The application of emulsion formulations *via* dermatological, oral, and parenteral routes, and methods for their manufacture have been reviewed in the literature (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004,

Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

ii. Microemulsions

5 In one embodiment of the present invention, the compositions of iRNAs and nucleic acids are formulated as microemulsions. A microemulsion can be defined as a system of water, oil, and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution (see *e.g.*, Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in
10 *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Typically microemulsions are systems that are prepared by first dispersing an oil in an aqueous surfactant solution and then adding a sufficient amount of a fourth component, generally an intermediate chain-length alcohol to form a transparent system. Therefore, microemulsions have also been described as thermodynamically stable, isotropically clear dispersions
15 of two immiscible liquids that are stabilized by interfacial films of surface-active molecules (Leung and Shah, in: *Controlled Release of Drugs: Polymers and Aggregate Systems*, Rosoff, M., Ed., 1989, VCH Publishers, New York, pages 185-215).

iii. Microparticles

20 An iRNA of the invention may be incorporated into a particle, *e.g.*, a microparticle. Microparticles can be produced by spray-drying, but may also be produced by other methods including lyophilization, evaporation, fluid bed drying, vacuum drying, or a combination of these techniques.

25 *iv. Penetration Enhancers*

In one embodiment, the present invention employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly iRNAs, to the skin of animals. Most drugs are present in solution in both ionized and nonionized forms. However, usually only lipid soluble or lipophilic drugs readily cross cell membranes. It has been discovered that even non-lipophilic drugs can cross
30 cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs.

Penetration enhancers can be classified as belonging to one of five broad categories, *i.e.*, surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (see *e.g.*,
35 Malmsten, M. *Surfactants and polymers in drug delivery*, Informa Health Care, New York, NY, 2002; Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p.92). Each of the above

mentioned classes of penetration enhancers and their use in manufacture of pharmaceutical compositions and delivery of pharmaceutical agents are well known in the art.

v. Excipients

5 In contrast to a carrier compound, a “pharmaceutical carrier” or “excipient” is a pharmaceutically acceptable solvent, suspending agent, or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient can be liquid or solid and is selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, etc., when combined with a nucleic acid and the other components of a given
10 pharmaceutical composition. Such agent are well known in the art.

vi. Other Components

The compositions of the present invention can additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for
15 example, the compositions can contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or can contain additional materials useful in physically formulating various dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the
20 biological activities of the components of the compositions of the present invention. The formulations can be sterilized and, if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings, or aromatic substances, and the like which do not deleteriously interact with the nucleic acid(s) of the formulation.

25 Aqueous suspensions can contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol, or dextran. The suspension can also contain stabilizers.

In some embodiments, pharmaceutical compositions featured in the invention include (a) one or more iRNA and (b) one or more agents which function by a non-iRNA mechanism and which are
30 useful in treating an AGT-associated disorder, *e.g.*, hypertension.

Toxicity and prophylactic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose prophylactically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it
35 can be expressed as the ratio LD50/ED50. Compounds that exhibit high therapeutic indices are preferred.

The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of compositions featured herein in the invention lies generally within a range of circulating concentrations that include the ED50, such as, an ED80 or ED90, with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the methods featured in the invention, the prophylactically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range of the compound or, when appropriate, of the polypeptide product of a target sequence (*e.g.*, achieving a decreased concentration of the polypeptide) that includes the IC50 (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) or higher levels of inhibition as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography.

In addition to their administration, as discussed above, the iRNAs featured in the invention can be administered in combination with other known agents used for the prevention or treatment of an AGT-associated disorder, *e.g.*, hypertension. In any event, the administering physician can adjust the amount and timing of iRNA administration on the basis of results observed using standard measures of efficacy known in the art or described herein.

VI. Methods For Inhibiting AGT Expression

The present invention also provides methods of inhibiting expression of an AGT gene in a cell. The methods include contacting a cell with an RNAi agent, *e.g.*, double stranded RNA agent, in an amount effective to inhibit expression of AGT in the cell, thereby inhibiting expression of AGT in the cell. In some embodiments of the disclosure, expression of an AGT gene is inhibited preferentially in the liver (*e.g.*, hepatocytes).

Contacting of a cell with an iRNA, *e.g.*, a double stranded RNA agent, may be done *in vitro* or *in vivo*. Contacting a cell *in vivo* with the iRNA includes contacting a cell or group of cells within a subject, *e.g.*, a human subject, with the iRNA. Combinations of *in vitro* and *in vivo* methods of contacting a cell are also possible. Contacting a cell may be direct or indirect, as discussed above. Furthermore, contacting a cell may be accomplished *via* a targeting ligand, including any ligand described herein or known in the art. In some embodiments, the targeting ligand is a carbohydrate moiety, *e.g.*, a GalNAc₃ ligand, or any other ligand that directs the RNAi agent to a site of interest.

The term “inhibiting,” as used herein, is used interchangeably with “reducing,” “silencing,” “downregulating”, “suppressing”, and other similar terms, and includes any level of inhibition.

The phrase “inhibiting expression of an AGT” is intended to refer to inhibition of expression of any AGT gene (such as, *e.g.*, a mouse AGT gene, a rat AGT gene, a monkey AGT gene, or a human AGT gene) as well as variants or mutants of an AGT gene. Thus, the AGT gene may be a

wild-type AGT gene, a mutant AGT gene, or a transgenic AGT gene in the context of a genetically manipulated cell, group of cells, or organism.

“Inhibiting expression of an AGT gene” includes any level of inhibition of an AGT gene, *e.g.*, at least partial suppression of the expression of an AGT gene. The expression of the AGT gene may be assessed based on the level, or the change in the level, of any variable associated with AGT gene expression, *e.g.*, AGT mRNA level or AGT protein level. This level may be assessed in an individual cell or in a group of cells, including, for example, a sample derived from a subject.

Inhibition may be assessed by a decrease in an absolute or relative level of one or more variables that are associated with AGT expression compared with a control level. The control level may be any type of control level that is utilized in the art, *e.g.*, a pre-dose baseline level, or a level determined from a similar subject, cell, or sample that is untreated or treated with a control (such as, *e.g.*, buffer only control or inactive agent control).

In some embodiments of the methods of the invention, expression of an AGT gene is inhibited by at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or to below the level of detection of the assay. In some embodiments, expression of an AGT gene is inhibited by at least 70%. It is further understood that inhibition of AGT expression in certain tissues, *e.g.*, in liver, without a significant inhibition of expression in other tissues, *e.g.*, brain, may be desirable. In some embodiments, expression level is determined using the assay method provided in Example 2 with a 10 nM siRNA concentration in the appropriate species matched cell line.

In certain embodiments, inhibition of expression *in vivo* is determined by knockdown of the human gene in a rodent expressing the human gene, *e.g.*, an AAV-infected mouse expressing the human target gene (*i.e.*, AGT), *e.g.*, when administered as a single dose, *e.g.*, at 3 mg/kg at the nadir of RNA expression. Knockdown of expression of an endogenous gene in a model animal system can also be determined, *e.g.*, after administration of a single dose at, *e.g.*, 3 mg/kg at the nadir of RNA expression. Such systems are useful when the nucleic acid sequence of the human gene and the model animal gene are sufficiently close such that the human iRNA provides effective knockdown of the model animal gene. RNA expression in liver is determined using the PCR methods provided in Example 2.

Inhibition of the expression of an AGT gene may be manifested by a reduction of the amount of mRNA expressed by a first cell or group of cells (such cells may be present, for example, in a sample derived from a subject) in which an AGT gene is transcribed and which has or have been treated (*e.g.*, by contacting the cell or cells with an iRNA of the invention, or by administering an iRNA of the invention to a subject in which the cells are or were present) such that the expression of an AGT gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has not or have not been so treated (control cell(s) not treated with an iRNA or not treated with an iRNA targeted to the gene of interest). In some embodiments, the inhibition is assessed by the method provided in Example 2 using a 10nM siRNA concentration in

the species matched cell line and expressing the level of mRNA in treated cells as a percentage of the level of mRNA in control cells, using the following formula:

$$\frac{(\text{mRNA in control cells}) - (\text{mRNA in treated cells})}{(\text{mRNA in control cells})} \bullet 100\%$$

In other embodiments, inhibition of the expression of an AGT gene may be assessed in terms of a reduction of a parameter that is functionally linked to AGT gene expression, *e.g.*, AGT protein level in blood or serum from a subject. AGT gene silencing may be determined in any cell expressing AGT, either endogenous or heterologous from an expression construct, and by any assay known in the art.

Inhibition of the expression of an AGT protein may be manifested by a reduction in the level of the AGT protein that is expressed by a cell or group of cells or in a subject sample (*e.g.*, the level of protein in a blood sample derived from a subject). As explained above, for the assessment of mRNA suppression, the inhibition of protein expression levels in a treated cell or group of cells may similarly be expressed as a percentage of the level of protein in a control cell or group of cells, or the change in the level of protein in a subject sample, *e.g.*, blood or serum derived therefrom.

A control cell, a group of cells, or subject sample that may be used to assess the inhibition of the expression of an AGT gene includes a cell, group of cells, or subject sample that has not yet been contacted with an RNAi agent of the invention. For example, the control cell, group of cells, or subject sample may be derived from an individual subject (*e.g.*, a human or animal subject) prior to treatment of the subject with an RNAi agent or an appropriately matched population control.

The level of AGT mRNA that is expressed by a cell or group of cells may be determined using any method known in the art for assessing mRNA expression. In one embodiment, the level of expression of AGT in a sample is determined by detecting a transcribed polynucleotide, or portion thereof, *e.g.*, mRNA of the AGT gene. RNA may be extracted from cells using RNA extraction techniques including, for example, using acid phenol/guanidine isothiocyanate extraction (RNAzol B; Biogenesis), RNeasyTM RNA preparation kits (Qiagen®) or PAXgeneTM (PreAnalytixTM, Switzerland). Typical assay formats utilizing ribonucleic acid hybridization include nuclear run-on assays, RT-PCR, RNase protection assays, northern blotting, *in situ* hybridization, and microarray analysis.

In some embodiments, the level of expression of AGT is determined using a nucleic acid probe. The term “probe”, as used herein, refers to any molecule that is capable of selectively binding to a specific AGT. Probes can be synthesized by one of skill in the art, or derived from appropriate biological preparations. Probes may be specifically designed to be labeled. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

Isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or northern analyses, polymerase chain reaction (PCR) analyses and probe arrays.

One method for the determination of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to AGT mRNA. In one embodiment, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as

nitrocellulose. In an alternative embodiment, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix® gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in determining the level of AGT mRNA.

An alternative method for determining the level of expression of AGT in a sample involves the process of nucleic acid amplification or reverse transcriptase (to prepare cDNA) of for example mRNA in the sample, *e.g.*, by RT-PCR (the experimental embodiment set forth in Mullis, 1987, U.S. Patent No. 4,683,202), ligase chain reaction (Barany (1991) *Proc. Natl. Acad. Sci. USA* 88:189-193), self sustained sequence replication (Guatelli *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.* (1988) *Bio/Technology* 6:1197), rolling circle replication (Lizardi *et al.*, U.S. Patent No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. In particular aspects of the invention, the level of expression of AGT is determined by quantitative fluorogenic RT-PCR (*i.e.*, the TaqMan™ System). In some embodiments, expression level is determined by the method provided in Example 2 using, *e.g.*, a 10 nM siRNA concentration, in the species matched cell line.

The expression levels of AGT mRNA may be monitored using a membrane blot (such as used in hybridization analysis such as northern, Southern, dot, and the like), or microwells, sample tubes, gels, beads or fibers (or any solid support comprising bound nucleic acids). See U.S. Patent Nos. 5,770,722, 5,874,219, 5,744,305, 5,677,195 and 5,445,934, which are incorporated herein by reference. The determination of AGT expression level may also comprise using nucleic acid probes in solution.

In some embodiments, the level of mRNA expression is assessed using branched DNA (bDNA) assays or real time PCR (qPCR). The use of these methods is described and exemplified in the Examples presented herein. In some embodiments, expression level is determined by the method provided in Example 2 using a 10nM siRNA concentration in the species matched cell line.

The level of AGT protein expression may be determined using any method known in the art for the measurement of protein levels. Such methods include, for example, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, fluid or gel precipitin reactions, absorption spectroscopy, a colorimetric assays, spectrophotometric assays, flow cytometry, immunodiffusion (single or double),

immunoelectrophoresis, western blotting, radioimmunoassay (RIA), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays, electrochemiluminescence assays, and the like.

In some embodiments, the efficacy of the methods of the invention are assessed by a decrease in AGT mRNA or protein level (*e.g.*, in a liver biopsy).

5 In some embodiments, the efficacy of the methods of the invention can be monitored by detecting or monitoring a reduction in a symptom of an AGT-associate disorder. It is well within the ability of one skilled in the art to monitor efficacy of the methods by measuring any one of such parameters, or any combination of parameters.

10 In some embodiments of the methods of the invention, the iRNA is administered to a subject such that the iRNA is delivered to a specific site within the subject. The inhibition of expression of AGT may be assessed using measurements of the level or change in the level of AGT mRNA or AGT protein in a sample derived from fluid or tissue from the specific site within the subject (*e.g.*, liver or blood).

15 As used herein, the terms detecting or determining a level of an analyte are understood to mean performing the steps to determine if a material, *e.g.*, protein, RNA, is present. As used herein, methods of detecting or determining include detection or determination of an analyte level that is below the level of detection for the method used.

VII. Prophylactic and Treatment Methods of the Invention

20 The present invention also provides methods of using an iRNA of the invention or a composition containing an iRNA of the invention to inhibit expression of AGT, thereby preventing or treating an AGT-associated disorder, *e.g.*, hypertension. In the methods of the invention the cell may be contacted with the siRNA *in vitro* or *in vivo*, *i.e.*, the cell may be within a subject.

25 A cell suitable for treatment using the methods of the invention may be any cell that expresses an AGT gene, *e.g.*, a liver cell. A cell suitable for use in the methods of the invention may be a mammalian cell, *e.g.*, a primate cell (such as a human cell, including human cell in a chimeric non-human animal, or a non-human primate cell, *e.g.*, a monkey cell or a chimpanzee cell), or a non-primate cell. In certain embodiments, the cell is a human cell, *e.g.*, a human liver cell. In the methods of the invention, AGT expression is inhibited in the cell by at least 50, 55, 60, 65, 70, 75, 80, 85, 90, 30 or 95, or to a level below the level of detection of the assay.

The *in vivo* methods of the invention may include administering to a subject a composition containing an iRNA, where the iRNA includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of the AGT gene of the mammal to which the RNAi agent is to be administered. The composition can be administered by any means known in the art including, but not 35 limited to oral, intraperitoneal, or parenteral routes, including intracranial (*e.g.*, intraventricular, intraparenchymal, and intrathecal), intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), nasal, rectal, intraocular (*e.g.*, periocular, conjunctival, subtenon, intracameral, intravitreal,

intraocular, anterior or posterior juxtasceral, subretinal, subconjunctival, retrobulbar, or intracranial injection), intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), and topical (including buccal and sublingual) administration.

In certain embodiments, the compositions are administered by intravenous infusion or injection. In certain embodiments, the compositions are administered by subcutaneous injection. In certain embodiments, the compositions are administered by intramuscular injection.

The mode of administration may be chosen based upon whether local or systemic treatment is desired and based upon the area to be treated. The route and site of administration may be chosen to enhance targeting.

In one aspect, the present invention also provides methods for inhibiting the expression of an AGT gene in a mammal. The methods include administering to the mammal a composition comprising a dsRNA that targets an AGT gene in a cell of the mammal and maintaining the mammal for a time sufficient to obtain degradation of the mRNA transcript of the AGT gene, thereby inhibiting expression of the AGT gene in the cell. Reduction in gene expression can be assessed by any methods known in the art and by methods, *e.g.* qRT-PCR, described herein, *e.g.*, in Example 2. Reduction in protein production can be assessed by any methods known in the art, *e.g.* ELISA. In certain embodiments, a puncture liver biopsy sample serves as the tissue material for monitoring the reduction in the AGT gene or protein expression. In other embodiments, a blood sample serves as the subject sample for monitoring the reduction in the AGT protein expression.

The present invention further provides methods of treatment in a subject in need thereof, *e.g.*, a subject diagnosed with an AGT-associated disorder, such as hypertension.

The present invention further provides methods of prophylaxis in a subject in need thereof. The treatment methods of the invention include administering an iRNA of the invention to a subject, *e.g.*, a subject that would benefit from a reduction of AGT expression, in a prophylactically effective amount of a dsRNA targeting an AGT gene or a pharmaceutical composition comprising a dsRNA targeting an AGT gene.

In one aspect, the present invention provides methods of treating a subject having a disorder that would benefit from reduction in AGT expression, *e.g.*, an AGT-associated disorder, such as high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, hypertension associated with low plasma renin activity or plasma renin concentration, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal

disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR) , fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome.

In some embodiments, the RNAi agent is administered to a subject in an amount effective to inhibit AGT expression in a cell within the subject. The amount effective to inhibit AGT expression in a cell within a subject may be assessed using methods discussed above, including methods that involve assessment of the inhibition of AGT mRNA, AGT protein, or related variables, such as a reduction in the severity of a symptom of an AGT-associate disorder, *e.g.*, reduction in the severity of edema swelling of the extremities, face, larynx, upper respiratory tract, abdomen, trunk, and genitals, prodrome; laryngeal swelling; nonpruritic rash; nausea; vomiting; or abdominal pain.

An iRNA of the invention may be administered as a “free iRNA.” A free iRNA is administered in the absence of a pharmaceutical composition. The naked iRNA may be in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolarity of the buffer solution containing the iRNA can be adjusted such that it is suitable for administering to a subject.

Alternatively, an iRNA of the invention may be administered as a pharmaceutical composition, such as a dsRNA liposomal formulation.

Subjects that would benefit from an inhibition of AGT gene expression are subjects susceptible to or diagnosed with an AGT-associated disorder, such as high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, hypertension associated with low plasma renin activity or plasma renin concentration, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR) , fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome. In an embodiment, the method includes administering a composition featured herein such that expression of the target ab AGT gene is decreased, such as for about 1, 2, 3, 4, 5, 6, 1-6, 1-3, or 3-6 months per dose. In certain embodiments, the composition is administered once every 3-6 months.

In one embodiment, the iRNAs useful for the methods and compositions featured herein specifically target RNAs (primary or processed) of the target AGT gene. Compositions and methods for inhibiting the expression of these genes using iRNAs can be prepared and performed as described herein.

Administration of the iRNA according to the methods of the invention may result prevention or treatment of an AGT-associated disorder, *e.g.*, high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, hypertension associated with low plasma renin activity or plasma renin concentration, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR), fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome. Subjects can be administered a therapeutic amount of iRNA, such as about 0.01 mg/kg to about 200 mg/kg.

In one embodiment, the iRNA is administered subcutaneously, *i.e.*, by subcutaneous injection. One or more injections may be used to deliver the desired dose of iRNA to a subject. The injections may be repeated over a period of time.

The administration may be repeated on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. A repeat-dose regimen may include administration of a therapeutic amount of iRNA on a regular basis, such as once per month to once a year. In certain embodiments, the iRNA is administered about once per month to about once every three months, or about once every three months to about once every six months.

The invention further provides methods and uses of an iRNA agent or a pharmaceutical composition thereof for treating a subject that would benefit from reduction and/or inhibition of AGT gene expression, *e.g.*, a subject having an AGT-associated disorder, in combination with other pharmaceuticals and/or other therapeutic methods, *e.g.*, with known pharmaceuticals and/or known therapeutic methods, such as, for example, those which are currently employed for treating these disorders.

Accordingly, in some aspects of the invention, the methods which include administration of an iRNA agent of the invention, further include administering to the subject one or more additional therapeutic agents. For example, in certain embodiments, an iRNA targeting AGT is administered in

combination with, *e.g.*, a diuretic, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a beta-blocker, a vasodilator, a calcium channel blocker, an aldosterone antagonist, an alpha2-agonist, a renin inhibitor, an alpha-blocker, a peripheral acting adrenergic agent, a selective D1 receptor partial agonist, a nonselective alpha-adrenergic antagonist, a synthetic, a steroidal antimineralocorticoid agent, an angiotensin receptor-neprilysin inhibitors (ARNi), Entresto®, sacubitril/valsartan; or an endothelin receptor antagonist (ERA), sitaxentan, ambrisentan, atrasentan, BQ-123, zibotentan, bosentan, macitentan, and tezosentan; a combination of any of the foregoing; and a hypertension therapeutic agent formulated as a combination of agents.

The iRNA and additional therapeutic agents may be administered at the same time and/or in the same combination, *e.g.*, parenterally, or the additional therapeutic agent can be administered as part of a separate composition or at separate times and/or by another method known in the art or described herein.

The iRNA agent and an additional therapeutic agent and/or treatment may be administered at the same time and/or in the same combination, *e.g.*, parenterally, or the additional therapeutic agent can be administered as part of a separate composition or at separate times and/or by another method known in the art or described herein.

A. *Diagnostic Criteria, Risk Factors, and Treatments for Hypertension*

Recently practice guidelines for prevention and treatment of hypertension were revised. Extensive reports were published by Reboussin *et al.* (Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7. pii: S0735-1097(17)41517-8. doi: 10.1016/j.jacc.2017.11.004.) and Whelton *et al.* (2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7. pii: S0735-1097(17)41519-1. doi: 10.1016/j.jacc.2017.11.006.). Some highlights of the new Guidelines are provided below. However, the Guidelines should be understood as providing the knowledge of those of skill in the art regarding diagnostic and monitoring criteria and treatment for hypertension at the time of filing of this application and are incorporated herein by reference.

1. Diagnostic Criteria

Although a continuous association exists between higher blood pressure and increased cardiovascular disease risk, it is useful to categorize blood pressure levels for clinical and public health decision making. Blood pressure can be categorized into 4 levels on the basis of average blood

pressure measured in a healthcare setting (office pressures): normal, elevated, and stage 1 or 2 hypertension as shown in the table below (from Whelton *et al.*, 2017).

Blood Pressure Category	Systolic Blood Pressure		Diastolic Blood Pressure
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120-129 mm Hg	and	<80 mm Hg
Hypertension*			
Stage 1	130-139 mm Hg	or	80-89 mm Hg
Stage 2	≥ 140 mm Hg	or	≥ 90 mm Hg

*Individuals with systolic blood pressure and diastolic blood pressure in 2 categories should be designated to the higher blood pressure category.

Blood pressure indicates blood pressure based on an average of ≥ 2 careful readings obtained on ≥ 2 occasions. Best practices for obtaining careful blood pressure readings are detailed in Whelton *et al.*, 2017 and are known in the art.

This categorization differs from that previously recommended in the JNC 7 report (Chobanian *et al.*; the National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-52) with stage 1 hypertension now defined as a systolic blood pressure (SBP) of 130–139 or a diastolic blood pressure (DBP) of 80–89 mm Hg, and with stage 2 hypertension in the present document corresponding to stages 1 and 2 in the JNC 7 report. The rationale for this categorization is based on observational data related to the association between SBP/DBP and cardiovascular disease risk, randomized clinical trials of lifestyle modification to lower blood pressure, and randomized clinical trials of treatment with antihypertensive medication to prevent cardiovascular disease.

The increased risk of cardiovascular disease among adults with stage 2 hypertension is well established. An increasing number of individual studies and meta-analyses of observational data have reported a gradient of progressively higher cardiovascular disease risk going from normal blood pressure to elevated blood pressure and stage 1 hypertension. In many of these meta-analyses, the hazard ratios for coronary heart disease and stroke were between 1.1 and 1.5 for the comparison of SBP/DBP of 120–129/80–84 mm Hg versus <120/80 mm Hg and between 1.5 and 2.0 for the comparison of SBP/DBP of 130–139/85–89 mm Hg versus <120/80 mm Hg. This risk gradient was consistent across subgroups defined by sex and race/ethnicity. The relative increase in cardiovascular

disease risk associated with higher blood pressure was attenuated but still present among older adults. Lifestyle modification and pharmacological antihypertensive treatment are recommended for individuals with elevated blood pressure and stages 1 and 2 hypertension. Clinical benefit can be obtained by a reduction of the stage of elevated blood pressure, even if blood pressure is not normalized by a treatment.

2. Risk Factors

Hypertension is a complex disease that results from a combination of factors including, but not limited to, genetics, lifestyle, diet, and secondary risk factors. Hypertension can also be associated with pregnancy. It is understood that due to the complex nature of hypertension, it is understood that multiple interventions may be required for treatment of hypertension. Moreover, non-pharmacological interventions, including modification of diet and lifestyle, can be useful for the prevention and treatment of hypertension. Further, an intervention may provide a clinical benefit without fully normalizing blood pressure in an individual.

a. Genetic risk factors

Several monogenic forms of hypertension have been identified, such as glucocorticoid-remediable aldosteronism, Liddle's syndrome, Gordon's syndrome, and others in which single-gene mutations fully explain the pathophysiology of hypertension, these disorders are rare. The current tabulation of known genetic variants contributing to blood pressure and hypertension includes more than 25 rare mutations and 120 single nucleotide polymorphisms. However, although genetic factors may contribute to hypertension in some individuals, it is estimated that genetic variation accounts for only about 3.5% of blood pressure variability.

b. Diet and alcohol consumption

Common environmental and lifestyle risk factors leading to hypertension include poor diet, insufficient physical activity, and excess alcohol consumption. These factors can lead to a person to become overweight or obese, further increasing the likelihood of developing or exacerbating hypertension. Elevated blood pressure is even more strongly correlated with increased waist-to-hip ratio or other measures of central fat distribution. Obesity at a young age and ongoing obesity is strongly correlated with hypertension later in life. Achieving a normal weight can reduce the risk of developing high blood pressure to that of a person who has never been obese.

Intake of sodium, potassium, magnesium, and calcium can also have a significant effect on blood pressure. Sodium intake is positively correlated with blood pressure and accounts for much of the age-related increase in blood pressure. Certain groups are more sensitive to increased sodium consumption than others including black and older adults (≥ 65 years old), and those with a higher level of blood pressure or comorbidities such as chronic kidney disease, diabetes mellitus, or metabolic syndrome. In aggregate, these groups constitute more than half of all US adults. Salt sensitivity may be a marker for increased cardiovascular disease and all-cause mortality, independent

of blood pressure. Currently, techniques for recognition of salt sensitivity are impractical in a clinical setting. Therefore, salt sensitivity is best considered as a group characteristic.

Potassium intake is inversely related to blood pressure and stroke, and a higher level of potassium seems to blunt the effect of sodium on blood pressure. A lower sodium-potassium ratio is associated with a lower blood pressure than that noted for corresponding levels of sodium or potassium on their own. A similar observation has been made for risk of cardiovascular disease.

Alcohol consumption has long been associated with high blood pressure. In the US, it has been estimated that alcohol consumption accounts for about 10% of the population burden of hypertension, with the burden being greater in men than women.

It is understood that changes in diet or alcohol consumption can be an aspect of prevention or treatment of hypertension.

c. Physical activity

There is a well-established inverse correlation between physical activity/ physical fitness and blood pressure levels. Even modest levels of physical activity have been demonstrated to be beneficial in decreasing hypertension.

It is understood that an increase in physical activity can be an aspect of prevention or treatment of hypertension.

d. Secondary risk factors

Secondary hypertension can underlie severe elevation of blood pressure, pharmacologically resistant hypertension, sudden onset of hypertension, increased blood pressure in patients with hypertension previously controlled on drug therapy, onset of diastolic hypertension in older adults, and target organ damage disproportionate to the duration or severity of the hypertension. Although secondary hypertension should be suspected in younger patients (<30 years of age) with elevated blood pressure, it is not uncommon for primary hypertension to manifest at a younger age, especially in blacks, and some forms of secondary hypertension, such as renovascular disease, are more common at older age (≥ 65 years of age). Many of the causes of secondary hypertension are strongly associated with clinical findings or groups of findings that suggest a specific disorder. In such cases, treatment of the underlying condition may resolve the findings of elevated blood pressure without administering agents typically used for the treatment of hypertension.

e. Pregnancy

Pregnancy is a risk factor for high blood pressure, and high blood pressure during pregnancy is a risk factor for cardiovascular disease and hypertension later in life. A Report on pregnancy associated hypertension was published in 2013 by the American College of Obstetrics and Gynecology (ACOG) (American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol.* 2013;122:1122-31). Some highlights of the Report are provided below. However, the Report should

be understood as providing the knowledge of those of skill in the art regarding diagnostic and monitoring criteria and treatment for hypertension in pregnancy at the time of filing of this application and are incorporated herein by reference.'

- 5 The diagnostic criteria for preeclampsia are provided in the table below (from Table 1 of the ACOG report, 2013).

Blood Pressure	- ≥ 140 mm Hg diastolic or ≥ 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure - ≥ 160 mm Hg systolic or ≥ 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
and	
Proteinuria	- ≥ 300 mg per 24-hour urine collection (or this amount extrapolated for a timed collection) Or - Protein/ creatinine ratio ≥ 0.3 (each measured as mg/dL)
Or in the absence of proteinuria, new onset of hypertension with the new onset of an of the following:	
Thrombocytopenia	- Platelet count $\leq 100,000$ /microliter
Renal insufficiency	- Serum creatinine concentration ≥ 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
Impaired liver function	- Elevated blood concentrations of liver transaminases to twice normal concentration
Pulmonary edema	
Cerebral or visual symptoms	

Blood Pressure management during pregnancy is complicated by the fact that many commonly used antihypertensive agents, including ACE inhibitors and ARBs, are contraindicated

during pregnancy because of potential harm to the fetus. The goal of antihypertensive treatment during pregnancy includes prevention of severe hypertension and the possibility of prolonging gestation to allow the fetus more time to mature before delivery. A review of treatment for pregnancy-associated severe hypertension found insufficient evidence to recommend specific agents; rather, clinician experience was recommended in this setting (Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev. 2013;7:CD001449.).

3. Treatments

Treatment of high blood pressure is complex as it is frequently present with other comorbidities, often including reduced renal function, for which the subject may also be undergoing treatment. Clinicians managing adults with high blood pressure should focus on overall patient health, with a particular emphasis on reducing the risk of future adverse cardiovascular disease outcomes. All patient risk factors need to be managed in an integrated fashion with a comprehensive set of nonpharmacological and pharmacological strategies. As patient blood pressure and risk of future cardiovascular disease events increase, blood pressure management should be intensified.

Whereas treatment of high blood pressure with blood pressure-lowering medications on the basis of blood pressure level alone is considered cost effective, use of a combination of absolute cardiovascular disease risk and blood pressure level to guide such treatment is more efficient and cost effective at reducing risk of cardiovascular disease than is use of blood pressure level alone. Many patients started on a single agent will subsequently require ≥ 2 drugs from different pharmacological classes to reach their blood pressure goals. Knowledge of the pharmacological mechanisms of action of each agent is important. Drug regimens with complementary activity, where a second antihypertensive agent is used to block compensatory responses to the initial agent or affect a different pressor mechanism, can result in additive lowering of blood pressure. For example, thiazide diuretics may stimulate the renin-angiotensin-aldosterone system. By adding an ACE inhibitor or ARB to the thiazide, an additive blood pressure lowering effect may be obtained. Use of combination therapy may also improve adherence. Several 2- and 3-fixed-dose drug combinations of antihypertensive drug therapy are available, with complementary mechanisms of action among the components.

Table 18 from Whelton *et al.* 2017 listing oral antihypertensive drugs is provided below. Classes of therapeutic agents for the treatment of high blood pressure and drugs that fall within those classes are provided. Dose ranges, frequencies, and comments are also provided.

Class	Drug	Usual Dose, Range (mg/d)*	Daily Frequency	Comments
Primary agents				

Thiazide or thiazide-type diuretics	Chlorthalidone	12.5-25	1	- Chlorthalidone is preferred on the basis of prolonged half-life and proven trial reduction of CVD. - Monitor for hyponatremia and hypokalemia, uric acid and calcium levels. - Use with caution in patients with history of acute gout unless patient is on uric acid-lowering therapy.
	Hydrochlorothiazide	25-50	1	
	Indapamide	1.25-2.5	1	
	Metolazone	2.5-10	1	
ACE inhibitors	Benazepril	10-40	1 or 2	- Do not use in combination with ARBs or direct renin inhibitor - There is an increased risk of hyperkalemia, especially in patents with CKD or in those on K⁺ supplements or K⁺-sparing drugs. - There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. - Do not use if patient has history of angioedema with ACE inhibitors. - Avoid in pregnancy.
	Captopril	12.5-150	2 or 3	
	Enalapril	5-40	1 or 2	
	Fosinopril	10-40	1	
	Lisinopril	10-40	1	
	Moexipril	7.5-30	1 or 2	
	Perindopril	4-16	1	
	Quinapril	10-80	1 or 2	
	Ramipril	2.5-10	1 or 2	
	Trandolapril	1-4	1	
ARBs	Azilsartan	40-80	1	- Do not use in combination with ACE inhibitors or direct renin inhibitors. - There is an increased risk of hyperkalemia in CKD or in those on K⁺ supplements or K⁺-sparing drugs. - There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. - Do not use if patient has history of angioedema with ARBs. Patients with a history of angioedema with an ACE inhibitor can receive an ARB beginning 6 weeks after ACE inhibitor is discontinued. - Avoid in pregnancy.
	Candesartan	8-32	1	
	Eprosartan	600-800	1 or 2	
	Irbesartan	150-300	1	
	Losartan	50-100	1 or 2	
	Olmesartan	20-40	1	
	Telmisartan	20-80	1	
	Valsartan	80-320	1	
CCB-dihydropyridines	Amlodipine	2.5-10	1	- Avoid use in patients with HFrEF; amlodipine or felodipine may be used if required - They are associated with dose-related pedal edema,
	Felodipine	5-10	1	
	Isradipine	5-10	2	
	Nicardipine SR	5-20	1	
	Nifedipine LA	60-120	1	

	Nisoldipine	30-90	1	which is more common in women than men.
CCB-nondihydropyridines	Diltiazem SR	180-360	2	• Avoid routine use with beta blockers because of increased risk of bradycardia and heart block. • Do not use in patients with HF_rEF. • There are drug interactions with diltiazem and verapamil (<i>CYP3A4</i> major substrate and moderate inhibitor).
	Diltiazem ER	120-480	1	
	Verapamil IR	40-80	3	
	Verapamil SR	120-480	1 or 2	
	Verapamil-delayed onset ER (various forms)	100-480	1 (in the evening)	
Secondary agents				
Diuretics-loop	Bumetanide	0.5-4	2	• There are preferred diuretics in patients with symptomatic HF. They are preferred over thiazides in patients with moderate-to-severe CKD (e.g., GFR <30 mL/min).
	Furosemide	20-80	2	
	Torsemide	5-10	1	
Diuretics-potassium sparing	Amiloride	5-10	1 or 2	• These are monotherapy agents and minimally effective antihypertensive agents. • Combination therapy of potassium-sparing diuretic with a thiazide can be considered in patients with hypokalemia on thiazide monotherapy. • Avoid in patients with significant CKD (e.g. GFR <45 mL/min).
	Triamterene	50-100	1 or 2	
Diuretics-aldosterone antagonists	Eplerenone	50-100	12	• These are preferred agents in primary aldosteronism and resistant hypertension. • Spironolactone is associated with greater risk of gynecomastia and impotence as compared with eplerenone. • This is common add-on therapy in resistant hypertension. • Avoid use with K⁺ supplements, other K⁺-sparing diuretics, or significant renal dysfunction. • Eplerenone often requires twice-daily dosing for adequate BP lowering.
	Spironolactone	25-100	1	

Beta blockers-cardioselective	Atenolol	25-100	12	- Beta blockers are not recommended as first-line agents unless the patient has IHD or HF. - These are preferred in patients with bronchospastic airway disease requiring a beta blocker. - Bisoprolol and metoprolol succinate are preferred in patients with HF$\neq$EF. - Avoid abrupt cessation.
	Betaxolol	5-20	1	
	Bisoprolol	2.5-10	1	
	Metoprolol tartrate	100-400	2	
	Metoprolol succinate	50-200	1	
Beta blockers-cardioselective and vasodilatory	Nebivolol	5-40	1	- Nebivolol induces nitric oxide-induced vasodilation. - Avoid abrupt cessation.
Beta blockers-noncardioselective	Nadolol	40-120	1	- Avoid in patients with reactive airways disease. - Avoid abrupt cessation.
	Propranolol IR	160-480	2	
	Propranolol LA	80-320	1	
Beta blockers-intrinsic sympathomimetic activity	Acebutolol	200-800	2	- Generally avoid, especially in patients with IHD or HF. - Avoid abrupt cessation.
	Carteolol	2.5-10	1	
	Penbutolol	10-40	1	
	Pindolol	10-60	2	
Beta blockers-combined alpha-and beta receptor	Carvedilol	12.5-50	2	- Carvedilol is preferred in patients with HF$\neq$EF. - Avoid abrupt cessation.
	Carvedilol phosphate	20-80	1	
	Labetalol	200-800	2	
Direct renin inhibitor	Aliskiren	150-300	1	- Do not use in combination with ACE inhibitors or ARBs. - Aliskiren is very long acting. - There is an increased risk of hyperkalemia in CKD or in those on K⁺ supplements or K⁺-sparing drugs. - Aliskiren may cause acute renal failure in patients with severe bilateral renal artery stenosis. - Avoid in pregnancy.
Alpha-1-blockers	Doxazosin	1-8	1	These are associated with orthostatic hypotension, especially in older adults.
	Prazosin	2-20	2 or 3	

	Terazosin	1-20	1 or 2	They may be considered as second-line agent in patients with concomitant BPH.
Central α_1 -agonist and other centrally acting drugs	Clonidine oral	0.1-0.8	2	- These are generally reserved as last-line because of significant CNS adverse effects, especially in older adults. - Avoid abrupt discontinuation of clonidine, which may induce hypertensive crisis; clonidine must be tapered to avoid rebound hypertension.
	Clonidine patch	0.1-0.3	1 weekly	
	Methyldopa	250-1000	2	
	Guanfacine	0.5-2	1	
Direct vasodilators	Hydralazine	250-200	2 or 3	- These are associated with sodium and water retention and reflex tachycardia; use with a diuretic and beta blocker. - Hydralazine is associated with drug-induced lupus-like syndrome at higher doses. - Minoxidil is associated with hirsutism and required a loop diuretic. Minoxidil can induce pericardial effusion.
	Minoxidil	5-100	1-3	

*Dosages may vary from those listed in the FDA approved labeling (available at <https://dailymed.nlm.nih.gov/dailymed/>). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; BPH, benign prostatic hyperplasia; CCB, calcium channel blocker; CKD, chronic kidney disease; CNS, central nervous system; CVD, cardiovascular disease; ER, extended release; GFR, glomerular filtration rate; HF, heart failure; HF_rEF, heart failure with reduced ejection fraction; IHD, ischemic heart disease; IR, immediate release; LA, long-acting; and SR, sustained release.

From, Chobanian *et al.* (2003) The JNC 7 Report. *JAMA* 289(19):2560.

VIII. Kits

In certain aspects, the instant disclosure provides kits that include a suitable container containing a pharmaceutical formulation of a siRNA compound, *e.g.*, a double-stranded siRNA compound, or siRNA compound, (*e.g.*, a precursor, *e.g.*, a larger siRNA compound which can be processed into a siRNA compound, or a DNA which encodes an siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, or precursor thereof).

Such kits include one or more dsRNA agent(s) and instructions for use, *e.g.*, instructions for administering a prophylactically or therapeutically effective amount of a dsRNA agent(s). The dsRNA agent may be in a vial or a pre-filled syringe. The kits may optionally further comprise means for administering the dsRNA agent (*e.g.*, an injection device, such as a pre-filled syringe), or means for measuring the inhibition of AGT (*e.g.*, means for measuring the inhibition of AGT mRNA, AGT protein, and/or AGT activity). Such means for measuring the inhibition of AGT may comprise a

means for obtaining a sample from a subject, such as, *e.g.*, a plasma sample. The kits of the invention may optionally further comprise means for determining the therapeutically effective or prophylactically effective amount.

In certain embodiments the individual components of the pharmaceutical formulation may be provided in one container, *e.g.*, a vial or a pre-filled syringe. Alternatively, it may be desirable to provide the components of the pharmaceutical formulation separately in two or more containers, *e.g.*, one container for a siRNA compound preparation, and at least another for a carrier compound. The kit may be packaged in a number of different configurations such as one or more containers in a single box. The different components can be combined, *e.g.*, according to instructions provided with the kit. The components can be combined according to a method described herein, *e.g.*, to prepare and administer a pharmaceutical composition. The kit can also include a delivery device.

This invention is further illustrated by the following examples which should not be construed as limiting. The entire contents of all references, patents and published patent applications cited throughout this application, as well as the informal Sequence Listing and Figures, are hereby incorporated herein by reference.

EXAMPLES

Example 1. iRNA Synthesis

Source of reagents

Where the source of a reagent is not specifically given herein, such reagent can be obtained from any supplier of reagents for molecular biology at a quality/purity standard for application in molecular biology.

siRNA Design

siRNAs targeting the human angiotensinogen (AGT) gene (human: GenBank NM_001384479.1 or NM_000029.3, NCBI GeneID: 183) were designed using custom R and Python scripts. The human NM_001384479.1 REFSEQ mRNA, has a length of 2116 bases and the human NM_000029.3 REFSEQ mRNA, has a length of 2587 bases.

Detailed lists of the unmodified AGT sense and antisense strand nucleotide sequences are shown in Tables 2 and 4. Detailed lists of the modified AGT sense and antisense strand nucleotide sequences are shown in Tables 3 and 5.

It is to be understood that, throughout the application, a duplex name without a decimal is equivalent to a duplex name with a decimal which merely references the batch number of the duplex. For example, AD-959917 is equivalent to AD-959917.1.

5 siRNA Synthesis

siRNAs were designed, synthesized, and prepared using methods known in the art.

Briefly, siRNA sequences were synthesized on a 1 μ mol scale using a Mermade 192 synthesizer (BioAutomation) with phosphoramidite chemistry on solid supports. The solid support was controlled pore glass (500-1000 Å) loaded with a custom GalNAc ligand (3'-GalNAc
10 conjugates), universal solid support (AM Chemicals), or the first nucleotide of interest. Ancillary synthesis reagents and standard 2-cyanoethyl phosphoramidite monomers (2'-deoxy-2'-fluoro, 2'-O-methyl, RNA, DNA) were obtained from Thermo-Fisher (Milwaukee, WI), Hongene (China), or Chemgenes (Wilmington, MA, USA). Additional phosphoramidite monomers were procured from commercial suppliers, prepared in-house, or procured using custom synthesis from various CMOs.
15 Phosphoramidites were prepared at a concentration of 100 mM in either acetonitrile or 9:1 acetonitrile:DMF and were coupled using 5-Ethylthio-1H-tetrazole (ETT, 0.25 M in acetonitrile) with a reaction time of 400 s. Phosphorothioate linkages were generated using a 100 mM solution of 3-((Dimethylamino-methylidene) amino)-3H-1,2,4-dithiazole-3-thione (DDTT, obtained from Chemgenes (Wilmington, MA, USA)) in anhydrous acetonitrile/pyridine (9:1 v/v). Oxidation time
20 was 5 minutes. All sequences were synthesized with final removal of the DMT group ("DMT-Off").

Upon completion of the solid phase synthesis, solid-supported oligoribonucleotides were treated with 300 μ L of Methylamine (40% aqueous) at room temperature in 96 well plates for approximately 2 hours to afford cleavage from the solid support and subsequent removal of all additional base-labile protecting groups. For sequences containing any natural ribonucleotide linkages
25 (2'-OH) protected with a tert-butyl dimethyl silyl (TBDMS) group, a second deprotection step was performed using TEA.3HF (triethylamine trihydrofluoride). To each oligonucleotide solution in aqueous methylamine was added 200 μ L of dimethyl sulfoxide (DMSO) and 300 μ L TEA.3HF and the solution was incubated for approximately 30 mins at 60 °C. After incubation, the plate was allowed to come to room temperature and crude oligonucleotides were precipitated by the addition of
30 1 mL of 9:1 acetonitrile:ethanol or 1:1 ethanol:isopropanol. The plates were then centrifuged at 4 °C for 45 mins and the supernatant carefully decanted with the aid of a multichannel pipette. The oligonucleotide pellet was resuspended in 20 mM NaOAc and subsequently desalted using a HiTrap size exclusion column (5 mL, GE Healthcare) on an Agilent LC system equipped with an autosampler, UV detector, conductivity meter, and fraction collector. Desalted samples were collected
35 in 96 well plates and then analyzed by LC-MS and UV spectrometry to confirm identity and quantify the amount of material, respectively.

Duplexing of single strands was performed on a Tecan liquid handling robot. Sense and antisense single strands were combined in an equimolar ratio to a final concentration of 10 μ M in 1x PBS in 96 well plates, the plate sealed, incubated at 100 °C for 10 minutes, and subsequently allowed to return slowly to room temperature over a period of 2-3 hours. The concentration and identity of each duplex was confirmed and then subsequently utilized for *in vitro* screening assays.

Example 2. *In vitro* screening methods

Cell culture and 384-well transfections

Hep3b cells (ATCC, Manassas, VA) are grown to near confluence at 37°C in an atmosphere of 5% CO₂ in Eagle's Minimum Essential Medium (Gibco) supplemented with 10% FBS (ATCC) before being released from the plate by trypsinization. Transfection is carried out by adding 7.5 μ l of Opti-MEM plus 0.1 μ l of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 2.5 μ l of each siRNA duplex to an individual well in a 384-well plate. The mixture is then incubated at room temperature for 15 minutes. Forty μ l of complete growth media without antibiotic containing $\sim 1.5 \times 10^4$ cells are then added to the siRNA mixture. Cells are incubated for 24 hours prior to RNA purification. Single dose experiments are performed at 10 nM, 1 nM, and 0.1 nM final duplex concentration.

Total RNA isolation using DYNABEADS mRNA Isolation Kit (Invitrogen™, part #: 610-12)

Cells are lysed in 75 μ l of Lysis/Binding Buffer containing 3 μ L of beads per well and mixed for 10 minutes on an electrostatic shaker. The washing steps are automated on a Biotek EL406, using a magnetic plate support. Beads are washed (in 90 μ L) once in Buffer A, once in Buffer B, and twice in Buffer E, with aspiration steps in between. Following a final aspiration, complete 10 μ L RT mixture is added to each well, as described below.

cDNA synthesis using ABI High capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813)

A master mix of 1 μ l 10X Buffer, 0.4 μ l 25X dNTPs, 1 μ l Random primers, 0.5 μ l Reverse Transcriptase, 0.5 μ l RNase inhibitor and 6.6 μ l of H₂O per reaction are added per well. Plates are sealed, agitated for 10 minutes on an electrostatic shaker, and then incubated at 37 degrees C for 2 hours. Following this, the plates are agitated at 80 degrees C for 8 minutes.

Real time PCR

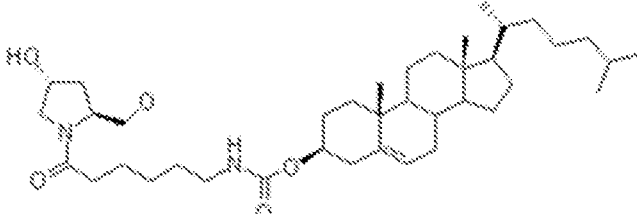
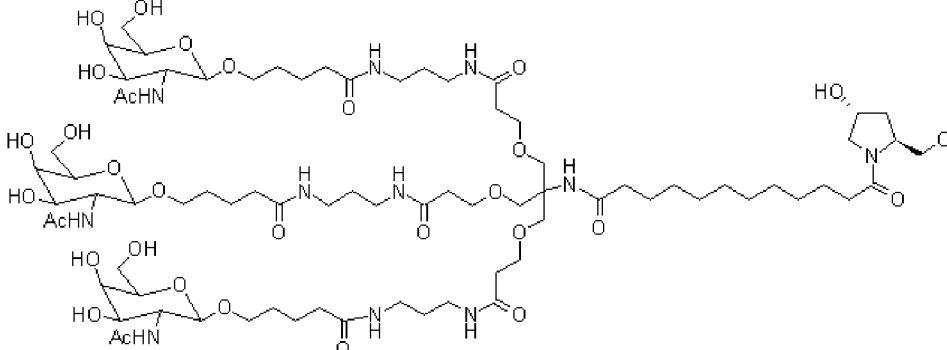
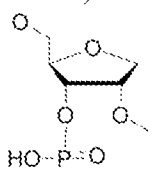
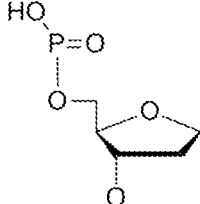
Two microlitre (μ l) of cDNA are added to a master mix containing 0.5 μ l of human GAPDH TaqMan Probe (4326317E), 0.5 μ l human AGT, 2 μ l nuclease-free water and 5 μ l Lightcycler 480

probe master mix (Roche Cat # 04887301001) per well in a 384 well plates (Roche cat # 04887301001). Real time PCR is done in a LightCycler480 Real Time PCR system (Roche).

To calculate relative fold change, data are analyzed using the $\Delta\Delta C_t$ method and normalized to assays performed with cells transfected with 10nM AD-1955, or mock transfected cells. IC₅₀s are calculated using a 4 parameter fit model using XLFit and normalized to cells transfected with AD-1955 or mock-transfected. The sense and antisense sequences of AD-1955 are: sense: cuuAcGcuGAGuAcuucGAdTsdT and antisense UCGAAGuACUcAGCGuAAGdTsdT.

- 10 **Table 1.** Abbreviations of nucleotide monomers used in nucleic acid sequence representation. It will be understood that these monomers, when present in an oligonucleotide, are mutually linked by 5'-3'-phosphodiester bonds; and it is understood that when the nucleotide contains a 2'-fluoro modification, then the fluoro replaces the hydroxy at that position in the parent nucleotide (*i.e.*, it is a 2'-deoxy-2'-fluoronucleotide).

Abbreviation	Nucleotide(s)
A	Adenosine-3'-phosphate
Ab	beta-L-adenosine-3'-phosphate
Abs	beta-L-adenosine-3'-phosphorothioate
Af	2'-fluoroadenosine-3'-phosphate
Afs	2'-fluoroadenosine-3'-phosphorothioate
As	adenosine-3'-phosphorothioate
C	cytidine-3'-phosphate
Cb	beta-L-cytidine-3'-phosphate
Cbs	beta-L-cytidine-3'-phosphorothioate
Cf	2'-fluorocytidine-3'-phosphate
Cfs	2'-fluorocytidine-3'-phosphorothioate
Cs	cytidine-3'-phosphorothioate
G	guanosine-3'-phosphate
Gb	beta-L-guanosine-3'-phosphate
Gbs	beta-L-guanosine-3'-phosphorothioate
Gf	2'-fluoroguanosine-3'-phosphate
Gfs	2'-fluoroguanosine-3'-phosphorothioate
Gs	guanosine-3'-phosphorothioate
T	5'-methyluridine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate
Ts	5-methyluridine-3'-phosphorothioate
U	Uridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine-3'-phosphorothioate
Us	uridine-3'-phosphorothioate
N	any nucleotide, modified or unmodified
a	2'-O-methyladenosine-3'-phosphate
as	2'-O-methyladenosine-3'-phosphorothioate

Abbreviation	Nucleotide(s)
c	2'-O-methylcytidine-3'-phosphate
cs	2'-O-methylcytidine-3'-phosphorothioate
g	2'-O-methylguanosine-3'-phosphate
gs	2'-O-methylguanosine-3'-phosphorothioate
t	2'-O-methyl-5-methyluridine-3'-phosphate
ts	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u	2'-O-methyluridine-3'-phosphate
us	2'-O-methyluridine-3'-phosphorothioate
s	phosphorothioate linkage
L10	N-(cholesterylcarboxamidocaproyl)-4-hydroxyprolinol (Hyp-C6-Chol) 
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl]-4-hydroxyprolinol (Hyp-(GalNAc-alkyl)3) 
Y34	2-hydroxymethyl-tetrahydrofuran-4-methoxy-3-phosphate (abasic 2'-OMe furanose) 
Y44	inverted abasic DNA (2-hydroxymethyl-tetrahydrofuran-5-phosphate) 
(Agn)	Adenosine-glycol nucleic acid (GNA) S-Isomer
(Cgn)	Cytidine-glycol nucleic acid (GNA) S-Isomer
(Ggn)	Guanosine-glycol nucleic acid (GNA) S-Isomer
(Tgn)	Thymidine-glycol nucleic acid (GNA) S-Isomer
P	Phosphate
VP	Vinyl-phosphonate

Abbreviation	Nucleotide(s)
dA	2'-deoxyadenosine-3'-phosphate
dAs	2'-deoxyadenosine-3'-phosphorothioate
dC	2'-deoxycytidine-3'-phosphate
dCs	2'-deoxycytidine-3'-phosphorothioate
dG	2'-deoxyguanosine-3'-phosphate
dGs	2'-deoxyguanosine-3'-phosphorothioate
dT	2'-deoxythymidine-3'-phosphate
dTs	2'-deoxythymidine-3'-phosphorothioate
dU	2'-deoxyuridine
dUs	2'-deoxyuridine-3'-phosphorothioate
(C2p)	cytidine-2'-phosphate
(G2p)	guanosine-2'-phosphate
(U2p)	uridine-2'-phosphate
(A2p)	adenosine-2'-phosphate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(Ghd)	2'-O-hexadecyl-guanosine-3'-phosphate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate

Table 2. Unmodified Sense and Antisense Strand Sequences of Angiotensinogen (AGT) dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1632736	AGAAAGCUGCCGUUGUUCUGGU		3-23	ACCAGAACAACGGCAGCUUCUUC		1-23
AD-1632737	GAAGCUGCCGUUGUUCUGGGU		4-24	ACCCAGAAACAACGGCAGCUUCUU		2-24
AD-1632738	AAGCUGCCGUUGUUCUGGGUU		5-25	AACCCAGAAACAACGGCAGCUUCU		3-25
AD-1632741	CUGCCGUUGUUCUGGGGUACUU		8-28	AAGUACCCAGAAACAACGGCAGCU		6-28
AD-1632745	CGUUGUUCUGGGGUACUACAGU		12-32	ACUGUAGUACCCAGAAACAACGGC		10-32
AD-1632752	CUGGGUACUACAGCAGAGAGGU		19-39	ACCUUCUGCUGUAGUACCCAGAA		17-39
AD-1632757	UACUACAGCAGAGAGGGUAUGU		24-44	ACAUACCCUUCUCUGCUGUAGUACC		22-44
AD-1632758	ACUACAGCAGAGAGGGUAUGCU		25-45	AGCAUACCCUUCUCUGCUGUAGUAC		23-45
AD-1632759	CUACAGCAGAGAGGGUAUGCGU		26-46	ACGCAUACCCUUCUCUGCUGUAGUA		24-46
AD-1632760	UACAGCAGAGAGGGUAUGCGGU		27-47	ACCGCAUACCCUUCUCUGCUGUAGU		25-47
AD-1632761	ACAGCAGAGAGGGUAUGCGGAU		28-48	AUCCGCAUACCCUUCUCUGCUGUAG		26-48
AD-1632763	AGCAGAGAGGGUAUGCGGAAGU		30-50	ACUUCGCAUACCCUUCUCUGCUGU		28-50
AD-1632852	AUCCACAAUGAGAGUACCCUGU		173-193	ACAGGUACUCUCAUUGUGGAUGA		171-193
AD-1632856	ACAAUGAGAGUACCCUGUGAGU		177-197	ACUCACAGGUACUCUCAUUGUGG		175-197
AD-1632898	UUCAUACCCUGCUCUCCAAUUCU		239-259	AUGAAUUUGGAGCAGGUAGUAAGG		237-259

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1632899	UCAUACCUGCUCCAUAUUCAGU		240-260	ACUGAAUUGGAGCAGGUAUGAAG		238-260
AD-1632900	CAUACCUGCUCCAUAUUCAGGU		241-261	ACCUGAAUUGGAGCAGGUAUGAA		239-261
AD-1632915	UGGAUGAAAAGGCCCUACAGU		276-296	ACUGUAGGGCCUUUUAUCCACA		274-296
AD-1632916	GGAUGAAAAGGCCCUACAGGU		277-297	ACCUGUAGGGCCUUUUAUCCAC		275-297
AD-1632944	GUGCUAGUCGUGCAAAACUU		305-325	AAGUUUUGCAGCGACUAGCACCA		303-325
AD-1632945	UGCUAGUCGUGCAAAACUUU		306-326	AAAGUUUUGCAGCGACUAGCAC		304-326
AD-1632946	GCUAGUCGUGCAAAACUUGU		307-327	ACAAGUUUUGCAGCGACUAGCAC		305-327
AD-1632955	UGCAAAACUUUGACACCGAAGU		316-336	ACUUCGGUGUCAAGUUUUGCAGC		314-336
AD-1632956	GCAAAACUUUGACACCGAAGAU		317-337	AUCUUCGGUGUCAAGUUUUGCAG		315-337
AD-1632963	UUGACACCGAAGACAAGUUGU		324-344	ACAACUUGUCUUUCGGUGUCAAGU		322-344
AD-1632964	UGACACCGAAGACAAGUUGAU		325-345	AUCAACUUGUCUUUCGGUGUCAAG		323-345
AD-1632966	ACACCGAAGACAAGUUGAGGU		327-347	ACCUCAACUUGUCUUUCGGUGUCA		325-347
AD-1632967	CACCGAAGACAAGUUGAGGGU		328-348	ACCCUCAACUUGUCUUUCGGUGUC		326-348
AD-1632977	AAGUUAGAGGGCCGCAAUUGGUU		338-358	AACCAUUGCGGGCCCUCAACUUGU		336-358
AD-1632998	GGGAUUCUGGGCCAACUUCUUU		359-379	AAAGAAGUUUGGCCAGCAUCCCCGA		357-379
AD-1633003	GCUGGCCAACUUCUUGGGCUU		364-384	AAGCCCAAGAAAGUUUGGCCAGCAU		362-384

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1633009	CAACUUCUUGGGCUUCCGUAAU		370-390	AUACGGAAAGCCCAAGAAAGUUGGC		368-390
AD-1633010	AACUUCUUGGGCUUCCGUAAU		371-391	AAUACGGAAAGCCCAAGAAAGUUGG		369-391
AD-1633011	ACUUCUUGGGCUUCCGUAAU		372-392	AUAUACGGAAAGCCCAAGAAAGUUG		370-392
AD-1633014	UCUUGGGCUUCCGUAAUAAU		375-395	AAUAUAUACGGAAAGCCCAAGAAAG		373-395
AD-1633016	UUGGGCUUCCGUAAUAUAGGU		377-397	ACCAUAUAUACGGAAAGCCCAAGA		375-397
AD-1633029	UAUAUGGCAUGCACAGUGAGU		390-410	ACUCACUGUGCAUUGCCCAUAUAUA		388-410
AD-1633034	GCAUGCACAGUGAGCUAUGGU		396-416	ACCAUAGCUCACUGUGCAUGCCCA		394-416
AD-1633064	CUCUAUCUGGGAGCCUUGGAU		476-496	AUCCAAGGCUCCCAAGAUAGAGAG		474-496
AD-1633094	GACAGGCUACAGGCAAUCCUU		506-526	AAGGAUUGCCUGUAGCCUGUCAG		504-526
AD-1633095	ACAGGCUACAGGCAAUCCUGU		507-527	ACAGGAUUGCCUGUAGCCUGUCA		505-527
AD-1633101	UACAGGCAAUCCUGGGUGUUU		513-533	AAACACCCAGGAUUGCCUGUAGC		511-533
AD-1633102	ACAGGCAAUCCUGGGUGUUUCU		514-534	AGAAACACCCAGGAUUGCCUGUAG		512-534
AD-1633105	GGCAAUCCUGGGUGUUCCUUU		517-537	AAAGGAACACCCAGGAUUGCCUG		515-537
AD-1633106	GCAAUCCUGGGUGUUCCUUUGU		518-538	ACAAGGAACACCCAGGAUUGCCU		516-538
AD-1633108	AAUCCUGGGUGUUCCUUUGGAU		520-540	AUCCAAGGAACACCCAGGAUUUGC		518-540
AD-1633110	UCCUGGGUGUUCCUUUGGAAGU		522-542	ACUUCCAAAGGAACACCCAGGAUU		520-542

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1633121	CCUUGGAAGGACAAGAACUGU		533-553	ACAGUUCUUGUCCUCCAAGGAA		531-553
AD-1633254	CACCUGAAGCAGCCGUUUGUU		692-712	AACAAACGGCUGCUUCAGGUGCA		690-712
AD-1633295	CUCUGGACUUCACAGAACUGU		753-773	ACAGUUCUGUGAAGUCCAGAGAG		751-773
AD-1633296	UCUGGACUUCACAGAACUGGU		754-774	ACCAGUUCUGUGAAGUCCAGAGA		752-774
AD-1633299	GGACUUCACAGAACUGGAUGU		757-777	ACAUCCAGUUCUGUGAAGUCCAG		755-777
AD-1633301	ACUUCACAGAACUGGAUGUUU		759-779	AAACAUCCAGUUCUGUGAAGUCC		757-779
AD-1633302	CUUCACAGAACUGGAUGUUGU		760-780	ACAACAUCCAGUUCUGUGAAGUC		758-780
AD-1633305	CACAGAACUGGAUGUUGCUGU		763-783	ACAGCAACAUCCAGUUCUGUGAA		761-783
AD-1633306	ACAGAACUGGAUGUUGCUGCU		764-784	AGCAGCAACAUCCAGUUCUGUGA		762-784
AD-1633317	UGUUGCUGCUGAGAGAAUUGU		775-795	ACAAUCUUCUCAGCAGCAACAUC		773-795
AD-1633319	UUGCUGCUGAGAGAAUUGACU		777-797	AGUCAAUUCUUCUCAGCAGCAACA		775-797
AD-1633321	GCUGCUGAGAGAAUUGACAGU		779-799	ACUGUCAAUUCUUCUCAGCAGCAA		777-799
AD-1633335	ACAGGUUCAUGCAGGCUGUGU		795-815	ACACAGCCUGCAUGAACCUUGUCA		793-815
AD-1633343	AUGCAGGCUGUGACAGGAUGU		803-823	ACAUCCUGUACACAGCCUGCAUGA		801-823
AD-1633345	GCAGGCUGUGACAGGAUGGAU		805-825	AUCCAUCCUGUACACAGCCUGCAU		803-825
AD-1633397	GACAGCACCCUGGCUUUCAAU		857-877	AUUGAAAGCCAGGGUGCUGUCCA		855-877

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1633406	CUGGCUUUCAACACCUACGUU		866-886	AACGUAGGUGUUUAAAAGCCAGGG		864-886
AD-1633409	GCUUUC AACACCUACGUCCAU		869-889	AUGGACGUAGGUGUUUAAAAGCCA		867-889
AD-1633417	CACCUACGUCCACUUC CAAGU		877-897	ACUUGGAAAGUGGACGUAGGUGUU		875-897
AD-1633425	UCCACUCCAAAGGGAAGAUGU		885-905	ACAUCUCCCUUGGAAAGUGGACG		883-905
AD-1633428	ACUUCCAAAGGGAAGAUGAAGU		888-908	ACUUCAUCUUCUCCCUUGGAAAGUGG		886-908
AD-1633429	CUUCCAAAGGGAAGAUGAAGGU		889-909	ACCUUCAUCUUCUCCCUUGGAAAGUG		887-909
AD-1633431	UCCAAAGGGAAGAUGAAGGGCU		891-911	AGCCCUUCAUCUUCUCCCUUGGAAAG		889-911
AD-1633440	AGAUGAAGGGCUUCUCCCUUGU		900-920	ACAGGGAGAAGCCCUUCAUCUUC		898-920
AD-1633464	GGACAACAGCACCCUCAGUGUU		946-966	AACACUGAGGUGCUGUUGUCCAC		944-966
AD-1633465	GACAACAGCACCCUCAGUGUCU		947-967	AGACACUGAGGUGCUGUUGUCCA		945-967
AD-1633467	CAACAGCACCCUCAGUGUCUGU		949-969	ACAGACACUGAGGUGCUGUUGUC		947-969
AD-1633474	ACCUCAGUGUCUGUUC CCAUU		956-976	AAUGGGAAACAGACACUGAGGUGC		954-976
AD-1633478	CAGUGUCUGUUC CCAUGCUCU		960-980	AGAGCAUGGGAAACAGACACUGAG		958-980
AD-1633482	GUCUGUUC CCAUGCUCUCUGU		964-984	ACAGAGAGCAUGGGAAACAGACAC		962-984
AD-1633483	UCUGUUC CCAUGCUCUCUGGU		965-985	ACCAGAGAGCAUGGGAAACAGACA		963-985
AD-1633528	GACAUC CAGGACAAACUUCUCU		1010-1030	AGAGAAAGUUGUCCUUGGAUGUCAC		1008-1030

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1633529	ACAUCCAGGACAAACUUCUCGU		1011-1031	ACGAGAAGUUGUCCUGGAUGUCA		1009-1031
AD-1633530	CAUCCAGGACAAACUUCUGGU		1012-1032	ACCGAGAAGUUGUCCUGGAUGUC		1010-1032
AD-1633531	AUCCAGGACAAACUUCUGGUU		1013-1033	AACCGAGAAGUUGUCCUGGAUGU		1011-1033
AD-1633532	UCCAGGACAAACUUCUGGUGU		1014-1034	ACACCGAGAAGUUGUCCUGGAUG		1012-1034
AD-1633533	CCAGGACAAACUUCUGGUGAU		1015-1035	AUCACCGAGAAGUUGUCCUGGAU		1013-1035
AD-1633534	CAGGACAAACUUCUGGUGACU		1016-1036	AGUCACCGAGAAGUUGUCCUGGA		1014-1036
AD-1633541	ACUUCUGGUGACUCAAGUGU		1023-1043	ACACUUGAGUCACCGAGAAAGUUG		1021-1043
AD-1633542	CUUCUGGUGACUCAAGUGCU		1024-1044	AGCACUUGAGUCACCGAGAAAGUU		1022-1044
AD-1633551	GACUCAAGUGCCCUUCACUGU		1033-1053	ACAGUGAAGGGCACUUGAGUCAC		1031-1053
AD-1633553	CUCAAAGUGCCCUUCACUGAGU		1035-1055	ACUCAGUGAAGGGCACUUGAGUC		1033-1055
AD-1633587	GCUGAUCCAGCCUACUAUGU		1069-1089	ACAUAGUGAGGCUGGAUCAGCAG		1067-1089
AD-1633624	GUGGAGGGUUCACAUUUCCAU		1106-1126	AUGGAAAAGUGAGACCCUCCACCU		1104-1126
AD-1633633	CUCACUUUCCAGCAAAACUCU		1115-1135	AGAGUUUUGCUGGAAAAGUGAGAC		1113-1135
AD-1633642	CAGCAAAACUCCCUCAACUGU		1124-1144	ACAGUUUGAGGGAGUUUUGCUGGA		1122-1144
AD-1633643	AGCAAAACUCCCUCAACUGGU		1125-1145	ACCAGUUUGAGGGAGUUUUGCUGG		1123-1145
AD-1633646	AAAACUCCCUCAACUGGAUGU		1128-1148	ACAUCCAGUUGAGGGAGUUUUUGC		1126-1148

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1633649	ACUCCCUCAACUGGAUGAAGU		1131-1151	ACUUCAUCCAGUUUGAGGGAGUUU		1129-1151
AD-1633658	CUGGAUGAAGAAACUAUCUCU		1141-1161	AGAGAUAGUUUCUUCAUCCAGUU		1139-1161
AD-1633666	ACUGGUGCUGCAAGGAUCUUU		1189-1209	AAAGAUCUUGCAGCACCAGUUG		1187-1209
AD-1633669	GGUGCUGCAAGGAUCUUUAUGU		1192-1212	ACAUAAAGAUCCUUGCAGCACCAG		1190-1212
AD-1633670	GUGCUGCAAGGAUCUUUAUGAU		1193-1213	AUCAUAAAGAUCCUUGCAGCACCA		1191-1213
AD-1633671	UGCUGCAAGGAUCUUUAUGACU		1194-1214	AGUCAUAAAGAUCCUUGCAGCACCC		1192-1214
AD-1633683	CUUAUGACCUGCAGGACCUGU		1206-1226	ACAGGUCCUGCAGGUCAUAAGAU		1204-1226
AD-1633732	CGAGCUGAACCCUGCAAAAUAU		1261-1281	AAUUUUUGCAGGUUCAGCUCGGU		1259-1281
AD-1633733	GAGCUGAACCCUGCAAAAUAU		1262-1282	AAAUUUUUUGCAGGUUCAGCUCGG		1260-1282
AD-1633734	AGCUGAACCCUGCAAAAUAUUGU		1263-1283	ACAAUUUUUUUGCAGGUUCAGCUCG		1261-1283
AD-1633735	GCUGAACCCUGCAAAAUAUUGAU		1264-1284	AUCAUUUUUUUGCAGGUUCAGCUC		1262-1284
AD-1633736	CUGAACCCUGCAAAAUAUUGAGU		1265-1285	ACUCAUUUUUUUGCAGGUUCAGCU		1263-1285
AD-1633737	UGAACCCUGCAAAAUAUUGAGCU		1266-1286	AGCUCAAAUUUUUGCAGGUUCAGC		1264-1286
AD-1633743	UGCAAAAAAUUGAGCAAUAGACU		1272-1292	AGUCAUUUGCUCAAAUUUUUGCAGG		1270-1292
AD-1633745	CAAAAAUUUGAGCAAUUGACCGU		1274-1294	ACGGUCAUUUGCUCAAAUUUUUGCA		1272-1294
AD-1633751	UUGAGCAAUUGACCGCAUUCAGU		1280-1300	ACUGAUGCGGUCAUUGCUCAAUU		1278-1300

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1633752	UGAGCAAUGACCGCAUCAGGU		1281-1301	ACCUGAUGCGGUCAUUGCUCAAU		1279-1301
AD-1633754	AGCAAUGACCGCAUCAGGGUU		1283-1303	AACCCUGAUGCGGUCAUUGCUCA		1281-1303
AD-1633759	GAGGUGCUGAACACAGCAUUUUU		1307-1327	AAAAAUGCUGUUCAGCACCUCCC		1305-1327
AD-1633761	UUGAGCUUUGAAGCGGAUGAGU		1329-1349	ACUCAUCCGCUUCAAGCUCAAAA		1327-1349
AD-1633795	GUCUACCCCAACAGCUUUAACAU		1363-1383	AUGUUAAGCUGUUGGGUAGACUC		1361-1383
AD-1633796	UCUACCCCAACAGCUUUAACAAU		1364-1384	AUUGUUAAAGCUGUUGGGUAGACU		1362-1384
AD-1633797	CUACCCCAACAGCUUUAACAAAGU		1365-1385	ACUUGUUAAGCUGUUGGGUAGAC		1363-1385
AD-1633801	CCAAACAGCUUUAACAAAGCCUGU		1369-1389	ACAGGCUUGUUAAGCUGUUGGGU		1367-1389
AD-1633804	ACAGCUUUAACAAAGCCUGAGGU		1372-1392	ACCUCAGGCUUGUUAAGCUGUUG		1370-1392
AD-1633808	CUUAACAAAGCCUGAGGUCUUU		1376-1396	AAAGACCUCAGGCUUGUUAAGCU		1374-1396
AD-1633809	UUAACAAAGCCUGAGGUCUUUGU		1377-1397	ACAAGACCUCAGGCUUGUUAAGC		1375-1397
AD-1633810	UAACAAAGCCUGAGGUCUUUGGU		1378-1398	ACCAAGACCUCAGGCUUGUUAAG		1376-1398
AD-1633811	AACAAAGCCUGAGGUCUUUGGAU		1379-1399	AUCCAAGACCUCAGGCUUGUUA		1377-1399
AD-1633812	ACAAGCCUGAGGUCUUUGGAGU		1380-1400	ACUCCAAGACCUCAGGCUUGUUA		1378-1400
AD-1633813	CAAGCCUGAGGUCUUUGGAGGU		1381-1401	ACCUCCAAGACCUCAGGCUUGUU		1379-1401
AD-1633841	AACCGCCCAUUCUUGUUUGCU		1409-1429	AGCAAACAGGAAUGGGCGGUUCA		1407-1429

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1633842	ACCGCCCAUUCUGUUUGCUU		1410-1430	AAGCAAACAGGAUUGGCGGUUC		1408-1430
AD-1633843	CCGCCCAUUCUGUUUGCUGU		1411-1431	ACAGCAAACAGGAUUGGCGGUU		1409-1431
AD-1633844	CGCCCAUUCUGUUUGCUGUU		1412-1432	AACAGCAAACAGGAUUGGCGGU		1410-1432
AD-1633848	AUUCUGUUUGCUGUGUAUGU		1417-1437	ACAUACACAGCAAACAGGAUUG		1415-1437
AD-1633850	UCCUGUUUGCUGUGUAUGAUU		1419-1439	AAUCAUACACAGCAAACAGGAU		1417-1439
AD-1633857	UGCUGUGUAUGAUCAAAGCGU		1426-1446	ACGCUUUGAUCAUACACAGCAA		1424-1446
AD-1633858	GCUGUGUAUGAUCAAAGCGCU		1427-1447	AGCGCUUUGAUCAUACACAGCAA		1425-1447
AD-1633859	CUGUGUAUGAUCAAAGCGCCU		1428-1448	AGGCGCUUUGAUCAUACACAGCA		1426-1448
AD-1633937	AGGCCAGCAGCAGAUAAACAAU		1557-1577	AUUGUUAUCUGCUGCUGGCCUUU		1555-1577
AD-1633940	CGGACAAAUACAGCGAUGUGUU		1580-1600	AACACAUCGCUGAUUUUGCCGG		1578-1600
AD-1633941	GGACAAAUACAGCGAUGUGUCU		1581-1601	AGACACAUCGCUGAUUUUGCCGG		1579-1601
AD-1633947	CUCCCCACCUUUUCUUCUAAUU		1610-1630	AAUUAGAAAGAAAAGGUGGGAGAC		1608-1630
AD-1633948	UCCCACCUUUUCUUCUAAUGU		1611-1631	ACAUUAGAAAGAAAAGGUGGGAGA		1609-1631
AD-1633949	CCCACCUUUUCUUCUAAUGAU		1612-1632	AUCAUUAGAAAGAAAAGGUGGGAG		1610-1632
AD-1633954	UUUUCUUCUAAUAGAGUCGACU		1618-1638	AGUCGACUCAUUAGAAAGAAAAGG		1616-1638
AD-1633955	UUUCUUCUAAUAGAGUCGACUU		1619-1639	AAGUCGACUCAUUAGAAAGAAAAG		1617-1639

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1633956	UUCUUCUAAUGAGUCGACUUU		1620-1640	AAAGUCGACUCAUUAGAAGAAA		1618-1640
AD-1633958	CUUCUAAUGAGUCGACUUUGU		1622-1642	ACAAAGUCGACUCAUUAGAAGAA		1620-1642
AD-1633959	UUCUAAUGAGUCGACUUUGAU		1623-1643	AUCAAAAGUCGACUCAUUAGAAGA		1621-1643
AD-1633960	UCUAAUGAGUCGACUUUGAGU		1624-1644	ACUCAAAAGUCGACUCAUUAGAAG		1622-1644
AD-1633961	CUAAUGAGUCGACUUUGAGCU		1625-1645	AGCUCAAAAGUCGACUCAUUAGAA		1623-1645
AD-1633962	UAAUGAGUCGACUUUGAGCUU		1626-1646	AAGCUCAAAAGUCGACUCAUUAGA		1624-1646
AD-1633971	GACUUUGAGCUGGAAAGCAGU		1635-1655	ACUGCUUUUCCAGCUCAAAAGUCGA		1633-1655
AD-1633977	GAGCUGGAAAGCAGCCGUUUU		1641-1661	AAAAACGGCUGCUUUUCCAGCUCAA		1639-1661
AD-1633978	AGCUGGAAAGCAGCCGUUUUCU		1642-1662	AGAAACGGCUGCUUUUCCAGCUCA		1640-1662
AD-1633979	GCUGGAAAGCAGCCGUUUUCUU		1643-1663	AAGAAACGGCUGCUUUUCCAGCUC		1641-1663
AD-1633980	CUGGAAAGCAGCCGUUUUCUCU		1644-1664	AGAGAAACGGCUGCUUUUCCAGCU		1642-1664
AD-1633982	GGAAAGCAGCCGUUUUCUCCUU		1646-1666	AAGGAGAAACGGCUGCUUUUCCAG		1644-1666
AD-1633984	AAAGCAGCCGUUUUCUCCUUUGU		1648-1668	ACAAGGAGAAACGGCUGCUUUUCC		1646-1668
AD-1633986	AGCAGCCGUUUUCUCCUUUGGUU		1650-1670	AACCAAGGAGAAACGGCUGCUUUU		1648-1670
AD-1633987	GCAGCCGUUUUCUCCUUUGGUCU		1651-1671	AGACCAAGGAGAAACGGCUGCUUU		1649-1671
AD-1633988	CAGCCGUUUUCUCCUUUGGUCUU		1652-1672	AAGACCAAGGAGAAACGGCUGCU		1650-1672

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1633992	CGUUUCUCCUUGGUCUAAGUU		1656-1676	AACUUAGACCAAGGAGAAACGGC		1654-1676
AD-1633993	GUUUUCUCCUUGGUCUAAGUGU		1657-1677	ACACUUAGACCAAGGAGAAACGG		1655-1677
AD-1633994	UUUCUCCUUGGUCUAAGUGUU		1658-1678	AACACUUAGACCAAGGAGAAACG		1656-1678
AD-1633995	UUCUCCUUGGUCUAAGUGUGU		1659-1679	ACACACUUAGACCAAGGAGAAAC		1657-1679
AD-1633996	UCUCCUUGGUCUAAGUGUCU		1660-1680	AGCACACUUAGACCAAGGAGAAA		1658-1680
AD-1633998	UCCUUGGUCUAAGUGUGCUGU		1662-1682	ACAGCACACUUAGACCAAGGAGA		1660-1682
AD-1634005	UCUAAUGUGUGCUGCAUGGAGU		1669-1689	ACUCCAUGCAGCACACUUAAGACC		1667-1689
AD-1634009	AGUGUGCUGCAUGGAGUGAGU		1673-1693	ACUCACUCCAUGCAGCACACUUA		1671-1693
AD-1634018	CAUGGAGUGAGCAGUAGAAGU		1682-1702	ACUUUCUACUGCUCACUCCAUGCA		1680-1702
AD-1634022	GAGUGAGCAGUAGAAGCCUGU		1686-1706	ACAGGCUUUCUACUGCUCACUCCA		1684-1706
AD-1634050	CAA AUGCACCUCCCAAGUUUGU		1714-1734	ACAAACUGGGAGGUGCAUUUGUG		1712-1734
AD-1634051	AA AUGCACCUCCCAAGUUUUGCU		1715-1735	AGCAAACUGGGAGGUGCAUUUGU		1713-1735
AD-1634052	AAUGCACCUCCCAAGUUUGCUU		1716-1736	AAGCAAACUGGGAGGUGCAUUUG		1714-1736
AD-1634053	AUGCACCUCCCAAGUUUGCUGU		1717-1737	ACAGCAAACUGGGAGGUGCAUUU		1715-1737
AD-1634054	UGCACCUCCCAAGUUUGCUGGU		1718-1738	ACCAGCAAACUGGGAGGUGCAUU		1716-1738
AD-1634059	CUCCCAAGUUUGCUGGGUUUAU		1723-1743	AUAAACCCAGCAAACUGGGAGGU		1721-1743

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1634061	CCCAGUUUGCUGGGUUUAUUU		1725-1745	AAAUAAACCCAGCAAAACUGGGAG		1723-1745
AD-1634062	CCAGUUUGCUGGGUUUAUUU		1726-1746	AAAAUAAACCCAGCAAAACUGGGA		1724-1746
AD-1634063	CAGUUUGCUGGGUUUAUUU		1727-1747	AAAAUAAACCCAGCAAAACUGGG		1725-1747
AD-1634064	AGUUUGCUGGGUUUAUUU		1728-1748	AUAAAAUAAACCCAGCAAAACUGG		1726-1748
AD-1634065	GUUUUGCUGGGUUUAUUU		1729-1749	ACUAAAAUAAACCCAGCAAAACUG		1727-1749
AD-1634066	UUUGCUGGGUUUAUUU		1730-1750	AUCUAAAAUAAACCCAGCAAAACU		1728-1750
AD-1634067	UUGCUGGGUUUAUUU		1731-1751	ACUCUAAAAUAAACCCAGCAAAAC		1729-1751
AD-1634068	UGCUGGGUUUAUUU		1732-1752	AUCUCUAAAAUAAACCCAGCAAA		1730-1752
AD-1634071	GGGUUAUUUAGAGAAUGGU		1736-1756	ACCAUUCUCUAAAAUAAACCCAG		1734-1756
AD-1634072	GGGAGGCAAGAACCCAGUGUUU		1761-1781	AAACACUGGUUUCUUGCCUCCCCA		1759-1781
AD-1634073	GGAGGCAAGAACCCAGUGUUU		1762-1782	AAACACUGGUUUCUUGCCUCCCC		1760-1782
AD-1634075	AGGCAAGAACCCAGUGUUU		1764-1784	ACUAAACACUGGUUUCUUGCCUCC		1762-1784
AD-1634076	GGCAAGAACCCAGUGUUU		1765-1785	AGCUAAACACUGGUUUCUUGCCUC		1763-1785
AD-1634088	UGUUUAGCGCGGGACUACUGU		1777-1797	ACAGUAGUCCCCGCGCUAAACACU		1775-1797
AD-1634100	GACUACUGUUCCAAAAAGAAU		1789-1809	AUUCUUUUUGGAACAGUAGUCCC		1787-1809
AD-1634104	ACUGUCCAAAAAGAAUCCU		1793-1813	AGGAUUUCUUUUUGGAACAGUAG		1791-1813

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1634105	CUGUUCACAAAAGAAUUC		1794-1814	AUGGAAUUCUUUUUGGAACAGUA		1792-1814
AD-1634111	CAAAAAGAAUUCACACCGACU		1800-1820	AGUCGGUUGGAAUUCUUUUUGGA		1798-1820
AD-1634123	ACCGACAGCUUGUUUGAU		1814-1834	AUCACAAACAAAGCUGGUCGGUUG		1812-1834
AD-1634131	AAAGUUGUCCCUUUUCAAGUU		1840-1860	AACUUGAAAAGGGAACACUUUUU		1838-1860
AD-1634133	AGUGUCCCUUUUCAAGUUGU		1842-1862	ACAACUUGAAAAGGGAACACUUU		1840-1862
AD-1634134	GUGUCCCUUUUCAAGUUGAU		1843-1863	AUCAACUUGAAAAGGGAACACUU		1841-1863
AD-1634135	UGUCCCUUUUCAAGUUGAGU		1844-1864	ACUCAACUUGAAAAGGGAACACU		1842-1864
AD-1634136	GUUCCCUUUUCAAGUUGAGAU		1845-1865	AUCUCAACUUGAAAAGGGAACAC		1843-1865
AD-1634146	CAAGUUGAGAACAAAAUUGU		1855-1875	ACAAUUUUUGUUCUCAACUUGAA		1853-1875
AD-1634147	AAGUUGAGAACAAAAUUGGU		1856-1876	ACCAAUUUUUGUUCUCAACUUGA		1854-1876
AD-1634148	GUUGAGAACAAAAUUGGGUU		1858-1878	AACCCAAUUUUUGUUCUCAACUU		1856-1878
AD-1634149	UUGAGAACAAAAUUGGGUUU		1859-1879	AAACCCAAUUUUUGUUCUCAACU		1857-1879
AD-1634150	UGAGAACAAAAUUGGGUUUU		1860-1880	AAAACCCAAUUUUUGUUCUCAAC		1858-1880
AD-1634151	GAGAACAAAAUUGGGUUUUU		1861-1881	AAAAACCCAAUUUUUGUUCUCAAA		1859-1881
AD-1634152	AGAAACAAAAUUGGGUUUUU		1862-1882	AUAAACCCAAUUUUUGUUCUCA		1860-1882
AD-1634153	GAACAAAAUUGGGUUUUAAU		1863-1883	AUUAAAAACCCAAUUUUUGUUCUC		1861-1883

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1634163	GUAAUACAUUUUUUGCAUUGCCU		1890-1910	AGGCAUUGCAAAA AUGUAUACUU		1888-1910
AD-1634165	AUACAUUUUUUGCAUUGCCUUU		1892-1912	AAAGGCAUUGCAAAA AUGUAUAC		1890-1912
AD-1634168	CAUUUUUGCAUUGCCUUCGGU		1895-1915	ACCGAAGGCAUUGCAAAA AUGUA		1893-1915
AD-1634169	AUUUUUGCAUUGCCUUCGGUU		1896-1916	AACCGAAGGCAUUGCAAAA AUGU		1894-1916
AD-1634170	UUUUUGCAUUGCCUUCGGUUU		1897-1917	AAACCGAAGGCAUUGCAAAA AUG		1895-1917
AD-1634171	UUUUUGCAUUGCCUUCGGUUUU		1898-1918	AAAACCGAAGGCAUUGCAAAA AU		1896-1918
AD-1634172	UUUGCAUUGCCUUCGGUUUGU		1899-1919	ACAAACCGAAGGCAUUGCAAAA		1897-1919
AD-1634173	UUGCAUUGCCUUCGGUUUGUU		1900-1920	AACAAACCGAAGGCAUUGCAAAA		1898-1920
AD-1634174	UGCAUUGCCUUCGGUUUGUAU		1901-1921	AUACAACCGAAGGCAUUGCAAA		1899-1921
AD-1634175	GCAUUGCCUUCGGUUUGUAUU		1902-1922	AAUACAACCGAAGGCAUUGCAA		1900-1922
AD-1634176	CAUUGCCUUCGGUUUGUAUUU		1903-1923	AAAUACAACCGAAGGCAUUGCA		1901-1923
AD-1634177	AUUGCCUUCGGUUUGUAUUUU		1904-1924	AAAAUACAACCGAAGGCAAUUGC		1902-1924
AD-1634178	UUGCCUUCGGUUUGUAUUUAU		1905-1925	AUAAAUAACAACCGAAGGCAAUUG		1903-1925
AD-1634179	UGCCUUCGGUUUGUAUUUAGU		1906-1926	ACUAAAUAACAACCGAAGGCAAU		1904-1926
AD-1634180	GCCUUCGGUUUGUAUUUAGUU		1907-1927	AACUAAAUAACAACCGAAGGCAA		1905-1927
AD-1634181	CCUUCGGUUUGUAUUUAGUGU		1908-1928	ACACUAAAUAACAACCGAAGGCA		1906-1928

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1634182	CUUCGGUUUUGUAUUUAGUGUUU		1909-1929	AACACUAAAUAACAACCCGAAGGC		1907-1929
AD-1634186	GGUUUGUAUUUAGUGUCUUUGU		1913-1933	ACAAAGACACUAAAUAACAAACCGA		1911-1933
AD-1634190	UGUAUUUAGUGUCUUUGAAUGU		1917-1937	ACAUUCAAGACACUAAAUAACAAA		1915-1937
AD-1634192	UAUUUAGUGUCUUUGAAUGUAU		1919-1939	AUACAUUCAAGACACUAAAUAACA		1917-1939
AD-1634194	UUUAGUGUCUUUGAAUGUAAGU		1921-1941	ACUUACAUUCAAGACACUAAAUA		1919-1941
AD-1634200	GUCUUUGAAUGUAAGAAACAUGU		1927-1947	ACAUGUUCUUACAUAUCAAAGACAC		1925-1947
AD-1634209	GUAAACAUGACCCUCCGUGU		1936-1956	ACACGGAGGUCAUGUUUCUUACAU		1934-1956
AD-1634210	UAAGAACAUAGACCUCCGUGUU		1937-1957	AACACGGAGGUCAUGUUUCUUACA		1935-1957
AD-1634211	AAGAACAUAGACCUCCGUGUAU		1938-1958	AUACACGGAGGUCAUGUUUCUUAC		1936-1958
AD-1634212	AGAACAUAGACCUCCGUGUAGU		1939-1959	ACUACACGGAGGUCAUGUUUCUUA		1937-1959
AD-1634213	GAACAUGACCUCCGUGUAGUU		1940-1960	AACUACACGGAGGUCAUGUUUCUU		1938-1960
AD-1634214	AACAUGACCUCCGUGUAGUGU		1941-1961	ACACUACACGGAGGUCAUGUUUCU		1939-1961
AD-1634215	ACAUGACCUCCGUGUAGUGUU		1942-1962	AACACUACACGGAGGUCAUGUUUC		1940-1962
AD-1634218	UGACCUCCGUGUAGUGUCUGU		1945-1965	ACAGACACUACACGGAGGUCAUG		1943-1965
AD-1634224	CCGUGUAGUGUCUGUAAUACU		1951-1971	AGUAUUACAGACACUACACGGAG		1949-1971
AD-1634225	CGUGUAGUGUCUGUAAUACCU		1952-1972	AGGUAAUACAGACACUACACGGA		1950-1972

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1634226	GUGUAGUGUCUGUAAUACCUU		1953-1973	AAGGUUUACAGACACUACACGG		1951-1973
AD-1634227	UGUAGUGUCUGUAAUACCUUU		1954-1974	AAAGGUUUACAGACACUACACG		1952-1974
AD-1634230	AGUGUCUGUAAUACCUUAGUU		1957-1977	AACUAAAGGUUUACAGACACUAC		1955-1977
AD-1634231	GUGUCUGUAAUACCUUAGUUU		1958-1978	AAACUAAAGGUUUACAGACACUA		1956-1978
AD-1634232	UGUCUGUAAUACCUUAGUUUU		1959-1979	AAAACUAAAGGUUUACAGACACU		1957-1979
AD-1634233	GUCUGUAAUACCUUAGUUUUU		1960-1980	AAAAACUAAAGGUUUACAGACAC		1958-1980
AD-1634234	UUUCCACAGAUGCUUUGUGAUU		1979-1999	AAUCACAAAGCAUCUGUGGAAAAA		1977-1999
AD-1634238	CACAGAUGCUUUGUGAUUUUUU		1983-2003	AAAAAAUUCACAAAGCAUCUGUGGA		1981-2003
AD-1634239	ACAGAUGCUUUGUGAUUUUUUGU		1984-2004	ACAAAAAUUCACAAAGCAUCUGUGG		1982-2004
AD-1634240	CAGAUGCUUUGUGAUUUUUUGAU		1985-2005	AUCAAAAAUUCACAAAGCAUCUGUG		1983-2005
AD-1634241	AGAUGCUUUGUGAUUUUUUGAAU		1986-2006	AUUCAAAAAUUCACAAAGCAUCUGU		1984-2006
AD-1634242	GAUGCUUUGUGAUUUUUUGAACU		1987-2007	AGUUCAAAAAUUCACAAAGCAUCUG		1985-2007
AD-1634248	UGUGAUUUUUUGAACAAUACGU		1993-2013	ACGUUUUUUUUCAA AAAAUUCACAAAG		1991-2013
AD-1634249	GUGAUUUUUUGAACAAUACGUU		1994-2014	AACGUUUUUUUUCAA AAAAUUCACAA		1992-2014
AD-1634250	UGAUUUUUUGAACAAUACGUGU		1995-2015	ACACGUUUUUUUUCAA AAAAUUCACA		1993-2015
AD-1634251	GAUUUUUUUGAACAAUACGUGAU		1996-2016	AUCACGUUUUUUUUCAA AAAAUUCAC		1994-2016

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1634252	AUUUUUGAACAAUACGUGAAU		1997-2017	AUUCACGUUUUGUUCAAAAUAUCA		1995-2017
AD-1634257	UGAACAAUACGUGAAAGAUGU		2002-2022	ACAUCUUUCACGUUUUGUUCAAAA		2000-2022
AD-1634273	GAUGCAAGCACCCUGAAUUUCU		2018-2038	AGAAUUUCAGGUGCUUGCAUCUU		2016-2038
AD-1634274	AUGCAAGCACCCUGAAUUUCU		2019-2039	AAGAAUUUCAGGUGCUUGCAUCU		2017-2039
AD-1634275	UGCAAGCACCCUGAAUUUCUGU		2020-2040	ACAGAAUUUCAGGUGCUUGCAUC		2018-2040
AD-1634276	GCAAGCACCCUGAAUUUCUGU		2021-2041	AACAGAAUUUCAGGUGCUUGCAU		2019-2041
AD-1634277	CAAGCACCCUGAAUUUCUGUUU		2022-2042	AAACAGAAUUUCAGGUGCUUGCA		2020-2042
AD-1634278	AAGCACCCUGAAUUUCUGUUUU		2023-2043	AAAAACAGAAUUUCAGGUGCUUGC		2021-2043
AD-1634279	AGCACCCUGAAUUUCUGUUUGU		2024-2044	ACAAACAGAAUUUCAGGUGCUUG		2022-2044
AD-1634280	GCACCUGAAUUUCUGUUUGAU		2025-2045	AUCAACACAGAAUUUCAGGUGCUU		2023-2045
AD-1634281	CACCUGAAUUUCUGUUUGAAU		2026-2046	AUUCAAACAGAAUUUCAGGUGCU		2024-2046
AD-1634282	ACCUGAAUUUCUGUUUGAAUU		2027-2047	AAUUCAAAACAGAAUUUCAGGUGC		2025-2047
AD-1634283	CCUGAAUUUCUGUUUGAAUGU		2028-2048	ACAUUCAACAGAAUUUCAGGUG		2026-2048
AD-1634285	UGAAUUUCUGUUUGAAUGCGU		2030-2050	ACGCAUUCAAACAGAAUUUCAGG		2028-2050
AD-1634286	GAAUUUCUGUUUGAAUGCGGU		2031-2051	ACCGCAUUUCAACAGAAUUUCAG		2029-2051
AD-1634287	AAUUUCUGUUUGAAUGCGGAU		2032-2052	AUCCGCAUUUCAACAGAAUUUCA		2030-2052

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1634296	UUGAAUGCGGAACCAUAGCUU		2041-2061	AAGCUAUGGUUCCGCAUUCAAAC		2039-2061
AD-1634297	UGAAUGCGGAACCAUAGCUGU		2042-2062	ACAGCUAUGGUUCCGCAUUCAAA		2040-2062
AD-1634298	GAAUGCGGAACCAUAGCUGGU		2043-2063	ACCAGCUAUGGUUCCGCAUUCAA		2041-2063
AD-1634303	CGGAACCAUAGCUGGUUAUUU		2048-2068	AAAUAAACCAGCUAUGGUUCCGCA		2046-2068
AD-1634304	GGAAACCAUAGCUGGUUAUUU		2049-2069	AAAAUAAACCAGCUAUGGUUCCGC		2047-2069
AD-1634305	GAACCAUAGCUGGUUAUUUCU		2050-2070	AGAAAUAAACCAGCUAUGGUUCCG		2048-2070
AD-1634306	AACCAUAGCUGGUUAUUUCUU		2051-2071	AAGAAUAAACCAGCUAUGGUUCC		2049-2071
AD-1634307	ACCAUAGCUGGUUAUUUCUCU		2052-2072	AGAGAAUAAACCAGCUAUGGUUC		2050-2072
AD-1634308	CCAUAGCUGGUUAUUUCUCCU		2053-2073	AGGAGAAUAAACCAGCUAUGGUU		2051-2073
AD-1634309	CAUAGCUGGUUAUUUCUCCCU		2054-2074	AGGGAGAAUAAACCAGCUAUGGU		2052-2074
AD-1634314	CUGGUUAUUUCUCCCUUGUGU		2059-2079	ACACAAGGGAGAAUAAACCAGCU		2057-2079
AD-1634315	UGGUUAUUUCUCCCUUGUGUU		2060-2080	AACACAAGGGAGAAUAAACCAGC		2058-2080
AD-1634316	GGUUAUUUCUCCCUUGUGUUU		2061-2081	AAACACAAGGGAGAAUAAACCAG		2059-2081
AD-1634318	UUAAUUUCUCCCUUGUGUUAGU		2063-2083	ACUAAACACAAGGGAGAAUAAACC		2061-2083
AD-1634319	UAUUUCUCCCUUGUGUUAGUU		2064-2084	AACUAAACACAAGGGAGAAUAAAC		2062-2084
AD-1634320	AUUUCUCCCUUGUGUUAGUAAU		2065-2085	AUACUAAACACAAGGGAGAAUAA		2063-2085

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1
AD-1634321	UUUCUCCCUUGUGUUAGUAAU		2066-2086	AUUACUAAACACAAAGGGAGAAUA		2064-2086
AD-1634325	UCCCUUGUGUUAGUAAAUAU		2070-2090	AUUUAUUACUAAACACAAAGGGAGA		2068-2090
AD-1634326	CCCUUGUGUUAGUAAUAAACU		2071-2091	AGUUUAUUACUAAACACAAAGGGAG		2069-2091
AD-1634327	CCUUGUGUUAGUAAUAAACGU		2072-2092	ACGUUUUUUUACUAAACACAAAGGGA		2070-2092
AD-1634328	CUUGUGUUAGUAAUAAACGUU		2073-2093	AACGUUUUUUUACUAAACACAAAGGG		2071-2093
AD-1634329	UUGUGUUAGUAAUAAACGUCU		2074-2094	AGACGUUUUUUUACUAAACACAAAGG		2072-2094
AD-1634330	UGUGUUAGUAAUAAACGUCUU		2075-2095	AAGACGUUUUUUUACUAAACACAAAG		2073-2095
AD-1634331	GUGUUAGUAAUAAACGUCUUU		2076-2096	AAAGACGUUUUUUUACUAAACACAA		2074-2096
AD-1634332	UGUUAGUAAUAAACGUCUUGU		2077-2097	ACAAGACGUUUUUUUACUAAACACA		2075-2097
AD-1634333	GUUAGUAAUAAACGUCUUGCU		2078-2098	AGCAAGACGUUUUUUUACUAAACAC		2076-2098
AD-1634334	UUAGUAAUAAACGUCUUGCCU		2079-2099	AGGCAAGACGUUUUUUUACUAAACA		2077-2099
AD-1634342	AAACGUCUUUGCCACAAUUAAGU		2087-2107	ACUUUUUUGUGGCAAGACGUUUUAU		2085-2107
AD-1634343	AACGUCUUUGCCACAAUUAAGCU		2088-2108	AGCUUUAUUUGUGGCAAGACGUUUA		2086-2108
AD-1634344	ACGUCUUUGCCACAAUUAAGCCU		2089-2109	AGGCUUUAUUUGUGGCAAGACGUUU		2087-2109
AD-68585	AGUUGAGAACAAUUAUUGGGU		1857-1877	ACCCAAUUUUUUUGUUCUCAACUUG		1855-1877

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1632736	asgsaagcUfgCfCfGfuunguucugguL96		asCfscagAfaCfAfaecgCfaGfeucnuse		GAAGAAAGCUGCCGUUGUUCUGGG	
AD-1632737	gsasageuGfcCfGfUfuguucuggguL96		asCfsecaGfaAfCfaacGfcAfgcucnusu		AAGAAAGCUGCCGUUGUUCUGGGU	
AD-1632738	asasgcugCfcGfUfUfguucuggguuL96		asAfseccAfgAfAfaaacGfgCfagcunscsu		AGAAGCUGCCGUUGUUCUGGGUA	
AD-1632741	csusgccgUfuGfUfUfcuggguaacuL96		asAfsguaCfcCfAfaaacAfaCfggcagscsu		AGCUGCCGUUGUUCUGGGUACUA	
AD-1632745	csgsunguUfcUfGfGfguaacuagL96		asCfsuguAfgUfAfceccaGfaAfaaacgsgsc		GCCGUUGUUCUGGGUACUACAGC	
AD-1632752	csusggguAfcUfAfCfagcagaaggL96		asCfseuuCfuGfCfuguaGfuAfceccagsasa		UUCUGGGUACUACAGCAGAAGGG	
AD-1632757	usascuacAfgCfAfGfaaggguauL96		asCfsauaCfcCfUfuengCfuGfuaguascsc		GGUACUACAGCAGAAGGGUAUGC	
AD-1632758	asesuacaGfcAfGfAfaggguaugcL96		asGfseauAfcCfCfuenGfcUfguaagusasc		GUACUACAGCAGAAGGGUAUGC	
AD-1632759	csusacagCfaGfAfAfgguaugcguL96		asCfsgcaUfaCfCfenneUfgCfuguagususa		UACUACAGCAGAAGGGUAUGC	
AD-1632760	usascagcAfgAfAfGfguaugcggL96		asCfsegcAfuAfCfceuUfuGfuguuasgsu		ACUACAGCAGAAGGGUAUGC	
AD-1632761	asesagcaGfaAfGfGfguaugcggauL96		asUfseccGfaUfAfcecuUfcUfgcugusasg		CUACAGCAGAAGGGUAUGC	
AD-1632763	asgscagaAfgGfGfUfauggcgaaL96		asCfsuueCfgCfAfuaceCfuUfucugcugsu		ACAGCAGAAGGGUAUGC	
AD-1632852	asusccacAfaUfGfAfaguaucugL96		asCfsaggUfaCfUfcaUfuGfuggausgsa		UCAUCCACAAGAGAGUACCUGU	
AD-1632856	asesaauGafGfGfUfaccugugagL96		asCfsucaCfaGfGfuacuCfuCfaungsgsg		CCACAAGAGAGUACCUGAGC	
AD-1632898	ususcauaCfcUfGfCfuceaauuL96		asUfsgaaUfuGfGfagcaGfgUfaugaasgsg		CCUUCAUACCUGCUCCAAUUCAG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1632899	uscsauacCfuGfCfUfccaauucaguuL96		asCfsugaAfuUfGfgagcAfgGfuauagasag		CUUCAUACCCUGCUCUCCAAUUCAGG	
AD-1632900	csasuaccUfgCfUfccaauucagguL96		asCfscugAfaUfUfggagCfaGfguauagsasa		UUCAUACCCUGCUCUCCAAUUCAGGC	
AD-1632915	usgsaugAfaAfAfGfgccuacaguuL96		asCfsuguAfgGfgfccuUfuCfauccasesa		UGUGGAUGAAAAGGCCCUACAGG	
AD-1632916	gsgsaugAfaAfGfgccuacaguuL96		asCfscugUfaGfGfgccuUfuUfcauccsasc		GUGGAUGAAAAGGCCCUACAGGA	
AD-1632944	gsusguaGfuCfGfCfugcaaaaacuuL96		asAfsuuUfuGfCfagcAfeUfagcacsca		UGGUGCUAGUCGCGUGCAAAAACUU	
AD-1632945	usgsuagUfcGfCfUfccaauucuuL96		asAfsaguUfuUfGfagcGfaCfuagcascsc		GGUGCUAGUCGCGUGCAAAAACUUUG	
AD-1632946	gscsuagUfcGfCfUfccaauucuuL96		asCfsaagUfuUfUfgcagCfGfcauagcsasc		GUGCUAGUCGCGUGCAAAAACUUUGA	
AD-1632955	usgsaaaAfeUfUfGfcaaccgaaguuL96		asCfsuucGfgUfGfcaaaGfuUfuuagcsasc		GCUGCAAAAACUUUGACACCCGAAGA	
AD-1632956	gscsaaaCfuUfGfAfcaccgaaguuL96		asUfscuuCfgGfUfgucaAfgUfuuagcsasc		CUGCAAAAACUUUGACACCCGAAGAC	
AD-1632963	usugacaCfcGfAfgacaaguuuuL96		asCfsaacUfuGfUfcuucGfgUfgucaagsu		ACUUGACACCGAAGACAAGUUUGA	
AD-1632964	usgsaacCfcGfAfgacaaguuuuL96		asUfscacCfuUfGfucuuCfGfugucasasc		CUUGACACCGAAGACAAGUUUGAG	
AD-1632966	ascsaccGfAfaGfAfcfaaguuaguuL96		asCfscucAfaCfUfugucUfuCfggguuscsa		UGACACCGAAGACAAGUUUGAGGG	
AD-1632967	csasccgaAfgAfcfAfaaguuaguuuuL96		asCfscuuCfaAfcfuuguCfuUfaggguususc		GACACCGAAGACAAGUUUGAGGGC	
AD-1632977	asasguuAfgGfGfCfcgaauuguuuuL96		asAfsccaUfuGfCfaggccCfuCfaacuugsu		ACAAGUUAGAGGGCCGCAAAUGGUUC	
AD-1632998	gsgsgauCfuGfGfCfcaacuucuuuuL96		asAfsagaAfgUfUfaggccAfgCfauccccgsa		UCGGGAUGCUGGGCCCAACUUCUUUG	
AD-1633003	gscsuggcCfaAfcUfucuuaggguuuL96		asAfsgccCfaAfcGfaaguUfgGfcaagcsasu		AUGCUGGCCCAACUUCUUGGGGUU	

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1633121	cscsuugcAfaGfGfAfcagaacugulL96		asCfsaguUfcUfUfguccUfuCfcaaggsasa		UUCCUUGGAAGGACAAGAACUGC	
AD-1633254	csascuugAfaGfCfAfcgcuuuuuL96		asAfscaaAfcGfGfucgUfuCfagguugsasa		UGCACCUGAAGCAGCCGUUUGUG	
AD-1633295	csuscugAfcUfUfCfacaagaacugulL96		asCfsaguUfcUfGfugaGfuCfcaaggsasg		CUCUCUGGACUUCACAGAACUGG	
AD-1633296	uscsuggaCfuUfCfAfcagaacugulL96		asCfscagUfuCfUfgugaAfgUfccaggsasa		UCUCUGGACUUCACAGAACUGGA	
AD-1633299	gsgsacuuCfaCfAfcgaacuggaugulL96		asCfsaucCfaGfUfucugUfgAfaguccsasg		CUGGACUUCACAGAACUGGAUGU	
AD-1633301	ascsuucaCfaGfAfcuggauguuuL96		asAfsacaUfcCfAfguuUfgUfgaaguscsc		GGACUUCACAGAACUGGAUGUUUG	
AD-1633302	csusucacAfgAfAfcfuggauguuuL96		asCfisaacAfuCfCfaguuCfuGfugaagsusc		GACUUCACAGAACUGGAUGUUUGC	
AD-1633305	csascagaAfcUfGfGfanguugcugulL96		asCfsagcAfaCfAfucaGfuUfengugsasa		UUCACAGAACUGGAUGUUUGCUGC	
AD-1633306	ascsagaaCfuGfGfAfuugucugulL96		asGfscagCfaAfCfauccAfgUfucugusgsa		UCACAGAACUGGAUGUUUGCUGCU	
AD-1633317	usgsuugcUfgCfUfGfagaagaauuL96		asCfsaauCfuUfCfucagCfaGfcaacasusc		GAUGUUGCUGCUGAGAGAAAUUGA	
AD-1633319	ususgcugCfuGfAfcgaagaugaculL96		asGfsucaAfuCfUfucucAfgCfagaasasa		UGUUGCUGCUGAGAGAAAUUGACA	
AD-1633321	gscsuugcuGfaGfAfcgaugacagulL96		asCfsuguCfaAfUfucuuUfcAfgcagcsasa		UUGCUGCUGAGAGAAAUUGACAGG	
AD-1633335	ascsagguUfcAfUfGfagcugcugulL96		asCfsacaGfcCfUfgcauGfaAfcuugusasa		UGACAGGUUCAUGCAGGCUGUGA	
AD-1633343	asusgcagGfcUfGfUfgacaggaugulL96		asCfsaucCfuGfUfcaCaGfcCfugaugsasa		UCAUGCAGGCUGUGACAGGAUGG	
AD-1633345	gscsagguUfgUfGfAfcaggaugauL96		asUfsecaUfcCfUfgucaCfaGfcaugcsasu		AUGCAGGCUGUGACAGGAUGGAA	
AD-1633397	gsascagcAfcCfCfUfgcucuuaauL96		asUfsugaAfaGfCfcaaggGfuGfcugucscasa		UGGACAGCACCCUGGCUUUUAAC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1633406	csusggcuUfuCfAfAfcacucaguuL96		asAfscguAfgGfUfguugAfaAfgccagsgsg		CCCUGGCUUUCAACACCUACGUC	
AD-1633409	gscsuuucAfaCfAfCfcuacguccauL96		asUfsggaCfGfUfAfggugUfuGfaaaagcsca		UGGCUUUCAACACCUACGUCCAC	
AD-1633417	csasccuaCfGfUfCfCfacuuccaaguuL96		asCfcsuugGfaAfGfuggaCfGfUfagguusuu		AACACCUACGUCCACCUUCCAAGG	
AD-1633425	uscsacuUfcCfAfAfggaagaaguuL96		asCfcsaucUfuCfCfcuugGfaAfguggascsG		CGUCCACUUCCAAGGGAAGAUGA	
AD-1633428	ascsuuccAfaGfGfGfaagaagaaguuL96		asCfcsuucAfuCfUfucccUfuGfagaagsgsg		CCACUUCCAAGGGAAGAUGAAGG	
AD-1633429	csusuccaAfgGfGfAfagaagaaguuL96		asCfscuuCfaUfCfuuccCfuUfagaagsgsg		CACUUCCAAGGGAAGAUGAAGGG	
AD-1633431	uscsaagGfGfAfAfGfagaagaaguuL96		asGfscceUfuCfAfucuuCfcCfuuggasasg		CUUCCAAGGGAAGAUGAAGGGGCU	
AD-1633440	asgsaagaAfgGfGfCfuuccuccuguuL96		asCfsaggGfaGfAfagccCfuUfcaucusuc		GAAGAUGAAGGGCUUCCCCUGC	
AD-1633464	gsgsacaaCfaGfCfAfccuacaguuL96		asAfscacUfgAfggugcUfgUfuguccsasc		GUGGACAAACAGCACCCUCAGUGUC	
AD-1633465	gsascaacAfgCfAfCfcuacaguguuL96		asGfsacaCfuGfAfggugCfuGfuuugscsa		UGGACAAACAGCACCCUCAGUGUCU	
AD-1633467	csasacagCfaCfCfUfcaagugucuuL96		asCfsagaCfaCfUfagggUfgCfuuugsuusc		GACAAACAGCACCCUCAGUGUCUGU	
AD-1633474	ascsuuccGfuGfUfCfGfuguuuccauL96		asAfsuggGfaAfCfagacAfcUfagguusgsc		GCACCUCAGUGUCUGUUGUCCCCAUG	
AD-1633478	csasguguCfuGfUfUfUfcccagucuuL96		asGfsagcAfuGfGfagaacAfgAfcacugssag		CUCAGUGUCUGUUGUCCCCAUGCUCU	
AD-1633482	gsuscuugUfcCfCfAfugcucucuuL96		asCfsagaGfaGfCfauugGfaAfcagacsasc		GUGUCUGUUGUCCCCAUGCUCUCUGG	
AD-1633483	uscsuuguuCfcCfAfUfgeucucuguuL96		asCfscagAfgAfgfcaugGfGfAfacagascsa		UGUCUGUUGUCCCCAUGCUCUCUGGC	
AD-1633528	gsascaucCfaGfGfAfcacuuucuuL96		asGfsagaAfgUfUfguccUfgGfauugcsasc		GUGACAUCCAGGACAACUUCUCG	

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1633649	ascsuccUfcAfaCfuggaugauL96		asCfsuucAfuCfCfaguuGfaGfggagususu		AAACUCCCUCAACUGGAUGAAGA	
AD-1633658	csusggauGfaAfaGfaaauuauL96		asGfsagaUfaGfUfuuuUfcAfucaagsusu		AACUGGAUGAAAGAAACUAUCUCC	
AD-1633666	ascusggUfcUfGfCfaaggaucuuuL96		asAfsagaUfcCfUfugcaGfcAfcagususg		CAACUGGUGCUGCAAGGAUCUUA	
AD-1633669	gsgugcuGfcAfaGfgaucuuauL96		asCfsauaAfgAfuuccuGfcAfgcaccsag		CUGGUGCUGCAAGGAUCUUAUGA	
AD-1633670	gsgugcuGfaAfaGfGfaucuuauL96		asUfscuuAfaGfAfuuccUfgCfagcacsca		UGGUGCUGCAAGGAUCUUAUGAC	
AD-1633671	usgscugAfaGfGfAfuuuuagauL96		asGfsucaUfaAfgfaucUfuGfcagascsc		GGUGCUGCAAGGAUCUUAUGACC	
AD-1633683	csusuauAfcCfUfgfcaggaccguL96		asCfsaggUfcCfUfgcagGfuCfaaagsasu		AUCUUAUGACCUUGCAGGACCUGC	
AD-1633732	csgsagcuGfaAfaCfCfugcaaaaauL96		asAfsuuUfuGfCfagguUfcAfgcucgsgu		ACCGAGCUGAACCUUGCAAAAUAU	
AD-1633733	gsasgcuAfaCfCfUfgcaaaaauuL96		asAfsauUfuUfgfcaggUfuCfagcucsgg		CCGAGCUGAACCUUGCAAAAUAUUG	
AD-1633734	asgscugaAfcCfUfgfcaaaaauuL96		asCfsauUfuUfUfgcagGfuUfcagcuscg		CGAGCUGAACCUUGCAAAAUAUGA	
AD-1633735	gsgsugaCfcUfGfCfaaaaauuL96		asUfscuuUfuUfUfugcaGfgUfucagcusc		GAGCUGAACCUUGCAAAAUAUGAG	
AD-1633736	csusgaacCfuGfCfaaaaauuL96		asCfsucaAfuUfUfugcAfgGfuucagscsu		AGCUGAACCUUGCAAAAUAUGAGC	
AD-1633737	usgsaacUfgCfAfaaaaugagcuL96		asGfscucAfaUfUfuuuGfCfaGfguucagsc		GCUGAACCUUGCAAAAUAUGAGCA	
AD-1633743	usgscaaaAfaUfUfGfagcaaugacuL96		asGfsucaUfuGfCfucuaUfuUfuugcagsg		CCUGCAAAAUAUGAGCAAAUGACC	
AD-1633745	csasaaaaUfuGfAfgfcaaugaccguL96		asCfsgguCfaUfUfugcAfaUfuuuugscsa		UGCAAAAUAUGAGCAAAUGACCGC	
AD-1633751	ususgagcAfaUfGfAfcgcaucauL96		asCfsugaUfgCfGfgucaUfuGfcucaasusu		AAUUGAGCAAAUGACCGCAUCAGG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1633752	usgsagcaAfuGfAfCfGcaucaggguL96		asCfscugAfuGfCfGgucAfuUfgucasasu		AUUGAGCAAUGACCGCAUCAGGG	
AD-1633754	asgscaauGfaCfCfGfcaucaggguL96		asAfscccUfgAfUfgcggUfcAfuugcscsa		UGAGCAAUGACCGCAUCAGGGUG	
AD-1633759	gsasggugCfuGfAfAfcafcagcauuuuL96		asAfsaaaUfgCfUfguucAfgCfaccucscsc		GGGAGGUGCUGAACAGCAUUUUUU	
AD-1633761	ususgagcUfuGfAfAfGfgcgauagguL96		asCfsucaUfcCfGfGuucAfaGfcauasasa		UUUUGAGCUUGAAGCGGAUGAGA	
AD-1633795	gsuucuacCfcAfAfCfagcuuaacauL96		asUfsguuAfaGfCfuguuGfgGfuagacsuc		GAGUCUACCCACACAGCUUAACAA	
AD-1633796	uscsuaccCfaAfCfAfGcuuaacauL96		asUfsuguUfaAfGfcuguUfgGfguagasesu		AGUCUACCCAAACAGCUUAACAAAG	
AD-1633797	csusagccAfaCfAfGfcuuaacagguL96		asCfsuugUfuAfAfGfcugUfuGfgguagsasc		GUCUACCCAACACAGCUUAACAAAGC	
AD-1633801	cscsaacaGfcUfuUfAfacaagccuguL96		asCfsagcCfuUfGfuuuaaGfcUfguuugsgsu		ACCCAACAGCUUAACAAAGCCUGA	
AD-1633804	ascsgagUfaAfCfAfagccugaggguL96		asCfscucAfgGfCfuuguUfaAfGfcugusug		CAACAGCUUAACAAAGCCUGAGGU	
AD-1633808	csusuaacAfaGfCfCfugaggucuuuL96		asAfsagaCfcUfCfagggcUfuGfuuuaagscsu		AGCUUAACAAAGCCUGAGGUCUUUG	
AD-1633809	ususaacaAfgCfCfUfgaggucuuuL96		asCfsaagAfcCfUfcagggCfuUfguuuaagsgc		GCUUAACAAAGCCUGAGGUCUUUGG	
AD-1633810	usasacaaGfcCfUfGfaggucuuuL96		asCfscaagGfaCfCfucagGfcUfuguuaasag		CUUAACAAGCCUGAGGUCUUUGGA	
AD-1633811	asascaagCfcUfGfAfGgucuuuL96		asUfscaaAfgAfCfcaGfgCfuguuasasa		UUAAACAAGCCUGAGGUCUUUGGAG	
AD-1633812	ascsaagcCfuGfAfGfgucuuuL96		asCfsuccAfaGfAfcuucAfgGfciuugususa		UAACAAGCCUGAGGUCUUUGGAGG	
AD-1633813	csasagccUfgAfGfGfucuuuL96		asCfscucCfaAfGfaccuCfaGfgcuuugssu		AACAAGCCUGAGGUCUUUGGAGGU	
AD-1633841	asascgccCfcAfUfuUfccuuuuuL96		asGfscaaAfcAfGfgaauGfgGfgcuuuscscsa		UGAAACCGCCCAUUCUGUUUGCU	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1633842	ascsgccCfaUfuCfcguguuugcuuL96		asAfsgeaAfaCfaAfggaaUfgGfgeggususc		GAACCGCCCAUCCUGUUUUGCUG	
AD-1633843	cscsgcccAfuUfCfcfuguuuugcuuL96		asCfsageAfaAfcAfcaggAfuGfgegggsusu		AACCGCCCAUCCUGUUUUGCUGU	
AD-1633844	csgscccaUfuCfCfUfguuugcuuL96		asAfsagCfaAfaAfcaggAfaUfgggcgsgsu		ACCGCCCAUCCUGUUUUGCUGUG	
AD-1633848	asusuccuGfuUfUfGfcuguguuauL96		asCfsauaCfaCfaAfgcaaAfcAfggausgsg		CCAUCCUGUUUUGCUGUGUAUGA	
AD-1633850	uscsccguUfuGfCfUfguguaugauL96		asAfsucaUfaCfaAfcagcAfaAfcaggasasu		AUCCUGUUUUGCUGUGUAUGAUC	
AD-1633857	usgscuguGfuAfuUfGfaucaaagcuL96		asCfsgcuUfuGfAfucauAfaAfcagcasasa		UUUGCUGUGUAUGAUCAAAGCGC	
AD-1633858	gscsugugUfaUfGfAfuaaaagcuL96		asGfscgcUfuUfGfaucaUfaCfacagcsasa		UUGCUGUGUAUGAUCAAAGCGCC	
AD-1633859	csusguguAfuGfAfUfcaaaagccuL96		asGfsgcgCfuUfUfgaucAfuAfcacagsesa		UGCUGUGUAUGAUCAAAAGCGCCA	
AD-1633937	asgsgccaGfcAfcGfcfagauaacaauL96		asUfsuguUfaUfcfugcuGfcUfgggccususu		AAAGGCCAGCAGCAGAUAAACAAC	
AD-1633940	csgsgacaAfaUfCfAfcggauguguL96		asAfsacAfuCfGfcugaUfuUfguccgsgsg		CCCGGACAAAUACAGCGAUGUGUC	
AD-1633941	gsgsacaaAfuCfAfcgfcgaugugucuL96		asGfsacaCfaUfCfcgcuAfuUfguccsgsg		CCGGACAAAUACAGCGAUGUGUCA	
AD-1633947	csuscccaCfcUfuUfUfucuucaauL96		asAfsuuuGfaAfcGfaaaaGfgUfgggagsasc		GUCUCCCAUCCUUUUCUUCUAAUG	
AD-1633948	uscsccacCfuUfuUfUfucuucaauguL96		asCfsauuAfgAfaAfgaaaAfgGfugggagsga		UCUCCCAUCCUUUUCUUCUAAUGA	
AD-1633949	cscscaccUfuUfuUfCfuucuaaauL96		asUfscuuUfaGfAfaagaaAfaGfuggggsasg		CUCCCAUCCUUUUCUUCUAAUGAG	
AD-1633954	ususuuuuUfcUfAfaAfcagugacuL96		asGfsucgAfcUfCfauuuAfaAfgaaaasgsg		CCUUUUCUUCUAAUGAGUCGACU	
AD-1633955	ususuuuuCfuAfaAfuUfgagugacuL96		asAfsugcGfaCfuUfcauuAfgAfgaaaasasg		CUUUUUCUUCUAAUGAGUCGACUU	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1633956	ususcucUfaAfUfGfagucgacuuuL96		asAfsaguCfGfAfCfucuuUfaGfagaasasa		UUUUCUUUUA AUGAGUCGACUUU	
AD-1633958	csusucuaAfuGfAfGfucgacuuuL96		asCfsaaaGfuCfGfagucAfuUfagaasasa		UUCUUUUA AUGAGUCGACUUUGA	
AD-1633959	ususcuaUfgAfGfUfGfagucuuuL96		asUfscuaAfgUfCfGfagucCfuUfagaasgsa		UCUUCUUA AUGAGUCGACUUUGAG	
AD-1633960	uscsuaaGfaGfUfCfGfagucuuuL96		asCfsucaAfaGfUfGfagucUfcAfuagagasg		CUUCUUA AUGAGUCGACUUUGAGC	
AD-1633961	csusaauGfUfCfGfagucuuuL96		asGfscucAfaAfGfucgCfuCfauuagsasa		UUCUUA AUGAGUCGACUUUGAGCU	
AD-1633962	usasaugGfuCfGfAfCfucuuuL96		asAfsagCfaAfAfGfucgAfcUfcauuagsa		UCUUA AUGAGUCGACUUUGAGCUG	
AD-1633971	gsascuuGfaGfCfUfGfagaaGcaguL96		asCfsugCfuUfCfagucUfcAfaugucgsa		UCGACUUUUGAGCUGGAAAGCAGC	
AD-1633977	gsasgcuGfaAfAfGfagccguuuuL96		asAfsaacGfGfCfUfGfucuuUfcCfagucgsa		UUGAGCUGGAAAGCAGCAGCCGUUUC	
AD-1633978	asgscugAfaAfGfCfagccguuuuL96		asGfsaaaCfGfCfugcuUfuCfagucgsa		UGAGCUGGAAAGCAGCAGCCGUUUCU	
AD-1633979	gscsuGgaAfaGfCfAfGfagccguuuuL96		asAfsaaaAfcGfGfagucUfuUfCfagucsu		GAGCUGGAAAGCAGCAGCCGUUUCUC	
AD-1633980	csusggaaAfgCfAfGfagccguuuuL96		asGfsagaAfaCfGfagucCfuUfCfagucsu		AGCUGGAAAGCAGCAGCCGUUUCUCC	
AD-1633982	ggsaaagCfaGfCfCfGfagccguuuuL96		asAfsagaGfaAfaAfcggCfuCfuuuacsag		CUGGAAAGCAGCAGCCGUUUCUCCUU	
AD-1633984	asasaGcaGfcCfGfUfucucuuuL96		asCfsaaGfAfaGfAfaacGfCfuuuucsc		GGAAAGCAGCAGCCGUUUCUCCUUGG	
AD-1633986	asgscagCfGfUfUfUfucuuuL96		asAfscaaAfgGfAfgaaaCfGfagucsu		AAAGCAGCCGUUUCUCCUUGGUC	
AD-1633987	gscsagccGfuUfUfCfucuuuL96		asGfsaccAfaGfGfagaaAfcGfagucsu		AAGCAGCCGUUUCUCCUUGGUCU	
AD-1633988	csasgcccUfuUfCfUfucuuuL96		asAfsagCfaAfGfagaaAfaCfagucsu		AGCAGCCGUUUCUCCUUGGUCUA	

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1634061	cscscagUfuGfCfUfggguuuuuuL96		asAfsauaAfaCfCfcagcAfaAfcuagggsasg		CUCCCAGUUUGCUGGGUUUAUUUU	
AD-1634062	cscscaguuUfgCfUfgfguuuuuuuuL96		asAfsauuAfaAfcCfcagCfaAfacuagggsa		UCCCAGUUUGCUGGGUUUAUUUU	
AD-1634063	csasguuuGfcUfGfGfguuuuuuuuL96		asAfsaaaUfaAfaAfcceGfcAfaacugsgsg		CCCAGUUUGCUGGGUUUAUUUUUA	
AD-1634064	asgsuuuGfGfGfGfuuuuuuuuuL96		asUfsaaaAfuAfaAfcceAfcCfaaacusgsg		CCAGUUUGCUGGGUUUAUUUUAG	
AD-1634065	gsusuuGfGfGfUfuuuuuuuuuL96		asCfsuaaAfaUfaAaccCfaGfcaaacusg		CAGUUUGCUGGGUUUAUUUUAGA	
AD-1634066	ususugcuGfGfUfuuuuuuuuuL96		asUfscuaAfaAfuAfaacCfcAfgcaaaacsu		AGUUUGCUGGGUUUAUUUUAGAG	
AD-1634067	ususgcugGfGfUfuUfauuuuuagauL96		asCfsucuAfaAfaAfaaaCfcCfcagcaasac		GUUUGCUGGGUUUAUUUUAGAGA	
AD-1634068	usgscuggGfuUfuAfuuuuagagauL96		asUfscueUfaAfaAfaaaAfcCfcagcasasa		UUUGCUGGGUUUAUUUUAGAGAA	
AD-1634071	gsgsguuuAfuUfuUfagagauuuL96		asCfscauUfcUfCfuuaaAfuAfaacccsasg		CUGGGUUUAUUUUAGAGAAUAGGG	
AD-1634072	gsgsgaggCfaAfgfAfaaccaguuuuL96		asAfsacaCfuGfGfuuuUfGfCfucuccscsa		UGGGGAGGCAAGAACCAGUGUUU	
AD-1634073	gsgsaggcAfaGfAfaAfcaguuuuuuL96		asAfsaacAfcUfGfguuUfuGfucuccscsc		GGGGAGGCAAGAACCAGUGUUUA	
AD-1634075	asgsgcaaGfaAfcCfaguuuuuuuL96		asCfsuaaAfcAfcfuguuUfcUfugcucscsc		GGAGGCAAGAACCAGUGUUUAGC	
AD-1634076	gsgscagAfaCfCfaguuuuuuuL96		asGfscuaAfaCfAfcuaggUfuCfuugccsusc		GAGGCAAGAACCAGUGUUUAGCG	
AD-1634088	usgssuuuGfcCfCfGfgacuacuuL96		asCfsaguAfgUfCfcccGfcUfaaacacsu		AGUGUUUAGCGCGGGGACUACUGU	
AD-1634100	gsascuacUfgUfuUfCfcaaaaagaauL96		asUfsucuUfuUfUfggaaCfaGfuagucscsc		GGGACUACUGUUUCCAAAAAAGAAU	
AD-1634104	ascsguuCfcAfaAfaagaauuuL96		asGfsgaaUfuCfuUfuuuuGfgAfacagisag		CUACUGUUUCCAAAAAAGAAUUCCA	

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1634182	csusueggUfuUfGfUfaunuaguguuL96		asAfscaeUfaAfaFuacaAfaCfegaagsgc		GCCUUCGGUUUGUAUUUAGUGUC	
AD-1634186	gsusuuugUfaUfUfUfagugucuguuL96		asCfsaagAfcAfcFuaaaUfaCfaaacsgsa		UCGGUUUGUAUUUAGUGUCUUUA	
AD-1634190	usgsuauuUfaGfUfGfucuuagauguL96		asCfsauuCfaAfGfiacaeUfaAfaucasasa		UUUGUAUUUAGUGUCUUUGAAUGU	
AD-1634192	usasuuaGfuGfUfCfugaaguauuL96		asUfsacaUfuCfAfagacAfcUfaauascsa		UGUAUUUAGUGUCUUUGAAUGUAA	
AD-1634194	ususuaGfuCfUfUfgaauaaguL96		asCfsuuaCfaUfUfcaagAfcAfcuaaasusa		UAUUUAGUGUCUUUGAAUGUAGA	
AD-1634200	gsuscungAfaUfGfUfaagaacaguL96		asCfsaugUfuCfUfuacaUfuCfaagacsasc		GUGUCUUUGAAUGUAAGAACAUAGA	
AD-1634209	gsusaagaAfcAfuGfUfGfaccuccuguuL96		asCfsacgGfaGfGfucauGfuUfcuuaacsasu		AUGUAAGAACAUAGACCUCUCCGUGU	
AD-1634210	usasagaCfaUfGfAfcuccuguuL96		asAfscaeGfgAfGfgucaUfgUfcuuaascsa		UGUAAGAACAUAGACCUCUCCGUGUA	
AD-1634211	asasgaacAfuGfAfcuccuguuauL96		asUfsacaCfGfAfggucAfuGfucuuasasc		GUAAGAACAUAGACCUCUCCGUGUAG	
AD-1634212	asgsaacaUfgAfcCfuccuguuaguL96		asCfsuacAfcGfGfagguCfaUfguucususua		UAAGAACAUAGACCUCUCCGUGUAGU	
AD-1634213	gsasacauGfaCfCfUfGfGfuguaguL96		asAfsucaCfaCfGfagggUfcAfguucususu		AAGAACAUAGACCUCUCCGUGUAGUG	
AD-1634214	asascaugAfcCfUfCfGfGfuguaguL96		asCfsacuAfcAfcGfagGfuCfauguuacsu		AGAACAUAGACCUCUCCGUGUAGUGU	
AD-1634215	ascsaagaCfcUfCfGfGfuguaguL96		asAfscaeUfaCfAfcgggaGfgUfcaugususc		GAACAUAGACCUCUCCGUGUAGUGUC	
AD-1634218	usgsaccuCfcGfUfGfGfuguagucuguL96		asCfsagaCfaCfUfacacGfgAfggucacug		CAUGACCUCUCCGUGUAGUGUCUGU	
AD-1634224	csesguguAfgUfGfUfGfGfuguauacuL96		asGfsuauUfaCfAfgacaCfuAfcacgggsag		CUCCGUGUAGUGUCUGUAAUUAACC	
AD-1634225	csesguguaGfuGfUfCfGfGfuguauacuL96		asGfsguaUfuAfcfagacAfcUfacacgsgsa		UCCGUGUAGUGUCUGUAAUUAACCU	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1634226	gsusguagUfgUfCfUfguaauaccuuL96		asAfsaggUfaUfAfcagaCfaCfuacacsosg		CCGUGUAGUGUCUGUAAUACCUU	
AD-1634227	usgsuaguGfuCfUfGfuauaccuuuL96		asAfsaggUfaUfUfacagAfcAfcuacacsosg		CGUGUAGUGUCUGUAAUACCUUA	
AD-1634230	asgsugucUfgUfAfAfuaaccuuaguL96		asAfsucaAfcGfUfauuaCfaGfacacuscasc		GUAGUGUCUGUAAUACCUUAGUU	
AD-1634231	gsusguacuGfuAfAfUfaccuuaguuuL96		asAfsacuAfaGfGfuuuAfcAfcacacsusa		UAGUGUCUGUAAUACCUUAGUUU	
AD-1634232	usgsucugUfaAfUfAfcuuaguuuuL96		asAfsaacUfaAfGfguuUfaCfagacacsu		AGUGUCUGUAAUACCUUAGUUUU	
AD-1634233	gsuscuguAfaUfAfCfcuuaguuuuL96		asAfsaaaCfuAfAfguaUfuAfcagacuscasc		GUGUCUGUAAUACCUUAGUUUUU	
AD-1634234	ususucaCfaGfAfUfgcuugugauL96		asAfsucaCfaAfcgaucUfgUfggaaasasa		UUUUUCCACAGAUAGCUUUGUGAUU	
AD-1634238	csascagaUfgCfUfUfguaauuuuL96		asAfsaaaAfuCfAfcagCfaUfcugugsgsa		UCCACAGAUAGCUUUGUGAUUUUUUG	
AD-1634239	ascsagauGfcUfUfGfugaauuuuL96		asCfsaaaAfaUfCfacaGfcAfuucugsgsg		CCACAGAUAGCUUUGUGAUUUUUUGA	
AD-1634240	csasgaugCfuUfGfUfgaauuuuL96		asUfscaaAfaAfUfcacaAfgCfaucugsgsg		CACAGAUAGCUUUGUGAUUUUUUGAA	
AD-1634241	asgsaugcUfuGfUfGfaauuuuL96		asUfsucaAfaAfAfucacAfaGfcaucugsgsu		ACAGAUAGCUUUGUGAUUUUUUGAAC	
AD-1634242	gsasugcuUfgUfGfAfuuuuuL96		asGfsuucAfaAfAfaucAfaAfgcaucugsg		CAGAUAGCUUUGUGAUUUUUUGAACA	
AD-1634248	usgsugauUfuUfUfGfaaauacguL96		asCfsguaUfuGfUfuaaAfaAfuacacascg		CUUGUGAUUUUUUGAACAAUACGU	
AD-1634249	gsusgaunUfuUfGfAfacaauacguL96		asAfsaguAfuUfGfuaaAfaAfaucacsasa		UUGUGAUUUUUUGAACAAUACGUG	
AD-1634250	usgsaunUfuGfAfAfaaauacguL96		asCfsagUfaUfUfguucAfaAfaucacsasa		UGUGAUUUUUUGAACAAUACGUGA	
AD-1634251	gsasuuuuUfgAfAfCfaaauacguL96		asUfscacGfuAfUfuguCfaAfaaauacsasc		GUGAUUUUUUGAACAAUACGUGAA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1634252	asusuuuuGfaAfCfAfaucgugaauL96		asUfsucaCfGfUfAfuuuUfCfAfaaauscsa		UGAUUUUUUGAACAAUACGUGAAA	
AD-1634257	usgsaacaAfuAfCfGfugaagauguL96		asCfsaueUfuUfCfagcuAfuUfguucasasa		UUUGAACAAUACGUGAAAAGAUGC	
AD-1634273	gsasugcaAfgCfAfCfCfugaauuuuL96		asGfsaaaUfuCfAfagguCfuUfgcaucsusu		AAGAUGCAAGCACCUGAAUUUCU	
AD-1634274	asusgcaaGfcAfCfCfugaauuuuL96		asAfsгааAfuUfCfagguGfcUfugcauscsu		AGAUGCAAGCACCUGAAUUUCUG	
AD-1634275	usgscaagCfaCfCfUfgaauuuuL96		asCfsagaAfaUfUfcaggUfgCfuugcasusc		GAUGCAAGCACCUGAAUUUCUGU	
AD-1634276	gscsaagcAfcCfUfGfaauuuuL96		asAfsagAfaAfuUfcagGfuGfcuugcsasu		AUGCAAGCACCUGAAUUUCUGUU	
AD-1634277	csasagcaCfcUfGfAfaauuuuL96		asAfsacaGfaAfAfuucaGfgUfgcuugscsa		UGCAAGCACCUGAAUUUCUGUUU	
AD-1634278	asasgcacCfuGfAfAfuuuuL96		asAfsaacAfgAfAfaaucAfgGfuguugsgc		GCAAGCACCUGAAUUUCUGUUUG	
AD-1634279	asgscaccUfgAfAfUfucuguuuL96		asCfsaaaCfaGfAfaauuCfaGfgugcuscusg		CAAGCACCUGAAUUUCUGUUUGA	
AD-1634280	gscsaccuGfaAfUfUfucuguuuL96		asUfscaaAfcAfGfaauUfCfAfgguugcsusu		AAGCACCUGAAUUUCUGUUUGAA	
AD-1634281	csasccugAfaUfUfUfCfugaauuL96		asUfsucaAfaCfAfgaaaUfuCfagguugscsu		AGCACCUGAAUUUCUGUUUGAAU	
AD-1634282	ascsccugaAfuUfUfCfugaauuL96		asAfsuucAfaAfcfagaaAfuUfcagguugsc		GCACCUGAAUUUCUGUUUGAAUG	
AD-1634283	csesugaaUfuUfCfUfguuuL96		asCfsaauCfaAfAfcagaAfaUfucagguugsg		CACCUGAAUUUCUGUUUGAAUGC	
AD-1634285	usgsaauUfcUfGfUfugaauuL96		asCfsfgcaUfuCfAfaacaGfaAfaauucsgsg		CCUGAAUUUCUGUUUGAAUGCGG	
AD-1634286	gsasaauuUfuGfUfugaauuL96		asCfscgcAfuUfCfaaacAfgAfaauucsasg		CUGAAUUUCUGUUUGAAUGCGGA	
AD-1634287	asasuucUfgUfUfUfgaauuL96		asUfscgcCfaUfUfcaaaaCfaGfaaauscsa		UGAAUUUCUGUUUGAAUGCGGAA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1634296	ususgaauGfcGfAfaccuagcuuL96		asAfsacuAfuGfGfuuccGfcAfuucaasasc		GUUUGAAUGCGGAACCAUAGCUG	
AD-1634297	usgsaauGfcGfAfaccuagcuuL96		asCfsageUfaUfGfguucCfcGfaucacasasa		UUUGAAUGCGGAACCAUAGCUGG	
AD-1634298	gsasauGfcGfAfCfcauagcuuL96		asCfscagCfuAfuGfguuCfcGfcauucsasa		UUGAAUGCGGAACCAUAGCUGGU	
AD-1634303	csgsgaacCfaUfAfGfcuuguuuuuL96		asAfsauaAfcCfAfgcuUfGfGfuuccgscsa		UGCGGAACCAUAGCUGGUUAUUU	
AD-1634304	gsgsaaccAfuAfgCfGfuguuuuuuL96		asAfsaauAfaCfCfagcuAfuGfGfuuccsgsc		GCGGAACCAUAGCUGGUUAUUUC	
AD-1634305	gsasaccaUfaGfCfUfguuuuuuuL96		asGfsaaaUfaAfcCfcageUfaUfGfguucscsg		CGGAACCAUAGCUGGUUAUUUCU	
AD-1634306	asasccauAfgCfUfGfguuuuuuuL96		asAfsгааAfuAfaCfcagCfuAfuGfguucscsc		GGAACCAUAGCUGGUUAUUUCUC	
AD-1634307	ascscauGfcUfGfGfuuuuuuuL96		asGfsagaAfaUfaCfaccGfcUfaugguususc		GAACCAUAGCUGGUUAUUUCUCC	
AD-1634308	csesauagCfuGfGfUfuuuuuuuuL96		asGfsagagAfaAfuAfaaccAfgCfuauuggsusu		AACCAUAGCUGGUUAUUUCUCCCC	
AD-1634309	csasuagCfuGfGfUfuuuuuuuuL96		asGfsagaGfaAfaAfuAfaaccCfaGfcauuggsusu		ACCAUAGCUGGUUAUUUCUCCCCU	
AD-1634314	csusgguuAfuUfUfCfuccuuuguuL96		asCfsacaAfgGfGfagaaAfuAfaaccagscu		AGCUGGUUAUUUCUCCCCUUGUGU	
AD-1634315	usgsguuuUfuUfCfUfcccuuuguuL96		asAfsacAfaGfGfagaaAfaUfaaccagscu		GCUGGUUAUUUCUCCCCUUGUGUU	
AD-1634316	gsgsuuuUfuUfCfUfcccuuuguuL96		asAfsacaCfaAfgGfgagAfaUfaaccagscu		CUGGUUAUUUCUCCCCUUGUGUUA	
AD-1634318	ususauuuCfuCfCfCfuuguuuuuL96		asCfsuuaCfaCfAfgggAfgAfaauaascsc		GGUUAUUUCUCCCCUUGUGUUAAGU	
AD-1634319	usasuuuUfcCfCfUfuguuuuuL96		asAfscauAfcAfcfaaggGfaGfaauaasasc		GUUAUUUCUCCCCUUGUGUUAAGUA	
AD-1634320	asusuucuCfcCfUfUfuguuuuuL96		asUfsacuAfaCfAfcaggGfgAfgaaauasasa		UUUAUUUCUCCCCUUGUGUUAAGUAA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1634321	usuuuucCfcUfUfGfuguuaauL96		asUfsuacUfaAfcfacaGfGfagaasusa		UAUUUCUCCCCUUGUGUUAGUAAU	
AD-1634325	uscsccuGfuGfUfUfaguuaauL96		asUfsuuuUfuAfcfuaacAfcAfgggasgsa		UCUCCCCUUGUGUUAGUAAUAAAC	
AD-1634326	csccsuuUfgUfUfAfguaauaacuL96		asGfsuuuAfuUfAfcuaaCfaCfaaggsasg		CUCCCCUUGUGUUAGUAAUAAACG	
AD-1634327	csccsuuGfuUfAfcfuaauaacguL96		asCfsuuUfaUfUfuaaAfcAfcaggsgsa		UCCCCUUGUGUUAGUAAUAAACGU	
AD-1634328	csusugUfUfAfcfuaauaacguL96		asAfcsgUfuUfUfuaaAfaCfaagsgsg		CCCUUGUGUUAGUAAUAAACGUC	
AD-1634329	ususguUfaGfUfAfaaaacgucL96		asGfsagUfuUfAfuuaUfaAfcacaasgsg		CCUUGUGUUAGUAAUAAACGUCU	
AD-1634330	usgsuGuAfGfUfAfaaaacgucL96		asAfsagGfuUfUfaaaCfuAfacacasag		CUUGUGUUAGUAAUAAACGUCUU	
AD-1634331	gsusguGfuAfaUfaaaacgucL96		asAfsagaCfGfUfuaaAfcUfaacacsasa		UUGUGUUAGUAAUAAACGUCUUG	
AD-1634332	usgsuuGfUfaUfAfaacgucL96		asCfsaagAfcGfUfuuaUfaCfuaacacsasa		UGUGUUAGUAAUAAACGUCUUGC	
AD-1634333	gsusuaguAfaUfAfaacgucL96		asGfscaaGfaCfGfuuaUfuAfcuaacsasc		GUGUUAGUAAUAAACGUCUUGCC	
AD-1634334	ususaguAfuAfaAfcgucL96		asGfsgcaAfgAfcfguuAfuUfaaacsasa		UGUUAGUAAUAAACGUCUUGCCA	
AD-1634342	asasagUcfUfGfCfcacaaagL96		asCfsuuUfuGfUfggcaAfgAfcguuasasu		AUAAACGUCUUGGCCACAAUAAAGC	
AD-1634343	asascgUcfUfGfCfcacaaagL96		asGfscuuAfuUfGfuggcAfaGfacguusasa		UAAACGUCUUGGCCACAAUAAAGCC	
AD-1634344	ascsugUfgCfCfAfaaaagccL96		asGfsgcuUfaUfUfuggCfaAfgacguususu		AAACGUCUUGGCCACAAUAAAGCCU	
AD-68585	asgsuuGfaAfcAfaaaagggL96		asCfscgaAfuUfUfuuuUfcUfaacacususg		CAAGUUGAGAAACAAAAAUUGGGU	

Table 4. Unmodified Sense and Antisense Strand Sequences of Angiotensinogen (AGT) dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_001384479.1	Antisense Sequence 5' to 3'	SEQ ID NO:	Range on NM_001384479.1
AD-1657992	AGCCUGAGGGCCACCAUCCUU		86-106	AAGGAUGGUGCCCUACAGGCUCA		84-106
AD-1657994	CCUGAGGGCCACCAUCCUCUU		88-108	AAGAGGAUGGUGGCCCUACAGGCU		86-108
AD-1657998	AGGGCCACCAUCCUCUGCCUU		92-112	AAGGCAGAGGATGUGGCCCUCA		90-112
AD-1658030	GUGACCGGGUGUACAUACACU		138-158	AGUGTATGUACACCCGGUACACCU		136-158
AD-1658032	CUUCCACCUCGUAUCCACAU		160-180	ATGUGGAUACGAGGUGGAAGG		158-180
AD-1658033	UUCCACCUCGUAUCCACAAU		161-181	ATUGTGGAUACGAGGUGGAAG		159-181
AD-1658034	UCCACCUCGUAUCCACAAU		162-182	AAUUGUGGAUACGAGGUGGAAG		160-182
AD-1658035	CCACCUCGUAUCCACAAUGU		163-183	ACAUTGTGGAUACGAGGUGGAA		161-183
AD-1658036	CACCUCGUAUCCACAAUGAU		164-184	ATCATUGUGGATGACGAGGUGGA		162-184
AD-1658037	ACCUCGUAUCCACAAUGAGU		165-185	ACUCAUTGUGGAUACGAGGUGG		163-185
AD-1658038	CCUCGUAUCCACAAUGAGAU		166-186	ATCUCATUGUGGAUACGAGGUG		164-186
AD-1658039	CUCGUAUCCACAAUGAGAGU		167-187	ACUCTCAUUGUGGAUACGAGAGU		165-187
AD-1658040	UCGUAUCCACAAUGAGAGUU		168-188	AACUCUCAUUGTGGAUACGAGG		166-188
AD-1658041	CGUCAUCCACAAUGAGAGUAU		169-189	ATACTCTCAUUGUGGAUACGAG		167-189

AD-1658042	GUCAUCCACAAUGAGAGUACU	170-190	AGUACUCUCAUTGUGGAUGACGA	168-190
AD-1658043	UCAUCCACAAUGAGAGUACCU	171-191	AGGUACTCUCATUGUGGAUGACG	169-191
AD-1658044	CAUCCACAAUGAGAGUACCUU	172-192	AAGGTACUCUCUCAUUGUGGAUGAC	170-192
AD-1658045	AUCCACAAUGAGAGUACCUUGU	173-193	ACAGGUACUCUCUCAUUGUGGAUGA	171-193
AD-1658046	UCCACAAUGAGAGUACCUUGU	174-194	AACAGGTACUCTCAUUGUGGAUG	172-194
AD-1658047	CCACAAUGAGAGUACCUUGUGU	175-195	ACACAGGUACUCUCUCAUUGUGGAU	173-195
AD-1658048	CACAAUGAGAGUACCUUGUGAU	176-196	ATCACAGGUACTCUCUCAUUGUGGA	174-196
AD-1658049	ACAAUGAGAGUACCUUGUGAGU	177-197	ACUCACAGGUACUCUCUCAUUGUGG	175-197
AD-1658050	CAAUGAGAGUACCUUGUGAGCU	178-198	AGCUCACAGGUACUCUCUCAUUGUG	176-198
AD-1658051	AAUGAGAGUACCUUGUGAGCAU	179-199	ATGCTCACAGGTACUCUCUCAUUGU	177-199
AD-1658052	AUGAGAGUACCUUGUGAGCAGU	180-200	ACUGCUCACAGGUACUCUCUCAUUG	178-200
AD-1658053	UGAGAGUACCUUGUGAGCAGCU	181-201	AGCUGCTCACAGGUACUCUCUCAU	179-201
AD-1658054	GAGAGUACCUUGUGAGCAGCUU	182-202	AAGCTGCUCACAGGUACUCUCUCAU	180-202
AD-1658055	AGAGUACCUUGUGAGCAGCUGU	183-203	ACAGCUGCUCACAGGUACUCUCA	181-203
AD-1658056	GAGUACCUUGUGAGCAGCUGGU	184-204	ACCAGCTGCUCACAGGUACUCUC	182-204
AD-1658057	AGUACCUUGUGAGCAGCUGGCU	185-205	AGCCAGCUGCUCACAGGUACUCUCU	183-205
AD-1658058	GUACCUUGUGAGCAGCUGGCAU	186-206	ATGCCAGCUGCTCACAGGUACUC	184-206

AD-1658059	UACCUUGUGAGCAGCUGGCAAU	187-207	ATUGCCAGCUGCUCACAGGUACU	185-207
AD-1658184	AAUGGUCGGGAUGCUGGCCAU	352-372	ATGGCCAGCAUCCCGACCAUUGC	350-372
AD-1658185	AUGUCGGGAUGCUGGCCAAU	353-373	ATUGGCCAGCATCCCGACCAUUG	351-373
AD-1658186	UGGUCGGGAUGCUGGCCAAU	354-374	AGUUGGCCAGCAUCCCGACCAUU	352-374
AD-1658187	GGUCGGGAUGCUGGCCAAU	355-375	AAGUTGGCCAGCAUCCCGACCAU	353-375
AD-1658188	GUCGGGAUGCUGGCCAAU	356-376	AAAGTUGGCCAGCAUCCCGACCA	354-376
AD-1658189	UCGGGAUGCUGGCCAAU	357-377	AGAAAGTUGGCCAGCAUCCCGACC	355-377
AD-1658190	CGGGAUGCUGGCCAAU	358-378	AAGAAAGTUGGCCAGCAUCCCGAC	356-378
AD-1658191	GGGAUGCUGGCCAAU	359-379	AAAGAAAGUUGGCCAGCAUCCCGA	357-379
AD-1658192	GGAUGCUGGCCAAU	360-380	ACAAGAAGUUGGCCAGCAUCCCG	358-380
AD-1658193	GAUGCUGGCCAAU	361-381	ACCAAGAAGUUGGCCAGCAUCC	359-381
AD-1658196	GCUGGCCAAU	364-384	AAGCCCCAAGAAGUUGGCCAGCAU	362-384
AD-1658197	CUGGCCAAU	365-385	AAAGCCCCAAGAAGUUGGCCAGCA	363-385
AD-1658200	GCCAAU	368-388	ACGGAAGCCCCAAGAAGUUGGCCA	366-388
AD-1658201	CCAAU	369-389	AACGGAAGCCCCAAGAAGUUGGCC	367-389
AD-1658202	CAACU	370-390	ATACGGAAGCCCCAAGAAGUUGGC	368-390
AD-1658203	AACU	371-391	AAUACGGAAGCCCCAAGAAGUUGG	369-391

AD-1658204	ACUUCUUGGGCUUCCGUUAU		372-392	ATAUACGGAAAGCCCAAGAAAGUUUG		370-392
AD-1658205	CUUCUUGGGCUUCCGUUAU		373-393	AAUATACGGAAGCCCAAGAAAGUU		371-393
AD-1658206	UUCUUGGGCUUCCGUUAU		374-394	ATAUAUACGGAAGCCCAAGAAAGU		372-394
AD-1658207	UCUUGGGCUUCCGUUAU		375-395	AAUATATACGGAAGCCCAAGAAAG		373-395
AD-1658208	CUUGGGCUUCCGUUAU		376-396	ACAUUAUACGGAAGCCCAAGAA		374-396
AD-1658209	UUGGGCUUCCGUUAU		377-397	ACCATATAUACGGAAGCCCAAGA		375-397
AD-1658210	UGGGCUUCCGUUAU		378-398	AGCCAUUAUACGGAAGCCCAAG		376-398
AD-1658211	GGGCUUCCGUUAU		379-399	ATGCCATAUAUACGGAAGCCCA		377-399
AD-1658212	GGCUUCCGUUAU		380-400	AAUGCCAUUAUATACGGAAAGCCCA		378-400
AD-1658213	GCUUCCGUUAU		381-401	ACAUGCCAUUAUACGGAAGCC		379-401
AD-1658220	UAUAUUGGCAUGCACAGUGU		388-408	ACACTGTGCAUGGCCAUUAUACG		386-408
AD-1658221	AUAUUGGCAUGCACAGUGAU		389-409	ATCACUGUGCATGCCAUUAUAC		387-409
AD-1658222	UAUAUGGCAUGCACAGUGAGU		390-410	ACUCACTGUGCAUGGCCAUUAUA		388-410
AD-1658223	AUAUGGCAUGCACAGUGAGCU		391-411	AGCUCACUGUGCAUGGCCAUUAU		389-411
AD-1658224	UAUGGCAUGCACAGUGAGCUU		392-412	AAGCTCACUGUGCAUGGCCAUUA		390-412
AD-1658225	AUGGCAUGCACAGUGAGCUAU		393-413	ATAGCUCACUGTGCAUGGCCAUU		391-413
AD-1658226	UGGCAUGCACAGUGAGCUAUU		394-414	AAUAGCTCACUGUGCAUGGCCAU		392-414

AD-1658227	GGCAUGCACAGUGAGCUAUGU		395-415	ACAUAGCUCACCTGUGCAUGCCAU		393-415
AD-1658228	GCAUGCACAGUGAGCUAUGGU		396-416	ACCATAGCUCACUGUGCAUGCCA		394-416
AD-1658242	UGGACCCUUGGCCUCUCUCUU		460-480	AAGAGAGAGGCCAGGGUGCCAAA		458-480
AD-1658243	GGCACCCUUGGCCUCUCUCUAU		461-481	ATAGAGAGAGGCCAGGGUGCCAA		459-481
AD-1658288	GACAGGCUACAGGCAAUCCUU		506-526	AAGGAUTGCCUGUAGCCUGUCAG		504-526
AD-1658289	ACAGGCUACAGGCAAUCCUGU		507-527	ACAGGATUGCCTGUAGCCUGUCA		505-527
AD-1658313	UUCCUUGGAAGGACAAAGAAU		531-551	AGUUCUTGUCCTUCCAAAGGAACA		529-551
AD-1658315	CCUUGGAAAGGACAAAGAACUGU		533-553	ACAGTUCUUUGUCCUUCCAAAGGAA		531-553
AD-1658316	CUUGGAAGGACAAAGAACUGCU		534-554	AGCAGUTCUUUGTCCUUCCAAAGGA		532-554
AD-1658448	CACCUGAAGCAGCCGUUUGUU		692-712	AACAAACGGCUGCUUCAGGUGCA		690-712
AD-1658451	CUGAAGCAGCCGUUUGUGCAU		695-715	ATGCACAAACGGCUGCUUCAGGU		693-715
AD-1658463	UUUGUGCAGGGCCUGGCUCUU		707-727	AAGAGCCAGGGCCUUGCACAAACG		705-727
AD-1658464	UUGUGCAGGGCCUGGCUCUCU		708-728	AGAGAGCCAGGGCCUUGCACAAAC		706-728
AD-1658465	UGUGCAGGGCCUGGCUCUCUU		709-729	AAGAGAGCCAGGGCCUUGCACAAA		707-729
AD-1658466	GUGCAGGGCCUGGCUCUCUAU		710-730	ATAGAGAGCCAGGGCCUUGCACAA		708-730
AD-1658467	UGCAGGGCCUGGCUCUCUAUU		711-731	AAUAGAGAGCCAGGGCCUUGCACA		709-731
AD-1658484	ACGCUCUCUGGACUUCACAGU		748-768	ACUGTGAAGUCCAGAGAGCCGUGG		746-768

AD-1658485	CGCUCUCUGGACUUCACAGAU	749-769	ATCUGUGAAGUCCAGAGAGCGUG	747-769
AD-1658519	CUGAGAAAGAUUGACAGGUUCU	783-803	AGAACCTGUCAAUCUUCUCAGCA	781-803
AD-1658520	UGAGAAAGAUUGACAGGUUCAU	784-804	ATGAAACCUGUCAAUUCUUCACAGC	782-804
AD-1658521	GAGAAAGAUUGACAGGUUCAU	785-805	AAUGAACCCUGUCAAUUCUUCACAG	783-805
AD-1658522	AGAAAGAUUGACAGGUUCAUGU	786-806	ACAUGAACCCUGTGCAAUCUUCUCA	784-806
AD-1658523	GAAAGAUUGACAGGUUCAUGCU	787-807	AGCATGAACCUGUCAAUUCUUCUC	785-807
AD-1658524	AAGAUUGACAGGUUCAUGCAU	788-808	ATGCAUGAACCCTGUCAAUCUUCU	786-808
AD-1658525	AGAUUGACAGGUUCAUGCAGU	789-809	ACUGCATGAACCUGUCAAUUCUUC	787-809
AD-1658526	GAUUGACAGGUUCAUGCAGGU	790-810	ACCUGCAUGAACCCUGUCAAUUCU	788-810
AD-1658527	AUUGACAGGUUCAUGCAGGCU	791-811	AGCCTGCAUGAACCCUGUCAAUUCU	789-811
AD-1658528	UUGACAGGUUCAUGCAGGCUU	792-812	AAGCCUGCAUGAACCCUGUCAAUUC	790-812
AD-1658529	UGACAGGUUCAUGCAGGCGU	793-813	ACAGCCTGCAUGAACCCUGUCAAU	791-813
AD-1658530	GACAGGUUCAUGCAGGCGU	794-814	AACAGCCUGCATGAACCUGUCA	792-814
AD-1658531	ACAGGUUCAUGCAGGCGUGUGU	795-815	ACACAGCCUGCAUGAACCCUGUCA	793-815
AD-1658535	GUUCAUGCAGGCGUGUGACAGU	799-819	ACUGTCACAGCCUGCAUGAACCCU	797-819
AD-1658539	AUGCAGGCGUGUGACAGGAUGU	803-823	ACAUCCTGUCACAGCCUGCAUGA	801-823
AD-1658541	GCAGGCGUGUGACAGGAUGGAU	805-825	ATCCAUCUGUCACAGCCUGCAU	803-825

AD-1658542	CAGGCUGUGACAGGAUGGAAU	806-826	ATUCCATCCUGTCACAGCCUGCA	804-826
AD-1658605	GCUUUAACACCCUACGUCCAU	869-889	ATGGACGUAGGTGUUGAAAGCCA	867-889
AD-1658650	GAGUUCUGGGUGGACAACAGU	935-955	ACUGTUGUCCACCCAGAACUCCU	933-955
AD-1658661	GGACAACAGCACCCUCAGUGUU	946-966	AACACUGAGGUGCUGUUGUCCAC	944-966
AD-1658662	GACAACAGCACCCUCAGUGUCU	947-967	AGACACTGAGGTGCUGUUGUCCA	945-967
AD-1658663	ACAACAGCACCCUCAGUGUCUU	948-968	AAGACACUGAGGUGCUGUUGUCC	946-968
AD-1658664	CAACAGCACCCUCAGUGUCUGU	949-969	ACAGACACUGAGGUGCUGUUGUC	947-969
AD-1658665	AACAGCACCCUCAGUGUCUGUU	950-970	AACAGACACUGAGGUGCUGUUGU	948-970
AD-1658801	AUGCCUCUGACCCUGGACAAGU	1086-1106	ACUUGUCCAGGTACAGAGGCAUAG	1084-1106
AD-1658802	UGCCUCUGACCCUGGACAAGGU	1087-1107	ACCUTGTCCAGGUCAGAGGCAUA	1085-1107
AD-1658818	AAGGUGGAGGGUCUCACUUUU	1103-1123	AAAAAGUGAGACCCUCCACCUUGU	1101-1123
AD-1658819	AGGUGGAGGGUCUCACUUUCU	1104-1124	AGAAAAGTGAGACCCUCCACCUUG	1102-1124
AD-1658820	GGUGGAGGGUCUCACUUUCCU	1105-1125	AGGAAAAGUGAGACCCUCCACCUU	1103-1125
AD-1658821	GUGGAGGGUCUCACUUUCCAU	1106-1126	ATGGAAAAGUGAGACCCUCCACCU	1104-1126
AD-1658824	GAGGGUCUCACUUUCCAGCAU	1109-1129	ATGCTGGAAAAGTGAGACCCUCCU	1107-1129
AD-1658825	AGGGUCUCACUUUCCAGCAAU	1110-1130	ATUGCUGGAAAAGUGAGACCCUCC	1108-1130
AD-1658826	GGGUCUCACUUUCCAGCAAAU	1111-1131	ATUUGCTGGAAAAGUGAGACCCUC	1109-1131

AD-1658827	GGUCUCACUUUCCAGCAAAAU	1112-1132	ATUUTGCUUGAAAGUGAGACCCU	1110-1132
AD-1658828	GUCUCACUUUCCAGCAAAACU	1113-1133	AGUUTGCUUGAAAGUGAGACCC	1111-1133
AD-1658829	UCUCACUUUCCAGCAAAACUU	1114-1134	AAGUTUTGCUUGAAAGUGAGACC	1112-1134
AD-1658830	CUCACUUUCCAGCAAAACUCU	1115-1135	AGAGTUTGCUUGAAAGUGAGAC	1113-1135
AD-1658831	UCACUUUCCAGCAAAACUCCU	1116-1136	AGGAGUTUUGCTGGAAGUGAGA	1114-1136
AD-1658832	CACUUUCCAGCAAAACUCCCU	1117-1137	AGGGAGTUUUGCUGGAAAGUGAG	1115-1137
AD-1658833	ACUUUCCAGCAAAACUCCCUU	1118-1138	AAGGGAGUUUUGCUGGAAAGUGA	1116-1138
AD-1658834	CUUUUCCAGCAAAACUCCCUU	1119-1139	AGAGGGAGUUUTGCUUGGAAAGUG	1117-1139
AD-1658835	UUUCCAGCAAAACUCCCUCAU	1120-1140	ATGAGGGAGUUUTGCUUGGAAAGU	1118-1140
AD-1658836	UUCAGCAAAACUCCCUCAAU	1121-1141	ATUGAGGGAGUTUUGCUGGAAAG	1119-1141
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AD-1658840	AGCAAAACUCCCUCAACUGGU	1125-1145	ACCAGUTGAGGGAGUUUUGCUGG	1123-1145
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AD-1658842	CAAAACUCCCUCAACUGGAUU	1127-1147	AAUCCAGUUUGAGGGAGUUUUGCU	1125-1147
AD-1658843	AAAACUCCCUCAACUGGAUGU	1128-1148	ACAUCCAGUUUGAGGGAGUUUUGC	1126-1148

AD-1658844	AAACUCCCUCAACUGGAUGAU	1129-1149	ATCATCCAGUUUGAGGGAGUUUUG	1127-1149
AD-1658845	AACUCCCUCAACUGGAUGAAU	1130-1150	ATUCAUCCAGUTGAGGGAGUUUU	1128-1150
AD-1658846	ACUCCCUCAACUGGAUGAAGU	1131-1151	ACUUCATCCAGTUGAGGGAGUUU	1129-1151
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AD-1658848	UCCCUCAACUGGAUGAAGAAU	1133-1153	ATUCTUCAUCCAGUUUGAGGGAGU	1131-1153
AD-1658849	CCCUCAACUGGAUGAAGAAAU	1134-1154	ATUUCUTCAUCCAGUUUGAGGGAG	1132-1154
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AD-1658875	AGGAUCUUUAUGACCUUGCAGGU	1201-1221	ACCUGCAGGUCAUUAAGAUCUUG	1199-1221
AD-1658880	CUUAUGACCUUGCAGGACCUGU	1206-1226	ACAGGUCCUGCAGGUCAUAAGAU	1204-1226
AD-1658929	CGAGCUGAACCUUGCAAAAUAU	1261-1281	AAUUTUTGCAGGUUCAGCUCGGU	1259-1281
AD-1658930	GAGCUGAACCUUGCAAAAUAU	1262-1282	AAAUTUTUGCAGGUUCAGCUCGG	1260-1282
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AD-1658958	UGCUGAACAGCAUUUUUUUU	1311-1331	AAAAAAUUGCUGUUUCAGCACCC	1309-1331
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AD-1659059	CGCCCAUUCUGUUUGCUGUU	1412-1432	AACAGCAAAACAGGAAUGGGCGGU	1410-1432
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AD-1659064	AUUCCUGUUUGCUGUGUAUGU	1417-1437	ACAUACACAGCAAAACAGGAAUGG	1415-1437
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AD-1659069	UGUUUGCUGUGUAUGAUCAAU	1422-1442	ATUGAUCAUACACAGCAAAACAGG	1420-1442
AD-1659070	GUUUGCUGUGUAUGAUCAAAU	1423-1443	ATUUGATCAUACACAGCAAAACAG	1421-1443
AD-1659071	UUUGCUGUGUAUGAUCAAAAGU	1424-1444	ACUUTGAUCAUACACAGCAAAACA	1422-1444
AD-1659161	CAGUCUCCCCACCUUUUCUUCU	1606-1626	AGAAGAAAAAGGTGGGAGACUGGG	1604-1626
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AD-1659208	CCGUUUCUCUCCUUGGUCUAAAGU	1655-1675	ACUUAAGACCAAGGAGAAACGGCU	1653-1675
AD-1659209	CGUUUCUCUCCUUGGUCUAAAGUU	1656-1676	AACUTAGACCAAGGAGAAACGGC	1654-1676
AD-1659210	GUUUCUCCUUGGUCUAAAGUGU	1657-1677	ACACTUAGACCAAGGAGAAACGG	1655-1677
AD-1659282	GUUUGCUGGGUUUAUUUUAGU	1729-1749	ACUAAAUAUAAACCCAGCAAACUG	1727-1749
AD-1659283	UUUGCUGGGUUUAUUUUAGAU	1730-1750	ATCUAAAUAUAAACCCAGCAAACU	1728-1750
AD-1659284	UUGCUGGGUUUAUUUUAGAGU	1731-1751	ACUCTAAAUAUAAACCCAGCAAAC	1729-1751
AD-1659285	UGCUGGGUUUAUUUUAGAGAU	1732-1752	ATCUCUAAAUAUAAACCCAGCAAA	1730-1752
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AD-1659288	UGGGUUUAUUUUAGAGAAUGU	1735-1755	ACAUTCTCUAAAUAUAAACCCAGC	1733-1755
AD-1659289	GGGUUUAUUUUAGAGAAUGGU	1736-1756	ACCATUCUCUAAAUAUAAACCCAG	1734-1756
AD-1659290	GAGGCAAGAACCAAGUGUUUAU	1763-1783	ATAAACACUGGTUCUUGCCUCCC	1761-1783
AD-1659291	AGGCAAGAACCAAGUGUUUAUGU	1764-1784	ACUAAACACACUGGUUCUUGCCUCC	1762-1784
AD-1659292	GGCAAGAACCAAGUGUUUAAGCU	1765-1785	AGCUAAACACACUGGUUCUUGCCUC	1763-1785
AD-1659293	GCAAGAACCAAGUGUUUAAGCGU	1766-1786	ACGCTAAACACTGGUUCUUGCCU	1764-1786

AD-1659294	CAAGAACCAAGUGUUUAGCGCU	1767-1787	AGCGCUAAACACACUGGUUCUUGCC	1765-1787
AD-1659295	AAGAACCAAGUGUUUAGCGCGU	1768-1788	ACGCGCTAAACACACUGGUUCUUGC	1766-1788
AD-1659296	AGAACCAAGUGUUUAGCGCGGU	1769-1789	ACCGCGCUAAACACACUGGUUCUUG	1767-1789
AD-1659297	GAAACAGUGUUUAGCGCGGGU	1770-1790	ACCCGCGCUAAACACACUGGUUCUU	1768-1790
AD-1659298	AACCAGUGUUUAGCGCGGGAU	1771-1791	ATCCCGCGCUAAACACACUGGUUCU	1769-1791
AD-1659321	CUGUCCAAAAAGAAUUCCAU	1794-1814	ATGGAAATUCUUTUUUGGAACAGUA	1792-1814
AD-1659322	UGUUCCAAAAAAGAAUUCCAAU	1795-1815	ATUGGAAUUCUTUUUGGAACAGU	1793-1815
AD-1659323	GUUCCAAAAAGAAUUCCAAACU	1796-1816	AGUUGGAAUUCTUUUUUGGAACAG	1794-1816
AD-1659325	UCCAAAAAGAAUUCCAAACCGU	1798-1818	ACGGTUGGAAUTCUUUUUUGGAAC	1796-1818
AD-1659326	CCAAAAAGAAUUCCAAACCGAU	1799-1819	ATCGGUTGGAATUCUUUUUUGGAA	1797-1819
AD-1659327	CAAAAAGAAUUCCAAACCGACU	1800-1820	AGUCGGTUGGAAUUCUUUUUUGGA	1798-1820
AD-1659328	AAAAAGAAUUCCAAACCGACCU	1801-1821	AGGUCCGUUGGAAUUCUUUUUUGG	1799-1821
AD-1659329	AAAAGAAUUCCAAACCGACCAU	1802-1822	ATGGTCGGUUGGAAUUCUUUUUUG	1800-1822
AD-1659330	AAAGAAUUCCAAACCGACCAU	1803-1823	ACUGGUCGGUUGGAAUUCUUUUUU	1801-1823
AD-1659331	AAGAAUUCCAAACCGACCAU	1804-1824	AGCUGGTCGGUTGGAUUUCUUUUU	1802-1824
AD-1659332	AGAAUUCCAAACCGACCAU	1805-1825	AAGCTGGUCGGTUGGAAUUCUUU	1803-1825
AD-1659333	GAAUUCCAAACCGACCAU	1806-1826	AAAGCUGGUCGGUUGGAAUUCUU	1804-1826

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AD-1659334	AAUUCCAAACCGACACGCUUGU	1807-1827	ACAAGCTGGUCGGUUGGAAUUCU	1805-1827
AD-1659335	AUUCCAAACCGACACGCUUGUU	1808-1828	AACAAAGCUGGUCGGUUGGAAUUC	1806-1828
AD-1659336	UUCCAAACCGACACGCUUGUUU	1809-1829	AAACAAGCUGGTCTGGUUGGAAUU	1807-1829
AD-1659337	UCCAAACCGACACGCUUGUUUU	1810-1830	AAAAACAAGCUGGUCGGUUGGAAU	1808-1830
AD-1659338	CCAAACCGACACGCUUGUUUGU	1811-1831	ACAAAACAAGCUGGUCGGUUGGAA	1809-1831
AD-1659339	CAACCGACACGCUUGUUUGUU	1812-1832	AACAACAAGCTGGUCGGUUGGA	1810-1832
AD-1659340	AACCGACACGCUUGUUUGUGU	1813-1833	ACACAACAAGCUGGUCGGUUGG	1811-1833
AD-1659341	ACCGACACGCUUGUUUGUGAU	1814-1834	ATCACAACAAGCUGGUCGGUUG	1812-1834
AD-1659342	CCGACACGCUUGUUUGUGAAU	1815-1835	ATUCACAACAAGCUGGUCGGUU	1813-1835
AD-1659343	CGACACGCUUGUUUGUGAAAU	1816-1836	ATUUCACAACAAGCUGGUCGGU	1814-1836
AD-1659344	GACCAGCUUGUUUGUGAAACU	1817-1837	AGUUTCACAACAAGCUGGUCGG	1815-1837
AD-1659345	ACCAGCUUGUUUGUGAAACAU	1818-1838	ATGUTUCACAACAAGCUGGUCG	1816-1838
AD-1659346	CCAGCUUGUUUGUGAAACAAU	1819-1839	ATUGTUTCACAACAAGCUGGUC	1817-1839
AD-1659347	CAGCUUGUUUGUGAAACAAAU	1820-1840	ATUUGUTUCACAACAAGCUGGU	1818-1840
AD-1659348	AGCUUGUUUGUGAAACAAAAU	1821-1841	ATUUTGTUUCACAACAAGCUGG	1819-1841
AD-1659350	CUUGUUUGUGAAACAAAAAU	1823-1843	ATUUTUTGUUUUCACAACAAGCU	1821-1843
AD-1659351	UUGUUUGUGAAACAAAAAAGU	1824-1844	ACUUTUTUGUUTCACAACAAGC	1822-1844

AD-1659371	UGUUCUUUUUUCAGUUGAGU	1844-1864	ACUCAACUUUAGAAAAGGGAACACU	1842-1864
AD-1659372	GUUCCUUUUUCAAGUUGAGAU	1845-1865	ATCUCACUUUAGAAAAGGGAACAC	1843-1865
AD-1659373	UUCUUUUUUCAGUUGAGAAU	1846-1866	ATUCTAACUUUGAAAAGGGAACA	1844-1866
AD-1659382	CAAGUUGAGAACAAAAUUUGU	1855-1875	ACAATUTUUGUTCUCACUUUGAA	1853-1875
AD-1659383	AAGUUGAGAACAAAAUUUGGU	1856-1876	ACCAAUTUUUGTUCUCAAACUUGA	1854-1876
AD-1659384	AGUUGAGAACAAAAUUGGGU	1857-1877	ACCCAAUUUUUGUUCUCAAACUUG	1855-1877
AD-1659385	GUUGAGAACAAAAUUGGGUU	1858-1878	AACCCAAUUUUTGUUCUCAAACUU	1856-1878
AD-1659386	UUGAGAACAAAAUUGGGUUU	1859-1879	AAACCCAAUUUTGUUCUCAAACU	1857-1879
AD-1659387	UGAGAACAAAAUUGGGUUUU	1860-1880	AAAACCCAAUUTUUUGUUCUCAAC	1858-1880
AD-1659388	GAGAACAAAAUUGGGUUUUU	1861-1881	AAAAACCCAAUTUUUGUUCUCAAA	1859-1881
AD-1659389	AGAACAAAAUUGGGUUUUUAU	1862-1882	ATAAAACCCCAATUUUUGUUCUCA	1860-1882
AD-1659390	GAACAAAAUUGGGUUUUUAU	1863-1883	ATUAAAACCCCAUUUUUUGUUCUC	1861-1883
AD-1659391	AACAAAAUUGGGUUUUUAAU	1864-1884	ATUUAAAACCCCAUUUUUUGUUCU	1862-1884
AD-1659399	AGUAUACAUUUUUGCAUUGCU	1889-1909	AGCAAUGCAAAAUGUAUACUUU	1887-1909
AD-1659400	GUAUACAUUUUUGCAUUGCCU	1890-1910	AGGCAATGCAAAAAUGUAUACUU	1888-1910
AD-1659401	UAUACAUUUUUGCAUUGCCUU	1891-1911	AAGGCAUUGCAAAAUGUAUACU	1889-1911
AD-1659402	AUACAUUUUUGCAUUGCCUUU	1892-1912	AAAGGCAUUGCAAAAUGUAUAC	1890-1912

AD-1659405	CAUUUUUGCAUUGCCUUCGGU	1895-1915	ACCGAAGGCAATGCAAAAUGUA	1893-1915
AD-1659406	AUUUUUGCAUUGCCUUCGGUU	1896-1916	AACCGAAGGCAUUGCAAAAUGU	1894-1916
AD-1659407	UUUUUGCAUUGCCUUCGGUUU	1897-1917	AAACCGAAGGCAUUGCAAAAUG	1895-1917
AD-1659408	UUUUUGCAUUGCCUUCGGUUUU	1898-1918	AAAAACCGAAGGCAUUGCAAAAUA	1896-1918
AD-1659409	UUUGCAUUGCCUUCGGUUUGU	1899-1919	ACAAAACCGAAGGCAUUGCAAAA	1897-1919
AD-1659410	UUGCAUUGCCUUCGGUUUGUU	1900-1920	AACAAAACCGAAGGCAUUGCAAAA	1898-1920
AD-1659411	UGCAUUGCCUUCGGUUUUGUAU	1901-1921	ATACAAAACCGAAGGCAUUGCAAA	1899-1921
AD-1659412	GCAUUGCCUUCGGUUUUGUAUU	1902-1922	AAUACAAAACCGAAGGCAUUGCAA	1900-1922
AD-1659413	CAUUGCCUUCGGUUUUGUAUUU	1903-1923	AAAUACAAAACCGAAGGCAUUGCA	1901-1923
AD-1659414	AUUGCCUUCGGUUUUGUAUUUU	1904-1924	AAAAATACAAAACCGAAGGCAAUUGC	1902-1924
AD-1659415	UUGCCUUCGGUUUUGUAUUUAU	1905-1925	ATAAAUACAAAACCGAAGGCAAUUG	1903-1925
AD-1659416	UGCCUUCGGUUUUGUAUUUAGU	1906-1926	ACUAAAATACAAAACCGAAGGCAAU	1904-1926
AD-1659417	GCCUUCGGUUUUGUAUUUAGUU	1907-1927	AACUAAAUACAAAACCGAAGGCAA	1905-1927
AD-1659418	CCUUCGGUUUUGUAUUUAGUGU	1908-1928	ACACTAAAUACAAAACCGAAGGCA	1906-1928
AD-1659419	CUUCGGUUUUGUAUUUAGUGUU	1909-1929	AACACUAAAUAACAAACCGAAGGC	1907-1929
AD-1659420	UUCGGUUUUGUAUUUAGUGUCU	1910-1930	AGACACTAAAUACAAACCGAAGG	1908-1930
AD-1659421	UCGGUUUUGUAUUUAGUGUCUU	1911-1931	AAGACACUAAATACAAACCGAAG	1909-1931

AD-1659422	CGGUUUGUAUUUAGUGUCUUU	1912-1932	AAAGACACUAAAUAACAAACCGAA		1910-1932
AD-1659423	GGUUUGUAUUUAGUGUCUUUGU	1913-1933	ACAAGACACUAAAUAACAAACCGA		1911-1933
AD-1659424	GUUUGUAUUUAGUGUCUUUGAU	1914-1934	ATCAAGACACUAAAUAACAAACCG		1912-1934
AD-1659425	UUUGUAUUUAGUGUCUUUGAAU	1915-1935	ATUCAAGACACTAAAUACAAACC		1913-1935
AD-1659426	UUGUAUUUAGUGUCUUUGAAUU	1916-1936	AUUUCAAGACACUAAAUAACAAAC		1914-1936
AD-1659427	UGUAUUUAGUGUCUUUGAAUGU	1917-1937	ACAUTCAAGACACUAAAUAACAAA		1915-1937
AD-1659428	GUAUUUAGUGUCUUUGAAUGUU	1918-1938	AACATUCAAGACACUAAAUAACAA		1916-1938
AD-1659429	UAUUUAGUGUCUUUGAAUGUAU	1919-1939	ATACAUTCAAGACACUAAAUAACA		1917-1939
AD-1659430	AUUUAGUGUCUUUGAAUGUAAU	1920-1940	ATUACATUCAAGACACUAAAUAUAC		1918-1940
AD-1659431	UUUAGUGUCUUUGAAUGUAAAGU	1921-1941	ACUUACAUUUCAAGACACUAAAUA		1919-1941
AD-1659432	UUAGUGUCUUUGAAUGUAAAGAU	1922-1942	ATCUTACAUUUCAAGACACUAAAUA		1920-1942
AD-1659433	UAGUGUCUUUGAAUGUAAAGAAU	1923-1943	ATUCTUACAUUUCAAGACACUAAA		1921-1943
AD-1659434	AGUGUCUUUGAAUGUAAAGAACU	1924-1944	AGUUCUTACAUTCAAGACACUAA		1922-1944
AD-1659436	UGUCUUUGAAUGUAAAGAACAUU	1926-1946	AAUGTUCUUACAUUCAAGACACU		1924-1946
AD-1659437	GUCUUUGAAUGUAAAGAACAUUGU	1927-1947	ACAUGUTCUUACAUUCAAGACAC		1925-1947
AD-1659440	UUGAAUGUAAAGAACAUAGACCU	1930-1950	AGGUCATGUUUCTUACAUUUCAAGA		1928-1950
AD-1659446	GUAAGAACAUAGACCUCCGUGU	1936-1956	ACACGGAGGUGUCAUGUUCUUAUACAU		1934-1956

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AD-1659447	UAAGAAACAUGACCUCGUGUU	1937-1957	AACACGGAGGUCAUGUUCUACA	1935-1957
AD-1659448	AAGAAACAUGACCUCGUGUAU	1938-1958	ATACACGGAGGTCAUGUUCUAC	1936-1958
AD-1659449	AGAAACAUGACCUCGUGUAGU	1939-1959	ACUACACGGAGGUCAUGUUCUUA	1937-1959
AD-1659450	GAAACAUGACCUCGUGUAGUU	1940-1960	AACUACACGGAGGUCAUGUUCUU	1938-1960
AD-1659451	AACAUGACCUCGUGUAGUGU	1941-1961	ACACTACACGGAGGUCAUGUUCU	1939-1961
AD-1659452	ACAUGACCUCGUGUAGUGUU	1942-1962	AACACUACACGGAGGUCAUGUUC	1940-1962
AD-1659453	CAUGACCUCGUGUAGUGUCU	1943-1963	AGACACTACACGGAGGUCAUGUU	1941-1963
AD-1659454	AUGACCUCGUGUAGUGUCUU	1944-1964	AAGACACUACACGGAGGUCAUGU	1942-1964
AD-1659481	CUUAGUUUUUUUCCACAGAUGU	1971-1991	ACAUCUGUGGAAAAAACUAAGGU	1969-1991
AD-1659482	UUAGUUUUUUUCCACAGAUGCU	1972-1992	AGCATCTGUGGAAAAAACUAAGG	1970-1992
AD-1659483	UAGUUUUUUUCCACAGAUGCUU	1973-1993	AAGCAUCUGUGGAAAAAACUAAG	1971-1993
AD-1659484	AGUUUUUUUCCACAGAUGCUUU	1974-1994	AAAGCATCUGUGGAAAAAACUAA	1972-1994
AD-1659485	GUUUUUUUUCCACAGAUGCUUGU	1975-1995	ACAAGCAUCUGTGGAACAAACUA	1973-1995
AD-1659487	UUUUUCCACAGAUGCUUUGUGU	1977-1997	ACACAAAGCAUCTGUGGAAAAAAC	1975-1997
AD-1659488	UUUUUCCACAGAUGCUUUGUGAU	1978-1998	ATCACAAAGCAUCUGUGGAAAAAA	1976-1998
AD-1659489	UUUCCACAGAUGCUUUGUGAUU	1979-1999	AAUCACAAAGCATCUGUGGAAAAA	1977-1999
AD-1659490	UUCCACAGAUGCUUUGUGAUUU	1980-2000	AAAUACAAAGCAUCUGUGGAAAA	1978-2000

AD-1659491	UCCACAGAUAGCUUGUGAUUUU	1981-2001	AAAATCACAAGCAUCUGUGGAAA		1979-2001
AD-1659492	CCACAGAUGCUUGUGAUUUUU	1982-2002	AAAAAUCACAAGCAUCUGUGGAA		1980-2002
AD-1659493	CACAGAUGCUUGUGAUUUUUU	1983-2003	AAAAAATCACAAGCAUCUGUGGA		1981-2003
AD-1659537	ACCUGAAUUUCUGUUUGAAUU	2027-2047	AAUUCAAAACAGAAAUUCAGGUGC		2025-2047
AD-1659538	CCUGAAUUUCUGUUUGAAUGU	2028-2048	ACAUTCAAACAGAAAUUCAGGUG		2026-2048
AD-1659559	GGAAACCAUAGCUGGUUAUUUU	2049-2069	AAAATAACCCAGCUAUGGUUCCGC		2047-2069
AD-1659560	GAAACCAUAGCUGGUUAUUUCU	2050-2070	AGAAAUAAACCAGCUAUGGUUCCG		2048-2070
AD-1659561	AACCAUAGCUGGUUAUUUCUU	2051-2071	AAGAAATAACCCAGCUAUGGUUCC		2049-2071
AD-1659562	ACCAUAGCUGGUUAUUUCUCU	2052-2072	AGAGAAAUAAACCAGCUAUGGUUC		2050-2072
AD-1659563	CCAUAGCUGGUUAUUUCUCCU	2053-2073	AGGAGAAAUAAACCAGCUAUGGUU		2051-2073
AD-1659582	CCUUGUGUUAAGUAAUAAACGU	2072-2092	ACGUTUAUUACTAACACAAAGGGA		2070-2092
AD-1659583	CUUGUGUUAAGUAAUAAACGUU	2073-2093	AACGTUTAUUACUAAACACAAAGGG		2071-2093
AD-1659584	UUGUGUUAAGUAAUAAACGUCU	2074-2094	AGACGUTUAUUACUAAACACAAAGG		2072-2094
AD-1659585	UGUGUUAAGUAAUAAACGUCUU	2075-2095	AAGACGTUUUAUTACUAAACACAAG		2073-2095
AD-1659586	GUGUUAAGUAAUAAACGUCUUU	2076-2096	AAAGACGUUUUAUTACUAAACACAA		2074-2096
AD-1659587	UGUUAGUAAUAAACGUCUUUGU	2077-2097	ACAAGACGUUUUAUUACUAAACACA		2075-2097
AD-1659588	GUUAGUAAUAAACGUCUUGCU	2078-2098	AGCAAGACGUUTAUUACUAAACAC		2076-2098

AD-1321384	UCUCCACCUUUUCUUAU	1609-1629	ATUAGAAGAAAAGUGGAGACU	1607-1629
AD-1321390	CCUCAAACUGGAUGAAGAAACU	1135-1155	AGUUTCTUCAUCCAGUUGAGGGA	1133-1155

Table 5. Modified Sense and Antisense Strand Sequences of Angiotensinogen (AGT) dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1657992	asgscucgagGfGfCfcaccauccuL96		asdAsggdAudGguggdCcCfcucaggcsa		UGAGCCUGAGGGCCACCAUCCUC	
AD-1657994	csesugagggCfCfAfcaccauccuL96		asdAsgadGgdAuggdGgCfcucaggcsu		AGCCUGAGGGCCACCAUCCUCUG	
AD-1657998	asgsgggcacCfAfufccucugccuL96		asdAsggdCadGaggadTgGfugggccscsa		UGAGGGCCACCAUCCUCUGCCUC	
AD-1658030	gsusgacggGfUfGfuacauacauL96		asdGsugdTadTguacdAcCfcgucacscsu		AGGUGACCGGGUGUACAUAACACC	
AD-1658032	csusuccaccUfCfGfucaccauL96		asdTsgudGgdAugacdGaGfugggagsgsg		CCCUUCCACCUUGUCAUCCACAA	
AD-1658033	ususcaccuCfGfUfcauccaauL96		asdTsugdTgdGaugadCgAfggggaaagsg		CCUUCCACCUUGUCAUCCACAAU	
AD-1658034	uscsaccucGfUfCfauccacaauL96		asdAsuudGudGgaugdAcGfaggggasag		CUUCCACCUUGUCAUCCACAAUG	
AD-1658035	csesaccucUfCfAfucaacaauL96		asdCsaudTgdTggandGaCfagggggsasa		UUCACCUUGUCAUCCACAAUGA	
AD-1658036	csasccucgCfAfUfcaacaauL96		asdTscadTudGuggadTgAfcgaggugsgsa		UCCACCUUGUCAUCCACAAUGAG	
AD-1658037	ascsccugacAfUfCfcaacaugauL96		asdCsucdAudTguggdAuGfagggugsgsg		CCACCUUGUCAUCCACAAUGAGA	
AD-1658038	csesuegucUfCfCfacaauagauL96		asdTscudCadTugudGaUfagggagsgusg		CACCUCGUCAUCCACAAUGAGAG	
AD-1658039	csuscgucacCfCfAfcacaugagauL96		asdCsucdTcdAuugudGgAfugagggagsgsu		ACCUCGUCAUCCACAAUGAGAGU	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1658040	usesgucaucCfAfCfaugagaguuL96		asdAscudCudCaungdTgGfauagacgasgsg		CCUCGUCAUCCACAAUGAGAGUA	
AD-1658041	csgsucauccAfCfAfaugagaguuL96		asdTsacdTcdTcaundGuGfgaugacgsasg		CUCGUCAUCCACAAUGAGAGUAC	
AD-1658042	gsuscauccaCfAfAfugagaguacuL96		asdGsuadCudCucadTgUfggaugacsaga		UCGUCAUCCACAAUGAGAGUACC	
AD-1658043	usesauccacAfAfUfgagaguaccuL96		asdGsgudAcdTcucadTuGfuggaugascsg		CGUCAUCCACAAUGAGAGUACCU	
AD-1658044	csusuccacaAfUfGfagaguaccuuL96		asdAsggdTadCucudAuUfguggaugsasc		GUCAUCCACAAUGAGAGUACCUG	
AD-1658045	asusccacaaUfGfAfagaguaccuguL96		asdCsagdgudAcucudCaUfuguggausgsa		UCAUCCACAAUGAGAGUACCUGU	
AD-1658046	uscsacaaUfGfAfagaguaccuguL96		asdAscadGgdTadTcUfuguggausgsu		CAUCCACAAUGAGAGUACCUGUG	
AD-1658047	csesacaangAfGfAfguaccuguL96		asdCsacdAgdGuacudCuCfaunguggsasu		AUCCACAAUGAGAGUACCUGUGA	
AD-1658048	csascaangaGfAfGfuaccuguL96		asdTscadCadGguacdTcUfcaunguggsa		UCCACAAUGAGAGUACCUGUGAG	
AD-1658049	ascsaungagAfGfUfaccugugaguL96		asdCsucdAcdAgguadCuCfucanuugsgsg		CCACAAUGAGAGUACCUGUGAGC	
AD-1658050	csasaugagaGfUfAfccugugagcuL96		asdGscudCadCagguAdUfcucauugsgsg		CACAAUGAGAGUACCUGUGAGCA	
AD-1658051	asasuugagUfAfCfcugugagcauL96		asdTsgcdTcdAcaggdTaCfucanuugsgsu		ACAAUGAGAGUACCUGUGAGCAG	
AD-1658052	asusgagaguAfCfCfugugagcaguL96		asdCsugdCudCacagdGuAfcuenuausgsu		CAAUGAGAGUACCUGUGAGCAGC	
AD-1658053	usgsagaguaCfCfUfgugagcaguL96		asdGscudGcdTcacadGgUfacuenuausu		AAUGAGAGUACCUGUGAGCAGCU	
AD-1658054	gsasagaguacCfUfGfugagcagcuL96		asdAsgcdTgdCucacdAgGfuacuenuasuu		AUGAGAGUACCUGUGAGCAGCUG	
AD-1658055	asgsaguaccUfGfUfgagcagcuL96		asdCsagdCudGcudCaGfguacuenuasuu		UGAGAGUACCUGUGAGCAGCUGG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1658056	gsasguaccuGfUfGfagcagcugguL96		asdCscadGedTgcuedAcAfgguacuusc		GAGAGUACCUGUGAGCAGCUGGGC	
AD-1658057	asgsuaccugUfGfAfgcagcugguL96		asdGscddAgdCugcudCaCfagguacuusc		AGAGUACCUGUGAGCAGCUGGGCA	
AD-1658058	gsusaccuGuGfAfgcagcugguL96		asdTsgcdCadGcugedTcAfeagguacuusc		GAGUACCUGUGAGCAGCUGGGCAA	
AD-1658059	usasccuGuGfAfgcagcugguL96		asdTsugdCcdAgcugdCuCfagguacuusc		AGUACCUGUGAGCAGCUGGGCAA	
AD-1658184	asasugguGfGfAfgcugggccauL96		asdTsggdCcdAgcaudCcCfaggaucuuusc		GCAAUGGUCGGGAUGCUGGGCCAA	
AD-1658185	asusggucGfAfgcugggccauL96		asdTsugdGcdCagcadTcCfaggaucuuusc		CAAUGGUCGGGAUGCUGGGCCAAC	
AD-1658186	usgsugcggGfUfGfugggccauL96		asdGsuudGgdCcagcdAuCfaggaucuuusc		AAUGGUCGGGAUGCUGGGCCAAACU	
AD-1658187	gsusugcggGfUfGfugggccauL96		asdAsgudTgdGccagdCaUfaggaucuuusc		AUGGUCGGGAUGCUGGGCCAAACU	
AD-1658188	gsuscgggGfUfGfugggccauL96		asdAsagdTudGccagdGcAfuaggaucuuusc		UGGUCGGGAUGCUGGGCCAAACUUC	
AD-1658189	uscsugggGfUfGfugggccauL96		asdGsaadGudTggccdAgCfaggaucuuusc		GGUCGGGAUGCUGGGCCAAACUUCU	
AD-1658190	csusggauGfUfGfugggccauL96		asdAsgadAgdTuggdCaGfaggaucuuusc		GUCCGGGAUGCUGGGCCAAACUUCU	
AD-1658191	gsusgaugGfUfGfugggccauL96		asdAsagdAadGuuggdCcAfggaucuuusc		UCGGGAUGCUGGGCCAAACUUCUUG	
AD-1658192	gsusgaugGfUfGfugggccauL96		asdCsaadGadAguugdGcCfaggaucuuusc		CGGGGAUGCUGGGCCAAACUUCUUGG	
AD-1658193	gsasugcggGfUfGfugggccauL96		asdCscadAgdAguugdGcCfaggaucuuusc		GGGAUGCUGGGCCAAACUUCUUGGG	
AD-1658196	gsesuggGfUfGfugggccauL96		asdAsgddCcdAagaadGuUfaggaucuuusc		AUGCUGGGCCAAACUUCUUGGGCUU	
AD-1658197	csusggccGfUfUfugggccauL96		asdAsagdCcdCaagadAgUfaggaucuuusc		UGCUGGGCCAAACUUCUUGGGCUUC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1658200	gscscacauuCUfUfGgggcuuccguL96		asdCsggdAadGcccadAGAfaguunggscsa		UGGCCAACUUCUUGGGCUUCCGU	
AD-1658201	cscsaacuncUfUfGfggcuuccguuL96		asdAscgdGadAgcccdAaGfaaguuaggscsc		GGCCAAACUUCUUGGGCUUCCGUA	
AD-1658202	csasacuncuUfGfGfgcuuccguauL96		asdTsacdGgdAagccdCaAfgaaguuaggsc		GCCAAACUUCUUGGGCUUCCGUAU	
AD-1658203	asascuuncuGfGfGfGfcuuccguauuL96		asdAsuadCgdGaaagdCcAfagaaguuaggsg		CCAAACUUCUUGGGCUUCCGUUAU	
AD-1658204	ascsuuuncuGfGfGfGfcuuccguauauL96		asdTsaudAcdGgaagdCcCfaagaaguuagg		CAACUUCUUGGGCUUCCGUUAU	
AD-1658205	csuscuungGfGfUfGfGfGfcuuccguauuL96		asdAsuadTadCggaadGcCfcaagaaguuasu		AACUUCUUGGGCUUCCGUUAU	
AD-1658206	ususcuuaggGfGfUfGfGfGfGfcuuccguauuL96		asdTsaudAudAcgggadAGCfcaagaaguuasu		ACUUCUUGGGCUUCCGUUAU	
AD-1658207	uscsuungggCfUfGfGfGfGfGfGfcuuccguauuL96		asdAsuadTadTaccggdAaGfccaagaaguuasu		CUUCUUGGGCUUCCGUUAU	
AD-1658208	csusungggcuUfCfCfGfGfGfGfGfGfGfcuuccguauuL96		asdCsaudAudAuacgdGaAfgcccaagaaguuasu		UUCUUGGGCUUCCGUUAU	
AD-1658209	ususgggcuUfCfGfGfGfGfGfGfGfGfGfcuuccguauuL96		asdCscadTadTauacdGgAfagcccaagaaguuasu		UCUUGGGCUUCCGUUAU	
AD-1658210	usgsggcuUfGfGfGfGfGfGfGfGfGfGfGfGfcuuccguauuL96		asdGscdAudAuauadCgGfagggcccaagaaguuasu		CUUGGGCUUCCGUUAU	
AD-1658211	gsgsgcuUfGfGfGfGfGfGfGfGfGfGfGfGfGfcuuccguauuL96		asdTsacdCadTauaudAcGfgaagggcccaagaaguuasu		UUGGGCUUCCGUUAU	
AD-1658212	gsgscuuccUfAfUfGfGfGfGfGfGfGfGfGfGfGfGfcuuccguauuL96		asdAsugdCcdAuauadTaCfGgaagggcccaagaaguuasu		UGGGCUUCCGUUAU	
AD-1658213	gscsuuccguAfUfAfGfGfGfGfGfGfGfGfGfGfGfGfcuuccguauuL96		asdCsaudGcdCauaudAuAfcggaagggcccaagaaguuasu		GGGCUUCCGUUAU	
AD-1658220	usasuauagGfCfAfGfGfGfGfGfGfGfGfGfGfGfGfcuuccguauuL96		asdCsacdTgdTgcaudGcCfauauauuagggcccaagaaguuasu		CGUAUAUAUGGGCAUGCACAGUA	
AD-1658221	asusauuaggCfAfUfGfGfGfGfGfGfGfGfGfGfGfGfcuuccguauuL96		asdTsacdCudGugcadTgCfcauauuagggcccaagaaguuasu		GUUAUAUAUGGGCAUGCACAGUGAG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1658222	usasuauaggcAfUfGfcaagagagauL96		asdCsuedAcdTgugedAuGfccaauuasusa		UAUAUAUGGCAUGCACAGUGAGC	
AD-1658223	asusauaggcAUfGfCfcaagagagcuL96		asdGscudCadCugugdCaUfGCCAUuasusa		AUAUAUGGCAUGCACAGUGAGCU	
AD-1658224	usauaggcAUfGfCfcaagagagcuL96		asdAsgcdTcdAcugudGcAfugccaauasusa		UAUAUGGCAUGCACAGUGAGCUA	
AD-1658225	asusaggcAUfGfCfcaagagagcuL96		asdTsagdTcdCacugdTgCfaugccaasusa		AUAUGGCAUGCACAGUGAGCUAU	
AD-1658226	usgsaggcAUfGfCfcaagagagcuL96		asdAsuadGcdTcaudGuGfcaugccasusa		UAUGGCAUGCACAGUGAGCUAUG	
AD-1658227	gsagcaggcAUfGfCfcaagagagcuL96		asdCsaudAgdCucacdTgUfcaugccasusa		AUGGCAUGCACAGUGAGCUAUGG	
AD-1658228	gsasaggcAUfGfCfcaagagagcuL96		asdCscadTadGcucadCuGfcaugccasusa		UGGCAUGCACAGUGAGCUAUGGG	
AD-1658242	usgsaggcAUfGfCfcaagagagcuL96		asdAsgadGadGaggcdCaGfaggugccasusa		UUUGGCACCCUGGCCUCUCUCUA	
AD-1658243	gsagcaggcAUfGfCfcaagagagcuL96		asdTsagdTadGcucadCuGfcaugccasusa		UUGGCACCCUGGCCUCUCUCUAU	
AD-1658288	gsasaggcAUfGfCfcaagagagcuL96		asdAsggdAudTgucudGuAfGCCUgucsa		CUGACAGGCUACAGGCAAUCCUG	
AD-1658289	ascsaggcAUfGfCfcaagagagcuL96		asdCsagdTadGcucadCuGfcaugccasusa		UGACAGGCUACAGGCAAUCCUGG	
AD-1658313	ususcaggcAUfGfCfcaagagagcuL96		asdGsuudCudTgucudTuCfcaaggagcsa		UGUCCUUGGAAGGACAAGAACU	
AD-1658315	csesaggcAUfGfCfcaagagagcuL96		asdCsagdTudCuugudCcUfuccaaggcsa		UUCUUGGAAGGACAAGAACUGC	
AD-1658316	csusaggcAUfGfCfcaagagagcuL96		asdGscadGudTcuugdTcCfuuccaaggcsa		UCCUUGGAAGGACAAGAACUGCA	
AD-1658448	csasaggcAUfGfCfcaagagagcuL96		asdAscadAadCggcudGcUfuccaaggcsa		UGCACCUUGAAGGAGCCGUUUGUG	
AD-1658451	csusaggcAUfGfCfcaagagagcuL96		asdTsgcdAcdAaacgdGcUfGCCUgucsa		ACCUGAAGCAGCCGUUUGUGCAG	

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1658528	ususgacaggUfUfCfauagcaggcuuL96		asdAsgcdCudGgaugdAaCfcugucaasuc		GAUUGACAGGUUCAUGCAGGCUG	
AD-1658529	usgsacagguUfCfAfugeaggcuL96		asdCsagdCcdTtgcaudGaAfcuguecasu		AUUGACAGGUUCAUGCAGGCUGU	
AD-1658530	gsascaggguCfAfUfgcaggcuuL96		asdAscadGcdCugcadTgAfaccugucsasa		UUGACAGGUUCAUGCAGGCUGUG	
AD-1658531	asesaggguCfAfUfgcaggcuL96		asdCsacdAagdCcuagdAuGfaaccuguscsa		UGACAGGUUCAUGCAGGCUGUGA	
AD-1658535	gsuscaugcAfGfGfcugugacaguL96		asdCsugdTedAcagcdCuGfcaugaaacsu		AGGUUCAUGCAGGCUGUGACAGG	
AD-1658539	asusgcaggcUfGfUfgacaggauL96		asdCsaudCcdTtgucadCaGfcaugcausgsa		UCAUGCAGGCUGUGACAGGAUGG	
AD-1658541	gsesaggcuUfGfAfcaaggauL96		asdTsccdAudCcuagdCaCfagccugcsasu		AUGCAGGCUGUGACAGGAUGGAA	
AD-1658542	csasggcuguGfAfCfaggauL96		asdTsuedCadTccugdTcAfcagccugcsa		UGCAGGCUGUGACAGGAUGGAAG	
AD-1658605	gsesuucaaaCfAfCfcauaguccauL96		asdTsggdAcdGuaggdTgUfugaagcsa		UGGCUUUAACACCUACGUCCAC	
AD-1658650	gsasguucugGfGfUfgacacaguL96		asdCsugdTudGuccadCcCfagaucscsu		AGGAGUUCUGGGUGGACACACAGC	
AD-1658661	gsasacaacaGfCfAfcuacaguguuL96		asdAscadCudGaggudGcUfguugccsasc		GUGGACAACAGCACCUACAGUGUC	
AD-1658662	gsasacaagCfAfCfcauagugucL96		asdGsacdAcdTgaggdTgCfugugucscsa		UGGACAACAGCACCUACAGUGUCU	
AD-1658663	asesaacagCfAfCfcauaguguuL96		asdAsgadCadCugagdGuGfugugugscsc		GGACAACAGCACCUACAGUGUCUG	
AD-1658664	csasacagcaCfCfUfcagugucugL96		asdCsagdAcdAcuagdGgUfgcugugususc		GACAACAGCACCUACAGUGUCUGU	
AD-1658665	asascagcacCfUfCfagugucuguuL96		asdAscadGadCacugdAgGfugcugugusgu		ACAACAGCACCUACAGUGUGUUI	
AD-1658801	asusgccuucGfAfCfcaaggacaaguL96		asdCsnuudGudCaggdTcAfcaggcausag		CUAUGCCUCUGACCUAGGACAAGG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1658802	usgsccucugAfCfCfuggacaagguL96		asdCscudTgdTccagdGuCfagaggcausasa		UAUGCCUCUGACCUUGGACAAGGU	
AD-1658818	asasgggugaGfGfGfucacuuuuL96		asdAasaadGudGagaedCcUfccacuuusgu		ACAAGGUGGAGGGUCUCACUUUUC	
AD-1658819	asgsugggaggGfGfUfucacuuuuL96		asdGsaadAgdTlgagadCcCfuccaccuusg		CAAGGUGGAGGGUCUCACUUUUC	
AD-1658820	gsusgggaggGfUfCfucacuuuuL96		asdGsgadAadGugagdAcCfuccaccuusuu		AAGGUGGAGGGUCUCACUUUCCA	
AD-1658821	gsusgggaggUfCfUfcauuuuL96		asdTsggdAadAgugadGaCfuccaccuscu		AGGUGGAGGGUCUCACUUUCCAG	
AD-1658824	gsasgggucucAfCfUfuuuccagcauL96		asdTsgcdTgdGaaagdTgAfgaccuucscsa		UGGAGGGUCUCACUUUCCAGCAA	
AD-1658825	asgsgggucucAfCfUfuuuccagcauL96		asdTsgcdCudGgaadGuGfagaccuucsc		GGAGGGUCUCACUUUCCAGCAAA	
AD-1658826	gsusgucucaCfUfUfuccagcaauL96		asdTsuudGedTggadAgUfgagaccusuc		GAGGGUCUCACUUUCCAGCAAAA	
AD-1658827	gsusgucucacUfUfUfuccagcaauL96		asdTsuudTgdCuggadAgGfugagaccuscu		AGGGUCUCACUUUCCAGCAAAAC	
AD-1658828	gsusgucacuUfUfCfagcaaaacuL96		asdGsuudTudGcuggdAaAfgugagaccsc		GGGUCUCACUUUCCAGCAAAACU	
AD-1658829	uscsucacuUfCfCfagcaaaacuL96		asdAsgudTudTgcuagdGaAfgugagaccsc		GGUCUCACUUUCCAGCAAAACUC	
AD-1658830	csuscacuuuUfCfAfgcaaaacuL96		asdGsgadTudTugcudGgAfgugagaccsc		GUCUCACUUUCCAGCAAAACUCC	
AD-1658831	uscsacuuuUfCfAfgcaaaacuL96		asdGsgadGudTuuagdGgAfgugagaccsc		UCUCACUUUCCAGCAAAACUCCC	
AD-1658832	csascuuuUfCfAfgcaaaacuL96		asdGsggdAgdTuuuagdCuGfgaaagugaccsc		CUCACUUUCCAGCAAAACUCCCU	
AD-1658833	asesuuuUfCfAfgcaaaacuL96		asdAsggdGadGuuuudGcUfggaaagugaccsc		UCACUUUCCAGCAAAACUCCUC	
AD-1658834	csusuuccagCfAfgcaaaacuL96		asdGsgadGgdAguuudTgCfuggaaagugaccsc		CACUUUCCAGCAAAACUCCUCA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1658835	usuuuccagcAfAfAfacuuccuauL96		asdTsgadGgdGagudTuGfcuggaasgsu		ACUUUCCAGCAAAAACUCCCCUCAA	
AD-1658836	usuccagcaAfAfAfuccuccuauL96		asdTsugdAgdGagudTuUfgcuggaasasg		CUUCCAGCAAAAACUCCCCUCAAC	
AD-1658837	usescagcaaAfAfCfuccuccuauL96		asdGsuudGadGggagdTuUfugcuggasasa		UUUCCAGCAAAAACUCCCCUCAACU	
AD-1658838	cscsagcaaaaAfCfUfccuccuauL96		asdAsgudTgdAgggadGuUfuugcugggsasa		UUCCAGCAAAAACUCCCCUCAACUG	
AD-1658839	csasgcacaaaCfUfCfccuccuauL96		asdCsagdTudGagggdAgUfuugcugggsa		UCCAGCAAAAACUCCCCUCAACUGG	
AD-1658840	asgscaaaacUfCfCfuccuacugulL96		asdCscadGudTgaggdGaGfuunucgusgs		CCAGCAAAAACUCCCCUCAACUGGA	
AD-1658841	gscsaaaacuCfCfCfuccuacugulL96		asdTscddAgdTugagdGgAfguunucgusg		CAGCAAAAACUCCCCUCAACUGGAU	
AD-1658842	csasaaacucCfCfUfcaacuggaauL96		asdAsuedCadGuugadGgGfaguunucgscu		AGCAAAAACUCCCCUCAACUGGAUG	
AD-1658843	asasaaacuccCfUfCfaacuggaugulL96		asdCsaudCcdAguugdAgGfagguunucgsc		GCAAAAACUCCCCUCAACUGGAUGA	
AD-1658844	asasacuccUfCfAfacuuggaugulL96		asdTscadTcdCaguudGaGfagguunucsg		CAAAAACUCCCCUCAACUGGAUGAA	
AD-1658845	asascuccucCfAfAfacuuggaugulL96		asdTsuedAudCagudTgAfaggagguunusu		AAAACUCCCCUCAACUGGAUGAAG	
AD-1658846	ascsuccucAfAfCfuggauggaugulL96		asdCsnuudCadTccagdTuGfaggagguunusu		AAACUCCCCUCAACUGGAUGAAGA	
AD-1658847	csusccuccaAfCfUfagggauggaugulL96		asdTscudTcdAuccadGuUfaggagguunusu		AACUCCCCUCAACUGGAUGAAGAA	
AD-1658848	uscsuccuacCfUfGfaggauggaugulL96		asdTsuedTudCauccdAgUfaggagguunusu		ACUCCCCUCAACUGGAUGAAGAAA	
AD-1658849	cscsccuacUfGfGfaggauggaugulL96		asdTsnuudCudTcauedCaGfuugagggsasg		CUCCCCUCAACUGGAUGAAGAAAC	
AD-1658850	csuscaacugGfAfUfgauggaugulL96		asdAsgudTudCuucadTcCfaguugagggs		CCCUCAACUGGAUGAAGAAACUA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1658874	asasggaucUfAfUfgaccugcagU96		asdCsuugdCadGgucadTaAfgauccuugsc		GCAAGGAUCUUUAUGACCUGCAGG	
AD-1658875	asgsngaucuuAfUfGfaccugcagguL96		asdCscudGedAgguedAuAfagaucucusg		CAAGGAUCUUUAUGACCUGCAGGA	
AD-1658880	csusuaugacCfUfGfagaggaccugU96		asdCsagdGudCcguedAgGfucuaaagsasu		AUCUUUAUGACCUGCAGGACCUGC	
AD-1658929	csasgacugaaAfCfCfugcaaaaauuL96		asdAsuudTudTgcagdGuUfcagcucsgsu		ACCGAGCUGAACCCUGCAAAAAUUU	
AD-1658930	gsasgcugaaCfCfUfgcaaaaauuuL96		asdAsaudTudTugcadGgUfcagcucsgsg		CCGAGCUGAACCCUGCAAAAAUUUG	
AD-1658931	asgsugaacCfUfGfcaaaaauuuL96		asdCsaadTudTuugcdAgGfuucagcuscsg		CGAGCUGAACCCUGCAAAAAUUUGA	
AD-1658932	gscsugaaccUfGfCfaaaaauuuL96		asdTscadAudTuungdCaGfguucagcusc		GAGCUGAACCCUGCAAAAAUUUGAG	
AD-1658933	csusgaaccUfGfCfaaaaauuuL96		asdCsuedAadTuunudGcAfgguucagcsu		AGCUGAACCCUGCAAAAAUUUGAGC	
AD-1658934	usgsaaccugCfAfAfaaaungagcuL96		asdGscudCadAuuuudTgCfagguucasgsc		GCUGAACCCUGCAAAAAUUUGAGCA	
AD-1658935	gsasaccugCfAfAfaaaungagcauL96		asdTsgcdTcdAuuuudTuGfcagguucasag		CUGAACCCUGCAAAAAUUUGAGCAA	
AD-1658940	usgscaaaaUfUfGfagcaaugacuL96		asdGsuedAudTgcuedAaUfuuuugcagsgsg		CCUGCAAAAAUUUGAGCAAUUGACC	
AD-1658954	gsasggugcuGfAfAfcagcauuuuuL96		asdAsaadAudGcugudTcAfgcaccucscsc		GGGAGGUGCUGAACACAGCAUUUUUU	
AD-1658955	asgsgugcuGfAfCfagcauuuuuuL96		asdAsaadAadTgcugdTuCfagcaccucsc		GGAGGUGCUGAACACAGCAUUUUUUU	
AD-1658956	gsgsugcuGfAfCfAfgcauuuuuuuL96		asdAsaadAadAugcudGuUfcagcaccusc		GAGGUGCUGAACACAGCAUUUUUUU	
AD-1658957	gsusgcugaaCfAfGfcauuuuuuuuL96		asdAsaadAadAaugdTgUfcagcaccscsu		AGGUGCUGAACACAGCAUUUUUUUU	
AD-1658958	usgscugaacAfGfCfauuuuuuuuuuL96		asdAsaadAadAaaugdCuGfuucagcascsc		GGUGCUGAACACAGCAUUUUUUUUUG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1658959	gsesugaacaGfCfAfuuuuuuuuuL96		asdCsaadAadAaaaadGcUfguuacagsasc		GUGCUGAACAGCAUUUUUUUUUGA	
AD-1658960	csusgaacagCfAfUfuuuuuuuuuL96		asdTscadAadAaaaadTgCfuguuacagsesa		UGCUGAACAGCAUUUUUUUUUGAG	
AD-1658992	usgsagagagAfGfCfcacacagaguuL96		asdAscudCudGuggggdCuCfucucucasusc		GAUGAGAGAGAGCCCCACAGAGUC	
AD-1658994	asgsagagagCfCfCfacacagagucuuL96		asdAsgadCudCugugdGgCfucucucusc		UGAGAGAGAGCCCCACAGAGUCUA	
AD-1658995	gsasgagagCfCfAfcagagucuuL96		asdTsagdAcdTcugudGgGfucucucusc		GAGAGAGAGCCCCACAGAGUCUAC	
AD-1659055	gsasaccgcccCfAfUfuccuguuuuL96		asdCsaadAcdAggaadTgGfggggguucsaag		CUGAACCGCCCCAUUCCUGUUUUGC	
AD-1659056	asasccgcccAfUfUfuccuguuuuL96		asdGscadAadCaggadAuGfggggguucsa		UGAACCGCCCCAUUCCUGUUUUGCU	
AD-1659057	ascscgcccUfUfCfucuguuuuL96		asdAsgcdAadAcaggdAaUfgggggguususc		GAACCGCCCCAUUCCUGUUUUGCUG	
AD-1659058	cscsgcccUfCfCfuguuuuL96		asdCsagdCadAacagdGaAfuggggggsusu		AACCGCCCCAUUCCUGUUUUGCUGU	
AD-1659059	csgscccUfCfUfuuuuuuL96		asdAscadGcdAaacadGgAfauggggcgsgsu		ACCGCCCCAUUCCUGUUUUGCUGUG	
AD-1659060	gscccauuccCfUfGfuuuuuuL96		asdCsacdAgdCaacdAgGfaauggcgsgsg		CCGCCCCAUUCCUGUUUUGCUGUGU	
AD-1659061	cscscuuuccUfGfUfuuuuuuL96		asdAscadCadGcaaadCaGfgaauggcgsgsg		CGCCCCAUUCCUGUUUUGCUGUGUA	
AD-1659062	cscsaauuccUfUfUfuguuuuL96		asdTsacdAcdAgcaadAcAfgaauggcgsgsc		GCCCCAUUCCUGUUUUGCUGUGUAU	
AD-1659063	csaauuccUfUfUfuguuuuL96		asdAsuadCadCaggadAaCfaggaugsgsg		CCCAUUCCUGUUUUGCUGUGUAUG	
AD-1659064	asusuccuUfUfGfuguuuuL96		asdCsaudAcdAcagcdAaAfcaggaugsgsg		CCAUUCCUGUUUUGCUGUGUAUGA	
AD-1659065	ususuccuUfGfCfuguuuuL96		asdTscadTadCacagdCaAfacaggausgsg		CAUUCCUGUUUUGCUGUGUAUGAU	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1659066	usescguguuGfCfUfguguaugauuL96		asdAsucdAudAcacadGcAfaacaggasasu		AUCCUGUUUGCUGUGUAUGAUC	
AD-1659067	cscsguuguuGfUfGfuguaugauuL96		asdGsaudCadTacadAgCfaaacagggsasa		UUCUGUUUGCUGUGUAUGAUC	
AD-1659068	csusguuugcUfGfUfguaugauuL96		asdTsgadTcdAuacadCaGfcaaacaggsgsa		UCCUGUUUGCUGUGUAUGAUC	
AD-1659069	usgsuuugcuGfUfGfuaugaucaauL96		asdTsugdAudCauacdAcAfgcaaacaggsgg		CCUGUUUGCUGUGUAUGAUC	
AD-1659070	gsusuuugcuUfGfUfaugaucuuL96		asdTsuidGadTcauadCaCfagcaaacgsag		CUGUUUGCUGUGUAUGAUC	
AD-1659071	ususugcuGfUfAfuagaucuuL96		asdCsuidTgdAucaudAcAfcagcaaacscsa		UGUUUGCUGUGUAUGAUC	
AD-1659161	csasguuuccCfAfCfcuuuuuuuuL96		asdGsaadGadAaaggdTgGfagagacugsgsg		CCCAGUCUCCCCACCUUUUUCUUCU	
AD-1659162	gsusuccccaCfCfufuuuuuuuuL96		asdTsagdAadGaaadGgUfgggagacugsg		CAGUCUCCCCACCUUUUUCUUCU	
AD-1659163	csuscccaceUfUfUfuuuuuuuuL96		asdAsuidAgdAagaadAaGfuggggagsgasc		GUCUCCCCACCUUUUUCUUCU	
AD-1659164	usescaccuUfUfUfuuuuuuuuL96		asdCsaudTadGaagadAaAfgguggggagsgsa		UCUCCCCACCUUUUUCUUCU	
AD-1659165	cscsaccuuUfUfCfuuuuuuuL96		asdTscadTudAgaagdAaAfgguggggagsg		CUCCCCACCUUUUUCUUCU	
AD-1659166	cscsaccuuUfCfUfuuuuuuL96		asdCsudAudTagaadGaAfaaggggagsgsa		UCCCCACCUUUUUCUUCU	
AD-1659167	csasccuuuuCfUfUfuuuuuuL96		asdAscudCadTuagadAgAfaaagggagsgsg		CCCACCUUUUUCUUCU	
AD-1659168	ascscuuuuUfUfCfuuaugagucL96		asdGsacdTcdAuuaadAaGfaaagggagsgsg		CCACCUUUUUCUUCU	
AD-1659208	cscsguuuuCfCfUfugguuuuuL96		asdCsuidAgdAccaadGgAfgaaaggsgscsu		AGCCGUUUUCUCCUUGGUCU	
AD-1659209	csgsuuuuucCfUfUfgguuuuuL96		asdAscudTadGaccadAgGfagaaggsgsc		GCCGUUUUCUCCUUGGUCU	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1659210	gsusuuuuccUfUfGfugcuuagugul96		asdCsacdTudAgaccdAaGfagagaaacsug		CCGUUUUCUCCUUGGUCUUAAGUGU	
AD-1659282	gsusuuuugcGfGfUfuuuuuuuagul96		asdCsuaadAadAuaaadCcCfagcaacsusg		CAGUUUGCUGGGUUUAUUUUAGA	
AD-1659283	ususugcugGfUfUfuuuuuuagaul96		asdTscudAadAuaaadAcCfcagcaascsu		AGUUUUGCUGGGUUUAUUUUAGAG	
AD-1659284	ususgcugggUfUfUfuuuuuagagul96		asdCsuedTadAaaudAaCfccagcaasasc		GUUUGCUGGGUUUAUUUUAGAGA	
AD-1659285	usgscugggUfUfAfuuuuagagaul96		asdTscudCudAaaudAaAfccagcaasasa		UUUGCUGGGUUUAUUUUAGAGAA	
AD-1659286	gscsugggguUfAfuuuuagagaaul96		asdTsuedTcdTaaadTaAfaccagcsasa		UUGCUGGGUUUAUUUUAGAGAAU	
AD-1659287	csusgggguuAfUfUfuuuagagaauul96		asdAsuudCudCuuaadAuAfaaccagcsasa		UGCUGGGUUUAUUUUAGAGAAUG	
AD-1659288	usgsggguuUfUfUfuagagaauugul96		asdCsaudTcdTcuuadAaUfaaaccagcsc		GCUGGGUUUAUUUUAGAGAAUGG	
AD-1659289	gsgsgguuuUfUfUfagagaauugul96		asdCscadTudCueuadAaAfuuaaccsasc		CUGGGUUUAUUUUAGAGAAUGGG	
AD-1659290	gsasgggcaagAfAfCfcaguguuuauul96		asdTsaadAcdAcuggdTuCfuugccucscsc		GGGAGGCAAGAACCCAGUGUUUAG	
AD-1659291	asgsgcaagaAfCfCfcaguguuuagul96		asdCsuaadAadCacugdGuUfcuugccucscsc		GGAGGCAAGAACCCAGUGUUUAGC	
AD-1659292	gsgscaagaaCfCfAfguguuuagcguL96		asdGscudAadAcacudGgUfucuuuuccuisc		GAGGCAAGAACCCAGUGUUUAGCG	
AD-1659293	gscsaagaacCfAfGfuguuuagcguL96		asdCsgcdTadAaacadTgGfuuuuugcscsu		AGGCAAGAACCCAGUGUUUAGCGC	
AD-1659294	csasagaaccAfGfUfguuuagcgcguL96		asdGscgdCudAaacadCuGfguuuugcscsc		GGCAAGAACCCAGUGUUUAGCGCG	
AD-1659295	asasgaaccaGfUfGfuuuagcgcguL96		asdCsgcdGcdTaaacdAcUfgguuucugsc		GCAAGAACCCAGUGUUUAGCGCGG	
AD-1659296	asgsaaccagUfGfUfuuagcgcgcguL96		asdCsccdCgdCuuaadCaCfugguuucusug		CAAGAACCCAGUGUUUAGCGCGGG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1659297	gsasaccaguGfUfUfagcgcggguL96		asdCscddGedGcuadAcAfcugguucsusu		AAGAAACCAGUGUUUAGCGCGGGA	
AD-1659298	asasccagugUfUfUfagcgcggguL96		asdTscddCgdCgcuaaAaCfacugguuscsu		AGAAACCAGUGUUUAGCGCGGGAC	
AD-1659321	csusguuccaAfAfAfagaauuccauL96		asdTsggdAadTucundTuUfugaacagsusa		UACUGUUCCAAAAAGAAAUUCCAA	
AD-1659322	usgsuuccaaAfAfAfagaauuccauL96		asdTsggdGadAunucdTuUfugaacagsu		ACUGUUCCAAAAAGAAAUUCCAAC	
AD-1659323	gsusuccaaaAfAfGfaauuccaauL96		asdGsuudGgdAaunucdTuUfugaacagsu		CUGUUCCAAAAAGAAAUUCCAAACC	
AD-1659325	uscsaaaaaGfAfAfuaucacccguL96		asdCsggdTudGgaudTuUfuuuuggasasc		GUUCCAAAAAGAAAUUCCAAACCGA	
AD-1659326	csasaaaagAfAfUfuccaaccguL96		asdTscgdGudTggadTuCfuuuuuggsasa		UUCCAAAAAGAAAUUCCAAACCGAC	
AD-1659327	csasaaaagaAfUfUfccaaccgaculL96		asdGsuudGgdTuggadAuUfuuuuuuggsa		UCCAAAAAGAAAUUCCAAACCGACC	
AD-1659328	asasaaaagaUfUfCfaaccgaccuL96		asdGsgudCgdGuuggdAaUfuuuuuuugsg		CCAAAAAGAAAUUCCAAACCGACCA	
AD-1659329	asasagaauUfCfCfaaccgaccuL96		asdTsggdTcdGuuggdGaAfuuuuuuuusg		CAAAAAGAAAUUCCAAACCGACCAG	
AD-1659330	asasagaauCfCfAfaccgaccuL96		asdCsuudGudCgguudGgAfauuuuuuusuu		AAAAAGAAAUUCCAAACCGACCAGC	
AD-1659331	asasagaauCfCfAfaccgaccuL96		asdGscudGgdTcggudTuGfauuuuuuusuu		AAAAGAAAUUCCAAACCGACCAGCU	
AD-1659332	asgsaauuccAfAfCfcgaccagcuL96		asdAsgcdTgdGucggdTuGfgaauuuusuu		AAAGAAAUUCCAAACCGACCAGCUU	
AD-1659333	gsasaauuccAfCfCfcgaccagcuL96		asdAsagdCudGgucggdGuUfggaauuuusuu		AAGAAAUUCCAAACCGACCAGCUUG	
AD-1659334	asasuuccaaCfCfGfaccagcuuL96		asdCsaadGedTggudGgUfugaauuuusuu		AGAAAUUCCAAACCGACCAGCUUGU	
AD-1659335	asusuuccaaCfGfAfaccagcuuL96		asdAscadAgdCuggdCgGfuuuugaauusuu		GAAUUCCAACCGACCAGCUUGUU	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1659336	ususccaaccGfAfCfcagcuuuuuL96		asdAsacdAadGcuggdTcGfguuggaasusu		AAUUCCAAACCGACCCAGCUUUGUUU	
AD-1659337	uscsaaccgAfCfCfagcuuuuuuuL96		asdAsaadCadAgcugdGuCfkguuggasasu		AUUCCAAACCGACCCAGCUUUGUUUG	
AD-1659338	csesaaccgaCfCfAfGcuuuuuuuL96		asdCsaadAcdAagcudGgUfegguuugsasa		UUCCAAACCGACCCAGCUUUGUUUGU	
AD-1659339	csasaccgacCfAfGfuuuuuuuuL96		asdAscadAadCaagcdTgGfuegguugsasa		UCCAACCGACCCAGCUUUGUUUGUG	
AD-1659340	asasccgaccAfGfCfuuuuuuuuL96		asdCsacdAadAcaagdCuGfgucggguusgsg		CCAACCGACCCAGCUUUGUUUGUGA	
AD-1659341	ascscgaccaGfCfUfuuuuuuuuL96		asdTscadCadAcaadGcUfkgucggguusg		CAACCGACCCAGCUUUGUUUGUGAA	
AD-1659342	csesgaccagCfUfUfuuuuuuuuL96		asdTsucdAcdAaacadAgCfkgucggguususu		AACCGACCCAGCUUUGUUUGUGAAA	
AD-1659343	csesgaccageUfUfGfuuuuuuuuL96		asdTsuudCadCaacdAaGfkgucggguusgsu		ACCGACCCAGCUUUGUUUGUGAAAC	
AD-1659344	gsasccagcuUfGfUfuuuuuuuuL96		asdGsuudTedAcaaadCaAfkgucggguusgsg		CCGACCCAGCUUUGUUUGUGAAACA	
AD-1659345	ascscagcuUfUfUfuuuuuuuuL96		asdTsgudTudCacaadAcAfkgucggguuscsg		CGACCCAGCUUUGUUUGUGAAACAA	
AD-1659346	csesagcuUfUfUfuuuuuuuuL96		asdTsuugdTudTcacadAaCfaagcuuggsusc		GACCCAGCUUUGUUUGUGAAACAAA	
AD-1659347	csasgcuuUfUfGfuuuuuuuuL96		asdTsuudGudTucadAaAfcaagcuuggsusu		ACCAGCUUUGUUUGUGAAACAAA	
AD-1659348	asgscuuUfUfGfUfuuuuuuuuL96		asdTsuudTgdTuucadCaAfcaagcuuggsug		CCAGCUUUGUUUGUGAAACAAAA	
AD-1659350	csusuuuuUfGfAfacaacaaaaaL96		asdTsuudTudTguudCaCfaaacaggsesu		AGCUUUGUUUGUGAAACAAAAAG	
AD-1659351	ususuuuuUfGfAfafacaaaaaaL96		asdCsuudTudTuguudTcAfcaaacagsgc		GCUUUGUUUGUGAAACAAAAAGU	
AD-1659371	usgsuuuccuUfUfUfcaaguuuuuuL96		asdCsucdAadCuugadAaAfgggaaacascsu		AGUGUUCCCUUUUCAAGUUGAGA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1659372	gsusuccuuUfUfCfaaguuagauL96		asdTscudCadAcuugdAaAfaggggaacsasc		GUGUUCCCCUUUUAAGUUUGAGAA	
AD-1659373	ususccuuUfCfAfaguuagagauL96		asdTsuedTcdAacuudGaAfaaggggaacsca		UGUUCCCCUUUUAAGUUUGAGAAC	
AD-1659382	csasaguugaGfAfAfaaaaaauuL96		asdCsaadTudTuungudTcUfcaacuugsasa		UUCAAGUUUGAGAACAAAAUUUGG	
AD-1659383	asasguugagAfAfCfaaaaaauuL96		asdCscadAudTuungdTcUfcaacuugsasa		UCAAGUUUGAGAACAAAAUUUGGG	
AD-1659384	asgsuugagaAfCfAfaaaauuL96		asdCscddAadTuunudGuUfcaacuugsasc		CAAGUUUGAGAACAAAAUUUGGGU	
AD-1659385	gsusugagaaCfAfAfaaauggguuL96		asdAscddCadAuuuudTgUfcaacuugsasu		AAGUUUGAGAACAAAAUUUGGGUU	
AD-1659386	ususgagaaCfAfAfaaauggguuL96		asdAsacdCcdAuuuudTuGfuucuaacsusu		AGUUUGAGAACAAAAUUUGGGUUU	
AD-1659387	usgsagaacaAfAfAfaaauggguuuL96		asdAsaadCcdCaauudTuUfguucuaacsasc		GUUGAGAACAAAAUUUGGGUUUU	
AD-1659388	gsasgaacaaAfAfAfaaauggguuuuL96		asdAsaadAcdCcaudTuUfguucuaacsasa		UUGAGAACAAAAUUUGGGUUUUA	
AD-1659389	asgsaacaaaAfAfUfuggguuuuauL96		asdTsacdAadCccadTuUfuuuuuacsca		UGAGAACAAAAUUUGGGUUUUAAA	
AD-1659390	gsasacaaaaAfUfUfuggguuuuauuL96		asdTsuaadAadAccadAuUfuuuuuacsusc		GAGAACAAAAUUUGGGUUUUAAA	
AD-1659391	asasacaaaaUfUfGfggguuuuuuL96		asdTsuaadAadAaccadAaUfuuuuuacsusu		AGAACAAAAUUUGGGUUUUAAA	
AD-1659399	asgsuaaacaUfUfUfugcauuL96		asdGscadAudGcaaadAaUfguaauacsusu		AAAGUAUACAUUUUUUGCAUUGGCC	
AD-1659400	gsusauaacaUfUfUfugcauuL96		asdGsgcdAadTgcaadAaAfguaauacsusu		AAGUAUACAUUUUUUGCAUUGGCCU	
AD-1659401	usasuaaauUfUfUfugcauuL96		asdAsggcdCadAugcadAaAfauguaacsusu		AGUAUACAUUUUUUGCAUUGCCUU	
AD-1659402	asusacauuuUfUfGfcauuL96		asdAsagcdGcdAugcadAaAfauguaacsusc		GUUAUACAUUUUUUGCAUUGCCUUC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1659405	csasuuuuuGcFfAfUfugccuucggulL96		asdCscgdAadGgcaadTgCfaaaaaugsusa		UACAUUUUUGCAUUUGCCCUUCGGGU	
AD-1659406	asuuuuuGcAfUfUfugccuucggulL96		asdAascdGadAggcaadAuGfcaaaaaugsu		ACAUUUUUGCAUUUGCCCUUCGGGU	
AD-1659407	usuuuuuGcAfUfUfugccuucggulL96		asdAsacdCgdAaggdAaUfGcaaaaausg		CAUUUUUGCAUUUGCCCUUCGGGU	
AD-1659408	usuuuuuGcAfUfUfugccuucggulL96		asdAsaadCcdGaaggdCaAfugcaaaaasasu		AUUUUUGCAUUUGCCCUUCGGGU	
AD-1659409	usuuuuuGcAfUfUfugccuucggulL96		asdCsaadAcdCgaaggdGcAfauGcaaaasasa		UUUUUGCAUUUGCCCUUCGGGU	
AD-1659410	usuuuuuGcAfUfUfugccuucggulL96		asdAscadAadCcggaadGgCfaugcaasasa		UUUUUGCAUUUGCCCUUCGGGU	
AD-1659411	usuuuuuGcAfUfUfugccuucggulL96		asdTsacdAadAccgadAgGfcaaugcasasa		UUUGCAUUUGCCCUUCGGGU	
AD-1659412	gscsuuuGcUfUfUfugccuucggulL96		asdAsuadCadAaccgdAaGfGcaaugcsasa		UUGCAUUUGCCCUUCGGGU	
AD-1659413	csasuuuuGcUfUfUfugccuucggulL96		asdAsaudAcdAaaccdGaAfGgcaaugscsa		UGCAUUUGCCCUUCGGGU	
AD-1659414	asuuuuuGcUfUfUfugccuucggulL96		asdAsaadTadCaacdCgAfagGcaaugsc		GCAUUUGCCCUUCGGGU	
AD-1659415	usuuuuuGcUfUfUfugccuucggulL96		asdTsaudAudAcaaadCcGfaagGcaaugsg		CAUUGCCCUUCGGGU	
AD-1659416	usuuuuuGcUfUfUfugccuucggulL96		asdCsaudAadTacaadAcCfGagGcaaugsg		AUUGCCCUUCGGGU	
AD-1659417	gscsuuuGcUfUfUfugccuucggulL96		asdAscudAadAuacadAaCfGagGcaaugsg		UUGCCCUUCGGGU	
AD-1659418	csuuuuuGcUfUfUfugccuucggulL96		asdCsacdTadAuauadAaAfcGagGcaaugsg		UGCCCUUCGGGU	
AD-1659419	csuuuuuGcUfUfUfugccuucggulL96		asdAscudCudAauadCaAfaceGagGcaaugsg		GCCCUUCGGGU	
AD-1659420	usuuuuuGcUfUfUfugccuucggulL96		asdGsacdAcdTaaudAcAfaceGagGcaaugsg		CCCUUCGGGU	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1659421	uscsgguuuUfAfUfuuaugugucuuL96		asdAsgadCadCuuaadTaCfaaacggasag		CUUCGGUUUGUAUUUAGUGUCUUU	
AD-1659422	csrgsuuuUfUfUfuuaugugucuuL96		asdAsagdAcdAcuuadAuAfaaacccgsasa		UUCGGUUUGUAUUUAGUGUCUUUG	
AD-1659423	gsgsuuuUfUfUfagugucuuL96		asdCsaadGadCacuadAaUfacaacccgsa		UCGGUUUGUAUUUAGUGUCUUUGA	
AD-1659424	gsusuuuuUfUfAfugugucuuL96		asdTscadAgaAcacudAaAfuacaaacsag		CGGUUUUGUAUUUAGUGUCUUUGAA	
AD-1659425	ususuuuuUfAfGfugucuuL96		asdTsucdAadGacacdTaAfaucaaacsac		GGUUUUUGUAUUUAGUGUCUUUGAAU	
AD-1659426	ususuuuuUfGfUfugucuuL96		asdAsuudCadAgacacdCuAfaucacacsac		GUUUUUUGUAUUUAGUGUCUUUGAAUG	
AD-1659427	usgsuuuuUfGfUfugucuuL96		asdCsauudTcdAagacdAcUfaauuacacsasa		UUUUUUUGUAUUUAGUGUCUUUGAAUGU	
AD-1659428	gsusuuuuUfGfUfucuuL96		asdAscadTudCaagadCaCfuuaauacsasa		UUGUAUUUAGUGUCUUUGAAUGUA	
AD-1659429	usasuuuuUfGfUfucuuL96		asdTsacdAudTcaagAcAfcuaauacsasa		UGUAUUUAGUGUCUUUGAAUGUAA	
AD-1659430	asusuuuuUfCfUfugaauL96		asdTsuaudCadTucadGaCfacuaauacsac		GUUUUUAGUGUCUUUGAAUGUAAAG	
AD-1659431	ususuuuuUfUfUfugaauL96		asdCsauudAcdAuucadAgAfcuaauacsasa		UAUUUUAGUGUCUUUGAAUGUAAAGA	
AD-1659432	ususuuuuUfUfGfugaauL96		asdTsauudTadCaauudAaGfacuaauacsasu		AUUUUAGUGUCUUUGAAUGUAAAGAA	
AD-1659433	usasuuuuUfGfAfugaauL96		asdTsucdTudAcauudCaAfgacuaacsasa		UUUUUUAGUGUCUUUGAAUGUAAAGAAC	
AD-1659434	asgsuuuuUfGfAfugaauL96		asdGsauudCudTcauudTcAfgacuaacsasa		UUUUUUAGUGUCUUUGAAUGUAAAGAAC	
AD-1659436	usgsuuuuUfGfUfugaauL96		asdAsuudTudCuuaudAuUfcauagacacsu		AGUGUCUUUGAAUGUAAAGAACAUUG	
AD-1659437	gsusuuuuUfGfUfugaauL96		asdCsauudGudTcuuadCaUfcauagacacsac		GUGUCUUUGAAUGUAAAGAACAUUGA	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1659440	ususgaauuuAfAfGfaacauagaccuL96		asdGsgudCadTgguuedTuAfaauucaasgsa		UCUUGAAUGUAAAGAAACAUGACCU	
AD-1659446	gsusaaagaacAfUfGfaaccuccuguguL96		asdCsacdGgdAgguuedAuGfuucuuuacsasu		AUGUAAAGAAACAUGACCUCCCGUGU	
AD-1659447	usasagaacaUfGfAfcuuccuguguuL96		asdAscadCgdGaggudCaUfguucuuuacsasa		UGUAAAGAAACAUGACCUCCCGUGUA	
AD-1659448	asasgaacauGfAfCfcuuccuguguauL96		asdTsacdAcdGgaggdTcAfuguuuuacsasc		GUAAGAAACAUGACCUCCCGUGUAG	
AD-1659449	asgsaacaugAfCfCfuccuguguaguL96		asdCsudCadCggaggdGuCfaguuuuacsusa		UAAGAAACAUGACCUCCCGUGUAGU	
AD-1659450	gsasacaugaCfCfUfcguguguaguL96		asdAscudAcdAcgggdGgUfcauguuuacsusu		AAGAAACAUGACCUCCCGUGUAGUG	
AD-1659451	asascaugacCfUfCfuguguaguL96		asdCsacdTadCacggdAgGfcauguuuacsusu		AGAACAUGACCUCCCGUGUAGUGU	
AD-1659452	ascsaugaceUfCfCfuguguaguL96		asdAscadCudAcaggdGaGfcauguuuacsusc		GAACAUGACCUCCCGUGUAGUGUC	
AD-1659453	csasugaccuCfCfGfuguguaguL96		asdGsacdAcdTaccadGgAfggucauguusu		AACAUGACCUCCCGUGUAGUGUCU	
AD-1659454	asusgaccucCfGfUfguagugucuuL96		asdAsgadCadCuacadCgGfaggucaugsusu		ACAUGACCUCCCGUGUAGUGUCUG	
AD-1659481	csusuaguuuuUfUfUfccacagauL96		asdCsaudCudGuggadAaAfaacuaaagsusu		ACCUUAGUUUUUUUCCACACAGAUGC	
AD-1659482	ususaguuuuUfUfCfcacagauL96		asdGsacdTcdTguggdAaAfaaauaasgsu		CCUUAGUUUUUUUCCACACAGAUGC	
AD-1659483	usasguuuuuUfCfCfacagauL96		asdAsgcdAudCugugdGaAfaaauaasgsu		CUUAGUUUUUUUCCACACAGAUGC	
AD-1659484	asgsuuuuuuCfCfAfcagauL96		asdAsagdCadTcugudGgAfaaauaasgsu		UUAGUUUUUUUCCACACAGAUGC	
AD-1659485	gsusuuuuuuCfAfCfagauL96		asdCsacdGcdAucugdTgGfaaauaacsusa		UAGUUUUUUUCCACACAGAUGC	
AD-1659487	ususuuuuuCaAfGfagauL96		asdCsacdAadGcauedTgUfggaaaaasasc		GUUUUUUCCACACAGAUGC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1659488	usuuuuccacAfGfAfugcuuugauL96		asdTscadCadAgcaudCuGfuggaaaasasa		UUUUUCCACAGAUCCUUGUGAU	
AD-1659489	usuuuccacaGfAfUfgeuugugauuL96		asdAsucdAcdAagcadTcUfugugaaasasa		UUUUUCCACAGAUCCUUGUGAUU	
AD-1659490	usuuccacagAfUfGfuuugugauuuL96		asdAsaudCadCaagedAuCfuguggaasasa		UUUUCCACAGAUCCUUGUGAUUU	
AD-1659491	uscsacagaUfGfCfuugugauuuuL96		asdAsaadTcdAcaagdCaUfcuuguggasasa		UUUCCACAGAUCCUUGUGAUUUU	
AD-1659492	csesacagauGfCfUfugugauuuuL96		asdAsaadAudCacaadGcAfucuguggsasa		UUCCACAGAUCCUUGUGAUUUUU	
AD-1659493	csasacagauGfUfUfugugauuuuL96		asdAsaadAadTcacadAgCfaucuguggsa		UCCACAGAUCCUUGUGAUUUUUG	
AD-1659537	ascscugauUfUfCfuguuugaauL96		asdAsuudCadAacagdAaAfucaggugsc		GCACCUGAAUUUCUGUUUGAAUG	
AD-1659538	csesugaauUfCfUfguuugaauL96		asdCsaudTcdAaacadGaAfaucaggugsg		CACCUGAAUUUCUGUUUGAAUUGC	
AD-1659559	gsgsaaccuAfGfCfuguuuauuuL96		asdAsaadTadAccagdCuAfugguucscsg		GCGGAACCAUAGCUGGUUAUUUC	
AD-1659560	gsasaccuagGfCfUfguuauuuuL96		asdGsaadAudAaccadGcUfaugguucscsg		CGGAACCAUAGCUGGUUAUUUCU	
AD-1659561	asasccuagCfUfGfguuauuuuL96		asdAsgadAadTaacedAgCfuaugguuscsc		GGAACCAUAGCUGGUUAUUUCUC	
AD-1659562	ascscuagCfUfGfGuuauuuuL96		asdGsgadAadAuaacdCaGfuaugguuscsc		GAACCAUAGCUGGUUAUUUCUCC	
AD-1659563	csesauagCfUfUfauuuucuuL96		asdGsgadGadAuaadCcAfgcuagguusu		AACCAUAGCUGGUUAUUUCUCCC	
AD-1659582	csesuugugUfAfGfuaauaaacguL96		asdCsugdTuadAuuacdTaAfcacaaggsgsa		UCCCUUGUGUUAGUAAUAAACGU	
AD-1659583	csusuugugUfAfGfUfaauaaacguL96		asdAscgdTuadTuuadCuAfacacaaggsgsg		CCCUUGUGUUAGUAAUAAACGUC	
AD-1659584	ususuuguuGfUfAfauaaacguL96		asdGsacdGudTuuuadAcUfaacacaaggsg		CCUUGUGUUAGUAAUAAACGUCU	

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Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1659585	usgsuguuagUfAfAfuaacgucuuL96		asdAsgadCgdTuuaudTACfuaacacacasag		CUUGUGUUAGUAAUAAACGUCUUU	
AD-1659586	gsusguuaguAfAfUfaaacgucuuuL96		asdAsagdAcdGuuuadTuAfcuaacacsasa		UUGUGUUAGUAAUAAACGUCUUG	
AD-1659587	usgsuuaguAfUfAfaacgucuuuL96		asdCsaadGadCguuudAuUfuaacacascsa		UGUGUUAGUAAUAAACGUCUUUGC	
AD-1659588	gsusuaguuaUfAfAfagcucuuuL96		asdGscadAgdAaguuuTaUfuaacacsasc		GUGUUAGUAAUAAACGUCUUGCC	
AD-1321384	uscsucccacCfUfUfuucuuuaauL96		asdTsuadGadAgaadAgGfugggagascsu		AGUCUCCCACCUUUUCUUCUAAU	
AD-1321390	cscsucaacuGfGfAfugaagaacuuL96		asdGsuudTcdTuaudCcAfguugaggsgsa		UCCCUCACUGGAUGAAGAAACU	

Example 3. Additional Duplexes Targeting angiotensinogen (AGT)

Additional agents targeting angiotensinogen gene were designed using custom R and Python scripts and synthesized as described above.

A detailed list of the unmodified AGT sense and antisense strand nucleotide sequences is shown in Table 6. A detailed list of the modified AGT sense and antisense strand nucleotide sequences is shown in Table 7.

For transfections, 7.5 μ l of Opti-MEM plus 0.1 μ l of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) was added to 2.5 μ l of each siRNA duplex to an individual well in a 384-well plate. The mixture was then incubated at room temperature for 15 minutes. Forty μ l of complete growth media without antibiotic containing $\sim 1.5 \times 10^4$ Hep3B was then added to the siRNA mixture. Cells are incubated for 24 hours prior to RNA purification. Single dose experiments were performed at 10 nM, 1 nM, and 0.1 nM final duplex concentration.

Total RNA isolation was performed using DYNABEADS. Briefly, cells were lysed in 10 μ l of Lysis/Binding Buffer containing 3 μ L of beads per well were mixed for 10 minutes on an electrostatic shaker. The washing steps were automated on a Biotek EL406, using a magnetic plate support. Beads were washed (in 3 μ L) once in Buffer A, once in Buffer B, and twice in Buffer E, with aspiration steps in between. Following a final aspiration, complete 12 μ L RT mixture was added to each well, as described below.

For cDNA synthesis, a master mix of 1.5 μ l 10X Buffer, 0.6 μ l 10X dNTPs, 1.5 μ l Random primers, 0.75 μ l Reverse Transcriptase, 0.75 μ l RNase inhibitor and 9.9 μ l of H₂O per reaction was added per well. Plates were sealed, agitated for 10 minutes on an electrostatic shaker, and then incubated at 37 degrees C for 2 hours. Following this, the plates were agitated at 80 degrees C for 8 minutes.

RT-qPCR was performed as described above and relative fold change was calculated as described above. The results of the single dose screen of the agents in Tables 6 and 7 in Hep3b cells are shown in Table 8.

Table 6. Unmodified Sense and Antisense Strand Sequences of Angiotensinogen (AGT) dsRNA Agents

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1321384.2	UCUCCACCUUUUUCUUAU		1609-1629	ATUAGAAAGAAAGGUGGGAGACU		1607-1629
AD-1321390.2	CCUCAACUGGAUGAAGAAACU		1135-1155	AGUUTCTUACUCCAGUUGAGGGA		1133-1155
AD-1632799.1	AGCCUGAGGGCCACCAUCCUU		86-106	AAGGAUGGUGGCCCCUCAGGCUC		84-106
AD-1632801.1	CCUGAGGGCCACCAUCCUUCU		88-108	AAGAGGAUGGUGGCCUUCAGGCU		86-108
AD-1632805.1	AGGGCCACCAUCCUCUGCCUU		92-112	AAGGCAGAGGAUGGUGGCCUUC		90-112
AD-1632836.1	GUCAUCCACAAUGAGAGUACU		170-190	AGUACUCUCAUUUGUGGAUGACGA		168-190
AD-1632838.1	GUGACCGGGUGUACAUAACAU		138-158	AGUGUAUGUACACCCGGUACCCU		136-158
AD-1632840.1	CUUCCACCUCGUAUCCACAU		160-180	AUGUGGAUGACGAGGUGGAAAGG		158-180
AD-1632841.1	UUCCACCUCGUAUCCACAAU		161-181	AUUGUGGAUGACGAGGUGGAAAG		159-181
AD-1632842.1	UCCACCUCGUAUCCACAAU		162-182	AAUUGUGGAUGACGAGGUGGAAAG		160-182
AD-1632843.1	CCACCUCGUAUCCACAAUGU		163-183	ACAUUUGUGGAUGACGAGGUGGAA		161-183
AD-1632844.1	CACCUCGUAUCCACAAUGAU		164-184	AUCAUUUGUGGAUGACGAGGUGGA		162-184
AD-1632846.1	CCUCGUAUCCACAAUGAGAU		166-186	AUCUCAUUUGUGGAUGACGAGGUG		164-186
AD-1632847.1	CUCGUAUCCACAAUGAGAGU		167-187	ACUCUCAUUUGUGGAUGACGAGGU		165-187
AD-1632848.1	UCGUAUCCACAAUGAGAGUU		168-188	AACUCUCAUUUGUGGAUGACGAGG		166-188
AD-1632849.1	CGUAUCCACAAUGAGAGUAU		169-189	AUACUCUCAUUUGUGGAUGACGAG		167-189
AD-1632850.1	UCAUCCACAAUGAGAGUACCU		171-191	AGGUACUCUCAUUUGUGGAUGACG		169-191
AD-1632851.1	CAUCCACAAUGAGAGUACCUU		172-192	AAGGUACUCUCAUUUGUGGAUGAC		170-192
AD-1632852.1	AUCCACAAUGAGAGUACCUU		173-193	ACAGGUACUCUCAUUUGUGGAUGA		171-193
AD-1632853.1	UCCACAAUGAGAGUACCUU		174-194	AACAGGUACUCUCAUUUGUGGAUG		172-194
AD-1632854.1	CCACAAUGAGAGUACCUUGU		175-195	ACACAGGUACUCUCAUUUGUGGAU		173-195
AD-1632855.1	CACAAUGAGAGUACCUUGAU		176-196	AUCACAGGUACUCUCAUUUGUGGA		174-196
AD-1632856.1	ACAAUGAGAGUACCUUGAGU		177-197	ACUCACAGGUACUCUCAUUUGUGG		175-197

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1632857.1	CAAUGAGAGUACCUUGAGAGCU		178-198	AGCUCACAGGUACUCUCAUUGUG		176-198
AD-1632858.1	AAUGAGAGUACCUUGAGAGCAU		179-199	AUGCUCACAGGUACUCUCAUUGU		177-199
AD-1632859.1	AUGAGAGUACCUUGAGAGCAGU		180-200	ACUGCUCACAGGUACUCUCAUUG		178-200
AD-1632860.1	UGAGAGUACCUUGAGAGCAGCU		181-201	AGCUGCUCACAGGUACUCUCAU		179-201
AD-1632861.1	GAGAGUACCUUGAGAGCAGCUU		182-202	AAGCUGCUCACAGGUACUCUCAU		180-202
AD-1632862.1	AGAGUACCUUGAGAGCAGCUGU		183-203	ACAGCUGCUCACAGGUACUCUCA		181-203
AD-1632863.1	GAGUACCUUGAGAGCAGCUGGU		184-204	ACCAGCUGCUCACAGGUACUCUC		182-204
AD-1632864.1	AGUACCUUGAGAGCAGCUGGCU		185-205	AGCCAGCUGCUCACAGGUACUCU		183-205
AD-1632865.1	GUACCUUGAGAGCAGCUGGCAU		186-206	AUGCCAGCUGCUCACAGGUACUC		184-206
AD-1632866.1	UACCUUGAGAGCAGCUGGCAAU		187-207	AUUGCCAGCUGCUCACAGGUACU		185-207
AD-1632991.1	AAUGGUCGGGAUGCUGGCCAAU		352-372	AUGGCCAGCAUCCCGACCAUUGC		350-372
AD-1632992.1	AUGGUCGGGAUGCUGGCCAAU		353-373	AUUGGCCAGCAUCCCGACCAUUG		351-373
AD-1632993.1	UGGUCGGGAUGCUGGCCAACU		354-374	AGUUGGCCAGCAUCCCGACCAU		352-374
AD-1632994.1	GGUCGGGAUGCUGGCCAACUU		355-375	AAGUUGGCCAGCAUCCCGACCAU		353-375
AD-1632995.1	GUCGGGAUGCUGGCCAACUUU		356-376	AAAGUUGGCCAGCAUCCCGACCA		354-376
AD-1632996.1	UCGGGAUGCUGGCCAACUUCU		357-377	AGAAGUUGGCCAGCAUCCCGACC		355-377
AD-1632997.1	CGGGAUGCUGGCCAACUUCUU		358-378	AAGAAGUUGGCCAGCAUCCCGAC		356-378
AD-1632998.1	GGGAUGCUGGCCAACUUCUUU		359-379	AAAGAAGUUGGCCAGCAUCCCGA		357-379
AD-1632999.1	GGAUGCUGGCCAACUUCUUGU		360-380	ACAAGAAGUUGGCCAGCAUCCCG		358-380
AD-1633000.1	GAUGCUGGCCAACUUCUUGGU		361-381	ACCAAGAAGUUGGCCAGCAUCCC		359-381
AD-1633003.1	GCUGGCCAACUUCUUGGGCUU		364-384	AAGCCCCAAGAAGUUGGGCCAGCAU		362-384
AD-1633004.1	CUGGCCAACUUCUUGGGCUUU		365-385	AAAGCCCCAAGAAGUUGGGCCAGCA		363-385
AD-1633007.1	GCCAAUCUUCUUGGGCUUCCGU		368-388	ACGGAAGCCCCAAGAAGUUGGGCCA		366-388
AD-1633008.1	CCAAUCUUCUUGGGCUUCCGUU		369-389	AACGGAAGCCCCAAGAAGUUGGGCC		367-389

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1633009.1	CAACUUCUUGGGCUUCCGUAAU		370-390	AUACGGAAGCCCAAGAAUUUGGC		368-390
AD-1633010.1	AACUUCUUGGGCUUCCGUAAU		371-391	AAUACGGAAGCCCAAGAAUUUGG		369-391
AD-1633011.1	ACUUCUUGGGCUUCCGUAAU		372-392	AUAUACGGAAGCCCAAGAAUUUG		370-392
AD-1633012.1	CUUCUUGGGCUUCCGUAAU		373-393	AAUAUACGGAAGCCCAAGAAUU		371-393
AD-1633013.1	UUCUUGGGCUUCCGUAAU		374-394	AUAUAUACGGAAGCCCAAGAAU		372-394
AD-1633014.1	UCUUGGGCUUCCGUAAU		375-395	AAUAUAUACGGAAGCCCAAGAA		373-395
AD-1633015.1	CUUGGGCUUCCGUAAU		376-396	ACAUUAUACGGAAGCCCAAGAA		374-396
AD-1633016.1	UUGGGCUUCCGUAAU		377-397	ACCAUAUAUACGGAAGCCCAAGA		375-397
AD-1633018.1	GGGCUUCCGUAAU		379-399	AUGCCAUUAUACGGAAGCCCAA		377-399
AD-1633019.1	GGCUUCCGUAAU		380-400	AAUGCCAUUAUACGGAAGCCCA		378-400
AD-1633020.1	GCUUCCGUAAU		381-401	ACAUGCCAUUAUACGGAAGCC		379-401
AD-1633027.1	UAUAUUGGCAUGCACAGUGU		388-408	ACACUGGCAUGCCAUUAUACG		386-408
AD-1633028.1	AUAUAUGGCAUGCACAGUGAU		389-409	AUCACUGGCAUGCCAUUAUAC		387-409
AD-1633029.1	UAUAUGGCAUGCACAGUGAGU		390-410	ACUCACUGGCAUGCCAUUAUA		388-410
AD-1633030.1	AUAUGGCAUGCACAGUGAGCU		391-411	AGCUCACUGGCAUGCCAUUAU		389-411
AD-1633031.1	UAUGGCAUGCACAGUGAGCUU		392-412	AAGCUCACUGGCAUGCCAUUA		390-412
AD-1633032.1	UGGCAUGCACAGUGAGCUAAU		394-414	AAUAGCUCACUGGCAUGCCAU		392-414
AD-1633033.1	GGCAUGCACAGUGAGCUAUGU		395-415	ACAUAGCUCACUGGCAUGCCAU		393-415
AD-1633034.1	GCAUGCACAGUGAGCUAUGGU		396-416	ACCAUAGCUCACUGGCAUGCCA		394-416
AD-1633048.1	UGGCACCCUGGCCUCUCUCUU		460-480	AAGAGAGAGGCCAGGGUGCCAAA		458-480
AD-1633049.1	GGCACCCUGGCCUCUCUCUAU		461-481	AUAGAGAGAGGCCAGGGUGCCAA		459-481
AD-1633094.1	GACAGGCUACAGGCAAUCCUU		506-526	AAGGAUUGCCUGUAGCCUGUCAG		504-526
AD-1633095.1	ACAGGCUACAGGCAAUCCUGU		507-527	ACAGGAUUGCCUGUAGCCUGUCA		505-527
AD-1633119.1	UUCUUGGAAGGACAAGAACU		531-551	AGUUCUUGGUCCUCCAAAGGAACA		529-551

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1633121.1	CCUUGGAAGGACAAGAACUGU		533-553	ACAGUUCUUGUCCUCCAAAGGAA		531-553
AD-1633122.1	CUUGGAAGGACAAGAACUGCU		534-554	AGCAGUUCUUGUCCUCCAAAGGA		532-554
AD-1633254.2	CACCUGAAGCAGCCGUUUGUU		692-712	AACAAACGGCUGCUUCAGGUGCA		690-712
AD-1633257.2	CUGAAGCAGCCGUUUGUGCAU		695-715	AUGCACAAACGGCUGCUUCAGGU		693-715
AD-1633269.2	UUUGUCAGGGCCUGGCUCUU		707-727	AAGAGCCAGGCCUUGCACAACG		705-727
AD-1633270.2	UUGUCAGGGCCUGGCUCUCU		708-728	AGAGAGCCAGGCCUUGCACAAC		706-728
AD-1633271.2	UGUCAGGGCCUGGCUCUCUU		709-729	AAGAGAGCCAGGCCUUGCACA		707-729
AD-1633272.2	GUGCAGGGCCUGGCUCUCUAU		710-730	AUAGAGAGCCAGGCCUUGCACA		708-730
AD-1633273.2	UGCAGGGCCUGGCUCUCUAU		711-731	AAUAGAGAGCCAGGCCUUGCACA		709-731
AD-1633290.2	ACGCUCUCUGGACUUCACAGU		748-768	ACUGUGAAGUCCAGAGAGCGUG		746-768
AD-1633291.2	CGCUCUCUGGACUUCACAGAU		749-769	AUCUGUGAAGUCCAGAGAGCGUG		747-769
AD-1633324.2	CUGAGAAGAUUGACAGGUUCU		783-803	AGAACCUUGUCAAUUCUUCACGCA		781-803
AD-1633325.2	GAGAAAGAUUGACAGGUUCAU		785-805	AAUGAACCUUGUCAAUUCUUCACG		783-805
AD-1633326.2	AGAAAGAUUGACAGGUUCAUGU		786-806	ACAUGAACCUUGUCAAUUCUUCUCA		784-806
AD-1633327.2	GAAGAUUGACAGGUUCAUGCU		787-807	AGCAUGAACCUUGUCAAUUCUUCUC		785-807
AD-1633328.2	AAGAUUGACAGGUUCAUGCAU		788-808	AUGCAUGAACCUUGUCAAUUCUUCU		786-808
AD-1633329.2	AGAUUGACAGGUUCAUGCAGU		789-809	ACUGCAUGAACCUUGUCAAUUCUUC		787-809
AD-1633330.2	GAUUGACAGGUUCAUGCAGGU		790-810	ACCUGCAUGAACCUUGUCAAUUCUU		788-810
AD-1633331.2	AUUGACAGGUUCAUGCAGGCU		791-811	AGCCUGCAUGAACCUUGUCAAUUCU		789-811
AD-1633332.2	UUGACAGGUUCAUGCAGGCUU		792-812	AAGCCUGCAUGAACCUUGUCAAUUC		790-812
AD-1633333.2	UGACAGGUUCAUGCAGGCGUGU		793-813	ACAGCCUGCAUGAACCUUGUCAAU		791-813
AD-1633334.2	GACAGGUUCAUGCAGGCGUGUU		794-814	AACAGCCUGCAUGAACCUUGUCA		792-814
AD-1633335.2	ACAGGUUCAUGCAGGCGUGUGU		795-815	ACACAGCCUGCAUGAACCUUGUCA		793-815
AD-1633343.2	AUGCAGGCGUGACAGGAUGU		803-823	ACAUCCUGUCACAGCCUGCAUGA		801-823

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM 000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM 000029.3
AD-1633345.2	GCAGGCUGUGACAGGAUGGAU		805-825	AUCCAUCCUGUCACAGCCUGCAU		803-825
AD-1633346.2	CAGGCUGUGACAGGAUGGAU		806-826	AUCCAUCCUGUCACAGCCUGCA		804-826
AD-1633349.2	GCUUUAACACCUACGUCCAU		869-889	AUGGACGUAGGUUUGAAAGCCA		867-889
AD-1633353.2	GAGUUCUGGUGGACAAACAGU		935-955	ACUGUUGUCCACCCAGAACUCCU		933-955
AD-1633364.2	GGACAACAGCACCUCAGUGUU		946-966	AACACUGAGGUGCUGUUGUCCAC		944-966
AD-1633365.2	GACAACAGCACCUCAGUGUCU		947-967	AGACACUGAGGUGCUGUUGUCCA		945-967
AD-1633366.2	ACAACAGCACCUCAGUGUCUU		948-968	AAGACACUGAGGUGCUGUUGUCC		946-968
AD-1633367.2	CAACAGCACCUCAGUGUCUGU		949-969	ACAGACACUGAGGUGCUGUUGUC		947-969
AD-1633368.2	AACAGCACCUCAGUGUCUGUU		950-970	AACAGACACUGAGGUGCUGUUGU		948-970
AD-1633369.2	AUGCCUCUGACCCUGGACAAAGU		1086-1106	ACUUGUCCAGGUCAGAGGCAUAG		1084-1106
AD-1633372.2	AAGGUGGAGGUCUCACUUUUU		1103-1123	AAAAGUGAGACCCUCCACCUUGU		1101-1123
AD-1633373.2	AGGUGGAGGUCUCACUUUUU		1104-1124	AGAAAGUGAGACCCUCCACCUUG		1102-1124
AD-1633374.2	GGUGGAGGUCUCACUUUUUUU		1105-1125	AGGAAAGUGAGACCCUCCACCUU		1103-1125
AD-1633375.2	GAGGUCUCACUUUUUCCAGCAU		1109-1129	AUGCUGGAAAGUGAGACCCUCCA		1107-1129
AD-1633376.2	AGGUCUCACUUUUUCCAGCAAU		1110-1130	AUUGCUGGAAAGUGAGACCCUCC		1108-1130
AD-1633377.2	GGUCUCACUUUUUCCAGCAAAAU		1112-1132	AUUUUUGCUGGAAAGUGAGACCCU		1110-1132
AD-1633378.2	GUCUCACUUUUUCCAGCAAAACU		1113-1133	AGUUUUUGCUGGAAAGUGAGACCC		1111-1133
AD-1633379.2	UCUCACUUUUUCCAGCAAAACUU		1114-1134	AAGUUUUUGCUGGAAAGUGAGACC		1112-1134
AD-1633380.2	CUCACUUUUUCCAGCAAAACUCU		1115-1135	AGAGUUUUUGCUGGAAAGUGAGAC		1113-1135
AD-1633381.2	UCACUUUUUCCAGCAAAACUCCU		1116-1136	AGGAGUUUUUGCUGGAAAGUGAGA		1114-1136
AD-1633382.2	CACUUUUUCCAGCAAAACUCCCU		1117-1137	AGGGAGUUUUUGCUGGAAAGUGAG		1115-1137
AD-1633383.2	ACUUUUUCCAGCAAAACUCCCUU		1118-1138	AAGGAGUUUUUGCUGGAAAGUGA		1116-1138
AD-1633384.2	CUUUUUUCCAGCAAAACUCCCUU		1119-1139	AGAGGAGUUUUUGCUGGAAAGUG		1117-1139
AD-1633385.2	UUUUUUUCCAGCAAAACUCCCUCAU		1120-1140	AUGAGGAGUUUUUGCUGGAAAGU		1118-1140

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1633639.1	UUC CAG CAA A A C U C C C U C A A U		1121-1141	A U U G A G G G A G U U U U G C U G G A A A G		1119-1141
AD-1633640.1	U C C A G C A A A A A C U C C C U C A A C U		1122-1142	A G U U G A G G G A G U U U U G C U G G A A A		1120-1142
AD-1633641.1	C C A G C A A A A C U C C C U C A A C U U		1123-1143	A A G U U G A G G G A G U U U U G C U G G A A		1121-1143
AD-1633642.1	C A G C A A A A C U C C C U C A A C U G U		1124-1144	A C A G U U G A G G G A G U U U U G C U G G A		1122-1144
AD-1633643.1	A G C A A A C U C C C U C A A C U G G U		1125-1145	A C C A G U U G A G G G A G U U U U G C U G G		1123-1145
AD-1633644.1	G C A A A A C U C C C U C A A C U G G A U		1126-1146	A U C C A G U U G A G G G A G U U U U G C U G		1124-1146
AD-1633645.1	C A A A A C U C C C U C A A C U G G A U U		1127-1147	A A U C C A G U U G A G G G A G U U U U G C U		1125-1147
AD-1633646.1	A A A C U C C C U C A A C U G G A U G U		1128-1148	A C A U C C A G U U G A G G G A G U U U U G C		1126-1148
AD-1633647.1	A A A C U C C C U C A A C U G G A U G A U		1129-1149	A U C A U C C A G U U G A G G G A G U U U U G		1127-1149
AD-1633648.1	A A C U C C U C A A C U G G A U G A A U		1130-1150	A U U C A U C C A G U U G A G G G A G U U U U		1128-1150
AD-1633649.1	A C U C C C U C A A C U G G A U G A A G U		1131-1151	A C U U C A U C C A G U U G A G G G A G U U U		1129-1151
AD-1633650.1	C U C C C U C A A C U G G A U G A A G A U		1132-1152	A U C U U C A U C C A G U U G A G G G A G U U		1130-1152
AD-1633651.1	U C C C U C A A C U G G A U G A A G A A U		1133-1153	A U U C U U C A U C C A G U U G A G G G A G U		1131-1153
AD-1633652.1	C C C U C A A C U G G A U G A A G A A A U		1134-1154	A U U U C U U C A U C C A G U U G A G G G A G		1132-1154
AD-1633653.1	C U C A A C U G G A U G A A G A A A C U U		1136-1156	A A G U U U C U U C A U C C A G U U G A G G G		1134-1156
AD-1633678.1	A G G A U C U U A U G A C C U G C A G G U		1201-1221	A C C U G C A G G U C A U A A G A U C C U U G		1199-1221
AD-1633683.1	C U U A U G A C C U G C A G G A C C U G U		1206-1226	A C A G G U C C U G C A G G U C A U A A G A U		1204-1226
AD-1633732.1	C G A G C U G A A C C U G C A A A A A U U		1261-1281	A A U U U U U G C A G G U U C A G C U C G G U		1259-1281
AD-1633733.1	G A G C U G A A C C U G C A A A A A U U U		1262-1282	A A A U U U U U G C A G G U U C A G C U C G G		1260-1282
AD-1633734.1	A G C U G A A C C U G C A A A A A U U G U		1263-1283	A C A A U U U U U G C A G G U U C A G C U C G		1261-1283
AD-1633735.1	G C U G A A C C U G C A A A A A A U U G A U		1264-1284	A U C A A U U U U U G C A G G U U C A G C U C		1262-1284
AD-1633736.1	C U G A A C C U G C A A A A A A U U G A G U		1265-1285	A C U C A A U U U U U G C A G G U U C A G C U		1263-1285
AD-1633737.1	U G A A C C U G C A A A A A A U U G A G C U		1266-1286	A G C U C A A U U U U U G C A G G U U C A G C		1264-1286
AD-1633738.1	G A A C C U G C A A A A A A U U G A G C A U		1267-1287	A U G C U C A A U U U U U U G C A G G U U C A G		1265-1287

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1633739.1	AACCUAGCAAAAUUAGCAAU		1268-1288	AUUGCUCAAUUUUUGCAGGUUCA		1266-1288
AD-1633740.1	ACCUGCAAAAUUAGCAAU		1269-1289	AAUUGCUCAAUUUUUGCAGGUUC		1267-1289
AD-1633741.1	CCUGCAAAAUUAGCAAUGU		1270-1290	ACAUUGCUCAAUUUUUGCAGGUU		1268-1290
AD-1633742.1	CUGCAAAAUUAGCAAUGAU		1271-1291	AUCAUUGCUCAAUUUUUGCAGGU		1269-1291
AD-1633743.1	UGCAAAAUUAGCAAUGACU		1272-1292	AGUCAUUGCUCAAUUUUUGCAGG		1270-1292
AD-1633759.1	GAGGUGCUGAACAGCAUUUUU		1307-1327	AAAAAUGCUGUUCAGCACCUCCC		1305-1327
AD-1633777.1	UGAGAGAGAGCCACAGAGUU		1345-1365	AACUCUGUGGGCUCUCUCUCAUC		1343-1365
AD-1633779.1	AGAGAGAGCCACAGAGUCUU		1347-1367	AAGACUCUGUGGGCUCUCUCUCA		1345-1367
AD-1633780.1	GAGAGAGCCACAGAGUCUAU		1348-1368	AUAGACUCUGUGGGCUCUCUCUC		1346-1368
AD-1633840.1	GAACCGCCCAUCCUGUUUGU		1408-1428	ACAAACAGGAUUGGGCGGUUCAG		1406-1428
AD-1633841.1	AACCGCCCAUCCUGUUUGCU		1409-1429	AGCAAACAGGAUUGGGCGGUUCA		1407-1429
AD-1633842.1	ACCGCCCAUCCUGUUUGCUU		1410-1430	AAGCAAACAGGAUUGGGCGGUUC		1408-1430
AD-1633843.1	CCGCCCAUCCUGUUUGCUGU		1411-1431	ACAGCAAACAGGAUUGGGCGGUU		1409-1431
AD-1633844.1	CGCCCAUCCUGUUUGCUGUU		1412-1432	AACAGCAAACAGGAUUGGGCGGU		1410-1432
AD-1633845.1	GCCCAUCCUGUUUGCUGUGU		1413-1433	ACACAGCAAACAGGAUUGGGCGG		1411-1433
AD-1633846.1	CCCAUCCUGUUUGCUGUGUU		1414-1434	AACACAGCAAACAGGAUUGGGCG		1412-1434
AD-1633847.1	CAUCCUGUUUGCUGUGUAUU		1416-1436	AAUACACAGCAAACAGGAUUGGG		1414-1436
AD-1633848.1	AUCCUGUUUGCUGUGUAUGU		1417-1437	ACAUACACAGCAAACAGGAUUGG		1415-1437
AD-1633849.1	UCCUGUUUGCUGUGUAUGAU		1418-1438	AUCAUACACAGCAAACAGGAUUG		1416-1438
AD-1633850.1	UCCUGUUUGCUGUGUAUGAUU		1419-1439	AAUCAUACACAGCAAACAGGAUU		1417-1439
AD-1633851.1	CCUGUUUGCUGUGUAUGAUCU		1420-1440	AGAUCAUACACAGCAAACAGGAA		1418-1440
AD-1633852.1	CUGUUUGCUGUGUAUGAUCAU		1421-1441	AUGAUCAUACACAGCAAACAGGA		1419-1441
AD-1633853.1	UGUUUGCUGUGUAUGAUCAAU		1422-1442	AUUGAUCAUACACAGCAAACAGG		1420-1442
AD-1633854.1	GUUUGCUGUGUAUGAUCAAAU		1423-1443	AUUUGAUCAUACACAGCAAACAG		1421-1443

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1633855.1	UUUGCUGUGUAUGAUCAAAAGU		1424-1444	ACUUUGAUCUAACACAGCAACA		1422-1444
AD-1633946.1	GUCUCCACCUUUUCUUCUAU		1608-1628	AUAGAAGAAAAGGUGGGAGACUG		1606-1628
AD-1633947.1	CUCCACCUUUUCUUCUAAUU		1610-1630	AAUAGAAGAAAAGGUGGGAGAC		1608-1630
AD-1633948.1	UCCACCUUUUCUUCUAAUGU		1611-1631	ACAUUAGAAGAAAAGGUGGGAGA		1609-1631
AD-1633949.1	CCCACCUUUUCUUCUAAUGAU		1612-1632	AUCAUUAGAAGAAAAGGUGGGAG		1610-1632
AD-1633950.1	CACCUUUUCUUCUAAUGAGUU		1614-1634	AACUCAUUAGAAGAAAAGGUGGG		1612-1634
AD-1633951.1	ACCUUUUCUUCUAAUGAGUCU		1615-1635	AGACUCAUUAGAAGAAAAGGUGG		1613-1635
AD-1633991.1	CCGUUUCUCCUUGGUCUAAAGU		1655-1675	ACUUAGACCAAGGAGAAAACGGCU		1653-1675
AD-1633992.1	CGUUUCUCCUUGGUCUAAAGUU		1656-1676	AACUUAGACCAAGGAGAAAACGGC		1654-1676
AD-1633993.1	GUUUCUCCUUGGUCUAAAGUGU		1657-1677	ACACUUAGACCAAGGAGAAAACGG		1655-1677
AD-1634065.1	GUUUGCUGGGUUUAUUUUAGU		1729-1749	ACUAAAAUAAACCCAGCAAAACUG		1727-1749
AD-1634066.1	UUUGCUGGGUUUAUUUUAGAU		1730-1750	AUCUAAAAUAAACCCAGCAAAACU		1728-1750
AD-1634067.1	UUGCUGGGUUUAUUUUAGAGU		1731-1751	ACUCUAAAAUAAACCCAGCAAAAC		1729-1751
AD-1634068.1	UGCUGGGUUUAUUUUAGAGAU		1732-1752	AUCUCUAAAAUAAACCCAGCAAA		1730-1752
AD-1634069.1	CUGGGUUUAUUUUAGAGAAUU		1734-1754	AAUUCUCUAAAAUAAACCCAGCA		1732-1754
AD-1634070.1	UGGGUUUAUUUUAGAGAAUGU		1735-1755	ACAUUCUCUAAAAUAAACCCAGC		1733-1755
AD-1634071.1	GGGUUUAUUUUAGAGAAUGGU		1736-1756	ACCAUUCUCUAAAAUAAACCCAG		1734-1756
AD-1634072.1	GGGAGGCAAGAACCAAGUGUUU		1761-1781	AAACACUGGUUUCUUGCCUCCCCA		1759-1781
AD-1634073.1	GGAGGCAAGAACCAAGUGUUUU		1762-1782	AAAACACUGGUUUCUUGCCUCCCC		1760-1782
AD-1634074.1	GAGGCAAGAACCAAGUGUUUAU		1763-1783	AUAAACACUGGUUUCUUGCCUCCC		1761-1783
AD-1634075.1	AGGCAAGAACCAAGUGUUUAUGU		1764-1784	ACUAAACACUGGUUUCUUGCCUCC		1762-1784
AD-1634076.1	GGCAAGAACCAAGUGUUUAAGCU		1765-1785	AGCUAAACACUGGUUUCUUGCCUC		1763-1785
AD-1634077.1	GCAAGAACCAAGUGUUUAAGCGU		1766-1786	ACGCUAAACACUGGUUUCUUGCCU		1764-1786
AD-1634078.1	CAAGAACCAAGUGUUUAAGCGCU		1767-1787	AGCGCUAAACACUGGUUUCUUGCC		1765-1787

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1634079.1	AAGAACACAGUGUUUAGCGCGU		1768-1788	ACGCGCUAAACACUGGUUUCUUGC		1766-1788
AD-1634080.1	AGAACACAGUGUUUAGCGCGU		1769-1789	ACGCGCUAAACACUGGUUUCUUG		1767-1789
AD-1634081.1	GAACACAGUGUUUAGCGCGGU		1770-1790	ACCCGCGCUAAACACUGGUUUCU		1768-1790
AD-1634082.1	AACACAGUGUUUAGCGCGGAU		1771-1791	AUCCCGCGCUAAACACUGGUUCU		1769-1791
AD-1634105.1	CUGUCCAAAAGAAUCCAU		1794-1814	AUGGAAUUCUUUUUGGACAGUA		1792-1814
AD-1634107.1	GUUCCAAAAGAAUCCAAACU		1796-1816	AGUUGGAAUUCUUUUUGGACAG		1794-1816
AD-1634109.1	UCCAAAAGAAUCCAAACCGU		1798-1818	ACGGUUGGAAUUCUUUUUGGAAC		1796-1818
AD-1634110.1	CCAAAAGAAUCCAAACCGAU		1799-1819	AUCGGUUGGAAUUCUUUUUGGAA		1797-1819
AD-1634111.1	CAAAAAGAAUCCAAACCGACU		1800-1820	AGUCGGUUGGAAUUCUUUUUGGA		1798-1820
AD-1634112.1	AAAAAGAAUCCAAACCGACCU		1801-1821	AGGUCGGUUGGAAUUCUUUUUGG		1799-1821
AD-1634113.1	AAAAAGAAUCCAAACCGACCAU		1802-1822	AUGGUCGGUUGGAAUUCUUUUUG		1800-1822
AD-1634114.1	AAAGAAUCCAAACCGACCAU		1803-1823	ACUGGUCGGUUGGAAUUCUUUUU		1801-1823
AD-1634115.1	AAGAAUCCAAACCGACCAU		1804-1824	AGCUGGUCGGUUGGAAUUCUUUU		1802-1824
AD-1634116.1	GAAUCCAAACCGACCAUUCU		1806-1826	AAAGCUGGUCGGUUGGAAUUCUU		1804-1826
AD-1634117.1	AUUCCAAACCGACCAUUGU		1807-1827	ACAAGCUGGUCGGUUGGAAUUCU		1805-1827
AD-1634118.1	AUUCCAAACCGACCAUUGUU		1808-1828	AACAAGCUGGUCGGUUGGAAUUC		1806-1828
AD-1634119.1	UCCAAACCGACCAUUGUUU		1810-1830	AAACAAGCUGGUCGGUUGGAAU		1808-1830
AD-1634120.1	CCAACCGACCAUUGUUUGU		1811-1831	ACAAACAAGCUGGUCGGUUGGAA		1809-1831
AD-1634121.1	CAACCGACCAUUGUUUGUU		1812-1832	AACAACAAGCUGGUCGGUUGGA		1810-1832
AD-1634122.1	AACCGACCAUUGUUUGUGU		1813-1833	ACACAACAAGCUGGUCGGUUGG		1811-1833
AD-1634123.1	ACCGACCAUUGUUUGUGAU		1814-1834	AUCACAACAAGCUGGUCGGUUG		1812-1834
AD-1634124.1	CCGACCAUUGUUUGUGAAU		1815-1835	AUUCACAACAAGCUGGUCGGUU		1813-1835
AD-1634125.1	CGACCAUUGUUUGUGAAAU		1816-1836	AUUUCACAACAAGCUGGUCGGU		1814-1836
AD-1634126.1	GACCAUUGUUUGUGAAAU		1817-1837	AGUUUCACAACAAGCUGGUCGG		1815-1837

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1634127.1	ACCAGCUUGUUUGUGAAACAUAU		1818-1838	AUGUUUCACAAACAAGCUGGUCG		1816-1838
AD-1634128.1	CCAGCUUGUUUGUGAAACAUAU		1819-1839	AUUGUUUCACAAACAAGCUGGUC		1817-1839
AD-1634129.1	CAGCUUGUUUGUGAAACAUAU		1820-1840	AUUUGUUUCACAAACAAGCUGGU		1818-1840
AD-1634130.1	AGCUUGUUUGUGAAACAUAU		1821-1841	AUUUGUUUCACAAACAAGCUGG		1819-1841
AD-1634135.1	UGUUCCCUUUUCAAAGUUGAGU		1844-1864	ACUCAACUUGAAAAGGGAACACU		1842-1864
AD-1634136.1	GUUCCCUUUUCAAAGUUGAGAU		1845-1865	AUCUCAACUUGAAAAGGGAACAC		1843-1865
AD-1634137.1	UUCUUUUUCAAAGUUGAGAAU		1846-1866	AUUCUCAACUUGAAAAGGGAACA		1844-1866
AD-1634146.1	CAAGUUGAGAACAAAAAUUGU		1855-1875	ACAAUUUUUGUUCUCAAACUUGAA		1853-1875
AD-1634147.1	AAGUUGAGAACAAAAAUUGGU		1856-1876	ACCAAUUUUUGUUCUCAAACUUGA		1854-1876
AD-1634148.1	GUUGAGAACAAAAAUUGGGUU		1858-1878	AACCCAAUUUUUGUUCUCAAACUU		1856-1878
AD-1634149.1	UUGAGAACAAAAAUUGGGUUU		1859-1879	AAACCCAAUUUUUGUUCUCAAACU		1857-1879
AD-1634150.1	UGAGAACAAAAAUUGGGUUUU		1860-1880	AAACCCAAUUUUUGUUCUCAAAC		1858-1880
AD-1634151.1	GAGAACAAAAAUUGGGUUUUU		1861-1881	AAAAACCCAAUUUUUGUUCUCAA		1859-1881
AD-1634152.1	AGAACAAAAAUUGGGUUUUUAU		1862-1882	AUAAAAACCCAAUUUUUGUUCUCA		1860-1882
AD-1634153.1	GAACAAAAAUUGGGUUUUUAU		1863-1883	AUUAAAAACCCAAUUUUUGUUCUC		1861-1883
AD-1634162.1	AGUAUACAUUUUUGCAUUGCU		1889-1909	AGCAAUGCAAAAAAUGUAUACUUU		1887-1909
AD-1634163.1	GUUAUACAUUUUUGCAUUGCCU		1890-1910	AGGCAAUGCAAAAAAUGUAUACUU		1888-1910
AD-1634164.1	UAUACAUUUUUGCAUUGCCUU		1891-1911	AAGGCAAUGCAAAAAAUGUAUACU		1889-1911
AD-1634165.1	AUACAUUUUUGCAUUGCCUUU		1892-1912	AAAGGCAAUGCAAAAAAUGUAUAC		1890-1912
AD-1634169.1	AUUUUUGCAUUGCCUUCGGUU		1896-1916	AACCGAAGGCAAAUGCAAAAAAUGU		1894-1916
AD-1634170.1	UUUUUGCAUUGCCUUCGGUUU		1897-1917	AAACCGAAGGCAAAUGCAAAAAAUG		1895-1917
AD-1634171.1	UUUUUGCAUUGCCUUCGGUUUU		1898-1918	AAACCGAAGGCAAAUGCAAAAAAU		1896-1918
AD-1634172.1	UUUGCAUUGCCUUCGGUUUGU		1899-1919	ACAAACCGAAGGCAAAUGCAAAAA		1897-1919
AD-1634173.1	UUGCAUUGCCUUCGGUUUGUU		1900-1920	AACAAACCGAAGGCAAAUGCAAAA		1898-1920

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1634174.1	UGCAUUGCCUUCGGUUUGUAU		1901-1921	AUACAAACCCGAAAGGCAAUGCAA		1899-1921
AD-1634175.1	GCAUUGCCUUCGGUUUGUAU		1902-1922	AAUACAAACCCGAAAGGCAAUGCAA		1900-1922
AD-1634176.1	CAUUGCCUUCGGUUUGUAU		1903-1923	AAUACAAACCCGAAAGGCAAUGCA		1901-1923
AD-1634177.1	AUUGCCUUCGGUUUGUAU		1904-1924	AAAUACAAACCCGAAAGGCAAUGC		1902-1924
AD-1634178.1	UUGCCUUCGGUUUGUAU		1905-1925	AUAAAUACAAACCCGAAAGGCAAUG		1903-1925
AD-1634179.1	UGCCUUCGGUUUGUAU		1906-1926	ACUAAAUACAAACCCGAAAGGCAAU		1904-1926
AD-1634180.1	GCCUUCGGUUUGUAU		1907-1927	AACUAAAUACAAACCCGAAAGGCAA		1905-1927
AD-1634181.1	CCUUCGGUUUGUAU		1908-1928	ACACUAAAUACAAACCCGAAAGGCA		1906-1928
AD-1634182.1	CUUCGGUUUGUAU		1909-1929	AACACUAAAUACAAACCCGAAAGGC		1907-1929
AD-1634183.1	UUCGGUUUGUAU		1910-1930	AGACACUAAAUACAAACCCGAAAGG		1908-1930
AD-1634184.1	UCGGUUUGUAU		1911-1931	AAGACACUAAAUACAAACCCGAAAG		1909-1931
AD-1634185.1	CGGUUUGUAU		1912-1932	AAAGACACUAAAUACAAACCCGAA		1910-1932
AD-1634186.1	GGUUUGUAU		1913-1933	ACAAGACACUAAAUACAAACCCGA		1911-1933
AD-1634187.1	GUUUGUAU		1914-1934	AUCAAGACACUAAAUACAAACCCG		1912-1934
AD-1634188.1	UUUGUAU		1915-1935	AUUCAGACACUAAAUACAAACCC		1913-1935
AD-1634189.1	UUGUAU		1916-1936	AAUUCAGACACUAAAUACAAAC		1914-1936
AD-1634190.1	UGUAU		1917-1937	ACAUUCAAGACACUAAAUACAAA		1915-1937
AD-1634191.1	GUUAU		1918-1938	AACAUUCAAGACACUAAAUACAA		1916-1938
AD-1634192.1	UAUUAGUGUCUUUGAAUGUAU		1919-1939	AUACAUUCAAGACACUAAAUACA		1917-1939
AD-1634193.1	AUUUAGUGUCUUUGAAUGUAU		1920-1940	AUUACAUUCAAGACACUAAAUAC		1918-1940
AD-1634194.1	UUUAGUGUCUUUGAAUGUAU		1921-1941	ACUUACAUUCAAGACACUAAAU		1919-1941
AD-1634195.1	UUAGUGUCUUUGAAUGUAU		1922-1942	AUCUUACAUUCAAGACACUAAAU		1920-1942
AD-1634196.1	UAGUGUCUUUGAAUGUAU		1923-1943	AUUCUUACAUUCAAGACACUAAA		1921-1943
AD-1634197.1	AGUGUCUUUGAAUGUAU		1924-1944	AGUUCUUACAUUCAAGACACUAA		1922-1944

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1634199.1	UGUCUUGAAUGUAGAACAUAU		1926-1946	AAUGUUUUACAUAUCAAAGACACU		1924-1946
AD-1634200.1	GUCUUUGAAUGUAGAACAUGU		1927-1947	ACAUGUUUUACAUAUCAAAGACAC		1925-1947
AD-1634203.1	UUGAAUGUAGAACAUGACCU		1930-1950	AGGUCAUUUUUACAUAUCAAAGA		1928-1950
AD-1634209.1	GUAGAACAUGACCUCCGUGU		1936-1956	ACACGGAGGUCAUGUUUUACAUA		1934-1956
AD-1634210.1	UAAGAACAUGACCUCCGUGUU		1937-1957	AACACGGAGGUCAUGUUUUACA		1935-1957
AD-1634211.1	AAGAACAUGACCUCCGUGUAU		1938-1958	AUACACGGAGGUCAUGUUUUAC		1936-1958
AD-1634212.1	AGAAACAUGACCUCCGUGUAGU		1939-1959	ACUACACGGAGGUCAUGUUUUUA		1937-1959
AD-1634213.1	GAACAUGACCUCCGUGUAGUU		1940-1960	AACUACACGGAGGUCAUGUUUUU		1938-1960
AD-1634214.1	AACAUGACCUCCGUGUAGUGU		1941-1961	ACACUACACGGAGGUCAUGUUUCU		1939-1961
AD-1634215.1	ACAUGACCUCCGUGUAGUGUU		1942-1962	AACACUACACGGAGGUCAUGUUC		1940-1962
AD-1634216.1	CAUGACCUCCGUGUAGUGUCU		1943-1963	AGACACUACACGGAGGUCAUGUU		1941-1963
AD-1634217.1	AUGACCUCCGUGUAGUGUCUU		1944-1964	AAGACACUACACGGAGGUCAUGU		1942-1964
AD-1634234.1	UUUCCACAGAUUCUUUGUGAUU		1979-1999	AAUCACAAAGCAUUCUGUGGAAAA		1977-1999
AD-1634235.1	UUCCACAGAUUCUUUGUGAUUU		1980-2000	AAAUACAAAGCAUUCUGUGGAAAA		1978-2000
AD-1634236.1	UCCACAGAUUCUUUGUGAUUUU		1981-2001	AAAUACAAAGCAUUCUGUGGAAA		1979-2001
AD-1634237.1	CCACAGAUUCUUUGUGAUUUUU		1982-2002	AAAAAUACAAAGCAUUCUGUGGAA		1980-2002
AD-1634238.1	CACAGAUUCUUUGUGAUUUUUU		1983-2003	AAAAAUACAAAGCAUUCUGUGGA		1981-2003
AD-1634282.1	ACCUGAAUUUCUGUUUUGAAUU		2027-2047	AAUUCAAACAGAAAUUUCAGGUGC		2025-2047
AD-1634283.1	CCUGAAUUUCUGUUUUGAAUGU		2028-2048	ACAUUCAACAGAAAUUUCAGGUG		2026-2048
AD-1634304.1	GGAAACCAUAGCUGGUUAUUUUU		2049-2069	AAAUUAAACAGCUAUGGUUCCGC		2047-2069
AD-1634305.1	GAACCAUAGCUGGUUAUUUUU		2050-2070	AGAAAUAAACAGCUAUGGUUCCG		2048-2070
AD-1634306.1	AACCAUAGCUGGUUAUUUCUU		2051-2071	AAGAAAUAAACAGCUAUGGUUCC		2049-2071
AD-1634307.1	ACCAUAGCUGGUUAUUUCUCU		2052-2072	AGAGAAAUAAACAGCUAUGGUUC		2050-2072
AD-1634308.1	CCAUAGCUGGUUAUUUCUCCU		2053-2073	AGGAGAAAUAAACAGCUAUGGUU		2051-2073

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1634327.1	CCUUGUGUUAGUAAUAAACGU		2072-2092	ACGUUUUUUUACUAAACAAAGGGA		2070-2092
AD-1634328.1	CUUGUGUUAGUAAUAAACGUU		2073-2093	AACGUUUUUUUACUAAACAAAGGG		2071-2093
AD-1634329.1	UUUGUUUAGUAAUAAACGUCU		2074-2094	AGACGUUUUUUUACUAAACAAAGG		2072-2094
AD-1634330.1	UGUGUUAGUAAUAAACGUCUU		2075-2095	AAGACGUUUUUUUACUAAACAAAG		2073-2095
AD-1634331.1	GUGUUAGUAAUAAACGUCUUU		2076-2096	AAGACGUUUUUUUACUAAACAA		2074-2096
AD-1634332.1	UGUUAGUAAUAAACGUCUUUGU		2077-2097	ACAAGACGUUUUUUUACUAAACACA		2075-2097
AD-1634333.1	GUUAGUAAUAAACGUCUUUGCU		2078-2098	AGCAAGACGUUUUUUUACUAAACAC		2076-2098
AD-1657992.1	AGCCUGAGGGCCACCAUCCUU		86-106	AAGGAUUGGUGGCCCCUCAGGCUCA		84-106
AD-1657994.1	CCUGAGGGCCACCAUCCUCUU		88-108	AAGAGGAUGGUGGCCCCUCAGGCU		86-108
AD-1657998.1	AGGGCCACCAUCCUCUGCCUU		92-112	AAGGCAGAGGATGGUGGCCCCUCA		90-112
AD-1658030.1	GUGACCGGGUGUACAUACACU		138-158	AGUGTATGUACACCCGGUCACCU		136-158
AD-1658032.1	CUUCCACCCUCGUAUCCACAU		160-180	ATGUGGAUGACGAGGUGGGAAGG		158-180
AD-1658033.1	UUCCACCCUCGUAUCCACAAU		161-181	ATUGTGAUGACGAGGUGGGAAGG		159-181
AD-1658034.1	UCCACCCUCGUAUCCACAAUU		162-182	AAUUGUGGAUGACGAGGUGGGAAG		160-182
AD-1658035.1	CCACCCUCGUAUCCACAAUGU		163-183	ACAUTGTGAUGACGAGGUGGGA		161-183
AD-1658036.1	CACCCUCGUAUCCACAAUGAU		164-184	ATCATUGUGGATGACGAGGUGGA		162-184
AD-1658038.1	CCUCGUAUCCACAAUGAGAU		166-186	ATCUCATUGUGGAUGACGAGGUG		164-186
AD-1658039.1	CUCGUAUCCACAAUGAGAGU		167-187	ACUCTCAUUUGGGAUGACGAGGU		165-187
AD-1658040.1	UCGUAUCCACAAUGAGAGUU		168-188	AACUCUCAUUUGTGAUGACGAGG		166-188
AD-1658041.1	CGUAUCCACAAUGAGAGUAU		169-189	ATACTCTCAUUUGGGAUGACGAG		167-189
AD-1658042.1	GUAUCCACAAUGAGAGUAU		170-190	AGUACUCUCAUTGUGGAUGACGA		168-190
AD-1658043.1	UCAUCCACAAUGAGAGUACCU		171-191	AGGUACTCUCATUGUGGAUGACG		169-191
AD-1658044.1	CAUCCACAAUGAGAGUAUCCUU		172-192	AAGGTACUCUCAUUUGGGAUGAC		170-192
AD-1658045.1	AUCCACAAUGAGAGUAUCCUGU		173-193	ACAGGUACUCUCAUUUGGGAUGA		171-193

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1658046.1	UCCACAAUGAGAGUACCUGUU		174-194	AACAGGTACUCTCAUUGUGGAUG		172-194
AD-1658047.1	CCACA AUGAGAGUACCUGUGU		175-195	ACACAGGUACUCUCAUUGUGGAU		173-195
AD-1658048.1	CACAAUGAGAGUACCUGUGAU		176-196	ATCACAGGUACTCUCAUUGUGGA		174-196
AD-1658049.1	ACAAUGAGAGUACCUGUGAGU		177-197	ACUCACAGGUACUCUCAUUGUGG		175-197
AD-1658050.1	CAAUGAGAGUACCUGUGAGCU		178-198	AGCUCACAGGUACUCUCAUUGUG		176-198
AD-1658051.1	AAUGAGAGUACCUGUGAGCAU		179-199	ATGCTCACAGGTACUCUCAUUGU		177-199
AD-1658052.1	AUGAGAGUACCUGUGAGCAGU		180-200	ACUGCUCACAGGUACUCUCAUUG		178-200
AD-1658053.1	UGAGAGUACCUGUGAGCAGCU		181-201	AGCUGCTCACAGGUACUCUCAUU		179-201
AD-1658054.1	GAGAGUACCUGUGAGCAGCUU		182-202	AAGCTGCUCACAGGUACUCUCAU		180-202
AD-1658055.1	AGAGUACCUGUGAGCAGCUGU		183-203	ACAGCUGCUCACAGGUACUCUCA		181-203
AD-1658056.1	GAGUACCUGUGAGCAGCUGGU		184-204	ACCAGCTGCUCACAGGUACUCUC		182-204
AD-1658057.1	AGUACCUGUGAGCAGCUGGCU		185-205	AGCCAGCUGCUCACAGGUACUCU		183-205
AD-1658058.1	GUACCUGUGAGCAGCUGGCAU		186-206	ATGCCAGCUGCTCACAGGUACUC		184-206
AD-1658059.1	UACCUGUGAGCAGCUGGCAAU		187-207	ATUGCCAGCUGCUCACAGGUACU		185-207
AD-1658184.1	AAUGGUCGGGAUGCUGGCCAU		352-372	ATGGCCAGCAUCCCGACCAUUGC		350-372
AD-1658185.1	AUGGUCGGGAUGCUGGCCAAU		353-373	ATUGGCCAGCATCCCGACCAUUG		351-373
AD-1658186.1	UGGUCGGGAUGCUGGCCAACU		354-374	AGUUGGCCAGCAUCCCGACCAUU		352-374
AD-1658187.1	GGUCGGGAUGCUGGCCAACUU		355-375	AAGUTGGCCAGCAUCCCGACCAU		353-375
AD-1658188.1	GUCGGGAUGCUGGCCAACUUU		356-376	AAAGTUGGCCAGCAUCCCGACCA		354-376
AD-1658189.1	UCGGGAUGCUGGCCAACUUCU		357-377	AGAAGUTGGCCAGCAUCCCGACC		355-377
AD-1658190.1	CGGGAUGCUGGCCAACUUCUU		358-378	AAGAAGTUGGCCAGCAUCCCGAC		356-378
AD-1658191.1	GGGAUGCUGGCCAACUUCUUU		359-379	AAAGAAGUUGGCCAGCAUCCCGA		357-379
AD-1658192.1	GGGAUGCUGGCCAACUUCUUGU		360-380	ACAAGAAGUUGGCCAGCAUCCCG		358-380
AD-1658193.1	GAUGCUGGCCAACUUCUUGGU		361-381	ACCAAGAAGUUGGCCAGCAUCCC		359-381

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1658196.1	GCUGGCCAACUUCUUGGGCUU		364-384	AAGCCCAAGAAAGUUGGCCAGCAU		362-384
AD-1658197.1	CUGGCCAACUUCUUGGGCUU		365-385	AAGCCCAAGAAAGUUGGCCAGCA		363-385
AD-1658200.1	GCCAAACUUCUUGGGCUUCCGU		368-388	ACGGAAGCCCAAGAAAGUUGGCCA		366-388
AD-1658201.1	CCAAACUUCUUGGGCUUCCGUU		369-389	AACGGAAGCCCAAGAAAGUUGGCC		367-389
AD-1658202.1	CAACUUCUUGGGCUUCCGUU		370-390	ATACGGAAGCCCAAGAAAGUUGGC		368-390
AD-1658203.1	AACUUCUUGGGCUUCCGUU		371-391	AAUACGGAAGCCCAAGAAAGUUGG		369-391
AD-1658204.1	ACUUCUUGGGCUUCCGUU		372-392	ATAUACGGAAGCCCAAGAAAGUUG		370-392
AD-1658205.1	CUUCUUGGGCUUCCGUU		373-393	AAUATACGGAAGCCCAAGAAAGU		371-393
AD-1658206.1	UUCUUGGGCUUCCGUU		374-394	ATAUUAUACGGAAGCCCAAGAAAGU		372-394
AD-1658207.1	UCUUGGGCUUCCGUU		375-395	AAUATATACGGAAGCCCAAGAAAG		373-395
AD-1658208.1	CUUGGGCUUCCGUU		376-396	ACAUUAUACGGAAGCCCAAGAA		374-396
AD-1658209.1	UUGGGCUUCCGUU		377-397	ACCATATAUACGGAAGCCCAAGAA		375-397
AD-1658211.1	GGGCUUCCGUU		379-399	ATGCCATAUUAUACGGAAGCCCA		377-399
AD-1658212.1	GGCUUCCGUU		380-400	AAUGCCAUUAUATACGGAAGCCCA		378-400
AD-1658213.1	GCUUCCGUU		381-401	ACAUGCCAUUAUACGGAAGCCCA		379-401
AD-1658220.1	UAUAUUGGCAUGCACAGUGU		388-408	ACACTGTGCAUGCCCAUAUAUACG		386-408
AD-1658221.1	AUAUAUGGCAUGCACAGUGAU		389-409	ATCACUGUGCATGCCAUUAUAUAC		387-409
AD-1658222.1	UAUAUGGCAUGCACAGUGAGU		390-410	ACUCACTGUGCAUGCCCAUAUAUA		388-410
AD-1658223.1	AUAUGGCAUGCACAGUGAGCU		391-411	AGCUCACUGUGCAUGCCCAUAUAU		389-411
AD-1658224.1	UAUGGCAUGCACAGUGAGCUU		392-412	AAGCTCACUGUGCAUGCCCAUAUA		390-412
AD-1658225.1	AUGGCAUGCACAGUGAGCUU		393-413	ATAGCUCACUGUGCAUGCCCAUAU		391-413
AD-1658226.1	UGGCAUGCACAGUGAGCUU		394-414	AAUAGCTCACUGUGCAUGCCCAUA		392-414
AD-1658227.1	GGCAUGCACAGUGAGCUU		395-415	ACAUAGCUCACUGUGCAUGCCCAU		393-415
AD-1658228.1	GCAUGCACAGUGAGCUU		396-416	ACCATAGCUCACUGUGCAUGCCCA		394-416

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1658242.1	UGGCACCCUGGCCUCUCUCUU		460-480	AAGAGAGAGGCCAGGGUGCCAAA		458-480
AD-1658243.1	GGCACCCUGGCCUCUCUCUAU		461-481	ATAGAGAGAGGCCAGGGUGCCAA		459-481
AD-1658288.1	GACAGGCUACAGGCAAUCCUU		506-526	AAGGAUTGCCUGUAGCCUGUCAG		504-526
AD-1658289.1	ACAGGCUACAGGCAAUCCUGU		507-527	ACAGGATUGCCTGUAGCCUGUCA		505-527
AD-1658313.1	UUCUUGGAAGGACAAGAACU		531-551	AGUUCUTGUCCTUCCAGGAACA		529-551
AD-1658315.1	CCUUGGAAGGACAAGAACUGU		533-553	ACAGTUCUUGUCCUCCAAAGGA		531-553
AD-1658316.1	CUUGGAAGGACAAGAACUGCU		534-554	AGCAGUTCUUGTCCUCCAAAGGA		532-554
AD-1658448.2	CACCUGAAGCAGCCGUUUGUU		692-712	AACAAACGGCUGCUUCAGGUGCA		690-712
AD-1658451.2	CUGAAGCAGCCGUUUGUGCAU		695-715	ATGCACAAACGGCUGCUUCAGGU		693-715
AD-1658463.2	UUUGUCAGGGCCUGGCUCUU		707-727	AAGAGCCAGGCCUUGCACAACG		705-727
AD-1658464.2	UUGUCAGGGCCUGGCUCUCU		708-728	AGAGAGCCAGGCCUUGCACAAC		706-728
AD-1658465.2	UGUCAGGGCCUGGCUCUCUU		709-729	AAGAGAGCCAGGCCUUGCACA		707-729
AD-1658466.2	GUGCAGGGCCUGGCUCUCUAU		710-730	ATAGAGAGCCAGGCCUUGCACA		708-730
AD-1658467.2	UGCAGGGCCUGGCUCUCUAU		711-731	AAUAGAGAGCCAGGCCUUGCACA		709-731
AD-1658484.2	ACGCUCUCUGGACUUCACAGU		748-768	ACUGTGAAGUCCAGAGAGCGUGG		746-768
AD-1658485.2	CGCUCUCUGGACUUCACAGAU		749-769	ATCUGUGAAGUCCAGAGAGCGUG		747-769
AD-1658519.2	CUGAGAAGAUUGACAGGUUCU		783-803	AGAACCTGTUCAAUUCUUCAGCA		781-803
AD-1658520.2	UGAGAAGAUUGACAGGUUCAU		784-804	ATGAACCUGUCAAUUCUUCAGC		782-804
AD-1658521.2	GAGAAGAUUGACAGGUUCAU		785-805	AAUGAACCCUGUCAAUUCUUCAG		783-805
AD-1658522.2	AGAAAGAUUGACAGGUUCAUGU		786-806	ACAUGAACCCUGTCAAUUCUUCU		784-806
AD-1658523.2	GAAAGAUUGACAGGUUCAUGCU		787-807	AGCATGAACCUGUCAAUUCUUC		785-807
AD-1658524.2	AAGAUGACAGGUUCAUGCAU		788-808	ATGCAUGAACCTGTUCAAUUCUUC		786-808
AD-1658525.2	AGAUUGACAGGUUCAUGCAGU		789-809	ACUGCATGAACCUGUCAAUUCUUC		787-809
AD-1658526.2	GAUUGACAGGUUCAUGCAGGU		790-810	ACCUGCAUGAACCCUGUCAAUUCU		788-810

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM 000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM 000029.3
AD-1658527.2	AUUGACAGGUUCAUGCAGGCU		791-811	AGCCTGCAUGAACCCUGUCAUUC		789-811
AD-1658528.2	UUGACAGGUUCAUGCAGGCUU		792-812	AAGCCUGCAUGAACCCUGUCAUUC		790-812
AD-1658529.2	UGACAGGUUCAUGCAGGCUU		793-813	ACAGCCTGCAUGAACCCUGUCAUUC		791-813
AD-1658530.2	GACAGGUUCAUGCAGGCUU		794-814	AACAGCCUGCATGAACCCUGUCAUUC		792-814
AD-1658531.2	ACAGGUUCAUGCAGGCUU		795-815	ACACAGCCUGCAUGAACCCUGUCAUUC		793-815
AD-1658539.2	AUGCAGGCUUGACAGGAUUG		803-823	ACAUCCTGUCACAGCCUGCAUGA		801-823
AD-1658541.2	GCAGGCUUGACAGGAUUGAU		805-825	ATCCAUCUUGUCACAGCCUGCAUUC		803-825
AD-1658542.2	CAGGCUUGACAGGAUUGAAU		806-826	ATUCCATCCUGTCAACAGCCUGCAUUC		804-826
AD-1658605.2	GCUUUCACACCUACGUCCAU		869-889	ATGGACGUAGGTGUUGAAAGCCA		867-889
AD-1658650.2	GAGUUCUGGGUGGACAAACAGU		935-955	ACUGTUGUCCACCCAGAACUCCU		933-955
AD-1658661.2	GGACAACAGCACCUCAGUGUU		946-966	AACACUGAGGUGCUGUUUGUCCAC		944-966
AD-1658662.2	GACAACAGCACCUCAGUGUCU		947-967	AGACACTGAGGTGCUUGUUGUCCA		945-967
AD-1658663.2	ACAACAGCACCUCAGUGUCUU		948-968	AAGACACUGAGGUGCUGUUUGUCC		946-968
AD-1658664.2	CAACAGCACCUCAGUGUCUGU		949-969	ACAGACACUGAGGUGCUGUUUGUC		947-969
AD-1658665.2	AACAGCACCUCAGUGUCUGUU		950-970	AACAGACACUGAGGUGCUGUUUGU		948-970
AD-1658801.2	AUGCCUCUGACCCUGGACAAGU		1086-1106	ACUUGUCCAGGTCAAGAGGCAUAG		1084-1106
AD-1658818.2	AAGGUGGAGGGUCUCACUUUU		1103-1123	AAAAGUGAGACCCUCCACCCUUGU		1101-1123
AD-1658819.2	AGGUGGAGGGUCUCACUUUU		1104-1124	AGAAAAGTGAGACCCUCCACCCUUG		1102-1124
AD-1658820.2	GGUGGAGGGUCUCACUUUU		1105-1125	AGGAAAAGUGAGACCCUCCACCCU		1103-1125
AD-1658824.2	GAGGUCUCACUUUCCAGCAU		1109-1129	ATGCTGGAAGTGAGACCCUCCA		1107-1129
AD-1658825.2	AGGUCUCACUUUCCAGCAU		1110-1130	ATUGCUGGAAAAGUGAGACCCUCC		1108-1130
AD-1658827.2	GGUCUCACUUUCCAGCAAAA		1112-1132	ATUUTGUGGAAAAGUGAGACCCU		1110-1132
AD-1658828.2	GUCUCACUUUCCAGCAAAA		1113-1133	AGUUTGUGGAAAAGUGAGACCC		1111-1133
AD-1658829.2	UCUCACUUUCCAGCAAAA		1114-1134	AAGUTUTGUGGAAAAGUGAGACC		1112-1134

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1658830.1	CUCACUUUCCAGCAAAACUCU		1115-1135	AGAGTUTUGCUGGAAAGUGAGAC		1113-1135
AD-1658831.1	UCACUUUCCAGCAAAACUCCU		1116-1136	AGGAGUTUUGCTGGAAGUGAGA		1114-1136
AD-1658832.1	CACUUUCCAGCAAAACUCCCU		1117-1137	AGGGAGTUUUGCUGGAAAGUGAG		1115-1137
AD-1658833.1	ACUUUCCAGCAAAACUCCCU		1118-1138	AAGGGAGUUUUGCUGGAAAGUGA		1116-1138
AD-1658834.1	CUUCCAGCAAAACUCCCU		1119-1139	AGAGGAGUUUUGCUGGAAAGUG		1117-1139
AD-1658835.1	UUUCCAGCAAAACUCCCU		1120-1140	ATGAGGGAGUUUUGCUGGAAAGU		1118-1140
AD-1658836.1	UCCAGCAAAACUCCCU		1121-1141	ATUGAGGGAGUUUUGCUGGAAAG		1119-1141
AD-1658837.1	UCCAGCAAAACUCCCU		1122-1142	AGUUGAGGGAGTUUUGCUGGAAA		1120-1142
AD-1658838.1	CCAGCAAAACUCCCU		1123-1143	AAGUTGAGGGAGUUUUGCUGGAA		1121-1143
AD-1658839.1	CAGCAAAACUCCCU		1124-1144	ACAGTUGAGGGAGUUUUGCUGGA		1122-1144
AD-1658840.1	AGCAAAACUCCCU		1125-1145	ACCAGUTGAGGGAGUUUUGCUGG		1123-1145
AD-1658841.1	GCAAAACUCCCU		1126-1146	ATCCAGTUGAGGGAGUUUUGCUG		1124-1146
AD-1658842.1	CAAAACUCCCU		1127-1147	AAUCCAGUUGAGGGAGUUUUGCU		1125-1147
AD-1658843.1	AAACUCCCU		1128-1148	ACAUCCAGUUGAGGGAGUUUUGC		1126-1148
AD-1658844.1	AAACUCCCU		1129-1149	ATCATCCAGUUGAGGGAGUUUUG		1127-1149
AD-1658845.1	AACUCCCU		1130-1150	ATUCAUCCAGUTGAGGGAGUUUU		1128-1150
AD-1658846.1	ACUCCCU		1131-1151	ACUUCATCCAGTUGAGGGAGUUU		1129-1151
AD-1658847.1	CUCCCU		1132-1152	ATCUTCAUCCAGUUUGAGGGAGUU		1130-1152
AD-1658848.1	UCCCU		1133-1153	ATUCTUCAUCCAGUUUGAGGGAGU		1131-1153
AD-1658849.1	CCCU		1134-1154	ATUUCUTCAUCCAGUUUGAGGGAG		1132-1154
AD-1658850.1	CUCACUUGGAUAGAAACUU		1136-1156	AAGUTUCUUCATCCAGUUUGAGGG		1134-1156
AD-1658875.1	AGGAUCUUUAGACCU		1201-1221	ACCUGCAGGUCAUAAAGAUCCUUG		1199-1221
AD-1658880.1	CUUAUGACCU		1206-1226	ACAGGUCCUGCAGGUCAUAAAGAU		1204-1226
AD-1658929.1	CGAGCUGAACCU		1261-1281	AAUUTUTGCAGGUUCAGCUCGGU		1259-1281

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1658930.1	GAGCUGAACCCUGCAAAAAUUU		1262-1282	AAAUTUTUUGCAGGUUCAGCUCGG		1260-1282
AD-1658931.1	AGCUGAACCCUGCAAAAAUUUGU		1263-1283	ACAAATUTUUGCAGGUUCAGCUCG		1261-1283
AD-1658932.1	GCUGAACCCUGCAAAAAUUUGAU		1264-1284	ATCAAATUUUUGCAGGUUCAGCUC		1262-1284
AD-1658933.1	CUGAACCCUGCAAAAAUUUGAGU		1265-1285	ACUCAATUUUUGCAGGUUCAGCU		1263-1285
AD-1658934.1	UGAACCCUGCAAAAAUUUGAGCU		1266-1286	AGCUCAAUUUUTGCAGGUUCAGC		1264-1286
AD-1658935.1	GAACCCUGCAAAAAUUUGAGCAU		1267-1287	ATGCTCAAUUUTUGCAGGUUCAG		1265-1287
AD-1658936.1	AACCCUGCAAAAAUUUGAGCAAU		1268-1288	ATUGCUCAAUUTUUGCAGGUUCA		1266-1288
AD-1658937.1	ACCUGCAAAAAUUUGAGCAAUU		1269-1289	AAUUGCTCAAUTUUUUGCAGGUUC		1267-1289
AD-1658938.1	CCUGCAAAAAUUUGAGCAAUGU		1270-1290	ACAUTGCUCAATUUUUGCAGGUU		1268-1290
AD-1658939.1	CUGCAAAAAUUUGAGCAAUGAU		1271-1291	ATCATUGCUCAAUUUUUGCAGGU		1269-1291
AD-1658940.1	UGCAAAAAUUUGAGCAAUGACU		1272-1292	AGUCAUTGCUCAAUUUUUUGCAGG		1270-1292
AD-1658954.1	GAGGUGCUGAACAGCAUUUUU		1307-1327	AAAAAUGCUGUTCAGCACCUCCC		1305-1327
AD-1658955.1	AGGUGCUGAACAGCAUUUUUU		1308-1328	AAAAAATGCUGTUCAGCACCUCC		1306-1328
AD-1658956.1	GGUGCUGAACAGCAUUUUUUU		1309-1329	AAAAAAUUGCUGUUCAGCACCU		1307-1329
AD-1658957.1	GUGCUGAACAGCAUUUUUUUU		1310-1330	AAAAAAUUGCTGUUCAGCACCU		1308-1330
AD-1658958.1	UGCUGAACAGCAUUUUUUUUU		1311-1331	AAAAAAAUUGCUGUUCAGCAC		1309-1331
AD-1658959.1	GCUGAACAGCAUUUUUUUUUGU		1312-1332	ACAAAAAAUUGCUGUUCAGCAC		1310-1332
AD-1658960.1	CUGAACAGCAUUUUUUUUUGAU		1313-1333	ATCAAAAAAAATGCUGUUCAGCA		1311-1333
AD-1658992.1	UGAGAGAGAGCCACAGAGUU		1345-1365	AACUCUGUGGGCUCUCUCUCAUC		1343-1365
AD-1658994.1	AGAGAGAGCCACAGAGUCUU		1347-1367	AAGACUCUGUGGGCUCUCUCUCA		1345-1367
AD-1658995.1	GAGAGAGCCACAGAGUCUAU		1348-1368	ATAGACTCUGUGGGCUCUCUCUC		1346-1368
AD-1659055.1	GAACCGCCCAUCCUGUUUGU		1408-1428	ACAAACAGGAATGGGCGGUUCAG		1406-1428
AD-1659056.1	AACCGCCCAUCCUGUUUGCU		1409-1429	AGCAAACAGGAUUGGGCGGUUCA		1407-1429
AD-1659057.1	ACCGCCCAUCCUGUUUGCUU		1410-1430	AAGCAACAGGAUUGGGCGGUUC		1408-1430

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1659058.1	CCGCCCAUUCUUGUUUGCUGU		1411-1431	ACAGCAAAACAGGAUUGGGCGGUU		1409-1431
AD-1659059.1	CGCCCAUUCUUGUUUGCUGU		1412-1432	AACAGCAAAACAGGAUUGGGCGGU		1410-1432
AD-1659060.1	GCCCAUUCUUGUUUGCUGU		1413-1433	ACACAGCAAAACAGGAUUGGGCGG		1411-1433
AD-1659061.1	CCCAUUCUUGUUUGCUGU		1414-1434	AACACAGCAAAACAGGAUUGGGCG		1412-1434
AD-1659062.1	CCAUUCUUGUUUGCUGU		1415-1435	ATACACAGCAAAACAGGAUUGGGC		1413-1435
AD-1659063.1	CAUUCUUGUUUGCUGU		1416-1436	AAUACACAGCAAAACAGGAUUGGG		1414-1436
AD-1659064.1	AUUCUUGUUUGCUGU		1417-1437	ACAUACACAGCAAAACAGGAUUGG		1415-1437
AD-1659065.1	UUCUUGUUUGCUGU		1418-1438	ATCATACACAGCAAAACAGGAUUG		1416-1438
AD-1659066.1	UCCUUGUUUGCUGU		1419-1439	AAUCAUACACAGCAAAACAGGAU		1417-1439
AD-1659067.1	CCGUUUGCUGU		1420-1440	AGAUCATACACAGCAAAACAGGAA		1418-1440
AD-1659068.1	CUGUUGCUGU		1421-1441	ATGATCAUACACAGCAAAACAGGA		1419-1441
AD-1659069.1	UGUUUGCUGU		1422-1442	ATUGAUCAUACACAGCAAAACAGG		1420-1442
AD-1659070.1	GUUUGCUGU		1423-1443	ATUUGATCAUACACAGCAAAACAG		1421-1443
AD-1659071.1	UUUGCUGU		1424-1444	ACUUTGAUCAUACACAGCAAAACA		1422-1444
AD-1659162.1	GUCUCCACCUUUUCUUCU		1608-1628	ATAGAAGAAAAGGUGGGAGACUG		1606-1628
AD-1659163.1	CUCCACCUUUUCUUCU		1610-1630	AAUUAGAAGAAAAGGUGGGAGAC		1608-1630
AD-1659164.1	UCCACCUUUUCUUCU		1611-1631	ACAUTAGAAGAAAAGGUGGGAGA		1609-1631
AD-1659165.1	CCCACCUUUUCUUCU		1612-1632	ATCATUAGAAGAAAAGGUGGGAG		1610-1632
AD-1659166.1	CCACCUUUUCUUCU		1613-1633	ACUCAUTAGAAGAAAAGGUGGGGA		1611-1633
AD-1659167.1	CACCUUUUCUUCU		1614-1634	AACUCATUAGAAGAAAAGGUGGG		1612-1634
AD-1659168.1	ACCUUUUCUUCU		1615-1635	AGACTCAUUGAAGAAAAGGUGG		1613-1635
AD-1659208.1	CCGUUUCUCCUUGGUCU		1655-1675	ACUUAAGACCAAGGAGAAAACGGCU		1653-1675
AD-1659209.1	CGUUUCUCCUUGGUCU		1656-1676	AACUTAGACCAAGGAGAAAACGGC		1654-1676
AD-1659210.1	GUUUCUCCUUGGUCU		1657-1677	ACACTUAGACCAAGGAGAAAACGG		1655-1677

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1659282.1	GUUUGCUGGGUUUAUUUAGAU		1729-1749	ACUAAAAUAAACCCAGCAAAACUG		1727-1749
AD-1659283.1	UUUGCUGGGUUUAUUUAGAU		1730-1750	ATCUAAAAUAAACCCAGCAAAACU		1728-1750
AD-1659284.1	UUUGCUGGGUUUAUUUAGAGU		1731-1751	ACUCTAAAAUAAACCCAGCAAAAC		1729-1751
AD-1659285.1	UGCUGGGUUUAUUUAGAGAU		1732-1752	ATCUCUAAAAUAAACCCAGCAAAA		1730-1752
AD-1659286.1	GCUGGGUUUAUUUAGAGAAU		1733-1753	ATUUCTTAAAAATAAACCCAGCAA		1731-1753
AD-1659287.1	CUGGGUUUAUUUAGAGAAUU		1734-1754	AAUUCUCUAAAAUAAACCCAGCA		1732-1754
AD-1659288.1	UGGGUUUAUUUAGAGAAUGU		1735-1755	ACAUTCTCUAAAAUAAACCCAGC		1733-1755
AD-1659289.1	GGGUUUAUUUAGAGAAUGGU		1736-1756	ACCATUCUCUAAAAUAAACCCAG		1734-1756
AD-1659290.1	GAGGCAAGAACCCAGUGUUUAU		1763-1783	ATAAACACUGGTUCUUGCCUCCC		1761-1783
AD-1659291.1	AGGCAAGAACCCAGUGUUUAGU		1764-1784	ACUAAACACUGGUUUCUUGCCUCC		1762-1784
AD-1659292.1	GGCAAGAACCCAGUGUUUAGCU		1765-1785	AGCUAAACACUGGUUUCUUGCCUC		1763-1785
AD-1659293.1	GCAAGAACCCAGUGUUUAGCGU		1766-1786	ACGCTAAACACTGGUUCUUGCCU		1764-1786
AD-1659294.1	CAAGAACCCAGUGUUUAGCGCU		1767-1787	AGCGCUAAACACUGGUUUCUUGCC		1765-1787
AD-1659295.1	AAGAACCCAGUGUUUAGCGCGU		1768-1788	ACGCGCTAAACACACUGGUUCUUGC		1766-1788
AD-1659296.1	AGAACCCAGUGUUUAGCGCGGU		1769-1789	ACCGGCGUAAACACUGGUUUCUUG		1767-1789
AD-1659297.1	GAACCCAGUGUUUAGCGCGGGU		1770-1790	ACCCGCGCUAAACACACUGGUUCUU		1768-1790
AD-1659298.1	AACCCAGUGUUUAGCGCGGGAU		1771-1791	ATCCCCGCGCUAAACACACUGGUUCU		1769-1791
AD-1659321.1	CUGUCCAAAAAGAAUUCCAU		1794-1814	ATGGAATUCUUTUUUGGAACAGUA		1792-1814
AD-1659323.1	GUUCCAAAAAGAAUUCCAAACU		1796-1816	AGUUGGAAUUCUUTUUUGGAACAG		1794-1816
AD-1659325.1	UCCAAAAAGAAUUCCAAACCGU		1798-1818	ACGGTUGGAAUTCUUUUUGGAAC		1796-1818
AD-1659326.1	CCAAAAAGAAUUCCAAACCGAU		1799-1819	ATCGGUTGGAATUCUUUUUGGAA		1797-1819
AD-1659327.1	CAAAAAGAAUUCCAAACCGACU		1800-1820	AGUCGGTUGGAAUUCUUUUUGGA		1798-1820
AD-1659328.1	AAAAAGAAUUCCAAACCGACCU		1801-1821	AGGUCCGUUGGAAUUCUUUUUGG		1799-1821
AD-1659329.1	AAAAAGAAUUCCAAACCGACCAU		1802-1822	ATGGTCGGUUGGAAUUCUUUUUG		1800-1822

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1659330.1	AAAGAAUUCCAACCGACCAGU		1803-1823	ACUGGUCGGUUGGAAUUCUUUUU		1801-1823
AD-1659331.1	AAGAAUUCCAACCGACCAGCU		1804-1824	AGCUGGTGGGUTGGAAUUCUUUU		1802-1824
AD-1659332.1	AGAAUUCCAACCGACCAGCUU		1805-1825	AAGCTGGUCGGTUGGAAUUCUUU		1803-1825
AD-1659333.1	GAAUUCCAACCGACCAGCUUU		1806-1826	AAAGCUGGUCGGUUGGAAUUCUU		1804-1826
AD-1659334.1	AUUUCCAACCGACCAGCUUGU		1807-1827	ACAAGCTGGUCGGUUGGAAUUCU		1805-1827
AD-1659335.1	AUUCCAACCGACCAGCUUGUU		1808-1828	AACAAGCUGGUCGGUUGGAAUUC		1806-1828
AD-1659336.1	UUCCAACCGACCAGCUUGUUU		1809-1829	AAACAAGCUGGTGCGGUUGGAAUU		1807-1829
AD-1659337.1	UCCAACCGACCAGCUUGUUUU		1810-1830	AAACAAGCUGGUCGGUUGGAAU		1808-1830
AD-1659338.1	CCAACCGACCAGCUUGUUUGU		1811-1831	ACAACAAGCUGGUCGGUUGGAA		1809-1831
AD-1659339.1	CAACCGACCAGCUUGUUUGUU		1812-1832	AACAACAAGCTGGUCGGUUGGA		1810-1832
AD-1659340.1	AACCGACCAGCUUGUUUGUGU		1813-1833	ACACAACAAGCUGGUCGGUUGG		1811-1833
AD-1659341.1	ACCGACCAGCUUGUUUGUGAU		1814-1834	ATCACAAACAAGCUGGUCGGUUG		1812-1834
AD-1659342.1	CCGACCAGCUUGUUUGUGAAU		1815-1835	ATUCACAAACAAGCUGGUCGGUU		1813-1835
AD-1659343.1	CGACCAGCUUGUUUGUGAAAU		1816-1836	ATUUCACAAACAAGCUGGUCGGU		1814-1836
AD-1659344.1	GACCAGCUUGUUUGUGAAACU		1817-1837	AGUUTCACAAACAAGCUGGUCGG		1815-1837
AD-1659345.1	ACCAGCUUGUUUGUGAAACAU		1818-1838	ATGUTUCACAAACAAGCUGGUCG		1816-1838
AD-1659346.1	CCAGCUUGUUUGUGAAACAAU		1819-1839	ATUGTUTCACAAACAAGCUGGUC		1817-1839
AD-1659347.1	CAGCUUGUUUGUGAAACAAAU		1820-1840	ATUUGUTUCACAAACAAGCUGGU		1818-1840
AD-1659348.1	AGCUUGUUUGUGAAACAAAUU		1821-1841	ATUUTGTUUCACAAACAAGCUGG		1819-1841
AD-1659349.1	GCUUGUUUGUGAAACAAAUU		1822-1842	ATUUTUGUUUCACAAACAAGCUG		1820-1842
AD-1659350.1	CUUGUUUGUGAAACAAAUUUU		1823-1843	ATUUTUTGUUUCACAAACAAGCU		1821-1843
AD-1659351.1	UUGUUUGUGAAACAAAUUUAGU		1824-1844	ACUUTUTUGUUTCACAAACAAGC		1822-1844
AD-1659371.1	UGUUCCCCUUUUCAGUUGAGU		1844-1864	ACUCAACUUGAAAAGGGAACACU		1842-1864
AD-1659372.1	GUUCCCCUUUUCAGUUGAGAU		1845-1865	ATCUCAACUUGAAAAGGGAACAC		1843-1865

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1659373.1	UCCCCUUUUC AAGUUGAGAAU		1846-1866	ATUCTCAACUUGAAAAGGGAACA		1844-1866
AD-1659382.1	CAAGUUGAGAACAAA AUUGU		1855-1875	ACAATUTUUGUTCUCAACUUGAA		1853-1875
AD-1659383.1	AAGUUGAGAACAAA AUUGGU		1856-1876	ACCAAUTUUUGTUCUCAACUUGA		1854-1876
AD-1659384.1	AGUUGAGAACAAA AUUGGU		1857-1877	ACCCAATUUUGUUCUCAACUUG		1855-1877
AD-1659385.1	GUUGAGAACAAA AUUGGUU		1858-1878	AACCCAAUUUTGUUCUCAACU		1856-1878
AD-1659386.1	UUGAGAACAAA AUUGGUUU		1859-1879	AAACCCAAUUUTGUUCUCAACU		1857-1879
AD-1659387.1	UGAGAACAAA AUUGGUUUU		1860-1880	AAACCCAAUUUTGUUCUCAAC		1858-1880
AD-1659388.1	GAGAACAAA AUUGGUUUUU		1861-1881	AAAAACCCAAUTUUUGUUCUCA		1859-1881
AD-1659389.1	AGAACAAA AUUGGUUUUAU		1862-1882	ATAAAACCCAAUTUUUGUUCUCA		1860-1882
AD-1659390.1	GAACAAA AUUGGUUUUAU		1863-1883	ATUAAAACCCAAUUUUUGUUCUC		1861-1883
AD-1659399.1	AGUAUACAUUUUUGCAUUGCU		1889-1909	AGCAAUGCAAAA AUGUAUACUUU		1887-1909
AD-1659400.1	GUUAUACAUUUUUGCAUUGCCU		1890-1910	AGGCAATGCAAAA AUGUAUACUU		1888-1910
AD-1659401.1	UAUACAUUUUUGCAUUGCCUU		1891-1911	AAGGCAUUGCAAAA AUGUAUACU		1889-1911
AD-1659402.1	AUACAUUUUUGCAUUGCCUUU		1892-1912	AAAGGCAUUGCAAAA AUGUAUAC		1890-1912
AD-1659406.1	AUUUUUGCAUUGCCUUCGGUU		1896-1916	AACCGAAGGCA AUGCAAAA AUGU		1894-1916
AD-1659407.1	UUUUUGCAUUGCCUUCGGUUU		1897-1917	AAACCGAAGGCA AUGCAAAA AUG		1895-1917
AD-1659408.1	UUUUUGCAUUGCCUUCGGUUUU		1898-1918	AAACCGAAGGCA AUGCAAAA AU		1896-1918
AD-1659409.1	UUUGCAUUGCCUUCGGUUUGU		1899-1919	ACAAACCGAAGGCA AUGCAAAA		1897-1919
AD-1659410.1	UUGCAUUGCCUUCGGUUUGUU		1900-1920	AACAAACCGAAGGCA AUGCAAAA		1898-1920
AD-1659411.1	UGCAUUGCCUUCGGUUUGUAU		1901-1921	ATACAAACCGAAGGCA AUGCAAA		1899-1921
AD-1659412.1	GCAUUGCCUUCGGUUUGUAUU		1902-1922	AAUACAAACCGAAGGCA AUGCAA		1900-1922
AD-1659413.1	CAUUGCCUUCGGUUUGUAUUU		1903-1923	AAUACAAACCGAAGGCA AUGCA		1901-1923
AD-1659414.1	AUUGCCUUCGGUUUGUAUUUU		1904-1924	AAATACAAACCGAAGGCA AUGC		1902-1924
AD-1659415.1	UUGCCUUCGGUUUGUAUUUAU		1905-1925	ATAAAUACAAACCGAAGGCA AUG		1903-1925

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1659416.1	UGCCUUCGGUUUUGUAUUUAGU		1906-1926	ACUAAATACAAACCCGAAGCAAU		1904-1926
AD-1659417.1	GCCUUCGGUUUUGUAUUUAGUU		1907-1927	AACUAAAUACAAACCCGAAGCAA		1905-1927
AD-1659418.1	CCUUCGGUUUUGUAUUUAGUGU		1908-1928	ACACTAAAUACAAACCCGAAGGCA		1906-1928
AD-1659419.1	CUUCGGUUUUGUAUUUAGUGUU		1909-1929	AACACUAAAUACAAACCCGAAGGC		1907-1929
AD-1659420.1	UUCGGUUUUGUAUUUAGUGUCU		1910-1930	AGACACTAAAUACAAACCCGAAGG		1908-1930
AD-1659421.1	UCGGUUUUGUAUUUAGUGUCUU		1911-1931	AAGACACUAAATACAAACCCGAAG		1909-1931
AD-1659422.1	CGGUUUGUAUUUAGUGUCUUU		1912-1932	AAAGACACUAAAUACAAACCCGAA		1910-1932
AD-1659423.1	GGUUUGUAUUUAGUGUCUUUGU		1913-1933	ACAAGACACUAAAUACAAACCCGA		1911-1933
AD-1659424.1	GUUUGUAUUUAGUGUCUUUGAU		1914-1934	ATCAAGACACUAAAUACAAACCCG		1912-1934
AD-1659425.1	UUUGUAUUUAGUGUCUUUGAAU		1915-1935	ATUCAAGACACTAAAUACAAACC		1913-1935
AD-1659426.1	UUGUAUUUAGUGUCUUUGAAUU		1916-1936	AAUUCAAAGACACUAAAUACAAAC		1914-1936
AD-1659427.1	UGUAUUUAGUGUCUUUGAAUGU		1917-1937	ACAUTCAAGACACUAAAUACAAA		1915-1937
AD-1659428.1	GUUUUAGUGUCUUUGAAUGUU		1918-1938	AACATUCAAGACACUAAAUACAA		1916-1938
AD-1659429.1	UAUUUAGUGUCUUUGAAUGU		1919-1939	ATACAUTCAAGACACUAAAUACA		1917-1939
AD-1659430.1	AUUUAGUGUCUUUGAAUGUAAU		1920-1940	ATUACATUCAAGACACUAAAUAC		1918-1940
AD-1659431.1	UUUAGUGUCUUUGAAUGUAAAGU		1921-1941	ACUUACAUUCAAGACACUAAAU		1919-1941
AD-1659432.1	UUAGUGUCUUUGAAUGUAAAGAU		1922-1942	ATCUTACAUUCAAGACACUAAAU		1920-1942
AD-1659433.1	UAGUGUCUUUGAAUGUAAAGAAU		1923-1943	ATUCTUACAUUCAAGACACUAAA		1921-1943
AD-1659434.1	AGUGUCUUUGAAUGUAAAGAACU		1924-1944	AGUUCUTACAUUCAAGACACUAA		1922-1944
AD-1659436.1	UGUCUUUGAAUGUAAAGAACAUU		1926-1946	AAUGTUCUUUCAUUAAGACACU		1924-1946
AD-1659437.1	GUCUUUGAAUGUAAAGAACAUUGU		1927-1947	ACAUGUTCUUACAUAAGACACAC		1925-1947
AD-1659440.1	UUGAAUGUAAAGAACAUAGACCU		1930-1950	AGGUCATGUUUCTUACAUAUCAAGA		1928-1950
AD-1659446.1	GUAAGAACAUAGACCUCCGUGU		1936-1956	ACACGGAGGUCUAUUAUUAUACA		1934-1956
AD-1659447.1	UAAGAACAUAGACCUCCGUGUU		1937-1957	AACACGGAGGUCUAUUAUUAACA		1935-1957

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1659448.1	AAGAACAUAGACCUCCGUGUAU		1938-1958	ATACACGGAGGTCAUGUUCUAC		1936-1958
AD-1659449.1	AGAACAUAGACCUCCGUGUAGU		1939-1959	ACUACACGGAGGUCAUGUUCUUA		1937-1959
AD-1659450.1	GAACAUGACCUCCGUGUAGUU		1940-1960	AACUACACGGAGGUCAUGUUCUU		1938-1960
AD-1659451.1	AACAUGACCUCCGUGUAGUGU		1941-1961	ACACTACACGGAGGUCAUGUUCU		1939-1961
AD-1659452.1	ACAUGACCUCCGUGUAGUGUU		1942-1962	AACACUACACGGAGGUCAUGUUC		1940-1962
AD-1659453.1	CAUGACCUCCGUGUAGUGUCU		1943-1963	AGACACTACACGGAGGUCAUGUU		1941-1963
AD-1659454.1	AUGACCUCCGUGUAGUGUCUU		1944-1964	AAGACACUACACGGAGGUCAUGU		1942-1964
AD-1659481.1	CUUAGUUUUUUCACACAGAUGU		1971-1991	ACAUCUGUGGAAAAAACUAAGGU		1969-1991
AD-1659482.1	UUAGUUUUUUCACACAGAUGCU		1972-1992	AGCATCTGUGGAAAAAACUAAGG		1970-1992
AD-1659483.1	UAGUUUUUUCACACAGAUGCUU		1973-1993	AAGCAUCUGUGGAAAAAACUAAG		1971-1993
AD-1659485.1	GUUUUUUUCACACAGAUGCUUGU		1975-1995	ACAAGCAUCUCGTGGAAAAAACUA		1973-1995
AD-1659487.1	UUUUUCCACACAGAUGCUUGUGU		1977-1997	ACACAAGCAUCTGUGGAAAAAAC		1975-1997
AD-1659488.1	UUUUCCACACAGAUGCUUGUGAU		1978-1998	ATCACAAGCAUCUGUGGAAAAAAA		1976-1998
AD-1659489.1	UUUCCACACAGAUGCUUGUGAUU		1979-1999	AAUCACAAGCATCUGUGGAAAAAA		1977-1999
AD-1659490.1	UUCCACAGAUGCUUGUGAUUUU		1980-2000	AAUUCACAAGCAUCUGUGGAAAA		1978-2000
AD-1659491.1	UCCACAGAUGCUUGUGAUUUU		1981-2001	AAAATCACAAGCAUCUGUGGAAA		1979-2001
AD-1659492.1	CCACAGAUGCUUGUGAUUUUU		1982-2002	AAAAAUCACAAGCAUCUGUGGAA		1980-2002
AD-1659493.1	CACAGAUGCUUGUGAUUUUUU		1983-2003	AAAAATCACAAGCAUCUGUGGGA		1981-2003
AD-1659537.1	ACCUGAAUUUCUGUUUGAAUU		2027-2047	AAUUCAAACAGAAAUUCAGGUGC		2025-2047
AD-1659538.1	CCUGAAUUUCUGUUUGAAUGU		2028-2048	ACAUTCAAACAGAAAUUCAGGUG		2026-2048
AD-1659559.1	GGAAACCAUAGCUGGUUAUUUU		2049-2069	AAAATAACCAAGCUAUGGUUCCGC		2047-2069
AD-1659560.1	GAACCAUAGCUGGUUAUUUCU		2050-2070	AGAAAAAACCAAGCUAUGGUUCCG		2048-2070
AD-1659561.1	AACCAUAGCUGGUUAUUUCUU		2051-2071	AAGAAATAACCAAGCUAUGGUUCC		2049-2071
AD-1659562.1	ACCAUAGCUGGUUAUUUCUCU		2052-2072	AGAGAAAUAAACCAAGCUAUGGUUC		2050-2072

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM 000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM 000029.3
AD-1659563.1	CCAUAGCUGGUUAAUUCUCCU		2053-2073	AGGAGAAUAAACCAGCUAUGGUU		2051-2073
AD-1659582.1	CCUUGUGUUAAGUAAUAAACGU		2072-2092	ACGUTUAUUACTAAACACAAGGA		2070-2092
AD-1659583.1	CUUGUGUUAAGUAAUAAACGUU		2073-2093	AACGTUTAUUACUAAACACAAGGG		2071-2093
AD-1659584.1	UUGUGUUAAGUAAUAAACGUCU		2074-2094	AGACGUTUAUUAACUAAACACAAGG		2072-2094
AD-1659585.1	UGUGUUAAGUAAUAAACGUCUU		2075-2095	AAGACGTUUAUTACUAAACACAAG		2073-2095
AD-1659586.1	GUGUUAAGUAAUAAACGUCUUU		2076-2096	AAAGACGUUUATUACUAAACACAA		2074-2096
AD-1659587.1	UGUUAGUAAUAAACGUCUUUGU		2077-2097	ACAAGACGUUUAUUACUAAACACA		2075-2097
AD-1659588.1	GUUAGUAAUAAACGUCUUGCU		2078-2098	AGCAAGACGUUTAUUACUAAACAC		2076-2098
AD-1684490.1	CCGGGUGUACAUACACCCCUU		142-162	AAGGGGUGUAUGUACACCCGGUC		140-162
AD-1684491.1	CCGGGUGUACAUACACCCCUU		142-162	AAGGGGTGU AUGUACACCCGGUC		140-162
AD-1684492.1	CGGGUGUACAUACACCCCUUU		143-163	AAAGGGGUGUAUGUACACCCGGU		141-163
AD-1684493.1	CGGGUGUACAUACACCCCUUU		143-163	AAAGGGGUGUATGUACACCCGGU		141-163
AD-1684494.1	GGGUGUACAUACACCCCUUCU		144-164	AGAAGGGGUGUAUGUACACCCGG		142-164
AD-1684495.1	GGGUGUACAUACACCCCUUCU		144-164	AGAAGGGGUGUAUGUACACCCGG		142-164
AD-1684496.1	GGUGUACAUACACCCCUUCCU		145-165	AGGAAGGGGUGUAUGUACACCCG		143-165
AD-1684497.1	GGUGUACAUACACCCCUUCCU		145-165	AGGAAGGGGUGTAUGUACACCCG		143-165
AD-1684498.1	GUGUACAUACACCCCUUCCAU		146-166	AUGGAAGGGGUGUAUGUACACCC		144-166
AD-1684499.1	GUGUACAUACACCCCUUCCAU		146-166	ATGGAAGGGGUGUAUGUACACCC		144-166
AD-1684500.1	UGUACAUACACCCCUUCCACU		147-167	AGUGGAAGGGGUGUAUGUACACC		145-167
AD-1684501.1	UGUACAUACACCCCUUCCACU		147-167	AGUGGAAGGGGTGU AUGUACACC		145-167
AD-1684502.1	GUACAUACACCCCUUCCACCU		148-168	AGGUGGAAGGGGUGUAUGUACAC		146-168
AD-1684503.1	GUACAUACACCCCUUCCACCU		148-168	AGGUGGAAGGGGUGUAUGUACAC		146-168
AD-1684504.1	UACAUACACCCCUUCCACCUU		149-169	AAGGUGGAAGGGGUGUAUGUACA		147-169
AD-1684505.1	UACAUACACCCCUUCCACCUU		149-169	AAGGTGGAAGGGGUGUAUGUACA		147-169

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1684506.1	ACAUACACCCCUUCCACCUCU		150-170	AGAGGUGGAAGGGGUGUAUGUAC		148-170
AD-1684507.1	ACAUACACCCCUUCCACCUCU		150-170	AGAGGUGGAAGGGGUGUAUGUAC		148-170
AD-1684508.1	CAUACACCCCUUCCACCUCGU		151-171	ACGAGGUGGAAGGGGUGUAUGUA		149-171
AD-1684509.1	CAUACACCCCUUCCACCUCGU		151-171	ACGAGGTGGAAGGGGUGUAUGUA		149-171
AD-1684510.1	AUACACCCCUUCCACCUCGUU		152-172	AACGAGGUGGAAGGGGUGUAUGU		150-172
AD-1684511.1	AUACACCCCUUCCACCUCGUU		152-172	AACGAGGUGGAAGGGGUGUAUGU		150-172
AD-1684512.1	CCUUCACCCUCGUAUCCAU		158-178	AUGGAUGACGAGGUGGAAGGGGU		156-178
AD-1684513.1	CCUUCACCCUCGUAUCCAU		158-178	ATGGAUGACGAGGUGGAAGGGGU		156-178
AD-1684514.1	CCUUCACCCUCGUAUCCACU		159-179	AGUGGAUGACGAGGUGGAAGGGG		157-179
AD-1684515.1	CCUUCACCCUCGUAUCCACU		159-179	AGUGGATGACGAGGUGGAAGGGG		157-179
AD-1684516.1	CAUGCACAGUGAGCUAUGGGU		397-417	ACCCAUAGCUCACUGUGCAUGCC		395-417
AD-1684517.1	CAUGCACAGUGAGCUAUGGGU		397-417	ACCCAUAGCUCACUGUGCAUGCC		395-417
AD-1684518.1	AUGCACAGUGAGCUAUGGGGU		398-418	ACCCCAUAGCUCACUGUGCAUGC		396-418
AD-1684519.1	AUGCACAGUGAGCUAUGGGGU		398-418	ACCCCATAGCUCACUGUGCAUGC		396-418
AD-1684520.1	CCUCUCCCCAACGGCUGUCUU		439-459	AAGACAGCCGUUGGGGAGAGGAC		437-459
AD-1684521.1	CCUCUCCCCAACGGCUGUCUU		439-459	AAGACAGCCGUUGGGGAGAGGAC		437-459
AD-1684522.1	AGGUGCUGAACAGCAUUUUUU		1308-1328	AAAAAAUGCUGUUCAGCACCCUCC		1306-1328
AD-1684523.1	GGUGCUGAACAGCAUUUUUUU		1309-1329	AAAAAAUGCUGUUCAGCACCCUC		1307-1329
AD-1684524.1	GUGCUGAACAGCAUUUUUUUU		1310-1330	AAAAAAUGCUGUUCAGCACCCU		1308-1330
AD-1684525.1	UGCUGAACAGCAUUUUUUUUU		1311-1331	AAAAAAUGCUGUUCAGCACCC		1309-1331
AD-1684526.1	GCUGAACAGCAUUUUUUUUUGU		1312-1332	ACAAAAAAUUGCUGUUCAGCAC		1310-1332
AD-1684527.1	CUGAACAGCAUUUUUUUUUGAU		1313-1333	AUCAAATAAAUUGCUGUUCAGCA		1311-1333
AD-1684528.1	CCCCAGUCUCCCCACCUUUUCU		1603-1623	AGAAAAGGUGGGAGACUGGGGGU		1601-1623
AD-1684529.1	CCCCAGUCUCCCCACCUUUUCU		1603-1623	AGAAAAGGUGGGAGACUGGGGGU		1601-1623

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1684530.1	CCCAGUCUCCACCCUUUUUCUU		1604-1624	AAGAAAAGGUGGGAGACUGGGGG		1602-1624
AD-1684531.1	CCCAGUCUCCACCCUUUUUCUU		1604-1624	AAGAAAAGGUGGGAGACUGGGGG		1602-1624
AD-1684532.1	CCAGUCUCCACCCUUUUUCUUU		1605-1625	AAAGAAAAGGUGGGAGACUGGGGG		1603-1625
AD-1684533.1	CCAGUCUCCACCCUUUUUCUUU		1605-1625	AAAGAAAAGGUGGGAGACUGGGGG		1603-1625
AD-1684534.1	AGUCUCCACCCUUUUUCUUU		1607-1627	AAGAAGAAAAGGUGGGAGACUGGG		1605-1627
AD-1684535.1	AGUCUCCACCCUUUUUCUUU		1607-1627	AAGAAGAAAAGGUGGGAGACUGGG		1605-1627
AD-1684536.1	GGUUUAUUUAGAGAAUGGGU		1737-1757	ACCCAUAUCUUAUAAUAAACCCA		1735-1757
AD-1684537.1	GGUUUAUUUAGAGAAUGGGU		1737-1757	ACCCAUTCUCUAAAAUAAACCCA		1735-1757
AD-1684538.1	GUUUUUUUUAGAGAAUGGGU		1738-1758	ACCCAUAUCUCUAAAAUAAACCC		1736-1758
AD-1684539.1	GUUUUUUUUAGAGAAUGGGU		1738-1758	ACCCCATUCUCTAAAAUAAACCC		1736-1758
AD-1684540.1	UUUUAUUUAGAGAAUGGGGU		1739-1759	ACCCCAUAUCUCUAAAAUAAACC		1737-1759
AD-1684541.1	UUUUAUUUAGAGAAUGGGGU		1739-1759	ACCCCAUAUCUCUAAAAUAAACC		1737-1759
AD-1684542.1	AGAAUGGGGUGGGAGGGCAU		1749-1769	AUGCCUCCCCACCCCCAUUCUCU		1747-1769
AD-1684543.1	AGAAUGGGGUGGGAGGGCAU		1749-1769	ATGCCUCCCCACCCCCAUUCUCU		1747-1769
AD-1684544.1	GAUUGGGGUGGGAGGGCAAU		1750-1770	AUUGCCUCCCCACCCCCAUUCUC		1748-1770
AD-1684545.1	GAAUGGGGUGGGAGGGCAAU		1750-1770	ATUGCCTCCCCACCCCCAUUCUC		1748-1770
AD-1684546.1	AAUGGGGUGGGAGGGCAAGU		1751-1771	ACUUGCCUCCCCACCCCCAUUCU		1749-1771
AD-1684547.1	AAUGGGGUGGGAGGGCAAGU		1751-1771	ACUUGCCUCCCCACCCCCAUUCU		1749-1771
AD-1684548.1	AUGGGGUGGGAGGGCAAGAU		1752-1772	AUCUUGCCUCCCCACCCCCAUUC		1750-1772
AD-1684549.1	AUGGGGUGGGAGGGCAAGAU		1752-1772	ATCUTGCCUCCCCACCCCCAUUC		1750-1772
AD-1684550.1	UGGGGUGGGAGGGCAAGAAU		1753-1773	AUUCUUGCCUCCCCACCCCCAUU		1751-1773
AD-1684551.1	UGGGGUGGGAGGGCAAGAAU		1753-1773	ATUCTUGCCUCCCCACCCCCAUU		1751-1773
AD-1684552.1	GGGGUGGGAGGGCAAGAAU		1754-1774	AGUUCUUGCCUCCCCACCCCCAU		1752-1774
AD-1684553.1	GGGGUGGGAGGGCAAGAAU		1754-1774	AGUUCUTGCCUCCCCACCCCCAU		1752-1774

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-1684554.1	GUGGGAGGCAAGAACACAGUU		1758-1778	AACUGGUUCUUUGCCUCCCCACCC		1756-1778
AD-1684555.1	GUGGGAGGCAAGAACACAGUU		1758-1778	AACUGGTUCUUUGCCUCCCCACCC		1756-1778
AD-1684556.1	UGGGGAGGCAAGAACACAGUGU		1759-1779	ACACUGGUUCUUUGCCUCCCCACCC		1757-1779
AD-1684557.1	UGGGGAGGCAAGAACACAGUGU		1759-1779	ACACTGGUUCUTGCCUCCCCACCC		1757-1779
AD-1684558.1	GGGGAGGCAAGAACACAGUGUU		1760-1780	AACACUGGUUCUUUGCCUCCCCAC		1758-1780
AD-1684559.1	GGGGAGGCAAGAACACAGUGUU		1760-1780	AACACUGGUUCUTGCCUCCCCAC		1758-1780
AD-1684560.1	GGGAGGCAAGAACACAGUGUUU		1761-1781	AAACACTGGUUCUUUGCCUCCCCA		1759-1781
AD-1684561.1	GGAGGCAAGAACACAGUGUUUU		1762-1782	AAACACUGGUTCUUUGCCUCCCC		1760-1782
AD-1684562.1	GCUUGUUUGUGAAACAAAAAU		1822-1842	AUUUUUGUUUCACAAACAAGCUG		1820-1842
AD-1684563.1	CUUGUUUGUGAAACAAAAAU		1823-1843	AUUUUUGUUUCACAAACAAGCU		1821-1843
AD-1684564.1	UUGUUUGUGAAACAAAAAAGU		1824-1844	ACUUUUUUGUUUCACAAACAAGC		1822-1844
AD-1684565.1	CUUAGUUUUUCCACAGAUUGU		1971-1991	ACAUCUGUGGAAAAAACUAAGGU		1969-1991
AD-1684566.1	UUAGUUUUUCCACAGAUUGCU		1972-1992	AGCAUCUGUGGAAAAAACUAAGG		1970-1992
AD-1684567.1	UAGUUUUUCCACAGAUUGCUU		1973-1993	AAGCAUCUGUGGAAAAAACUAAG		1971-1993
AD-1684568.1	GUUUUUUCCACAGAUUGCUUGU		1975-1995	ACAAGCAUCUGUGGAAAAAACUA		1973-1995
AD-1684569.1	UUUUUCCACAGAUUGCUUGUGU		1977-1997	ACACAAGCAUCUGUGGAAAAAAC		1975-1997
AD-1684570.1	UUUUCCACAGAUUGCUUGUGAU		1978-1998	AUCACAAGCAUCUGUGGAAAAAA		1976-1998
AD-67328.2	UCUCCCAACCUUUUCUUCUAAU		1609-1629	AUUAGAAAGAAAAAGGUGGGAGACU		1607-1629
AD-68579.2	UUCCAAACCGACACAGCUUGUUU		1809-1829	AAACAAGCUGGUGCGGUUGGAAUU		1807-1829
AD-68585.2	AGUUGAGAAACAAAAAUUGGGU		1857-1877	ACCCAAUUUUUGUUCUCAACUUG		1855-1877
AD-84700.2	CCACCUUUUCUUCUAAUGAGU		1613-1633	ACUCAUUAGAAAGAAAAAGGUGGA		1611-1633
AD-84707.2	CCUCAACUGGAUGAAGAAACU		1135-1155	AGUUUCUUCAUCCAGUUAGGGA		1133-1155
AD-84712.2	CCAUUCCUGUUUGCUGUGUAU		1415-1435	AUACACAGCAAAACAGGAUUGGGC		1413-1435
AD-84724.2	AGAAUUCCAACCGACCAAGCUU		1805-1825	AAGCUGGUGCGGUUGGAAUUCUUU		1803-1825

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Range in NM_000029.3
AD-84730.2	GCUGGGUUUAUUUAGAGAAU		1733-1753	AUUCUCUAAAAUAAACCCAGCAA		1731-1753
AD-84731.2	AUGGCAUGCACAGUGAGCUAU		393-413	AUAGCUCACUGUGCAUGCCAUU		391-413
AD-84739.5	UGAGAAGAUUGACAGGUUCAU		784-804	AUGAACCUUGUCAUUCUUCAGC		782-804

Table 7. Modified Sense and Antisense Strand Sequences of Angiotensinogen (AGT) dsRNA Agents

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence 5' to 3'	SEQ ID NO:
AD-1321384.2	uscsuacccacCfUfUfuucuuucaaL96		asdTsuadGadAgaadAgGfugggagascsu		AGUCCCCACCUUUUCUUAU	
AD-1321390.2	cscsucaacuGfGfAfugaagaacuuL96		asdGsnudTcdTucadCcAfguugagsgsa		UCCCUCAACUGGAUGAAGAAACU	
AD-1632799.1	asgsecugAfgGfGfCfcaucauL96		asAfsaggAfgGfUfggccCfuCfaggcscsa		UGAGCCUGAGGGCCACCAUCCUC	
AD-1632801.1	cscsuagagGfgCfCfAfcauuccuuL96		asAfsaggGfaUfGfuggCfcCfueaggsu		AGCCUGAGGGCCACCAUCCUCUG	
AD-1632805.1	asgsggccAfcCfAfUfcuucgcuuL96		asAfsaggAfgAfGfauugGfuGfccccscsa		UGAGGGCCACCAUCCUCUGCCUC	
AD-1632836.1	gsuscaucCfaCfAfAfugagaguauL96		asGfsuacUfcUfCfauugUfgGfauagcsasa		UCGUCAUCCACAAUGAGAGUACC	
AD-1632838.1	gsusgaccGfgGfUfGfuacauacuuL96		asGfsuguAfuGfUfacaacCfcGfugacscsu		AGGUGACCGGGUGUACAUAACACC	
AD-1632840.1	csusucaCfcUfCfGfucacuccauL96		asUfsgugGfaUfGfacaGfgUfggaagsgsg		CCCUUCCACCUUGUGUCAUCCACAA	
AD-1632841.1	ususcacCfuCfGfUfcauccacaaL96		asUfsguguGfgAfUfgacgAfgGfuggaasgs		CCUCCACCUUGUGUCAUCCACAAU	
AD-1632842.1	uscsacacUfcGfUfCfauccacaaL96		asAfsuugUfgGfAfugacGfaGfugggasasg		CUUCCACCUUGUGUCAUCCACAAUG	
AD-1632843.1	cscsacuuCfGfUfCfAfuccacaaL96		asCfsauuGfuGfGfauaCfGfagguggsasa		UUCCACCUUGUGUCAUCCACAAUGA	
AD-1632844.1	csasccucGfuCfAfUfcaacaaL96		asUfscuuUfgUfGfauagAfcGfagguggsa		UCCACCUUGUGUCAUCCACAAUGAG	
AD-1632846.1	cscsugcuCfaUfCfCfacaauagauL96		asUfscucAfuUfGfuggaUfgAfcgaggusug		CACCUUGUCAUCCACAAUGAGAG	
AD-1632847.1	csuscgucAfuCfCfAfcauagagauL96		asCfsuucCfaUfUfuggAfuGfagagsgsu		ACCUUGUCAUCCACAAUGAGAGU	
AD-1632848.1	uscsuicaUfcCfAfCfaugagaguuL96		asAfsuicUfcAfuUfuggGfaUfgagagsgsg		CCUUGUCAUCCACAAUGAGAGUA	

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AD-1633991.1	cscsguuuCfuCfCfUfugucuaaguiL96			asCfsuuuGfaCfCfaaggAfgAfaacggscsu	AGCCGUUUUCCUUGGUCUAAAGU
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AD-1634077.1	gscaagaAfcCfAfGfuuuagL96		asCfsguuAfaAfCfagguUfuUfuuuagcsc		AGGCAAGAACCCAGUGUUUAAGCGC
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DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 253

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 253

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of angiotensinogen (AGT) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of
5 complementarity to an mRNA encoding AGT, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-7.

2. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising
10 at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

3. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising
15 at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

4. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising
20 at least 15 contiguous nucleotides differing by no more than one nucleotide from any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising at least 15 contiguous nucleotides differing by no more than one nucleotide from any one
25 of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

5. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising a nucleotide sequence selected from the group consisting of any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising a nucleotide sequence
30 selected from the group consisting of any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

6. The dsRNA agent of claim 1, wherein the dsRNA agent comprises at least one modified nucleotide.

7. The dsRNA agent of claim 1 or 6, wherein substantially all of the nucleotides of the sense strand are modified nucleotides; substantially all of the nucleotides of the antisense strand are modified nucleotides; or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides.

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8. The dsRNA agent of any one of claims 1, 6 or 7, wherein all of the nucleotides of the sense strand are modified nucleotides; all of the nucleotides of the antisense strand are modified nucleotides; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

10

9. The dsRNA agent of any one of claims 6-8, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythymidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, a 2'-5'-linked ribonucleotide (3'-RNA), an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a vinyl-phosphonate nucleotide, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), a nucleotide comprising a 2' phosphate, and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

25

10. The dsRNA agent of any one of claims 6-8, wherein at least one of the modified nucleotides is selected from the group consisting of LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C-allyl, 2'-fluoro, 2'-deoxy, 2'-hydroxyl, and glycol; and combinations thereof.

30

11. The dsRNA agent of any one of claims 6-8, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), a nucleotide comprising a 2' phosphate, and a nucleotide comprising a phosphorothioate group; and combinations thereof.

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12. The dsRNA agent of any one of claims 6-8, wherein at least one of the modified nucleotides is a nucleotide modified with a thermally destabilizing nucleotide modification.

13. The dsRNA agent of claim 12, wherein the thermally destabilizing nucleotide modification is selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; a destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an unlocked nucleic acid (UNA), and a glycerol nucleic acid (GNA).

14. The dsRNA agent of any one of claims 1-13, wherein the double stranded region is 19-30 nucleotide pairs in length.

15. The dsRNA agent of claim 14, wherein the double stranded region is 19-25 nucleotide pairs in length.

16. The dsRNA agent of claim 14, wherein the double stranded region is 19-23 nucleotide pairs in length.

17. The dsRNA agent of claim 14, wherein the double stranded region is 23-27 nucleotide pairs in length.

18. The dsRNA agent of claim 14, wherein the double stranded region is 21-23 nucleotide pairs in length.

19. The dsRNA agent of any one of claims 1-18, wherein each strand is independently no more than 30 nucleotides in length.

20. The dsRNA agent of any one of claims 1-19, wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.

21. The dsRNA agent of any one of claims 1-20, wherein the region of complementarity is at least 17 nucleotides in length.

22. The dsRNA agent of any one of claims 1-21, wherein the region of complementarity is between 19 and 23 nucleotides in length.

23. The dsRNA agent of any one of claims 1-22, wherein the region of complementarity is 19 nucleotides in length.

24. The dsRNA agent of any one of claims 1-23, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

25. The dsRNA agent of any one of claims 1-23, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

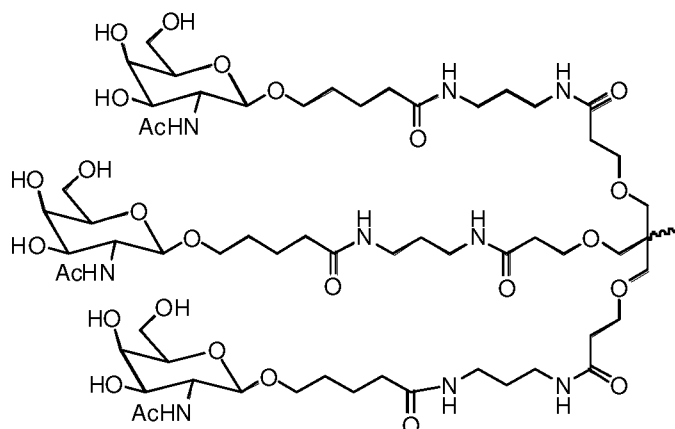
26. The dsRNA agent of any one of claims 1-25, further comprising a ligand.

27. The dsRNA agent of claim 26, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

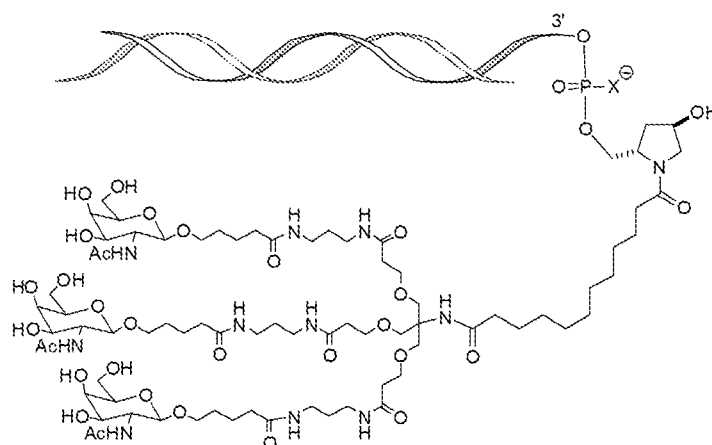
28. The dsRNA agent of claim 26 or 27, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

29. The dsRNA agent of any one of claims 26-28, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

30. The dsRNA agent of claim 28 or 29, wherein the ligand is



31. The dsRNA agent of claim 30, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

32. The dsRNA agent of claim 31, wherein the X is O.

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33. The dsRNA agent of any one of claims 1-32, wherein the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

34. The dsRNA agent of claim 33, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

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35. The dsRNA agent of claim 34, wherein the strand is the antisense strand.

36. The dsRNA agent of claim 34, wherein the strand is the sense strand.

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37. The dsRNA agent of claim 33, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand.

38. The dsRNA agent of claim 37, wherein the strand is the antisense strand.

20

39. The dsRNA agent of claim 37, wherein the strand is the sense strand.

40. The dsRNA agent of claim 33, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at both the 5'- and 3'-terminus of one strand.

25

41. The dsRNA agent of claim 40, wherein the strand is the antisense strand.

42. The dsRNA agent of any one of claims 1-41, wherein the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair.

43. A cell containing the dsRNA agent of any one of claims 1-42.

5

44. A pharmaceutical composition for inhibiting expression of a gene encoding angiotensinogen (AGT) comprising the dsRNA agent of any one of claims 1-42 and a pharmaceutically acceptable carrier.

10 45. The pharmaceutical composition of claim 44, wherein dsRNA agent is in an unbuffered solution.

46. The pharmaceutical composition of claim 45, wherein the unbuffered solution is saline or water.

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47. The pharmaceutical composition of claim 44, wherein said dsRNA agent is in a buffer solution.

20 48. The pharmaceutical composition of claim 47, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

49. The pharmaceutical composition of claim 48, wherein the buffer solution is phosphate buffered saline (PBS).

25 50. A method of inhibiting expression of an angiotensinogen (AGT) gene in a cell, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-42, or the pharmaceutical composition of any one of claims 44-49, thereby inhibiting expression of the AGT gene in the cell.

30 51. The method of claim 50, wherein the cell is within a subject.

52. The method of claim 51, wherein the subject is a human.

53. The method of claim 51, wherein the subject has an AGT-associated disorder.

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54. The method of claim 53, wherein the AGT-associated disorder is selected from the group consisting of high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, hypertension associated with low plasma renin activity or plasma renin concentration, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR), fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome.

55. The method of claim 54, wherein the subject has a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 80 mm Hg.

56. The method of claim 54, wherein the subject has a systolic blood pressure of at least 140 mm Hg and a diastolic blood pressure of at least 80 mm Hg.

57. The method of claim 54, the subject is part of a group susceptible to salt sensitivity, is overweight, is obese, or is pregnant.

58. The method of any one of claims 50-57, wherein contacting the cell with the dsRNA agent inhibits the expression of AGT by at least 50%, 60%, 70%, 80%, 90%, or 95%.

59. The method of any one of claims 50-58, wherein inhibiting expression of AGT decreases AGT protein level in serum of the subject by at least 50%, 60%, 70%, 80%, 90%, or 95%.

60. A method of treating a subject having a disorder that would benefit from reduction in angiotensinogen (AGT) expression, comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-42, or the pharmaceutical composition of any one of claims 44-49, thereby treating the subject having the disorder that would benefit from reduction in AGT expression.

61. A method of preventing at least one symptom in a subject having a disorder that would benefit from reduction in angiotensinogen (AGT) expression, comprising administering to the subject a prophylactically effective amount of the dsRNA agent of any one of claims 1-42, or the pharmaceutical composition of any one of claims 44-49, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in AGT expression.

62. The method of claim 60 or 61, wherein the disorder is an AGT-associated disorder.

63. The method of claim 62, wherein the AGT-associated disorder is selected from the group consisting of high blood pressure, hypertension, borderline hypertension, primary hypertension, secondary hypertension isolated systolic or diastolic hypertension, pregnancy-associated hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, hypertension associated with low plasma renin activity or plasma renin concentration, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, systolic hypertension, labile hypertension; hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiac myopathy, glomerulosclerosis, coarctation of the aorta, aortic aneurism, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth restriction (IUGR), fetal growth restriction, obesity, liver steatosis/ fatty liver, non-alcoholic Steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD); glucose intolerance, type 2 diabetes (non-insulin dependent diabetes), and metabolic syndrome.

64. The method of claim 63, wherein the subject has a systolic blood pressure of at least 130 mm Hg or a diastolic blood pressure of at least 80 mm Hg.

65. The method of claim 63, wherein the subject has a systolic blood pressure of at least 140 mm Hg and a diastolic blood pressure of at least 80 mm Hg.

66. The method of claim 63, the subject is part of a group susceptible to salt sensitivity, is overweight, is obese, or is pregnant.

67. The method of any one of claims 60-66, wherein the subject is a human.

68. The method of any one of claims 60-67, wherein administration of the dsRNA agent to the subject causes a decrease in AGT protein accumulation in the subject.

69. The method of any one of claims 60-68, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

5 70. The method of any one of claims 60-69, wherein the dsRNA agent is administered to the subject subcutaneously.

71. The method of any one of claims 60-70, further comprising determining the level of AGT in a sample(s) from the subject.

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72. The method of claim 71, wherein the level of AGT in the subject sample(s) is an AGT protein level in a blood or serum or urine or liver tissue sample(s).

15 73. The method of any one of claims 60-72, further comprising determining the level of bradykinin, prekallikrein, or blood pressure in the subject.

74. The method of any one of claims 60-73, further comprising administering to the subject an additional therapeutic agent for treatment of an AGT-associated disorder.

20 75. The method of claim 74, wherein the additional therapeutic agent is selected from the group consisting of a diuretic, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a beta-blocker, a vasodilator, a calcium channel blocker, an aldosterone antagonist, an alpha2-agonist, a renin inhibitor, an alpha-blocker, a peripheral acting adrenergic agent, a selective D1 receptor partial agonist, a nonselective alpha-adrenergic antagonist, a synthetic,
25 a steroidal antimineralocorticoid agent, an angiotensin receptor-neprilysin inhibitors (ARNi), Entresto®, sacubitril/valsartan; or an endothelin receptor antagonist (ERA), sitaxentan, ambrisentan, atrasentan, BQ-123, zibotentan, bosentan, macitentan, and tezosentan; a combination of any of the foregoing; and a hypertension therapeutic agent formulated as a combination of agents.

30 76. The method of claim 74, wherein the additional therapeutic agent comprises an angiotensin II receptor antagonist.

77. The method of claim 76, wherein the angiotensin II receptor antagonist is selected from the group consisting of losartan, valsartan, olmesartan, eprosartan, and azilsartan.

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78. A kit comprising the dsRNA agent of any one of claims 1-42 or the pharmaceutical composition of any one of claims 44-49.

5 79. A vial comprising the dsRNA agent of any one of claims 1-42 or the pharmaceutical composition of any one of claims 44-49.

80. A syringe comprising the dsRNA agent of any one of claims 1-42 or the pharmaceutical composition of any one of claims 44-49.

10 81. An RNA-induced silencing complex (RISC) comprising an antisense strand of any of the dsRNA agents of claims 1-42.

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