

IRNA COMPOSITIONS AND METHODS FOR SILENCING ANGIOTENSINOGEN (AGT)**RELATED APPLICATIONS**

This application claims the benefit of priority to U.S. Provisional Application No. 63/229085,
5 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
10 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
15 (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
20 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
25 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
30 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
35 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
- 5 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

10 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

- 15 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
- 20 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

25 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.

- 30 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
- 35 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'-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 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.

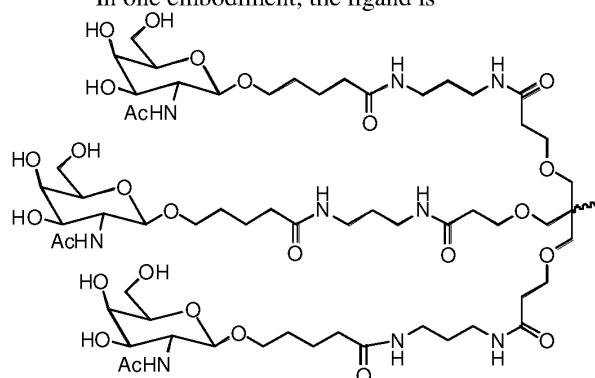
5 In one embodiment, the dsRNA agent further comprises a ligand.

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

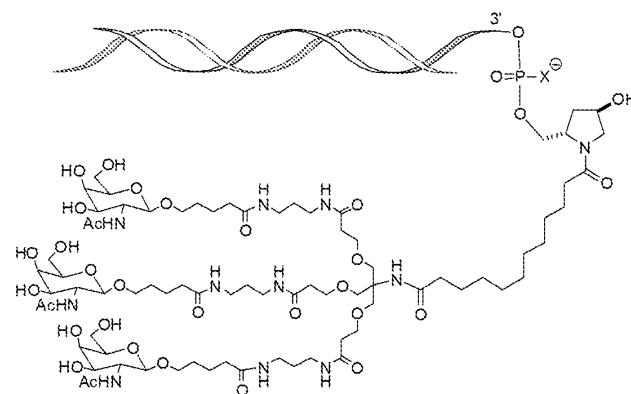
In one embodiment, the ligand is an N-acetylgalactosamine (GalNAc) derivative.

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 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).

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
15 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 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
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

5 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

10 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

15 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

20 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

25 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

30 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,

35 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

5 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".

15 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.

20 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.

25 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.

30 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 (unttranslated); 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
5 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-
10 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
15 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
20 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,
25 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
30 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
35 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,

5 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
10 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
15 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
20 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
25 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.*,
30 "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.

35 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%, 35%, 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
 5 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
 10 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
 15 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
 20 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
 25 (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
 30 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,”
 35 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

5 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

10 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

15 *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

20 (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

25 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

30 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

35 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.

15 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
5 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
10 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,
15 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
20 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
25 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.

30 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;
35 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
- 5 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
- 10 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
- 15 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).
- 20 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
- 25 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.
- 30 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,
- 35 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

5 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, these disclosed by Englisch *et al.*, *Angewandte Chemie*, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y S., Chapter 15, *dsRNA Research and*

10 *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

15 (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

20 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.

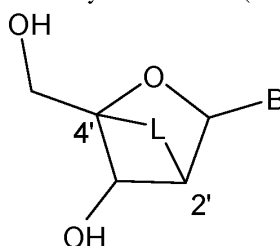
25 In some embodiments, an RNAi agent of the disclosure can also be modified to include one or more bicyclic sugar moieties. A "bicyclic sugar" is a furanosyl ring modified by a ring formed by the bridging of two carbons, whether adjacent or non-adjacent. A "bicyclic nucleoside" ("BNA") is a nucleoside 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

30 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'

35 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
 5 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).
 15 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
 20 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).
 25

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
 30

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 Fluiters *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” from 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” from 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.

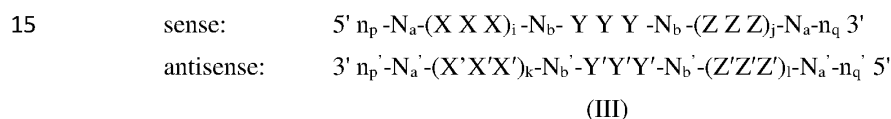
35 In some embodiments, the sense strand of the dsRNAi agent may contain YYY motif occurring at 9, 10, and 11 positions of the strand when the duplex region is 21 nt, the count starting from the first nucleotide from the 5'-end, or optionally, the count starting at the first paired nucleotide within 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):



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;

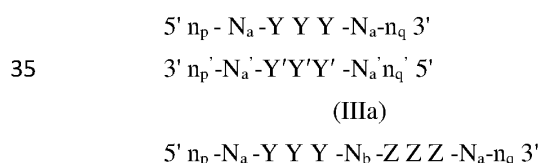
each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

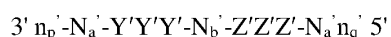
wherein each n_p , n_p , n_q , and n_q , each of which may or may not be present, independently represents an overhang nucleotide; and

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.

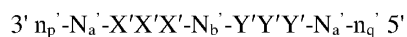
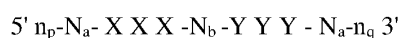
In one embodiment, i is 0 and j is 0; or i is 1 and j is 0; or i is 0 and j is 1; or both i and j are 0; or both i and j are 1. In another embodiment, k is 0 and l is 0; or k is 1 and l is 0; or k is 0 and l is 1; or both k and l are 0; or both k and l are 1.

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





(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 (III_d), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications. In other embodiments, when the RNAi agent is represented by formula (III_d), 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 (III_d), 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* 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
10 embodiments, when the RNAi agent is represented by formula (III_d), 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* 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.
15

In some embodiments, when the dsRNAi agent is represented by formula (III_a), 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* 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.
20

In some embodiments, the dsRNAi agent is a multimer containing at least two duplexes represented by formula (III), (III_a), (III_b), (III_c), and (III_d), wherein the duplexes are 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.
25

In some embodiments, the dsRNAi agent is a multimer containing three, four, five, six, or more duplexes represented by formula (III), (III_a), (III_b), (III_c), and (III_d), wherein the duplexes are 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.
30

In one embodiment, two dsRNAi agents represented by at least one of formulas (III), (III_a), (III_b), (III_c), and (III_d) are linked to each other at the 5' end, and one or both of the 3' ends, and are 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.
35

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

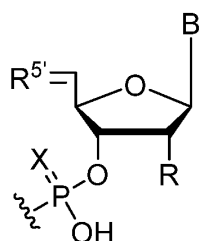
5 nucleotides with a 2'-fluoro modification, *e.g.*, 4 nucleotides with a 2'-fluoro modification in the sense strand and 6 nucleotides with a 2'-fluoro modification in the antisense strand. In another specific embodiment, the RNAi agent of the invention contains 6 nucleotides with a 2'-fluoro modification, *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.

10 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

15 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.

20 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;

25 R is hydrogen, hydroxy, fluoro, or C₁₋₂₀alkoxy (*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.

30 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.

5 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,
10 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
15 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
20 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
25 "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
30 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
35 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, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxaliny, pyridazinonyl, tetrahydrofuryl, and decalin. In one embodiment, the acyclic group is a serinol backbone or diethanolamine backbone.

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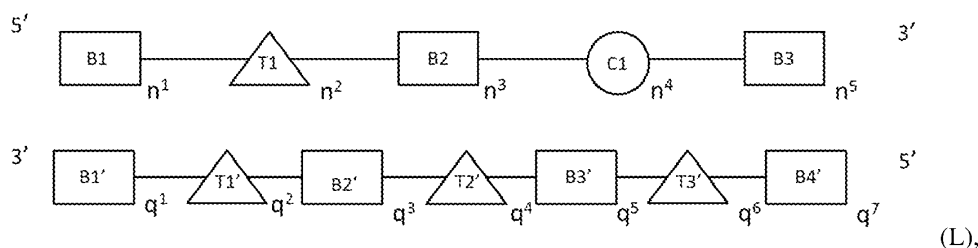
i. Thermally Destabilizing Modifications

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 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 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.

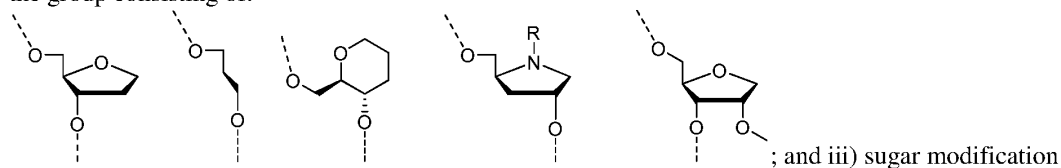
It has been discovered that dsRNAs with an antisense strand comprising at least one thermally destabilizing modification of the duplex within the first 9 nucleotide positions, counting from the 5' end, of the antisense strand have reduced off-target gene silencing activity. Accordingly, in some embodiments, 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 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.

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):

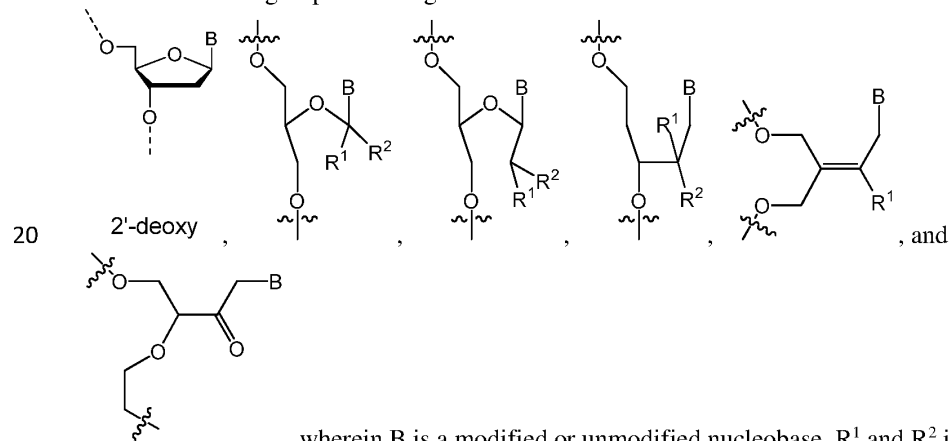


In formula (L), B1, B2, B3, B1', B2', B3', and B4' each are independently a nucleotide containing a modification selected from the group consisting of 2'-O-alkyl, 2'-substituted alkoxy, 2'-substituted alkyl, 2'-halo, ENA, and BNA/LNA. In one embodiment, B1, B2, B3, B1', B2', B3', and B4' each contain 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:

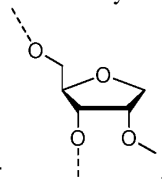


selected from the group consisting of:



, wherein B is a modified or unmodified nucleobase, R¹ and R² independently are 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).

5 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).

10 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.

15 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).

20 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.

25 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).

30 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 1, B3' is 2'-OMe or 2'-F, q⁵ is 6, T3' is 2'-F, q⁶ is 1, B4' is 2'-OMe, 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, T2' is 2'-F, q⁴ is 1, B3' is 2'-OMe or 2'-F, q⁵ is 6, T3' is 2'-F, q⁶ is 1, B4' is 2'-OMe, 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 5, T2' is 2'-F, q⁴ is 1, 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; 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, 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 5, T2' is 2'-F, q⁴ is 1, 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; 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, 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.

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 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).

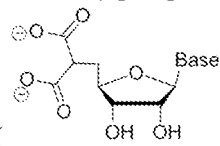
In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-F,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

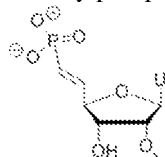
In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, q⁴ is 0, B3' is 2'-OMe or 2'-F, q⁵ is 7, T3' is 2'-F, q⁶ is 1, B4' is 2'-F, and q⁷ is 1.

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).

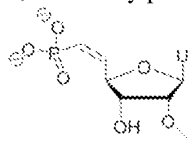
The RNAi agent can comprise a phosphorus-containing group at the 5'-end of the sense strand or antisense strand. The 5'-end phosphorus-containing group can be 5'-end phosphate (5'-P), 5'-end phosphorothioate (5'-PS), 5'-end phosphorodithioate (5'-PS₂), 5'-end vinylphosphonate (5'-

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 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, 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 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, 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 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, 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 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, 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 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'-OMe, 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'-OMe, and q⁷ is 1. The dsRNA agent also comprises a 5'-PS.

- 5 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. The RNAi agent also comprises a 5'-VP. The 5'-VP may be 5'-E-VP, 5'-Z-VP, or combination thereof.
- 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, 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. The RNAi agent also comprises a 5'-PS₂.

- 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, 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. The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl.

- 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, 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'-P.

- 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, 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'-PS.
- 30

- 35 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'-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,

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. 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, 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.

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.

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'-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, 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'-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,

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

5 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'-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, 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. The RNAi agent also comprises a 5'-PS.

15 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. 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. 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, 25 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. 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'-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.

35 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

5 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

10 (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.

30 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.

5 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
10 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
15 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
20 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
30 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
35 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:

- 5 (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,
10 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:

- 15 (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);
20 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:

- 25 (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
30 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:

35 (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
5 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
10 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
15 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
20 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
25 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
30 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
35 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;
- (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
5 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
10 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,
15 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
20 (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,
25 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-carbonyloxycholesterol moiety (Crooke *et al.*, *J. Pharmacol.
Exp. Ther.*, 1996, 277:923-937).

30 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.

35 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 polyphosphazene. 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-κB.

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
5 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,
10 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
15 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
20 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,
25 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
30 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
35 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

5 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
10 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
15 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.

20 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
25 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).

30 *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
35 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 Tat protein (GRKKRRQRRRPPQ (SEQ ID NO:16) and the Drosophila Antennapedia protein
- 15 (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.

- 25 An RGD peptide for use in the compositions and methods of the invention may be linear or cyclic, and may be modified, *e.g.*, glycosylated or methylated, to facilitate targeting to a specific tissue(s). RGD-containing peptides and peptidomimetics 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.

- 30 A “cell permeation peptide” is capable of permeating a cell, *e.g.*, a microbial cell, such as a 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.

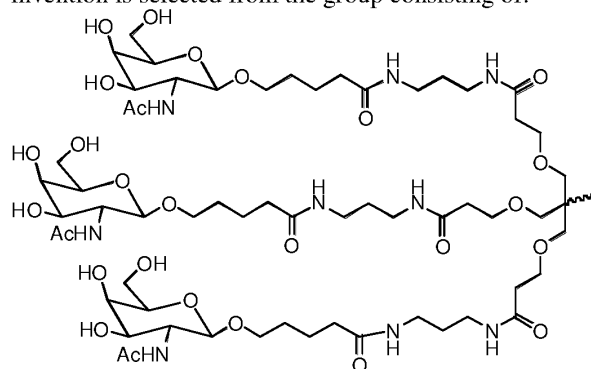
In certain embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a bivalent linker. In yet other embodiments of the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

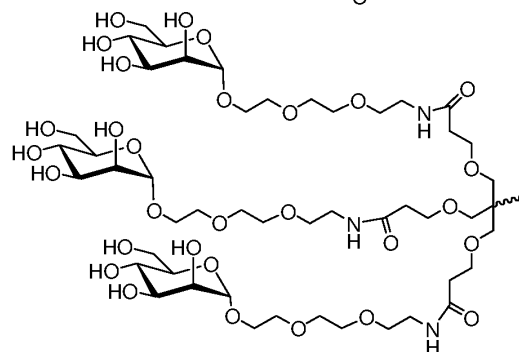
In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of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

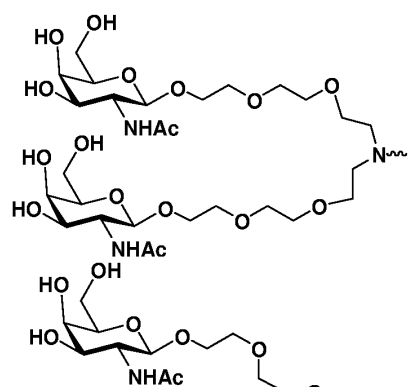
In one embodiment, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



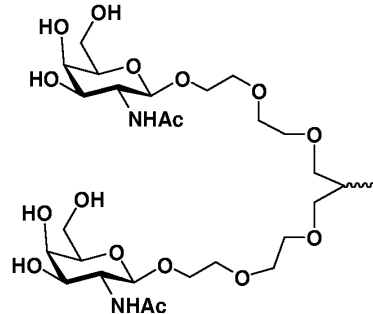
Formula II,



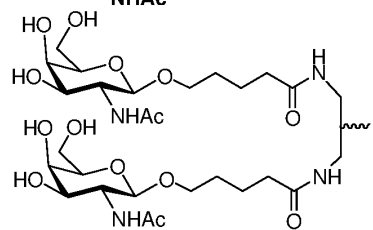
Formula III,



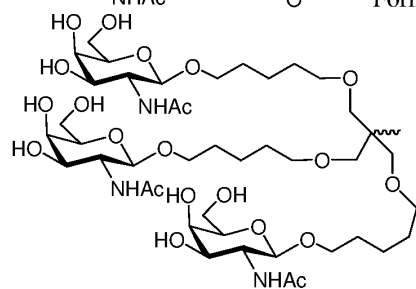
Formula IV,



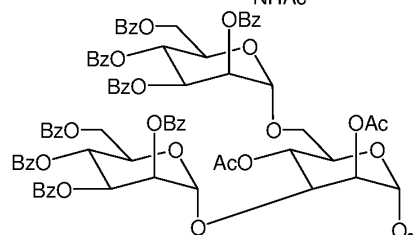
Formula V,



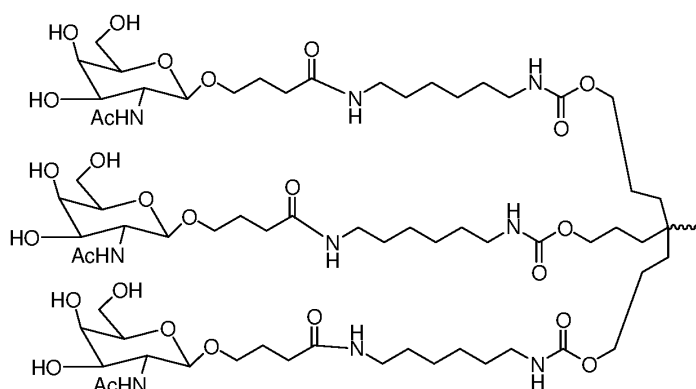
Formula VI,



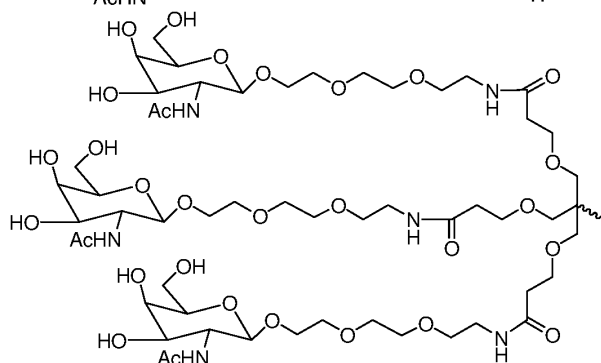
Formula VII,



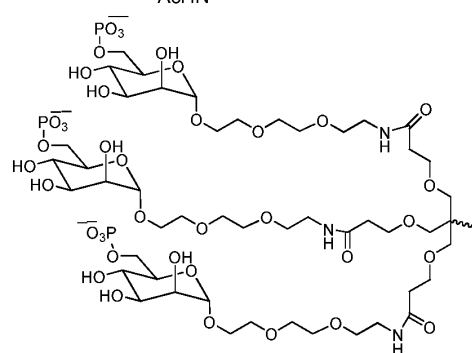
Formula VIII,



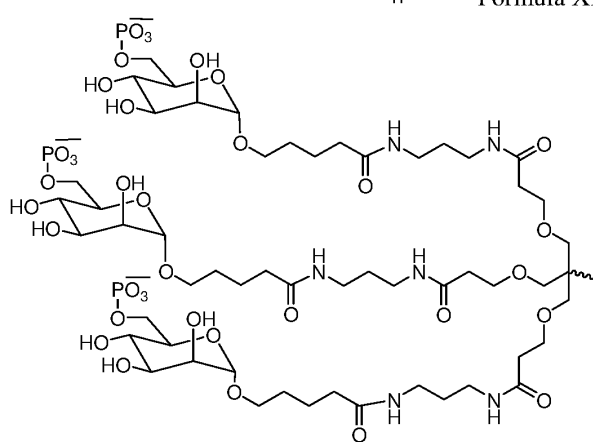
Formula IX,



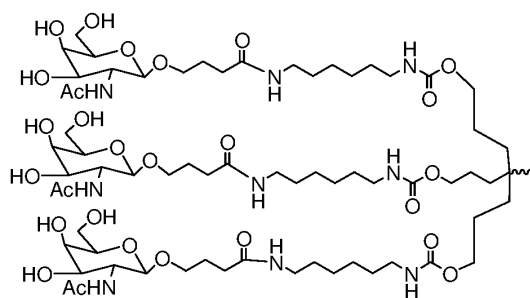
Formula X,



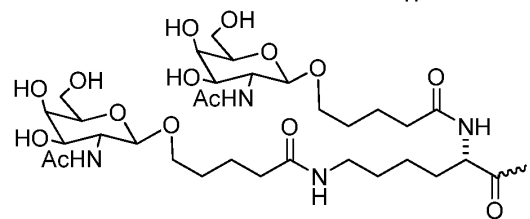
Formula XI,



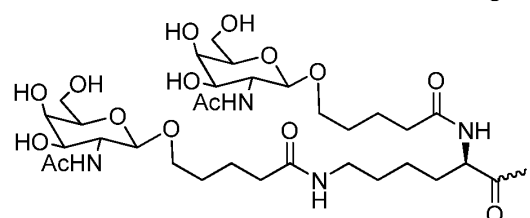
Formula XII,



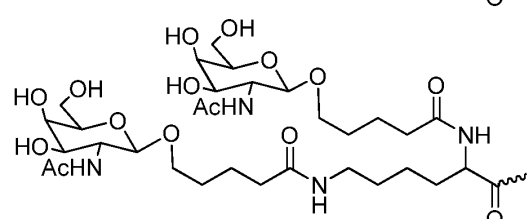
Formula XIII,



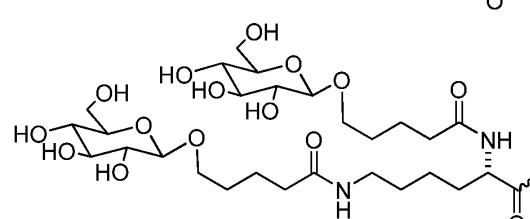
Formula XIV,



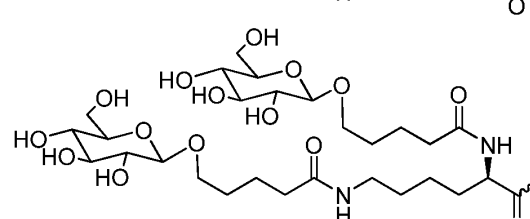
Formula XV,



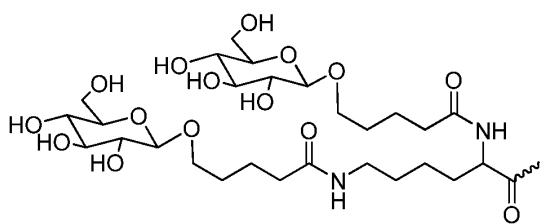
Formula XVI,



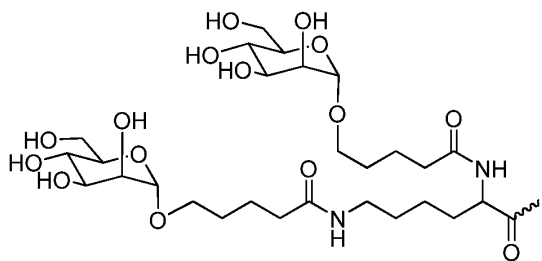
Formula XVII,



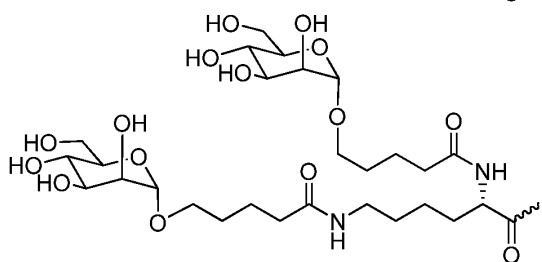
Formula XVIII,



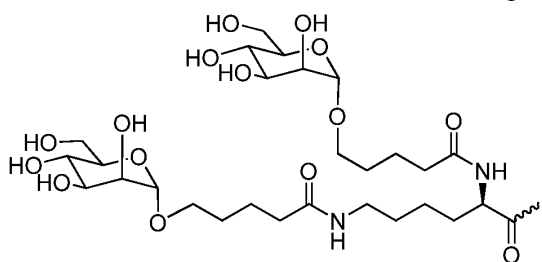
Formula XIX,



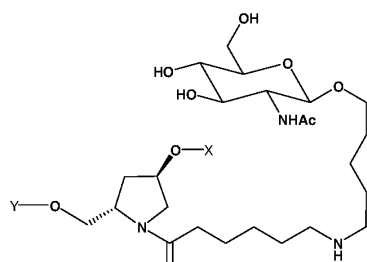
Formula XX,



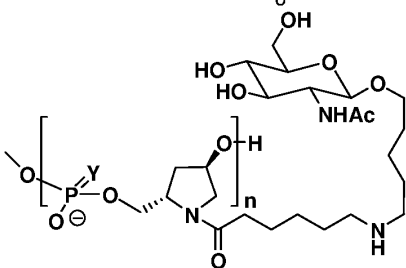
Formula XXI,



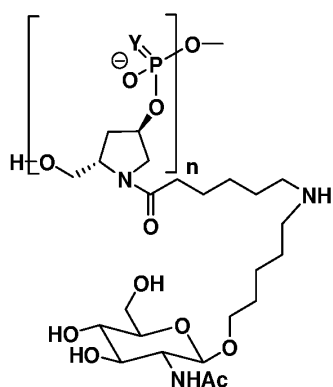
Formula XXII,



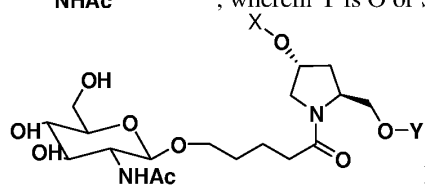
Formula XXIII;



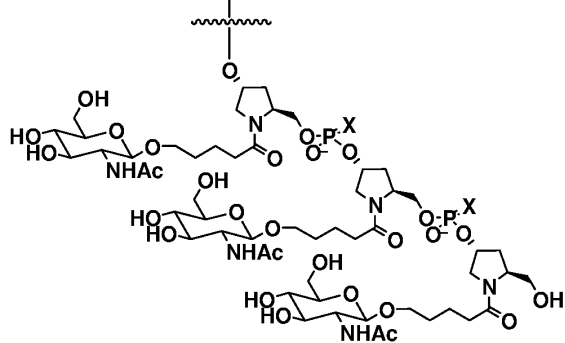
, wherein Y is O or S and n is 3 -6 (Formula XXIV);



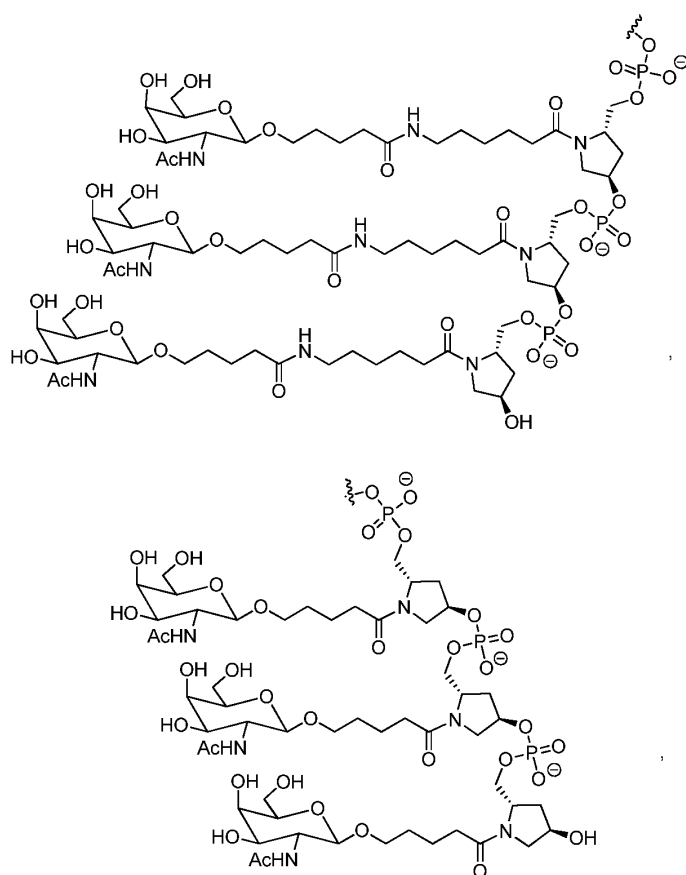
, wherein Y is O or S and n is 3-6 (Formula XXV);



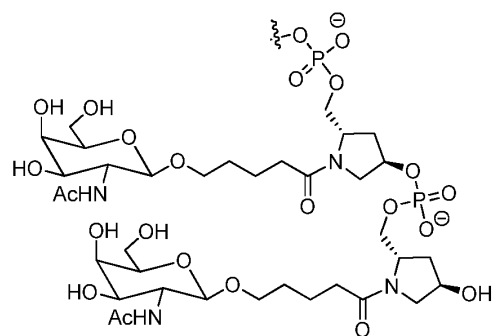
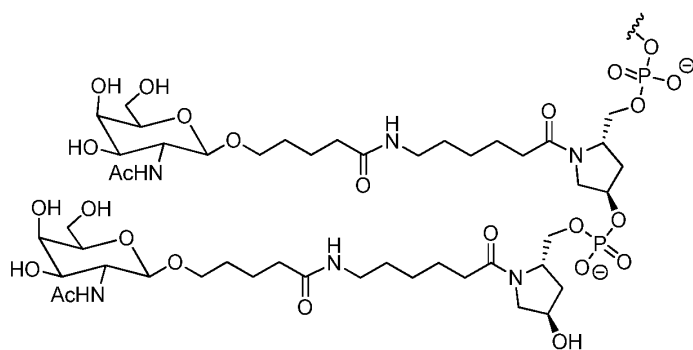
Formula XXVI;



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

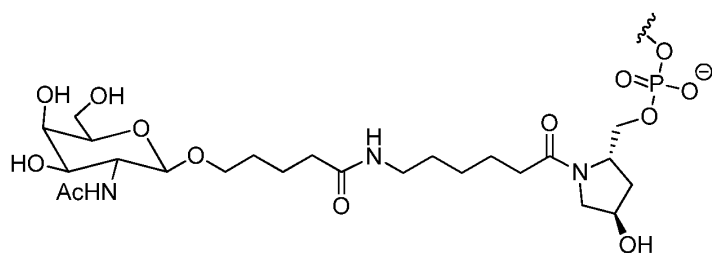


Formula XXVII; Formula XXIX;

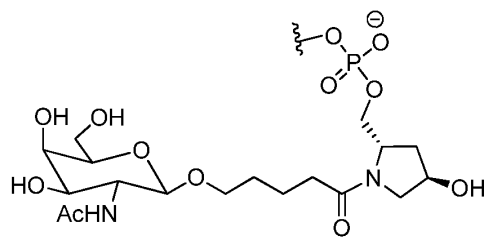


Formula XXX;

Formula XXXI;

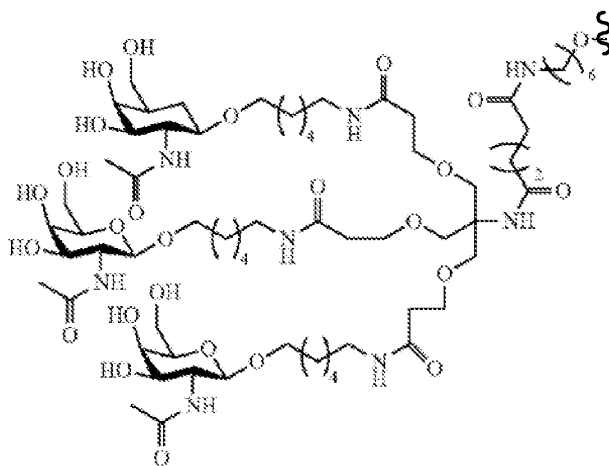


, and



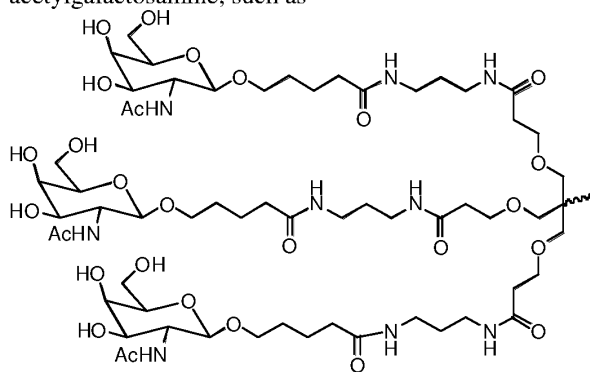
Formula XXXII;

5 Formula XXXIII.



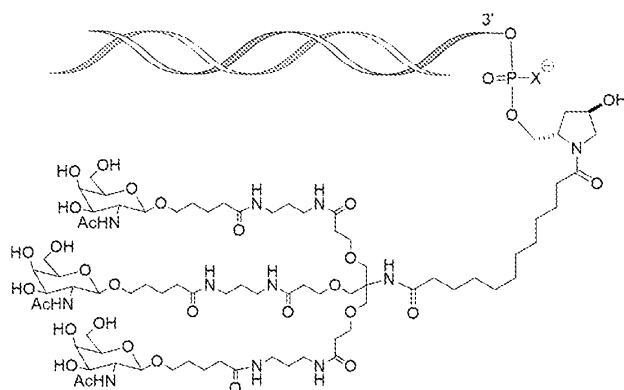
Formula XXXIV.

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

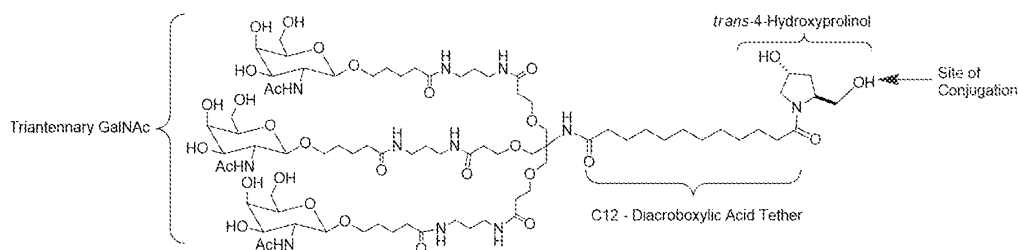


Formula II.

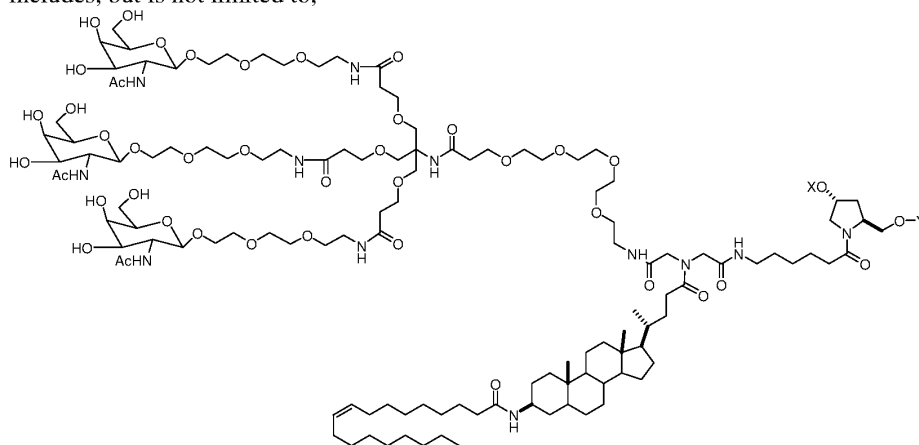
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate *via* a linker as shown in the following schematic, wherein X is O or S.



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,

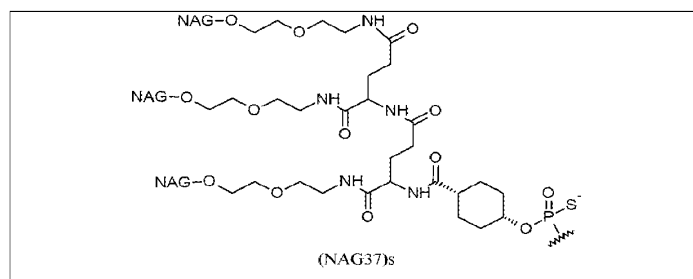


(Formula XXXVI), when one of X or Y is an oligonucleotide, the other is a hydrogen.

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:

5

10



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

15 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

20 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

25 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

30 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

35 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
 5 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,
 10 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
 20 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
 25 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
 30 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
 35 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.

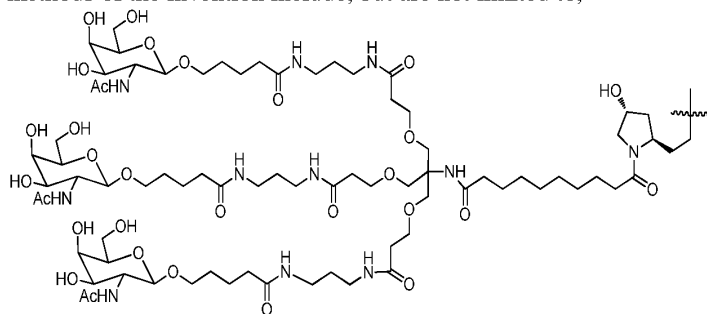
iv. *Ester-based linking groups*

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.

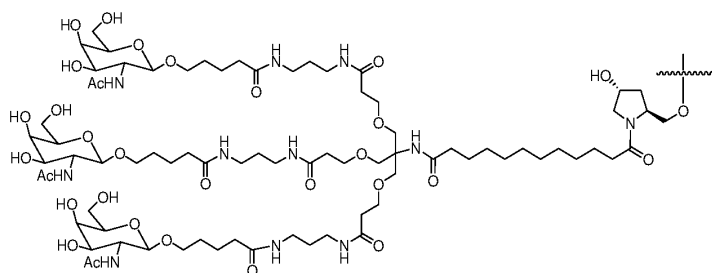
v. *Peptide-based cleaving groups*

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.

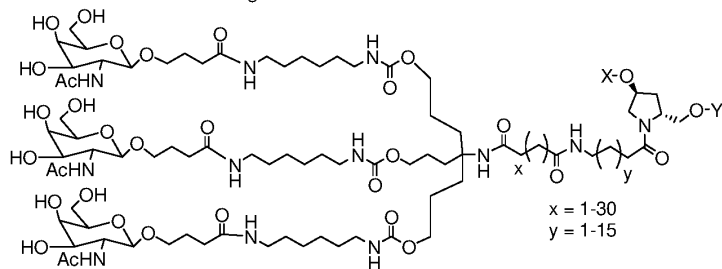
In some embodiments, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



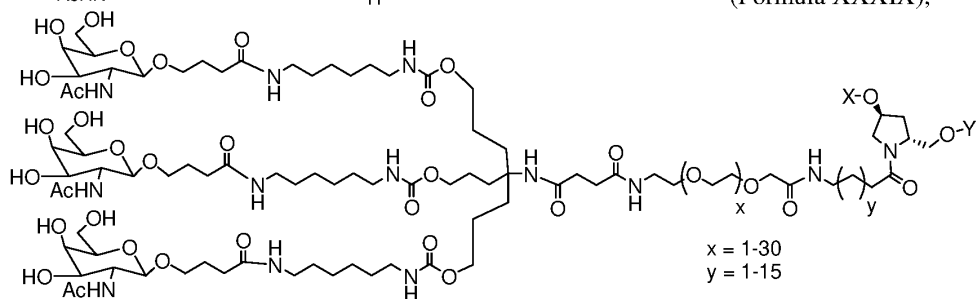
(Formula XXXVII),



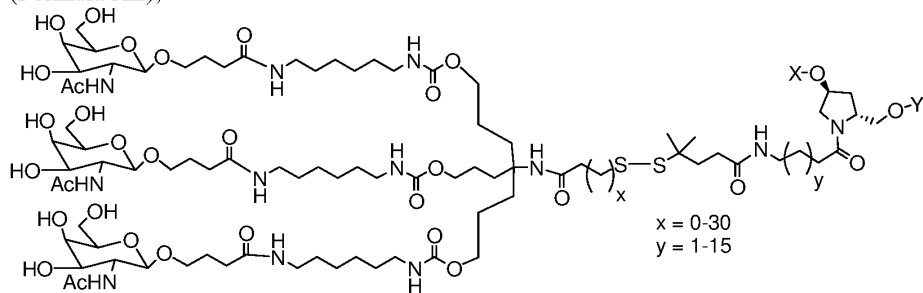
(Formula XXXVIII),



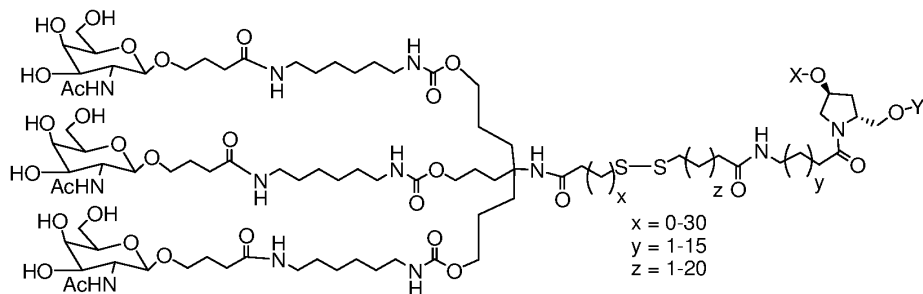
(Formula XXXIX),



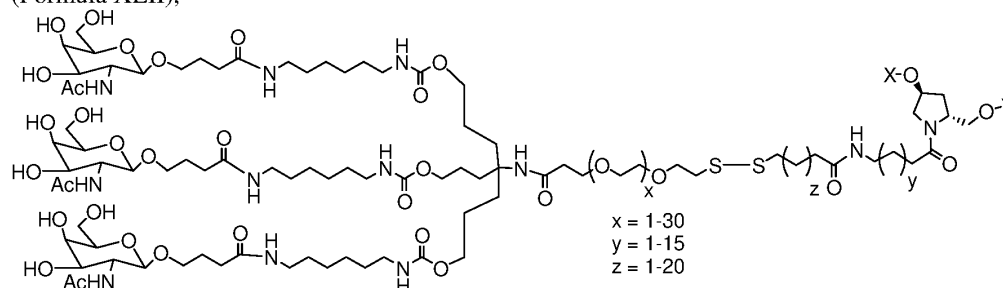
(Formula XL),



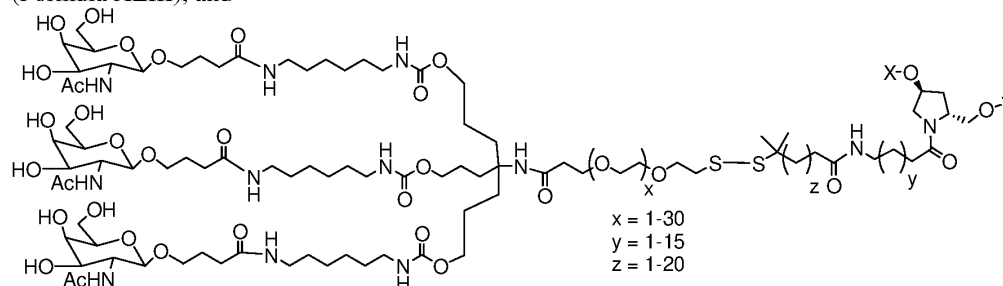
(Formula XLI),



(Formula XLII).



(Formula XLIII), and

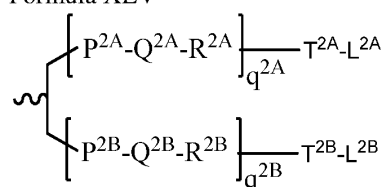


- 5 (Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

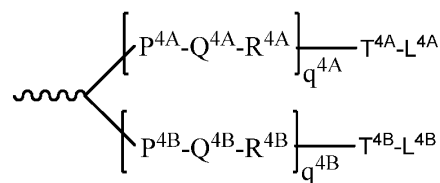
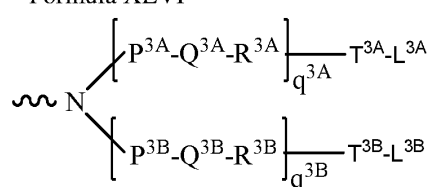
In certain embodiments of the compositions and methods of the invention, a ligand is one or more “GalNAc” (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

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

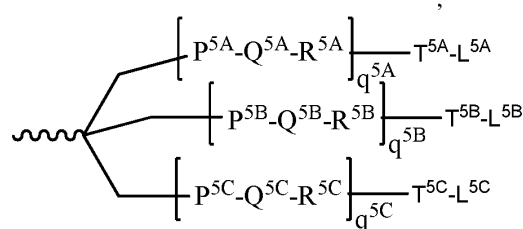
Formula XLV



Formula XLVI



Formula XLVII



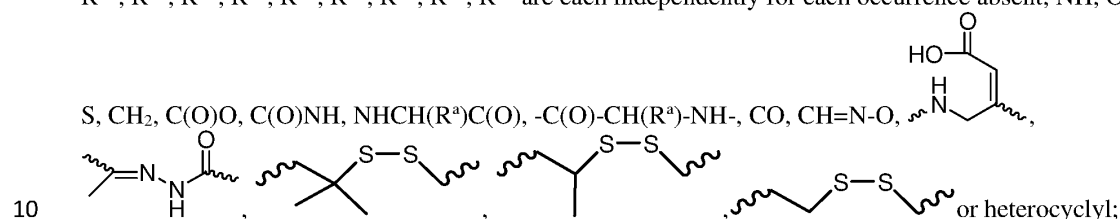
Formula XLVIII

- 15 wherein:

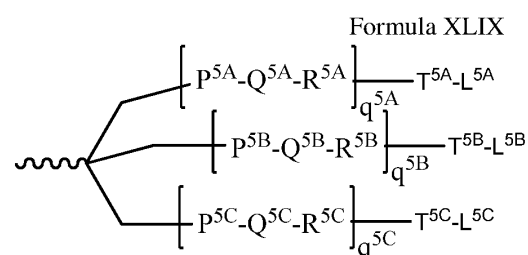
q2A, q2B, q3A, q3B, q4A, q4B, q5A, q5B and q5C represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different;

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
- 15 target gene, such as those of formula (XLIX):



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

- 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.
- 20

- 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;
- 25

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 juxtascleral, subretinal, subconjunctival, retrobulbar, or intracanalicular 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
5 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
10 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
15 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
20 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,
25 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,
30 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
35 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.

5 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, 10 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, 15 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 20 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 25 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 30 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.

35 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
 5 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
 10 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
 15 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.

20 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
 25 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,
 30 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
 35 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

5 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

10 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

15 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

20 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

25 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.

30 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

35 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	
Proteinurea	- ≥ 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 proteinurea, 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 if 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/EF. • 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 HFrEF. - 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 HFrEF. - 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/EF, 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

- 10 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).
- 15 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
- 20

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

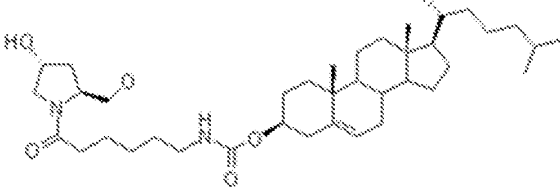
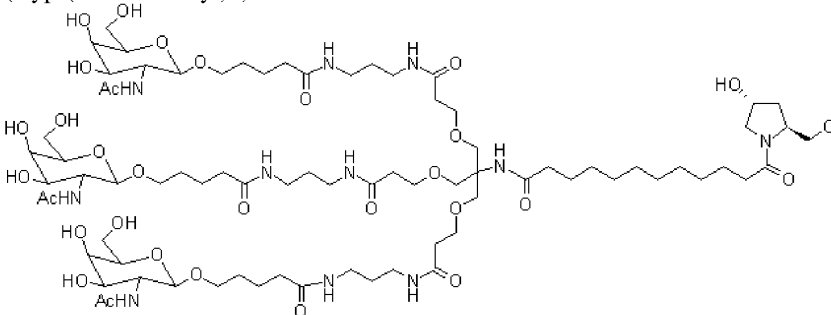
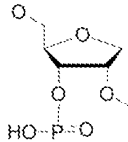
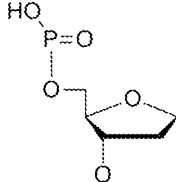
Two microlitre (μ L) of cDNA are added to a master mix containing 0.5 μ L of human GAPDH TaqMan Probe (4326317E), 0.5 μ L human AGT, 2 μ L nuclease-free water and 5 μ L Lightcycler 480

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	ACCAGAACAAACGGCAGCUUCUUC		1-23
AD-1632737	GAAGCUGCCGUUGUUCUGGGU		4-24	ACCCAGAACAAACGGCAGCUUCUU		2-24
AD-1632738	AAGCUGCCGUUGUUCUGGGUU		5-25	AACCCAGAACAAACGGCAGCUUCU		3-25
AD-1632741	CUGCCGUUGUUCUGGGUACUU		8-28	AAGUACCCAGAACAAACGGCAGCU		6-28
AD-1632745	CGUUGUUCUGGGUACUACAGU		12-32	ACUGUAGUACCCAGAACAAACGGC		10-32
AD-1632752	CUGGGUACUACAGCAGAAAGGU		19-39	ACCUUCUGCUGUAGUACCCAGAA		17-39
AD-1632757	UACUACAGCAGAAAGGUUUGU		24-44	ACAUACCCUUCUGCUGUAGUACC		22-44
AD-1632758	ACUACAGCAGAAAGGUUUGCU		25-45	AGCAUACCCUUCUGCUGUAGUAC		23-45
AD-1632759	CUACAGCAGAAAGGUUUGCGU		26-46	ACGCAUACCCUUCUGCUGUAGUA		24-46
AD-1632760	UACAGCAGAAAGGUUUGCGGU		27-47	ACCGCAUACCCUUCUGCUGUAGU		25-47
AD-1632761	ACAGCAGAAAGGUUUGCGGAU		28-48	AUCCGCAUACCCUUCUGCUGUAG		26-48
AD-1632763	AGCAGAGGGUUAUGCGGAAGU		30-50	ACUUCGCAUACCCUUCUGCUGU		28-50
AD-1632852	AUCCACAAUGAGAGUACCUUGU		173-193	ACAGGUACUCUCAUUGUGGAUGA		171-193
AD-1632856	ACAAUGAGAGUACCUUGUGAGU		177-197	ACUCACAGGUACUCUCAUUGUGG		175-197
AD-1632898	UUCAUACCUUGCUCCAAUUCU		239-259	AUGAAUUGGAGCAGGUUAGAAAGG		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	UCAUACCUUGCUCCAAUUCAGU		240-260	ACUGAAUUGGAGCAGGUAUGAAG		238-260
AD-1632900	CAUACCUUGCUCCAAUUCAGGU		241-261	ACCUGAAUUGGAGCAGGUAUGAA		239-261
AD-1632915	UGGAUGAAAAAGGCCCUACAGU		276-296	ACUGAGGGCCUUUUCAUCCACA		274-296
AD-1632916	GGAUGAAAAAGGCCCUACAGGU		277-297	ACCUGAGGGCCUUUUCAUCCAC		275-297
AD-1632944	GUUCUAGUCGCUUGCAAAACUU		305-325	AAGUUUUGCAGCGACUAGCACCA		303-325
AD-1632945	UGCUAGUCGCUUGCAAAACUUU		306-326	AAAGUUUUGCAGCGACUAGCACCC		304-326
AD-1632946	GCUAGUCGCUUGCAAAACUUGU		307-327	ACAAGUUUUGCAGCGACUAGCAC		305-327
AD-1632955	UGCAAAACUUUGACACCCGAAGU		316-336	ACUUCGGUGUCAAGUUUUUGCAGC		314-336
AD-1632956	GC AAAACUUUGACACCCGAAGAU		317-337	AUCUUCGGUGUCAAGUUUUUGCAG		315-337
AD-1632963	UUUGACACCCGAAGACAAGUUGU		324-344	ACAACUUGUCUUCGGUGUCAAGU		322-344
AD-1632964	UGACACCCGAAGACAAGUUGAU		325-345	AUCAACUUGUCUUCGGUGUCAAG		323-345
AD-1632966	ACACCCGAAGACAAGUUGAGGU		327-347	ACCUCAACUUGUCUUCGGUGUCA		325-347
AD-1632967	CACCGAAGACAAGUUGAGGGU		328-348	ACCCUCAACUUGUCUUCGGUGUC		326-348
AD-1632977	AAGUUGAGGGCCGCAUUGGUU		338-358	AACCAUUGCGGGCCCUCAACUUGU		336-358
AD-1632998	GGGAUGCUGGCCCAACUUCUUU		359-379	AAAGAAUUGGCCCAGCAUCCCGA		357-379
AD-1633003	GCUGGCCCAACUUCUUGGGCUU		364-384	AAGCCCAAGAAAGUUGGCCAGCAU		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	AUACGGAAGCCCAAGAAAGUUUGG		368-390
AD-1633010	AACUUCUUGGGCUUCCGUAAU		371-391	AAUACGGAAGCCCAAGAAAGUUUGG		369-391
AD-1633011	ACUUCUUGGGCUUCCGUAAU		372-392	AUAUACGGAAGCCCAAGAAAGUUUG		370-392
AD-1633014	UCUUGGGCUUCCGUAAUAAU		375-395	AAUAUAUACGGAAGCCCAAGAAAG		373-395
AD-1633016	UUGGGCUUCCGUAAUAAUUGGU		377-397	ACCAUAUAUACGGAAGCCCAAGAAAG		375-397
AD-1633029	UAUAUGGCAUGCACAGUGAGU		390-410	ACUCACUGUGCAUGGCCAUAAUAUA		388-410
AD-1633034	GCAUGCACAGUGAGCUAUGGU		396-416	ACCAUAGCUCACUGUGCAUGCCCA		394-416
AD-1633064	CUCUAUCUGGGAGCCUUGGAU		476-496	AUCCAAGGCUCUCCAGAUAGAGAG		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	AGAACACCCAGGAUUGCCUGUAG		512-534
AD-1633105	GGCAAUCCUGGGUGUUCUUU		517-537	AAAGGAACACCCAGGAUUUGCCUG		515-537
AD-1633106	GCAAUCCUGGGUGUUCUUUGU		518-538	ACAAGGAACACCCAGGAUUUGCCU		516-538
AD-1633108	AUCCUGGGUGUUCUUUGGAU		520-540	AUCCAAGGAACACCCAGGAUUUGC		518-540
AD-1633110	UCCUGGGUGUUCUUUGGAAGU		522-542	ACUCCAAGGAACACCCAGGAUU		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	CCUUGGAAGGACAAAGAACUGU		533-553	ACAGUUCUUGUCCUCCAAAGGAA		531-553
AD-1633254	CACCUGAAGCAGCCGUUUGUU		692-712	AACAAACGGCUGCUUCAGGUGCA		690-712
AD-1633295	CUCUGGACUUCACAGAACUGU		753-773	ACAGUUCUGUGAAAGUCCAGAGAG		751-773
AD-1633296	UCUGGACUUCACAGAACUGGU		754-774	ACCAGUUCUGUGAAAGUCCAGAGA		752-774
AD-1633299	GGACUUCACAGAACUGGAUGU		757-777	ACAUCCAGUUCUGUGAAGUCCAG		755-777
AD-1633301	ACUUCACAGAACUGGAUUGUU		759-779	AAACAUCAGUUCUGUGAAGUCC		757-779
AD-1633302	CUUCACAGAACUGGAUUGUU		760-780	ACAACAUCAGUUCUGUGAAGUCC		758-780
AD-1633305	CACAGAACUGGAUUGUUGCUGU		763-783	ACAGCAACAUCAGUUCUGUGAA		761-783
AD-1633306	ACAGAACUGGAUUGUUGCUGU		764-784	AGCAGCAACAUCAGUUCUGUGA		762-784
AD-1633317	UGUUGCUGCUGAGAGAAUUGU		775-795	ACAUCUUCUCAGCAGCAACAUC		773-795
AD-1633319	UUGCUGCUGAGAGAAUUGACU		777-797	AGUCAAUUCUUCAGCAGCAACA		775-797
AD-1633321	GCUGCUGAGAGAAUUGACAGU		779-799	ACUGUCAAUUCUUCAGCAGCAAA		777-799
AD-1633335	ACAGGUUCAUGCAGGCUGUGU		795-815	ACACAGCCUGCAUGAACCCUGUCA		793-815
AD-1633343	AUGCAGGCUGUGACAGGAUGU		803-823	ACAUCCUGUCACAGCCUGCAUGA		801-823
AD-1633345	GCAGGCUGUGACAGGAUGGAU		805-825	AUCCAUCUUGUCACAGCCUGCAU		803-825
AD-1633397	GACAGCACCCUGGCUUUCAAU		857-877	AUUGAAAAGCCAGGGUGCUGUCCA		855-877

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	CUGGCUUUAACACACCUACGUU		866-886	AACGUAGGUGUUUAGAAAGCCAGGG		864-886
AD-1633409	GCUUUAACACCUACGUCCAU		869-889	AUGGACGUAGGUGUUGAAAGCCA		867-889
AD-1633417	CACCUACGUCCACUUCCAAAGU		877-897	ACUUGGAAGUGGACGUAGGUGUU		875-897
AD-1633425	UCCACUUCCAAAGGGAAGAUGU		885-905	ACAUCUCCCUUGGAAAGUGGACG		883-905
AD-1633428	ACUUCCAAAGGGAAGAUGAAGU		888-908	ACUUCAUCUCCCCUUGGAAGUGG		886-908
AD-1633429	CUUCCAAGGGAAGAUGAAGGU		889-909	ACCUUCAUCUCCCCUUGGAAGUG		887-909
AD-1633431	UCCAAGGGAAGAUGAAGGGCU		891-911	AGCCCCUUAUCUCCCCUUGGAAG		889-911
AD-1633440	AGAUGAAGGGCUUCUCCCCUGU		900-920	ACAGGGAGAAAGCCCUUCAUCUUC		898-920
AD-1633464	GGACAACAGCACCCUCAGUGUU		946-966	AACACUGAGGUGUGUUGUCCAC		944-966
AD-1633465	GACAACAGCACCCUCAGUGUCU		947-967	AGACACUGAGGUGUGUUGUCCCA		945-967
AD-1633467	CAACAGCACCCUCAGUGUCUGU		949-969	ACAGACACUGAGGUGUGUGUUGUC		947-969
AD-1633474	ACCUCAGUGUCUGUUUCCCAUU		956-976	AAUGGGAACAGACACUCUGAGGUGC		954-976
AD-1633478	CAGUGUCUGUUUCCCAUGCUCU		960-980	AGAGCAUGGGAACAGACACUCAG		958-980
AD-1633482	GUCUGUUCCCAUGCUCUCUCUGU		964-984	ACAGAGAGCAUGGGAACAGACAC		962-984
AD-1633483	UCUGUUCCCAUGCUCUCUCUGGU		965-985	ACCAGAGAGCAUGGGAACAGACA		963-985
AD-1633528	GACAUCCAGGACAAACUUCUCU		1010-1030	AGAGAAGUUUCCUUGGAUGUCAC		1008-1030

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	ACGAGAAUUUGUCCUGGAUGUCA		1009-1031
AD-1633530	CAUCCAGGACAAACUUCUCGGU		1012-1032	ACCGAGAAUUUGUCCUGGAUGUC		1010-1032
AD-1633531	AUCCAGGACAAACUUCUCGGUU		1013-1033	AACCGAGAAUUUGUCCUGGAUGU		1011-1033
AD-1633532	UCCAGGACAAACUUCUCGGUGU		1014-1034	ACACCGAGAAUUUGUCCUGGAUG		1012-1034
AD-1633533	CCAGGACAAACUUCUCGGUGAU		1015-1035	AUCACCGAGAAUUUGUCCUGGAU		1013-1035
AD-1633534	CAGGACAAACUUCUCGGUGACU		1016-1036	AGUCACCGAGAAUUUGUCCUGGA		1014-1036
AD-1633541	ACUUCUCGGUGACUCAAGUGU		1023-1043	ACACUUGAGUCACCGAGAAUUUG		1021-1043
AD-1633542	CUUCUCGGUGACUCAAGUGCU		1024-1044	AGCACUUGAGUCACCGAGAAUUU		1022-1044
AD-1633551	GACUCAAGUGGCCCUUCACUGU		1033-1053	ACAGUGAAGGGCACUUGAGUCAC		1031-1053
AD-1633553	CUCAAGUGCCCUUCACUGAGU		1035-1055	ACUCAGUGAAGGGCACUUGAGUC		1033-1055
AD-1633587	GCUGAUCCAGCCUCACUAUGU		1069-1089	ACAUAUGAGAGGCUGGAUCAGCAG		1067-1089
AD-1633624	GUGGAGGGUUCACAUUCCAU		1106-1126	AUGGAAAGUGAGACCCUCCACCU		1104-1126
AD-1633633	CUCACUUCAGCAAAACUCU		1115-1135	AGAGUUUUGCUGGAAAGUGAGAC		1113-1135
AD-1633642	CAGCAAAACUCCCUCAACUGU		1124-1144	ACAGUUGAGGGAGUUUUGCUGGA		1122-1144
AD-1633643	AGCAAAACUCCCUCAACUGGU		1125-1145	ACCAUUUGAGGGAGUUUUGCUGG		1123-1145
AD-1633646	AAAACUCCCUCAACUGGAUGU		1128-1148	ACAUCCAGUUUGAGGGAGUUUUGC		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	AGAGAUAGUUUUCUUCAUCCAGUU		1139-1161
AD-1633666	ACUGGUGCUGCAAGGAUCUUU		1189-1209	AAAGAUCCUUGCAGCACCCAGUUUG		1187-1209
AD-1633669	GGUGCUGCAAGGAUCUUUAUGU		1192-1212	ACAUAAAGAUCCUUGCAGCACCCAG		1190-1212
AD-1633670	GUGCUGCAAGGAUCUUUAUGAU		1193-1213	AUCAUAAAGAUCCUUGCAGCACCCA		1191-1213
AD-1633671	UGCUGCAAGGAUCUUUAUGACU		1194-1214	AGUCAUAAAGAUCCUUGCAGCACCC		1192-1214
AD-1633683	CUUAUGACCUGCAGGACCUGU		1206-1226	ACAGGUCCUGCAGGUCAUAAAGAU		1204-1226
AD-1633732	CGAGCUGAACCUUGCAAAAUUU		1261-1281	AAUUUUUGCAGGUUCAGCUCGGU		1259-1281
AD-1633733	GAGCUGAACCUUGCAAAAUUU		1262-1282	AAUUUUUGCAGGUUCAGCUCGG		1260-1282
AD-1633734	AGCUGAACCUUGCAAAAUUUGU		1263-1283	ACAAUUUUUGCAGGUUCAGCUCG		1261-1283
AD-1633735	GCUGAACCUUGCAAAAUUUGAU		1264-1284	AUCAUUUUUGCAGGUUCAGCUC		1262-1284
AD-1633736	CUGAACCUUGCAAAAUUUGAGU		1265-1285	ACUCAUUUUUGCAGGUUCAGCU		1263-1285
AD-1633737	UGAACCUUGCAAAAUUUGAGCU		1266-1286	AGCUCAUUUUUGCAGGUUCAGC		1264-1286
AD-1633743	UGCAAAAUUUGAGCAAUUGACU		1272-1292	AGUCAUUUGCUCAAUUUUUGCAGG		1270-1292
AD-1633745	CAAAAUUUGAGCAAUUGACCGU		1274-1294	ACGGUCAUUUGCUCAAUUUUUGCA		1272-1294
AD-1633751	UUAGAGCAAUUGACCGCAUCAGU		1280-1300	ACUGAUGCGGUCAUUGCUCAAUU		1278-1300

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	AACCCUGAUGCGGUCAUUGCUCUA		1281-1303
AD-1633759	GAGGUGCUGAACAGCAUUUUU		1307-1327	AAAAAUGCUGUUACAGCACCUCCC		1305-1327
AD-1633761	UUAGGCUUGAAGCGGAUGAGU		1329-1349	ACUCAUCCGCUUCAAAGCUCAAAA		1327-1349
AD-1633795	GUCUACCCCAACAGCUUAACAU		1363-1383	AUGUUAAGCUGUUGGGUAGACUC		1361-1383
AD-1633796	UCUACCCCAACAGCUUAACAAU		1364-1384	AUUGUUAAGCUGUUGGGUAGACU		1362-1384
AD-1633797	CUACCCCAACAGCUUAACAAU		1365-1385	ACUUGUUAAGCUGUUGGGUAGAC		1363-1385
AD-1633801	CCAAACAGCUUAACAAAGCCUGU		1369-1389	ACAGGCUUGUUAAGCUGUUGGGU		1367-1389
AD-1633804	ACAGCUUAACAAAGCCUGAGGU		1372-1392	ACCUCAGGCUUGUUAAGCUGUUG		1370-1392
AD-1633808	CUUAACAAAGCCUGAGGUCUUU		1376-1396	AAAGACCUCAGGCUUGUUAAGCU		1374-1396
AD-1633809	UUAACAAGCCUGAGGUCUUUGU		1377-1397	ACAAGACCUCAGGCUUGUUAAGC		1375-1397
AD-1633810	UAAACAAGCCUGAGGUCUUUGGU		1378-1398	ACCAAGACCUCAGGCUUGUUAAG		1376-1398
AD-1633811	AACAAGCCUGAGGUCUUGGAU		1379-1399	AUCCAAGACCUCAGGCUUGUUA		1377-1399
AD-1633812	ACAAGCCUGAGGUCUUGGAGU		1380-1400	ACUCCAAGACCUCAGGCUUGUUA		1378-1400
AD-1633813	CAAGCCUGAGGUCUUGGAGGU		1381-1401	ACCUCCAAGACCUCAGGCUUGUU		1379-1401
AD-1633841	AACCGCCCAUUCUUGUUGCU		1409-1429	AGCAAACAGGAAUUGGCGGUUCA		1407-1429

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	ACCGCCCAUCCUGUUUUGCUU		1410-1430	AAGCAACACAGGAUUGGGCGGUUC		1408-1430
AD-1633843	CCGCCCAUCCUGUUUUGCUGU		1411-1431	ACAGCAACACAGGAUUGGGCGGUU		1409-1431
AD-1633844	CGCCCAUCCUGUUUUGCUGUU		1412-1432	AACAGCAACACAGGAUUGGGCGGU		1410-1432
AD-1633848	AUUCUGUUUUGCUGUGUAUGU		1417-1437	ACAUACACAGCAAAACAGGAUUGG		1415-1437
AD-1633850	UCCUGUUUUGCUGUGUAUGAUU		1419-1439	AAUCAUACACAGCAAAACAGGAUU		1417-1439
AD-1633857	UGCUGUGUAUGAUCAAAAGCGU		1426-1446	ACGCUUUGAUCAUACACAGCAAA		1424-1446
AD-1633858	GCUGUGUAUGAUCAAAAGCGCU		1427-1447	AGCGCUUUGAUCAUACACAGCAA		1425-1447
AD-1633859	CUGUGUAUGAUCAAAAGCGCCU		1428-1448	AGGCGCUUUGAUCAUACACAGCA		1426-1448
AD-1633937	AGGCCAGCAGCAGAUAAACAAU		1557-1577	AUUGUUAUCUGCUGCGGCCUUU		1555-1577
AD-1633940	CGGACAAAUACGCGAUGUGUU		1580-1600	AACACAUCGCUGAUUUUGUCCGGG		1578-1600
AD-1633941	GGACAAAUACGCGAUGUGUCU		1581-1601	AGACACAUCGCUGAUUUUGUCCGG		1579-1601
AD-1633947	CUCCACCCUUUUUCUUAUU		1610-1630	AAUUAGAAGAAAAGGUGGGAGAC		1608-1630
AD-1633948	UCCACCCUUUUUCUUAUU		1611-1631	ACAUUAGAAGAAAAGGUGGGAGA		1609-1631
AD-1633949	CCCACCCUUUUUCUUAUU		1612-1632	AUCAUAGAAGAAAAGGUGGGAG		1610-1632
AD-1633954	UUUUCUUAUUUAGAGUCGACU		1618-1638	AGUCGACUCAUUUAGAAAGAAAGG		1616-1638
AD-1633955	UUUCUUAUUUAGAGUCGACUU		1619-1639	AAGUCGACUCAUUUAGAAAGAAAG		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	UUUUUUAUAGAGUCGACUUU		1620-1640	AAAGUCGACUCAUUAGAAAGAAA		1618-1640
AD-1633958	CUUCUAAUGAGUCGACUUUGU		1622-1642	ACAAAAGUCGACUCAUUAGAAAGAA		1620-1642
AD-1633959	UUCUAAUGAGUCGACUUUGAU		1623-1643	AUCAAAGUCGACUCAUUAGAAAGA		1621-1643
AD-1633960	UCUAAUGAGUCGACUUUGAGU		1624-1644	ACUCAAAGUCGACUCAUUAGAAAG		1622-1644
AD-1633961	CUAAUGAGUCGACUUUGAGCU		1625-1645	AGCUCAAAAGUCGACUCAUUAGAA		1623-1645
AD-1633962	UAAUGAGUCGACUUUGAGCUU		1626-1646	AAAGCUCAAAAGUCGACUCAUUAGA		1624-1646
AD-1633971	GACUUUGAGCUGGAAAGCAGU		1635-1655	ACUGCUUUUCCAGCUCAAAAGUCGA		1633-1655
AD-1633977	GAGCUGGAAAGCAGCCGUUUU		1641-1661	AAAACGGCUGCUUUUCCAGCUCAA		1639-1661
AD-1633978	AGCUGGAAAGCAGCCGUUUUCU		1642-1662	AGAAACGGCUGCUUUUCCAGCUCUA		1640-1662
AD-1633979	GCUGGAAAGCAGCCGUUUUCU		1643-1663	AAGAAACGGCUGCUUUUCCAGCUC		1641-1663
AD-1633980	CUGGAAAGCAGCCGUUUUCUCU		1644-1664	AGAGAAACGGCUGCUUUUCCAGCU		1642-1664
AD-1633982	GGAAAGCAGCCGUUUUCUCCU		1646-1666	AAGGAGAAACGGCUGCUUUUCCAG		1644-1666
AD-1633984	AAAGCAGCCGUUUUCUCCUUGU		1648-1668	ACAAGGAGAAACGGCUGCUUUUCC		1646-1668
AD-1633986	AGCAGCCGUUUUCUCCUUGGUU		1650-1670	AACCAAGGAGAAACGGCUGCUUUU		1648-1670
AD-1633987	GCAGCCGUUUUCUCCUUGGUUCU		1651-1671	AGACCAAGGAGAAACGGCUGCUUU		1649-1671
AD-1633988	CAGCCGUUUUCUCCUUGGUUCU		1652-1672	AAGACCAAGGAGAAACGGCUGCU		1650-1672

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	GUUUCUCCUUGGUCUAAGUGU		1657-1677	ACACUUAGACCAAGGAGAAACGG		1655-1677
AD-1633994	UUUCUCCUUGGUCUAAGUGUU		1658-1678	AACACUUAGACCAAGGAGAAACG		1656-1678
AD-1633995	UUUCUCCUUGGUCUAAGUGUGU		1659-1679	ACACACUUAGACCAAGGAGAAAC		1657-1679
AD-1633996	UCUCCUUGGUCUAAGUGUGCU		1660-1680	AGCACACUUAGACCAAGGAGAAA		1658-1680
AD-1633998	UCCUUGGUCUAAGUGUGCUGU		1662-1682	ACAGCACACUUAGACCAAGGAGA		1660-1682
AD-1634005	UCUAAGUGUGCUGCAUGGAGU		1669-1689	ACUCCAUUGCAGCACACUUAGACC		1667-1689
AD-1634009	AGUGUGCUGCAUGGAGUGAGU		1673-1693	ACUCACUCCAUUGCAGCACACUUA		1671-1693
AD-1634018	CAUGGAGUGAGCAGUAGAAAGU		1682-1702	ACUUCUACUUGCUCACUCCAUUGCA		1680-1702
AD-1634022	GAGUGAGCAGUAGAAAGCCUGU		1686-1706	ACAGGCUUCUACUGCUCACUCCA		1684-1706
AD-1634050	CAA AUGCACCUCUCCAGUUUUGU		1714-1734	ACAAACUGGGAGGUGCAUUUUGUG		1712-1734
AD-1634051	AAUGCACCUCUCCAGUUUUGCU		1715-1735	AGCAAAACUGGGAGGUGCAUUUUGU		1713-1735
AD-1634052	AAUGCACCUCUCCAGUUUUGCUU		1716-1736	AAGCAAAACUGGGAGGUGCAUUUUG		1714-1736
AD-1634053	AUGCACCUCUCCAGUUUUGCUGU		1717-1737	ACAGCAAAACUGGGAGGUGCAUUU		1715-1737
AD-1634054	UGCACCUCUCCAGUUUUGCUGGU		1718-1738	ACCAGCAAAACUGGGAGGUGCAUU		1716-1738
AD-1634059	CUCCAGUUUUGCUGGGUUUAU		1723-1743	AUAAACCCAGCAAAACUGGGAGGU		1721-1743

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	AAAUAAACCCAGCAAACUGGGAG		1723-1745
AD-1634062	CCAGUUUGCUGGGUUUAUUU		1726-1746	AAAUAAACCCAGCAAACUGGGA		1724-1746
AD-1634063	CAGUUUGCUGGGUUUAUUU		1727-1747	AAAUAAACCCAGCAAACUGGG		1725-1747
AD-1634064	AGUUUGCUGGGUUUAUUU		1728-1748	AUAAAUAAACCCAGCAAACUGG		1726-1748
AD-1634065	GUUUUGCUGGGUUUAUUU		1729-1749	ACUAAAUAAACCCAGCAAACUG		1727-1749
AD-1634066	UUUGCUGGGUUUAUUU		1730-1750	AUCUAAAUAAACCCAGCAAACU		1728-1750
AD-1634067	UUGCUGGGUUUAUUU		1731-1751	ACUCUAAAUAAACCCAGCAAAC		1729-1751
AD-1634068	UGCUGGGUUUAUUU		1732-1752	AUCUCUAAAUAAACCCAGCAA		1730-1752
AD-1634071	GGGUUAUUUAGAGAAUGGU		1736-1756	ACCAUUCUCUAAAAAUAAACCCAG		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	AGCUAAACACUGGUUUCUUGCCUCC		1763-1785
AD-1634088	UGUUUAGCGCGGGACUACUGU		1777-1797	ACAGUAGUCCCGCGGCUAAACACU		1775-1797
AD-1634100	GACUACUGUUCCAAAAAGAAU		1789-1809	AUUCUUUUUGGAACAGUAGUCCC		1787-1809
AD-1634104	ACUGUUCCAAAAAGAAUUCU		1793-1813	AGGAAUUCUUUUUGGAACAGUAG		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	CUGUUCACAAAAAGAAUUCACU		1794-1814	AUGGAAUUCUUUUUUGGAAACAGUA		1792-1814
AD-1634111	CAAAAAGAAUUCACACCGACU		1800-1820	AGUCGGUUGGAAUUCUUUUUGGA		1798-1820
AD-1634123	ACCGACAGCUUGUUUGUGAU		1814-1834	AUCACAAACAAAGCUGGUCGGUUG		1812-1834
AD-1634131	AAAGUUUCCCUUUUCAAGUU		1840-1860	AACUUGAAAAGGGAACACUUUUU		1838-1860
AD-1634133	AGUGUUCCCUUUUCAAGUUGU		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	CAAGUUGAGAACAAAAAUUGU		1855-1875	ACAAUUUUUGUUUCUACAACUUGAA		1853-1875
AD-1634147	AAGUUGAGAACAAAAAUUGGU		1856-1876	ACCAUUUUUGUUUCUACAACUUGA		1854-1876
AD-1634148	GUUGAGAACAAAAAUUGGGUU		1858-1878	AACCCAAUUUUUGUUUCUACAACUU		1856-1878
AD-1634149	UUAGAGAACAAAAAUUGGGUUU		1859-1879	AAACCCAAUUUUUGUUUCUACAACU		1857-1879
AD-1634150	UGAGAACAAAAAUUGGGUUUU		1860-1880	AAAACCCAAUUUUUGUUUCUACAAC		1858-1880
AD-1634151	GAGAACAAAAAUUGGGUUUUU		1861-1881	AAAAACCCAAUUUUUGUUUCUACA		1859-1881
AD-1634152	AGAACAAAAAUUGGGUUUUUAU		1862-1882	AUAAAAACCCAAUUUUUGUUUCUCA		1860-1882
AD-1634153	GAACAAAAAUUGGGUUUUUAU		1863-1883	AUUAAAAACCCAAUUUUUGUUUCUC		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	GUUACAUUUUUUGCAUUGCCU		1890-1910	AGGCAUUGCAAAAUAUGUAUACUU		1888-1910
AD-1634165	AUACAUUUUUUGCAUUGCCUUU		1892-1912	AAAGGCAUUGCAAAAUAUGUAUAC		1890-1912
AD-1634168	CAUUUUUGCAUUGCCUUCGGU		1895-1915	ACCGAAGGCAUUGCAAAAUAUGUA		1893-1915
AD-1634169	AUUUUUGCAUUGCCUUCGGUU		1896-1916	AACCGAAGGCAUUGCAAAAUAUGU		1894-1916
AD-1634170	UUUUUGCAUUGCCUUCGGUUU		1897-1917	AAACCGAAGGCAUUGCAAAAUAUG		1895-1917
AD-1634171	UUUUUGCAUUGCCUUCGGUUUU		1898-1918	AAACCGAAGGCAUUGCAAAAUAU		1896-1918
AD-1634172	UUUGCAUUGCCUUCGGUUUUGU		1899-1919	ACAAACCGAAGGCAUUGCAAAA		1897-1919
AD-1634173	UUGCAUUGCCUUCGGUUUUGUU		1900-1920	AACAAACCGAAGGCAUUGCAAAA		1898-1920
AD-1634174	UGCAUUGCCUUCGGUUUUGUAU		1901-1921	AUACAAACCGAAGGCAUUGCAAAA		1899-1921
AD-1634175	GCAUUGCCUUCGGUUUUGUAUU		1902-1922	AAUACAAACCGAAGGCAUUGCAA		1900-1922
AD-1634176	CAUUGCCUUCGGUUUUGUAUUU		1903-1923	AAAUACAAACCGAAGGCAUUGCA		1901-1923
AD-1634177	AUUGCCUUCGGUUUUGUAUUUU		1904-1924	AAAUACAAACCGAAGGCAUUGC		1902-1924
AD-1634178	UUUGCCUUCGGUUUUGUAUUUAU		1905-1925	AUAAAUAACAAACCGAAGGCAUUG		1903-1925
AD-1634179	UGCCUUCGGUUUUGUAUUUAGU		1906-1926	ACUAAAUAACAAACCGAAGGCAAU		1904-1926
AD-1634180	GCCUUCGGUUUUGUAUUUAGUU		1907-1927	AACUAAAUAACAAACCGAAGGCAA		1905-1927
AD-1634181	CCUUCGGUUUUGUAUUUAGUGU		1908-1928	ACACUAAAUAACAAACCGAAGGCA		1906-1928

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	CUUCGGUUUUGUAUUUAGUGUU		1909-1929	AACACUAAAUACAAACCCGAAGGC		1907-1929
AD-1634186	GGUUUGUAUUUAGUGUCUUUGU		1913-1933	ACAAGACACUAAAUACAAACCGA		1911-1933
AD-1634190	UGUAUUUAGUGUCUUGAAUGU		1917-1937	ACAUUCAAGACACUAAAUACAAA		1915-1937
AD-1634192	UAUUUAGUGUCUUUGAAUGUAU		1919-1939	AUACAUUCAAGACACUAAAUACA		1917-1939
AD-1634194	UUUAGUGUCUUUGAAUGUAAGU		1921-1941	ACUUACAUUCAAGACACUAAAUAA		1919-1941
AD-1634200	GUCUUUGAAUGUAAGAACAUGU		1927-1947	ACAUGUUUCUUAACAUAUCAAAGACAC		1925-1947
AD-1634209	GUAAAGAACAUAGACCUCGCCGUGU		1936-1956	ACACGGGAGGUCAUGUUCUUACA		1934-1956
AD-1634210	UAAGAACAUAGACCUCGCCGUGUU		1937-1957	AACACGGGAGGUCAUGUUCUUACA		1935-1957
AD-1634211	AAGAACAUAGACCUCGCCGUGUAU		1938-1958	AUACACGGGAGGUCAUGUUCUUAC		1936-1958
AD-1634212	AGAACAUAGACCUCGCCGUGUAGU		1939-1959	ACUACACGGGAGGUCAUGUUCUUUA		1937-1959
AD-1634213	GAACAUGACCUCGCCGUGUAGUU		1940-1960	AACUACACGGGAGGUCAUGUUCUU		1938-1960
AD-1634214	AACAUGACCUCGCCGUGUAGUGU		1941-1961	ACACUACACGGGAGGUCAUGUUCU		1939-1961
AD-1634215	ACAUGACCUCGCCGUGUAGUGUU		1942-1962	AACACUACACGGGAGGUCAUGUUC		1940-1962
AD-1634218	UGACCUCGCCGUGUAGUGUCUGU		1945-1965	ACAGACACUACACGGGAGGUCAUG		1943-1965
AD-1634224	CCGUGUAGUGUCUGUAAUACU		1951-1971	AGUAUUACAGACACUACACGGAG		1949-1971
AD-1634225	CGUGUAGUGUCUGUAAUACCU		1952-1972	AGGUUUACAGACACUACACGGGA		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	GUUAGUGUCUGUAAUACCUU		1953-1973	AAGGUUUACAGACACUACACGG		1951-1973
AD-1634227	UGUAGUGUCUGUAAUACCUU		1954-1974	AAAGGUUUACAGACACUACACG		1952-1974
AD-1634230	AGUGUCUGUAAUACCUUAGUU		1957-1977	AACUAAAGGUUUACAGACACUAC		1955-1977
AD-1634231	GUUUCUGUAAUACCUUAGUUU		1958-1978	AAACUAAAGGUUUACAGACACUA		1956-1978
AD-1634232	UGUCUGUAAUACCUUAGUUU		1959-1979	AAAACUAAAGGUUUACAGACACU		1957-1979
AD-1634233	GUCUGUAAUACCUUAGUUUUU		1960-1980	AAAAACUAAAGGUUUACAGACAC		1958-1980
AD-1634234	UUUCCACAGAUUCUUGUGAUU		1979-1999	AAUCACAAGCAUCUUGUGGAAAAA		1977-1999
AD-1634238	CACAGAUCCUUGUGAUUUUUU		1983-2003	AAAAAUUCACAAAGCAUCUGUGGA		1981-2003
AD-1634239	ACAGAUCCUUGUGAUUUUUUGU		1984-2004	ACAAAAUUCACAAAGCAUCUGUGG		1982-2004
AD-1634240	CAGAUCCUUGUGAUUUUUUGAU		1985-2005	AUCAAAAAUUCACAAAGCAUCUGUG		1983-2005
AD-1634241	AGAUGCUUGUGAUUUUUUGAAU		1986-2006	AUUCAAAAAUUCACAAAGCAUCUGU		1984-2006
AD-1634242	GAUGCUUGUGAUUUUUUGAACU		1987-2007	AGUUCAAAAAUUCACAAAGCAUCUG		1985-2007
AD-1634248	UGUGAUUUUUUGAACAAUACGU		1993-2013	ACGUUUUGUUCAAAAAUUCACAAAG		1991-2013
AD-1634249	GUGAUUUUUUGAACAAUACGUU		1994-2014	AACGUUUUGUUCAAAAAUUCACAA		1992-2014
AD-1634250	UGAUUUUUUGAACAAUACGUGU		1995-2015	ACACGUUUUGUUCAAAAAUUCACA		1993-2015
AD-1634251	GAUUUUUUUGAACAAUACGUGAU		1996-2016	AUCACGUUUUGUUCAAAAAUUCAC		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	AUUCACGUUUUUUCAAUCAAUUA		1995-2017
AD-1634257	UGAACAAUACGUGAAAGAUU		2002-2022	ACAUCUUUCACGUUUUUUCAAUUA		2000-2022
AD-1634273	GAUGCAAGCACCCUGAAUUUCU		2018-2038	AGAAUUUCAGGUGCUUGCAUUCU		2016-2038
AD-1634274	AUGCAAGCACCCUGAAUUUCU		2019-2039	AAGAAUUUCAGGUGCUUGCAUUCU		2017-2039
AD-1634275	UGCAAGCACCCUGAAUUUCUGU		2020-2040	ACAGAAUUUCAGGUGCUUGCAUUC		2018-2040
AD-1634276	GCAAGCACCCUGAAUUUCUGUU		2021-2041	AACAGAAUUUCAGGUGCUUGCAU		2019-2041
AD-1634277	CAAGCACCCUGAAUUUCUGUUU		2022-2042	AAACAGAAUUUCAGGUGCUUGCA		2020-2042
AD-1634278	AAGCACCCUGAAUUUCUGUUUU		2023-2043	AAAACAGAAUUUCAGGUGCUUGC		2021-2043
AD-1634279	AGCACCCUGAAUUUCUGUUUGU		2024-2044	ACAAACAGAAUUUCAGGUGCUUG		2022-2044
AD-1634280	GCACCCUGAAUUUCUGUUUGAU		2025-2045	AUCAAACAGAAUUUCAGGUGCUU		2023-2045
AD-1634281	CACCUGAAUUUCUGUUUGAAU		2026-2046	AUCAAACAGAAUUUCAGGUGCU		2024-2046
AD-1634282	ACCUGAAUUUCUGUUUGAAUU		2027-2047	AAUCAAACAGAAUUUCAGGUGC		2025-2047
AD-1634283	CCUGAAUUUCUGUUUGAAUGU		2028-2048	ACAUCAAACAGAAUUUCAGGUG		2026-2048
AD-1634285	UGAAUUUCUGUUUGAAUGCGU		2030-2050	ACGCAUUCAAACAGAAUUUCAGG		2028-2050
AD-1634286	GAAUUUCUGUUUGAAUGCGGU		2031-2051	ACCGCAUUCAAACAGAAUUUCAG		2029-2051
AD-1634287	AAUUUCUGUUUGAAUGCGGAU		2032-2052	AUCCGCAUUCAAACAGAAUUUA		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	UUUGAAUGCGGAACCAUAGCUU		2041-2061	AAGCUAUGGUUCCCGCAUUAAC		2039-2061
AD-1634297	UGAAUGCGGAACCAUAGCUGU		2042-2062	ACAGCUAUGGUUCCCGCAUUAAC		2040-2062
AD-1634298	GAAUGCGGAACCAUAGCUGGU		2043-2063	ACCAGCUAUGGUUCCCGCAUUAAC		2041-2063
AD-1634303	CGGAACCAUAGCUGGUUAUUU		2048-2068	AAUAACCAAGCUAUGGUUCCGCA		2046-2068
AD-1634304	GGAACCAUAGCUGGUUAUUUU		2049-2069	AAAUAACCAAGCUAUGGUUCCGCA		2047-2069
AD-1634305	GAACCAUAGCUGGUUAUUUCU		2050-2070	AGAAUAACCAAGCUAUGGUUCCG		2048-2070
AD-1634306	AACCAUAGCUGGUUAUUUCUU		2051-2071	AAGAAUAACCAAGCUAUGGUUCC		2049-2071
AD-1634307	ACCAUAGCUGGUUAUUUCUCU		2052-2072	AGAGAAUAACCAAGCUAUGGUUCC		2050-2072
AD-1634308	CCAUAAGCUGGUUAUUUCUCCU		2053-2073	AGGAGAAUAACCAAGCUAUGGUU		2051-2073
AD-1634309	CAUAGCUGGUUAUUUCUCCCU		2054-2074	AGGGAGAAUAACCAAGCUAUGGU		2052-2074
AD-1634314	CUGGUUAUUUCUCCCUUGUGU		2059-2079	ACACAAGGGAGAAUAACCAAGCU		2057-2079
AD-1634315	UGGUUAUUUCUCCCUUGUGUU		2060-2080	AACACAAGGGAGAAUAACCAAGC		2058-2080
AD-1634316	GGUUAUUUCUCCCUUGUGUUU		2061-2081	AAACAAGGGAGAAUAACCAAG		2059-2081
AD-1634318	UUAUUUCUCCCUUGUGUUAAGU		2063-2083	ACUAACACAAGGGAGAAUAAC		2061-2083
AD-1634319	UAUUUCUCCCUUGUGUUAAGU		2064-2084	AACUAACACAAGGGAGAAUAAC		2062-2084
AD-1634320	AUUUCUCCCUUGUGUUAAGU		2065-2085	AUACUAACACAAGGGAGAAUAAC		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	AUUACUAACACAAGGGGAGAAAUA		2064-2086
AD-1634325	UCCCUUGUGUUAGUAAUAAAU		2070-2090	AUUUAUUACUAAACACAAGGGAGA		2068-2090
AD-1634326	CCCUGUGUUAGUAAUAAACU		2071-2091	AGUUUAUUACUAAACACAAAGGGAG		2069-2091
AD-1634327	CCUUGUGUUAGUAAUAAACGU		2072-2092	ACGUUUAUUACUAAACACAAGGGA		2070-2092
AD-1634328	CUUGUGUUAGUAAUAAACGUU		2073-2093	AACGUUUAUUACUAAACACAAGGG		2071-2093
AD-1634329	UUUGUGUUAGUAAUAAACGUCU		2074-2094	AGACGUUUAUUACUAAACACAAGG		2072-2094
AD-1634330	UGUGUUAGUAAUAAACGUCUU		2075-2095	AAGACGUUUAUUACUAAACACAAG		2073-2095
AD-1634331	GUGUUAGUAAUAAACGUCUUU		2076-2096	AAAGACGUUUAUUACUAAACACAA		2074-2096
AD-1634332	UGUUAGUAAUAAACGUCUUGU		2077-2097	ACAAGACGUUUAUUACUAAACACA		2075-2097
AD-1634333	GUUAGUAAUAAACGUCUUUGC		2078-2098	AGCAAGACGUUUAUUACUAAACAC		2076-2098
AD-1634334	UUAGUAAUAAACGUCUUUGCCU		2079-2099	AGGCAAGACGUUUAUUACUAAACA		2077-2099
AD-1634342	AAACGUCUUGCCACAAUAAAGU		2087-2107	ACUUAUUUGGGCAAGACGUUUUU		2085-2107
AD-1634343	AACGUCUUGCCACAAUAAAGC		2088-2108	AGCUUAUUUGGGCAAGACGUUUUA		2086-2108
AD-1634344	ACGUCUUGCCACAAUAAAGCCU		2089-2109	AGGCUUAUUUGGGCAAGACGUUUU		2087-2109
AD-68585	AGUUUGAGAACAAAAUUUGGGHU		1857-1877	ACCCAATUUUUUUUUUUGUUCTTCAACTUUG		1855-1877

Table 3. 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-1632736	asgsaaagcUfgCfGfugnuucggguL96		asCfscagAfaCfAfacaggCfaGfcuucusuc		GAAGAAAGCUGCCGUUGUUUCUGGG	
AD-1632737	gsasagcuGfcCfGfuUfugnuucggguL96		asCfsccaGfaAfCfaacgGfcAfgcucusu		AAGAAGCUGCCGUUGUUUCUGGGU	
AD-1632738	asasgcugCfcGfUfUfgnuucggguuL96		asAfseccAfgAfAfcaacGfgCfagcuuscu		AGAAGCUGCCGUUGUUUCUGGGUA	
AD-1632741	csusgccgUfuGFUfUfcugnguaauL96		asAfsguaCfcCfAfgaacAfaCfggcgagscu		AGCUGCCGUUGUUUCUGGGUACUA	
AD-1632745	csgsuuguUfcUFGfGfguaacuaguuL96		asCfsuguAfgUfAfcecaGfaAfaacgsgsc		GCCGUUGUUUCUGGGUACUACAGC	
AD-1632752	csusggguAfcUFAfCfagcagaagguL96		asCfscuuCfuGfCfuguaGfuAfeccegasa		UUCUGGGUACUACAGCAGAGAGGG	
AD-1632757	usascuacAfgCfAfGfaggguauguuL96		asCfsauaCfcCTufueugCfuGfuaguascsc		GGUACUACAGCAGAGAGGGUAUGC	
AD-1632758	ascsuacaGfcAfGfAfaggguaugcuL96		asGfscuuAfcCfCfuucuGfcUfguaigusasc		GUACUACAGCAGAGAGGGUAUGCG	
AD-1632759	csusacagCfaCfAfafggguaugcuuL96		asCfsgcaUfaCfCfceuucUfgCfugaugsusa		UACUACAGCAGAGAGGGUAUGCGG	
AD-1632760	usascagcAfgAfAfGfguaugcgguL96		asCfscgcAfuAfCfcuuuCfuGfcuaguasgu		ACUACAGCAGAGAGGGUAUGCGGA	
AD-1632761	ascsaageaGfaAfGfGfguaugcggauiL96		asUfsecgCfaUfAfAfeeCUfcUfpgcuigasg		CUACAGCAGAGAGGGUAUGCGGAA	
AD-1632763	asgscaeaAfgGfGfUfaugcggaaguuL96		asCfsuucCfgCfAfuaacCfuUfcpuugusgu		ACAGCAGAGAGGGUAUGCGGGAAGC	
AD-1632852	asusccacAfaUfGfAfaggaaccuuuL96		asCfsagglUfaCTufeucaUfuGfuggausgsa		UCAUCCACA AUGAGAGUACCUGU	
AD-1632856	ascsaaugAfgAfGTUfaccugugaguuL96		asCfsucaCfaGfGhuacuCfuCfaunugusgg		CCACAAUGAGAGUACCUGUGAGC	
AD-1632898	ususcauaCfcUfGfGfuccaaucauL96		asUfsgaaUfuGfGfagcaGfgUfaugaasgsg		CCUUCAUACCUGGUCCAUAUUCAG	

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	uscsauacCfuUfGfCUfccaauucaguL96		asCfsugaAfuUfGfgagcAfgGfuaugasag		CUUCAUACCUGCUCCAAAUUCAGG	
AD-1632900	csasuaccUfgCUfGfcauuucagguL96		asCfscugAfaUfUfggagCfaGfguaugsasa		UUCAUACCUGCUCCAAAUUCAGGC	
AD-1632915	usgsaugAfaAfAfgGgcccacaguL96		asCfsuguAfgGfGfcuuUfuCfauccasca		UGUGGAUGAAAAGGCCCUACAGG	
AD-1632916	gsgsaugaAfaAfGfGfccuacaggul96		asCfscugUfaGfGfgcuUfuUfcauccsasc		GUGGAUGAAAAAGGGCCCUACAGGA	
AD-1632944	gssugcuafCuCFgCFugcaaaacuL96		asAfsguuUfuGfCFagcgAfeUfagcacscsa		UGGUGCUAGUCGCGUGCAAACUU	
AD-1632945	usgsuagUfCfGfCUfGcaaaaacuul96		asAfsaguUfuUfGfcagcGfaCfuagcasesc		GGUGCUAGUCGCGUGCAAACUUUG	
AD-1632946	gscsuagnCfGCUfGfcaaacuugul96		asCfsaagUfuUfUfgcagCfGaFenaagsasc		GUGCUAGUCGCGUGCAAACUUUA	
AD-1632955	usgscaaaaAfeUfUfGfiacacgaagul96		asCfsuucGfgUfGfucaagFuUfuuigcagssc		GCUGCAAAAACUUUGACACCCGAAGA	
AD-1632956	gscsaaaaCfuUfGfAfcaacgaagul96		asUfscuuCfGfGfUfgueaAfgUfuuuigsasg		CUGCAAAAACUUUGACACCCGAAGAC	
AD-1632963	ususgacaCfcGfAfAfagacaagugul96		asCfsaacUfuGfUfcauicGfgUfgucaasgsu		ACUUGACACCCGAAGACAAGUUGA	
AD-1632964	usgsacacCfGfAfAfGfacaaugugul96		asUfsecaaCfuUfGfueuuCfGfGfueasasg		CUUGACACCCGAAGACAAGUUGAG	
AD-1632966	ascsaccgAfaGfAfCfaaungaggul96		asCfscuicAfaCfUfugucUfuCfGguguscса		UGACACCGAAGACAAGUUGAGGG	
AD-1632967	csascegaAfgAfCfAfagunagggul96		asCfscuicCfaAfCfuuiguCfuUfCgngugnsc		GACACCGAAGACAAGUUGAGGGC	
AD-1632977	asasgnugAfgGfGfCfcgauggguL96		asAfsecaaUfuGfCfGggccCfuCfaacuugsu		ACAAGUUGAGGGCCCGCA AUGGUC	
AD-1632998	gsgsgaugCfuGfGfCfcaacuucuul96		asAfsagaAfgUfUfGggccAfgCfauccesgsa		UCGGGAUGCUGGCCCAACUUCUUG	
AD-1633003	gscsnagaCfaAfCfUfueuagagguL96		asAfsaccCfaAfGfcauuUfGfcaaccasau		AUGCTGGCCAACUUCUUGGGCTUI	

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-1633009	csasacuuCfuUfGfGfGcuccgguauL96		asUfsacgGfaAfGfcccAfGfaguugsgc		GCCAAACUUCUUGGGCUUCCGUAU	
AD-1633010	asascuucUfuGfGfGfGcuccgguauL96		asAfsuacGfgAfAfGcccAfGfaguugsgg		CCAACUUCUUGGGCUUCCGUAAU	
AD-1633011	ascsmucUfGfGfGfCfuuccgguauL96		asUfsauaCfGfGfAfagccCfaAfgaaguuug		CAACUUCUUGGGCUUCCGUAU	
AD-1633014	uscsmuggGfcUfUfCfGguauauuuL96		asAfsuauAfuAfCfggaaGfcCfaagaaasag		CUUCUUGGGCUUCCGUAAUAUG	
AD-1633016	ususgggcUfuCfCfGfuauauaugguL96		asCfscuuAfuAfUfacggAfGfcccAasga		UCUUGGGCUUCCGUAAUAUAGGC	
AD-1633029	usasuauGfCfAfUfGfcacagugaguL96		asCfsucaCfuGfuUfGcauGfcCfaauauasua		UAUAUAUGGCAUGCACAGUGAGC	
AD-1633034	gscsaugcAfcAfGfUfGgcauauugguL96		asCfscuuAfgCfuUfcacuGfuGfcaugcsesa		UGGCAUGCACAGUGAGCUAUGGG	
AD-1633064	csuscuauCfuGfGfGfGcuccugguauL96		asUfsecaAfgGfCfuccAfGfAfuagagsag		CUCUCUAUCUGGGAGCCUUGGAC	
AD-1633094	gsascaggCfuAfCfAfGgcauccuuL96		asAfsaggUfuGfCfcuguAfGfCfcugcsesa		CUGACAGGCUACAGGCAAUCCUG	
AD-1633095	ascsaggcUfaCfAfGfGcauccugguL96		asCfsaggAfuUfGfccugUfaGfCfcugcsesa		UGACAGGCUACAGGCAAUCCUGG	
AD-1633101	usascaggCfaAfUfCfGgugugguuuL96		asAfsacaCfcCfAfggauUfgCfcuguasgsc		GCUACAGGCAAUCCUGGGGUGUUC	
AD-1633102	ascsaggcAfaUfCfCfGgguguguuL96		asGfsaacAfcCfCfagggaUfuGfCfcuguisag		CUACAGGCAAUCCUGGGGUGUUC	
AD-1633105	gsgscauCfcUfGfGfGguguccuuL96		asAfsaggAfaCfAfcccGfGfAfuugccusug		CAGGCAAUCCUGGGGUGUUCUUG	
AD-1633106	gscsaucCfuCfGfGfGuguccugguL96		asCfsaagGfaAfCfaccCfGfGfauugcsesu		AGGCAAUCCUGGGGUGUUCUUGG	
AD-1633108	asasuucGfgGfUfGfGfGcuccugguL96		asUfsecaAfgGfAfacacCfcAfggaauugsc		GCAAUCCUGGGGUGUUCUUGGAA	
AD-1633110	uscscuucCfuGfUfUfCfGgcauauL96		asCfsuucCfaAfGfGaaCfCfCfagrasuu		AATUCCUGGGUGUUCUUGGAAGG	

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	ccscnuuggAfaGfGfAfaagaacugul96		asCfsaguUfcUfUfguccUfuCfcaaggsasa		UUCCUUUGGAAGGACAAGAACUGC	
AD-1633254	csascuugAfaGfCfAfcccguuuugul96		asAfscaaAfcGfGfucgUfuCfaggugcsa		UGCAACCUGAAGCAGCCGUUUGUG	
AD-1633295	csuscuuggAfcUfUfCfacaagaacugul96		asCfsaguUfcUfGfugaaGfuCfcaaggsasg		CUCUCUGGACUUCACAGAACUGG	
AD-1633296	uscsuuggaCfuUfCfAfcagaacugul96		asCfsacgUfuCfUfugaaAfgUfccaggsa		UCUCUGGACUUCACAGAACUGGA	
AD-1633299	gsgsacuuCfaCfAfGfaacuggaugul96		asCfsaucCfaGfUfucugUfgAfaaguccsasg		CUGGACUUCACAGAACUGGAUGU	
AD-1633301	ascsuucaCfaGfAfAfcuggauguuul96		asAfsacaUfcCfAfgnuucUfgUfgaagusc		GGACUUCACAGAACUGGAUGUUG	
AD-1633302	csusucacAfgAfaCfCfuggauguuul96		asCfsaacAfuCfCfaguuCfuGfugaaggsusc		GACUUCACAGAACUGGAUGUUGC	
AD-1633305	csascagaAfcUfGfGfaugugugul96		asCfsacgAfaCfAfuccaGfuUfcugugcsa		UUCACAGAACUGGAUGUUGCUGC	
AD-1633306	ascsaagaCfuGfGfAfugugugugul96		asGfscagCfaAfCfauccAfgUfucugugsa		UCACAGAACUGGAUGUUGCUGCU	
AD-1633317	usgsuugcUfgCfUfGfagaagaugul96		asCfsaanCfuUfCfucagCfaGfcaacasusc		GAUGUUGCUGCUGAGAGAAGAUUGA	
AD-1633319	ususgcugCfuGfAfGfaagaugagacul96		asGfsucaAfuCfUfucncAfgCfagaacsca		UGUUGCUGCUGAGAGAAGAUUGACA	
AD-1633321	gscsuugcuGfaGfAfAfgauugacagul96		asCfsuugCfaAfUfcuucUfcAfgcagcsa		UUGCUGCUGAGAGAAGAUUGACAGG	
AD-1633335	ascsaagguUfcAfuUfGfcaagcugugul96		asCfsacaGfcCfUfugeauGfaAfcugusca		UGACAGGUUUAUGCAGGCUGUGA	
AD-1633343	asusacagGfcUfGfUfcaaggaugul96		asCfsaucCfuGfUfcacaGfcCfugeausga		UCAUGCAGGCUGUGACAGGAUGG	
AD-1633345	gscsaaggeUfgUfGfAfcaggaugauul96		asUfsccaUfcCfUfuguaCfaGfcccugcsasu		AUGCAGGCUGUGACAGGAUGGAA	
AD-1633397	gsascagcAfcCfCfUfugcuuucanul96		asUfsugaAfaGfCfcaaggGfuGfueugcsca		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	csusggcuUfuCfAfAfcaccuacguuL96		asAfscguAfgGfUfguuGfAfaGfccagsgg		CCCUGGCUUUCAAACACCUACGUC	
AD-1633409	gscsuuucAfaCfAfCfcuacguccauL96		asUfsggaCfGfUfAfGggugUfuGfaaagcsca		UGGCUUUUCAAACACCUACGUCCAC	
AD-1633417	csasccuaCfGfUfCfCfacuuccaagL96		asCfsuugGfaAfGfuggaCfGfUfaggugusuu		AACACCUACGUCCACUUCUCCAAGG	
AD-1633425	uscscauUfcCfAfAfagggaagauL96		asCfsaucUfuCfCfcuugGfaAfugggascsg		CGUCCACUUCCAAAGGGAAGAUGA	
AD-1633428	ascsuuccAfaCfGfGfaagaagaagL96		asCfsuucAfucUfuUuccUfuGfgaugusgg		CCACUUCCAAAGGGAAGAUGAAGG	
AD-1633429	csusucaAfgGfGfAfagaagaagguL96		asCfscuuCfaUfCfuuccCfuUfagaugusug		CACUUCCAAAGGGAAGAUGAAGGG	
AD-1633431	uscscaagGfGfAfAfGfaagaaggguL96		asGfscceUfuCfAfucuuCfcCfuuggasasg		CUUCCAAAGGGAAGAUGAAGGGCU	
AD-1633440	asgsaugaAfgGfGfCfuuuccuuguL96		asCfsaggGfaGfAfagccCfuUfcauucusuc		GAAGAUGAAGGGCUUCUCCCUGC	
AD-1633464	gsgsacaaCfaCfAfccuacuguuL96		asAfscacUfgAfGfguacUfgUfuguccasac		GUGGACAAACAGCACCCUCAGUGUC	
AD-1633465	gsascaacAfgCfAfCfcuacugucuL96		asGfsacaCfuGfAfGfgugCfuGfuuugcsca		UGGACAAACAGCACCCUCAGUGUCU	
AD-1633467	csasacagCfaCfUfcaugucuguL96		asCfsagaCfaCfUfagaggUfgCfuuuugsuc		GACAAACAGCACCCUCAGUGUCUGU	
AD-1633474	ascsucaGfuGfUfCfuguuccauuL96		asAfsuggGfaAfCfagacAfcUfaggugsgc		GCACCUACAGUGUCUGUUCUCCCAUG	
AD-1633478	csasguguCfuGfUfUfccaucguuL96		asGfsagcAfuGfGfgaacAfgAfcacugsasg		CUCAGUGUCUGUUCUCCCAUGCUCU	
AD-1633482	gusucguUfcCfCfAfugucucuguL96		asCfsagaGfaGfCfauggGfaAfcagacsasc		GUGUCUGUUCUCCCAUGCUCUCUGG	
AD-1633483	uscsuguuCfcCfAfUfgcucucuguL96		asCfscagAfgAfGfcaugGfgAfacagascsa		UGUCUGUUCUCCCAUGCUCUCUGGC	
AD-1633528	gcascacCfaGfGfAfcacucucuL96		asGfsacaAfuUfUfmcuUfcaGfaumcsasc		GUGACAUCCACGGGAACAACUUCUGC	

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-1633529	ascsauccAfgGfAfCfaacuuucugul96		asCfsgagAfaGfUfufugucCfuGfgaugusca		UGACAUC CAGGACAACUUCUCGG	
AD-1633530	csasuccaGfgAfCfAfaucuuucggul96		asCfscgaGfaAfGfuuugCfcUfpgaugusuc		GACAUC CAGGACAACUUCUCGGU	
AD-1633531	asusccagGfaCfAfAfcuuucggul96		asAfscgAfgAfAfguuGfCfuggaugsu		ACAUC CAGGACAACUUCUCGGUG	
AD-1633532	uscsccaggAfcAfAfCfuuucggugul96		asCfsaccGfaGfAfaguuGfuCfugggasusg		CAUCCAGGACAACUUCUCGGUGA	
AD-1633533	csccsaggGfaAfCfUfuuucggugul96		asUfscacCfGfAfGfaaguUfGfucuggsasu		AUCCAGGACAACUUCUCGGUGAC	
AD-1633534	csasgggacAfaCfUfUfuuucggugul96		asGfsucaCfcGfAfagaagUfuGfuuucuggsca		UCCAGGACAACUUCUCGGUGACU	
AD-1633541	ascsuuucCfGfUfGfuuucggugul96		asCfsacuUfgAfGfuuacCfGfagaagusug		CAACUUCUCGGUGAGACUCAAUGUC	
AD-1633542	csusuuucGfgUfGfAfcucaaagugul96		asGfscacUfuGfAfagucacCfcGfagaaggsusu		AACUUCUCGGUGAGACUCAAUGGCC	
AD-1633551	gsasuccaAfgUfGfCfcuuucacugul96		asCfsaguGfaAfGfggcaCfuUfagugcsasc		GUGACUCAAGUGGCCUUCACUGA	
AD-1633553	csuscaagUfgCfCfCfuuucacugul96		asCfsucaGfuGfAfagggCfaCfuugaggsuc		GACUCAAGUGGCCUUCACUGAGA	
AD-1633587	gscsuugauCfcAfGfCfcuacuaugul96		asCfsauaGfuGfAfggguGfgAfucagesasg		CUGCUGAUCCAGCCUACUUAUGC	
AD-1633624	gsusggagGfgUfCfUfCfuuucacul96		asUfsggaAfaGfUfagagCfcCfuaccscsu		AGGUGGAGGUGUCACUUAUCCAG	
AD-1633633	csuscaacuUfuCfCfAfagcaaacucul96		asGfsaguUfuUfGfucggAfaAfugaggsasc		GUCUCACUUUCCAGCAAAACUCC	
AD-1633642	csasgcaaAfaCfUfCfcucaaucugul96		asCfsaguUfgAfGfggagUfuUfugcuggsa		UCCAGCAAAACUCCUCAAACUGG	
AD-1633643	asgscaaaAfcUfCfCfcucaaucugul96		asCfscagUfuGfAfgggaGfuUfuuugcugsg		CCAGCAAAACUCCUCAAACUGGA	
AD-1633646	asasaacuCfcCfUfCfaacuggaugul96		asCfsaucCfaGfUfufugGfgAfguuuusgsc		GCAAAACUCCUCAAACUGGAUGA	

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	ascsucceUfcAfAfCfuggaugagauL96		asCfsuucAfuCfCfaguuGfaGfgagagusu		AAACUCCCUC AACUGGAUGAAGA	
AD-1633658	csusggauGfaAfGfAfaacuaucueuL96		asGfsagaUfaGfUfuucUfUfcAfuccagusu		AACUGGAUGAAGAAACUAUCUCC	
AD-1633666	ascsugguGfcUfGfCfaggaucuuuL96		asAfsagaUfcCfUfugeaGfcAfecagusu		CAACUGGUGCUGCAAGGAUCUUA	
AD-1633669	gsgsugcuGfcAfAfGfgaucuuuagauL96		asCfsauaAfgAfUfueuGfcAfgeaccsag		CUGGUGCUGCAAGGAUCUUAUGA	
AD-1633670	gsusgeugCfaAfGfGfaucuuuagauL96		asUfscuuAfaGfAfuceuUfgCfagcacsea		UGGUGCUGCAAGGAUCUUAUGAC	
AD-1633671	usgsuugcAfaGfGfAfuuuuagauL96		asGfsucaUfaAfGfaucUfuGfagcasc		GGUGCUGCAAGGAUCUUAUGACC	
AD-1633683	csusuauGfCfUfGfagaccuL96		asCfsaggUfcCfUfgeagGfuCfauaagsasu		AUCUU AUGACCU GCGAGGACCUGC	
AD-1633732	csgsagcuGfaAfCfCfugcaaaaauuL96		asAfsuuUfuGfCfagguUfcAfgeucgsgu		ACCGAGCUGAACCU GCAAAAAUU	
AD-1633733	gsasgcugAfaCfCfUfGcaaaaauuuL96		asAfsauUfuUfGfagguUfuCfagcucsgg		CCGAGCUGAACCU GCAAAAAUUUG	
AD-1633734	asgsuugaAfcCfUfGfcaaaaauuuL96		asCfsauUfuUfUfgeagGfuUfagcucsg		CGAGCUGAACCU GCAAAAAUUUGA	
AD-1633735	gscsuugaCfcUfGfCfaaaaauuuL96		asUfscuuUfuUfUfugeaGfgUfucagcusc		GAGCUGAACCU GCAAAAAUUUGAG	
AD-1633736	csusgaacCfuGfCfAfaaaaauuuL96		asCfsucaAfuUfUfuugcAfgGfuucagcsu		AGCUGAACCU GCAAAAAUUUGAGC	
AD-1633737	usgsaaccUfgCfAfAfaaaugagcuL96		asGfscucAfaUfUfuugCfaGfguuacsgc		GCUGAACCU GCAAAAAUUUGAGCA	
AD-1633743	usgscaaaaAfaUfUfGfagcauagcuL96		asGfsucaUfuGfCfucaUfuUfuugcagsg		CCUGCAAAAAUUUGAGCAUUGACC	
AD-1633745	csasaaaaUfuGfAfGfcaauagaccuL96		asCfsgguCfaUfUfgeucAfaUfuuuugscsa		UGCAAAAAUUUGAGCAUUGACCGC	
AD-1633751	ususgagcAfaUfGfAfccgaucagauL96		asCfsugaUfgCfGfugaUfuGfcauasu		AAUUGAGCAAUUGACCGCAUUCAGG	

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	usgsagcaAfuGfAfCfCgcaucaggulL96		asCfscugAfuGfCfCgugcAfuUfgcucasasu		AUUGAGCAAUGACCGCAUCAGGG	
AD-1633754	asgscaauGfaCfCfGfcaucaggguuL96		asAfseccUfgAfUfgggUfcAfuugcusesa		UGAGCAAUGACCGCAUCAGGGGUG	
AD-1633759	gsasggugCfuGfAfAfCfagcauuuuuL96		asAfsaaaUfgCfUfguucAfgCfaccucscsc		GGGAGGUGCUGAACACAGCAUUUUU	
AD-1633761	ususgagcUfuGfAfAfCfCggaugagguL96		asCfsucaUfcCfGfCfuucAfaGfCfcaasasa		UUUUGAGCUUUGAAGCGGGAUGAGA	
AD-1633795	gsuscuacCfcAfAfCfCfagcuuaacauL96		asUfsguuAfaGfCfCfuguuGfgGfuaagacsuc		GAGUCUACCCAAACAGCUUAACAA	
AD-1633796	uscsuaccCfaAfCfAfCfagcuuaacauL96		asUfsuguUfaAfGfCfuguUfgGfguagacsu		AGUCUACCCAAACAGCUUAACAAAG	
AD-1633797	csusacccAfaCfAfGfCfuaaacaaguL96		asCfsungUfuAfAfCfCfuguUfuGfgguagsasc		GUCUACCCAAACAGCUUAACAAAGC	
AD-1633801	cscsaacaGfcUfuUfAfacaagccugulL96		asCfsagcCfuUfGfuaaGfcUfguuaggsgsu		ACCCAAACAGCUUAACAAAGCCUGA	
AD-1633804	ascsaagcuUfaAfCfAfCfagccugagguL96		asCfscucAfgGfCfuguUfaAfCfCfugusug		CAACAGCUUAACAAAGCCUGAGGU	
AD-1633808	csusuaacAfaGfCfCfugagguuuuL96		asAfsagaCfcUfCfagcUfuGfuaaagcsu		AGCUUAACAAAGCCUGAGGUCUUG	
AD-1633809	ususaacaAfgCfCfUfgagguuuuL96		asCfsaagAfcCfUfCagcCfuUfguuuagsg		GCUUAAACAAAGCCUGAGGUCUUGG	
AD-1633810	usasacaaGfcCfuUfGfagguuuuL96		asCfscaaGfaCfCfucagGfcUfuguuuaasag		CUUAAACAAAGCCUGAGGUCUUGGA	
AD-1633811	asascaagCfcUfGfAfCfagguuuuL96		asUfsecaAfgAfCfcaGfgCfuuguuuisasa		UUAAACAAAGCCUGAGGUCUUGGAG	
AD-1633812	ascsaagcCfuGfAfGfCfagguuuuL96		asCfsuccAfaGfAfCfCfCfagGfgCfuuuuisusa		UAACAAAGCCUGAGGUCUUGGAGG	
AD-1633813	csasagccUfgAfGfGfCfagguuuuL96		asCfscucCfaAfGfCfCfCfagGfgCfuuuuisusu		AACAAGCCUGAGGUCUUGGAGGU	
AD-1633841	asasccgcCfcAfuUfUfCfCfagguuuuL96		asGfscacAfCfAfGfCfCfagGfgCfuuuuisusa		UGAACCGCCCAUUCUUGUUGCU	

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	ascsgccCfaUfUfCfugunugcuuL96		asAfsgeaAfaCfAfggaaUfgGfgcggnusuc		GAACCGCCCAUUCUGUUUGCUG	
AD-1633843	cscsgcccAfuUfCfCfugunugcuuL96		asCfsagcAfaAfcfaggaAfuGfgcggsusu		AACCGCCCAUUCUGUUUGCUGU	
AD-1633844	csgseccaUfuCfCfUfgunugcuuL96		asAfsagcCfaAfcfaggaAfuUfgggcgsgsu		ACCGCCCAUUCUGUUUGCUGUG	
AD-1633848	asusuccuGfuUfUfGfuguguguaugL96		asCfsauaCfaCfaAfgcaAfcAfggaauagsg		CCAUUCCUGUUUGCUGUGUAUGA	
AD-1633850	uscscuguUfuGfCfUfguguaugauL96		asAfsucaUfaCfAfcagcAfaAfcaggasasu		AUUCUGUUUGCUGUGUAUGAUC	
AD-1633857	usgscuguGfuAfuGfaucaaaagcuL96		asCfsgcuUfuGfAfucauAfcAfcagcasasa		UUUGCUGUGUAUGAUCAAAAGCGC	
AD-1633858	gscsugugUfaUfGfAfucaaaagcuL96		asGfscgcUfuUfGfaucaUfaCfagagcsasa		UUGCUGUGUAUGAUCAAAAGCGCC	
AD-1633859	csusugugAfuGfAfucaaaagccuL96		asGfsgcgCfuUfUfgaucAfuAfcacagcsesa		UGCUGUGUAUGAUCAAAAGCGCCA	
AD-1633937	asgsgccaGfcAfgGfCfagauaacaauL96		asUfsuguUfaUfCfugcuGfcUfggcccusuu		AAAGGCCAGCAGCAGAUAAACAAC	
AD-1633940	csgsgacaAfaUfCfAfggauguguuL96		asAfscaAfuCfGfugaUfuUfguuccsgsg		CCCGGACAAAUCAGCGAUGUGUC	
AD-1633941	gsgsacaaAfuCfAfggauguguuL96		asGfsacaCfaUfCfugcuAfuUfuguccsgsg		CCGGACAAAUCAGCGAUGUGUCA	
AD-1633947	csuscccaCfcUfuUfUfucuaaauuL96		asAfsuaaGfaAfgfaaaAfgUfgggaggsac		GUCUCCCACCUUUUCUUAUAUG	
AD-1633948	uscseccacCfuUfuUfUfucuaaauuL96		asCfsauuAfgAfaAfgaaAfgGfugggaggsa		UCUCCCACCUUUUCUUAUAUGA	
AD-1633949	cscscaccUfuUfUfCfucuaaauuL96		asUfscuuUfaGfAfgaaAfaGfuggggsag		CUCCCCACCUUUUCUUAUAUGAG	
AD-1633954	ususuuuuUfcUfaAfuagugugacuL96		asGfsucgAfcUfCfaauaGfaAfgaaasgsg		CCUUUUUCUUAUAUGAGUCGACU	
AD-1633955	ususuuuuCfuAfuUfgagugugacuL96		asAfsugcGfaCfUfcauuAfgAfgaaasag		CUUUUUUCUUAUAUGAGUCGACUU	

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	ususcucUfaAfUfGfagucagacuuL96		asAfsaguCfGfAfCfucauUfaGfaagaasasa		UUUUCUUUAAGAGAGUCGACUUU	
AD-1633958	csusucuaAfufGfAfGfucagcuuL96		asCfsaaaGfuCfGfucAfufUfagaagsasa		UUCUUUUAAGAGAGUCGACUUUGA	
AD-1633959	ususcuaaUfgAfGfUfGfagcuuL96		asUfscaaAfgUfCfGacuCfaUfuagaagsa		UCUUUAAGAGAGUCGACUUUGAG	
AD-1633960	uscsuaauGfaGfUfGfagcuuL96		asCfsucaAfaGfUfGfagUfcAfuuaagasag		CUUCUAAUGAGAGUCGACUUUGAGC	
AD-1633961	csusaauGfUfCfGfagcuuL96		asGfscucAfaAfGfucgaCfuCfauuagsasa		UUCUAAUGAGAGUCGACUUUGAGCU	
AD-1633962	usasaugaGfuCfGfAfcuuuL96		asAfsucuCfaAfAfGfuegAfcUfcauuagsa		UCUAAUGAGAGUCGACUUUGAGCUG	
AD-1633971	gsascuuuGfaGfCfUfgaaagcuL96		asCfsugcUfuUfCfagcUfcAfaagucgsa		UCGACUUUAGAGCUGGAAAGCAGC	
AD-1633977	gsasgcuGfaAfAfGfagccguuL96		asAfsaacGfgCfUfGcuUfCfagcucsasa		UUGAGCUGGAAAGCAGCAGCCGUUUC	
AD-1633978	asgscuggAfaAfGfCfagccguuL96		asGfsaaaCfGfGfCfugcuUfuCfagcucsasa		UGAGCUGGAAAGCAGCAGCCGUUUCU	
AD-1633979	gsasgugaAfaGfCfAfGccguuL96		asAfsaaaAfcGfGfugcUfuUfcagcsusc		GAGCUGGAAAGCAGCAGCCGUUUCUC	
AD-1633980	csusggaaAfgCfAfGfagcuuL96		asGfsagaAfaCfGfugcCfuUfuaccagsesu		AGCUGGAAAGCAGCAGCCGUUUCUCC	
AD-1633982	gsasaaGfCfaGfCfGfuuuL96		asAfsagaGfaAfAfGgCfUfGfuuuacsag		CUGGAAAGCAGCAGCCGUUUCUCCUU	
AD-1633984	asasagcaGfCfGfUfuucuuL96		asCfsaagGfaGfAfaagGfCfGfuuuuncsc		GGAAAGCAGCAGCCGUUUCUCCUUGG	
AD-1633986	asgsagcCfGfUfUfUfuccuuL96		asAfscaaAfgGfAfgaaCfGfGfuccuusu		AAAGCAGCCGUUUCUCCUUGGUC	
AD-1633987	gsasagccGfuUfUfGfuccuuL96		asGfsaccAfaGfGfagaaAfcGfGfuccuusu		AAGCAGCCGUUUCUCCUUGGUCU	
AD-1633988	csasagccUfaUfCfUfGfuuuL96		asAfsaacCfaAfGfGfacaAfaCfagcuuncsc		AGCAGCCGUUUCUCCUUGGUCTA	

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-1633992	csgsuuucUfcCfUfUfgucuaaguuL96		asAfscuuAfgAfCfaagGfaGfaaacgsgsc		GCCGUUUUCUCCUUGGUCUAAAGUG	
AD-1633993	gsusuucUfcCfUfUfgucuaaguuL96		asCfsacuUfaGfAfccaaGfgAfgaacgsgsg		CCGUUUUCUCCUUGGUCUAAAGUGU	
AD-1633994	ususuucUfcCfUfUfgucuaaguuL96		asAfscacUfuAfGfaccAfgGfagaacsgsg		CGUUUCUCCUUGGUCUAAAGUGUG	
AD-1633995	ususeuceUfuGfUfcuaaguguuL96		asCfsacaCfuUfAfGfaccAfaGfagaacsgsc		GUUUUCUCCUUGGUCUAAAGUGUGC	
AD-1633996	usesuccuUfgGfUfcuaaguguuL96		asGfscacAfcUfUfagacCfaAfgagagasa		UUUCUCCUUGGUCUAAAGUGUGCU	
AD-1633998	usesucugGfuCfUfAfaguguguuL96		asCfsagcAfcAfCfuagAfcCfaagagsgsa		UCUCCUUGGUCUAAAGUGUGCUGC	
AD-1634005	usesuaagUfgUfGfCfugcauguuL96		asCfsuccAfuGfCfagcaCfaCfuagagsgsc		GGUCUAAAGUGUGCUGCAUGGAGU	
AD-1634009	asgsugugCfuGfCfAfugaguguuL96		asCfsucaCfuCfCfagcAfgCfacacusa		UAAAGUGUGCUGCAUGGAGUGAGC	
AD-1634018	csasuggaGfuGfAfGfcauguaaguuL96		asCfsuucUfaCfUfGfucAfcUfcaugsgsa		UGCAUGGAGUGAGCAGUAGAAGC	
AD-1634022	gsasuggaGfcAfGfUfagaagccuuL96		asCfsagcCfuUfCfuacuGfcUfcaucsgsa		UGGAGUGAGCAGUAGAAGCCUGC	
AD-1634050	csasaauGfCfCfUfcccaguuuuL96		asCfsaaaCfuGfGfagagUfgCfaauusgsg		CACAAAUGCACCCUCCAGUUUUGC	
AD-1634051	asasaugcAfcCfUfCfcaaguuuuL96		asGfscacAfcUfGfagagGfuGfcauuusgsu		ACAAAUGCACCCUCCAGUUUUGCU	
AD-1634052	asasugcaCfcUfCfCfcaaguuuuL96		asAfsagaAfaCfUfGfagagGfuGfcauuusgsu		CAAAUGCACCCUCCAGUUUUGCUG	
AD-1634053	asusgacCfuCfCfCfaguuuuuuL96		asCfsagcAfaAfCfugggAfgGfugcausuu		AAAUGCACCCUCCAGUUUUGCUGG	
AD-1634054	usgscaceUfcCfCfAfguuuuguuL96		asCfscagCfaAfAfcaugGfaGfugcausuu		AAUGCACCCUCCAGUUUUGCUGGG	
AD-1634059	csuseccaGfuUfUfGfuggguuuuL96		asUfsaaaCfcCfAfGcaaAfcUfGfagagsgsu		ACCUCCAGUUUUGCUGGGUUUAU	

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	cscscaguUfuGfCfUfggguuuuuuL96		asAfsauaAfaCfCfcagcAfaAfcugggsasg		CUCCCAGUUUGCUGGGUUUAUUU	
AD-1634062	cscsaguuUfgCfUfggguuuuuuL96		asAfsauaAfaAfcfcagcCfaAfaucggsa		UCCCAGUUUGCUGGGUUUAUUU	
AD-1634063	csasguuuGfcUfGfGfguuuuuuL96		asAfsaaaUfaAfaAfccecaGfcAfaucggsa		CCCAGUUUGCUGGGUUUAUUUUA	
AD-1634064	asgsuuugCfuGfGfGfuuuuuuuL96		asUfsaaaAfuAfaAfacecAfgCfaaacusgs		CCAGUUUGCUGGGUUUAUUUUAG	
AD-1634065	gsusuuugCfuGfGfGfuuuuuuuL96		asCfsuaaAfaUfaAaccCfaGfaaacusg		CAGUUUGCUGGGUUUAUUUUAGA	
AD-1634066	ususugcuGfgGfUfUfauuuuuuL96		asUfseuaAfaAfuAfaaacCfcAfgcaaacsu		AGUUUGCUGGGUUUAUUUUAGAG	
AD-1634067	ususgcugGfgUfUfUfauuuuuuL96		asCfsucuAfaAfaAfuuaaCfcCfagcaasac		GUUUGCUGGGUUUAUUUUAGAGA	
AD-1634068	usgsuugGfuUfUfAfuuuuuuuL96		asUfseucUfaAfaAfauaaAfcCfcagcasasa		UUUGCUGGGUUUAUUUUAGAGAA	
AD-1634071	gsugsuuuAfuUfUfUfagagauguuL96		asCfscauUfcUfCfuuaaAfuAfaaccsasg		CUGGGUUUAUUUUAGAGAAUGGG	
AD-1634072	gsugsaggCfaAfaAfaaccaguuuuL96		asAfsacaCfuGfGfuucUfGfCfuecccsa		UGGGGAGGCAAGAACCACAGUGUU	
AD-1634073	gsugsaggCfaAfaAfaaccaguuuuL96		asAfsaacAfcUfGfGfuucUfuGfCfueccsc		GGGGAGGCAAGAACCACAGUGUUUA	
AD-1634075	asgsucaaGfaAfcCfaguguuuuL96		asCfsuaaAfcAfcfugguUfcUfugcuscsc		GGAGGCAAGAACCACAGUGUUUAGC	
AD-1634076	gsgscaagAfaCfCfAfguguuuuL96		asGfseuaAfaCfAfcuggUfuCfuugcuscsc		GAGGCAAGAACCACAGUGUUUAGCG	
AD-1634088	usgsuuuaGfcGfCfGfgacuuuuL96		asCfsaguAfgUfCfcgcGfcUfaaacascu		AGUGUUUAAGCGCGGACUACUGU	
AD-1634100	gsascuacUfgUfUfCfcaaaaagaauL96		asUfsucuUfuUfUfggaaCfaGfuaugcsc		GGGACUACUGUUUCCAAAAAGAAU	
AD-1634104	ascsnuguCfcAfaAfaagaauuuL96		asGfsгааUfuCfUfuuuuGfgAfacagusasg		CUACUGUUUCCAAAAAGAAUUCCA	

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-1634105	csusguucCfaAfAfAfaaauccauL96		asUfsggaAfuUfCfuuuUfGfGfaacagsusa		UACUGUUUCCAAAAAGAAUUUCCAA	
AD-1634111	csasaaaaGfaAfUfUfcaacccgacuL96		asGfsucGfuUfGfgaauUfcUfuuuugsgsa		UCCAAAAAGAAUUUCCAAACCGACC	
AD-1634123	ascscgacCfaGfCfUfuguuugugauL96		asUfscacAfaAfCfaagcUfgGfucggusug		CAACCGACCAAGCUUGUUUGUGAA	
AD-1634131	asasagugUfuCfCfCfuuuucaaguL96		asAfseuGfaAfAfagggAfaCfaacuususu		AAAAAGUGUUCUUUUUCCAAGUU	
AD-1634133	asgsuguuCfcCfUfUfuaaagugauL96		asCfsaacUfuGfAfaaagGfgAfaacususu		AAAGUGUUCUUUUUCCAAGUUGA	
AD-1634134	gsusguucCfcUfUfUfuaaagugauL96		asUfseaaCfuUfGffaaaGfgGfaacacusu		AAGUGUUCUUUUUCCAAGUUGAG	
AD-1634135	usgsuuccCfuUfUfUfcaagugagauL96		asCfsucaAfcUfUfUfgaaaAfgGfgaacacsu		AGUGUUCUUUUUCCAAGUUGAGA	
AD-1634136	gsusueccUfuUfUfCfaagugagauL96		asUfseucAfaCfUfUfgaaAfaGfggaacsasc		GUGUUCUUUUUCCAAGUUGAGAA	
AD-1634146	csasaguuGfaGfaAfcaaaaauugauL96		asCfsaaUfuUfUfUfguucUfcAfaauugsasa		UUCAAGUUGAGAACAAAAAUUGG	
AD-1634147	asasguugAfgAfAfCfaaaaauugauL96		asCfscaaUfuUfUfUfguuCfuCfaacuugsasa		UCAAGUUGAGAACAAAAAUUGGG	
AD-1634148	gsusugagAfaCfaAfaaaugggauL96		asAfseccAfaUfUfUfuugUfuCfuaacususu		AAGUUGAGAACAAAAAUUGGGUU	
AD-1634149	usugagaAfcAfAfAfaaauugggauL96		asAfsaccCfaAfUfuuuuGfuUfueucaacsu		AGUUGAGAACAAAAAUUGGGUUU	
AD-1634150	usgsagaaCfaAfAfAfaauggguuuL96		asAfsaacCfcAfAfuuuUfGfUfueucasasc		GUUGAGAACAAAAAUUGGGUUUU	
AD-1634151	gsasgaacAfaAfAfAfauggguuuuL96		asAfsaaaCfcCfAfauuuUfuGfueucsa		UUUGAGAACAAAAAUUGGGUUUUA	
AD-1634152	asgsaacaAfaAfAfUfuggguuuuL96		asUfsaaaAfcCfcfaauUfuUfugueucsa		UGAGAACAAAAAUUGGGUUUUA	
AD-1634153	gsasacaaAfaAfUfUfuggguuuuauL96		asUfsuaaAfaCfCfaauUfuUfugueucsc		GAGAACAAAAAUUGGGUUUUAAA	

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-1634163	gsusauacAfuUfUfUfugcauugccuL96		asGfsgcaAfuGfCfaaaaAfuGfuauacsusu		AAGUAUACAUUUUUUGCAUUGCCU	
AD-1634165	asusacauUfuUfUfGfcauugccuL96		asAfsaggCfaAfuUfgcaAfaAfuauasac		GUAUACAUUUUUUGCAUUGCCUUC	
AD-1634168	csasuuuuUfgCfAfuUfugccuugcuL96		asCfscgaAfgGfCfaaagCfaAfaaugsusa		UACAUUUUUUGCAUUGCCUUCGGU	
AD-1634169	asusuuuuGfcAfuUfUfgccuugcuL96		asAfscegAfaGfGfcauGfcAfaaausgsu		ACAUUUUUUGCAUUGCCUUCGGU	
AD-1634170	ususuuugCfaUfUfGfcccugcuL96		asAfsaccGfaAfgGcaUfgCfaaaausug		CAUUUUUGCAUUGCCUUCGGU	
AD-1634171	ususuuugCfaUfUfGfcccugcuL96		asAfsaacCfcaAfgGcaAfuGfcaaaaasasu		AUUUUUGCAUUGCCUUCGGU	
AD-1634172	ususugcaUfuGfCfCfuucgguuL96		asCfsaaaCfcaAfgGcaAfuUfgcaaaaasasa		UUUUUGCAUUGCCUUCGGU	
AD-1634173	ususgcauUfgCfCfuucgguuL96		asAfscaaAfcCfGfaaggCfaAfuGcaasasa		UUUUUGCAUUGCCUUCGGU	
AD-1634174	usgscauuGfcCfuUfUfggguuL96		asUfsacaAfaCfCfgaagGfcAfaugcasasa		UUUGCAUUGCCUUCGGU	
AD-1634175	gsccsaugCfcUfuUfCfGguuL96		asAfsuacAfaAfcCfGgaGfgCfaaugsasa		UUGCAUUGCCUUCGGU	
AD-1634176	csasuuugCfuUfCfGfuuuL96		asAfsauaCfaAfaCfGgaAfgGfcaaugscsa		UGCAUUGCCUUCGGU	
AD-1634177	asusugccUfuCfGfGfuuuL96		asAfsauaAfcAfaCfGgaAfgGfcaaugsc		GCAUUGCCUUCGGU	
AD-1634178	ususgcuUfcGfGfuuuL96		asUfsaaaUfaCfaCfaaccGfaAfggcaasug		CAUUGCCUUCGGU	
AD-1634179	usgsccuuCfGfUfuUfuguaauL96		asCfsuaaAfuAfaCfaaacCfGfagccasasu		AUUGCCUUCGGU	
AD-1634180	gsccsuucGfgUfuUfUfguaauL96		asAfsuuaAfaUfaCfaaaaCfcGfaaggcsasa		UUGCCUUCGGU	
AD-1634181	cscsuucGfuUfuUfGfuuuL96		asCfsacuAfaUfaCfaaaaAfcCfagaggcsa		UGCCUUCGGU	

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	csusucggUfuUfGfUfaunuauguguuL96		asAfscaUfaAfAfiacaAfaCfcgaagsgsc		GCCUUCGGUUUUGUAUUUAGUGUC	
AD-1634186	gsgsuuugUfaUfUfUfagugucuuuuL96		asCfsaagAfcAfCfuaaaUfaCfaaacsgsa		UCGGUUUUGUAUUUAGUGUCUUGA	
AD-1634190	usgsuaauUfaGfUfGfucuuugaauuuL96		asCfsauUfaAfGfiacacUfaAfaauacasasa		UUUGUAUUUAGUGUCUUGAAGUUG	
AD-1634192	usasuuuuGfuGfUfCfuuugaauuuuuL96		asUfsacaUfuCfAfagacAfcUfaaauascsa		UGUAUUUAGUGUCUUGAAGUUA	
AD-1634194	ususuauguGfuCfUfUfugaauuuuuuuL96		asCfsuuUfaUfUfcaagAfcAfcuaaasusa		UAUUUAGUGUCUUGAAGUUAAGA	
AD-1634200	gsusecuugAfaUfGfUfaagaauuuuuL96		asCfsaugUfuCfUfuaaUfuCfaagacsasc		GUGUCUUGAAGUUAAGAACAUAGA	
AD-1634209	gsusaagaAfcAfUfGfaccuccuguuL96		asCfsagGfaGfGfucacUfuUfcuuacsasu		AUGUAAGAACAUAGACCUCUCCGUGU	
AD-1634210	usasagaCfaUfGfAfccuccuguuuuL96		asAfscaGfgAfGfguaUfgUfucuuascsa		UGUAAGAACAUAGACCUCUCCGUGUA	
AD-1634211	asasgaacAfuGfAfCfcuccuguuuuL96		asUfsacaCfGfGfAfggncAfuGfuuuuasasc		GUAAAGAACAUAGACCUCUCCGUGUAG	
AD-1634212	asgsaacaUfgAfcCfuccuguuuuuuL96		asCfsuacAfcGfGfagguCfaUfguuuusu		UAAGAACAUAGACCUCUCCGUGUAGU	
AD-1634213	gsasacauGfaCfCfUfcccuguuuuuuL96		asAfsuaCfaCfGfagggUfcAfuuguuucsusu		AAGAACAUAGACCUCUCCGUGUAGUG	
AD-1634214	asascaugAfcCfUfCfcccuguuuuuuL96		asCfsacuAfcAfcGfgagGfuCfauguuucsusu		AGAACAUAGACCUCUCCGUGUAGUGU	
AD-1634215	ascsaugaCfcUfCfCfCfuguuuuuuuuL96		asAfscaUfaCfAfccgaGfgUfcauguuusc		GAACAUAGACCUCUCCGUGUAGUGUC	
AD-1634218	usgsaccuCfcGfUfGfuaugucuuuuL96		asCfsagaCfaCfUfacacGfgAfguacasu		CAUGACCUCUCCGUGUAGUGUCUGU	
AD-1634224	cscsguguAfgUfGfUfCfuguaauuuuuL96		asGfsuaUfaCfAfagacaCfuAfcacggsasg		CUCCGUGUAGUGUCUUGUAUUAACC	
AD-1634225	csgsguaGfuGfUfCfuguaauuuuuL96		asGfsuaUfaCfAfagacaCfuAfcacggsasa		UCCGUGUAGUGUCUUGUAUUAACCU	

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	gsusguagUfgUfcUfUfguaauaccuuL96		asAfsnguAfuUfAfcagaCfaCfuacacsgsg		CCGUGUAGUGUCUGUAAUACCUU	
AD-1634227	usgsuaguGfuCfuUfGfuauaccuuuL96		asAfsaggUfaUfUfacagAfcAfcuacasesg		CGUGUAGUGUCUGUAAUACCUUA	
AD-1634230	asgsugucUfgUfAfAfuaccuaguuuL96		asAfsucaAfgGfUfaunaCfaGfacacuasac		GUAGUGUCUGUAAUACCUUAGUU	
AD-1634231	gsusguenGfuAfAfUfaccuaguuuL96		asAfsacuAfaGfGfuuuAfcAfgcacacsua		UAGUGUCUGUAAUACCUUAGUUU	
AD-1634232	usgsucugUfaAfUfAfccuaguuuuL96		asAfsaacUfaAfGfguuUfaCfagacacsesu		AGUGUCUGUAAUACCUUAGUUUU	
AD-1634233	gsuscuguAfaUfAfCfcuaguuuuuL96		asAfsaaaCfuAfAffgguUfuAfcagacacasc		GUGUCUGUAAUACCUUAGUUUUU	
AD-1634234	ususucaCfaGfAfUfgcuugugauuL96		asAfsucaCfaAfGfcaucUfgUfggaasasa		UUUUUCCACAGAUAGCUUGUGUGAUU	
AD-1634238	csasagaUfgCfUfUfugugauuuuuuL96		asAfsaaaAfuCfAfcaagCfaUfcugugsgsa		UCCACAGAUAGCUUGUGAUUUUUUG	
AD-1634239	ascsagauGfcUfUfGfugauuuuuuL96		asCfsaaaAfaUfCfacaGfAfucugusgsg		CCACAGAUAGCUUGUGAUUUUUUGA	
AD-1634240	csasgaugCfuUfGfUfugauuuuuuL96		asUfscaaAfaAfUfcacaAfgCfaucugusug		CACAGAUAGCUUGUGAUUUUUUGAA	
AD-1634241	asgsauagCfuUfUfGfauuuuuuL96		asUfsucaAfaAfAfucacAfaGfcaucugsu		ACAGAUAGCUUGUGAUUUUUUGAAC	
AD-1634242	gsasugcuUfgUfGfAfuuuuuuL96		asGfsuucAfaAfAfaucaCfaAfgcaucsuug		CAGAUGCUUGUGAUUUUUUGAACA	
AD-1634248	usgsugauUfuUfUfGfacaauacguL96		asCfsignaUfuGfUfucaaAfaAfuacacasang		CUUGUGAUUUUUUGAACAAUACGU	
AD-1634249	gsusgaauUfuUfGfAfacaauacguuL96		asAfsnguAfuUfGfuucaAfaAfaucacasa		UUGUGAUUUUUUGAACAAUACGUG	
AD-1634250	usgsaauuUfuGfAfAfaauacguuL96		asCfsacgUfaUfUfguucAfaAfaucacasa		UGUGAUUUUUUGAACAAUACGUGA	
AD-1634251	gsasuuuuUfAfAfAfCfaauacguuL96		asUfscacGfuAfUfuguuCfaAfaaauacsasc		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		asUfsucaCfGfUfAfuuGUfCfAfaaauscsa		UGAUUUUUUGAACAAUACGUGAGAA	
AD-1634257	usgsaacaAfuAfCfGfugaagaugauL96		asCfsuacUfuUfCfGfaguAfuUfGfuucaasasa		UUUGAACAAAUACGUGAGAAUGAUGC	
AD-1634273	gsasugcaAfgCfAfCfcgaauuuuL96		asGfsaaaUfuCfAfGgugCfuUfGcaucsusu		AAGAUGCAAGCACCCUGAGAAUUUCU	
AD-1634274	asusgcaaGfcAfCfCfugaauuuuL96		asAfsaaaAfuUfCfGfaguGfcUfGcausesu		AGAUGCAAGCACCCUGAGAAUUUCUG	
AD-1634275	usgsaagCfaCfCfUfGfauuuuL96		asCfsagaAfaUfUfCfaggUfGfuuGcasusc		GAUGCAAGCACCCUGAGAAUUUCUGU	
AD-1634276	gsesaagCfcCfUfGfauuuuL96		asAfsaagAfaUfUfCfGfGfGfGfuuGcasu		AUGCAAGCACCCUGAGAAUUUCUGUU	
AD-1634277	csasagcaCfcUfGfAfauuuL96		asAfsacaGfaAfAfuucaGfGfGfuuGcsa		UGCAAGCACCCUGAGAAUUUCUGUUU	
AD-1634278	asasgcacCfuGfAfAfuuuuL96		asAfsaacAfgAfAfaucAfgGfGfuuGsgc		GCAAGCACCCUGAGAAUUUCUGUUUG	
AD-1634279	asgsaaceUfgAfAfUfuuuL96		asCfsaaaCfaGfAfaauCfaGfGfuuGcsu		CAAGCACCCUGAGAAUUUCUGUUUGA	
AD-1634280	gsasaccuGfaAfUfUfuuuL96		asUfscacAfcAfGfagaUfCfAfggugcsusu		AAGCACCCUGAGAAUUUCUGUUUGAA	
AD-1634281	csasaccuGfaAfUfUfuuuL96		asUfscacAfaCfAfgaaaUfuCfaggugcsu		AGCACCCUGAGAAUUUCUGUUUGAAU	
AD-1634282	ascsacugAfuUfUfCfuuuL96		asAfsuacAfaAfCfGfagaUfUfCfaggugsc		GCACCUGAGAAUUUCUGUUUGAUG	
AD-1634283	csasugaaUfuUfCfUfuuuL96		asCfsauuCfaAfAfcagaAfaUfucaggugsc		CACCUGAGAAUUUCUGUUUGAUGC	
AD-1634285	usgsaauUfcUfGfUfuuuL96		asCfsagaUfuCfAfaaGfaAfaauGcsug		CCUGAGAAUUUCUGUUUGAUGCGG	
AD-1634286	gsasauuuCfuGfUfUfuuuL96		asCfscgcAfuUfCfGfagaUfUfAfaauGcsu		CUGAGAAUUUCUGUUUGAUGCGGA	
AD-1634287	asasuuuUfgUfUfUfuuuL96		asUfscgcCfaUfUfCfGfagaUfUfAfaauGcsu		UGAGAAUUUCUGUUUGAUGCGGAA	

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	ususgaauGfcGfGfAfaceaagcuuL96		asAfsgeuAfuGfGfuuccGfcAfuuaasasc		GUUUGAAUGCGGAACCAUAGCUG	
AD-1634297	usgsaaugCfGfGfAfaceaagcugul96		asCfsagaUfaUfGfguucCfGfCfaucasasa		UUUGAAUGCGGAACCAUAGCUGG	
AD-1634298	gsasaugcGfGfAfaceaagcugul96		asCfscagCfuAfuUfgguuCfGfCfaucasasa		UUUGAAUGCGGAACCAUAGCUGGU	
AD-1634303	csgsaaacCfaUfAfaceaagcuuL96		asAfsauaAfcCfAfaceaUfGfGfuuccgsesa		UGCGGAACCAUAGCUGGUUAUUU	
AD-1634304	ggsaaaccAfuAfaceaagcuuL96		asAfsauaAfaCfCfagcuAfuGfguuccsgsc		GCGGAACCAUAGCUGGUUAUUUC	
AD-1634305	gsasaccaUfaGfCfUfgguuauuuL96		asGfsaaaUfaAfaceaUfaUfgguuccsg		CGGAACCAUAGCUGGUUAUUUCU	
AD-1634306	asasccauAfgCfUfgguuauuuL96		asAfsaaaAfuAfaceaCfuAfuGfguuccsc		GGAACCAUAGCUGGUUAUUUCUC	
AD-1634307	ascscuaaGfcUfGfGfuuaauuuL96		asGfsagaAfaUfAfaceaGfcUfaugguusc		GAACCAUAGCUGGUUAUUUCUCC	
AD-1634308	cscsaugCfuGfGfUfuuaauuuL96		asGfsagaAfaUfAfaceaAfgCfuuauggsusu		AACCAUAGCUGGUUAUUUCUCCCC	
AD-1634309	csasuagcUfGfUfUfaauuuL96		asGfsagaGfaAfaAfaceaCfaGfcauuggsu		ACCAUAGCUGGUUAUUUCUCCCCU	
AD-1634314	csusgguuAfuUfUfCfuccuugugul96		asCfsacaAfgGfGfagaAfaAfaceaagcsu		AGCUGGUUAUUUCUCCCCUUGUGU	
AD-1634315	usgsuuuaUfuUfCfUfuccuugugul96		asAfsacaAfaGfGfagaAfaUfaaccagsc		GCUGGUUAUUUCUCCCCUUGUGUU	
AD-1634316	gsgsuuauUfuCfUfCfuccuugugul96		asAfsacaCfaAfgfggagAfaAfaaaccsag		CUGGUUAUUUCUCCCCUUGUGUUA	
AD-1634318	ususauuuCfuCfCfCfuuguguaugul96		asCfsuaaCfaCfAfaceaAfgAfaaauascsc		GGUUAUUUCUCCCCUUGUGUUAAGU	
AD-1634319	usasuuuueUfcCfCfUfuguguaugul96		asAfsuaaAfcAfaceaGfGfagaAfaaauasc		GUUAUUUCUCCCCUUGUGUUAAGUA	
AD-1634320	asusuuuueCfcCfUfUfguguaugul96		asUfsacuAfaCfAfaceaGfGfagaAfaaauasc		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	usuuuucCfcUfUfGfuuuaguuauL96		asUfsuacUfaAfCfaacGfgGfagaasusa		UAUUUCUCCCUUGUGUUAGUAAU	
AD-1634325	uscscuuGfuGfUfUfaguuauaaauL96		asUfsuuaUfuAfCfuacAfCfagggsasa		UCUCCCUUGUGUUAGUAAUAAAC	
AD-1634326	cscscuugUfgUfUfAfguuauaaauL96		asGfsuuuAfuUfAfcuaaCfaCfaagggsasg		CUCCCUUGUGUUAGUAAUAAACG	
AD-1634327	cscsuuugUfuUfAfGfuuaaauaacguL96		asCfsguuUfaUfUfaeuafCfcaagggsa		UCCCUUGUGUUAGUAAUAAACGU	
AD-1634328	csusugUfuUfAfGfUfaaauaacguL96		asAfscguUfuUfUfuacuAfaCfacaaggsg		CCCUUGUGUUAGUAAUAAACGUC	
AD-1634329	usuuugUfuUfAfGfUfaaauaacguL96		asGfsacgUfuUfAfuacuUfaAfcaasgsg		CCUUGUGUUAGUAAUAAACGUCU	
AD-1634330	usgsuugUfGfUfAfAfuuaaacguL96		asAfsagGfuUfUfauuafCfaCfaacasag		CUUGUGUUAGUAAUAAACGUCUU	
AD-1634331	gsusguuaGfuAfAfUfaaacguuuL96		asAfsagaCfGfUfUfuuuafCfUfaacacsasa		UUUGUGUUAGUAAUAAACGUCUUG	
AD-1634332	usgsuuagUfaUfUfAfaacguuuL96		asCfsaagAfcGfUfuuauUfaCfuuaacsasa		UGUGUUAGUAAUAAACGUCUUGC	
AD-1634333	gsusuaguAfaUfAfAfaacguuuL96		asGfscuaGfaCfGfuuaUfuUfuaacsasc		GUGUUAGUAAUAAACGUCUUGCC	
AD-1634334	usuuagUfaUfUfAfaacguuuL96		asGfsgcaAfgAfCfguuuAfuUfauaacsasa		UGUUAGUAAUAAACGUCUUGCCA	
AD-1634342	asasacguCfuUfGfCfcaauuaaagL96		asCfsuuaUfuUfUfggcaAfgAfCguuuasau		AUAAACGUCUUGCCACAAUAAAGC	
AD-1634343	asasegucUfuGfCfCfaaauaaagL96		asGfscuuAfuUfGfuggcAfaGfaguuusasa		UAAACGUCUUGCCACAAUAAAGCC	
AD-1634344	ascsgucUfgCfCfcaauuaaagL96		asGfsgcuUfaUfUfguggCfaAfgacgususu		AAACGUCUUGCCACAAUAAAGCCU	
AD-68585	asgsuuugaGfaAfCfAfaaaauugguL96		asCfsecaAfuUfUfuuuuUfcaacuusug		CAAGUUGAGAACAAAAAUUGGGU	

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	AAGGAUGGUGGCCCUACAGGCUCA		84-106
AD-1657994	CCUGAGGGCCACCAUCCUCUU		88-108	AAGAGGAUGGUGGCCCUACAGGCUCU		86-108
AD-1657998	AGGGCCACCAUCCUCUGCCUU		92-112	AAGGCAGAGGATGGUGGCCCUCA		90-112
AD-1658030	GUGACCGGGUGUACAUAACAU		138-158	AGUGTATGUACACCCGGUACACCU		136-158
AD-1658032	CUUCCACCUCGUGCAUCCACAU		160-180	ATGUGGAUGACGAGGUGGAAAGGG		158-180
AD-1658033	UUCCACCUCGUGCAUCCACAAU		161-181	ATUGTGGAUGACGAGGUGGAAGG		159-181
AD-1658034	UCCACCUCGUGCAUCCACAAU		162-182	AAUUGUGGAUGACGAGGUGGAAG		160-182
AD-1658035	CCACCUCGUGCAUCCACAAUGU		163-183	ACAUTGTGGAUGACGAGGUGGAA		161-183
AD-1658036	CACCUCGUGCAUCCACAAUGAU		164-184	ATCATUGUGGATGACGAGGUGGA		162-184
AD-1658037	ACCUCGUGCAUCCACAAUGAGU		165-185	ACUCAUTGUGGAUGACGAGGUGG		163-185
AD-1658038	CCUCGUGCAUCCACAAUGAGAU		166-186	ATCUCATUGUGGAUGACGAGGUG		164-186
AD-1658039	CUCGUGCAUCCACAAUGAGAGU		167-187	ACUCTCAUUGUGGAUGACGAGGU		165-187
AD-1658040	UCGUGCAUCCACAAUGAGAGUU		168-188	AACUCUCAUUGTGGAUGACGAGG		166-188
AD-1658041	CGUGCAUCCACAAUGAGAGUAU		169-189	ATACTCTCAUUGUGGAUGACGAG		167-189

AD-1658042	GUCAUCCACAAUGAGAGUACU	170-190	AGUACUCUCAUTGUGGAUGACGA	168-190
AD-1658043	UCAUCCACAAUGAGAGUACCU	171-191	AGGUACTCUCATUGUGGAUGACG	169-191
AD-1658044	CAUCCACAAUGAGAGUACCUU	172-192	AAGGTACUCUCAUUGUGGAUGAC	170-192
AD-1658045	AUCCACAAUGAGAGUACCUUGU	173-193	ACAGGUACUCUCAUUGUGGAUGA	171-193
AD-1658046	UCCACAAUGAGAGUACCUUGU	174-194	AACAGGTACUCTCAUUGUGGAUG	172-194
AD-1658047	CCACAAUGAGAGUACCUUGUGU	175-195	ACACAGGUACUCUCAUUGUGGAU	173-195
AD-1658048	CACAAUGAGAGUACCUUGUGAU	176-196	ATCACAGGUACTCUCAUUGUGGA	174-196
AD-1658049	ACAAUGAGAGUACCUUGUGAGU	177-197	ACUCACAGGUACUCUCAUUGUGG	175-197
AD-1658050	CAAUGAGAGUACCUUGUGAGCU	178-198	AGCUCACAGGUACUCUCAUUGUG	176-198
AD-1658051	AAUGAGAGUACCUUGUGAGCAU	179-199	ATGCTCACAGGTACUCUCAUUGU	177-199
AD-1658052	AUGAGAGUACCUUGUGAGCAGU	180-200	ACUGCUCACAGGUACUCUCAUUG	178-200
AD-1658053	UGAGAGUACCUUGUGAGCAGCU	181-201	AGCUGCTCACAGGUACUCUCAU	179-201
AD-1658054	GAGAGUACCUUGUGAGCAGCUU	182-202	AAGCTGCUCACAGGUACUCUCAU	180-202
AD-1658055	AGAGUACCUUGUGAGCAGCUGU	183-203	ACAGCUGCUCACAGGUACUCUCA	181-203
AD-1658056	GAGUACCUUGUGAGCAGCUGGU	184-204	ACCAGCTGCUCACAGGUACUCUC	182-204
AD-1658057	AGUACCUUGUGAGCAGCUGGCU	185-205	AGCCAGCUGCUCACAGGUACUCU	183-205
AD-1658058	GUACCUUGUGAGCAGCUGGCAU	186-206	ATGCCAGCUGCTCACAGGUACUC	184-206

AD-1658059	UACCUGUGAGCAGCUGGGCAAU	187-207	ATUGCCAGCUCACAGGUACU	185-207
AD-1658184	AAUGGUCGGGAUGCUGGGCCAU	352-372	ATGGCCAGCAUCCCCGACCAUUGC	350-372
AD-1658185	AUGGUCGGGAUGCUGGGCCAAU	353-373	ATUGGCCAGCATCCCCGACCAUUG	351-373
AD-1658186	UGGUCGGGAUGCUGGGCCAAU	354-374	AGUUGGCCAGCAUCCCCGACCAUU	352-374
AD-1658187	GGUCGGGAUGCUGGGCCAAU	355-375	AAGUTGGCCAGCAUCCCCGACCAU	353-375
AD-1658188	GUCCGGGAUGCUGGGCCAAU	356-376	AAAGTUGGCCAGCAUCCCCGACCA	354-376
AD-1658189	UCGGGAUGCUGGGCCAAU	357-377	AGAAUTGGCCAGCAUCCCCGACCC	355-377
AD-1658190	CGGGAUGCUGGGCCAAU	358-378	AAGAAGTUGGCCAGCAUCCCCGAC	356-378
AD-1658191	GGGAUGCUGGGCCAAU	359-379	AAAGAAGUUGGCCAGCAUCCCCGA	357-379
AD-1658192	GGAUGCUGGGCCAAU	360-380	ACAAAGAAGUUGGCCAGCAUCCCCG	358-380
AD-1658193	GAUGCUGGGCCAAU	361-381	ACCAAAGAAGUUGGCCAGCAUCCCC	359-381
AD-1658196	GCUGGCCAAUUCUUGGGCUU	364-384	AAGCCCAAGAAAGUUGGCCAGCAU	362-384
AD-1658197	CUGGCCAAUUCUUGGGCUU	365-385	AAAGCCCAAGAAAGUUGGCCAGCA	363-385
AD-1658200	GCCAAUUCUUGGGCUU	368-388	ACGGAAAGCCCAAGAAAGUUGGCCA	366-388
AD-1658201	CCAAUUCUUGGGCUU	369-389	AACGGAAGCCCAAGAAAGUUGGCC	367-389
AD-1658202	CAACUUCUUGGGCUU	370-390	ATACGGAAAGCCCAAGAAAGUUGGC	368-390
AD-1658203	AACUUCUUGGGCUU	371-391	AAUACGGAAAGCCCAAGAAAGUUGG	369-391

AD-1658204	ACUUCUUGGGCUUCCGUUAU	372-392	ATAUACGGGAAGCCCAAGAAGUUG	370-392
AD-1658205	CUUCUUGGGCUUCCGUUAU	373-393	AAUATACGGGAAGCCCAAGAAGUU	371-393
AD-1658206	UUCUUGGGCUUCCGUUAU	374-394	ATAUAUACGGGAAGCCCAAGAAGU	372-394
AD-1658207	UCUUGGGCUUCCGUUAU	375-395	AAUATATACGGGAAGCCCAAGAAG	373-395
AD-1658208	CUUGGGCUUCCGUUAU	376-396	ACAUUAUACGGGAAGCCCAAGAA	374-396
AD-1658209	UUGGGCUUCCGUUAU	377-397	ACCATATAUACGGGAAGCCCAAGA	375-397
AD-1658210	UGGGCUUCCGUUAU	378-398	AGCCAUUAUACGGGAAGCCCAAG	376-398
AD-1658211	GGGCUUCCGUUAU	379-399	ATGCCATAUAUACGGGAAGCCCAA	377-399
AD-1658212	GGCUUCCGUUAU	380-400	AAUGCCAUAUATACGGGAAGCCCA	378-400
AD-1658213	GCUUCCGUUAU	381-401	ACAUGCCAUUAUACGGGAAGCCCC	379-401
AD-1658220	UAUAUAUGGCAUGCACAGUGU	388-408	ACACTGTGCAUGGCCAUUAUACG	386-408
AD-1658221	AUAUAUGGCAUGCACAGUGAU	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	UGGCAUGCACAGUGAGCUAU	394-414	AAUAGCTCACUGUGCAUGGCCAU	392-414

AD-1658227	GGCAUGCACAGUGAGCUAUGU		395-415	ACAUAGCUCACUGCAUGCCAU		393-415
AD-1658228	GCAUGCACAGUGAGCUAUGGU		396-416	ACCATAGCUCACUGUGCAUGCCA		394-416
AD-1658242	UGGCACCCUGGCCUCUCUCUU		460-480	AAGAGAGAGGCCAGGGUGCCAAA		458-480
AD-1658243	GGCACCCUGGCCUCUCUCUAU		461-481	ATAGAGAGAGGCCAGGGUGCCAA		459-481
AD-1658288	GACAGGCUACAGGCAAUCCUU		506-526	AAGGAUTGCCUGUAGCCUGUCAG		504-526
AD-1658289	ACAGGCUACAGGCAAUCCUGU		507-527	ACAGGATUGCCTGUAGCCUGUCA		505-527
AD-1658313	UUCUUUGGAAGGACAAGAAACU		531-551	AGUUCUTGUCCCTUCCAAGGAACA		529-551
AD-1658315	CCUUGGAAAGGACAAGAACUGU		533-553	ACAGTUCUUGUCCUCCAAAGGAA		531-553
AD-1658316	CUUGGAAAGGACAAGAACUGCU		534-554	AGCAGUTCUUGTCCUUCCAAAGGA		532-554
AD-1658448	CACCUGAAGCAGGCCGUUUUGUU		692-712	AACAAACGGCUGCUUUCAGGUGCA		690-712
AD-1658451	CUGAAGCAGCCGUUUUGUGCAU		695-715	ATGCACAAACGGCUGCUUCAGGU		693-715
AD-1658463	UUUGUGCAGGGCCUGGCUCUU		707-727	AAGAGCCAGGGCCUUGCACAAACG		705-727
AD-1658464	UUUGCAGGGCCUGGCUCUCU		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	ACUGTGAAAGUCCAGAGAGCGUGG		746-768

AD-1658485	CGCUCUCUGGACUUCACAGAU		749-769	ATCUGUGAAGUCCAGAGAGCGUG		747-769
AD-1658519	CUGAGAAAGAUUGACAGGUUCU		783-803	AGAACCTGUCAAUCUUCUCAGCA		781-803
AD-1658520	UGAGAAAGAUUGACAGGUUCAU		784-804	ATGAACCCUGUCAAUUCUUCAGC		782-804
AD-1658521	GAGAAAGAUUGACAGGUUCAUU		785-805	AAUGAACCCUGUCAAUUCUUCAG		783-805
AD-1658522	AGAAGAUUGACAGGUUCAUGU		786-806	ACAUGAACCCUGTCAAUCUUCUCA		784-806
AD-1658523	GAAGAUUGACAGGUUCAUGCU		787-807	AGCATGAACCCUGUCAAUUCUUC		785-807
AD-1658524	AAGAUUGACAGGUUCAUGCAU		788-808	ATGCAUGAACCTGUCAAUUCUUCU		786-808
AD-1658525	AGAUUGACAGGUUCAUGCAGU		789-809	ACUGCATGAACCCUGUCAAUUCUUC		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
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AD-1658531	ACAGGUUCAUGCAGGCGUGUGU		795-815	ACACAGCCUGCAUGAACCCUGUCA		793-815
AD-1658535	GUUCAUGCAGGCGUGUGACAGU		799-819	ACUGTCACAGCCUGCAUGAACCCU		797-819
AD-1658539	AUGCAGGCGUGUGACAGGAGU		803-823	ACAUCCTGUCACAGCCUGCAUGA		801-823
AD-1658541	GCAGGCGUGUGACAGGAGUUGAU		805-825	ATCCAUCCUGUCACAGCCUGCAU		803-825

AD-1658542	CAGGCUGUGACAGGAUGGAAU	806-826	ATUCCATCCUGTCACAGCCUGCA	804-826
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AD-1658650	GAGUUCUGGGUGGACAAACAGU	935-955	ACUGTUGUCCACCCAGAACUCCU	933-955
AD-1658661	GGACAACAGCACCCUCAGUGUU	946-966	AACACUGAGGUGCUGUUGUCCAC	944-966
AD-1658662	GACAACAGCACCCUCAGUGUCU	947-967	AGACACTGAGGTGCUGUUUGUCCA	945-967
AD-1658663	ACAACAGCACCCUCAGUGUCUU	948-968	AAGACACUGAGGUGCUGUUGUCC	946-968
AD-1658664	CAACAGCACCCUCAGUGUCUGU	949-969	ACAGACACUGAGGUGCUGUUGUC	947-969
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AD-1658802	UGCCUCUGACCCUGGACAAAGGU	1087-1107	ACCUTGTCCAGGUCAGAGGGCAUA	1085-1107
AD-1658818	AAGGUGGAGGGUCUCACUUUU	1103-1123	AAAAGUGAGACCCUCCACCCUUGU	1101-1123
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AD-1658820	GGUGGAGGGUCUCACUUUUCCU	1105-1125	AGGAAAGUGAGACCCUCCACCCUU	1103-1125
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AD-1658824	GAGGGUCUCACUUUUCCAGCAU	1109-1129	ATGCTGGAAAGTGAGACCCUCCA	1107-1129
AD-1658825	AGGGUCUCACUUUUCCAGCAAU	1110-1130	ATUGCUGGAAAGUGAGACCCUCC	1108-1130
AD-1658826	GGGUCUCACUUUUCCAGCAAU	1111-1131	ATUUGCTGGAAAGUGAGACCCUC	1109-1131

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AD-1658832	CACUUUCCAGCAAAACUCCCU	1117-1137	AGGGAGTUUUGCUGGAAAGUGAG	1115-1137
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AD-1658929	CGAGCUGAACCUUGCAAAAAUU	1261-1281	AAUUTUTGCAGGUUCAGCUCGGU	1259-1281
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AD-1659284	UUGCUGGGUUUAUUUUAGAGU	1731-1751	ACUCTAAAAUAAACCCAGCAAAAC	1729-1751
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AD-1659287	CUGGGUUUAUUUUAGAGAAUU	1734-1754	AAUUCUCUAAAAUAAACCCAGCA	1732-1754
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AD-1659289	GGGUUUUAUUUUAGAGAAUGGU	1736-1756	ACCATUCUCUAAAAUAAACCCAG	1734-1756
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AD-1659292	GGCAAGAACCCAGUGUUUAU	1765-1785	AGCUAAACACUGGUUUCUUGCCUC	1763-1785
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AD-1659322	UGUUCACAAAAAGAAUUCCAAU	1795-1815	ATUGGAAUUCUTUUUGGAACAGU	1793-1815
AD-1659323	GUUCCAAAAAGAAUUCCAACU	1796-1816	AGUUGGAAUUCTUUUUGGAACAG	1794-1816
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AD-1659326	CCAAAAAGAAUUCCAACCGAU	1799-1819	ATCGGUTGGAATUCUUUUUGGAA	1797-1819
AD-1659327	CAAAAAGAAUUCCAACCGACU	1800-1820	AGUCGGTUGGAAUUCUUUUUGGA	1798-1820
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AD-1659331	AAGAAUUCCAACCGACCAU	1804-1824	AGCUGGTCGGUTGGAUUCUUUU	1802-1824
AD-1659332	AGAAUUCCAACCGACCAU	1805-1825	AAGCTGGUCGGTUGGAAUUCUUU	1803-1825
AD-1659333	GAAUUCCAACCGACCAU	1806-1826	AAAGCUGGUCGGUUGGAAUUCUU	1804-1826

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AD-1659351	UUGUUUGUGAAACAAAU	1824-1844	ACUUTUTUGUUTCACAACAAGC	1822-1844

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AD-1659372	GUUCCCCUUUUUCAAGUUGAGAU	1845-1865	ATCUCACUUGAAAAAGGGAACAC	1843-1865
AD-1659373	UUCCCCUUUUUCAAGUUGAGAAU	1846-1866	ATUCTAACUUGAAAAAGGGAACA	1844-1866
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AD-1659386	UUGAGAACAAAAAUUGGGUUU	1859-1879	AAACCCAAUUUTUGUUUCUCAACU	1857-1879
AD-1659387	UGAGAACAAAAAUUGGGUUUU	1860-1880	AAAAACCCAAUUTUUGUUCUCAAC	1858-1880
AD-1659388	GAGAACAAAAAUUGGGUUUUU	1861-1881	AAAAACCCAAUUTUUUGUUCUCAAA	1859-1881
AD-1659389	AGAACAAAAAUUGGGUUUUUAU	1862-1882	ATAAAACCCCAATUUUUUGUUCUCA	1860-1882
AD-1659390	GAACAAAAAUUGGGUUUUUAAU	1863-1883	ATUAAAAACCCCAAUUUUUUGUUCUC	1861-1883
AD-1659391	AACAAAAAUUGGGUUUUUAAAU	1864-1884	ATUUAAAAACCCCAAUUUUUUGUUCU	1862-1884
AD-1659399	AGUAUACAUUUUUGCAUUGCU	1889-1909	AGCAAUGCAAAAAAUUGUAUACUUU	1887-1909
AD-1659400	GUUAUACAUUUUUGCAUUGCCU	1890-1910	AGGCAATGCAAAAAAUUGUAUACUU	1888-1910
AD-1659401	UAUAUACAUUUUUGCAUUGCCUU	1891-1911	AAGGCAUUGCAAAAAAUUGUAUACU	1889-1911
AD-1659402	AUAUAUUUUUGCAUUGCCUUU	1892-1912	AAAGGCAUUGCAAAAAAUUGUAUAC	1890-1912

AD-1659405	CAUUUUUGCAUUGCCUUCGGU	1895-1915	ACCGAAGGCAATGCAAAAAUGUA	1893-1915
AD-1659406	AUUUUUGCAUUGCCUUCGGUU	1896-1916	AACCGAAGGCAAUUGCAAAAAUGU	1894-1916
AD-1659407	UUUUUGCAUUGCCUUCGGUUU	1897-1917	AAACCGAAGGCAAUUGCAAAAAUG	1895-1917
AD-1659408	UUUUUGCAUUGCCUUCGGUUUU	1898-1918	AAACCGAAGGCAAUUGCAAAAAU	1896-1918
AD-1659409	UUUGCAUUGCCUUCGGUUUUUGU	1899-1919	ACAAACCGAAGGCAAUUGCAAAAA	1897-1919
AD-1659410	UUGCAUUGCCUUCGGUUUUUGUU	1900-1920	AACAAACCGAAGGCAAUUGCAAAA	1898-1920
AD-1659411	UGCAUUGCCUUCGGUUUUUGU	1901-1921	ATACAAACCGAAGGCAAUUGCAAA	1899-1921
AD-1659412	GCAUUGCCUUCGGUUUUUGUAUU	1902-1922	AAUACAAACCGAAGGCAAUUGCAA	1900-1922
AD-1659413	CAUUGCCUUCGGUUUUUGUAUUU	1903-1923	AAAUACAAACCGAAGGCAAUUGCA	1901-1923
AD-1659414	AUUGCCUUCGGUUUUUGUAUUUU	1904-1924	AAAATACAAACCGAAGGCAAUUGC	1902-1924
AD-1659415	UUGCCUUCGGUUUUUGUAUUUU	1905-1925	ATAAAUACAAACCGAAGGCAAUUG	1903-1925
AD-1659416	UGCCUUCGGUUUUUGUAUUUAGU	1906-1926	ACUAAATACAAACCGAAGGCAAU	1904-1926
AD-1659417	GCCUUCGGUUUUUGUAUUUAGUU	1907-1927	AACUAAAUACAAACCGAAGGCAA	1905-1927
AD-1659418	CCUUCGGUUUUUGUAUUUAGUGU	1908-1928	ACACTAAAUACAAACCGAAGGCA	1906-1928
AD-1659419	CUUCGGUUUUUGUAUUUAGUGUU	1909-1929	AACACUAAAUACAAACCGAAGGC	1907-1929
AD-1659420	UUCGGUUUUUGUAUUUAGUGUCU	1910-1930	AGACACTAAAUACAAACCGAAGG	1908-1930
AD-1659421	UCGGUUUUUGUAUUUAGUGUCUU	1911-1931	AAGACACUAAATACAAACCGAAG	1909-1931

AD-1659422	CGGUUUUGUAUUUAGUGUCUUU	1912-1932	AAAGACACUAAAAUACAAACCGAA	1910-1932
AD-1659423	GGUUUGUAUUUAGUGUCUUUGU	1913-1933	ACAAAGACACUAAAAUACAAACCGA	1911-1933
AD-1659424	GUUUGUAUUUAGUGUCUUUGAU	1914-1934	ATCAAGACACUAAAAUACAAACCG	1912-1934
AD-1659425	UUUGUAUUUAGUGUCUUUGAAU	1915-1935	ATUCAAGACACTAAAUACAAACC	1913-1935
AD-1659426	UUGUAUUUAGUGUCUUUGAAUU	1916-1936	AAUUCAAGACACUAAAAUACAAAC	1914-1936
AD-1659427	UGUAUUUAGUGUCUUUGAAUGU	1917-1937	ACAUTCAAGACACUAAAAUACAAA	1915-1937
AD-1659428	GUUUUUAGUGUCUUUGAAUGUU	1918-1938	AACATUCAAGACACUAAAAUACAA	1916-1938
AD-1659429	UAUUUAGUGUCUUUGAAUGUUAU	1919-1939	ATACAUTCAAGACACUAAAAUACA	1917-1939
AD-1659430	AUUUAGUGUCUUUGAAUGUAAU	1920-1940	ATUACATUCAAGACACUAAAAUAC	1918-1940
AD-1659431	UUUAGUGUCUUUGAAUGUAAAGU	1921-1941	ACUUACAUUUCAAGACACUAAAAUA	1919-1941
AD-1659432	UUAGUGUCUUUGAAUGUAAAGAU	1922-1942	ATCUTACAUUUCAAGACACUAAAAU	1920-1942
AD-1659433	UAGUGUCUUUGAAUGUAAAGAAU	1923-1943	ATUCTUACAUUUCAAGACACUAAAA	1921-1943
AD-1659434	AGUGUCUUUGAAUGUAAAGAACU	1924-1944	AGUUCUTACAUTCAAGACACUAA	1922-1944
AD-1659436	UGUCUUUGAAUGUAAAGAACAUU	1926-1946	AAUGTUCUUACAUUUCAAGACACU	1924-1946
AD-1659437	GUCUUUGAAUGUAAAGAACAUUGU	1927-1947	ACAUGUTCUUACAUUUCAAGACAC	1925-1947
AD-1659440	UUGAAUGUAAAGAACAUUGACCU	1930-1950	AGGUCATGUUCTUACAUAUUCAGA	1928-1950
AD-1659446	GUAAGAACAUUGACCUCCGUGU	1936-1956	ACACGGAGGUCAUGUUCUUAUACAU	1934-1956

AD-1659447	UAAGAAACAUGACCUCGUGUU	1937-1957	AACACGGAGGUCAUGUUCUACA	1935-1957
AD-1659448	AAGAAACAUGACCUCGUGUAU	1938-1958	ATACACGGAGGTCAUGUUCUUAAC	1936-1958
AD-1659449	AGAAACAUGACCUCGUGUAGU	1939-1959	ACUACACGGAGGUCAUGUUCUUA	1937-1959
AD-1659450	GAACAUGACCUCGUGUAGUU	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	CUUAGUUUUUUUCCACAGAU	1971-1991	ACAUCUGUGGAAAAAACUAAAGGU	1969-1991
AD-1659482	UUAGUUUUUUUCCACAGAU	1972-1992	AGCATCTGUGGAAAAAACUAAAGG	1970-1992
AD-1659483	UAGUUUUUUUCCACAGAU	1973-1993	AAGCAUCUGUGGAAAAAACUAAAG	1971-1993
AD-1659484	AGUUUUUUUCCACAGAU	1974-1994	AAAGCATCUGUGGAAAAAACUAA	1972-1994
AD-1659485	GUUUUUUUUCCACAGAU	1975-1995	ACAAAGCAUCUGTGGAACUAAACUA	1973-1995
AD-1659487	UUUUUUUCCACAGAU	1977-1997	ACACAAGCAUCTGUGGAAAAAAC	1975-1997
AD-1659488	UUUUUUUCCACAGAU	1978-1998	ATCACAAAGCAUCUGUGGAAAAAAC	1976-1998
AD-1659489	UUUUUUUCCACAGAU	1979-1999	AAUCACAAGCATCUGUGGAAAAAAC	1977-1999
AD-1659490	UUUUUUUCCACAGAU	1980-2000	AAAUCACAAGCAUCUGUGGAAAAAAC	1978-2000

AD-1659491	UCCACAGAGCUUGUGAUUUU	1981-2001	AAAAATCACAAGCAUCUGUGGAAA	1979-2001
AD-1659492	CCACAGAGCUUGUGAUUUUU	1982-2002	AAAAUACAAGCAUCUGUGGAA	1980-2002
AD-1659493	CACAGAGCUUGUGAUUUUUU	1983-2003	AAAAATCACAAGCAUCUGUGGA	1981-2003
AD-1659537	ACCUGAAUUUCUGUUUGAAUU	2027-2047	AAUUCAAACAGAAAUUUCAGGUGC	2025-2047
AD-1659538	CCUGAAUUUCUGUUUGAAUGU	2028-2048	ACAUTCAAACAGAAAUUUCAGGUG	2026-2048
AD-1659559	GGAACCAUAGCUGGUUAUUUU	2049-2069	AAAAATAACCAGCUAUGGUUCCGC	2047-2069
AD-1659560	GAACCAUAGCUGGUUAUUUCU	2050-2070	AGAAAUAAACCAGCUAUGGUUCCG	2048-2070
AD-1659561	AACCAUAGCUGGUUAUUUCUU	2051-2071	AAGAAATAACCAGCUAUGGUUCC	2049-2071
AD-1659562	ACCAUAGCUGGUUAUUUCUCU	2052-2072	AGAGAAAUAAACCAGCUAUGGUUCC	2050-2072
AD-1659563	CCAUAGCUGGUUAUUUCUCCU	2053-2073	AGGAGAAAUAAACCAGCUAUGGUUU	2051-2073
AD-1659582	CCUUGUGUUAGUAAUAAACGU	2072-2092	ACGUTUAUUUACTAACACAAAGGGA	2070-2092
AD-1659583	CUUGUGUUAGUAAUAAACGUU	2073-2093	AACGTUTAUUACUAAACACAAAGGG	2071-2093
AD-1659584	UUGUGUUAGUAAUAAACGUCU	2074-2094	AGACGUTUAUUUACUAAACACAAGG	2072-2094
AD-1659585	UGUGUUAGUAAUAAACGUCUU	2075-2095	AAGACGTUUAUTACUAAACACAAG	2073-2095
AD-1659586	GUGUUAGUAAUAAACGUCUUU	2076-2096	AAAGACGUUUATUACUAAACACAA	2074-2096
AD-1659587	UGUUAGUAAUAAACGUCUUUGU	2077-2097	ACAAAGACGUUUUUAUUAACUAAACACA	2075-2097
AD-1659588	GUUAGUAAUAAACGUCUUUGCU	2078-2098	AGCAAAGACGUUTAUUAACUAAACAC	2076-2098

AD-1321384	UCUCCACCUUUUCUUCUAAU	1609-1629	ATUAGAAGAAAAGUGGGAGACU	1607-1629
AD-1321390	CCUCAAUGGAUGAAGAAACU	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		asdAsggdAudGguggdCcCfcuagguccsa		UGAGCCUGAGGGCCACCAUCCUC	
AD-1657994	cscsugagggCfCfAfcaccauccuL96		asdAsggdGgdAuggudGgCfcuacaggsesu		AGCCUGAGGGCCACCAUCCUCUG	
AD-1657998	asgsggccacCfAfUfccucugccuL96		asdAsggdCadGaggadTgGfuggccuuccsa		UGAGGGCCACCAUCCUCUGCCUC	
AD-1658030	gsusgaccggGfUfGfhuacauacacL96		asdGsgudTadTguacdAcCfcgguccacscsu		AGGUGACCGGGGUGUACAUACACC	
AD-1658032	csusuccaccUfCfGfuccauctcauL96		asdTsgudGgdAugacdGaGfugggaggsagg		CCCUUCCACCCUCUGUCAUCCACAA	
AD-1658033	ususcaccuGfGfUfcauccacaauL96		asdTsgudTgdGaugadCcGfaggggaggsagg		CCUUCACCCUCUGUCAUCCACAAU	
AD-1658034	uscseaccuGfUfCfauccacaauuL96		asdAsuudGudGgaugdAcGfaggggaggsagg		CUUCCACCCUCUGUCAUCCACAAUG	
AD-1658035	cscsaccucgUfCfAfuccacaauL96		asdCsaudTgdTggudGaCfaggggaggsasa		UUCCACCCUCUGUCAUCCACAAUGA	
AD-1658036	csasccuuguCfAfUfccacaugauL96		asdTscadTudGuggadTgAfaggggaggsasa		UCCACCCUCUGUCAUCCACAAUGAG	
AD-1658037	ascscucgucAfUfCfcauauagauL96		asdCsudAudTggugdAuGfagggaggsagg		CCACCCUCUGUCAUCCACAAUGAGA	
AD-1658038	cscsugcucaUfCfCfacaugagauL96		asdTscudCadTugudGaUfagggaggsagg		CACCUCUGUCAUCCACAAUGAGAG	
AD-1658039	csuscgucauCfCfAfcuauagagauL96		asdCsudTcdAuugudGgAfugagggaggsagg		ACCUCUGUCAUCCACAAUGAGAGU	

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	uscsuaucaucCfAfCfaugagagaguuL96		asdAscudCudCaauudTgGfauagacgsg		CCUCGUCAUCCACAAUGAGAGUA	
AD-1658041	csuaucaucAfCfAfaugagaguuL96		asdTsacdTcdTcauudGuGfauagacgsg		CUCGUCAUCCACAAUGAGAGUAC	
AD-1658042	gsuaucaucCfAfAfugagaguuL96		asdGsuadCudCucudTgUfggagacgsg		UCGUCAUCCACAAUGAGAGUACC	
AD-1658043	usaucaucAfAfUfgagaguuL96		asdGsgudAcdTcuadTuGfauagacgsg		CGUCAUCCACAAUGAGAGUACCU	
AD-1658044	csaucaucAfUfGfagaguuL96		asdAsggdTadCucudAuUfggagacgsg		GUCAUCCACAAUGAGAGUACCUG	
AD-1658045	asuscaucaUfGfAfagaguuL96		asdCsagdTadCucudCaUfugagacgsg		UCAUCCACAAUGAGAGUACCUGU	
AD-1658046	uscaucaUfGfAfagaguuL96		asdAscagdTadCucudTcAfugagacgsg		CAUCCACAAUGAGAGUACCUGUG	
AD-1658047	cscaucaUfGfAfagaguuL96		asdCsacdAgdTcuadCuCfauagacgsg		AUCCACAAUGAGAGUACCUGUGA	
AD-1658048	cscaucaUfGfAfagaguuL96		asdTsacdCadGguadTcUfauagacgsg		UCCACAAUGAGAGUACCUGUGAG	
AD-1658049	ascaucaUfGfAfagaguuL96		asdCsacdAcdTcuadCuCfauagacgsg		CCACAAUGAGAGUACCUGUGAGC	
AD-1658050	csaucaucaUfGfAfagaguuL96		asdGscudCadCagudAcUfauagacgsg		CACAAUGAGAGUACCUGUGAGCA	
AD-1658051	asaucaucaUfGfAfagaguuL96		asdTsacdTcdAcagdTcCfauagacgsg		ACAAUGAGAGUACCUGUGAGCAG	
AD-1658052	asusgagagUfCfCfugagaguuL96		asdCsugdTadCacagdTcUfauagacgsg		CAAUGAGAGUACCUGUGAGCAGC	
AD-1658053	usgagagUfCfCfugagaguuL96		asdGscudGcdTcadGgUfauagacgsg		AAUGAGAGUACCUGUGAGCAGCU	
AD-1658054	gsasgagUfCfCfugagaguuL96		asdAsgdTgdTcuadAgGfauagacgsg		AUGAGAGUACCUGUGAGCAGCUG	
AD-1658055	asgsagUfCfCfugagaguuL96		asdCsagdTadCacagdTcUfauagacgsg		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		asdCscadGcdTgcudAcAfgguacuusc		GAGAGUACCUUGUGAGCAGCUGGC	
AD-1658057	asgsuaccugUfGfAfcagcugguL96		asdGscadAgdCugudCaCfagguacuusc		AGAGUACCUUGUGAGCAGCUGGCA	
AD-1658058	gsusaccugUfGfAfcagcugguL96		asdTsgcdCadGcugcdTcAfcagguacuusc		GAGUACCUUGUGAGCAGCUGGCAA	
AD-1658059	usasecuugAfGfCfagcuggeaL96		asdTsuagdCcdAgeugdCuCfagcagguascu		AGUACCUUGUGAGCAGCUGGCAAA	
AD-1658184	asasugguugGfGfAfcagcuggeaL96		asdTsggdCcdAgeaudCcCfagcagguasc		GCAAUGGUGCGGGAUGCUGGCGCAA	
AD-1658185	asusugguugGfAfuGfagcuggeaL96		asdTsuagdGcdCagcadTcCfagcagguasc		CAAUGGUGCGGGAUGCUGGCGCAAC	
AD-1658186	usgsugguugGfAfuGfagcuggeaL96		asdGsuudGgdCcagcdAuCfagcagguasc		AAUGGUGCGGGAUGCUGGCGCAACU	
AD-1658187	gsusugguugUfGfCfagcuggeaL96		asdAsgadTgdGccagdCaUfagcagguasc		AUGGUGCGGGAUGCUGGCGCAACUU	
AD-1658188	gsusugguugGfCfuGfagcuggeaL96		asdAsagdTudGgagdGcAfuagcagguasc		UGGUGCGGGAUGCUGGCGCAACUUC	
AD-1658189	uscsugguugCfUfGfagcagguL96		asdGsaadGudTggagdAgCfagcagguasc		GGUCCGGAUGCUGGCGCAACUUCU	
AD-1658190	csusugguugUfGfGfagcagguL96		asdAsgadAgdTugagdCaGfagcagguasc		GUCGGGAUGCUGGCGCAACUUCUU	
AD-1658191	gsusugguugGfGfCfagcagguL96		asdAsagdAadGunggdCcAfcagcagguasc		UCGGGAUGCUGGCGCAACUUCUUG	
AD-1658192	gsusugguugGfCfCfagcagguL96		asdCsaadGadAgunggdGcCfagcagguasc		CGGGAUGCUGGCGCAACUUCUUGG	
AD-1658193	gsasugguugCfCfAfcagcugguL96		asdCscadAgdAagundGgCfagcagguasc		GGGAUGCUGGCGCAACUUCUUGGG	
AD-1658196	gsusugguugAfcfUfagcugguL96		asdAsgadCcdAagaadGuUfagcagguasc		AUGCUGGCGCAACUUCUUGGGCUU	
AD-1658197	csusugguugCfUfUfagcugguL96		asdAsagdCcdCaagadAgUfagcagguasc		UGCUGGCGCAACUUCUUGGGCUUC	

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	gscscaacuuCfUfUfgggcuuccguL96		asdCsggdAadGeccadAgAfagnuugcscsa		UGGCCAACUUCUUGGGCUUCCGU	
AD-1658201	cscaaacuuUfUfGfggcuuccguL96		asdAsgcdGadAgcccdAaGfaaguuugscsc		GGCCAAACUUCUUGGGCUUCCGU A	
AD-1658202	csasacuuUfGfGfGcuuccguauL96		asdTsacdGgdAagcdCaAfgaaguugsgsc		GCCAAACUUCUUGGGCUUCCGU AU	
AD-1658203	asascuuUfGfGfGcuuccguauL96		asdAsuadCgdGagcdCcAfagaaguusgsg		CCAAACUUCUUGGGCUUCCGU AUA	
AD-1658204	ascsuuUfGfGfGcuuccguauL96		asdTsaudAcgGagcdCcCfaagaagugsg		CAACUUCUUGGGCUUCCGU AU AU	
AD-1658205	csusuuUfGfGfGcuuccguauL96		asdAsuadTadCggaadGcCfcaagaagsu		AACUUCUUGGGCUUCCGU AUAUA	
AD-1658206	usuuUfGfGfGcuuccguauL96		asdTsaudAudAcggadAgCfccaagaagsu		ACUUCUUGGGCUUCCGU AU AU AU	
AD-1658207	usuuUfGfGfGcuuccguauL96		asdAsuadTadTaeaggdAaGfccaagaasag		CUUCUUGGGCUUCCGU AU AU AUG	
AD-1658208	csuuUfGfGfGcuuccguauL96		asdCsaudAudAuacgdGaAfccccagaasasa		UUCUUGGGCUUCCGU AU AU AUGG	
AD-1658209	usuuUfGfGfGcuuccguauL96		asdCsaudTadTaeaggdGfAfgccccagaasga		UCUUGGGCUUCCGU AU AU AUGGC	
AD-1658210	usuuUfGfGfGcuuccguauL96		asdGscgdAudAuauadCgGfaagccccasag		CUUGGGCUUCCGU AU AU AUGGCA	
AD-1658211	gsguUfGfGfGcuuccguauL96		asdTsacdCadTaaudAcGfgaagccccasa		UUGGGCUUCCGU AU AU AUGGCAU	
AD-1658212	gsguUfGfGfGcuuccguauL96		asdAsuadCcdAuauadTaCfagaagccccsa		UGGGCUUCCGU AU AU AUGGCAUG	
AD-1658213	gscsuuUfGfGfGcuuccguauL96		asdCsaudGcdCauaudAuAfcgaagccsc		GGGCUUCCGU AU AU AUGGCAUGC	
AD-1658220	usuuUfGfGfGcuuccguauL96		asdCsaudTgdTgaudGcCfaauauascs		CGUAUAU AUGGCAUGCACAGUA	
AD-1658221	asuuUfGfGfGcuuccguauL96		asdTsaudCudGagcdTaCfaauauascs		GUAUAUAUUGGCAUGCACAGUAG	

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	usasuauggcAfUfGfcacagugaguuL96		asdCsucdAcdTgugcdAuGfccaauasusa		UAUAUAUGGCAUGCACAGAGAGC	
AD-1658223	asuauggcAUFfGfCfacagugaguuL96		asdGseudCadCuugudCaUfgecauauasasu		AUAUAUGGCAUGCACAGAGAGCU	
AD-1658224	usasugggcauGfCfAfcagugaguuL96		asdAsgcdTcdAcugudGcAfugecauauasusa		UAUAUGGCAUGCACAGAGAGCUA	
AD-1658225	asusggcangCfAfCfagugaguuL96		asdTtsagdCudCaeugdTGcfaugcauauasasu		AUAUGGCAUGCACAGAGAGCUAU	
AD-1658226	usggcangcAfCfAfcagugaguuL96		asdAsuadGcdTcaudGuGfcaugcauauasusa		UAUGGCAUGCACAGAGAGCUAUG	
AD-1658227	gsgcangcaCfAfGfugaguuL96		asdCsaudAgdCucacdTGfugecauauasasu		AUGGCAUGCACAGAGAGCUAUGG	
AD-1658228	gsgcangcacAfGfUfugaguuL96		asdCscadTadGcucadCuGfugecauauasasu		UGGCAUGCACAGAGAGCUAUGGG	
AD-1658242	usggcaccUfGfGfcuucuuL96		asdAsgadGadGaggcdCaGfugguagcaasasa		UUUGGCACCCUGGCCUCUCUCUA	
AD-1658243	gsgcaccuGfGfCfcuucuuL96		asdTtsagdAgdAgagudCcAfugguagcaasasa		UUGGCACCCUGGCCUCUCUCUAU	
AD-1658288	gsacagagcuAfCfAfcgaauccuuL96		asdAsgcdAudTgcuudGuAfgecuagcaasg		CUGACAGGCUACAGGCAAUCCUG	
AD-1658289	ascagagcuAfGfGfcauuccuuL96		asdCsagdGadTugcdTGfugecuagcaasasa		UGACAGGCUACAGGCAAUCCUGG	
AD-1658313	ususcuuugAfAfGfcaagaacuuL96		asdGsuudCudTgucudTuCfcaaggaasasa		UGUCCUUUGGAAGGACAAGAACU	
AD-1658315	cscsuuggaGfGfAfcagaagaacuuL96		asdCsagdTudCuugudCcUfuecaaggaasasa		UUGCCUUGGAAGGACAAGAACUGC	
AD-1658316	csusuggaagGfAfCfaagaacuuL96		asdGscadGudTcuugdTeCfucaaggaasasa		UCCUUGGAAGGACAAGAACUGCA	
AD-1658448	csaccuugaGfCfAfgecuuuuuL96		asdAscadAadCggcuudGcUfuecaaggaasasa		UGACCCUGAAGCAGCCGUUUUGUG	
AD-1658451	csusgaagcaGfCfCfuuuuuuL96		asdTsgcdAcdAaagcdGcUfuecaaggaasasa		ACCUGAAGCAGCCGUUUUGUGCAG	

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-1658463	ususugugcaGfGfGfcuggcucuuL96		asdAsgadGcdCaggcdCeUfgcacaascsg		CGUUUUGCAGGGCCUGGCUCUC	
AD-1658464	ususugugcagGfGfGfcuggcucuuL96		asdGrsagdAgdCaggcdCeCfugcacaasasc		GUUUUGCAGGGCCUGGCUCUCU	
AD-1658465	usgsugcaggGfCfCfuggcucuuL96		asdAsgadGadGccagdgGcCfugcacasasa		UUUUGCAGGGCCUGGCUCUCUA	
AD-1658466	gsusgcaggGfCfUfggcucueuauL96		asdTsgadAgdAgccadGgCfcccugcacsasa		UUUGCAGGGCCUGGCUCUCUAU	
AD-1658467	usgscaggGcCfUfggcucueuauL96		asdAsuadGadGagcdAgGfcccugcacsasa		UGUGCAGGGCCUGGCUCUCUAUA	
AD-1658484	ascsgeucucUfGfGfGfcacacaguuL96		asdCsuigdTgdAaguedCaGfagagcgusgsg		CCACGCUCUCUGGACUUCACAGA	
AD-1658485	csgseucucUfGfGfGfcacacaguuL96		asdTscudGudGaaugCdCafgagcgcsusg		CACGCUCUCUGGACUUCACAGAA	
AD-1658519	csusgagaagAfUfUfgacagguuuL96		asdGsaadCcdTgucadAuCfucucagcsasa		UGCUGAGAAGAUUGACAGGUUCA	
AD-1658520	usgsagaagaUfUfGfGfcagguuuL96		asdTsgadAcCdCuguedAaUfucucucagsgc		GCUGAGAAGAUUGACAGGUUCAU	
AD-1658521	gsasgaagauUfGfGfGfcagguuuL96		asdAsugdAadCcuugdCaAfucucucasag		CUGAGAAGAUUGACAGGUUCAUG	
AD-1658522	asgsaagauUfGfGfGfcagguuuL96		asdCsaudGadAccugdTcAfucucucasasa		UGAGAAGAUUGACAGGUUCAUGC	
AD-1658523	gsasagaauGfAfCfGfGfcagguuuL96		asdGscadTgdAaccudGuCfuaucucusc		GAGAAGAUUGACAGGUUCAUGCA	
AD-1658524	asasgaauGaCfAfGfGfcagguuuL96		asdTsgcdAudGaacedTgUfcaucucusc		AGAAGAUUGACAGGUUCAUGCAG	
AD-1658525	asgsaauGacAfGfGfGfcagguuuL96		asdCsuigdCadTgaacdCuCfuaucucusc		GAAGAUGACAGGUUCAUGCAGG	
AD-1658526	gsasuuGacaGfGfUfGfGfcagguuuL96		asdCseudGcdAugaadCeUfGfcaucucusc		AAGAUGACAGGUUCAUGCAGGC	
AD-1658527	asusugacagGfUfUfGfGfcagguuuL96		asdGscddTgdCaugadAcCfGfcaucucusc		AGAUGACAGGUUCAUGCAGGCU	

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	ususgacaggUfUfCfaugcaggcguL96		asdAsgcdCudGcaugdAaCfugucuaasuc		GAUUGACAGGUUCAUGCAGGCUG	
AD-1658529	usgsacagguUfCfAfu gcaggcguL96		asdCsagcdCedTgeaudGaAfcuugucasau		AUUGACAGGUUCAUGCAGGCUGU	
AD-1658530	gsascaggguCfAfUf gcaggcguL96		asdAscadGcdCugcadTgAfaccugucsasa		UUUGACAGGUUCAUGCAGGCUGUG	
AD-1658531	ascsaggguicAfUfGfcaaggcugguL96		asdCsacdAgdCcugcdAuGfaaccugucsasa		UGACAGGUUCAUGCAGGCUGUGA	
AD-1658535	gsusucaugcAfGfGfcaaggcagguL96		asdCsugdTcdAcagcdCuGfcaugaaacsu		AGGUUCAUGCAGGCUGUGACAGG	
AD-1658539	asusgcaggcUfGfUfcaaggcguL96		asdCsaudCcdTgeaudCaGfcaugcausgsa		UCAUGCAGGCUGUGACAGGAUGG	
AD-1658541	gsesaggcugUfGfAfcaggcguL96		asdTsccdAudCcugudCaCfagcugcsasu		AUGCAGGCUGUGACAGGAUGGAA	
AD-1658542	csasggcguGfAfCfaggcguL96		asdTsacdCadTcugdTcAfcagcugcsasa		UGCAGGCUGUGACAGGAUGGAAG	
AD-1658605	gsesuuucaCfAfCfcaaggcguL96		asdTsaggdAcdGuaggdTgUfugaagcsasa		UGGCUUUAACACACCUACGUCCAC	
AD-1658650	gsasguncugGfGfUf gcacaacagL96		asdCsugdTudGuccadCcCfagaacucscsu		AGGAGUUCUGGGUGGACACACAGC	
AD-1658661	gsasacaacaGfCfAfcuagcguL96		asdAscadCudGagagdGcUfguugucscasc		GUGGACAACAGCACCUACAGUGUC	
AD-1658662	gsascaacagCfAfCfcaaggcguL96		asdGsacdAcdTgaggdTgCfugugucscasa		UGGACAACAGCACCUACAGUGUCU	
AD-1658663	ascsaacagcAfCfCfcaaggcguL96		asdAsgadCadCugagdGuGfcaugugucscsc		GGACAACAGCACCUACAGUGUCUG	
AD-1658664	csasacaagcaCfCfUfcaaggcguL96		asdCsagdTcdAcuagdTgUfcaugugucscsc		GACAACAGCACCUACAGUGUGUCU	
AD-1658665	asascagcacCfUfCfcaaggcguL96		asdAscadGadCacugdAgGfugcugucsgsu		ACAACAGCACCUACAGUGUGUCUU	
AD-1658801	asusgccucUfGfAfcaggcagguL96		asdCsundGudCcaggdTcAfcaggcuaasag		CUAUGCCUCUGACCUUGGACAAGG	

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	usgscucugAfCfCfuggacaagguL96		asdCscudTgdTccagdGuCfagaggcasusa		UAUGCCUCUGACCUUGGACAAAGGU	
AD-1658818	asasggugggaGfGfucucacuuuuL96		asdAsaadGudGagacdCeUfccaccuusgsu		ACAAGGUGGAGGGGUCUCACUUUC	
AD-1658819	asgsugggagGfGfucucacuuuL96		asdGsaadAgdTgagadCeCfuccaccuusg		CAAGGUGGAGGGGUCUCACUUUCC	
AD-1658820	gsusggaggagGfUfCfucacuuuL96		asdGsgadAadGuagadAcCfuccaccuusuu		AAGGUGGAGGGGUCUCACUUUCCA	
AD-1658821	gsusggaggagUfCfucacuuuL96		asdTsggdAadAgugadGaCfuccaccuscu		AGGUGGAGGGGUCUCACUUUCCAG	
AD-1658824	gsasggggucuCfAfCfuuuL96		asdTsgcdTgdGaaagdTgAfagaccuscsa		UGGAGGGGUCUCACUUUCCAGCAA	
AD-1658825	asgsggucucAfCfufuuccagcauL96		asdTsuigdCudGgaadGuGfagaccuscsc		GGAGGGGUCUCACUUUCCAGCAAA	
AD-1658826	gsusgucucAfUfufuuccagcauL96		asdTsuudGcdTggadAgUfagaccuscsc		GAGGGGUCUCACUUUCCAGCAAAA	
AD-1658827	gsusgucucUfUfufcagcaaaL96		asdTsuudTgdCugadAaGfagaccuscsc		AGGGGUCUCACUUUCCAGCAAAAC	
AD-1658828	gsusucacuUfUfCfagcaaaL96		asdGsuudTudGcugdAaAfugagaccuscsc		GGGUCUCACUUUCCAGCAAAACU	
AD-1658829	uscsucacuUfCfCfagcaaaL96		asdAsgudTudTgcugdGaAfagugagascsc		GGUCUCACUUUCCAGCAAAACUC	
AD-1658830	csuscacuuuCfAfCfcaaaL96		asdGsaadTudTugcudGgAfagugagascsc		GUCUCACUUUCCAGCAAAACUCC	
AD-1658831	uscsacuuuCfAfGfcaaaL96		asdGsgadGudTuugdTgGfaaagugaggsa		UCUCACUUUCCAGCAAAACUCCC	
AD-1658832	csascuuuCCAfGfCfaaaL96		asdGsggdAgdTuuugdCuGfgaagugaggsa		CUCACUUUCCAGCAAAACUCCCU	
AD-1658833	ascsuuuCCaGfCfAfaaaL96		asdAsggdGadGuuuudGcUfGgaaguggsa		UCACUUUCCAGCAAAACUCCUC	
AD-1658834	csusuuccagCfAfAfaaL96		asdGsaadGgdAguuudTgCfuggaaguggsa		CACUUUCCAGCAAAACUCCCUCA	

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	usuuuccagcAfAfafuuccuccauL96		asdTsgadGgdGaguudTuGfucggaaasgsu		ACUUUCCAGCAAAAACUCCCUCAA	
AD-1658836	usuccagcaAfAfafuuccuccauL96		asdTsuagdAgdGgaguudTuUfucuggaasag		CUUUUCCAGCAAAAACUCCCUCAAC	
AD-1658837	uscscagcaaAfAfCfuccuccaacuL96		asdGsuudGadGggagdTuUfucugggasasa		UUUCCAGCAAAAACUCCCUCAACU	
AD-1658838	cscsagcaaaaAfCfUfccuccaacuL96		asdAsgudTgdAagggadGuUfuugcuggsasa		UUCCAGCAAAAACUCCCUCAACUG	
AD-1658839	csasgcaaaaCfUfCfccuccaacuL96		asdCsagdTudGagggdAgUfuugcuggsa		UCCAGCAAAAACUCCCUCAACUGG	
AD-1658840	asgseaaaacUfCfCfuccaacuL96		asdCsadGudTgaggdGaGfuuuugcussg		CCAGCAAAAACUCCCUCAACUGGA	
AD-1658841	gscsaaaaacuCfCfCfuccaacuL96		asdTsccdAgdTugagdGgAfguuuugcsusg		CAGCAAAAACUCCCUCAACUGGAU	
AD-1658842	csasaaaaacUfCfUfcaacuL96		asdAsuudCadGuugadGgGfaguuuugscsu		AGCAAAAACUCCCUCAACUGGAUG	
AD-1658843	asasaacuccCfUfCfcaacuL96		asdCsaudCcdAguugdAgGfaguuuuugsc		GCAAAAACUCCCUCAACUGGAUGA	
AD-1658844	asasacuccUfCfAfacuggaugauL96		asdTscadTcdCaguudGaGfaggaguuusug		CAAAAACUCCCUCAACUGGAUGAA	
AD-1658845	asasucccuCfAfAfucuggaugauL96		asdTsuedAudCcagudTgAfaggaguuusuu		AAAACUCCCUCAACUGGAUGAAG	
AD-1658846	ascsucuccUfCfUfuggaugaaagauL96		asdCsnuudCadTccagdTuGfaggaguuusuu		AAACUCCCUCAACUGGAUGAAGA	
AD-1658847	csusccuccAfCfUfuggaugaaagauL96		asdTscudTcdAuccadGuUfaggaguuusuu		AACUCCCUCAACUGGAUGAAGAA	
AD-1658848	uscscuccaaCfUfGfugaugaaagauL96		asdTsuedTudCauccdAgUfugagggasgsu		ACUCCCUCAACUGGAUGAAGAAA	
AD-1658849	cscseucaacUfGfGfugaugaaagauL96		asdTsnuudCudTcaudCaGfuugagggsasg		CUCCCUCAACUGGAUGAAGAAAC	
AD-1658850	csuscaacugGfAfUfugaagaaacuL96		asdAsgudTudCuucadTcCfaguugaggsg		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	asasggaucUfAfUfgaccugcagL96		asdCsugdCadGgucadTaAfgauccuugsc		GCAAGGAUCUUUAUGACCUGCAGG	
AD-1658875	asgsaauuuAfUfgaccugcagL96		asdCsugdGcdAaggucdAuAfgauccuugsc		CAAGGAUCUUUAUGACCUGCAGGA	
AD-1658880	csusuauagacCfUfgfagcaggaccuL96		asdCsagdGudCcuagcdAgGfucuaaaggsasu		AUCUUUAUGACCUGCAGGACCUGC	
AD-1658929	csagsagcugaAfCfCfugcaaaaauuL96		asdAsuudTudTgagcdGuUfagcagcucgsgsu		ACCGAGCUGAACCCUGCAAAAAUU	
AD-1658930	gsasgcugaaCfCfUfgcaaaaauuL96		asdAsauudTudTugcdGgUfucagcucsgsg		CCGAGCUGAACCCUGCAAAAAUUG	
AD-1658931	asgsuagaaCfUfgfcaaaaauuL96		asdCsauudTudTugcdAgGfucagcucsgsg		CGAGCUGAACCCUGCAAAAAUUGA	
AD-1658932	gsesuagaaccUfGfCfaaaaauuL96		asdTscadAudTuuugcdCaGfuuuacgcsuisc		GAGCUGAACCCUGCAAAAAUUGAG	
AD-1658933	csusgaaccUfGfCfaaaaauuL96		asdCsucdAadTuuuudGcAfgguuacgcsuisc		AGCUGAACCCUGCAAAAAUUGAGC	
AD-1658934	usgsaaccugCfAfAfaaaauugagcuL96		asdGscudCadAuuuudTgCfagguuacgsc		GCUGAACCCUGCAAAAAUUGAGCA	
AD-1658935	gsasaccugCfAfAfaaaauugagcuL96		asdTsgcdTcdAuuuudTuGfagguuacgsc		CUGAACCCUGCAAAAAUUGAGCAA	
AD-1658940	usgscaaaaaUfUfgfagcauagacuL96		asdGsucdAudTgucudAaUfuuuugcagsgsg		CCUGCAAAAAUUGAGCAAAUGACC	
AD-1658954	gsasgugcuGfAfCfagcauuuuuL96		asdAsaadAudGcuudTcAfgcaccucscsc		GGGAGGUGCUGAACAGCAUUUUUU	
AD-1658955	asgsugugcuGfAfCfagcauuuuuL96		asdAsaadAadTgucudTuCfagcaccucsc		GGAGGUGCUGAACAGCAUUUUUU	
AD-1658956	gsugugcuGfAfCfagcauuuuuL96		asdAsaadAadAugcdGuUfagcaccucsc		GAGGUGCUGAACAGCAUUUUUUUU	
AD-1658957	gsusugcuGfAfCfagcauuuuuL96		asdAsaadAadAugcdTgUfucagcaccscu		AGGUGCUGAACAGCAUUUUUUUU	
AD-1658958	usgsuagaacAfGfCfauuuuuuuuL96		asdAsaadAadAaaugCdUfuuuacgscsc		GGUGCUGAACAGCAUUUUUUUUUG	

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	gscsugaacaGfCfAfuuuuuuuuuL96		asdCsaadAadAaaaadGcUfguuucagscasc		GUGCUGAACACAGCAUUUUUUUUUGA	
AD-1658960	csusgaacagCfAfUfuuuuuuuuuL96		asdTscadAadAaaaadTgCfuuuucagscsa		UGCUGAACACAGCAUUUUUUUUUGAG	
AD-1658992	usgsagagagAfGfCfccacagaguuL96		asdAscudCudGugggdCuCfucucucastusc		GAUGAGAGAGAGACCCACACAGAGUC	
AD-1658994	asgsagagagCfCfCfacagagucuuL96		asdAsgadCudCugugdGgCfucucucucscsa		UGAGAGAGAGCCCCACAGAGUCUA	
AD-1658995	gsasagagagCfCfAfcagagucuuL96		asdTsagdAcdTeugudGgGfucucucucsc		GAGAGAGAGCCCCACAGAGUCUAC	
AD-1659055	gsasaccgccCfAfUfucucuguuuuL96		asdCsaadAcdAggaadTgGfaggguucscasg		CUGAACCGCCCCAUUCCUGUUUUGC	
AD-1659056	asaccgccCfAfUfucucuguuuuL96		asdGscadAadCaggadAuGfaggguucscsa		UGAACCGCCCCAUUCCUGUUUUGCU	
AD-1659057	ascscgcccUfUfCfcuguuuuuuL96		asdAsgadAadAcaggadAaUfaggcgguusc		GAACCGCCCCAUUCCUGUUUUGCUG	
AD-1659058	cscsgcccUfCfCfuuuuuuuuL96		asdCsaadCudAacagadGaAfuggcgguusuu		AACCGCCCCAUUCCUGUUUUGCUGU	
AD-1659059	csgcccUfCfUfuuuuuuuuL96		asdAscadGcdAaacadGgAfauaggcgsgsu		ACCGCCCCAUUCCUGUUUUGCUGUG	
AD-1659060	gscscauucCfUfGfuuuuuuuuL96		asdCsacdAgdCaaacdAgGfaauaggcgsgsg		CCGCCCCAUUCCUGUUUUGCUGUGU	
AD-1659061	cscscauuccUfGfUfuuuuuuuuL96		asdAscadCadGcaaadCaGfcauaggcgsgsg		CGCCCCAUUCCUGUUUUGCUGUGUA	
AD-1659062	cscsaauccUfUfUfuuuuuuuuL96		asdTsacdAcdAgcaadAcaAfggaauaggsgsc		GCCCCAUUCCUGUUUUGCUGUGUAU	
AD-1659063	csasauccUfUfUfuuuuuuuuL96		asdAsuadCadCagcadAaCfaggaauaggsgsg		CCCAUUCCUGUUUUGCUGUGUAUG	
AD-1659064	asusuccUfUfUfGfuuuuuuuuL96		asdCsaudAcdAcagadAaAfcaggaauaggsgsg		CCAUUCCUGUUUUGCUGUGUAUGA	
AD-1659065	ususcuccUfUfGfCfuuuuuuuuL96		asdTsacdTadCacagadCaAfacaggaauaggsgsg		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	uscsuguuuGfCfUfGfuguaugauuL96		asdAsuudAudAcacacGcAfaacaggasasu		AUUCUGUUUGCUGUGUAUGAUC	
AD-1659067	cscsuguuuGfUfGfuguaugauuL96		asdGsaudCadTaaadAgCfaaacaggasasa		UUCCUGUUUGCUGUGUAUGAUC	
AD-1659068	csusguuuGcUfGfUfGuaugaucauL96		asdTsgadTcdAuacacCaGfaaacaggsgsa		UCCUGUUUGCUGUGUAUGAUC	
AD-1659069	usgsuuuGcuGfUfGfuaugaucaauL96		asdTsuudAudCauadAcAfgcaaacagsgsg		CCUGUUUGCUGUGUAUGAUC	
AD-1659070	gsusuuuGcuGfUfGfuaugaucaauL96		asdTsuudGadTcauadCaGfaaacagsgsg		CUGUUUGCUGUGUAUGAUC	
AD-1659071	ususugcuGcuGfUfAfugaucacaaagL96		asdCsnuudTgdAucaudAcAfgcaaacagsgsa		UGUUUGCUGUGUAUGAUC	
AD-1659161	csasgucuccCfAfCfcuuuuuuuuL96		asdGsaudGadAaaagdGgUfggagagacsgsg		CCCAGUCUCCCCACCUUUUUCUUCU	
AD-1659162	gsusuccccaCfCfUfuuuuuuuuL96		asdTsagadAadGaaadGgUfggagagacsgsg		CAGUCUCCCCACCUUUUUCUUCU	
AD-1659163	csusccaccUfUfUfucuuuuuuL96		asdAsnuudAgdAgaadAaGfggggagagsg		GUCUCCCCACCUUUUUCUUCU	
AD-1659164	uscsccaccUfUfUfucuuuuuuL96		asdCsaudTadGaagadAaAfggggagagsgsa		UCUCCCCACCUUUUUCUUCU	
AD-1659165	cscscaccuuUfUfCfuuuuuuuuL96		asdTscadTudAgaagdAaAfggggagagsg		CUCCCCACCUUUUUCUUCU	
AD-1659166	cscsaccuuuUfCfUfucuuuuuuL96		asdCsnuudAudTagaadGaAfaaggggagsgsa		UCCCCACCUUUUUCUUCU	
AD-1659167	csasccuuuuCfUfUfcauuuuuuL96		asdAscudCadTuagadAgAfaaggggagsgsg		CCCACCUUUUUCUUCU	
AD-1659168	ascscuuuuCfUfCfuaauuuuuL96		asdGsaudTcdAuuaagdAaGfaaaagggsgsg		CCACCUUUUUCUUCU	
AD-1659208	cscsguuuuCfCfUfuguuuuuuL96		asdCsnuudAgdAccaadGgAfgaaagggsgsu		AGCCGUUUUUCUUCUUGGUCU	
AD-1659209	csgsuuuuuCfUfUfuguuuuuuL96		asdAscudTadGaccadAgGfagaagggsgsc		GCCGUUUUUCUUCUUGGUCU	

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	gsusuuuccUfUfGfgucuaaguuL96		asdCsacdTudAgaccdAaGfgagaaacsosg		CCGUUUCUCCUUGGUCUAAAGUGU	
AD-1659282	gsusuuugcugGfGfufuuuuuuuaguuL96		asdCsuaadAadAuaaadCcCfagcaacsosg		CAGUUUGCUGGGUUUAUUUUAGA	
AD-1659283	ususugcugGfUfufuuuuuaguuL96		asdTscudAadAuaaadAcCfagcaaaacsu		AGUUUGCUGGGUUUAUUUUAGAG	
AD-1659284	ususgcugcgUfUfufuuuuuaguuL96		asdCsucdTadAaauadAaCfccagcaasase		GUUUGCUGGGUUUAUUUUAGAGA	
AD-1659285	usgscugcgUfUfAfuuuagaguuL96		asdTscudCudAaaudAaAfccagcasasa		UUUGCUGGGUUUAUUUUAGAGAA	
AD-1659286	gscsugggguUfAfufuuuagaguuL96		asdTsnudTcdTaaadTaAfaccagcsasa		UUGCUGGGUUUAUUUUAGAGAAU	
AD-1659287	csusgggguuAfUfufuuuagagaaunL96		asdAsuudCudCuuaadAuAfaaccagcsesa		UGCUGGGUUUAUUUUAGAGAAUG	
AD-1659288	usgsggguuuaUfUfufuagagaauguuL96		asdCsaudTcdTcuadAaUfaaaccagsgc		GCUGGGUUUAUUUUAGAGAAUGG	
AD-1659289	gsgsguuuaUfUfufagagaauguuL96		asdCscaadTudCucuaadAaAfuaaaccsasg		CUGGGUUUAUUUUAGAGAAUGGG	
AD-1659290	gsasggcaagAfAfCfcaguguuuuuL96		asdTsaadAcdAcuggdTuCfugccucscsc		GGGAGGCAAGAACCAGUGUUUAG	
AD-1659291	asgsgcaagaAfCfCfaguguuuuuaguuL96		asdCsuaadAadCaecudGuUfcuugccusesc		GGAGGCAAGAACCCAGUGUUUAGC	
AD-1659292	gsgscaagaaCfCfAfuguguuuaguuL96		asdGscudAadAcacudGgUfcuugccesusc		GAGGCAAGAACCCAGUGUUUAGCG	
AD-1659293	gscsaagaacCfAfGfguuuagcguuL96		asdCsugdTadAaacadTgGfuuuugcscsu		AGGCAAGAACCCAGUGUUUAGCGC	
AD-1659294	csasagaaccAfGfUfguuuagcguuL96		asdGsgcdCudAaacadCuGfguuuugcscsc		GGCAAGAACCCAGUGUUUAGCGCG	
AD-1659295	asasgaaccaGfUfGfuuuagcguuL96		asdCsugdGcdTaaacdAcUfgguuucuscsc		GCAAGAACCCAGUGUUUAGCGGG	
AD-1659296	asgsaagacaaUfGfUfuuuagcguuuL96		asdCsacdCcdCuuaadCaCfuuuucuscsc		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	gsasaccaguGfUfUfuagcgcgggauL96		asdCscddGcdGcuadAcAfcugguucsu		AAGAAACCAAGUGUUUAGCGGGGA	
AD-1659298	asasccagugUfUfUfagcgcgggauL96		asdTscddCgdCgeuadAaCfagugguucsu		AGAAACCAAGUGUUUAGCGGGGAC	
AD-1659321	csusguuccaAfAfAfagaauuccauL96		asdTsggdAadTucudTuUfggaacagsa		UACUGUUCCAAAAAGAAUUCCAA	
AD-1659322	usgsuuccaaAfAfAfagaauuccauL96		asdTtsugdGadAuuudTuUfuggaacagsu		ACUGUUCCAAAAAGAAUUCCAAAC	
AD-1659323	gsusuccaaaAfAfFfaauuccaauL96		asdGsuudGgdAauudTuUfuggaacsag		CUGUUCCAAAAAGAAUUCCAAACC	
AD-1659325	uscsaaaaaGfAfAfuaucacccguL96		asdCsaggdTudGgaudTeUfuuuuggasac		GUUCCAAAAAGAAUUCCAAACCGA	
AD-1659326	csesaaaaagAfAfUfucaaccgauL96		asdTscgdGudTggadTuCfuuuuuggsasa		UUCCAAAAAGAAUUCCAAACCGAC	
AD-1659327	csasaaaaagaAfUfUfccaacggacuL96		asdGsuedGgdTuggadAuUfuuuuuuggsa		UCCAAAAAGAAUUCCAAACCGACC	
AD-1659328	asasaaagaaUfUfCfcaaccgaccuL96		asdGsgudCgdGuuggdAaUfucuuuuugsg		CCAAAAAGAAUUCCAAACCGACCA	
AD-1659329	asasagaauUfCfCfaccgaccacuL96		asdTsggdTcdGguugdGaAfuucuuuusug		CAAAAAAGAAUUCCAAACCGACCAG	
AD-1659330	asasagaauCfCfAfacegaccaguL96		asdCsugdGudCggudGgAfaucuuuusuu		AAAAAGAAUUCCAAACCGACCAGC	
AD-1659331	asasgaauucCfAfAfccgaccagcuL96		asdGscudGgdTcggudTgGfaauucuuusu		AAAAAGAAUUCCAAACCGACCAGCU	
AD-1659332	asgsaaauccAfAfCfcgaccagcuuL96		asdAsgcdTgdGuecgdTgGfaauucuuusu		AAAGAAUUCCAAACCGACCAGCUU	
AD-1659333	gsasaauuccAfCfCfaccagacuuuL96		asdAsagdCudGuecdGuUfggaauucsu		AAGAAUUCCAAACCGACCAGCUUG	
AD-1659334	asasaauccaaCfCfGfacegacuuuL96		asdCsaadGcdTggudGgUfuggaauucsu		AGAAUUCCAAACCGACCAGCUUGU	
AD-1659335	asusuccaacCfGfAfccagcuuuguuL96		asdAscadAgdCuggdCgGfuuggaauusc		GAAUUCCAAACCGACCAGCUUGUU	

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	usuccaaccGfAfCfcagcuuuuL96		asdAsacdAadGcuggdTcGfgnuuggaasusu		AAUUCCAACCGACCGACCGAGCUUGUUU	
AD-1659337	uscsaaccgAfCfCfagcuuuuuL96		asdAsaadCadAgeugdGuCfkguuggasasu		AUUCCAACCGACCGACCGAGCUUGUUUG	
AD-1659338	csesaaccgaCfCfAfgcuuuuuL96		asdCsaadAcdAageudGgUfcgguuggsasa		UUCCAACCGACCGACCGAGCUUGUUUUGU	
AD-1659339	csasaccgacCfAfGfcuuguuuuL96		asdAasadAadCaagcdTgGfucgguuuL96		UCCAACCGACCGACCGAGCUUGUUUUGUG	
AD-1659340	asasccgaccAfGfCfuuuuuuuL96		asdCsacdAadAcaagdCuGfgucgguuuL96		CCAACCGACCGACCGAGCUUGUUUUGUGA	
AD-1659341	ascsagaccGfCfUfuguuuuuuL96		asdTscadCadAcaadGcUfkgucgguuuL96		CAACCGACCGACCGAGCUUGUUUUGUGAA	
AD-1659342	csesgaccagCfUfUfuguuuuuuL96		asdTsacdAcdAaacadAgCfugucgguuuL96		AACCGACCGACCGAGCUUGUUUUGUGAAA	
AD-1659343	csesgaccagCfUfUfGfuuuuuuuL96		asdTsuudCadCaaacdAaGfucgucgguuuL96		ACCGACCGAGCUUGUUUUGUGUGAAAC	
AD-1659344	gsasccagcuUfGfUfuguuuuuuL96		asdGsuudTcdAcaaadCaAfgucgucgguuL96		CCGACCGAGCUUGUUUUGUGUGAAAAACA	
AD-1659345	ascsagcuUfUfUfuguuuuuuL96		asdTsgudTudCacaadAcAfgucgucgguuL96		CGACCGAGCUUGUUUUGUGUGAAAACAA	
AD-1659346	csesagcuUfUfUfuguuuuuuL96		asdTsuudTudTcacadAaCfaagucgguuL96		GACCGAGCUUGUUUUGUGUGAAAACAA	
AD-1659347	csasgcuUfUfUfGfugaacaaaL96		asdTsuudGudTucadAaAfcagucgguuL96		ACCAGCUUGUUUUGUGUGAAAACAAAA	
AD-1659348	asgsuuguuUfGfUfugaacaaaL96		asdTsuudTgdTuucadCaAfacagucgguuL96		CCAGCUUGUUUUGUGUGAAAACAAAA	
AD-1659350	csusgcuUfUfGfAfaacaaaaaL96		asdTsuudTudTguudCaCfaacaaaguuL96		AGCUUGUUUUGUGUGAAAACAAAAAG	
AD-1659351	usuguuuuGfAfAfaacaaaaaL96		asdCsuidTudTuguudTcAfaacaaaguuL96		GCUUGUUUUGUGUGAAAACAAAAAGU	
AD-1659371	usgsuucccuUfUfUfcaaguuuuL96		asdCsuidAadCuugadAaAfgggaacuuL96		AGUGUUCCCUUUUUCAGUUGUGAGA	

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	gsusuccuuUfUcfaaguuagauL96		asdTscudCadAcuugdAaAfagggaacsasc		GUGUCCCCUUUUCAGUUGAGAA	
AD-1659373	ususeccuuUfCfAfaaguuagaaL96		asdTscudTcdAacuudGaAfaagggaacsca		UGUCCCCUUUUCAGUUGAGAAC	
AD-1659382	csasaguugaGfAfAfcfaaaauugL96		asdCsaadTudTuugudTeUfcaacuugsasa		UUCAAAGUUGAGAGAACAAAAUUGG	
AD-1659383	asasguugagAfAfCfaaaauugguL96		asdCscadAudTuugudTuCfuaacuugsasa		UCAAAGUUGAGAGACAAAAAUUGGG	
AD-1659384	asgsuugagaAfCfAfaaaauugguL96		asdCscadAadTuunudGuUfcuaacuugsu		CAAGUUGAGAGACAAAAAUUGGGU	
AD-1659385	gsusugagaaCfAfAfaaaauugguL96		asdAsccdCadAuuudTgUfucuaacsusu		AAGUUGAGAGACAAAAAUUGGGUU	
AD-1659386	ususgagaacAfAfAfaauugguuuL96		asdAsacdCcdAuuudTuGfmucaacsusu		AGUUGAGAGACAAAAAUUGGGUUU	
AD-1659387	usgsagaacaAfAfAfaauuggguuuL96		asdAsaadCcdCaauudTuUfguuucasasc		GUUGAGAGACAAAAAUUGGGUUUU	
AD-1659388	gsasgaacaaAfAfAfuuggguuuuL96		asdAsaadAcdCcaudTuUfuguuucsasa		UUGAGAGACAAAAAUUGGGUUUUA	
AD-1659389	asgsaacaaaAfAfUfuggguuuuL96		asdTsaadAadCccadTuUfuguuucscsa		UGAGAGACAAAAAUUGGGUUUUA	
AD-1659390	gsasacaaaaAfUfUfgguuuuL96		asdTsuadAadAccadAuUfuuguuucsusc		GAGAACAAAAAUUGGGUUUUA	
AD-1659391	asascaaaaaUfUfGfgguuuuL96		asdTsuudAadAaccadAaUfuuuuguuucsusu		AGAACAAAAAUUGGGUUUUA	
AD-1659399	asgsuauacaUfUfUfuuuauugcuL96		asdGscadAudGcaaadAaUfguaucacsusu		AAAGUAUACAUUUUUGCAUUGGCC	
AD-1659400	gsusauacauUfUfUfugaauugccuL96		asdGsgcdAadTgcadAaAfuguuauacsusu		AAGUAUACAUUUUUGCAUUGCCU	
AD-1659401	usasuaauUfUfUfugaauugccuL96		asdAsggdCadAugcadAaAfauguauacsusu		AGUAUACAUUUUUGCAUUGCCUU	
AD-1659402	asusacaauUfUfGfcauugccuuL96		asdAsagcdGcdAugcdAaAfauguauacsusc		GUUAUACAUUUUUGCAUUGCCUUC	

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	csasuuuuugCfAfUfugccuucggguL96		asdCscgdAadGgcaadTgCfcaaaauggsa		UACAUUUUUUGCAUUGCCUUCGCGU	
AD-1659406	asuuuuuuugcAfUfUfugccuucggguL96		asdAascgdGadAgggcdAuGfcaaaauggsu		ACAUUUUUUGCAUUGCCUUCGCGUU	
AD-1659407	usuuuuuuugcaUfUfGfcccucggguuL96		asdAsacdCgdAaggcdAaUfgcaaaausug		CAUUUUUGCAUUGCCUUCGCGUUU	
AD-1659408	usuuuuuuugcaUfGfCfcccucggguuL96		asdAsaadCcdGaaggcdCaAfugcaaaaasuu		AUUUUUGCAUUGCCUUCGCGUUUG	
AD-1659409	usuuuuuuugcaUfGfCfcccucggguuL96		asdCsaadAcdCgaagcdGcAfauugcaaaasaa		UUUUUGCAUUGCCUUCGCGUUUGU	
AD-1659410	usuuuuuuugcaUfGfCfcccucggguuL96		asdAasadAadCcggaadGgCfauugcaaaasaa		UUUUUGCAUUGCCUUCGCGUUUGUA	
AD-1659411	usuuuuuuugcaUfGfCfcccucggguuL96		asdTsacdAadAccgaadAgGfcaauugcasaa		UUUGCAUUGCCUUCGCGUUUGUAU	
AD-1659412	gscsaauuuugccUfUfCfGfuuuuuaguuL96		asdAsaadCadAaccgdAaGfGcaauugcsaa		UUUGCAUUGCCUUCGCGUUUGUAUU	
AD-1659413	csasuuuuugccUfUfCfGfuuuuuaguuL96		asdAsaadAcdAaaccdGaAfGgcaauugcsaa		UGCAUUGCCUUCGCGUUUGUAUUU	
AD-1659414	asuuuuuuugccUfUfCfGfuuuuuaguuL96		asdAsaadTadCaaacdCgAfagGcaauugsc		GCAUUGCCUUCGCGUUUGUAUUUA	
AD-1659415	usuuuuuuugccUfUfGfuuuuuaguuL96		asdTsacdAadAcaaadCcGfagGcaauugsc		CAUUGCCUUCGCGUUUGUAUUUAG	
AD-1659416	usuuuuuuugccUfUfGfuuuuuaguuL96		asdCsuaadAadTacaadAcCfGaaagGcasuu		AUUGCCUUCGCGUUUGUAUUUAGU	
AD-1659417	gscsaauuuugccUfUfGfuuuuuaguuL96		asdAasadAadAuaaadAaCfGaaagGcasaa		UUUGCCUUCGCGUUUGUAUUUAGUG	
AD-1659418	csuuuuuuugccUfUfGfuuuuuaguuL96		asdCsacdTadAuaaadAaAfGaaagGcsaa		UGCCUUCGCGUUUGUAUUUAGUGU	
AD-1659419	csuuuuuuugccUfUfGfuuuuuaguuL96		asdAasadCudAaauadCaAfaccGaaagGsc		GCCUUCGCGUUUGUAUUUAGUGUC	
AD-1659420	usuuuuuuugccUfUfAfuuuuaguuL96		asdGsacdAcdTaaauadAcAfaccGaaagGsg		CCUUCGCGUUUGUAUUUAGUGUCU	

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	uscsggguugUfAfUfuagugucuuL96		asdAsgadCadCuaadTaCfaaacggasag		CUUCGGUUUGUAUUUAGUGUCUU	
AD-1659422	csgsguuuugUfAfUfuagugucuuuL96		asdAsgadAcdAcuaadAuAfaaacggsasa		UUCGGUUUGUAUUUAGUGUCUU	
AD-1659423	gsgsuuuugUfUfUfagugucuuL96		asdCsaadGadCacuadAaUfacaaaccgsa		UCGGUUUGUAUUUAGUGUCUU	
AD-1659424	gsusuuugUfUfAfugucuuL96		asdTscadAgtAcacudAaAfuacaacsag		CGGUUUUGUAUUUAGUGUCUU	
AD-1659425	usuuuuuuUfAfGfugucuuL96		asdTsucdAadGacacdTaaAfaaacaasc		GGUUUUUGUAUUUAGUGUCUU	
AD-1659426	usuuuuuuAfGfUfugucuuL96		asdAsuudCadAgacacCuAfaaacaasac		GUUUUUUGUAUUUAGUGUCUU	
AD-1659427	usuuuuuuGfUfGfucuuL96		asdCsaudTcdAagacdAeUfaaauacasasa		UUUUUUUGUAUUUAGUGUCUU	
AD-1659428	gsuuuuuuUfGfUfucuuL96		asdAscadTudCaagadCaCfaaauacasasa		UUUUUUUGUAUUUAGUGUCUU	
AD-1659429	usuuuuuuGfUfCfuuaaL96		asdTsacdAudTcaagdAeAfcuaaauascsa		UGUAUUUAGUGUCUUUGAAUGUAA	
AD-1659430	asuuuuuuUfCfUfuaaL96		asdTsuadCadTucadGaCfacuaaauasac		GUUUUUAGUGUCUUUGAAUGUAA	
AD-1659431	usuuuuuuCfUfUfuaaL96		asdCsuudAcdAuuacAdAgAfcuaaauasusa		UAUUUAGUGUCUUUGAAUGUAA	
AD-1659432	usuuuuuuUfUfGfaaL96		asdTscudTadCaauadAaGfacuaaauasasa		AUUUUAGUGUCUUUGAAUGUAA	
AD-1659433	usuuuuuuUfGfAfaaL96		asdTsucdTudAcauudCaAfgacuaaauasasa		UUUUAGUGUCUUUGAAUGUAA	
AD-1659434	asuuuuuuGfAfAfuuaaL96		asdGsuudCudTacaudTcAfaagacacusa		UUUUAGUGUCUUUGAAUGUAA	
AD-1659436	usuuuuuuAfUfGfuaaL96		asdAsuudTudCuuaadAuUfaaagacacsu		AGUGUCUUUGAAUGUAA	
AD-1659437	gsuuuuuuUfGfUfaaL96		asdCsaudGudTcuuadCaUfucaagacacsa		GUUUUUUGAAUGUAA	

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	ususgaauGuAfAfGfaacauGaccuL96		asdGsgudCadTguudTuAfaucuaasgsa		UCUUGAAUGUAAAGAACAUAGACCU	
AD-1659446	gsusaagaacAfUfGfaccuGugul96		asdCsacdGgdAggudAuGfucuuacsasu		AUGUAAAGAACAUAGACCUCCGUGU	
AD-1659447	usasagaacaUfGfAfcuGugul96		asdAscadCgdGagguCdUfguuuuasasa		UGUAAAGAACAUAGACCUCCGUGUA	
AD-1659448	asasgaacauGfAfCfuccGugul96		asdTsacdAcdGgagdTcAfuguuuacsasc		GUAAAGAACAUAGACCUCCGUGUAG	
AD-1659449	asgsaacauGfAfCfuccGugul96		asdCsacdCadCggagdGuCfauuuuacsusa		UAAGAACAUAGACCUCCGUGUAGU	
AD-1659450	gsasacaugaCfCfUfccGugul96		asdAscudAcdAcggadGgUfcauuuacsusu		AAGAACAUAGACCUCCGUGUAGUG	
AD-1659451	asascaugacCfUfCfGugul96		asdCsacdTadCacggdAgGfucuuuacsusu		AGAACAUAGACCUCCGUGUAGUGU	
AD-1659452	ascsaugaccUfCfCfGugul96		asdAscadCudAcacgdGaGfucuuuacsusc		GAACAUAGACCUCCGUGUAGUGUC	
AD-1659453	csasugaccuCfCfGfugul96		asdGscadAcdTaccdGgAfGgucuuuacsusu		AACAUAGACCUCCGUGUAGUGUCU	
AD-1659454	asusgaccucCfGfUfGugul96		asdAsgadCadCuacCdCgGfaguuuacsusu		ACAUGACCUCCGUGUAGUGUCUG	
AD-1659481	csusuaguuuUfUfUfccacagugul96		asdCsaudCudGuggdAaAfaacuuuacsusu		ACCUUAGUUUUUUUCCACAGAUAGC	
AD-1659482	ususaguuuuUfUfCfaccagugul96		asdGscadTcdTguggdAaAfaacuuuacsusu		CCUUAGUUUUUUUCCACAGAUAGCU	
AD-1659483	usasguuuuuUfCfCfaccagugul96		asdAsgcdAudCugudGaAfaaauuacsusu		CUUAGUUUUUUUCCACAGAUAGCUU	
AD-1659484	asgsuuuuuuCfCfAfcagugul96		asdAsagdCadTcuudGgAfaaauuacsusa		UUAGUUUUUUUCCACAGAUAGCUUG	
AD-1659485	gsusuuuuuuCfAfcfagugul96		asdCsacdGcdAucudTgGfaaauuacsusa		UAGUUUUUUUCCACAGAUAGCUUGU	
AD-1659487	ususuuuuuCaCfAfGfagugul96		asdCsacdAadGcaudTgUfGgaaauuacsasc		GUUUUUUUUCCACAGAUAGCUUGUGA	

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	usuuuuccacAfGfAfugcuugugauL96		asdTscadCadAgcadCuGfuggaaasasa		UUUUUUCCACAGAUGCUGUGAU	
AD-1659489	usuuuccacaGfAfUfGcuugugauL96		asdAsuadAcdAagcadTcUfugggaaasasa		UUUUUUCCACAGAUGCUGUGAUU	
AD-1659490	usuuccacagAfUfGfGcuugugauL96		asdAsauadCadCaagcdAuCfugggaaasasa		UUUUUUCCACAGAUGCUGUGAUUU	
AD-1659491	useseacagaUfGfCfuugugauuuL96		asdAsaadTcdAcaagdCaUfGcuugggasasa		UUUCCACAGAUGCUGUGAUUUUU	
AD-1659492	csesacagauGfCfUfugugauuuL96		asdAsaadAudCacaadGcAfGcuugggasasa		UUCCACAGAUGCUGUGAUUUUU	
AD-1659493	csasacagauGfUfUfugugauuuL96		asdAsaadAadTcaadAgCfauuuggggsa		UCCACAGAUGCUGUGAUUUUUUG	
AD-1659537	ascscugaaUfUfCfuguuugaaauL96		asdAsuudCadAacagdAaAfGcuagggsgsc		GCACCGAAUUUCUGUGUUUGAAUG	
AD-1659538	csesugaaUfCfUfGcuugaaugL96		asdCsauadTcdAaacadGaAfauuacaggsug		CACCUGAAUUUCUGUGUUUGAAUGC	
AD-1659559	gsgsaaccuAfGfCfugguuuuuL96		asdAsaadTadAccagdCuAfGguuuccsgsc		GCGGAACCAUAGCUGGUUAUUUC	
AD-1659560	gsasaccuafGfCfUfGguuuuuL96		asdGsaadAudAaccadGcUfauugguucsg		CGGAACCAUAGCUGGUUAUUUCU	
AD-1659561	asascuagCfUfGfGguuuuuL96		asdAsgadAadTaaacdAgCfuaugguucsc		GGAACCAUAGCUGGUUAUUUCUC	
AD-1659562	ascscuagCfUfGfGfuuuuuL96		asdGsaadAadAuaacdCaGfuaugguucsc		GAACCAUAGCUGGUUAUUUCUCC	
AD-1659563	csesauagcuGfGfUfuauuuuL96		asdGsgadGadAuaadCcAfGcuuuggsusu		AACCAUAGCUGGUUAUUUCUCCC	
AD-1659582	csesuuugguUfAfGfuaaauaacguL96		asdCsauadTudAuuaadTaAfcacaggsasa		UCCCUUGUGUUAGUAAUAAACGU	
AD-1659583	csuuugguUfAfGfUfaaauaacguL96		asdAsegdTudTuuuadCuAfacacaggsasa		CCCUUGUGUUAGUAAUAAACGUC	
AD-1659584	usuuugguuaGfUfAfuaaauaacguL96		asdGsacdGudTuuuadAcUfaacacaggsasa		CCCUUGUGUUAGUAAUAAACGUCU	

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	usgsuguuagUfAfAfaaacgucuuL96		asdAsgadCgdTuuauTtTaCfuacacacasa		CUUGUGUUAGUAAUAAACGUCUU	
AD-1659586	gsusguuuaguAfAfUfaaacgucuuuL96		asdAsagdAcdGuuuadTuAfcuaacacsasa		UUUGUGUUAGUAAUAAACGUCUUG	
AD-1659587	usgsuuaguaAfUfAfaacgucuuuguL96		asdCsaadGadCguuudAuUfacuaacacsasa		UGUGUUAGUAAUAAACGUCUUGC	
AD-1659588	gsusuaaguaaUfAfAfaacgucuuuguL96		asdGscadAgdAcguudTaUfuacuaacsasc		GUGUUAGUAAUAAACGUCUUGCC	
AD-1321384	uscsucccacCfUfUfuucuuuuaauL96		asdTsuadGadAgaadAgGfuggggagascsu		AGUCUCCCCACCUUUUUCUUCUAAU	
AD-1321390	csesucaacuGfGfAfugaagaagaauL96		asdGsuudTedTuaudCcAfguugaggaggsa		UCCCUCAACUGGAUGAAGAAACU	

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.

5 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 µl of Opti-MEM plus 0.1 µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) was added to 2.5 µl of each siRNA duplex to an individual well in a 384-well plate. The mixture was then incubated at room temperature for 15
10 minutes. Forty µl 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 10µl of Lysis/Binding Buffer containing 3 µL of beads per well were mixed for 10 minutes on an
15 electrostatic shaker. The washing steps were automated on a Biotek EL406, using a magnetic plate support. Beads were washed (in 3µL) once in Buffer A, once in Buffer B, and twice in Buffer E, with aspiration steps in between. Following a final aspiration, complete 12µL RT mixture was added to each well, as described below.

For cDNA synthesis, a master mix of 1.5µl 10X Buffer, 0.6µl 10X dNTPs, 1.5µl Random
20 primers, 0.75µl Reverse Transcriptase, 0.75µl RNase inhibitor and 9.9µl 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
25 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	UCUCCACCUUUUCUUAU		1609-1629	ATUAGAAAGAAAGGUGGAGACU		1607-1629
AD-1321390.2	CCUCAAACUGGAAGAAACU		1135-1155	AGUUTCTUCAUCCAGUUGAGGGA		1133-1155
AD-1632799.1	AGCCUGAGGGCCACCAUCCUU		86-106	AAGGAUGGUGGCCUACAGGCUCA		84-106
AD-1632801.1	CCUGAGGGCCACCAUCCUU		88-108	AAGAGGAUGGUGGCCUACAGGCU		86-108
AD-1632805.1	AGGGCCACCAUCCUUGCCUU		92-112	AAGGCAGAGGAUGGUGGCCUUA		90-112
AD-1632836.1	GUCAUCCACAAUGAGAGUACU		170-190	AGUACUCUCAUUGUGGAUGACGA		168-190
AD-1632838.1	GUGACCGGGUGUACAUACAU		138-158	AGUGUAUGUACACCCGGUCACCU		136-158
AD-1632840.1	CUUCCACCUUGUUAUCCACAU		160-180	AUGUGGAUGACGAGGUGGAAGGG		158-180
AD-1632841.1	UUCCACCUUGUUAUCCACAAU		161-181	AUUGUGGAUGACGAGGUGGAAGG		159-181
AD-1632842.1	UCCACCUUGUUAUCCACAAU		162-182	AUUGUGGAUGACGAGGUGGAAG		160-182
AD-1632843.1	CCACCUUGUUAUCCACAAU		163-183	ACAUUGUGGAUGACGAGGUGGA		161-183
AD-1632844.1	CACCUUGUUAUCCACAAU		164-184	AUCAUUGUGGAUGACGAGGUGGA		162-184
AD-1632846.1	CCUGUUAUCCACAAUAGAGAU		166-186	AUCUCAUUGUGGAUGACGAGGUG		164-186
AD-1632847.1	CUUGUUAUCCACAAUAGAGAU		167-187	ACUCUCAUUGUGGAUGACGAGGU		165-187
AD-1632848.1	UGGUUAUCCACAAUAGAGAU		168-188	AACUCUCAUUGUGGAUGACGAGG		166-188
AD-1632849.1	CGUCAUCCACAAUAGAGAU		169-189	AUACUCUCAUUGUGGAUGACGAG		167-189
AD-1632850.1	UCAUCCACAAUAGAGAUACCU		171-191	AGGUACUCUCAUUGUGGAUGACG		169-191
AD-1632851.1	CAUCCACAAUAGAGAUACCU		172-192	AAGGUACUCUCAUUGUGGAUGAC		170-192
AD-1632852.1	AUCCACAAUAGAGAUACCU		173-193	ACAGGUACUCUCAUUGUGGAUGA		171-193
AD-1632853.1	UCCACAAUAGAGAUACCU		174-194	AACAGGUACUCUCAUUGUGGAUG		172-194
AD-1632854.1	CCACAAUAGAGAUACCU		175-195	ACACAGGUACUCUCAUUGUGGAU		173-195
AD-1632855.1	CACAAUAGAGAUACCU		176-196	AUCACAGGUACUCUCAUUGUGGA		174-196
AD-1632856.1	ACAAUAGAGAUACCU		177-197	ACUCACAGGUACUCUCAUUGUGG		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	CAAGAGAGUACCUGUGAGCU		178-198	AGCUCACAGGUACUCUCAUUGUG		176-198
AD-1632858.1	AAUGAGAGUACCUGUGAGCAU		179-199	AUGCUCACAGGUACUCUCAUUGU		177-199
AD-1632859.1	AUGAGAGUACCUGUGAGCAGU		180-200	ACUGCUCACAGGUACUCUCAUUG		178-200
AD-1632860.1	UGAGAGUACCUGUGAGCAGCU		181-201	AGCUGCUCACAGGUACUCUCAUU		179-201
AD-1632861.1	GAGAGUACCUGUGAGCAGCUU		182-202	AAGCUGCUCACAGGUACUCUCAU		180-202
AD-1632862.1	AGAGUACCUGUGAGCAGCUGU		183-203	ACAGCUGCUCACAGGUACUCUCA		181-203
AD-1632863.1	GAGUACCUGUGAGCAGCUGGU		184-204	ACCAGCUGCUCACAGGUACUCUC		182-204
AD-1632864.1	AGUACCUGUGAGCAGCUGGCU		185-205	AGCCAGCUGCUCACAGGUACUCU		183-205
AD-1632865.1	GUACCUGUGAGCAGCUGGCAU		186-206	AUGCCAGCUGCUCACAGGUACUC		184-206
AD-1632866.1	UACCUGUGAGCAGCUGGGCAU		187-207	AUUGCCAGCUGCUCACAGGUACU		185-207
AD-1632991.1	AUGGUCGGGAUGCUGGGCCA		352-372	AUGGCCAGCAUCCCGACCAUUGC		350-372
AD-1632992.1	AUGGUCGGGAUGCUGGGCAU		353-373	AUUGGCCAGCAUCCCGACCAUUG		351-373
AD-1632993.1	UGGUCGGGAUGCUGGGCCAACU		354-374	AGUUGGCCAGCAUCCCGACCAU		352-374
AD-1632994.1	GGUCGGGAUGCUGGGCCAACUU		355-375	AAGUUGGCCAGCAUCCCGACCAU		353-375
AD-1632995.1	GUCGGGAUGCUGGGCCAACUUU		356-376	AAAGUUGGCCAGCAUCCCGACCA		354-376
AD-1632996.1	UCGGGAUGCUGGGCCAACUUCU		357-377	AGAAUUGGCCAGCAUCCCGACC		355-377
AD-1632997.1	CGGGGAUGCUGGGCCAACUUCUU		358-378	AAGAAUUGGCCAGCAUCCCGAC		356-378
AD-1632998.1	GGGAUGCUGGGCCAACUUCUUU		359-379	AAAGAAGUUGGCCAGCAUCCCGA		357-379
AD-1632999.1	GGGAUGCUGGGCCAACUUCUUGU		360-380	ACAAGAAGUUGGCCAGCAUCCCG		358-380
AD-1633000.1	GAUGCUGGGCCAACUUCUUGGU		361-381	ACCAAGAAGUUGGCCAGCAUCCC		359-381
AD-1633003.1	GCUGGGCCAACUUCUUGGGCUU		364-384	AAGCCCAAGAAGUUGGGCCAGCAU		362-384
AD-1633004.1	CUGGGCCAACUUCUUGGGCUUU		365-385	AAAGCCCAAGAAGUUGGGCCAGCA		363-385
AD-1633007.1	GCCAAUUCUUGGGCUUCCGU		368-388	ACGGAAGCCCAAGAAGUUGGGCCA		366-388
AD-1633008.1	CCAACUUCUUGGGCUUCCGUU		369-389	AACGGAAAGCCCAAGAAGUUGGGCC		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	AUACGGAAGCCCCAAGAAAGUUGG		368-390
AD-1633010.1	AACUUCUUGGGCUUCCGUAAU		371-391	AAUACGGAAGCCCCAAGAAAGUUGG		369-391
AD-1633011.1	ACUUCUUGGGCUUCCGUAAU		372-392	AUAUACGGAAGCCCCAAGAAAGUUG		370-392
AD-1633012.1	CUUCUUGGGCUUCCGUAAU		373-393	AAUAUACGGAAGCCCCAAGAAAGU		371-393
AD-1633013.1	UUCUUGGGCUUCCGUAAU		374-394	AUAUAUACGGAAGCCCCAAGAAAGU		372-394
AD-1633014.1	UCUUGGGCUUCCGUAAU		375-395	AAUAUAUACGGAAGCCCCAAGAAAG		373-395
AD-1633015.1	CUUGGGCUUCCGUAAU		376-396	ACAUUAUACGGAAGCCCCAAGAA		374-396
AD-1633016.1	UUGGGCUUCCGUAAU		377-397	ACCAUAUAUACGGAAGCCCCAAGA		375-397
AD-1633018.1	GGGCUUCCGUAAU		379-399	AUGCCAUAUAUACGGAAGCCCCAA		377-399
AD-1633019.1	GGCUUCCGUAAU		380-400	AAUGCCAUAUAUACGGAAGCCCCA		378-400
AD-1633020.1	GCUUCCGUAAU		381-401	ACAUGCCAUAUAUACGGAAGCCCC		379-401
AD-1633027.1	UAUAUAUGGCAUGCACAGUGU		388-408	ACACUGUGCAUGGCCAUUAUAACG		386-408
AD-1633028.1	AUAUAUGGCAUGCACAGUGAU		389-409	AUCACUGUGCAUGGCCAUUAUAUC		387-409
AD-1633029.1	UAUAUGGCAUGCACAGUGAGU		390-410	ACUCACUGUGCAUGGCCAUUAUA		388-410
AD-1633030.1	AUAUGGCAUGCACAGUGAGCU		391-411	AGCUCACUGUGCAUGGCCAUUAUAU		389-411
AD-1633031.1	UAUGGCAUGCACAGUGAGCUU		392-412	AAGCUCACUGUGCAUGGCCAUUA		390-412
AD-1633032.1	UGGCAUGCACAGUGAGCUAAU		394-414	AAUAGCUCACUGUGCAUGGCCAU		392-414
AD-1633033.1	GGCAUGCACAGUGAGCUAUGU		395-415	ACAUAGCUCACUGUGCAUGGCCAU		393-415
AD-1633034.1	GCAUGCACAGUGAGCUAUGGU		396-416	ACCAUAGCUCACUGUGCAUGGCCA		394-416
AD-1633048.1	UGGCACCCUGGCCUCUCUCUU		460-480	AAGAGAGAGGCCAGGGUGGCCAA		458-480
AD-1633049.1	GGCACCCUGGCCUCUCUCUAU		461-481	AUAGAGAGAGGCCAGGGUGGCCA		459-481
AD-1633094.1	GACAGGCUACAGGCAAUCCUU		506-526	AAGGAUUGCCUGUAGCCUGUCAG		504-526
AD-1633095.1	ACAGGCUACAGGCAAUCCUGU		507-527	ACAGGAUUGCCUGUAGCCUGUCA		505-527
AD-1633119.1	UUCCUUGGAAGGACAAAGAAU		531-551	AGUUCUUGUCCUCCAAAGGAACA		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	CCUUGGAAGGACAAAGAACUGU		533-553	ACAGUUCUUGUCCUUCACAAAGGA		531-553
AD-1633122.1	CUUGGAAGGACAAAGAACUGU		534-554	AGCAGUUCUUGUCCUUCACAAAGGA		532-554
AD-1633254.2	CACCUGAAGCAGCCGUUUGUU		692-712	AACAAACGGCUGCUUCAGGUGCA		690-712
AD-1633257.2	CUGAAGCAGCCGUUUGUGCAU		695-715	AUGCACAAACGGCUGCUUCAGGU		693-715
AD-1633269.2	UUUGUGCAGGGCCUGGCUCUU		707-727	AAGAGCCAGGCCUGGCACAAACG		705-727
AD-1633270.2	UUUGCAGGGCCUGGCUCUCU		708-728	AGAGAGCCAGGCCUGGCACAAAC		706-728
AD-1633271.2	UGUGCAGGGCCUGGCUCUCUU		709-729	AAGAGAGCCAGGCCUGGCACAAA		707-729
AD-1633272.2	GUGCAGGGCCUGGCUCUCUAU		710-730	AUAGAGAGCCAGGCCUGGCACAA		708-730
AD-1633273.2	UGCAGGGCCUGGCUCUCUAUU		711-731	AAUAGAGAGCCAGGCCUGGCACA		709-731
AD-1633290.2	ACGCUCUCUGGACUUCACAGU		748-768	ACUGUGAAGUCCAGAGAGCGUGG		746-768
AD-1633291.2	CGCUCUCUGGACUUCACAGAU		749-769	AUCUGUGAAGUCCAGAGAGCGUG		747-769
AD-1633324.2	CUGAGAAGAUUGACAGGUUCU		783-803	AGAACCUGUCAAUUCUUCACAGCA		781-803
AD-1633325.2	GAGAAGAUUGACAGGUUCAUU		785-805	AAUGAACCUUGUCAAUUCUUCUCAG		783-805
AD-1633326.2	AGAAGAUUGACAGGUUCAUGU		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	UUUGACAGGUUCAUGCAGGCUU		792-812	AAGCCUGCAUGAACCUUGUCAAUUC		790-812
AD-1633333.2	UGACAGGUUCAUGCAGGCGUGU		793-813	ACAGCCUGCAUGAACCUUGUCAAUU		791-813
AD-1633334.2	GACAGGUUCAUGCAGGCGUGUU		794-814	AACAGCCUGCAUGAACCUUGUCAAA		792-814
AD-1633335.2	ACAGGUUCAUGCAGGCGUGUGU		795-815	ACACAGCCUGCAUGAACCUUGUCA		793-815
AD-1633343.2	AUGCAGGCUGUGACAGGAUGU		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	GCAGGCGUGACAGGAUGGAU		805-825	AUCCAUCCUGUCACAGCCUGCAU		803-825
AD-1633346.2	CAGGCGUGACAGGAUGGAU		806-826	AUCCAUCCUGUCACAGCCUGCA		804-826
AD-1633409.2	GCUUCAACACCCUACGUCCAU		869-889	AUGGACGUAGGUGUUGAAAGCCA		867-889
AD-1633453.2	GAGUUCUGGGUGGACAAACAGU		935-955	ACUUGUUGCCACCCAGAACUCCU		933-955
AD-1633464.2	GGACAACAGCACCCUCAGUGUU		946-966	AACACUGAGGUGCUGUUGCCAC		944-966
AD-1633465.2	GACAACAGCACCCUCAGUGUCU		947-967	AGACACUGAGGUGCUGUUGUCCA		945-967
AD-1633466.2	ACAACAGCACCCUCAGUGUCUU		948-968	AAGACACUGAGGUGCUGUUGUCC		946-968
AD-1633467.2	CAACAGCACCCUCAGUGUCUGU		949-969	ACAGACACUGAGGUGCUGUUGUC		947-969
AD-1633468.2	AACAGCACCCUCAGUGUCUGUU		950-970	AACAGACACUGAGGUGCUGUUGU		948-970
AD-1633604.2	AUGCCUCUGACCCUGGACAAGU		1086-1106	ACUUGUCCAGGUCAGAGGCAUAG		1084-1106
AD-1633621.2	AAGGUGGAGGGUCUCACUUUUU		1103-1123	AAAAGUGAGACCCUCCACCUUGU		1101-1123
AD-1633622.2	AGGUGGAGGGUCUCACUUUCU		1104-1124	AGAAAGUGAGACCCUCCACCUUG		1102-1124
AD-1633623.2	GGUGGAGGGUCUCACUUUCCU		1105-1125	AGGAAAGUGAGACCCUCCACCUU		1103-1125
AD-1633627.2	GAGGGUCUCACUUUCCAGCAU		1109-1129	AUGCUGGAAAGUGAGACCCUCCA		1107-1129
AD-1633628.2	AGGGUCUCACUUUCCAGCAAU		1110-1130	AUUGCUGGAAAGUGAGACCCUCC		1108-1130
AD-1633630.2	GGUUCACUUUCCAGCAAAAU		1112-1132	AUUUUGCUGGAAAGUGAGACCCU		1110-1132
AD-1633631.2	GUUCACUUUCCAGCAAAACU		1113-1133	AGUUUUGCUGGAAAGUGAGACCC		1111-1133
AD-1633632.2	UCUCACUUUCCAGCAAAACUU		1114-1134	AAGUUUUGCUGGAAAGUGAGACC		1112-1134
AD-1633633.1	CUCACUUUCCAGCAAAACUCU		1115-1135	AGAGUUUUGCUGGAAAGUGAGAC		1113-1135
AD-1633634.1	UCACUUUCCAGCAAAACUCCU		1116-1136	AGGAGUUUUGCUGGAAAGUGAGA		1114-1136
AD-1633635.1	CACUUUCCAGCAAAACUCCCU		1117-1137	AGGGAGUUUUGCUGGAAAGUGAG		1115-1137
AD-1633636.1	ACUUUCCAGCAAAACUCCCUU		1118-1138	AAGGGAGUUUUGCUGGAAAGUGA		1116-1138
AD-1633637.1	CUUUCCAGCAAAACUCCCUU		1119-1139	AGAGGGAGUUUUGCUGGAAAGUG		1117-1139
AD-1633638.1	UUUCCAGCAAAACUCCCUCAU		1120-1140	AUGAGGGAGUUUUGCUGGAAAGU		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	UUCAGCAAAACUCCCUCAAU		1121-1141	AUUGAGGGAGUUUUGCUGGAAAG		1119-1141
AD-1633640.1	UCCAGCAAAACUCCCUCAACU		1122-1142	AGUUGAGGGAGUUUUGCUGGAAA		1120-1142
AD-1633641.1	CCAGCAAAACUCCCUCAACUU		1123-1143	AAGUUGAGGGAGUUUUGCUGGAA		1121-1143
AD-1633642.1	CAGCAAAACUCCCUCAACUGU		1124-1144	ACAGUUGAGGGAGUUUUGCUGGA		1122-1144
AD-1633643.1	AGCAAAACUCCCUCAACUGGU		1125-1145	ACCAUUUGAGGGAGUUUUGCUGG		1123-1145
AD-1633644.1	GCAAAACUCCCUCAACUGGAU		1126-1146	AUCCAGUUGAGGGAGUUUUGCUG		1124-1146
AD-1633645.1	CAAAACUCCCUCAACUGGAUU		1127-1147	AUCCAGUUGAGGGAGUUUUGCU		1125-1147
AD-1633646.1	AAACUCCCUCAACUGGAUGU		1128-1148	ACAUCCAGUUGAGGGAGUUUUGC		1126-1148
AD-1633647.1	AAACUCCCUCAACUGGAUGAU		1129-1149	AUCAUCCAGUUGAGGGAGUUUUG		1127-1149
AD-1633648.1	AACUCCCUCAACUGGAUGAAU		1130-1150	AUUAUCCAGUUGAGGGAGUUUU		1128-1150
AD-1633649.1	ACUCCCUCAACUGGAUGAAGU		1131-1151	ACUUAUCCAGUUGAGGGAGUUU		1129-1151
AD-1633650.1	CUCCCUCAACUGGAUGAAGAU		1132-1152	AUCUUAUCCAGUUGAGGGAGUU		1130-1152
AD-1633651.1	UCCCUCAACUGGAUGAAGAAU		1133-1153	AUUCUUAUCCAGUUGAGGGAGU		1131-1153
AD-1633652.1	CCCUCAACUGGAUGAAGAAAU		1134-1154	AUUUUAUUAUCCAGUUGAGGGAG		1132-1154
AD-1633653.1	CUCAACUGGAUGAAGAAACUU		1136-1156	AAGUUUCUUUAUUAUCCAGUUGAGGG		1134-1156
AD-1633678.1	AGGAUCUUUAUGACCUAGGCU		1201-1221	ACCUAGCAGGUCUAUUAAGAUCCUUG		1199-1221
AD-1633683.1	CUUAUGACCUAGCAGGACCUUGU		1206-1226	ACAGGUCCUAGCAGGUCUAUUAAGAU		1204-1226
AD-1633732.1	CGAGCUGAACCUAGCAAAAUU		1261-1281	AAUUUUUAGCAGGUUCAGCUCGGU		1259-1281
AD-1633733.1	GAGCUGAACCUAGCAAAAUUU		1262-1282	AAAUUUUUUAGCAGGUUCAGCUCGG		1260-1282
AD-1633734.1	AGCUGAACCUAGCAAAAUUUGU		1263-1283	ACAAUUUUUAGCAGGUUCAGCUCG		1261-1283
AD-1633735.1	GCUGAACCUAGCAAAAUUUGAU		1264-1284	AUCAUUUUUAGCAGGUUCAGCUC		1262-1284
AD-1633736.1	CUGAACCUAGCAAAAUUUGAGU		1265-1285	ACUCAUUUUUAGCAGGUUCAGCU		1263-1285
AD-1633737.1	UGAACCUAGCAAAAUUUGAGCU		1266-1286	AGCUCAAUUUUUAGCAGGUUCAGC		1264-1286
AD-1633738.1	GAACCUAGCAAAAUUUGAGCAU		1267-1287	AUGCUCAAUUUUUAGCAGGUUCAG		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	AACCCUGCAAAAAUUUGAGCAAU		1268-1288	AUUGCUCAAAAUUUUGCAGGUUCA		1266-1288
AD-1633740.1	ACCUGCAAAAAUUUGAGCAAUU		1269-1289	AAUUGCUCAAUUUUUGCAGGUUC		1267-1289
AD-1633741.1	CCUGCAAAAAUUUGAGCAAUGU		1270-1290	ACAUUGCUCAAUUUUUGCAGGUU		1268-1290
AD-1633742.1	CUGCAAAAAUUUGAGCAAUGAU		1271-1291	AUCAUUGCUCAAUUUUUGCAGGU		1269-1291
AD-1633743.1	UGCAAAAAUUUGAGCAAUGACU		1272-1292	AGUCAUUGCUCAAUUUUUGCAGG		1270-1292
AD-1633759.1	GAGGUGCUGAACAGCAUUUUU		1307-1327	AAAAAUGCUGUUUCAGCAUCCUCC		1305-1327
AD-1633777.1	UGAGAGAGAGCCCCACAGAGUU		1345-1365	AACUCUGUGGGCUCUCUCUCAUC		1343-1365
AD-1633779.1	AGAGAGAGCCCCACAGAGUCUU		1347-1367	AAGACUCUGUGGGCUCUCUCUCA		1345-1367
AD-1633780.1	GAGAGAGCCCCACAGAGUCUAU		1348-1368	AUAGACUCUGUGGGCUCUCUCUC		1346-1368
AD-1633840.1	GAACCGCCCAUUCUUGUUUGU		1408-1428	ACAAACAGGAAUUGGGCGGUUCAG		1406-1428
AD-1633841.1	AACCGCCCAUUCUUGUUUGCU		1409-1429	AGCAAACAGGAAUUGGGCGGUUCA		1407-1429
AD-1633842.1	ACCGCCCAUUCUUGUUUGCUU		1410-1430	AAGCAAACAGGAAUUGGGCGGUUC		1408-1430
AD-1633843.1	CCGCCCAUUCUUGUUUGCUGU		1411-1431	ACAGCAAACAGGAAUUGGGCGGUU		1409-1431
AD-1633844.1	CGCCCAUUCUUGUUUGCUGUU		1412-1432	AACAGCAAACAGGAAUUGGGCGGU		1410-1432
AD-1633845.1	GCCCAUUCUUGUUUGCUGUGU		1413-1433	ACACAGCAAACAGGAAUUGGGCGG		1411-1433
AD-1633846.1	CCCAUUCUUGUUUGCUGUGUU		1414-1434	AACACAGCAAACAGGAAUUGGGCG		1412-1434
AD-1633847.1	CAUUCUUGUUUGCUGUGUAUU		1416-1436	AAUACACAGCAAACAGGAAUUGG		1414-1436
AD-1633848.1	AUUCUUGUUUGCUGUGUAUGU		1417-1437	ACAUACACAGCAAACAGGAAUUG		1415-1437
AD-1633849.1	UUCCUGUUUGCUGUGUAUGAU		1418-1438	AUCAUACACAGCAAACAGGAAUG		1416-1438
AD-1633850.1	UCCUGUUUGCUGUGUAUGAUU		1419-1439	AUCAUACACAGCAAACAGGAAU		1417-1439
AD-1633851.1	CCUGUUUGCUGUGUAUGAUCU		1420-1440	AGAUAUACACAGCAAACAGGAA		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	UUUGCUGUGUAUGAUCAAAGU		1424-1444	ACUUUGAUCUAACACAGCAAAACA		1422-1444
AD-1633946.1	GUUCUCCACCUUUUUCUUAU		1608-1628	AUAGAAGAAAAGGUGGAGACUG		1606-1628
AD-1633947.1	CUCCACCUUUUUCUUAUUAU		1610-1630	AUUAGAAGAAAAGGUGGAGAC		1608-1630
AD-1633948.1	UCCACCUUUUUCUUAUUAU		1611-1631	ACUUAGAAGAAAAGGUGGAGAG		1609-1631
AD-1633949.1	CCCACCUUUUUCUUAUUAU		1612-1632	AUCAUUAGAAGAAAAGGUGGAG		1610-1632
AD-1633950.1	CACCUUUUUCUUAUUAUUAU		1614-1634	AACUCAUUAGAAGAAAAGGUGGG		1612-1634
AD-1633951.1	ACCUUUUUCUUAUUAUUAU		1615-1635	AGACUCAUUAGAAGAAAAGGUGG		1613-1635
AD-1633991.1	CCGUUUCUCCUUGGUCUAAGU		1655-1675	ACUUAGACCAAGGAGAAAACGGCU		1653-1675
AD-1633992.1	CGUUUCUCCUUGGUCUAAGU		1656-1676	AACUUAGACCAAGGAGAAAACGGC		1654-1676
AD-1633993.1	GUUUUCUCCUUGGUCUAAGU		1657-1677	ACACUUAGACCAAGGAGAAAACGG		1655-1677
AD-1634065.1	GUUUGCUGGGUUUAUUUUAGU		1729-1749	ACUAAAUAUAAACCCAGCAAAACUG		1727-1749
AD-1634066.1	UUUGCUGGGUUUAUUUUAGU		1730-1750	AUCUAAAUAUAAACCCAGCAAAACU		1728-1750
AD-1634067.1	UUUGCUGGGUUUAUUUUAGU		1731-1751	ACUCUAAAUAUAAACCCAGCAAAAC		1729-1751
AD-1634068.1	UGCUGGGUUUAUUUUAGAGU		1732-1752	AUCUCUAAAUAUAAACCCAGCAAA		1730-1752
AD-1634069.1	CUGGGUUUAUUUUAGAGAAU		1734-1754	AAUUCUCUAAAUAUAAACCCAGCA		1732-1754
AD-1634070.1	UGGGUUUAUUUUAGAGAAU		1735-1755	ACAUUCUCUAAAUAUAAACCCAGC		1733-1755
AD-1634071.1	GGGUUAUUUUAGAGAAUUGGU		1736-1756	ACCAUUCUCUAAAUAUAAACCCAG		1734-1756
AD-1634072.1	GGGAGGCAAGAACCAAGUGUUU		1761-1781	AAACACUGGUUUCUUGCCUCCCCA		1759-1781
AD-1634073.1	GGAGGCAAGAACCAAGUGUUU		1762-1782	AAACACUGGUUUCUUGCCUCCCC		1760-1782
AD-1634074.1	GAGGCAAGAACCAAGUGUUUAU		1763-1783	AUAAACACUGGUUUCUUGCCUCCC		1761-1783
AD-1634075.1	AGGCAAGAACCAAGUGUUUAU		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	AAGAACCAGUGUUUAGCGCGU		1768-1788	ACGCGCUAAACACUGGUUCUUGC		1766-1788
AD-1634080.1	AGAACCAGUGUUUAGCGCGGU		1769-1789	ACCGCGCUAAACACUGGUUCUUG		1767-1789
AD-1634081.1	GAACCAGUGUUUAGCGCGGU		1770-1790	ACCGCGCUAAACACUGGUUCU		1768-1790
AD-1634082.1	AACCAGUGUUUAGCGCGGAU		1771-1791	AUCCGCGCUAAACACUGGUUCU		1769-1791
AD-1634105.1	CUGUCCAAAAAGAAUCCAU		1794-1814	AUGGAUUCUUUUUGGAACAGUA		1792-1814
AD-1634107.1	GUUCCAAAAAGAAUCCAAU		1796-1816	AGUUGAAUUCUUUUUGGAACAG		1794-1816
AD-1634109.1	UCCAAAAAGAAUCCAAACCGU		1798-1818	ACGUUGGAUUCUUUUUGGAAC		1796-1818
AD-1634110.1	CCAAAAAGAAUCCAAACCGAU		1799-1819	AUCGGUUGGAUUCUUUUUGGAA		1797-1819
AD-1634111.1	CAAAAAAGAAUCCAAACCGACU		1800-1820	AGUCGGUUGGAUUCUUUUUGGA		1798-1820
AD-1634112.1	AAAAAGAAUCCAAACCGACCU		1801-1821	AGGUCGGUUGGAUUCUUUUUGG		1799-1821
AD-1634113.1	AAAGAAUCCAAACCGACCAU		1802-1822	AUGGUCGGUUGGAUUCUUUUUG		1800-1822
AD-1634114.1	AAAGAAUCCAAACCGACCAU		1803-1823	ACUGGUCGGUUGGAUUCUUUUU		1801-1823
AD-1634115.1	AAGAAUCCAAACCGACCAU		1804-1824	AGCUGGUCGGUUGGAUUCUUUU		1802-1824
AD-1634116.1	GAAUCCAAACCGACCAU		1806-1826	AAAGCUGGUCGGUUGGAUUCU		1804-1826
AD-1634117.1	AAUCCAAACCGACCAUUGU		1807-1827	ACAAGCUGGUCGGUUGGAUUCU		1805-1827
AD-1634118.1	AUCCAAACCGACCAUUGUU		1808-1828	AACAAGCUGGUCGGUUGGAUUC		1806-1828
AD-1634119.1	UCCAAACCGACCAUUGUUUU		1810-1830	AAACAAGCUGGUCGGUUGGAU		1808-1830
AD-1634120.1	CCAAACCGACCAUUGUUUGU		1811-1831	ACAAACAAGCUGGUCGGUUGGA		1809-1831
AD-1634121.1	CAACCGACCAUUGUUUGUU		1812-1832	AACAACAAGCUGGUCGGUUGGA		1810-1832
AD-1634122.1	AACCGACCAUUGUUUGUU		1813-1833	ACACAACAAGCUGGUCGGUUGG		1811-1833
AD-1634123.1	ACCGACCAUUGUUUGUGAU		1814-1834	AUCACAACAAGCUGGUCGGUUG		1812-1834
AD-1634124.1	CCGACCAUUGUUUGUGAAU		1815-1835	AUUCACAACAAGCUGGUCGGU		1813-1835
AD-1634125.1	CGACCAUUGUUUGUGAAU		1816-1836	AUUUCACAACAAGCUGGUCGGU		1814-1836
AD-1634126.1	GACCAUUGUUUGUGAAU		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	ACCAGCUUGUUUGUGAAAACAU		1818-1838	AUGUUUCACAAACAAAGCUGGUCG		1816-1838
AD-1634128.1	CCAGCUUGUUUGUGAAACAAU		1819-1839	AUUGUUUCACAAACAAAGCUGGUC		1817-1839
AD-1634129.1	CAGCUUGUUUGUGAAACAAAU		1820-1840	AUUUGUUUCACAAACAAAGCUGGU		1818-1840
AD-1634130.1	AGCUUGUUUGUGAAACAAAAU		1821-1841	AUUUGUUUCACAAACAAAGCUGG		1819-1841
AD-1634135.1	UGUCCCCUUUUCAGUUGAGU		1844-1864	ACUCAACUUGAAAAAGGGAACACU		1842-1864
AD-1634136.1	GUUCCCCUUUCAAGUUGAGAU		1845-1865	AUCUCAACUUGAAAAAGGGAACAC		1843-1865
AD-1634137.1	UUCUUUUUCAAGUUGAGAAU		1846-1866	AUUCUCAACUUGAAAAAGGGAACA		1844-1866
AD-1634146.1	CAAGUUGAGAACAAAAUUUGU		1855-1875	ACAAUUUUUGUUCUCAACUUGAA		1853-1875
AD-1634147.1	AAGUUGAGAACAAAAUUUGGU		1856-1876	ACCAUUUUUUGUUCUCAACUUGA		1854-1876
AD-1634148.1	GUUGAGAACAAAAUUUGGGUU		1858-1878	AACCCAAUUUUUGUUCUCAACUU		1856-1878
AD-1634149.1	UUGAGAACAAAAUUUGGGUUU		1859-1879	AAACCCAAUUUUUGUUCUCAACU		1857-1879
AD-1634150.1	UGAGAACAAAAUUUGGGUUUU		1860-1880	AAAACCCAAUUUUUGUUCUCAAC		1858-1880
AD-1634151.1	GAGAACAAAAUUUGGGUUUUU		1861-1881	AAAAACCCAAUUUUUGUUCUCA		1859-1881
AD-1634152.1	AGAACAAAAUUUGGGUUUUUAU		1862-1882	AUAAAACCCAAUUUUUGUUCUCA		1860-1882
AD-1634153.1	GAACAAAAAUUGGGUUUUUAU		1863-1883	AUUAAAACCCAAUUUUUGUUCUC		1861-1883
AD-1634162.1	AGUAUACAUUUUUUGCAUUGCU		1889-1909	AGCAAUGCAAAAAAUGUAUACUU		1887-1909
AD-1634163.1	GUUAUACAUUUUUUGCAUUGCCU		1890-1910	AGGCAUUGCAAAAAAUGUAUACUU		1888-1910
AD-1634164.1	UAUAUAUUUUUGCAUUGCCUU		1891-1911	AAGGCAUUGCAAAAAAUGUAUACU		1889-1911
AD-1634165.1	AUAUAUUUUUGCAUUGCCUUU		1892-1912	AAAGGCAUUGCAAAAAAUGUAUAC		1890-1912
AD-1634169.1	AUUUUUGCAUUGCCUUCGGUU		1896-1916	AACCGAAGGCAUUGCAAAAAAUGU		1894-1916
AD-1634170.1	UUUUUGCAUUGCCUUCGGUUU		1897-1917	AAACCGAAGGCAUUGCAAAAAAUG		1895-1917
AD-1634171.1	UUUUGCAUUGCCUUCGGUUUU		1898-1918	AAAACCGAAGGCAUUGCAAAAAAU		1896-1918
AD-1634172.1	UUUGCAUUGCCUUCGGUUUUGU		1899-1919	ACAAACCGAAGGCAUUGCAAAAA		1897-1919
AD-1634173.1	UUUGCAUUGCCUUCGGUUUUGUU		1900-1920	AACAAACCGAAGGCAUUGCAAAA		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	UGCAUUGCCUUCGCUUUGUAU		1901-1921	AUACAAACCGAAGGCAAU		1899-1921
AD-1634175.1	GCAUUGCCUUCGCUUUGUAU		1902-1922	AAUACAAACCGAAGGCAAU		1900-1922
AD-1634176.1	CAUUGCCUUCGCUUUGUAU		1903-1923	AAUACAAACCGAAGGCAAU		1901-1923
AD-1634177.1	AUUGCCUUCGCUUUGUAU		1904-1924	AAUACAAACCGAAGGCAAU		1902-1924
AD-1634178.1	UUGCCUUCGCUUUGUAU		1905-1925	AUAAUACAAACCGAAGGCAAU		1903-1925
AD-1634179.1	UGCCUUCGCUUUGUAU		1906-1926	ACUAAUACAAACCGAAGGCAAU		1904-1926
AD-1634180.1	GCCUUCGCUUUGUAU		1907-1927	AACUAAUACAAACCGAAGGCAAU		1905-1927
AD-1634181.1	CCUUCGCUUUGUAU		1908-1928	ACACUAAUACAAACCGAAGGCAAU		1906-1928
AD-1634182.1	CUUCGCUUUGUAU		1909-1929	AACACUAAUACAAACCGAAGGCAAU		1907-1929
AD-1634183.1	UUCGCUUUGUAU		1910-1930	AGACACUAAUACAAACCGAAGGCAAU		1908-1930
AD-1634184.1	UCGCUUUGUAU		1911-1931	AAGACACUAAUACAAACCGAAGGCAAU		1909-1931
AD-1634185.1	CGCUUUGUAU		1912-1932	AAAGACACUAAUACAAACCGAAGGCAAU		1910-1932
AD-1634186.1	GGUUGUAU		1913-1933	ACAAGACACUAAUACAAACCGAAGGCAAU		1911-1933
AD-1634187.1	GUUUGUAU		1914-1934	AUCAAGACACUAAUACAAACCGGCAAU		1912-1934
AD-1634188.1	UUUGUAU		1915-1935	AUUCAGACACUAAUACAAACCGGCAAU		1913-1935
AD-1634189.1	UUGUAU		1916-1936	AAUUCAGACACUAAUACAAACCGGCAAU		1914-1936
AD-1634190.1	UGUAU		1917-1937	ACAUUCAGACACUAAUACAAACCGGCAAU		1915-1937
AD-1634191.1	GUUUUAGUGUCUUGAAU		1918-1938	AACAUUCAGACACUAAUACAAACCGGCAAU		1916-1938
AD-1634192.1	UAUUUAGUGUCUUGAAU		1919-1939	AUACAUUCAGACACUAAUACAAACCGGCAAU		1917-1939
AD-1634193.1	AUUUAGUGUCUUGAAU		1920-1940	AUUACAUUCAGACACUAAUACAAACCGGCAAU		1918-1940
AD-1634194.1	UUUAGUGUCUUGAAU		1921-1941	ACUUACAUUCAGACACUAAUACAAACCGGCAAU		1919-1941
AD-1634195.1	UUAGUGUCUUGAAU		1922-1942	AUCUUACAUUCAGACACUAAUACAAACCGGCAAU		1920-1942
AD-1634196.1	UAGUGUCUUGAAU		1923-1943	AUUCUUACAUUCAGACACUAAUACAAACCGGCAAU		1921-1943
AD-1634197.1	AGUGUCUUGAAU		1924-1944	AGUUCUUACAUUCAGACACUAAUACAAACCGGCAAU		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	UGUCUUGAAUGUAAAGAACAUU		1926-1946	AAUGUUCUUACAUAUCAAAGACACU		1924-1946
AD-1634200.1	GUUCUUGAAUGUAAAGAACAUU		1927-1947	ACAUGUUCUUACAUAUCAAAGACAC		1925-1947
AD-1634203.1	UUUGAAUGUAAAGAACAUAGACCU		1930-1950	AGGUCAUGUUCUUACAUAUCAAAGA		1928-1950
AD-1634209.1	GUAAAGAACAUAGACCUCCGUGU		1936-1956	ACACGGAGGUCAUGUUCUUACAUA		1934-1956
AD-1634210.1	UAAGAACAUAGACCUCCGUGUU		1937-1957	AACACGGAGGUCAUGUUCUUACA		1935-1957
AD-1634211.1	AAGAACAUAGACCUCCGUGUAU		1938-1958	AUACACGGAGGUCAUGUUCUUAC		1936-1958
AD-1634212.1	AGAACAUAGACCUCCGUGUAGU		1939-1959	ACUACACGGAGGUCAUGUUCUUA		1937-1959
AD-1634213.1	GAACAUGACCUCCGUGUAGUU		1940-1960	AACUACACGGAGGUCAUGUUCUU		1938-1960
AD-1634214.1	AACAUGACCUCCGUGUAGUGU		1941-1961	ACACUACACGGAGGUCAUGUUCU		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	UUUCCACAGAUUCUUGUGAUU		1979-1999	AAUCACAAGCAUCUGUGGAAAAA		1977-1999
AD-1634235.1	UUCCACAGAUUCUUGUGAUUU		1980-2000	AAUUCACAAGCAUCUGUGGAAAA		1978-2000
AD-1634236.1	UCCACAGAUUCUUGUGAUUUU		1981-2001	AAAAUCACAAGCAUCUGUGGAAA		1979-2001
AD-1634237.1	CCACAGAUUCUUGUGAUUUUU		1982-2002	AAAAUCACAAGCAUCUGUGGAA		1980-2002
AD-1634238.1	CACAGAUUCUUGUGAUUUUUU		1983-2003	AAAAAUCACAAGCAUCUGUGGA		1981-2003
AD-1634282.1	ACCUGAAUUUCUGUUUGAAUU		2027-2047	AAUUCAAAACAGAAAUUCAGGUGC		2025-2047
AD-1634283.1	CCUGAAUUUCUGUUUGAAUGU		2028-2048	ACAUUCAAACAGAAAUUCAGGUG		2026-2048
AD-1634304.1	GGAAACCAUAGCUGGUUAUUUU		2049-2069	AAAAUAAACAGCUAUGGUUCCGC		2047-2069
AD-1634305.1	GAACCAUAGCUGGUUAUUUCU		2050-2070	AGAAUAAACAGCUAUGGUUCCG		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	CCUUGUGUUAGUAAUAAAACGU		2072-2092	ACGUUUUUUUACUAAACACAAGGGA		2070-2092
AD-1634328.1	CUUGUGUUAGUAAUAAAACGUU		2073-2093	AACGUUUUUUUACUAAACACAAGGG		2071-2093
AD-1634329.1	UUUGUGUUAGUAAUAAAACGUCU		2074-2094	AGACGUUUUUUUACUAAACACAAGG		2072-2094
AD-1634330.1	UGUGUUAGUAAUAAAACGUCUU		2075-2095	AAGACGUUUUUUUACUAAACACAAG		2073-2095
AD-1634331.1	GUGUUAGUAAUAAAACGUCUUU		2076-2096	AAAGACGUUUUUUUACUAAACACA		2074-2096
AD-1634332.1	UGUUAGUAAUAAAACGUCUUUGU		2077-2097	ACAAGACGUUUUUUUACUAAACACA		2075-2097
AD-1634333.1	GUUAGUAAUAAAACGUCUUUGCU		2078-2098	AGCAAGACGUUUUUUUACUAAACAC		2076-2098
AD-1657992.1	AGCCUGAGGGCCACCAUCCUU		86-106	AAGGAUGGUGGCCCCUCAGGCUC		84-106
AD-1657994.1	CCUGAGGGCCACCAUCCUCUU		88-108	AAGAGGAUGGUGGCCCCUCAGGCU		86-108
AD-1657998.1	AGGGCCACCAUCCUCUGCCUU		92-112	AAGGCAGAGGATGGUGGCCCUCA		90-112
AD-1658030.1	GUGACCGGGGUGUACAUACACU		138-158	AGUGTATGUACACCCGGUCACCU		136-158
AD-1658032.1	CUUCCACCUUGUUAUCCACAU		160-180	ATGUGGAUGACGAGGUGGAAGGG		158-180
AD-1658033.1	UUCCACCUUGUUAUCCACAAU		161-181	ATUGTGAUGACGAGGUGGAAGG		159-181
AD-1658034.1	UCCACCUUGUUAUCCACAAUU		162-182	AAUUGGAUGACGAGGUGGAAG		160-182
AD-1658035.1	CCACCUUGUUAUCCACAAUGU		163-183	ACAUTGTGAUGACGAGGUGGAA		161-183
AD-1658036.1	CACCUUGUUAUCCACAAUGAU		164-184	ATCATUGGATGACGAGGUGGA		162-184
AD-1658038.1	CCUGUUAUCCACAAUGAGAU		166-186	ATCUCATUGGGAUGACGAGGUG		164-186
AD-1658039.1	CUGUUAUCCACAAUGAGAGU		167-187	ACUCTCAUUGGGAUGACGAGGU		165-187
AD-1658040.1	UCGUUAUCCACAAUGAGAGUU		168-188	AACUCUCAUUGTGAUGACGAGG		166-188
AD-1658041.1	CGUUAUCCACAAUGAGAGU		169-189	ATACTCTCAUUGGGAUGACGAG		167-189
AD-1658042.1	GUCUAUCCACAAUGAGAGUACU		170-190	AGUACUCUCAUTGUGGAUGACGA		168-190
AD-1658043.1	UCAUCCACAAUGAGAGUACCU		171-191	AGGUACTCUCATUGGGAUGACG		169-191
AD-1658044.1	CAUCCACAAUGAGAGUACCUU		172-192	AAGGTACUCUCAUUGGGAUGAC		170-192
AD-1658045.1	AUCCACAAUGAGAGUACCUU		173-193	ACAGGUACUCUCAUUGGGAUGA		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	UCCACAUGAGAGUACCUGUU		174-194	AACAGGTACUCTCAUUGUGGAUG		172-194
AD-1658047.1	CCACAAUGAGAGUACCUGUGU		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	CAAAUGAGAGUACCUGUGAGCU		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	UACCUGUGAGCAGCUGGGCAAU		187-207	ATUGCCAGCUGCUCACAGGUACU		185-207
AD-1658184.1	AAUGGUCGGGAUGCUGGGCCAU		352-372	ATGGCCAGCAUCCCGACCAUUGC		350-372
AD-1658185.1	AUGGUCGGGAUGCUGGGCAAU		353-373	ATUGGCCAGCATCCCCACCAUUG		351-373
AD-1658186.1	UGGUCGGGAUGCUGGGCCAAU		354-374	AGUUGGCCAGCAUCCCGACCAUU		352-374
AD-1658187.1	GGUCGGGAUGCUGGGCCAAU		355-375	AAGUTGGCCAGCAUCCCGACCAU		353-375
AD-1658188.1	GUCGGGAUGCUGGGCCAAU		356-376	AAAGTUGGCCAGCAUCCCGACCA		354-376
AD-1658189.1	UCGGGAUGCUGGGCCAAU		357-377	AGAAGTUGGCCAGCAUCCCGACC		355-377
AD-1658190.1	CGGGAUGCUGGGCCAAU		358-378	AAGAAGTUGGCCAGCAUCCCGAC		356-378
AD-1658191.1	GGGAUGCUGGGCCAAU		359-379	AAAGAAGUUGGCCAGCAUCCCGA		357-379
AD-1658192.1	GGGAUGCUGGGCCAAU		360-380	ACAAGAAGUUGGCCAGCAUCCCG		358-380
AD-1658193.1	GAUGCUGGGCCAAU		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	AAGCCCCAAGAAUUGGCCAGCAU		362-384
AD-1658197.1	CUGGCCAACUUCUUGGGCUU		365-385	AAAGCCCCAAGAAUUGGCCAGCA		363-385
AD-1658200.1	GCCAAUUCUUGGGCUUCCGU		368-388	ACGGAAGCCCCAAGAAUUGGCCA		366-388
AD-1658201.1	CCAAUUCUUGGGCUUCCGUU		369-389	AACGGAAGCCCCAAGAAUUGGCC		367-389
AD-1658202.1	CAACUUCUUGGGCUUCCGUU		370-390	ATACGGAAGCCCCAAGAAUUGGC		368-390
AD-1658203.1	AACUUCUUGGGCUUCCGUU		371-391	AAUACGGAAGCCCCAAGAAUUGG		369-391
AD-1658204.1	ACUUCUUGGGCUUCCGUU		372-392	ATAUACGGAAGCCCCAAGAAUUG		370-392
AD-1658205.1	CUUCUUGGGCUUCCGUU		373-393	AAUATACGGAAGCCCCAAGAAU		371-393
AD-1658206.1	UUCUUGGGCUUCCGUU		374-394	ATAUACGGAAGCCCCAAGAAU		372-394
AD-1658207.1	UCUUGGGCUUCCGUU		375-395	AAUATATACGGAAGCCCCAAGAA		373-395
AD-1658208.1	CUUGGGCUUCCGUU		376-396	ACAUUACGGAAGCCCCAAGAA		374-396
AD-1658209.1	UUGGGCUUCCGUU		377-397	ACCATAUACGGAAGCCCCAAGA		375-397
AD-1658211.1	GGGCUUCCGUU		379-399	ATGCCATAUACGGAAGCCCCA		377-399
AD-1658212.1	GGCUUCCGUU		380-400	AAUGCCAUAUATACGGAAGCCCCA		378-400
AD-1658213.1	GCUCCGUU		381-401	ACAUGCCAUAUACGGAAGCCCC		379-401
AD-1658220.1	UAUAUUGGCAUGCACAGUGU		388-408	ACACTGTGCAUGCCAUAUAUACG		386-408
AD-1658221.1	AUAUAUGGCAUGCACAGUGAU		389-409	ATCACUGUGCATGCCAUUAUAUAC		387-409
AD-1658222.1	UAUAUGGCAUGCACAGUGAGU		390-410	ACUCACTGUGCAUGCCAUAUAUA		388-410
AD-1658223.1	AUAUGGCAUGCACAGUGAGCU		391-411	AGCUCACUGUGCAUGCCAUAUAU		389-411
AD-1658224.1	UAUGGCAUGCACAGUGAGCUU		392-412	AAGCTCACUGUGCAUGCCAUAUA		390-412
AD-1658225.1	AUGGCAUGCACAGUGAGCUU		393-413	ATAGCUCACUGTGCAUGCCAUAU		391-413
AD-1658226.1	UGGCAUGCACAGUGAGCUU		394-414	AAUAGCTCACUGUGCAUGCCAUA		392-414
AD-1658227.1	GGCAUGCACAGUGAGCUU		395-415	ACAUAGCUCACUGCAUGCCAUA		393-415
AD-1658228.1	GCAUGCACAGUGAGCUU		396-416	ACCATAGCUCACUGCAUGCCAUA		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	UUCUUUGGAAGGACAAGAAAU		531-551	AGUUCUTGUCCTUCCAAGGAACA		529-551
AD-1658315.1	CCUUGGAAGGACAAGAACUGU		533-553	ACAGTUCUUGUCCUCCAAAGGAA		531-553
AD-1658316.1	CUUGGAAGGACAAGAACUGCU		534-554	AGCAGUTCUUGTCCUCCAAAGGA		532-554
AD-1658448.2	CACCUAGAGCAGCCGUUUGUU		692-712	AACAAACGGCUGCUUCAGGUGCA		690-712
AD-1658451.2	CUGAAGCAGCCGUUUGUGCAU		695-715	ATGCACAAACGGCUGCUUCAGGU		693-715
AD-1658463.2	UUUGCAGGGCCUGGCUCUU		707-727	AAGAGCCAGGGCCUGGCACAAACG		705-727
AD-1658464.2	UUUGCAGGGCCUGGCUCUCU		708-728	AGAGAGCCAGGGCCUGGCACAAAC		706-728
AD-1658465.2	UGUGCAGGGCCUGGCUCUCUU		709-729	AAGAGAGCCAGGGCCUGGCACAAA		707-729
AD-1658466.2	GUGCAGGGCCUGGCUCUCUAU		710-730	ATAGAGAGCCAGGGCCUGGCACAA		708-730
AD-1658467.2	UGCAGGGCCUGGCUCUCUAUU		711-731	AAUAGAGAGCCAGGGCCUGGCACA		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	AGAACCTGUCAAUCUUCUCAGCA		781-803
AD-1658520.2	UGAGAAGAUUGACAGGUUCAU		784-804	ATGAACCUUGUCAAUUCUCAGC		782-804
AD-1658521.2	GAGAGAAGAUUGACAGGUUCAU		785-805	AAUGAACCUUGUCAAUUCUCAG		783-805
AD-1658522.2	AGAAGAUUGACAGGUUCAUGU		786-806	ACAUGAACCUUGTCAAUUCUUCUA		784-806
AD-1658523.2	GAAGAUUGACAGGUUCAUGCU		787-807	AGCATGAACCUUGUCAAUUCUUC		785-807
AD-1658524.2	AAGAUUGACAGGUUCAUGCAU		788-808	ATGCAUGAACCTGUCAAUUCUUCU		786-808
AD-1658525.2	AGAUUGACAGGUUCAUGCAGU		789-809	ACUGCATGAACCUUGUCAAUUCU		787-809
AD-1658526.2	GAUUGACAGGUUCAUGCAGGU		790-810	ACCUGCAUGAACCUUGUCAAUUCU		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	AGCCTGCAUGAACCUGUCAAUUC		789-811
AD-1658528.2	UUUGACAGGUUCAUGCAGGCUU		792-812	AAGCCUGCAUGAACCUGUCAAUUC		790-812
AD-1658529.2	UGACAGGUUCAUGCAGGCUU		793-813	ACAGCCTGCAUGAACCUGUCAAU		791-813
AD-1658530.2	GACAGGUUCAUGCAGGCUU		794-814	AACAGCCUGCATGAACCUGUCA		792-814
AD-1658531.2	ACAGGUUCAUGCAGGCUU		795-815	ACACAGCCUGCAUGAACCUGUCA		793-815
AD-1658539.2	AUGCAGGCUUGACAGGAU		803-823	ACAUCCTGUCACAGCCUGCAUGA		801-823
AD-1658541.2	GCAGGCUUGACAGGAU		805-825	ATCCAUCUGUCACAGCCUGCAU		803-825
AD-1658542.2	CAGGCUUGACAGGAU		806-826	ATUCCATCCUGTCAACAGCCUGCA		804-826
AD-1658605.2	GCUUUAACACACCUACGUCCA		869-889	ATGGACGUAGGTGUUGAAAGCCA		867-889
AD-1658650.2	GAGUUCUGGGUGGACAAACAGU		935-955	ACUGTUGUCCACCCAGAACUCCU		933-955
AD-1658661.2	GGACAACAGCACCCUCAGUGUU		946-966	AACACUGAGGUGCUGUUGUCCAC		944-966
AD-1658662.2	GACAACAGCACCCUCAGUGUCU		947-967	AGACACTGAGGTGCUGUUGUCCA		945-967
AD-1658663.2	ACAACAGCACCCUCAGUGUCU		948-968	AAGACACUGAGGUGCUGUUGUCC		946-968
AD-1658664.2	CAACAGCACCCUCAGUGUCU		949-969	ACAGACACUGAGGUGCUGUUGUCC		947-969
AD-1658665.2	AACAGCACCCUCAGUGUCU		950-970	AACAGACACUGAGGUGCUGUUGU		948-970
AD-1658801.2	AUGCCUCUGACCCUGGACAAGU		1086-1106	ACUUGUCCAGGTCAGAGGCAUAG		1084-1106
AD-1658818.2	AAGGUGGAGGGUCUCACUUUU		1103-1123	AAAAGUGAGACCCUCCACCUUGU		1101-1123
AD-1658819.2	AGGUGGAGGGUCUCACUUUU		1104-1124	AGAAAGTGAGACCCUCCACCUUG		1102-1124
AD-1658820.2	GGUGGAGGGUCUCACUUUU		1105-1125	AGGAAAGUGAGACCCUCCACCUU		1103-1125
AD-1658824.2	GAGGGUCUCACUUUCCAGCAU		1109-1129	ATGCTGGAAAGTGAGACCCUCCA		1107-1129
AD-1658825.2	AGGGUCUCACUUUCCAGCAU		1110-1130	ATUGCUGGAAAGUGAGACCCUCC		1108-1130
AD-1658827.2	GGUCUCACUUUCCAGCAAAU		1112-1132	ATUUTGCUGGAAAGUGAGACCCU		1110-1132
AD-1658828.2	GUUCACUUUCCAGCAAAACU		1113-1133	AGUUTUGCUGGAAAGUGAGACCC		1111-1133
AD-1658829.2	UCUCACUUUCCAGCAAAACU		1114-1134	AAGUTUTGCUGGAAAGUGAGACC		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	AGGAGUTUUGCTGGAAGAGAGAG		1114-1136
AD-1658832.1	CACUUUCCAGCAAAACUCCCU		1117-1137	AGGGAGTUUUGCUGGAAAGUGAG		1115-1137
AD-1658833.1	ACUUUCCAGCAAAACUCCCUU		1118-1138	AAGGAGUUUUUGCUGGAAAGUGA		1116-1138
AD-1658834.1	CUUUCAGCAAAACUCCCUU		1119-1139	AGAGGGAGUUU'GTCUGGAAAGUG		1117-1139
AD-1658835.1	UUUCCAGCAAAACUCCCUCAU		1120-1140	ATGAGGGAGUUU'GTCUGGAAAGU		1118-1140
AD-1658836.1	UUCCAGCAAAACUCCCUCAU		1121-1141	ATUGAGGGAGUTUUGCUGGAAAG		1119-1141
AD-1658837.1	UCCAGCAAAACUCCCUCAACU		1122-1142	AGUUGAGGGAGTUUUGCUGGAAA		1120-1142
AD-1658838.1	CCAGCAAAACUCCCUCAACUU		1123-1143	AAGUTGAGGGAGUUU'GTCUGGAA		1121-1143
AD-1658839.1	CAGCAAAACUCCCUCAACUGU		1124-1144	ACAGTUGAGGGAGUUU'GTCUGG		1122-1144
AD-1658840.1	AGCAAAACUCCCUCAACUGGU		1125-1145	ACCAGUTGAGGGAGUUU'GTCUGG		1123-1145
AD-1658841.1	GCAAAACUCCCUCAACUGGAU		1126-1146	ATCCAGTUGAGGGAGUUU'GTCUG		1124-1146
AD-1658842.1	CAAAACUCCCUCAACUGGAUU		1127-1147	AAUCCAGUUUGAGGGAGUUU'GCU		1125-1147
AD-1658843.1	AAACUCCCUCAACUGGAUGU		1128-1148	ACAUCCAGUUUGAGGGAGUUU'UGC		1126-1148
AD-1658844.1	AAACUCCCUCAACUGGAUGAU		1129-1149	ATCATCCAGUUUGAGGGAGUUU'UG		1127-1149
AD-1658845.1	AACUCCCUCAACUGGAUGAAU		1130-1150	ATUCAUCCAGUTGAGGGAGUUUU		1128-1150
AD-1658846.1	ACUCCCUCAACUGGAUGAAGU		1131-1151	ACUUCATCCAGTUGAGGGAGUUU		1129-1151
AD-1658847.1	CUCCCUCAACUGGAUGAAGAU		1132-1152	ATCUTCAUCCAGUUUGAGGGAGUU		1130-1152
AD-1658848.1	UCCCUCAACUGGAUGAAGAAU		1133-1153	ATUCTUCAUCCAGUUUGAGGGAGU		1131-1153
AD-1658849.1	CCCUCAACUGGAUGAAGAAU		1134-1154	ATUUCUTCAUCCAGUUUGAGGGAG		1132-1154
AD-1658850.1	CUCAACUGGAUGAAGAAACUU		1136-1156	AAGUTUCUUCATCCAGUUUGAGGG		1134-1156
AD-1658875.1	AGGAUCUUU'AU'GACCU'GCAGGU		1201-1221	ACCUGCAGGUCAU'AAAGAU'CCUUG		1199-1221
AD-1658880.1	CUUAUGACCU'GCAGGACCU'G		1206-1226	ACAGGUCCU'GCAGGUCAU'AAAGAU		1204-1226
AD-1658929.1	CGAGCUGAACCU'GCAAAAAUU		1261-1281	AAUUTUTGCAGGU'U'CA'GCUC'CGGU		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	AAAUUUUUGCAGGUUCAGCUCGG		1260-1282
AD-1658931.1	AGCUGAACCCUGCAAAAAUUU		1263-1283	ACAATUUUUGCAGGUUCAGCUCG		1261-1283
AD-1658932.1	GCUGAACCCUGCAAAAAUUU		1264-1284	ATCAAUUUUGCAGGUUCAGCUC		1262-1284
AD-1658933.1	CUGAACCCUGCAAAAAUUU		1265-1285	ACUCAUUUUGCAGGUUCAGCU		1263-1285
AD-1658934.1	UGAACCCUGCAAAAAUUU		1266-1286	AGCUCAAAAUUUUGCAGGUUCAGC		1264-1286
AD-1658935.1	GAACCCUGCAAAAAUUU		1267-1287	ATGCTCAUUUUGCAGGUUCAG		1265-1287
AD-1658936.1	AACCCUGCAAAAAUUU		1268-1288	ATUGCUCAAUUUUGCAGGUUCA		1266-1288
AD-1658937.1	ACCUGCAAAAAUUU		1269-1289	AAUUGCTCAAUUUUUGCAGGUUC		1267-1289
AD-1658938.1	CCUGCAAAAAUUU		1270-1290	ACAUTGCUCAATUUUUGCAGGUU		1268-1290
AD-1658939.1	CUGCAAAAAUUU		1271-1291	ATCATUGCUCAAUUUUGCAGGU		1269-1291
AD-1658940.1	UGCAAAAAUUU		1272-1292	AGUCAUTGCUCAUUUUGCAGG		1270-1292
AD-1658954.1	GAGGUGCUGAACAGCAUUUUU		1307-1327	AAAAAUGCUGUUTCAGCACCUCCC		1305-1327
AD-1658955.1	AGGUGCUGAACAGCAUUUUU		1308-1328	AAAAATGCUGTUCAGCACCUCC		1306-1328
AD-1658956.1	GGUGCUGAACAGCAUUUUU		1309-1329	AAAAAAUGCUGUUCAGCACCU		1307-1329
AD-1658957.1	GUGCUGAACAGCAUUUUU		1310-1330	AAAAAAAUGTGUUCAGCACCU		1308-1330
AD-1658958.1	UGCUGAACAGCAUUUUU		1311-1331	AAAAAAAUGCUGUUCAGCAC		1309-1331
AD-1658959.1	GCUGAACAGCAUUUUU		1312-1332	ACAAAAAAUGCUGUUCAGCAC		1310-1332
AD-1658960.1	CUGAACAGCAUUUUU		1313-1333	ATCAAAAAAATGCUGUUCAGCA		1311-1333
AD-1658992.1	UGAGAGAGAGCCACAGAGUU		1345-1365	AACUCUGUGGGCUCUCUCAUC		1343-1365
AD-1658994.1	AGAGAGAGCCACAGAGUCUU		1347-1367	AAGACUCUGUGGGCUCUCUCA		1345-1367
AD-1658995.1	GAGAGAGCCACAGAGUCUAU		1348-1368	ATAGACTCUGUGGGCUCUCUC		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	AAGCAAAACAGGAUUGGGCGGUUC		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	CCGCCAUUCCUGUUUGCUGU		1411-1431	ACAGCAAAACAGGAAUUGGGCGGU		1409-1431
AD-1659059.1	CGCCCAUUCUGUUUGCUGU		1412-1432	AACAGCAAAACAGGAAUUGGGCGGU		1410-1432
AD-1659060.1	GCCCAUUCUGUUUGCUGU		1413-1433	ACACAGCAAAACAGGAAUUGGGCGG		1411-1433
AD-1659061.1	CCCAUUCUGUUUGCUGU		1414-1434	AACACAGCAAAACAGGAAUUGGGCG		1412-1434
AD-1659062.1	CCAUUCUGUUUGCUGU		1415-1435	ATACACAGCAAAACAGGAAUUGGGC		1413-1435
AD-1659063.1	CAUUCUGUUUGCUGU		1416-1436	AAUACACAGCAAAACAGGAAUUGGG		1414-1436
AD-1659064.1	AUUCUGUUUGCUGU		1417-1437	ACAUACACAGCAAAACAGGAAUUGG		1415-1437
AD-1659065.1	UUCUGUUUGCUGU		1418-1438	ATCATACAGCAAAACAGGAAUUG		1416-1438
AD-1659066.1	UCCUGUUUGCUGU		1419-1439	AAUCAUACACAGCAAAACAGGAAU		1417-1439
AD-1659067.1	CCUGUUUGCUGU		1420-1440	AGAUCATACACAGCAAAACAGGAA		1418-1440
AD-1659068.1	CUGUUUGCUGU		1421-1441	ATGATCAUACACAGCAAAACAGGA		1419-1441
AD-1659069.1	UGUUUGCUGU		1422-1442	ATUGAUCAUACACAGCAAAACAGG		1420-1442
AD-1659070.1	GUUUUGCUGU		1423-1443	ATUUGATCAUACACAGCAAAACAG		1421-1443
AD-1659071.1	UUUUGCUGU		1424-1444	ACUUTGAUCAUACACAGCAAAACA		1422-1444
AD-1659162.1	GUCUCCCAUUCUUCU		1608-1628	ATAGAAGAAAAGGUGGGAGACUG		1606-1628
AD-1659163.1	CUCCCAUUCUUCU		1610-1630	AAUAGAAGAAAAGGUGGGAGAC		1608-1630
AD-1659164.1	UCCCAUUCUUCU		1611-1631	ACAUAGAAGAAAAGGUGGGAGA		1609-1631
AD-1659165.1	CCCAUUCUUCU		1612-1632	ATCATUAGAAGAAAAGGUGGGAG		1610-1632
AD-1659166.1	CCACCUUUCUUCU		1613-1633	ACUCAUTAGAAGAAAAGGUGGGA		1611-1633
AD-1659167.1	CACCUUUCUUCU		1614-1634	AACUCATUAGAAGAAAAGGUGGG		1612-1634
AD-1659168.1	ACCUUUCUUCU		1615-1635	AGACTCAUUAGAAGAAAAGGUGG		1613-1635
AD-1659208.1	CCGUUUCUCCUUGGUCU		1655-1675	ACUUAGACCAAGGAGAAACGGCU		1653-1675
AD-1659209.1	CGUUUCUCCUUGGUCU		1656-1676	AACUTAGACCAAGGAGAAACGGC		1654-1676
AD-1659210.1	GUUUCUCCUUGGUCU		1657-1677	ACACTUAGACCAAGGAGAAACGG		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	GUUUGCUGGGUUUAUUUUAGU		1729-1749	ACUAAAAUAAACCCAGCAAAACUG		1727-1749
AD-1659283.1	UUUGCUGGGUUUAUUUUAGAU		1730-1750	ATCUAAAAUAAACCCAGCAAAACU		1728-1750
AD-1659284.1	UUUGCUGGGUUUAUUUUAGAGU		1731-1751	ACUCTAAAAUAAACCCAGCAAAAC		1729-1751
AD-1659285.1	UGCUGGGUUUAUUUUAGAGAU		1732-1752	ATCUCUAAAAUAAACCCAGCAAAA		1730-1752
AD-1659286.1	GCUGGGUUUAUUUUAGAGAAU		1733-1753	ATUCTTAAATAAAACCCAGCAA		1731-1753
AD-1659287.1	CUGGGUUUAUUUUAGAGAAUU		1734-1754	AAUUCUCUAAAAUAAACCCAGCA		1732-1754
AD-1659288.1	UGGGUUUAUUUUAGAGAAUGU		1735-1755	ACAUUUCUAAAAUAAACCCAGC		1733-1755
AD-1659289.1	GGGUUUUAUUUUAGAGAAUGGU		1736-1756	ACCATUCUCUAAAAUAAACCCAG		1734-1756
AD-1659290.1	GAGGCAAGAACCCAGUGUUUAU		1763-1783	ATAAACACACUGGTUCUUGCCUCCC		1761-1783
AD-1659291.1	AGGCAAGAACCCAGUGUUUAU		1764-1784	ACUAAACACUGGUUCUUGCCUCC		1762-1784
AD-1659292.1	GGCAAGAACCCAGUGUUUAAGCU		1765-1785	AGCUAAACACUGGUUCUUGCCUC		1763-1785
AD-1659293.1	GCAAGAACCAGUGUUUAAGCGU		1766-1786	ACGCTAAACACTGGUUCUUGCCU		1764-1786
AD-1659294.1	CAAGAACCAGUGUUUAAGCGCU		1767-1787	AGCGCUAAACACUGGUUCUUGCC		1765-1787
AD-1659295.1	AAGAACCAGUGUUUAAGCGCGU		1768-1788	ACGGGCTAAACACUGGUUCUUGC		1766-1788
AD-1659296.1	AGAACCCAGUGUUUAAGCGCGGU		1769-1789	ACCGCGCUAAACACUGGUUCUUG		1767-1789
AD-1659297.1	GAACCAGUGUUUAAGCGCGGGU		1770-1790	ACCCGCGCUAAACACUGGUUCU		1768-1790
AD-1659298.1	AACCAGUGUUUAAGCGCGGGAU		1771-1791	ATCCCGCGCUAAACACUGGUUCU		1769-1791
AD-1659321.1	CUGUCCAAAAAGAAUUCCAU		1794-1814	ATGGAATUCUUTUUGGAACAGUA		1792-1814
AD-1659323.1	GUUCCAAAAAGAAUUCCAAACU		1796-1816	AGUUGGAAUUCUUTUUGGAACAG		1794-1816
AD-1659325.1	UCCAAAAAGAAUUCCAAACCGU		1798-1818	ACGGTUGGAAUUCUUTUUGGAAC		1796-1818
AD-1659326.1	CCAAAAAGAAUUCCAAACCGAU		1799-1819	ATCGGUTGGAATUCUUTUUGGAA		1797-1819
AD-1659327.1	CAAAAAAGAAUUCCAAACCGACU		1800-1820	AGUCGGTUGGAAUUCUUTUUGGA		1798-1820
AD-1659328.1	AAAAAGAAUUCCAAACCGACCU		1801-1821	AGGUCGGUUGGAAUUCUUTUUGG		1799-1821
AD-1659329.1	AAAAGAAUUCCAAACCGACCAU		1802-1822	ATGGTCGGUUGGAAUUCUUTUUG		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	AGCUGGTCGGUTGGAUUCUUUU		1802-1824
AD-1659332.1	AGAAUUCCAACCGACCAGCUU		1805-1825	AAGCTGGUCGGTUGGAAUUCUUU		1803-1825
AD-1659333.1	GAAUUCCAACCGACCAGCUUU		1806-1826	AAAGCUGGUCGGUUGGAAUUCUU		1804-1826
AD-1659334.1	AAUUCCAACCGACCAGCUUGU		1807-1827	ACAAGCTGGUCGGUUGGAAUUCU		1805-1827
AD-1659335.1	AUUCCAACCGACCAGCUUGUU		1808-1828	AACAAGCUGGUCGGUUGGAAUUC		1806-1828
AD-1659336.1	UUCCAACCGACCAGCUUGUUU		1809-1829	AACAAGCUGGTCGGUUGGAAUU		1807-1829
AD-1659337.1	UCCAAACCGACCAGCUUGUUU		1810-1830	AAAACAAGCUGGUCGGUUGGAAU		1808-1830
AD-1659338.1	CCAACCGACCAGCUUGUUUGU		1811-1831	ACAAACAAGCUGGUCGGUUGGAA		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	ATCACAAAACAAGCUGGUCGGUUG		1812-1834
AD-1659342.1	CCGACCAGCUUGUUUGUGAAU		1815-1835	ATUCACAAAACAAGCUGGUCGGUU		1813-1835
AD-1659343.1	CGACCAGCUUGUUUGUGAAAU		1816-1836	ATUUCACAAAACAAGCUGGUCGGU		1814-1836
AD-1659344.1	GACCAGCUUGUUUGUGAAACU		1817-1837	AGUUTCACAAAACAAGCUGGUCGG		1815-1837
AD-1659345.1	ACCAGCUUGUUUGUGAAACAU		1818-1838	ATGUTUCACAAAACAAGCUGGUCG		1816-1838
AD-1659346.1	CCAGCUUGUUUGUGAAACAAU		1819-1839	ATUGTUTCACAAAACAAGCUGGUC		1817-1839
AD-1659347.1	CAGCUUGUUUGUGAAACAAAU		1820-1840	ATUUGUTUCACAAAACAAGCUGGU		1818-1840
AD-1659348.1	AGCUUGUUUGUGAAACAAAAU		1821-1841	ATUUTGTUUCACAAAACAAGCUGG		1819-1841
AD-1659349.1	GCUUGUUUGUGAAACAAAAU		1822-1842	ATUUTUGUUUCACAAAACAAGCUG		1820-1842
AD-1659350.1	CUUGUUUGUGAAACAAAAAUU		1823-1843	ATUUTUTGUUUUCACAAAACAAGCU		1821-1843
AD-1659351.1	UUGUUUGUGAAACAAAAAAGU		1824-1844	ACUUTUTUGUUUTCACAAAACAAGC		1822-1844
AD-1659371.1	UGUCCCCUUUUCAGUUGAGU		1844-1864	ACUCAACUUGAAAAAGGGAACACU		1842-1864
AD-1659372.1	GUUCCCCUUUCAAGUUGAGAU		1845-1865	ATCUCACUUGAAAAAGGGAACAC		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	UUCCCCUUUCAAAGUUGAGAAU		1846-1866	ATUCTCAACUUAGAAAAGGGAACA		1844-1866
AD-1659382.1	CAAGUUGAGAACAAAAUUUGU		1855-1875	ACAATUUUGUTCUCAACUUGAA		1853-1875
AD-1659383.1	AAGUUGAGAACAAAAUUUGGU		1856-1876	ACCAAUUUUUGTUCUCAAUUGA		1854-1876
AD-1659384.1	AGUUGAGAACAAAAUUUGGU		1857-1877	ACCCAATUUUUUGUUCUCAAUUG		1855-1877
AD-1659385.1	GUUGAGAACAAAAUUUGGUU		1858-1878	AACCCAAUUUUUGUUCUCAAU		1856-1878
AD-1659386.1	UUAGAGAACAAAAUUUGGUUU		1859-1879	AAACCCAAUUUTUGUUCUCAAU		1857-1879
AD-1659387.1	UGAGAACAAAAUUUGGUUUU		1860-1880	AAACCCAAUUUTUGUUCUCAA		1858-1880
AD-1659388.1	GAGAACAAAAUUUGGUUUUU		1861-1881	AAAAACCCAAUUUUUGUUCUCAA		1859-1881
AD-1659389.1	AGAACAAAAUUUGGUUUUUU		1862-1882	ATAAAACCCCAATUUUUUGUUCU		1860-1882
AD-1659390.1	GAACAAAAUUUGGUUUUUAAU		1863-1883	ATUAAAACCCAAUUUUUGUUCUC		1861-1883
AD-1659399.1	AGUAUACAUUUUUGCAUUGCU		1889-1909	AGCAAUGCAAAAAUUGUAUACUU		1887-1909
AD-1659400.1	GUUAUACAUUUUUGCAUUGCCU		1890-1910	AGGCAATGCAAAAAUUGUAUACU		1888-1910
AD-1659401.1	UAUAUACAUUUUUGCAUUGCCUU		1891-1911	AAGGCAUUGCAAAAAUUGUAUACU		1889-1911
AD-1659402.1	AUAUAUUUUUGCAUUGCCUUU		1892-1912	AAAGGCAUUGCAAAAAUUGUAUAC		1890-1912
AD-1659406.1	AUUUUUGCAUUGCCUUCGGUU		1896-1916	AACCGAAGGCAAUUGCAAAAAUGU		1894-1916
AD-1659407.1	UUUUUGCAUUGCCUUCGGUUU		1897-1917	AAACCGAAGGCAAUUGCAAAAAUG		1895-1917
AD-1659408.1	UUUUGCAUUGCCUUCGGUUUU		1898-1918	AAAACCGAAGGCAAUUGCAAAAAU		1896-1918
AD-1659409.1	UUUGCAUUGCCUUCGGUUUUGU		1899-1919	ACAAACCGAAGGCAAUUGCAAAAA		1897-1919
AD-1659410.1	UUGCAUUGCCUUCGGUUUUGUU		1900-1920	AACAAACCGAAGGCAAUUGCAAAA		1898-1920
AD-1659411.1	UGCAUUGCCUUCGGUUUUGUAU		1901-1921	ATACAAACCGAAGGCAAUUGCAAA		1899-1921
AD-1659412.1	GCAUUGCCUUCGGUUUUGUAUU		1902-1922	AUAACAAACCGAAGGCAAUUGCAA		1900-1922
AD-1659413.1	CAUUGCCUUCGGUUUUGUAUUU		1903-1923	AAAUACAAACCGAAGGCAAUUGCA		1901-1923
AD-1659414.1	AUUGCCUUCGGUUUUGUAUUUU		1904-1924	AAAATACAAACCGAAGGCAAUUGC		1902-1924
AD-1659415.1	UUUGCCUUCGGUUUUGUAUUUUU		1905-1925	ATAAAUACAAACCGAAGGCAAUUG		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	UGCCUUCGGUUUGUAUUUAGU		1906-1926	ACUAAATACAAACCGAAGGCAAU		1904-1926
AD-1659417.1	GCCUUCGGUUUGUAUUUAGUU		1907-1927	AACUAAUACAAACCGAAGGCAA		1905-1927
AD-1659418.1	CCUUCGGUUUGUAUUUAGUGU		1908-1928	ACACTAAUACAAACCGAAGGCA		1906-1928
AD-1659419.1	CUUCGGUUUGUAUUUAGUGUU		1909-1929	AACACUAAUACAAACCGAAGGC		1907-1929
AD-1659420.1	UUCGGUUUGUAUUUAGUGUCU		1910-1930	AGACACTAAUACAAACCGAAGG		1908-1930
AD-1659421.1	UCGGUUUGUAUUUAGUGUCUU		1911-1931	AAGACACUAAATACAAACCGAAG		1909-1931
AD-1659422.1	CGGUUUGUAUUUAGUGUCUUU		1912-1932	AAAGACACUAAUACAAACCGAA		1910-1932
AD-1659423.1	GGUUUGUAUUUAGUGUCUUGU		1913-1933	ACAAGACACUAAUACAAACCGA		1911-1933
AD-1659424.1	GUUUUGUAUUUAGUGUCUUGAU		1914-1934	ATCAAGACACUAAUACAAACCG		1912-1934
AD-1659425.1	UUUGUAUUUAGUGUCUUGAAU		1915-1935	ATUCAAGACACTAAUACAAACC		1913-1935
AD-1659426.1	UUGUAUUUAGUGUCUUGAAUU		1916-1936	AAUCAAAGACACUAAUACAAAC		1914-1936
AD-1659427.1	UGUAUUUAGUGUCUUGAAUGU		1917-1937	ACAUTCAAGACACUAAUACAAA		1915-1937
AD-1659428.1	GUUUUAGUGUCUUGAAUGUU		1918-1938	AACATUCAAGACACUAAUACAA		1916-1938
AD-1659429.1	UAUUUAGUGUCUUGAAUGUUAU		1919-1939	ATACAUTCAAGACACUAAUACA		1917-1939
AD-1659430.1	AUUUAGUGUCUUGAAUGUAAU		1920-1940	ATUACATUCAAGACACUAAUAC		1918-1940
AD-1659431.1	UUUAGUGUCUUGAAUGUAAAGU		1921-1941	ACUUACAUIUCAAGACACUAAUA		1919-1941
AD-1659432.1	UUAGUGUCUUGAAUGUAAAGAU		1922-1942	ATCUTACAUIUCAAGACACUAAAU		1920-1942
AD-1659433.1	UAGUGUCUUGAAUGUAAAGAAU		1923-1943	ATUCTUACAUIUCAAGACACUAAA		1921-1943
AD-1659434.1	AGUGUCUUGAAUGUAAAGAACU		1924-1944	AGUUCUTACAUTCAAGACACUAA		1922-1944
AD-1659436.1	UGUCUUGAAUGUAAAGAACAUU		1926-1946	AAUGTUCUUACAUIUCAAGACACU		1924-1946
AD-1659437.1	GUCUUGAAUGUAAAGAACAUUGU		1927-1947	ACAUGUTCUUACAUIUCAAGACAC		1925-1947
AD-1659440.1	UUGAAUGUAAAGAACAUAGACCU		1930-1950	AGGUCATGUUCTUACAUIUCAAGA		1928-1950
AD-1659446.1	GUAAAGAACAUAGACCUCCGUGU		1936-1956	ACACGGAGGUCUAGUUCUUCACAU		1934-1956
AD-1659447.1	UAAGAACAUAGACCUCCGUGUU		1937-1957	AACACGGAGGUCUAGUUCUUCUACA		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	AAGAACAUAGACCUCGUGUAU		1938-1958	ATACACGGAGGTCAUGUUCUUAAC		1936-1958
AD-1659449.1	AGAACAUAGACCUCGUGUAU		1939-1959	ACUACACGGAGGUAUGUUCUUA		1937-1959
AD-1659450.1	GAACAUAGACCUCGUGUAU		1940-1960	AACUACACGGAGGUAUGUUCU		1938-1960
AD-1659451.1	AACAUAGACCUCGUGUAU		1941-1961	ACACTACACGGAGGUAUGUUCU		1939-1961
AD-1659452.1	ACAUGACCUCGUGUAU		1942-1962	AACACUACACGGAGGUAUGUUC		1940-1962
AD-1659453.1	CAUGACCUCGUGUAU		1943-1963	AGACACTACACGGAGGUAUGU		1941-1963
AD-1659454.1	AUGACCUCGUGUAU		1944-1964	AAGACACUACACGGAGGUAUGU		1942-1964
AD-1659481.1	CUUAGUUUUUCCACAGAUGU		1971-1991	ACAUCUGUGGAAAAACUAAAGGU		1969-1991
AD-1659482.1	UUAGUUUUUCCACAGAUGCU		1972-1992	AGCATCTGUGGAAAAACUAAAGG		1970-1992
AD-1659483.1	UAGUUUUUCCACAGAUGCUU		1973-1993	AAGCAUCUGUGGAAAAACUAAAG		1971-1993
AD-1659485.1	GUUUUUUCCACAGAUGCUUGU		1975-1995	ACAAGCAUCUGTGGAAAAACUA		1973-1995
AD-1659487.1	UUUUUCCACAGAUGCUUGUGU		1977-1997	ACACAAGCAUCTGUGGAAAAAC		1975-1997
AD-1659488.1	UUUCCACAGAUGCUUGUGAU		1978-1998	ATCACAAAGCAUCUGUGGAAAAA		1976-1998
AD-1659489.1	UUUCCACAGAUGCUUGUGAUU		1979-1999	AUACAAGCATCUGUGGAAAAA		1977-1999
AD-1659490.1	UUCCACAGAUGCUUGUGAUUU		1980-2000	AAAUACAAGCAUCUGUGGAAAA		1978-2000
AD-1659491.1	UCCACAGAUGCUUGUGAUUUU		1981-2001	AAAATCACAAAGCAUCUGUGGAAA		1979-2001
AD-1659492.1	CCACAGAUGCUUGUGAUUUUU		1982-2002	AAAAUACAAGCAUCUGUGGAAA		1980-2002
AD-1659493.1	CACAGAUGCUUGUGAUUUUUU		1983-2003	AAAAAATCACAAAGCAUCUGUGGA		1981-2003
AD-1659537.1	ACCUGAAUUUCUGUUUGAAUU		2027-2047	AUUUCAAACAGAAAUUCAGGUGC		2025-2047
AD-1659538.1	CCUGAAUUUCUGUUUGAAUGU		2028-2048	ACAUUCAAAACAGAAAUUCAGGUG		2026-2048
AD-1659559.1	GGAAACCAUAGCUGGUUAUUUU		2049-2069	AAAATAACCAAGCUAUGGUUCCGC		2047-2069
AD-1659560.1	GAACCAUAGCUGGUUAUUUCU		2050-2070	AGAAAUAAACCAAGCUAUGGUUCCG		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	CCAUAGCUGGUUAUUUCUCCU		2053-2073	AGGAGAAUAAACCAGCUAUGGUU		2051-2073
AD-1659582.1	CCUUGUGUAGUAAUAAACGU		2072-2092	ACGUTUAUUACTAACACAAGGA		2070-2092
AD-1659583.1	CUUGUGUAGUAAUAAACGUU		2073-2093	AACGTUTAUUACUAAACACAAGGG		2071-2093
AD-1659584.1	UUUGUGUAGUAAUAAACGUCU		2074-2094	AGACGUTUAUUACUAAACACAAGG		2072-2094
AD-1659585.1	UGUGUAGUAAUAAACGUCUU		2075-2095	AAGACGTUUAUTACUAAACACAAG		2073-2095
AD-1659586.1	GUGUAGUAAUAAACGUCUUU		2076-2096	AAAGACGUUUATUACUAAACACAA		2074-2096
AD-1659587.1	UGUUAGUAAUAAACGUCUUGU		2077-2097	ACAAGACGUUUUUUACUAAACACA		2075-2097
AD-1659588.1	GUUAGUAAUAAACGUCUUUGCU		2078-2098	AGCAAGACGUUTAUUACUAAACAC		2076-2098
AD-1684490.1	CCGGUGUACAUACACCCCUU		142-162	AAGGGUGUAUGUACACCCCGGUC		140-162
AD-1684491.1	CCGGUGUACAUACACCCCUU		142-162	AAGGGGTGUAUGUACACCCCGGUC		140-162
AD-1684492.1	CGGGUGUACAUACACCCCUUU		143-163	AAAGGGGUGUAUGUACACCCCGU		141-163
AD-1684493.1	CGGGUGUACAUACACCCCUUU		143-163	AAAGGGGUGUATGUACACCCCGGU		141-163
AD-1684494.1	GGGUGUACAUACACCCCUUCU		144-164	AGAAGGGGUGUAUGUACACCCCGG		142-164
AD-1684495.1	GGGUGUACAUACACCCCUUCU		144-164	AGAAGGGGUGUAUGUACACCCCGG		142-164
AD-1684496.1	GGUGUACAUACACCCCUUCCU		145-165	AGGAAGGGGUGUAUGUACACCCCG		143-165
AD-1684497.1	GGUGUACAUACACCCCUUCCU		145-165	AGGAAGGGGUGUATGUACACCCCG		143-165
AD-1684498.1	GUGUACAUACACCCCUUCCAU		146-166	AUGGAAGGGGUGUAUGUACACCCC		144-166
AD-1684499.1	GUGUACAUACACCCCUUCCAU		146-166	ATGGAAGGGGUGUAUGUACACCCC		144-166
AD-1684500.1	UGUACAUACACCCCUUCCACU		147-167	AGUGGAAGGGGUGUAUGUACACCC		145-167
AD-1684501.1	UGUACAUACACCCCUUCCACU		147-167	AGUGGAAGGGGTGUUUGUACACCC		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	ACAUACACCCCUUCCACCCUCU		150-170	AGAGGUGGAAGGGGUGUAUGUAC		148-170
AD-1684507.1	ACAUACACCCCUUCCACCCUCU		150-170	AGAGGUGGAAGGGGUGUAUGUAC		148-170
AD-1684508.1	CAUACACCCCUUCCACCCUCGU		151-171	ACGAGGUGGAAGGGGUGUAUGUA		149-171
AD-1684509.1	CAUACACCCCUUCCACCCUCGU		151-171	ACGAGGTGGAAGGGGUGUAUGUA		149-171
AD-1684510.1	AUACACCCCUUCCACCCUCGU		152-172	AACGAGGUGGAAGGGGUGUAUGU		150-172
AD-1684511.1	AUACACCCCUUCCACCCUCGU		152-172	AACGAGGUGGAAGGGGUGUAUGU		150-172
AD-1684512.1	CCCUUCCACCCUGUCAUCCAU		158-178	AUGGAUGACGAGGUGGAAGGGGU		156-178
AD-1684513.1	CCCUUCCACCCUGUCAUCCAU		158-178	ATGGAUGACGAGGUGGAAGGGGU		156-178
AD-1684514.1	CCUUCACCCUGUCAUCCACU		159-179	AGUGGAUGACGAGGUGGAAGGGG		157-179
AD-1684515.1	CCUUCACCCUGUCAUCCACU		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	ACCCATAGCUCACUGUGCAUGC		396-418
AD-1684520.1	CCUCUCCCCAACGGCUGUCUU		439-459	AAGACAGCCGUUGGGGAGAGGAC		437-459
AD-1684521.1	CCUCUCCCCAACGGCUGUCUU		439-459	AAGACAGCCGUTGGGGAGAGGAC		437-459
AD-1684522.1	AGGUGCUGAACAGCAUUUUUUU		1308-1328	AAAAAUUGCUGUUUCAGCACCUCC		1306-1328
AD-1684523.1	GGUGCUGAACAGCAUUUUUUU		1309-1329	AAAAAAUUGCUGUUUCAGCACCUCC		1307-1329
AD-1684524.1	GUGCUGAACAGCAUUUUUUUU		1310-1330	AAAAAAUUGCUGUUUCAGCACCU		1308-1330
AD-1684525.1	UGCUGAACAGCAUUUUUUUUU		1311-1331	AAAAAAUUGCUGUUUCAGCAC		1309-1331
AD-1684526.1	GCUGAACAGCAUUUUUUUUUGU		1312-1332	ACAAAAAAUUGCUGUUUCAGCAC		1310-1332
AD-1684527.1	CUGAACAGCAUUUUUUUUUGAU		1313-1333	AUCAAATAAAUUGCUGUUUCAGCA		1311-1333
AD-1684528.1	CCCCAGUCUCCACCUUUUCU		1603-1623	AGAAAAGGUGGGGAGACUGGGGU		1601-1623
AD-1684529.1	CCCCAGUCUCCACCUUUUCU		1603-1623	AGAAAAGGUGGGGAGACUGGGGU		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	AGUCUCCACCCUUUUUCUUUU		1607-1627	AAGAAAGAAAAGGUGGGAGACUGG		1605-1627
AD-1684535.1	AGUCUCCACCCUUUUUCUUUU		1607-1627	AAGAAAGAAAAGGUGGGAGACUGG		1605-1627
AD-1684536.1	GGUUUAUUUAGAGAAUGGGU		1737-1757	ACCCAUUUCUAAAAUAAACCCA		1735-1757
AD-1684537.1	GGUUUAUUUAGAGAAUGGGU		1737-1757	ACCCAUTCUCUAAAAUAAACCCA		1735-1757
AD-1684538.1	GUUUUUUUUAGAGAAUGGGU		1738-1758	ACCCAUUUCUAAAAUAAACCCA		1736-1758
AD-1684539.1	GUUUUUUUUAGAGAAUGGGU		1738-1758	ACCCCATUCUCTAAAAUAAACCCA		1736-1758
AD-1684540.1	UUUUUUUUUAGAGAAUGGGU		1739-1759	ACCCCAUUUCUAAAAUAAACCCA		1737-1759
AD-1684541.1	UUUUUUUUUAGAGAAUGGGU		1739-1759	ACCCCAUUUCUAAAAUAAACCCA		1737-1759
AD-1684542.1	AGAAUGGGGUGGGAGGCAU		1749-1769	AUGCCUCCCCACCCCAUUCUCU		1747-1769
AD-1684543.1	AGAAUGGGGUGGGAGGCAU		1749-1769	ATGCCUCCCCACCCCAUUCUCU		1747-1769
AD-1684544.1	GAAUGGGGUGGGAGGCAAU		1750-1770	AUUGCCUCCCCACCCCAUUCUC		1748-1770
AD-1684545.1	GAAUGGGGUGGGAGGCAAU		1750-1770	ATUGCCTCCCCACCCCAUUCUC		1748-1770
AD-1684546.1	AUUGGGGUGGGAGGCAAGU		1751-1771	ACUUGCCUCCCCACCCCAUUCU		1749-1771
AD-1684547.1	AUUGGGGUGGGAGGCAAGU		1751-1771	ACUUGCCUCCCCACCCCAUUCU		1749-1771
AD-1684548.1	AUGGGGUGGGAGGCAAGAU		1752-1772	AUCUUGCCUCCCCACCCCAUUC		1750-1772
AD-1684549.1	AUGGGGUGGGAGGCAAGAU		1752-1772	ATCUTGCCUCCCCACCCCAUUC		1750-1772
AD-1684550.1	UGGGGUGGGAGGCAAGAAU		1753-1773	AUUCUUGCCUCCCCACCCCAUUC		1751-1773
AD-1684551.1	UGGGGUGGGAGGCAAGAAU		1753-1773	ATUCTUGCCUCCCCACCCCAUUC		1751-1773
AD-1684552.1	GGGGUGGGGAGGCAAGAAU		1754-1774	AGUUCUUGCCUCCCCACCCCAUUC		1752-1774
AD-1684553.1	GGGGUGGGGAGGCAAGAAU		1754-1774	AGUUCUTGCCUCCCCACCCCAUUC		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	GUGGGAGGCAAGAACCCAGUU		1758-1778	AACUGGUUCUUGCCUCCCCACCC		1756-1778
AD-1684555.1	GUGGGAGGCAAGAACCCAGUU		1758-1778	AACUGGTUCUUGCCUCCCCACCC		1756-1778
AD-1684556.1	UGGGGAGGCAAGAACCCAGUGU		1759-1779	ACACUGGUUCUUGCCUCCCCACC		1757-1779
AD-1684557.1	UGGGGAGGCAAGAACCCAGUGU		1759-1779	ACACTGGUUCUTGCCUCCCCACC		1757-1779
AD-1684558.1	GGGGAGGCAAGAACCCAGUGUU		1760-1780	AACACUGGUUCUUGCCUCCCCAC		1758-1780
AD-1684559.1	GGGGAGGCAAGAACCCAGUGUU		1760-1780	AACACUGGUUCTUGCCUCCCCAC		1758-1780
AD-1684560.1	GGGAGGCAAGAACCCAGUGUUU		1761-1781	AAACACTGGUUCUUGCCUCCCCA		1759-1781
AD-1684561.1	GGAGGCAAGAACCCAGUGUUUU		1762-1782	AAAACACUGGUTCUUGCCUCCCC		1760-1782
AD-1684562.1	GCUUGUUUGUGAAACAAAAAU		1822-1842	AUUUUUGUUUCACAAACAAGCUG		1820-1842
AD-1684563.1	CUUGUUUGUGAAACAAAAAU		1823-1843	AUUUUUGUUUCACAAACAAGCU		1821-1843
AD-1684564.1	UUUUUUUGUGAAACAAAAAGU		1824-1844	ACUUUUUUUUUCACAAACAAGC		1822-1844
AD-1684565.1	CUUAGUUUUUUUCCACAGAUUGU		1971-1991	ACAUCUGUGGAAAAACUAAGGU		1969-1991
AD-1684566.1	UUAGUUUUUUUCCACAGAUUCU		1972-1992	AGCAUCUGUGGAAAAACUAAGG		1970-1992
AD-1684567.1	UAGUUUUUUUCCACAGAUUCUU		1973-1993	AAGCAUCUGUGGAAAAACUAAG		1971-1993
AD-1684568.1	GUUUUUUCCACAGAUUCUUGU		1975-1995	ACAAGCAUCUGUGGAAAAACUA		1973-1995
AD-1684569.1	UUUUUCCACAGAUUCUUGUGU		1977-1997	ACACAAGCAUCUGUGGAAAAAAC		1975-1997
AD-1684570.1	UUUUCCACAGAUUCUUGUGAU		1978-1998	AUCACAAGCAUCUGUGGAAAAAA		1976-1998
AD-67328.2	UCUCCACCUUUUCUUCUAAU		1609-1629	AUUAGAAGAAAAAGGUGGAGACU		1607-1629
AD-68579.2	UUCCAAACCGACCAAGCUUGUUU		1809-1829	AAACAAGCUGGUUCGGUUGGAAUU		1807-1829
AD-68585.2	AGUUGAGAAACAAAAAUUGGGU		1857-1877	ACCCAUUUUUUUGUUCUACAACUUG		1855-1877
AD-84700.2	CCACCUUUUUCUUCUAAUGAGU		1613-1633	ACUCAUUAGAAGAAAAAGGUGGGA		1611-1633
AD-84707.2	CCUCAACUGGGAUGAAGAAACU		1135-1155	AGUUUCUUCAUCCAGUUGAGGGA		1133-1155
AD-84712.2	CCAUUCCUGUUUUCUGUGUAU		1415-1435	AUACACAGCAACACAGGAUUGGGC		1413-1435
AD-84724.2	AGAAUUCCAAACCGACCAAGCUU		1805-1825	AAGCUGGUGGUGGAAUUCUUU		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	UGAGAAAGAUUGACAGGUUCAU		784-804	AUGAACCGUCUAAUCUUCUCAGC		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	uscsuccacCfUfUfucucuaauL96		asdTsuadGadAgaadAgGfugggagasesu		AGUCCCCACCUUUUCUUCUAAU	
AD-1321390.2	csesucaacuGfGfAfugaagaaculL96		asdGsuudTcdTtcaudCcAfguugaggsgsa		UCCCUCAAACUGGAUGAAGAAACU	
AD-1632799.1	asgsccugAfgGfGfCfcaccaucculL96		asAfsngaUfgGfUfggccCfuCfaggcusesa		UGAGCCUGAGGGCCACCAUCCUC	
AD-1632801.1	csesugagGfgCfCfAfcauccuculL96		asAfsnagGfaUfGfuggGfCfCfucaggscsu		AGCCUGAGGGCCACCAUCCUCUG	
AD-1632805.1	asgsggccAfcCfAfUfCfucucucculL96		asAfsngcAfgAfGfuggGfUfGfcccusesa		UGAGGGCCACCAUCCUCUGCCUC	
AD-1632836.1	gsuscaucCfaCfAfAfugagagaculL96		asGfsuacUfcUfCfaugUfgGfagacsgsa		UCGUCAUCCACAAUGAGAGUACC	
AD-1632838.1	gsusgaccGfgGfUfGfuaacaculL96		asGfsuguAfuGfUfacaCfCfGfucacscsu		AGGUGACCGGGUGUACAUACACC	
AD-1632840.1	csusuccaCfcUfCfGfuaucacaulL96		asUfsgugGfaUfGfagaGfUfGgaagsgsg		CCCUCCACCUUGUGUACUCCACAA	
AD-1632841.1	ususcacCfuCfGfUfcauccacaauL96		asUfsguGfgAfUfagcAfgGfuggaasgsg		CCUCCACCUUGUGUACUCCACAAU	
AD-1632842.1	uscsaccUfcGfUfCfauccacaauL96		asAfsungUfgGfAfugacGfaGfuggasasg		CUUCCACCUUGUGUACUCCACAAUG	
AD-1632843.1	csesaccuCfgUfCfAfuccacaugulL96		asCfsauuGfuGfGfagaCfGfagggsasa		UUCCACCUUGUGUACUCCACAAUGA	
AD-1632844.1	csasccucGfuCfAfUfcaacaugaulL96		asUfscuuUfgUfGfuggAfcGfagggsasa		UCCACCUUGUGUACUCCACAAUGAG	
AD-1632846.1	csesucguCfaUfCfCfacaugagaulL96		asUfscucAfuUfGfuggaUfgAfcagggsung		CACCUUGUACUCCACAAUGAGAG	
AD-1632847.1	csuscgucAfuCfCfAfcuaugagagulL96		asCfsucuCfaUfUfuggAfuGfagagsgsu		ACCUUGUACUCCACAAUGAGAGU	
AD-1632848.1	uscsucaUfcCfCfAfaugagagaulL96		asAfsucUfcAfuUfuggGfaUfagcagsgsg		CCUUGUACUCCACAAUGAGAGUA	

AD-1632849.1	csqsucacCfcAfCfAfaugagaguanL96	asUfsacuCfuCfuAfuuguGfgAfugacgsasg	CUCGUCAUCCACAAUGAGAGUAC
AD-1632850.1	uscsauccAfcAfAfUfagagaguacculL96	asGfsguaCfuCfuUfcauuGfuGfgauascs g	CGUCAUCCACAAUGAGAGUACCU
AD-1632851.1	csasuccaCfaAfUfGfagaguacculL96	asAfsaguAfcUfCfucauUfUfagauascs	GUCAUCCACAAUGAGAGUACCUUG
AD-1632852.1	asusceacAfaUfGfAfagaguacculL96	asCfsaggUfaCfuUfcaUfuGfuggausgsa	UCAUCCACAAUGAGAGUACCUUG
AD-1632853.1	uscsacaAfuGfAfGfagaguacculL96	asAfsagGfuAfcUfuecAfuUfuggausug	CAUCCACAAUGAGAGUACCUUGUG
AD-1632854.1	csacscaaUfgAfGfAfaguacculL96	asCfsacaGfgUfaAfcuacCfuUfugggsasu	AUCCACAAUGAGAGUACCUUGUGA
AD-1632855.1	csascauuGfaGfAfGfaguacculL96	asUfscacAfgGfuUfcaUfuAfuuggsusa	UCCACAAUGAGAGUACCUUGUGAG
AD-1632856.1	ascsaaugAfgAfGfUfaccugugagcuL96	asCfsucaCfaGfGfuaicuCfuCfauiugsgsg	CCACAAUGAGAGUACCUUGUGAGC
AD-1632857.1	csasaugaGfaGfUfAfcugugagcuL96	asGfscucAfcAfGfguacUfcUfcauiugsgsg	CACAAUGAGAGUACCUUGUGAGCA
AD-1632858.1	asasugagAfgUfAfcfugugagcuL96	asUfsgcuCfaCfaAfgguacCfuCfucauiugsu	ACAAUGAGAGUACCUUGUGAGCAG
AD-1632859.1	asusgagaGfuAfcUfGfugugagagcuL96	asCfsugeUfcAfcfagguAfcUfcauiugsg	CAUUGAGAGUACCUUGUGAGCAGC
AD-1632860.1	usgsagagUfaCfuUfGfugagagcuL96	asGfscugCfuCfuAfcaggUfaCfucauiugsu	AAUGAGAGUACCUUGUGAGCAGCU
AD-1632861.1	gsasgaguAfcCfuUfGfugagagcuL96	asAfsaguGfcUfCfagagGfuAfcuacuasuu	AUGAGAGUACCUUGUGAGCAGCUG
AD-1632862.1	asgsaguacCfcUfGfUfGfugagagcuL96	asCfsaggUfgCfuUfcaUfuGfugagagcuL96	UGAGAGUACCUUGUGAGCAGCUGG
AD-1632863.1	gsasguacCfuGfUfGfagagagcuL96	asCfsagCfuGfGfucacAfgGfuaucusc	GAGAGUACCUUGUGAGCAGCUGGC
AD-1632864.1	asgsuaccUfgUfGfAfgcagagcuL96	asGfscacGfcUfGfcaCfaGfguacusc	AGAGUACCUUGUGAGCAGCUGGCA
AD-1632865.1	gsusaccuGfuGfAfgcagagcuL96	asUfsgccAfgCfuUfcaUfuGfugagagcuL96	GAGUACCUUGUGAGCAGCUGGCAA
AD-1632866.1	usascuugUfgAfGfCfagcugagcuL96	asUfsgucCfaGfGfugcuCfaCfagguascu	AGUACCUUGUGAGCAGCUGGCAAA
AD-1632991.1	asasugguCfcGfGfAfgcugagcuL96	asUfsggcCfaGfCfauccCfGfAfcuauugsc	GCAAUGGUCGGGAUGCUGGCGCAA
AD-1632992.1	asusggucGfcGfAfuGcugagcuL96	asUfsgucCfcAfGfcaucCfcGfcauauug	CAAUGGUCGGGAUGCUGGCGCAAAC
AD-1632993.1	usgsugucGfgAfUfGfugagagcuL96	asGfsuugGfcCfAfgcuCfcCfagagagcuL96	AUGGUCGGGAUGCUGGCGCAAACU
AD-1632994.1	gsusugggGfaUfGfCfugagagcuL96	asAfsaguGfgCfCfagcAfuCfagagagcuL96	AUGGUCGGGAUGCUGGCGCAAACUU
AD-1632995.1	gsusgggaAfuGfCfUfggagagcuL96	asAfsaguUfgGfCfagcAfuCfagagagcuL96	UGGUCGGGAUGCUGGCGCAAACUUC
AD-1632996.1	uscsgggaUfgCfuUfggagagcuL96	asGfsagUfuGfGfcaCfuUfagagagcuL96	GGUCGGGAUGCUGGCGCAAACUUCU
AD-1632997.1	csusgggaGfcUfGfGfcauacuuL96	asAfsagaGfuUfGfGfcaGfcAfuacagagcuL96	GUCCGGGAUGCUGGCGCAAACUUCUU
AD-1632998.1	gsusgaugCfuGfGfCfcauacuuL96	asAfsagaAfgUfUfggagCfGfcauacagcuL96	UCGGGAUGCUGGCGCAAACUUCUUG
AD-1632999.1	gsusauccUfgGfCfcauacuuL96	asCfsagAfaGfUfugagCfAfgfcauacagcuL96	CGGGAUGCUGGCGCAAACUUCUUGG

AD-1633000.1	gsasugcuGfgCfcAfafacuncuggauL96		asCfscaaGfaAFgfuungCfcAfgcaucscsc	GGGAUGCUGGCCAACUUCUUGGG
AD-1633003.1	gscsuiggcCfaAfCFufucunngggcuL96		asAfsgccCfaAFGfaagnUfvgFgfccagcsasu	AUGCUGGCCAACUUCUUGGGCUU
AD-1633004.1	cnsuggccAfaCfuFUfcunngggcuuL96		asAfsagcCfcAfAfgaagUfnUGfcccagsca	UGCUGGCCAACUUCUUGGGCUUC
AD-1633007.1	gscsaacUfuCfuUFUfjggcuuccguL96		asCfsggaAfvgCfCfcaagAfaGfuungcsesa	UGGCCAACUUCUUGGGCUUCCGU
AD-1633008.1	cscsaacuUfcUfUFGfggcunccguuL96		asAfsccgAfaGFcfccaaGfaAfguungscsc	GGCCAAACUUCUUGGGCUUCCGUA
AD-1633009.1	csasaacuCfuUfGfGfgcunccguauL96		asUfsagcGfaAFGfccaaFvgAfguungscsc	GCCAACUUCUUGGGCUUCCGUAU
AD-1633010.1	asascuncUfuGfGfGfcmuccguauL96		asAfsuaecGfgAfAfgcccAfaGfaaguusgg	CCAAACUUCUUGGGCUUCCGUATA
AD-1633011.1	ascsmuncUfvgGfGfCfmuccguauauL96		asUfsaauCfvgGfAfagcgCfaAfgaagnusug	CAACUUCUUGGGCUUCCGUATAU
AD-1633012.1	csusuncuGfgGfCFufuccguauauL96		asAfsuauAfecGfGfaagcCfcAfagaagsusu	AACUUCUUGGGCUUCCGUATAUA
AD-1633013.1	ususuncugGfgCFUfufccguauauauL96		asUfsaauUfaCFGfgaagCfcCfaagaasgsu	ACUUCUUGGGCUUCCGUATAUAU
AD-1633014.1	uscsmuggcGfcUfuFCfguauauauL96		asAfsuauAfuAFCfggaAGfcCfcaagasug	CUUCUUGGGCUUCCGUATAUAUG
AD-1633015.1	csusunggcChuUfCfCfhuauauauL96		asCfsaauUfaUfAfccggaAfgCfccaagsasa	UUCUUGGGCUUCCGUATAUAUGG
AD-1633016.1	ususngggcUfnCfCFgfuaauauguL96		asCfscauAfuAFUfacggAfaGfcccagsasa	UCUUGGGCUUCCGUATAUAUGGC
AD-1633018.1	ggsggscmuCfcGfuFAfhuaunggcuaL96		asUfsgccAfuAFUfauaeGfgAfagcccsasa	UUGGGCUUCCGUATAUAUGGCAU
AD-1633019.1	ggsgcuncCfgUfAfUfuaunggcuaL96		asAfsugcCfaUfAfuaiaCfvgFgaagccsesa	UGGGCUUCCGUATAUAUGGCAUG
AD-1633020.1	gscsmuccGfuAFUfAfuaunggcuaL96		asCfsaugCfcAFUfauauAfcGfgaagcscsc	GGGCUUCCGUATAUAUGGCAUGC
AD-1633027.1	usasuaauUfgGfCFafaugcacaguuL96		asCfsacuGfnUGfCfaugcCfaUfauanaescg	CGUAUAUAUGGCAUGCACAGAGA
AD-1633028.1	asusaauGfgCfAFUfjgcacagugauL96		asUfscacUfvgUFGfcaugCfcAfuaunausac	GUUAUAUGGCAUGCACAGAGAG
AD-1633029.1	usasuaugGfcAFUfGfcaagugugauL96		asCfsucaChuGHUfgcauGfcCfauaunasusa	UAUAUAUGGCAUGCACAGUGAGC
AD-1633030.1	asusaugcCfaUfGfCfacagugugcuL96		asGfscucAfcUFGfugaUfvgCfcaunausasu	AUAUAUGGCAUGCACAGUGAGCU
AD-1633031.1	usasuggcAfuGfCFafaugagaguuL96		asAfsgeuCfaCHUfjgucAfuGfccaunasusa	UAUAUGGCAUGCACAGUGAGCUA
AD-1633032.1	usgsgcauGfcAfCFafjgugagucuaL96		asAfsuagChuCFafaeguGfcAfugccasusa	UAUGGCAUGCACAGUGAGGCUAUG
AD-1633033.1	ggsgcaugCfaCfAFGfjgagucuaL96		asCfsaauGfvcUFCfacugUfvgCfauugccsasu	AUGGCAUGCACAGUGAGGCUAUGG
AD-1633034.1	gscsaugcAfcAfGUfjgagucuaL96		asCfscauAfgCHUfcaeuGfnGfcaugcsesa	UGGCAUGCACAGUGAGGCUAUGGG
AD-1633048.1	usgsgcacCfcUfGfGfcecucucuL96		asAfsagagAfgAFGfgccaGfgGfugccasasa	UUUGGCACCCCUGGGCCUCUCUCA
AD-1633049.1	ggsgcaccChuGfGfCfecucucuaL96		asUfsagaGfaGfaGfgccAfgGfjgucssasa	UUGGCACCCCUGGGCCUCUCUCUAU
AD-1633094.1	gsascaggCfuAfCFafggcaaucuL96		asAfsggauFuGHCFceuguAfgCfjugucsasg	CUGACAGGCUACAGGCAAUCCUG

AD-1633095.1	ascsagcUfaCfAfGfgcaucugul96		ascfsaggAfuUfgfcgUfaGfgcugscsa	UGACAGGCUCACAGGCAAUCCUGG
AD-1633119.1	ususccuuGfgAFaFGfgacaagaacul96		asGfsuueUfuGFufecunCfcAfaggaasca	UGUCCUUGGAAGGACAAGAACU
AD-1633121.1	cscsuuggAfaGfGfAfcaagaacugul96		ascfsagnUfeUfUfguceUfuCfcaagggsasa	UUCUUUGGAAGGACAAGAACUGC
AD-1633122.1	csusuggaAfgGfAfChagaacugcul96		ascfscegUfuCFufugueChuUfccaaagsa	UCCUUGGAAGGACAAGAACUGCA
AD-1633254.2	esascceUfAfaGfCfAfccgcuuuugul96		asAfscaaAfeGfGfcugeUfuCfagugscsa	UGCACCUGAAGCAGCCCUGUUGUG
AD-1633257.2	csusgaagCfaGfCfCfgunnugcagul96		asUfsgcaCfaAfAfcfggcUfgCfnucagsgu	ACCUGAAGCAGGCCGUUUGUGCAG
AD-1633269.2	ususugucCfaGfGfGfgcgucucul96		asAfszagCfcAfGfgcccUfgCfcaaaescg	CGUUUGUGCAGGGCCUGGCUCUC
AD-1633270.2	ususugucAfgGfGfCfuggcucucul96		asGfsagaGfcCfAffgcecChuGfceaaase	GUUUGUGCAGGGCCUGGCUCUCU
AD-1633271.2	usugsugcaGfgGfCfCfhggcucucul96		asAfszagAfgCfCfaggcCfcUfgcacasasa	UUUGUGCAGGGCCUGGCUCUCUA
AD-1633272.2	gsusgcagGfgCfCfUfggcucuaul96		asUfsagaGfaGfCfcaggCfcChugacasasa	UUUGCAGGGCCUGGCUCUCUAU
AD-1633273.2	usgscaggGfcCfUfgfgcucucuaul96		asAfsuagAfgAfGfccagGfcCfcugcasasa	UGUGCAGGGCCUGGCUCUCUAUA
AD-1633290.2	ascsgneuCfcUfgGfGfacucaacagul96		asCfsugnGfaAFGfnuccGfaGfagegusgsg	CCACGCUUCUGGACUUCACAGA
AD-1633291.2	csgsgneuCfuGfGfAfcucaacagaul96		asUfscugUfgAfAfafgnccAfGfagcgsusg	CACGCUUCUGGACUUCACAGAA
AD-1633324.2	csusgagaAfgAFUfUfgacagguicul96		asCfsaacChuGFUfcaauChuUfcucagscsa	UGCUGAGAAGAUUGACAGGUUCA
AD-1633325.2	gsasgaagAfuUfgGfAfcagguucaul96		asAfsugaAfcCFUfgucaAfuCfnucesaag	CUGAGAAGAUUGACAGGUUCAUG
AD-1633326.2	asgsaagaUfuGfAfCfagguucaugul96		asCfsaugAfaCfCfugueAfaUfenucsesa	UGAGAAGAUUGACAGGUUCAUGC
AD-1633327.2	gsasaganUfgAfCfAfagguucaugul96		asGfscanGfaAfCfcnguCfaAfuenuscsc	GAGAAGAUUGACAGGUUCAUGCA
AD-1633328.2	asasganuGfaCfAfGfgmucagcaul96		asUfsgcaUfgAfAfaccugUfcAfauucscsu	AGAAGAUUGACAGGUUCAUGCAG
AD-1633329.2	asgsaanuGfAfcAfGfGfuaugcagul96		asCfsugeAfuGfAfaceuGfmCfaucustusc	GAAGAUUGACAGGUUCAUGCAGG
AD-1633330.2	gsasanugaCfaGfGfufucaugcaggul96		ascfscegCfaUfgfaaceUfgUfcaaucusu	AAGAUUGACAGGUUCAUGCAGGC
AD-1633331.2	asusugacAfgGfUfufcaugcagcul96		asGfscenGfcAfUfgaaCchuGfuaucscsu	AGAUUGACAGGUUCAUGCAGGCU
AD-1633332.2	ususgaacGfgUFUfCfaugcagguul96		asAfsgecUfgCfAfugaaCfcUfgucaausc	GAUUGACAGGUUCAUGCAGGCUG
AD-1633333.2	usgsacagGfuUfCfAfugcagguugul96		ascfsageChuGfCfaugaAfcCfngucasasu	AUUGACAGGUUCAUGCAGGCUGU
AD-1633334.2	gsascaggUfuCfAfUfgcagguul96		asAfscegCfcUfgfcaugAfaCfngucasasa	UUUGACAGGUUCAUGCAGGCUGUG
AD-1633335.2	ascsgagnUfcAfUfgfcaugcugugul96		asCfsaacGfcCfUfgcauGfaAfcugucsasa	UGACAGGUUCAUGCAGGCUGUGA
AD-1633343.2	asusgcagGfcUfgGfUfgcaggaugul96		ascfsaueChuGFUfcaGaGfcCfngcausgsa	UCAUGCAGGCUGUGACAGGAUGG
AD-1633345.2	gscsagocUfgUfgGfAfcaagaacugul96		aslffsccaUfcCfUfncCaCfaCfncacsasu	AUGCAGGCUGUGACAGGAUGGAA

AD-1633346.2	csasggcuGfuGfAfCfcaggaugaaunL96		asUfsuccAfuChfugueAfeAfgeucgsa	UGCAGGCUGACAGGAUGGAAG
AD-1633409.2	gscsuuncAfaCfAfCfeuaeguaeunL96		asUfsggaCfgeUFafggugUfuGfaaagsca	UGGUUUCAACACCUCGUCCAC
AD-1633453.2	gsasguucUfgGfgfUfggacaacaguL96		asCfsugnUfgUfcfaceCfaGfaacucesu	AGGAGUUUGGGUGGACAACAGC
AD-1633464.2	gsgsaacAfaGfCfafceucaguguunL96		asAfscaeUfgAfGfengeUfgUfugcesasc	GUGGACAACAGCACCUACAGUGUC
AD-1633465.2	gsascaacAfgCfAfCfeucaguguenL96		asGfsaacChuGFafggugChuGfuuguesca	UGGACAACAGCACCUACAGUGUCU
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AD-1684508.1	csasuacAfUfAfCfaccuuL96		asCfsagGfgGfGfaagGfUfguacacccsg	UACAUACACCCCUUCCACCU
AD-1684509.1	csasuacAfUfAfCfaccuuL96		asdCsgadGgdTggaadGfUfguacacccsg	UACAUACACCCCUUCCACCU
AD-1684510.1	asusacAfUfAfCfaccuuL96		asAfsagGfgUfGfgaagGfUfguacacccsg	ACAUACACCCCUUCCACCU
AD-1684511.1	asusacAfUfAfCfaccuuL96		asdAfsagGfgUfGfgaagGfUfguacacccsg	ACAUACACCCCUUCCACCU
AD-1684512.1	csesuacAfUfAfCfaccuuL96		asUfsggaUfgAfCfagGfUfguacacccsg	ACCCCUUCCACCUUCCACCU
AD-1684513.1	csesuacAfUfAfCfaccuuL96		asdTsggaAdGacgadGfUfguacacccsg	ACCCCUUCCACCUUCCACCU
AD-1684514.1	csesuacAfUfAfCfaccuuL96		asGfsuggAfUfAfcgagGfUfguacacccsg	CCCCCUUCCACCUUCCACCU
AD-1684515.1	csesuacAfUfAfCfaccuuL96		asdGsgadGadTggaadGfUfguacacccsg	CCCCCUUCCACCUUCCACCU
AD-1684516.1	csasugcaCfaGfUfguacacccuuL96		asCfsccaUfaGfGfUfguacacccsg	GGCAUGCACAGUAGAGCUAUGGGG
AD-1684517.1	csasugcaCfaGfUfguacacccuuL96		asdCscadAuaGcudAcUfguacacccsg	GGCAUGCACAGUAGAGCUAUGGGG
AD-1684518.1	asusgcacAfUfAfCfaccuuL96		asCfsccaAfUfAfcgagGfUfguacacccsg	GCAUGCACAGUAGAGCUAUGGGG

AD-1684519.1	asusgcacagUfGfAfgcuauuggguL96	asdCsecdCadTAgcudCaCfugcugcausgc	GCAUGCACAGUGAGCUAUGGGGC
AD-1684520.1	csesucucCfcCfAfAfagcgugucuuL96	asAfsagAfgCfCfugGfgGfagaggsasc	GUCCUCUCCCCAACGGCUGUCUU
AD-1684521.1	csesucuccCfAfAfagcgugucuuL96	asdAsgadCadGccgudTgGfgagaggsasc	GUCCUCUCCCCAACGGCUGUCUU
AD-1684522.1	asgsugucUfgAfAfCfagcauuuuuL96	asAfsaaaAfuGfCfuguCfaGfcacuscsc	GGAGGUGCUGAACAGCAUUUUUUU
AD-1684523.1	gsgsugcuGfaAfCfAfgcauuuuuuL96	asAfsaaaAfaUfgfuguUfcAfgaccusc	GAGGUGCUGAACAGCAUUUUUUUU
AD-1684524.1	gsgsugcuGfaAfCfAfgcauuuuuuL96	asAfsaaaAfaUfgcugUfuCfagcacscsu	AGGUGCUGAACAGCAUUUUUUUUU
AD-1684525.1	usgscugaAfcAfGfCfauuuuuuuuL96	asAfsaaaAfaAfAfugcuGfuUfcagcacsc	GGUGCUGAACAGCAUUUUUUUUUG
AD-1684526.1	gscsugaaCfaGfCfAfuuuuuuuuL96	asCfsaaaAfaAfAfaugcUfgUfucagcsasc	GUGCUGAACAGCAUUUUUUUUUGA
AD-1684527.1	csusgaacAfgCfAfUfuuuuuuuuL96	asUfscaaAfaAfAfaugCfuGfuucagcsa	UGCUGAACAGCAUUUUUUUUUGAG
AD-1684528.1	csesccagUfcUfCfCfcacuuuuuL96	asGfsaaaAfgGfUfgggaGfaCfugggsgsu	ACCCCCAGUCUCCCACCUUUUCU
AD-1684529.1	csesccagucUfCfCfcacuuuuuL96	asdGsaadAadGgugdGaGfacuggsgsu	ACCCCCAGUCUCCCACCUUUUCU
AD-1684530.1	csescaguCfuCfCfCfaccuuuuuL96	asAfsaaaAfaGfGfugggAfgAfcugggsg	CCCCCAGUCUCCCACCUUUUCU
AD-1684531.1	csescagucCfCfCfaccuuuuuL96	asdAsgadAadAggudGgAfcacuggsg	CCCCCAGUCUCCCACCUUUUCU
AD-1684532.1	csesagucUfcCfCfAfcuuuuuuL96	asAfsaaaAfaAfGfugGfaGfacuggsg	CCCCCAGUCUCCCACCUUUUCU
AD-1684533.1	csesagucCfCfCfAfcuuuuuuL96	asdAsgadAadAggudGgGfagacuggsg	CCCCCAGUCUCCCACCUUUUCU
AD-1684534.1	asgsucucCfcAfCfCfuuuuuuuL96	asAfsaaaGfaAfAfagguGfgGfagacugsg	CCAGUCUCCCACCUUUUCUCUA
AD-1684535.1	asgsucuccAfCfCfuuuuuuuL96	asdAsgadAgdAaaaGdGuGfggagacugsg	CCAGUCUCCCACCUUUUCUCUA
AD-1684536.1	gsgsuuuuUfuUfuUfAfagaauggguL96	asCfscaaUfuCfUfuuAfaUfaaaacsca	UGGGUUUAUUUUAGAGAAUGGGG
AD-1684537.1	gsgsuuuuuUfuUfAfagaauggguL96	asdCsecdAudTcucudAaAfauaaacsca	UGGGUUUAUUUUAGAGAAUGGGG
AD-1684538.1	gsgsuuuuUfuUfAfGfagaauggguL96	asCfscccAfuUfCfucuaAfaAfuaaacsca	GGUUUAUUUUAGAGAAUGGGG
AD-1684539.1	gsgsuuuuuUfAfGfagaauggguL96	asdCsecdCadTucudTaAfauaaacsca	GGUUUAUUUUAGAGAAUGGGG
AD-1684540.1	ususuauuUfuUfGfAfgaauggguL96	asCfscccCfaUfuUfuuAfaAfauaaacsca	GGUUUAUUUUAGAGAAUGGGGU
AD-1684541.1	ususuauuuAfGfAfgaauggguL96	asdCsecdCcdAmuudCuAfauaaacsca	GGUUUAUUUUAGAGAAUGGGGU
AD-1684542.1	asgsaaugGfgGfUfggggaggaauL96	asUfsgccUfcCfCfaccCfcCfaucuscscu	AGAGAAUGGGGUGGGGAGGCAA
AD-1684543.1	asgsaaugggGfgGfUfggggaggaauL96	asdTsgcdCudCcccdCcCfcauucscsu	AGAGAAUGGGGUGGGGAGGCAA
AD-1684544.1	gsasauggGfgGfUfggggaggaauL96	asUfsgcCfuCfCfaccCfcCfcauucsc	GAGAAUGGGGUGGGGAGGCAAAG
AD-1684545.1	gsasauggggGfUfgfgggaggaauL96	asdTsgdCcdTcccdAcCfccaucsc	GAGAAUGGGGUGGGGAGGCAAAG

AD-1684546.1	asasugggGfgUfgGfggagcaaguL96		asCfsuugCfcUfcfccaCfcCfccaunscsu	AGAUGGGGUGGGGAGGCAAGA
AD-1684547.1	asasugggggUfgUfgGfggagcaaguL96		asdCsuudGcdCucccdCaCfcccunscsu	AGAAUGGGGUGGGGAGGCAAGA
AD-1684548.1	asusggggGfuGfgGfggagcaaguL96		asUfscuuGfcCfuUfcccAfcCfccaunsc	GAAUGGGGUGGGGAGGCAAGAA
AD-1684549.1	asusggggGfuGfgGfggagcaaguL96		asdTscudTgdCucccdCcAfececaunsc	GAAUGGGGUGGGGAGGCAAGAA
AD-1684550.1	usgsggggUfgGfgGfggagcaaguL96		asUfscuuUfgCfuCfcccCfaCfcccunscsu	AAUGGGGUGGGGAGGCAAGAAC
AD-1684551.1	usgsggggGfuGfgGfggagcaaguL96		asdTscudTudGccudCcCfcccunscsu	AAUGGGGUGGGGAGGCAAGAAC
AD-1684552.1	gsusggggGfgGfgGfggagcaaguL96		asGfsuueUfuGfCfcccCfcAfececaunsc	AUGGGGUGGGGAGGCAAGAAC
AD-1684553.1	gsusggggGfgGfgGfggagcaaguL96		asGsuudCudTgceudCcCfcccunscsu	AUGGGGUGGGGAGGCAAGAAC
AD-1684554.1	gsusggggAfgGfgGfggagcaaguL96		asAfsuugGfuUfcfuuugCfuCfcccunsc	GGGUGGGGAGGCAAGAACAGUG
AD-1684555.1	gsusggggGfgGfgGfggagcaaguL96		asdAfsuudGgdTuccudGcCfcccunsc	GGGUGGGGAGGCAAGAACAGUG
AD-1684556.1	usgsgggaGfgCfAfAfgaaccaguuL96		asCfsacuGfgUfuUfcccCfcUfcccunsc	GGUGGGGAGGCAAGAACAGUGU
AD-1684557.1	usgsgggaGfgCfAfAfgaaccaguuL96		asdCsaadTgdGuccudTgCfcccunsc	GGUGGGGAGGCAAGAACAGUGU
AD-1684558.1	gsusgggaGfgCfAfAfgaaccaguuL96		asAfscaeUfgGfuUfcccCfcCfcccunsc	GUGGGGAGGCAAGAACAGUGUU
AD-1684559.1	gsusgggaAfgCfAfAfgaaccaguuL96		asdAfscaeCudGuccudTgCfcccunsc	GUGGGGAGGCAAGAACAGUGUU
AD-1684560.1	gsusgggaAfgCfAfAfgaaccaguuL96		asdAfscaeAcdTguccudCuUfcccunsc	UGGGGAGGCAAGAACAGUGUUU
AD-1684561.1	gsusgggaGfgCfAfAfgaaccaguuL96		asdAfscaeCadCuccudTgCfcccunsc	GGGGAGGCAAGAACAGUGUUUA
AD-1684562.1	gsusgggaUfuGfuGfgaaccaguuL96		asUfscuuUfgUfuUfcccCfaAfaaagcsug	CAGCUUGUUUGUGAAACAAAAA
AD-1684563.1	csusuguuUfgUfgGfgAfaaaccaguuL96		asUfscuuUfuGfuUfcccCfaAfaaagcsu	AGCUUGUUUGUGAAACAAAAAG
AD-1684564.1	usuguuuuGfuGfgAfaaaccaguuL96		asCfsuuuUfuUfgGfuUfcccCfaAfaaagcsu	GCUUUUUUUGUGAAACAAAAAAGU
AD-1684565.1	csusuguuUfuUfuUfcccaguuL96		asCfsuueUfgUfgGfaaaAfaAfaaagcsu	ACCUUAGUUUUUUUCCACAGAGUC
AD-1684566.1	usuguuuuUfuUfuUfcccaguuL96		asGfsuueUfuUfgGfaaaAfaAfaaagcsu	CCUUAGUUUUUUUCCACAGAGUCU
AD-1684567.1	usuguuuuUfuUfuUfcccaguuL96		asGfsuueUfuUfgGfaaaAfaAfaaagcsu	CUUAGUUUUUUUCCACAGAGUCUU
AD-1684568.1	gsusuuuuUfcCfAfAfgaaccaguuL96		asCfsuueUfuUfgGfaaaAfaAfaaagcsu	UAGUUUUUUUCCACAGAGAGUCUU
AD-1684569.1	usuuuuUfcCfAfAfgaaccaguuL96		asCfsuueUfuUfgGfaaaAfaAfaaagcsu	GUUUUUUUUCCACAGAGAGUCUGA
AD-1684570.1	usuuuuUfcCfAfAfgaaccaguuL96		asUfscuueAfcAfgGfaaaccaguuL96	UUUUUUUCCACAGAGAGAGUCUGAU
AD-67328.2	usuuuuUfcCfAfAfgaaccaguuL96		asUfscuueAfcAfgGfaaaccaguuL96	AGUCUUUUUCCACAGAGAGAGUCUU
AD-68579.2	usuuuuUfcCfAfAfgaaccaguuL96		asUfscuueAfcAfgGfaaaccaguuL96	AAUUUUUCCACAGAGAGAGUCUUU

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Table 8. AGT Single Dose Screen in Hep3b Cells

Duplex ID	Avg % message remaining $\pm$ STDEV			Duplex ID	Avg % message remaining $\pm$ STDEV		
	10 nM	1 nM	10 nM		10 nM	1 nM	10 nM
AD-1632799.1	88 $\pm$ 15	105 $\pm$ 23	90 $\pm$ 21	AD-1657992.1	55 $\pm$ 11	91 $\pm$ 9	73 $\pm$ 8
AD-1632801.1	6 $\pm$ 1	23 $\pm$ 4	33 $\pm$ 3	AD-1657994.1	2 $\pm$ 1	12 $\pm$ 3	15 $\pm$ 4
AD-1632805.1	82 $\pm$ 7	95 $\pm$ 7	83 $\pm$ 12	AD-1657998.1	43 $\pm$ 4	65 $\pm$ 16	66 $\pm$ 6
AD-1632838.1	58 $\pm$ 5	94 $\pm$ 7	92 $\pm$ 10	AD-1658030.1	64 $\pm$ 5	84 $\pm$ 7	82 $\pm$ 8
AD-1684490.1	50 $\pm$ 11	83 $\pm$ 26	80 $\pm$ 18	AD-1684491.1	38 $\pm$ 12	67 $\pm$ 14	73 $\pm$ 17
AD-1684492.1	28 $\pm$ 4	68 $\pm$ 7	71 $\pm$ 20	AD-1684493.1	19 $\pm$ 2	47 $\pm$ 12	70 $\pm$ 11
AD-1684494.1	92 $\pm$ 19	101 $\pm$ 10	116 $\pm$ 6	AD-1684495.1	18 $\pm$ 4	54 $\pm$ 9	60 $\pm$ 6
AD-1684496.1	24 $\pm$ 5	72 $\pm$ 8	99 $\pm$ 10	AD-1684497.1	4 $\pm$ 1	15 $\pm$ 3	42 $\pm$ 7
AD-1684498.1	8 $\pm$ 2	31 $\pm$ 9	66 $\pm$ 9	AD-1684499.1	34 $\pm$ 8	53 $\pm$ 10	79 $\pm$ 8
AD-1684500.1	4 $\pm$ 1	16 $\pm$ 5	33 $\pm$ 6	AD-1684501.1	2 $\pm$ 0	7 $\pm$ 2	24 $\pm$ 2
AD-1684502.1	98 $\pm$ 12	107 $\pm$ 8	98 $\pm$ 3	AD-1684503.1	78 $\pm$ 15	102 $\pm$ 10	112 $\pm$ 14
AD-1684504.1	12 $\pm$ 2	56 $\pm$ 6	78 $\pm$ 10	AD-1684505.1	1 $\pm$ 0	7 $\pm$ 3	18 $\pm$ 5
AD-1684506.1	16 $\pm$ 5	53 $\pm$ 12	58 $\pm$ 11	AD-1684507.1	10 $\pm$ 3	46 $\pm$ 9	54 $\pm$ 6
AD-1684508.1	31 $\pm$ 8	87 $\pm$ 10	101 $\pm$ 15	AD-1684509.1	5 $\pm$ 1	17 $\pm$ 2	52 $\pm$ 3
AD-1684510.1	95 $\pm$ 8	119 $\pm$ 9	131 $\pm$ 11	AD-1684511.1	30 $\pm$ 6	67 $\pm$ 5	96 $\pm$ 13
AD-1684512.1	2 $\pm$ 1	9 $\pm$ 3	24 $\pm$ 3	AD-1684513.1	4 $\pm$ 2	28 $\pm$ 3	49 $\pm$ 9
AD-1684514.1	39 $\pm$ 12	67 $\pm$ 8	82 $\pm$ 10	AD-1684515.1	44 $\pm$ 9	88 $\pm$ 10	100 $\pm$ 4
AD-1632840.1	17 $\pm$ 4	62 $\pm$ 5	77 $\pm$ 7	AD-1658032.1	7 $\pm$ 2	34 $\pm$ 3	52 $\pm$ 3
AD-1632841.1	9 $\pm$ 2	45 $\pm$ 8	70 $\pm$ 7	AD-1658033.1	2 $\pm$ 0	21 $\pm$ 4	32 $\pm$ 6
AD-1632842.1	62 $\pm$ 11	60 $\pm$ 4	67 $\pm$ 13	AD-1658034.1	29 $\pm$ 6	77 $\pm$ 17	72 $\pm$ 12
AD-1632843.1	6 $\pm$ 3	38 $\pm$ 6	45 $\pm$ 5	AD-1658035.1	3 $\pm$ 1	9 $\pm$ 1	18 $\pm$ 3
AD-1632844.1	7 $\pm$ 1	28 $\pm$ 5	45 $\pm$ 6	AD-1658036.1	3 $\pm$ 0	12 $\pm$ 2	20 $\pm$ 4
AD-1632846.1	7 $\pm$ 3	30 $\pm$ 7	54 $\pm$ 10	AD-1658038.1	5 $\pm$ 2	18 $\pm$ 2	38 $\pm$ 1
AD-1632847.1	9 $\pm$ 4	35 $\pm$ 7	47 $\pm$ 4	AD-1658039.1	2 $\pm$ 0	5 $\pm$ 1	15 $\pm$ 7
AD-1632848.1	67 $\pm$ 11	92 $\pm$ 8	108 $\pm$ 8	AD-1658040.1	5 $\pm$ 1	18 $\pm$ 2	34 $\pm$ 5
AD-1632849.1	4 $\pm$ 1	13 $\pm$ 2	22 $\pm$ 1	AD-1658041.1	7 $\pm$ 2	16 $\pm$ 0	31 $\pm$ 4
AD-1632836.1	1 $\pm$ 0	3 $\pm$ 2	7 $\pm$ 1	AD-1658042.1	1 $\pm$ 0	1 $\pm$ 0	3 $\pm$ 1
AD-1632850.1	26 $\pm$ 2	62 $\pm$ 7	70 $\pm$ 9	AD-1658043.1	2 $\pm$ 0	7 $\pm$ 1	14 $\pm$ 2
AD-1632851.1	17 $\pm$ 5	53 $\pm$ 8	74 $\pm$ 5	AD-1658044.1	1 $\pm$ 0	6 $\pm$ 2	12 $\pm$ 2
AD-1632852.1	4 $\pm$ 2	23 $\pm$ 4	46 $\pm$ 10	AD-1658045.1	2 $\pm$ 1	6 $\pm$ 2	16 $\pm$ 2
AD-1632853.1	16 $\pm$ 7	55 $\pm$ 14	62 $\pm$ 7	AD-1658046.1	2 $\pm$ 1	6 $\pm$ 1	19 $\pm$ 5
AD-1632854.1	40 $\pm$ 12	68 $\pm$ 11	74 $\pm$ 9	AD-1658047.1	6 $\pm$ 3	17 $\pm$ 1	30 $\pm$ 7
AD-1632855.1	2 $\pm$ 1	9 $\pm$ 1	13 $\pm$ 1	AD-1658048.1	3 $\pm$ 1	9 $\pm$ 3	18 $\pm$ 4
AD-1632856.1	21 $\pm$ 6	47 $\pm$ 8	75 $\pm$ 9	AD-1658049.1	1 $\pm$ 0	7 $\pm$ 1	16 $\pm$ 3
AD-1632857.1	8 $\pm$ 3	40 $\pm$ 5	43 $\pm$ 11	AD-1658050.1	5 $\pm$ 1	20 $\pm$ 5	29 $\pm$ 4
AD-1632858.1	6 $\pm$ 1	23 $\pm$ 6	48 $\pm$ 4	AD-1658051.1	6 $\pm$ 2	14 $\pm$ 1	31 $\pm$ 2
AD-1632859.1	3 $\pm$ 2	12 $\pm$ 3	43 $\pm$ 8	AD-1658052.1	2 $\pm$ 0	6 $\pm$ 0	17 $\pm$ 3

Duplex ID	Avg % message remaining $\pm$ STDEV			Duplex ID	Avg % message remaining $\pm$ STDEV		
	10 nM	1 nM	10 nM		10 nM	1 nM	10 nM
AD-1632860.1	9 $\pm$ 3	27 $\pm$ 4	57 $\pm$ 5	AD-1658053.1	6 $\pm$ 1	22 $\pm$ 2	51 $\pm$ 4
AD-1632861.1	10 $\pm$ 2	38 $\pm$ 5	63 $\pm$ 8	AD-1658054.1	2 $\pm$ 1	8 $\pm$ 4	22 $\pm$ 3
AD-1632862.1	53 $\pm$ 10	69 $\pm$ 10	100 $\pm$ 11	AD-1658055.1	12 $\pm$ 4	40 $\pm$ 5	69 $\pm$ 6
AD-1632863.1	13 $\pm$ 2	29 $\pm$ 5	75 $\pm$ 14	AD-1658056.1	18 $\pm$ 5	51 $\pm$ 1	80 $\pm$ 5
AD-1632864.1	61 $\pm$ 11	74 $\pm$ 9	113 $\pm$ 24	AD-1658057.1	67 $\pm$ 6	66 $\pm$ 16	96 $\pm$ 18
AD-1632865.1	37 $\pm$ 4	63 $\pm$ 10	86 $\pm$ 17	AD-1658058.1	19 $\pm$ 5	40 $\pm$ 6	56 $\pm$ 12
AD-1632866.1	17 $\pm$ 1	42 $\pm$ 8	62 $\pm$ 8	AD-1658059.1	12 $\pm$ 4	27 $\pm$ 6	41 $\pm$ 7
AD-1632991.1	18 $\pm$ 5	50 $\pm$ 2	74 $\pm$ 10	AD-1658184.1	10 $\pm$ 2	38 $\pm$ 9	58 $\pm$ 9
AD-1632992.1	63 $\pm$ 9	100 $\pm$ 20	90 $\pm$ 11	AD-1658185.1	38 $\pm$ 6	67 $\pm$ 12	86 $\pm$ 13
AD-1632993.1	50 $\pm$ 4	87 $\pm$ 8	102 $\pm$ 20	AD-1658186.1	5 $\pm$ 1	29 $\pm$ 1	55 $\pm$ 9
AD-1632994.1	6 $\pm$ 1	28 $\pm$ 2	65 $\pm$ 14	AD-1658187.1	3 $\pm$ 0	11 $\pm$ 1	32 $\pm$ 4
AD-1632995.1	35 $\pm$ 9	47 $\pm$ 4	75 $\pm$ 17	AD-1658188.1	4 $\pm$ 2	11 $\pm$ 3	26 $\pm$ 4
AD-1632996.1	13 $\pm$ 2	42 $\pm$ 8	76 $\pm$ 6	AD-1658189.1	7 $\pm$ 2	27 $\pm$ 4	56 $\pm$ 12
AD-1632997.1	5 $\pm$ 1	23 $\pm$ 4	50 $\pm$ 6	AD-1658190.1	4 $\pm$ 1	19 $\pm$ 6	31 $\pm$ 6
AD-1632998.1	8 $\pm$ 2	23 $\pm$ 2	58 $\pm$ 4	AD-1658191.1	13 $\pm$ 4	23 $\pm$ 3	48 $\pm$ 11
AD-1632999.1	41 $\pm$ 5	75 $\pm$ 4	83 $\pm$ 16	AD-1658192.1	21 $\pm$ 6	46 $\pm$ 10	77 $\pm$ 9
AD-1633000.1	106 $\pm$ 9	126 $\pm$ 8	96 $\pm$ 10	AD-1658193.1	25 $\pm$ 3	60 $\pm$ 5	83 $\pm$ 11
AD-1633003.1	4 $\pm$ 1	33 $\pm$ 7	64 $\pm$ 9	AD-1658196.1	2 $\pm$ 0	6 $\pm$ 2	22 $\pm$ 6
AD-1633004.1	55 $\pm$ 10	83 $\pm$ 11	122 $\pm$ 18	AD-1658197.1	8 $\pm$ 1	24 $\pm$ 5	32 $\pm$ 3
AD-1633007.1	6 $\pm$ 1	19 $\pm$ 2	69 $\pm$ 8	AD-1658200.1	2 $\pm$ 0	7 $\pm$ 1	22 $\pm$ 4
AD-1633008.1	26 $\pm$ 7	53 $\pm$ 8	53 $\pm$ 3	AD-1658201.1	19 $\pm$ 3	63 $\pm$ 12	89 $\pm$ 9
AD-1633009.1	5 $\pm$ 1	12 $\pm$ 3	30 $\pm$ 5	AD-1658202.1	10 $\pm$ 1	25 $\pm$ 5	50 $\pm$ 9
AD-1633010.1	5 $\pm$ 0	9 $\pm$ 3	13 $\pm$ 2	AD-1658203.1	1 $\pm$ 0	1 $\pm$ 0	4 $\pm$ 1
AD-1633011.1	3 $\pm$ 1	10 $\pm$ 2	26 $\pm$ 1	AD-1658204.1	1 $\pm$ 0	5 $\pm$ 1	16 $\pm$ 3
AD-1633012.1	5 $\pm$ 1	33 $\pm$ 4	64 $\pm$ 9	AD-1658205.1	2 $\pm$ 0	4 $\pm$ 1	10 $\pm$ 2
AD-1633013.1	3 $\pm$ 1	10 $\pm$ 3	25 $\pm$ 5	AD-1658206.1	1 $\pm$ 0	5 $\pm$ 1	14 $\pm$ 3
AD-1633014.1	3 $\pm$ 1	23 $\pm$ 4	35 $\pm$ 5	AD-1658207.1	4 $\pm$ 1	12 $\pm$ 3	22 $\pm$ 5
AD-1633015.1	16 $\pm$ 4	58 $\pm$ 5	72 $\pm$ 7	AD-1658208.1	4 $\pm$ 0	26 $\pm$ 6	39 $\pm$ 6
AD-1633016.1	21 $\pm$ 5	90 $\pm$ 5	104 $\pm$ 13	AD-1658209.1	14 $\pm$ 3	51 $\pm$ 4	71 $\pm$ 4
AD-1633018.1	84 $\pm$ 5	118 $\pm$ 17	109 $\pm$ 7	AD-1658211.1	84 $\pm$ 18	105 $\pm$ 10	102 $\pm$ 18
AD-1633019.1	8 $\pm$ 1	28 $\pm$ 0	50 $\pm$ 5	AD-1658212.1	2 $\pm$ 0	4 $\pm$ 1	8 $\pm$ 3
AD-1633020.1	27 $\pm$ 5	70 $\pm$ 6	96 $\pm$ 13	AD-1658213.1	9 $\pm$ 2	28 $\pm$ 6	56 $\pm$ 6
AD-1633027.1	17 $\pm$ 2	46 $\pm$ 7	65 $\pm$ 12	AD-1658220.1	4 $\pm$ 1	6 $\pm$ 1	15 $\pm$ 4
AD-1633028.1	15 $\pm$ 2	49 $\pm$ 8	63 $\pm$ 7	AD-1658221.1	5 $\pm$ 1	28 $\pm$ 4	49 $\pm$ 7
AD-1633029.1	113 $\pm$ 4	120 $\pm$ 14	108 $\pm$ 15	AD-1658222.1	28 $\pm$ 2	47 $\pm$ 4	58 $\pm$ 9
AD-1633030.1	19 $\pm$ 3	70 $\pm$ 13	86 $\pm$ 7	AD-1658223.1	4 $\pm$ 1	25 $\pm$ 7	36 $\pm$ 3

Duplex ID	Avg % message remaining $\pm$ STDEV			Duplex ID	Avg % message remaining $\pm$ STDEV		
	10 nM	1 nM	10 nM		10 nM	1 nM	10 nM
AD-1633031.1	6 $\pm$ 3	14 $\pm$ 2	40 $\pm$ 7	AD-1658224.1	4 $\pm$ 1	4 $\pm$ 0	10 $\pm$ 2
AD-84731.2	8 $\pm$ 1	16 $\pm$ 1	28 $\pm$ 7	AD-1658225.1	3 $\pm$ 1	6 $\pm$ 1	12 $\pm$ 2
AD-1633032.1	6 $\pm$ 2	14 $\pm$ 4	29 $\pm$ 7	AD-1658226.1	4 $\pm$ 1	6 $\pm$ 1	19 $\pm$ 4
AD-1633033.1	6 $\pm$ 1	12 $\pm$ 2	29 $\pm$ 3	AD-1658227.1	3 $\pm$ 1	5 $\pm$ 1	10 $\pm$ 3
AD-1633034.1	82 $\pm$ 12	92 $\pm$ 11	95 $\pm$ 16	AD-1658228.1	42 $\pm$ 8	75 $\pm$ 17	95 $\pm$ 13
AD-1684516.1	42 $\pm$ 11	83 $\pm$ 18	77 $\pm$ 23	AD-1684517.1	10 $\pm$ 2	30 $\pm$ 9	70 $\pm$ 6
AD-1684518.1	80 $\pm$ 10	107 $\pm$ 22	108 $\pm$ 20	AD-1684519.1	100 $\pm$ 7	107 $\pm$ 21	111 $\pm$ 21
AD-1684520.1	24 $\pm$ 6	75 $\pm$ 13	87 $\pm$ 8	AD-1684521.1	6 $\pm$ 1	15 $\pm$ 5	21 $\pm$ 2
AD-1633048.1	46 $\pm$ 9	82 $\pm$ 8	98 $\pm$ 10	AD-1658242.1	20 $\pm$ 6	43 $\pm$ 6	65 $\pm$ 10
AD-1633049.1	10 $\pm$ 2	28 $\pm$ 6	39 $\pm$ 10	AD-1658243.1	9 $\pm$ 1	19 $\pm$ 2	45 $\pm$ 4
AD-1633094.1	19 $\pm$ 7	31 $\pm$ 3	56 $\pm$ 7	AD-1658288.1	24 $\pm$ 4	53 $\pm$ 10	63 $\pm$ 13
AD-1633095.1	48 $\pm$ 15	63 $\pm$ 13	66 $\pm$ 11	AD-1658289.1	16 $\pm$ 5	36 $\pm$ 7	55 $\pm$ 7
AD-1633119.1	43 $\pm$ 8	72 $\pm$ 17	96 $\pm$ 16	AD-1658313.1	25 $\pm$ 3	49 $\pm$ 8	54 $\pm$ 5
AD-1633121.1	18 $\pm$ 5	53 $\pm$ 10	74 $\pm$ 13	AD-1658315.1	3 $\pm$ 1	11 $\pm$ 2	34 $\pm$ 9
AD-1633122.1	66 $\pm$ 18	85 $\pm$ 17	96 $\pm$ 15	AD-1658316.1	13 $\pm$ 4	40 $\pm$ 8	63 $\pm$ 8
AD-1633254.2	11 $\pm$ 4	21 $\pm$ 6	32 $\pm$ 5	AD-1658448.2	7 $\pm$ 1	16 $\pm$ 4	21 $\pm$ 9
AD-1633257.2	10 $\pm$ 2	27 $\pm$ 4	39 $\pm$ 7	AD-1658451.2	9 $\pm$ 1	23 $\pm$ 3	28 $\pm$ 3
AD-1633269.2	10 $\pm$ 0	18 $\pm$ 4	22 $\pm$ 2	AD-1658463.2	7 $\pm$ 1	9 $\pm$ 2	11 $\pm$ 1
AD-1633270.2	47 $\pm$ 3	68 $\pm$ 2	75 $\pm$ 12	AD-1658464.2	48 $\pm$ 4	69 $\pm$ 8	81 $\pm$ 13
AD-1633271.2	12 $\pm$ 3	29 $\pm$ 8	44 $\pm$ 10	AD-1658465.2	8 $\pm$ 3	17 $\pm$ 3	22 $\pm$ 4
AD-1633272.2	27 $\pm$ 6	35 $\pm$ 6	57 $\pm$ 4	AD-1658466.2	20 $\pm$ 3	27 $\pm$ 4	43 $\pm$ 7
AD-1633273.2	76 $\pm$ 2	78 $\pm$ 2	98 $\pm$ 17	AD-1658467.2	83 $\pm$ 6	76 $\pm$ 11	101 $\pm$ 11
AD-1633290.2	42 $\pm$ 4	68 $\pm$ 11	75 $\pm$ 9	AD-1658484.2	5 $\pm$ 1	16 $\pm$ 6	28 $\pm$ 3
AD-1633291.2	30 $\pm$ 5	50 $\pm$ 13	64 $\pm$ 11	AD-1658485.2	73 $\pm$ 15	97 $\pm$ 8	93 $\pm$ 20
AD-1633324.2	6 $\pm$ 2	14 $\pm$ 3	22 $\pm$ 5	AD-1658519.2	2 $\pm$ 0	4 $\pm$ 2	4 $\pm$ 1
AD-84739.5	2 $\pm$ 0	3 $\pm$ 1	3 $\pm$ 1	AD-1658520.2	2 $\pm$ 0	4 $\pm$ 1	8 $\pm$ 1
AD-1633325.2	2 $\pm$ 0	3 $\pm$ 1	5 $\pm$ 2	AD-1658521.2	1 $\pm$ 1	4 $\pm$ 1	5 $\pm$ 1
AD-1633326.2	3 $\pm$ 1	7 $\pm$ 1	17 $\pm$ 1	AD-1658522.2	1 $\pm$ 0	2 $\pm$ 0	3 $\pm$ 1
AD-1633327.2	20 $\pm$ 4	38 $\pm$ 5	49 $\pm$ 3	AD-1658523.2	12 $\pm$ 1	29 $\pm$ 6	58 $\pm$ 3
AD-1633328.2	7 $\pm$ 1	16 $\pm$ 2	27 $\pm$ 3	AD-1658524.2	4 $\pm$ 1	11 $\pm$ 1	28 $\pm$ 2
AD-1633329.2	7 $\pm$ 1	21 $\pm$ 4	44 $\pm$ 7	AD-1658525.2	2 $\pm$ 1	6 $\pm$ 1	12 $\pm$ 4
AD-1633330.2	14 $\pm$ 3	34 $\pm$ 2	58 $\pm$ 1	AD-1658526.2	6 $\pm$ 1	24 $\pm$ 7	33 $\pm$ 6
AD-1633331.2	112 $\pm$ 5	115 $\pm$ 6	123 $\pm$ 19	AD-1658527.2	31 $\pm$ 2	59 $\pm$ 5	80 $\pm$ 9
AD-1633332.2	12 $\pm$ 3	40 $\pm$ 8	61 $\pm$ 6	AD-1658528.2	8 $\pm$ 2	25 $\pm$ 3	33 $\pm$ 3
AD-1633333.2	2 $\pm$ 0	8 $\pm$ 2	15 $\pm$ 1	AD-1658529.2	3 $\pm$ 0	6 $\pm$ 1	12 $\pm$ 2
AD-1633334.2	9 $\pm$ 1	24 $\pm$ 4	50 $\pm$ 3	AD-1658530.2	6 $\pm$ 1	11 $\pm$ 2	18 $\pm$ 4
AD-1633335.2	105 $\pm$ 18	127 $\pm$ 10	140 $\pm$ 12	AD-1658531.2	27 $\pm$ 2	50 $\pm$ 5	73 $\pm$ 8
AD-1633343.2	63 $\pm$ 5	87 $\pm$ 7	100 $\pm$ 14	AD-1658539.2	32 $\pm$ 4	44 $\pm$ 5	69 $\pm$ 4

Duplex ID	Avg % message remaining $\pm$ STDEV			Duplex ID	Avg % message remaining $\pm$ STDEV		
	10 nM	1 nM	10 nM		10 nM	1 nM	10 nM
AD-1633345.2	29 $\pm$ 3	56 $\pm$ 5	87 $\pm$ 11	AD-1658541.2	13 $\pm$ 3	27 $\pm$ 3	49 $\pm$ 5
AD-1633346.2	5 $\pm$ 1	13 $\pm$ 3	27 $\pm$ 6	AD-1658542.2	5 $\pm$ 1	16 $\pm$ 5	20 $\pm$ 4
AD-1633409.2	4 $\pm$ 0	12 $\pm$ 4	21 $\pm$ 4	AD-1658605.2	4 $\pm$ 1	13 $\pm$ 5	23 $\pm$ 1
AD-1633453.2	67 $\pm$ 7	81 $\pm$ 13	102 $\pm$ 6	AD-1658650.2	25 $\pm$ 1	53 $\pm$ 3	82 $\pm$ 6
AD-1633464.2	14 $\pm$ 1	38 $\pm$ 4	67 $\pm$ 3	AD-1658661.2	5 $\pm$ 1	14 $\pm$ 2	27 $\pm$ 3
AD-1633465.2	5 $\pm$ 1	15 $\pm$ 3	39 $\pm$ 3	AD-1658662.2	4 $\pm$ 3	10 $\pm$ 6	12 $\pm$ 2
AD-1633466.2	11 $\pm$ 2	34 $\pm$ 10	61 $\pm$ 5	AD-1658663.2	3 $\pm$ 1	10 $\pm$ 1	19 $\pm$ 0
AD-1633467.2	6 $\pm$ 2	22 $\pm$ 1	39 $\pm$ 6	AD-1658664.2	3 $\pm$ 1	8 $\pm$ 2	13 $\pm$ 2
AD-1633468.2	85 $\pm$ 8	104 $\pm$ 9	114 $\pm$ 3	AD-1658665.2	52 $\pm$ 6	67 $\pm$ 5	89 $\pm$ 7
AD-1633604.2	82 $\pm$ 13	103 $\pm$ 14	118 $\pm$ 17	AD-1658801.2	51 $\pm$ 6	75 $\pm$ 6	106 $\pm$ 12
AD-1633621.2	4 $\pm$ 1	8 $\pm$ 1	21 $\pm$ 2	AD-1658818.2	3 $\pm$ 1	7 $\pm$ 2	16 $\pm$ 2
AD-1633622.2	24 $\pm$ 5	53 $\pm$ 5	84 $\pm$ 10	AD-1658819.2	25 $\pm$ 4	48 $\pm$ 13	75 $\pm$ 7
AD-1633623.2	46 $\pm$ 4	75 $\pm$ 9	118 $\pm$ 6	AD-1658820.2	10 $\pm$ 2	35 $\pm$ 4	58 $\pm$ 6
AD-1633627.2	6 $\pm$ 1	20 $\pm$ 4	34 $\pm$ 1	AD-1658824.2	4 $\pm$ 1	8 $\pm$ 2	19 $\pm$ 3
AD-1633628.2	4 $\pm$ 1	11 $\pm$ 2	19 $\pm$ 2	AD-1658825.2	2 $\pm$ 1	7 $\pm$ 1	14 $\pm$ 3
AD-1633630.2	41 $\pm$ 7	56 $\pm$ 5	67 $\pm$ 15	AD-1658827.2	15 $\pm$ 2	20 $\pm$ 5	53 $\pm$ 9
AD-1633631.2	5 $\pm$ 1	11 $\pm$ 2	22 $\pm$ 4	AD-1658828.2	3 $\pm$ 1	6 $\pm$ 1	10 $\pm$ 2
AD-1633632.2	3 $\pm$ 1	8 $\pm$ 1	17 $\pm$ 2	AD-1658829.2	3 $\pm$ 1	9 $\pm$ 3	17 $\pm$ 5
AD-1633633.1	4 $\pm$ 1	9 $\pm$ 1	33 $\pm$ 9	AD-1658830.1	3 $\pm$ 1	9 $\pm$ 2	20 $\pm$ 6
AD-1633634.1	3 $\pm$ 1	5 $\pm$ 1	19 $\pm$ 4	AD-1658831.1	1 $\pm$ 0	2 $\pm$ 0	6 $\pm$ 2
AD-1633635.1	20 $\pm$ 3	36 $\pm$ 6	71 $\pm$ 8	AD-1658832.1	4 $\pm$ 1	10 $\pm$ 2	29 $\pm$ 4
AD-1633636.1	1 $\pm$ 0	2 $\pm$ 0	6 $\pm$ 1	AD-1658833.1	1 $\pm$ 0	1 $\pm$ 0	4 $\pm$ 1
AD-1633637.1	9 $\pm$ 1	25 $\pm$ 7	54 $\pm$ 17	AD-1658834.1	2 $\pm$ 1	2 $\pm$ 0	5 $\pm$ 2
AD-1633638.1	24 $\pm$ 5	36 $\pm$ 9	71 $\pm$ 10	AD-1658835.1	7 $\pm$ 1	13 $\pm$ 1	30 $\pm$ 6
AD-1633639.1	1 $\pm$ 0	2 $\pm$ 0	5 $\pm$ 1	AD-1658836.1	3 $\pm$ 1	5 $\pm$ 2	12 $\pm$ 4
AD-1633640.1	4 $\pm$ 1	6 $\pm$ 1	17 $\pm$ 1	AD-1658837.1	3 $\pm$ 0	5 $\pm$ 1	18 $\pm$ 5
AD-1633641.1	7 $\pm$ 3	17 $\pm$ 3	31 $\pm$ 8	AD-1658838.1	2 $\pm$ 0	3 $\pm$ 1	8 $\pm$ 1
AD-1633642.1	39 $\pm$ 7	65 $\pm$ 11	71 $\pm$ 12	AD-1658839.1	2 $\pm$ 1	4 $\pm$ 1	10 $\pm$ 2
AD-1633643.1	23 $\pm$ 1	39 $\pm$ 9	70 $\pm$ 14	AD-1658840.1	8 $\pm$ 2	10 $\pm$ 2	34 $\pm$ 8
AD-1633644.1	3 $\pm$ 0	8 $\pm$ 2	25 $\pm$ 4	AD-1658841.1	2 $\pm$ 1	8 $\pm$ 1	16 $\pm$ 4
AD-1633645.1	9 $\pm$ 2	20 $\pm$ 3	37 $\pm$ 5	AD-1658842.1	2 $\pm$ 1	3 $\pm$ 1	8 $\pm$ 2
AD-1633646.1	42 $\pm$ 6	48 $\pm$ 8	55 $\pm$ 8	AD-1658843.1	19 $\pm$ 5	28 $\pm$ 3	48 $\pm$ 4
AD-1633647.1	87 $\pm$ 9	78 $\pm$ 10	89 $\pm$ 9	AD-1658844.1	66 $\pm$ 12	81 $\pm$ 11	93 $\pm$ 8
AD-1633648.1	8 $\pm$ 3	13 $\pm$ 3	32 $\pm$ 4	AD-1658845.1	2 $\pm$ 0	5 $\pm$ 0	14 $\pm$ 1
AD-1633649.1	27 $\pm$ 3	48 $\pm$ 8	87 $\pm$ 3	AD-1658846.1	2 $\pm$ 1	7 $\pm$ 3	19 $\pm$ 5
AD-1633650.1	31 $\pm$ 8	54 $\pm$ 7	82 $\pm$ 8	AD-1658847.1	17 $\pm$ 8	30 $\pm$ 5	53 $\pm$ 4
AD-1633651.1	44 $\pm$ 6	63 $\pm$ 4	75 $\pm$ 8	AD-1658848.1	19 $\pm$ 3	32 $\pm$ 5	53 $\pm$ 4
AD-1633652.1	10 $\pm$ 1	18 $\pm$ 5	28 $\pm$ 3	AD-1658849.1	17 $\pm$ 3	25 $\pm$ 4	46 $\pm$ 6
AD-84707.2	2 $\pm$ 1	5 $\pm$ 2	12 $\pm$ 2	AD-1321390.2	2 $\pm$ 0	3 $\pm$ 1	8 $\pm$ 2
AD-1633653.1	6 $\pm$ 1	15 $\pm$ 3	28 $\pm$ 7	AD-1658850.1	5 $\pm$ 1	10 $\pm$ 3	16 $\pm$ 4

Duplex ID	Avg % message remaining $\pm$ STDEV			Duplex ID	Avg % message remaining $\pm$ STDEV		
	10 nM	1 nM	10 nM		10 nM	1 nM	10 nM
AD-1633678.1	113 $\pm$ 6	99 $\pm$ 13	96 $\pm$ 9	AD-1658875.1	67 $\pm$ 7	103 $\pm$ 12	95 $\pm$ 2
AD-1633683.1	114 $\pm$ 14	118 $\pm$ 4	110 $\pm$ 8	AD-1658880.1	88 $\pm$ 8	96 $\pm$ 11	98 $\pm$ 10
AD-1633732.1	1 $\pm$ 0	3 $\pm$ 1	5 $\pm$ 2	AD-1658929.1	2 $\pm$ 1	5 $\pm$ 1	6 $\pm$ 2
AD-1633733.1	6 $\pm$ 2	10 $\pm$ 2	20 $\pm$ 2	AD-1658930.1	4 $\pm$ 1	8 $\pm$ 3	15 $\pm$ 2
AD-1633734.1	20 $\pm$ 3	32 $\pm$ 4	51 $\pm$ 6	AD-1658931.1	2 $\pm$ 0	3 $\pm$ 0	5 $\pm$ 2
AD-1633735.1	12 $\pm$ 4	21 $\pm$ 1	38 $\pm$ 6	AD-1658932.1	3 $\pm$ 1	9 $\pm$ 1	21 $\pm$ 5
AD-1633736.1	5 $\pm$ 1	8 $\pm$ 1	20 $\pm$ 2	AD-1658933.1	1 $\pm$ 0	2 $\pm$ 1	4 $\pm$ 1
AD-1633737.1	27 $\pm$ 3	41 $\pm$ 2	63 $\pm$ 5	AD-1658934.1	3 $\pm$ 1	8 $\pm$ 2	19 $\pm$ 3
AD-1633738.1	36 $\pm$ 3	47 $\pm$ 2	66 $\pm$ 3	AD-1658935.1	9 $\pm$ 2	15 $\pm$ 2	31 $\pm$ 5
AD-1633739.1	2 $\pm$ 1	4 $\pm$ 1	8 $\pm$ 2	AD-1658936.1	1 $\pm$ 0	2 $\pm$ 1	4 $\pm$ 1
AD-1633740.1	1 $\pm$ 0	2 $\pm$ 0	4 $\pm$ 1	AD-1658937.1	2 $\pm$ 0	2 $\pm$ 0	3 $\pm$ 1
AD-1633741.1	5 $\pm$ 1	10 $\pm$ 2	22 $\pm$ 2	AD-1658938.1	2 $\pm$ 0	4 $\pm$ 0	6 $\pm$ 1
AD-1633742.1	12 $\pm$ 1	22 $\pm$ 2	37 $\pm$ 8	AD-1658939.1	5 $\pm$ 1	8 $\pm$ 1	16 $\pm$ 1
AD-1633743.1	5 $\pm$ 2	6 $\pm$ 2	14 $\pm$ 3	AD-1658940.1	4 $\pm$ 1	6 $\pm$ 1	8 $\pm$ 2
AD-1633759.1	1 $\pm$ 0	2 $\pm$ 1	4 $\pm$ 1	AD-1658954.1	1 $\pm$ 0	2 $\pm$ 1	3 $\pm$ 2
AD-1684522.1	4 $\pm$ 2	7 $\pm$ 2	13 $\pm$ 3	AD-1658955.1	3 $\pm$ 1	6 $\pm$ 1	9 $\pm$ 2
AD-1684523.1	3 $\pm$ 1	6 $\pm$ 1	7 $\pm$ 2	AD-1658956.1	3 $\pm$ 1	5 $\pm$ 1	7 $\pm$ 1
AD-1684524.1	2 $\pm$ 1	3 $\pm$ 1	8 $\pm$ 2	AD-1658957.1	2 $\pm$ 0	3 $\pm$ 1	5 $\pm$ 1
AD-1684525.1	15 $\pm$ 5	18 $\pm$ 4	34 $\pm$ 5	AD-1658958.1	2 $\pm$ 1	4 $\pm$ 2	5 $\pm$ 3
AD-1684526.1	2 $\pm$ 1	3 $\pm$ 1	7 $\pm$ 1	AD-1658959.1	1 $\pm$ 0	1 $\pm$ 0	2 $\pm$ 1
AD-1684527.1	1 $\pm$ 1	3 $\pm$ 1	4 $\pm$ 1	AD-1658960.1	1 $\pm$ 1	2 $\pm$ 1	3 $\pm$ 1
AD-1633777.1	14 $\pm$ 3	18 $\pm$ 3	38 $\pm$ 5	AD-1658992.1	2 $\pm$ 1	5 $\pm$ 1	16 $\pm$ 2
AD-1633779.1	11 $\pm$ 4	27 $\pm$ 7	41 $\pm$ 7	AD-1658994.1	3 $\pm$ 1	6 $\pm$ 1	19 $\pm$ 4
AD-1633780.1	30 $\pm$ 5	52 $\pm$ 8	61 $\pm$ 11	AD-1658995.1	51 $\pm$ 6	52 $\pm$ 7	55 $\pm$ 9
AD-1633840.1	66 $\pm$ 13	91 $\pm$ 7	99 $\pm$ 13	AD-1659055.1	7 $\pm$ 1	19 $\pm$ 3	25 $\pm$ 3
AD-1633841.1	96 $\pm$ 13	99 $\pm$ 25	88 $\pm$ 9	AD-1659056.1	93 $\pm$ 10	103 $\pm$ 9	92 $\pm$ 11
AD-1633842.1	4 $\pm$ 2	22 $\pm$ 6	49 $\pm$ 10	AD-1659057.1	2 $\pm$ 1	13 $\pm$ 3	31 $\pm$ 5
AD-1633843.1	6 $\pm$ 1	36 $\pm$ 2	55 $\pm$ 13	AD-1659058.1	3 $\pm$ 1	12 $\pm$ 2	37 $\pm$ 7
AD-1633844.1	22 $\pm$ 3	47 $\pm$ 10	81 $\pm$ 9	AD-1659059.1	5 $\pm$ 1	27 $\pm$ 6	54 $\pm$ 8
AD-1633845.1	28 $\pm$ 4	83 $\pm$ 9	71 $\pm$ 7	AD-1659060.1	14 $\pm$ 2	41 $\pm$ 5	65 $\pm$ 13
AD-1633846.1	10 $\pm$ 2	32 $\pm$ 6	58 $\pm$ 14	AD-1659061.1	1 $\pm$ 0	12 $\pm$ 3	22 $\pm$ 8
AD-84712.2	2 $\pm$ 0	8 $\pm$ 1	17 $\pm$ 4	AD-1659062.1	1 $\pm$ 0	6 $\pm$ 2	12 $\pm$ 3
AD-1633847.1	14 $\pm$ 3	69 $\pm$ 10	86 $\pm$ 5	AD-1659063.1	5 $\pm$ 1	28 $\pm$ 8	54 $\pm$ 4
AD-1633848.1	12 $\pm$ 4	40 $\pm$ 2	80 $\pm$ 20	AD-1659064.1	3 $\pm$ 1	22 $\pm$ 6	31 $\pm$ 1
AD-1633849.1	8 $\pm$ 1	34 $\pm$ 3	64 $\pm$ 6	AD-1659065.1	6 $\pm$ 2	21 $\pm$ 5	50 $\pm$ 12
AD-1633850.1	2 $\pm$ 0	12 $\pm$ 3	23 $\pm$ 1	AD-1659066.1	2 $\pm$ 1	9 $\pm$ 1	27 $\pm$ 2
AD-1633851.1	6 $\pm$ 2	37 $\pm$ 5	52 $\pm$ 7	AD-1659067.1	3 $\pm$ 0	24 $\pm$ 5	46 $\pm$ 8
AD-1633852.1	8 $\pm$ 2	39 $\pm$ 5	62 $\pm$ 8	AD-1659068.1	7 $\pm$ 1	20 $\pm$ 6	39 $\pm$ 4
AD-1633853.1	1 $\pm$ 0	7 $\pm$ 2	17 $\pm$ 4	AD-1659069.1	1 $\pm$ 0	3 $\pm$ 1	14 $\pm$ 3
AD-1633854.1	22 $\pm$ 3	59 $\pm$ 9	85 $\pm$ 9	AD-1659070.1	7 $\pm$ 2	27 $\pm$ 4	52 $\pm$ 12

Duplex ID	Avg % message remaining $\pm$ STDEV			Duplex ID	Avg % message remaining $\pm$ STDEV		
	10 nM	1 nM	10 nM		10 nM	1 nM	10 nM
AD-1633855.1	21 $\pm$ 3	82 $\pm$ 14	91 $\pm$ 12	AD-1659071.1	2 $\pm$ 0	13 $\pm$ 3	35 $\pm$ 5
AD-1684528.1	7 $\pm$ 2	30 $\pm$ 5	61 $\pm$ 8	AD-1684529.1	3 $\pm$ 0	12 $\pm$ 3	34 $\pm$ 7
AD-1684530.1	3 $\pm$ 1	18 $\pm$ 1	45 $\pm$ 4	AD-1684531.1	2 $\pm$ 0	9 $\pm$ 1	33 $\pm$ 5
AD-1684532.1	7 $\pm$ 1	28 $\pm$ 3	44 $\pm$ 5	AD-1684533.1	3 $\pm$ 1	19 $\pm$ 8	47 $\pm$ 11
AD-1684534.1	3 $\pm$ 1	15 $\pm$ 1	30 $\pm$ 3	AD-1684535.1	4 $\pm$ 3	4 $\pm$ 0	12 $\pm$ 2
AD-1633946.1	3 $\pm$ 1	10 $\pm$ 3	22 $\pm$ 3	AD-1659162.1	1 $\pm$ 0	6 $\pm$ 2	19 $\pm$ 4
AD-67328.2	1 $\pm$ 0	7 $\pm$ 1	20 $\pm$ 3	AD-1321384.2	3 $\pm$ 0	9 $\pm$ 1	22 $\pm$ 4
AD-1633947.1	3 $\pm$ 1	10 $\pm$ 2	23 $\pm$ 1	AD-1659163.1	2 $\pm$ 1	10 $\pm$ 1	22 $\pm$ 3
AD-1633948.1	2 $\pm$ 1	17 $\pm$ 9	32 $\pm$ 5	AD-1659164.1	1 $\pm$ 0	4 $\pm$ 1	11 $\pm$ 3
AD-1633949.1	3 $\pm$ 1	21 $\pm$ 1	51 $\pm$ 8	AD-1659165.1	3 $\pm$ 0	12 $\pm$ 2	23 $\pm$ 2
AD-84700.2	11 $\pm$ 2	37 $\pm$ 3	66 $\pm$ 4	AD-1659166.1	2 $\pm$ 0	12 $\pm$ 1	25 $\pm$ 4
AD-1633950.1	1 $\pm$ 0	9 $\pm$ 2	29 $\pm$ 5	AD-1659167.1	1 $\pm$ 0	6 $\pm$ 2	18 $\pm$ 2
AD-1633951.1	5 $\pm$ 1	29 $\pm$ 6	60 $\pm$ 10	AD-1659168.1	4 $\pm$ 1	15 $\pm$ 1	33 $\pm$ 7
AD-1633991.1	3 $\pm$ 1	19 $\pm$ 3	46 $\pm$ 4	AD-1659208.1	2 $\pm$ 0	11 $\pm$ 2	26 $\pm$ 4
AD-1633992.1	14 $\pm$ 1	45 $\pm$ 5	77 $\pm$ 9	AD-1659209.1	3 $\pm$ 1	8 $\pm$ 2	23 $\pm$ 5
AD-1633993.1	27 $\pm$ 5	57 $\pm$ 10	73 $\pm$ 3	AD-1659210.1	11 $\pm$ 1	43 $\pm$ 5	70 $\pm$ 8
AD-1634065.1	13 $\pm$ 3	48 $\pm$ 6	79 $\pm$ 1	AD-1659282.1	4 $\pm$ 1	18 $\pm$ 4	44 $\pm$ 6
AD-1634066.1	45 $\pm$ 5	77 $\pm$ 9	98 $\pm$ 12	AD-1659283.1	30 $\pm$ 2	69 $\pm$ 14	80 $\pm$ 11
AD-1634067.1	25 $\pm$ 5	68 $\pm$ 6	87 $\pm$ 11	AD-1659284.1	24 $\pm$ 4	60 $\pm$ 2	71 $\pm$ 3
AD-1634068.1	10 $\pm$ 2	38 $\pm$ 4	58 $\pm$ 3	AD-1659285.1	11 $\pm$ 1	38 $\pm$ 2	64 $\pm$ 5
AD-84730.2	7 $\pm$ 1	19 $\pm$ 4	30 $\pm$ 8	AD-1659286.1	5 $\pm$ 1	21 $\pm$ 7	41 $\pm$ 6
AD-1634069.1	5 $\pm$ 1	19 $\pm$ 4	34 $\pm$ 6	AD-1659287.1	2 $\pm$ 1	12 $\pm$ 2	22 $\pm$ 5
AD-1634070.1	2 $\pm$ 1	12 $\pm$ 4	24 $\pm$ 4	AD-1659288.1	3 $\pm$ 1	13 $\pm$ 3	22 $\pm$ 2
AD-1634071.1	29 $\pm$ 3	65 $\pm$ 6	98 $\pm$ 16	AD-1659289.1	24 $\pm$ 6	55 $\pm$ 8	79 $\pm$ 12
AD-1684536.1	54 $\pm$ 6	83 $\pm$ 5	84 $\pm$ 5	AD-1684537.1	75 $\pm$ 4	105 $\pm$ 5	109 $\pm$ 19
AD-1684538.1	64 $\pm$ 6	103 $\pm$ 6	102 $\pm$ 20	AD-1684539.1	61 $\pm$ 5	105 $\pm$ 8	83 $\pm$ 8
AD-1684540.1	73 $\pm$ 5	65 $\pm$ 4	87 $\pm$ 9	AD-1684541.1	57 $\pm$ 9	67 $\pm$ 10	96 $\pm$ 15
AD-1684542.1	89 $\pm$ 22	65 $\pm$ 5	97 $\pm$ 9	AD-1684543.1	85 $\pm$ 10	78 $\pm$ 1	104 $\pm$ 19
AD-1684544.1	98 $\pm$ 15	87 $\pm$ 8	117 $\pm$ 19	AD-1684545.1	56 $\pm$ 9	56 $\pm$ 6	94 $\pm$ 6
AD-1684546.1	79 $\pm$ 9	84 $\pm$ 9	94 $\pm$ 12	AD-1684547.1	23 $\pm$ 3	45 $\pm$ 3	64 $\pm$ 8
AD-1684548.1	58 $\pm$ 9	62 $\pm$ 12	86 $\pm$ 18	AD-1684549.1	16 $\pm$ 1	44 $\pm$ 8	57 $\pm$ 8
AD-1684550.1	47 $\pm$ 7	63 $\pm$ 15	100 $\pm$ 17	AD-1684551.1	37 $\pm$ 3	50 $\pm$ 7	80 $\pm$ 3
AD-1684552.1	55 $\pm$ 5	74 $\pm$ 14	112 $\pm$ 20	AD-1684553.1	31 $\pm$ 5	54 $\pm$ 7	76 $\pm$ 9
AD-1684554.1	75 $\pm$ 8	98 $\pm$ 17	107 $\pm$ 18	AD-1684555.1	25 $\pm$ 2	50 $\pm$ 9	53 $\pm$ 5
AD-1684556.1	76 $\pm$ 10	82 $\pm$ 12	115 $\pm$ 26	AD-1684557.1	26 $\pm$ 7	45 $\pm$ 8	75 $\pm$ 20

Duplex ID	Avg % message remaining $\pm$ STDEV			Duplex ID	Avg % message remaining $\pm$ STDEV		
	10 nM	1 nM	10 nM		10 nM	1 nM	10 nM
AD-1684558.1	57 $\pm$ 9	65 $\pm$ 7	101 $\pm$ 14	AD-1684559.1	21 $\pm$ 6	41 $\pm$ 5	69 $\pm$ 6
AD-1634072.1	8 $\pm$ 1	19 $\pm$ 3	32 $\pm$ 8	AD-1684560.1	6 $\pm$ 0	15 $\pm$ 3	25 $\pm$ 4
AD-1634073.1	5 $\pm$ 1	13 $\pm$ 3	18 $\pm$ 3	AD-1684561.1	3 $\pm$ 1	10 $\pm$ 1	11 $\pm$ 3
AD-1634074.1	3 $\pm$ 0	8 $\pm$ 1	15 $\pm$ 3	AD-1659290.1	3 $\pm$ 1	9 $\pm$ 1	15 $\pm$ 1
AD-1634075.1	5 $\pm$ 1	15 $\pm$ 2	32 $\pm$ 9	AD-1659291.1	5 $\pm$ 1	15 $\pm$ 2	19 $\pm$ 3
AD-1634076.1	11 $\pm$ 2	36 $\pm$ 5	45 $\pm$ 4	AD-1659292.1	9 $\pm$ 1	25 $\pm$ 5	37 $\pm$ 9
AD-1634077.1	12 $\pm$ 2	30 $\pm$ 5	59 $\pm$ 8	AD-1659293.1	3 $\pm$ 2	10 $\pm$ 2	16 $\pm$ 1
AD-1634078.1	11 $\pm$ 3	29 $\pm$ 7	55 $\pm$ 8	AD-1659294.1	5 $\pm$ 1	13 $\pm$ 3	24 $\pm$ 4
AD-1634079.1	3 $\pm$ 1	10 $\pm$ 3	21 $\pm$ 4	AD-1659295.1	2 $\pm$ 0	4 $\pm$ 0	11 $\pm$ 1
AD-1634080.1	10 $\pm$ 3	34 $\pm$ 2	48 $\pm$ 7	AD-1659296.1	6 $\pm$ 2	15 $\pm$ 2	35 $\pm$ 7
AD-1634081.1	5 $\pm$ 1	20 $\pm$ 2	38 $\pm$ 8	AD-1659297.1	14 $\pm$ 2	26 $\pm$ 2	52 $\pm$ 7
AD-1634082.1	27 $\pm$ 3	60 $\pm$ 4	79 $\pm$ 11	AD-1659298.1	17 $\pm$ 3	34 $\pm$ 6	60 $\pm$ 10
AD-1634105.1	2 $\pm$ 0	4 $\pm$ 1	12 $\pm$ 2	AD-1659321.1	2 $\pm$ 1	5 $\pm$ 0	15 $\pm$ 2
AD-1634107.1	6 $\pm$ 2	21 $\pm$ 2	37 $\pm$ 9	AD-1659323.1	6 $\pm$ 1	13 $\pm$ 3	25 $\pm$ 2
AD-1634109.1	17 $\pm$ 2	40 $\pm$ 5	66 $\pm$ 8	AD-1659325.1	7 $\pm$ 2	17 $\pm$ 3	39 $\pm$ 6
AD-1634110.1	9 $\pm$ 2	26 $\pm$ 5	42 $\pm$ 2	AD-1659326.1	6 $\pm$ 1	19 $\pm$ 1	41 $\pm$ 6
AD-1634111.1	5 $\pm$ 2	11 $\pm$ 3	25 $\pm$ 3	AD-1659327.1	3 $\pm$ 1	14 $\pm$ 1	18 $\pm$ 2
AD-1634112.1	10 $\pm$ 1	32 $\pm$ 2	50 $\pm$ 9	AD-1659328.1	3 $\pm$ 1	10 $\pm$ 1	24 $\pm$ 6
AD-1634113.1	7 $\pm$ 2	17 $\pm$ 3	37 $\pm$ 4	AD-1659329.1	4 $\pm$ 1	15 $\pm$ 1	29 $\pm$ 6
AD-1634114.1	17 $\pm$ 5	33 $\pm$ 1	68 $\pm$ 8	AD-1659330.1	2 $\pm$ 1	5 $\pm$ 1	11 $\pm$ 2
AD-1634115.1	35 $\pm$ 5	63 $\pm$ 11	110 $\pm$ 7	AD-1659331.1	7 $\pm$ 1	24 $\pm$ 4	43 $\pm$ 7
AD-84724.2	24 $\pm$ 2	45 $\pm$ 6	61 $\pm$ 8	AD-1659332.1	5 $\pm$ 1	11 $\pm$ 1	24 $\pm$ 2
AD-1634116.1	5 $\pm$ 2	15 $\pm$ 3	33 $\pm$ 5	AD-1659333.1	3 $\pm$ 2	9 $\pm$ 1	17 $\pm$ 3
AD-1634117.1	9 $\pm$ 1	32 $\pm$ 3	45 $\pm$ 6	AD-1659334.1	10 $\pm$ 3	29 $\pm$ 1	42 $\pm$ 6
AD-1634118.1	25 $\pm$ 4	46 $\pm$ 5	79 $\pm$ 4	AD-1659335.1	6 $\pm$ 1	20 $\pm$ 3	31 $\pm$ 4
AD-68579.2	17 $\pm$ 5	41 $\pm$ 5	69 $\pm$ 6	AD-1659336.1	3 $\pm$ 1	10 $\pm$ 2	17 $\pm$ 3
AD-1634119.1	4 $\pm$ 1	14 $\pm$ 1	33 $\pm$ 4	AD-1659337.1	3 $\pm$ 0	10 $\pm$ 2	21 $\pm$ 2
AD-1634120.1	11 $\pm$ 3	33 $\pm$ 6	80 $\pm$ 5	AD-1659338.1	3 $\pm$ 1	8 $\pm$ 3	20 $\pm$ 1
AD-1634121.1	8 $\pm$ 2	22 $\pm$ 6	44 $\pm$ 4	AD-1659339.1	2 $\pm$ 1	6 $\pm$ 1	18 $\pm$ 3
AD-1634122.1	18 $\pm$ 13	29 $\pm$ 2	60 $\pm$ 7	AD-1659340.1	2 $\pm$ 0	15 $\pm$ 3	24 $\pm$ 4
AD-1634123.1	4 $\pm$ 1	14 $\pm$ 3	41 $\pm$ 1	AD-1659341.1	6 $\pm$ 1	23 $\pm$ 3	46 $\pm$ 8
AD-1634124.1	5 $\pm$ 1	17 $\pm$ 6	32 $\pm$ 5	AD-1659342.1	3 $\pm$ 0	12 $\pm$ 2	19 $\pm$ 3
AD-1634125.1	4 $\pm$ 1	11 $\pm$ 2	22 $\pm$ 2	AD-1659343.1	4 $\pm$ 1	10 $\pm$ 3	26 $\pm$ 5
AD-1634126.1	6 $\pm$ 1	16 $\pm$ 4	30 $\pm$ 4	AD-1659344.1	2 $\pm$ 0	8 $\pm$ 1	16 $\pm$ 3
AD-1634127.1	3 $\pm$ 0	7 $\pm$ 2	16 $\pm$ 1	AD-1659345.1	3 $\pm$ 0	6 $\pm$ 1	12 $\pm$ 2
AD-1634128.1	1 $\pm$ 0	1 $\pm$ 1	3 $\pm$ 2	AD-1659346.1	1 $\pm$ 0	2 $\pm$ 1	5 $\pm$ 1
AD-1634129.1	2 $\pm$ 1	6 $\pm$ 3	15 $\pm$ 2	AD-1659347.1	1 $\pm$ 0	1 $\pm$ 0	5 $\pm$ 2
AD-1634130.1	4 $\pm$ 1	13 $\pm$ 1	24 $\pm$ 4	AD-1659348.1	1 $\pm$ 1	1 $\pm$ 0	3 $\pm$ 1
AD-1684562.1	16 $\pm$ 4	33 $\pm$ 3	54 $\pm$ 7	AD-1659349.1	9 $\pm$ 2	23 $\pm$ 2	40 $\pm$ 1
AD-1684563.1	1 $\pm$ 0	1 $\pm$ 1	3 $\pm$ 0	AD-1659350.1	1 $\pm$ 0	1 $\pm$ 1	2 $\pm$ 1

Duplex ID	Avg % message remaining $\pm$ STDEV			Duplex ID	Avg % message remaining $\pm$ STDEV		
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AD-1634135.1	2 $\pm$ 1	7 $\pm$ 1	13 $\pm$ 4	AD-1659371.1	1 $\pm$ 0	2 $\pm$ 1	4 $\pm$ 1
AD-1634136.1	2 $\pm$ 1	7 $\pm$ 3	12 $\pm$ 1	AD-1659372.1	3 $\pm$ 1	9 $\pm$ 1	21 $\pm$ 4
AD-1634137.1	1 $\pm$ 0	2 $\pm$ 0	2 $\pm$ 1	AD-1659373.1	1 $\pm$ 1	2 $\pm$ 1	3 $\pm$ 1
AD-1634146.1	1 $\pm$ 0	2 $\pm$ 0	3 $\pm$ 1	AD-1659382.1	1 $\pm$ 0	1 $\pm$ 0	1 $\pm$ 0
AD-1634147.1	1 $\pm$ 0	4 $\pm$ 1	10 $\pm$ 3	AD-1659383.1	1 $\pm$ 1	2 $\pm$ 0	2 $\pm$ 0
AD-68585.2	5 $\pm$ 2	20 $\pm$ 2	29 $\pm$ 4	AD-1659384.1	2 $\pm$ 1	7 $\pm$ 1	11 $\pm$ 5
AD-1634148.1	2 $\pm$ 0	5 $\pm$ 1	9 $\pm$ 2	AD-1659385.1	1 $\pm$ 0	1 $\pm$ 0	1 $\pm$ 0
AD-1634149.1	1 $\pm$ 0	1 $\pm$ 0	3 $\pm$ 1	AD-1659386.1	1 $\pm$ 0	1 $\pm$ 0	3 $\pm$ 0
AD-1634150.1	1 $\pm$ 0	1 $\pm$ 0	4 $\pm$ 1	AD-1659387.1	1 $\pm$ 0	1 $\pm$ 0	2 $\pm$ 1
AD-1634151.1	0 $\pm$ 0	1 $\pm$ 0	2 $\pm$ 0	AD-1659388.1	0 $\pm$ 0	1 $\pm$ 0	1 $\pm$ 0
AD-1634152.1	1 $\pm$ 0	1 $\pm$ 0	2 $\pm$ 1	AD-1659389.1	1 $\pm$ 0	1 $\pm$ 0	2 $\pm$ 0
AD-1634153.1	2 $\pm$ 1	2 $\pm$ 1	5 $\pm$ 1	AD-1659390.1	1 $\pm$ 0	2 $\pm$ 0	5 $\pm$ 2
AD-1634162.1	3 $\pm$ 0	5 $\pm$ 2	12 $\pm$ 2	AD-1659399.1	3 $\pm$ 1	5 $\pm$ 1	8 $\pm$ 1
AD-1634163.1	4 $\pm$ 0	11 $\pm$ 2	18 $\pm$ 3	AD-1659400.1	9 $\pm$ 2	18 $\pm$ 5	30 $\pm$ 3
AD-1634164.1	29 $\pm$ 6	35 $\pm$ 3	48 $\pm$ 7	AD-1659401.1	26 $\pm$ 1	23 $\pm$ 3	33 $\pm$ 4
AD-1634165.1	19 $\pm$ 3	19 $\pm$ 2	30 $\pm$ 5	AD-1659402.1	20 $\pm$ 3	20 $\pm$ 5	24 $\pm$ 3
AD-1634169.1	65 $\pm$ 4	70 $\pm$ 7	79 $\pm$ 5	AD-1659406.1	63 $\pm$ 18	59 $\pm$ 11	53 $\pm$ 6
AD-1634170.1	84 $\pm$ 13	74 $\pm$ 9	72 $\pm$ 1	AD-1659407.1	58 $\pm$ 5	69 $\pm$ 8	68 $\pm$ 6
AD-1634171.1	81 $\pm$ 15	75 $\pm$ 8	85 $\pm$ 7	AD-1659408.1	86 $\pm$ 25	91 $\pm$ 9	81 $\pm$ 5
AD-1634172.1	50 $\pm$ 13	53 $\pm$ 7	67 $\pm$ 8	AD-1659409.1	58 $\pm$ 4	68 $\pm$ 6	65 $\pm$ 7
AD-1634173.1	60 $\pm$ 5	61 $\pm$ 5	56 $\pm$ 7	AD-1659410.1	49 $\pm$ 6	49 $\pm$ 2	52 $\pm$ 7
AD-1634174.1	69 $\pm$ 2	73 $\pm$ 5	77 $\pm$ 9	AD-1659411.1	36 $\pm$ 3	37 $\pm$ 4	39 $\pm$ 2
AD-1634175.1	61 $\pm$ 9	70 $\pm$ 9	81 $\pm$ 8	AD-1659412.1	36 $\pm$ 4	41 $\pm$ 7	42 $\pm$ 5
AD-1634176.1	70 $\pm$ 5	82 $\pm$ 5	88 $\pm$ 7	AD-1659413.1	64 $\pm$ 9	68 $\pm$ 4	74 $\pm$ 6
AD-1634177.1	57 $\pm$ 12	65 $\pm$ 9	67 $\pm$ 4	AD-1659414.1	52 $\pm$ 10	67 $\pm$ 3	67 $\pm$ 3
AD-1634178.1	63 $\pm$ 8	76 $\pm$ 6	74 $\pm$ 4	AD-1659415.1	58 $\pm$ 5	76 $\pm$ 4	67 $\pm$ 9
AD-1634179.1	79 $\pm$ 11	83 $\pm$ 18	103 $\pm$ 9	AD-1659416.1	65 $\pm$ 6	86 $\pm$ 7	92 $\pm$ 7
AD-1634180.1	47 $\pm$ 7	67 $\pm$ 10	72 $\pm$ 14	AD-1659417.1	58 $\pm$ 11	74 $\pm$ 7	73 $\pm$ 15
AD-1634181.1	71 $\pm$ 11	79 $\pm$ 6	72 $\pm$ 16	AD-1659418.1	54 $\pm$ 9	69 $\pm$ 7	56 $\pm$ 13
AD-1634182.1	62 $\pm$ 5	77 $\pm$ 3	86 $\pm$ 4	AD-1659419.1	57 $\pm$ 17	68 $\pm$ 7	76 $\pm$ 7
AD-1634183.1	61 $\pm$ 11	70 $\pm$ 11	81 $\pm$ 11	AD-1659420.1	63 $\pm$ 8	79 $\pm$ 11	86 $\pm$ 5
AD-1634184.1	64 $\pm$ 12	74 $\pm$ 9	80 $\pm$ 16	AD-1659421.1	33 $\pm$ 3	56 $\pm$ 8	62 $\pm$ 10
AD-1634185.1	58 $\pm$ 9	71 $\pm$ 9	76 $\pm$ 12	AD-1659422.1	58 $\pm$ 7	72 $\pm$ 18	61 $\pm$ 6
AD-1634186.1	60 $\pm$ 9	86 $\pm$ 12	86 $\pm$ 10	AD-1659423.1	62 $\pm$ 11	81 $\pm$ 15	82 $\pm$ 9
AD-1634187.1	43 $\pm$ 10	51 $\pm$ 9	42 $\pm$ 8	AD-1659424.1	81 $\pm$ 9	92 $\pm$ 11	82 $\pm$ 27
AD-1634188.1	37 $\pm$ 5	53 $\pm$ 8	48 $\pm$ 10	AD-1659425.1	42 $\pm$ 8	52 $\pm$ 14	73 $\pm$ 4
AD-1634189.1	49 $\pm$ 5	70 $\pm$ 17	87 $\pm$ 8	AD-1659426.1	47 $\pm$ 9	51 $\pm$ 9	67 $\pm$ 5
AD-1634190.1	50 $\pm$ 9	56 $\pm$ 10	72 $\pm$ 5	AD-1659427.1	46 $\pm$ 6	59 $\pm$ 16	76 $\pm$ 9
AD-1634191.1	44 $\pm$ 3	56 $\pm$ 7	65 $\pm$ 7	AD-1659428.1	56 $\pm$ 6	50 $\pm$ 8	80 $\pm$ 15

Duplex ID	Avg % message remaining $\pm$ STDEV			Duplex ID	Avg % message remaining $\pm$ STDEV		
	10 nM	1 nM	10 nM		10 nM	1 nM	10 nM
AD-1634192.1	45 $\pm$ 10	49 $\pm$ 5	61 $\pm$ 5	AD-1659429.1	34 $\pm$ 5	42 $\pm$ 7	50 $\pm$ 5
AD-1634193.1	47 $\pm$ 10	42 $\pm$ 8	62 $\pm$ 10	AD-1659430.1	63 $\pm$ 6	47 $\pm$ 7	69 $\pm$ 11
AD-1634194.1	49 $\pm$ 2	53 $\pm$ 2	62 $\pm$ 7	AD-1659431.1	49 $\pm$ 8	50 $\pm$ 7	63 $\pm$ 11
AD-1634195.1	52 $\pm$ 6	59 $\pm$ 11	80 $\pm$ 7	AD-1659432.1	59 $\pm$ 5	73 $\pm$ 7	82 $\pm$ 13
AD-1634196.1	57 $\pm$ 7	49 $\pm$ 3	71 $\pm$ 11	AD-1659433.1	50 $\pm$ 12	43 $\pm$ 7	68 $\pm$ 11
AD-1634197.1	52 $\pm$ 3	62 $\pm$ 4	70 $\pm$ 11	AD-1659434.1	52 $\pm$ 5	63 $\pm$ 5	72 $\pm$ 8
AD-1634199.1	61 $\pm$ 8	51 $\pm$ 5	60 $\pm$ 13	AD-1659436.1	65 $\pm$ 5	53 $\pm$ 3	78 $\pm$ 8
AD-1634200.1	62 $\pm$ 8	50 $\pm$ 5	73 $\pm$ 15	AD-1659437.1	57 $\pm$ 4	61 $\pm$ 3	55 $\pm$ 5
AD-1634203.1	77 $\pm$ 3	63 $\pm$ 7	86 $\pm$ 6	AD-1659440.1	65 $\pm$ 4	54 $\pm$ 6	64 $\pm$ 13
AD-1634209.1	91 $\pm$ 15	74 $\pm$ 8	112 $\pm$ 17	AD-1659446.1	78 $\pm$ 8	69 $\pm$ 3	88 $\pm$ 12
AD-1634210.1	73 $\pm$ 6	65 $\pm$ 6	85 $\pm$ 9	AD-1659447.1	72 $\pm$ 5	68 $\pm$ 6	93 $\pm$ 10
AD-1634211.1	74 $\pm$ 13	69 $\pm$ 8	85 $\pm$ 8	AD-1659448.1	66 $\pm$ 12	50 $\pm$ 9	78 $\pm$ 9
AD-1634212.1	43 $\pm$ 3	45 $\pm$ 3	68 $\pm$ 8	AD-1659449.1	68 $\pm$ 3	61 $\pm$ 5	91 $\pm$ 9
AD-1634213.1	71 $\pm$ 2	77 $\pm$ 17	98 $\pm$ 21	AD-1659450.1	73 $\pm$ 2	61 $\pm$ 6	103 $\pm$ 10
AD-1634214.1	85 $\pm$ 7	59 $\pm$ 5	85 $\pm$ 15	AD-1659451.1	52 $\pm$ 9	49 $\pm$ 9	56 $\pm$ 7
AD-1634215.1	82 $\pm$ 5	79 $\pm$ 9	108 $\pm$ 9	AD-1659452.1	67 $\pm$ 8	59 $\pm$ 6	83 $\pm$ 6
AD-1634216.1	76 $\pm$ 9	70 $\pm$ 6	113 $\pm$ 7	AD-1659453.1	77 $\pm$ 10	64 $\pm$ 3	90 $\pm$ 12
AD-1634217.1	92 $\pm$ 6	83 $\pm$ 1	116 $\pm$ 15	AD-1659454.1	75 $\pm$ 4	70 $\pm$ 6	101 $\pm$ 6
AD-1684565.1	85 $\pm$ 7	104 $\pm$ 15	84 $\pm$ 14	AD-1659481.1	49 $\pm$ 5	49 $\pm$ 5	61 $\pm$ 5
AD-1684566.1	122 $\pm$ 27	74 $\pm$ 9	98 $\pm$ 5	AD-1659482.1	67 $\pm$ 6	51 $\pm$ 4	108 $\pm$ 15
AD-1684567.1	85 $\pm$ 10	74 $\pm$ 7	98 $\pm$ 7	AD-1659483.1	89 $\pm$ 2	77 $\pm$ 9	102 $\pm$ 5
AD-1684568.1	71 $\pm$ 6	82 $\pm$ 12	107 $\pm$ 14	AD-1659485.1	67 $\pm$ 4	60 $\pm$ 6	91 $\pm$ 11
AD-1684569.1	68 $\pm$ 2	80 $\pm$ 4	100 $\pm$ 5	AD-1659487.1	68 $\pm$ 7	88 $\pm$ 15	91 $\pm$ 13
AD-1684570.1	78 $\pm$ 7	83 $\pm$ 6	123 $\pm$ 12	AD-1659488.1	79 $\pm$ 7	87 $\pm$ 13	111 $\pm$ 9
AD-1634234.1	45 $\pm$ 8	73 $\pm$ 12	91 $\pm$ 5	AD-1659489.1	81 $\pm$ 5	75 $\pm$ 10	97 $\pm$ 7
AD-1634235.1	65 $\pm$ 9	72 $\pm$ 6	91 $\pm$ 4	AD-1659490.1	47 $\pm$ 2	68 $\pm$ 4	89 $\pm$ 15
AD-1634236.1	70 $\pm$ 8	75 $\pm$ 9	96 $\pm$ 15	AD-1659491.1	32 $\pm$ 6	39 $\pm$ 3	48 $\pm$ 5
AD-1634237.1	75 $\pm$ 7	86 $\pm$ 14	113 $\pm$ 11	AD-1659492.1	36 $\pm$ 7	40 $\pm$ 4	48 $\pm$ 4
AD-1634238.1	79 $\pm$ 13	91 $\pm$ 11	96 $\pm$ 12	AD-1659493.1	74 $\pm$ 3	78 $\pm$ 4	104 $\pm$ 5
AD-1634282.1	64 $\pm$ 7	58 $\pm$ 8	72 $\pm$ 6	AD-1659537.1	63 $\pm$ 9	51 $\pm$ 8	61 $\pm$ 6
AD-1634283.1	76 $\pm$ 8	66 $\pm$ 3	97 $\pm$ 18	AD-1659538.1	59 $\pm$ 2	55 $\pm$ 5	71 $\pm$ 4
AD-1634304.1	69 $\pm$ 7	68 $\pm$ 8	102 $\pm$ 16	AD-1659559.1	70 $\pm$ 7	61 $\pm$ 11	85 $\pm$ 14
AD-1634305.1	51 $\pm$ 3	44 $\pm$ 4	50 $\pm$ 12	AD-1659560.1	49 $\pm$ 3	59 $\pm$ 3	55 $\pm$ 4
AD-1634306.1	61 $\pm$ 5	65 $\pm$ 5	74 $\pm$ 4	AD-1659561.1	51 $\pm$ 5	39 $\pm$ 5	73 $\pm$ 5
AD-1634307.1	83 $\pm$ 7	80 $\pm$ 7	103 $\pm$ 2	AD-1659562.1	74 $\pm$ 5	66 $\pm$ 8	93 $\pm$ 7
AD-1634308.1	61 $\pm$ 4	73 $\pm$ 7	82 $\pm$ 7	AD-1659563.1	69 $\pm$ 3	72 $\pm$ 4	98 $\pm$ 8

Duplex ID	Avg % message remaining $\pm$ STDEV			Duplex ID	Avg % message remaining $\pm$ STDEV		
	10 nM	1 nM	10 nM		10 nM	1 nM	10 nM
AD-1634327.1	61 $\pm$ 8	64 $\pm$ 7	80 $\pm$ 15	AD-1659582.1	49 $\pm$ 9	52 $\pm$ 2	74 $\pm$ 10
AD-1634328.1	64 $\pm$ 6	64 $\pm$ 9	91 $\pm$ 4	AD-1659583.1	44 $\pm$ 3	56 $\pm$ 4	70 $\pm$ 5
AD-1634329.1	65 $\pm$ 3	64 $\pm$ 7	85 $\pm$ 5	AD-1659584.1	60 $\pm$ 5	61 $\pm$ 9	88 $\pm$ 11
AD-1634330.1	56 $\pm$ 2	50 $\pm$ 6	54 $\pm$ 11	AD-1659585.1	72 $\pm$ 2	65 $\pm$ 7	81 $\pm$ 8
AD-1634331.1	44 $\pm$ 10	31 $\pm$ 6	49 $\pm$ 9	AD-1659586.1	53 $\pm$ 7	51 $\pm$ 9	72 $\pm$ 7
AD-1634332.1	46 $\pm$ 10	49 $\pm$ 13	81 $\pm$ 3	AD-1659587.1	34 $\pm$ 6	57 $\pm$ 1	52 $\pm$ 17
AD-1634333.1	67 $\pm$ 10	59 $\pm$ 15	84 $\pm$ 13	AD-1659588.1	64 $\pm$ 3	62 $\pm$ 11	97 $\pm$ 13

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.

5

Informal Sequence Listing

SEQ ID NO:1

>gi|188595658|ref|NM_000029.3| Homo sapiens angiotensinogen (serpin
 5 peptidase inhibitor, clade A, member 8) (AGT), mRNA
 ATCCCATGAGCGGGCAGCAGGGTCAGAAAGTGGCCCCGTTGGCTAAGCAAGACTCTCCCTGCCCTCT
 GCCCTCTGCACCTCCGGCTGCATGTCCCTGTGGCCTCTTGGGGGTACATCTCCGGGGCTGGGTCAGAA
 GGCTGGGTGGTTGGCCTCAGGCTGTACACACCTAGGGAGATGCTCCCGTTTCTGGGAACCTTGGCCCC
 GACTCCTGCAAACTTCGGTAAATGTGTAACCTCGACCTGCACCGGCTCACTCTGTTCAGCAGTGAAACTC
 10 TGCATCGATCACTAAGACTTCTTGAAGAGGTCCCAGCGTGAGTGTGCTTCTGGCATCTGTCTTCTTGG
 CCAGCCTGTGGTCTGGCCAAGTGATGTAAACCTCTCTCCAGCCTGTGCACAGGCAGCCTGGGAACAGCT
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 GTACTACAGCAGAAGGGTATGCGGAAGCGAGCACCCAGTCTGAGATGGCTCCTGCCGGTGTGAGCCTGA
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 15 CCACCTCGTATCCACAATGAGAGTACCTGTGAGCAGCTGGCAAAGGCCAATGCCGGGAAGCCAAAGAC
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 TGGTGCTAGTGTGCAAACTTGACACCGAAGACAAGTTGAGGGCCGCAATGGTCGGGATGCTGGCCAA
 CTCTTGGGCTTCGGTATATATGGCATGCACAGTGAGCTATGGGGCGTGGTCCATGGGGCCACCGTCTCT
 TCCCCAACGGCTGTCTTGGCACCCCTGGCCTCTCTCTATCTGGGAGCCTTGGACCACACAGCTGACAGGC
 20 TACAGGCAATCCTGGGTGTTCTTGGGAAGGACAAGAACTGCACCTCCCGGCTGGATGCGCACAAGGTCTT
 GTCTGCCCTGCAGGCTGTACAGGGCCTGTAGTGGCCAGGGCAGGGCTGATAGCCAGGCCCAGCTGCTG
 CTGTCCACGGTGGTGGGCGTGTTCACAGCCCCAGGCCTGCACCTGAAGCAGCCGTTTGTGAGGGCCTGG
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 TGACAGGTTTCATGCAGGCTGTGACAGGATGGAAGACTGGCTGCTCCCTGATGGGAGCCAGTGTGGACAGC
 25 ACCCTGGCTTTCAACACCTACGTCCACTTCCAAGGGAAGATGAAGGGCTTCTCCCTGCTGGCCGAGCCCC
 AGGAGTTCTGGGTGGACAACAGCACCTCAGTGTCTGTTCCCATGCTCTCTGGCATGGGCACCTTCCAGCA
 CTGGAGTGACATCCAGGACAACCTTCTCGGTGACTCAAGTGCCCTTCACTGAGAGCGCTGCCTGCTGCTG
 ATCCAGCCTCACTATGCCTCTGACCTGGACAAGGTGGAGGGTCTCACTTTCCAGCAAACTCCCTCAACT
 GGATGAAGAACTATCTCCCGGACCATCCACCTGACCATGCCCAACTGGTGTGCAAGGATCTTATGA
 30 CCTGCAGGACTGCTCGCCAGGCTGAGCTGCCCGCCATTCTGCACACCGAGCTGAACCTGCAAAAATTG
 AGCAATGACCCGATCAGGGTGGGGGAGGTGCTGAACAGCATTTTTTTTGTAGCTTGAAGCGGATGAGAGAG
 AGCCACAGAGTCTACCCAAACAGCTTAACAAGCCTGAGGTCTTGGAGGTGACCTGAACCGCCCCATTCTT
 GTTTGCTGTGTATGATCAAAGCGCCACTGCCCTGCATTTCTGGGCCGCGTGGCCAACCCGCTGAGCACA
 GCATGAGGCCAGGGCCCCAGAACACAGTGCTGGCAAGGCCTCTGCCCTGGCCTTTGAGGCAAAAGGCCA
 35 GCAGCAGATAACAACCCGGACAAATCAGCGATGTGTACCCCAAGTCTCCACCTTTTCTTAATGAG
 TCGACTTTGAGCTGGAAGCAGCCGTTTCTCTTGGTCTAAGTGTGCTGCATGGAGTGAGCAGTAGAAGC
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 CCAGTGTTTAGCGCGGGACTACTGTTCAAAAAGAATTCCAACCGACCAGCTTGTGTGAAACAAAAAA
 GTGTTCCCTTTTCAAGTTGAGAACAAAAATTGGGTTTTAAATTAAGTATACATTTTTGCAATTGCCCTT
 40 GGTGTTGATTTAGTGTCTTGAATGTAAGAATGACCTCCGTGTAGTGTCTGTAATACCTTAGTTTTTTC
 CACAGATGCTTGTGATTTTTGAACAATACGTGAAAGATGCAAGCACCTGAATTTCTGTTTGAATCGGGAA
 CCATAGCTGGTTATTTCTCCCTTGTGTTAGTAATAAACGCTTTGCCACAATAAGCCTCCAAAAAAA

SEQ ID NO:2

Reverse Complement of SEQ ID NO:1
 45 TTTTTTTGGAGGCTTATTGTGGCAAGACGTTTATTACTAACACAAGGGAGAAATAACCAGCTATGGTTCCGCAT
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20 GAGTGAGCCGGTGCAGGGTCGAGTTACACATTTACCGAAGTTTGCAGGAGTCGGGGCCAAGGTTCCAGAAACGG
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25 **SEQ ID NO: 3**
>NM_001384479.1 Homo sapiens angiotensinogen (AGT), transcript variant 1,
mRNA
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35 TTGGACCACACAGCTGACAGGCTACAGGCAATCCTGGGTGTTCTTGGAAAGACAAGAACTGCACCTCCC
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SEQ ID NO:4

Reverse Complement of SEQ ID NO:3

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SEQ ID NO:5

>gi|90075391|dbj|AB170313.1| Macaca fascicularis brain cDNA clone: QmoA-
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 proteinaseinhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member
 8) (AGT), mRNA, RefSeq: NM_000029.1
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SEQ ID NO:6

Reverse Complement of SEQ ID NO:5

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35 SEQ ID NO:7

>gi|113461997|ref|NM_007428.3| Mus musculus angiotensinogen (serpin
peptidase inhibitor, clade A, member 8) (Agt), mRNA
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SEQ ID NO:8

Reverse Complement of SEQ ID NO:7

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35 SEQ ID NO:9

>gi|51036672|ref|NM_134432.2| Rattus norvegicus angiotensinogen (serpin
peptidase inhibitor, clade A, member 8) (Agt), mRNA
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40 TAGCTGTGCTTGTCTGGGCTGGAGCTAAAGGACACACAGAAGCAAGTCCACAGATCCGTGATGACTCCCA
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45 CGCGATGATTGCCAACTTCATGGGTTTCCGCATGTACAAGATGCTGAGTGAGGCAAGAGGTGTAGCCAGT
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SEQ ID NO:10

Reverse Complement of SEQ ID NO:9

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SEQ ID NO:11

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SEQ ID NO:12
Reverse Complement of SEQ DI NO:11
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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 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 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 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 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.
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 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.

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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'-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 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

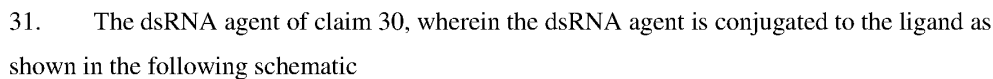
10. The dsRNA agent of any one of claims 6-8, wherein at least one of the modified nucleotides is selected from the group consisting of LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C-allyl, 2'-fluoro, 2'-deoxy, 2'-hydroxyl, and glycol; and combinations thereof.

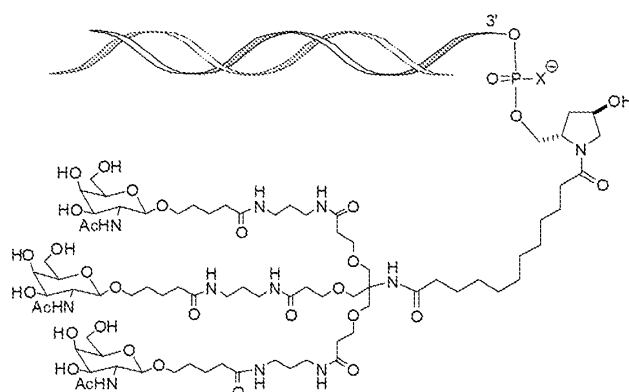
30 11. The dsRNA agent of any one of claims 6-8, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), a nucleotide 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
5 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
10 nucleotide pairs in length.
15. The dsRNA agent of claim 14, wherein the double stranded region is 19-25 nucleotide pairs in length.
- 15 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.
20
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
25 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.
- 30 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
35 between 19 and 23 nucleotides in length.

30. The dsRNA agent of claim 28 or 29, wherein the ligand is





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.
- 15 47. The pharmaceutical composition of claim 44, wherein said dsRNA agent is in a buffer solution.
48. The pharmaceutical composition of claim 47, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.
- 20 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.
- 10 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).
73. The method of any one of claims 60-72, further comprising determining the level of
- 15 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.
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.
81. An RNA-induced silencing complex (RISC) comprising an antisense strand of any of the dsRNA agents of claims 1-42.