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(54) **Title:** METHODS AND COMPOSITIONS FOR TREATING SUBJECTS HAVING OR AT RISK OF DEVELOPING A NON-PRIMARY HYPEROXALURIA DISEASE OR DISORDER

(57) **Abstract:** The present invention provides methods for treating subjects having or at risk of developing a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate, and compositions comprising nucleic acid inhibitors, e.g., double stranded ribonucleic acid (dsRNA) agents or single stranded antisense polynucleotide agents targeting lactate dehydrogenase A (LDHA), hydroxyacid oxidase (HAO1) and/or proline dehydrogenase 2 (PRODH2), for treating such subjects.

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METHODS AND COMPOSITIONS FOR TREATING SUBJECTS HAVING OR AT RISK OF DEVELOPING A NON-PRIMARY HYPEROXALURIA DISEASE OR DISORDER

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application No. 63/223,278, filed on July 19, 2021, the entire contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Oxalate ($C_2O_4^{2-}$) is the salt-forming ion of oxalic acid ($C_2H_2O_4$) that is widely distributed in both plants and animals. It is an unavoidable component of the human diet and a ubiquitous component of plants and plant-derived foods. Oxalate can also be synthesized endogenously *via* the metabolic pathways that occur in the liver. Dietary and endogenous contributions to urinary oxalate excretion are equal. Glyoxylate is an immediate precursor to oxalate and is derived from the oxidation of glycolate by the enzyme glycolate oxidase (GO), also known, and referred to herein, as hydroxyacid oxidase (HAO1), or by catabolism of hydroxyproline, a component of collagen, by proline dehydrogenase 2 (PRODH2, also known as HYPDH). Transamination of glyoxylate with alanine by the enzyme alanine-glyoxylate aminotransferase (AGXT) results in the formation of pyruvate and glycine. Excess glyoxylate is converted to oxalate by lactate dehydrogenase A (LDHA). The endogenous pathway for oxalate metabolism is illustrated in Figure 1.

Since oxalate binds with calcium in the kidney, urinary CaOx supersaturation may occur, resulting in the formation and deposition of CaOx crystals in renal tissue or collecting system, even in the presence of normal levels of oxalate. These CaOx crystals contribute to the formation of diffuse renal calcifications (nephrocalcinosis) and stones (nephrolithiasis). Subjects having diffuse renal calcifications or non-obstructing stones typically have no symptoms. However, obstructing stones can cause severe pain. Moreover, over time, these CaOx crystals cause injury and progressive inflammation to the kidney and, when secondary complications such as obstruction are present, these CaOx crystals may lead to decreased renal function and in severe cases even to end-stage renal failure and the need for dialysis.

Primary hyperoxaluria is a well-known disease associated with high levels of oxalate. Specifically, primary hyperoxaluria is characterized by impaired glyoxylate metabolism resulting in overproduction and accumulation of oxalate throughout the body, typically manifesting as kidney and bladder stones. There are three major types of primary hyperoxaluria that differ in their severity and genetic cause. Autosomal recessive mutations in the AGXT gene cause primary hyperoxaluria type 1 (PH1); autosomal recessive mutations in the GRHPR gene cause primary hyperoxaluria type 2 (PH2); and autosomal recessive mutations in the HOGA1 gene cause primary hyperoxaluria type 3 (PH3) (see, Figure 1). There are few treatment options for subjects having a hereditary hyperoxaluria. Ultimately, some subjects with hereditary hyperoxaluria develop end stage renal disease (ESRD) and require kidney/liver transplants.

Recently, two investigational therapeutics for the treatment of subjects having PH1 or PH2 that reduce oxalate have entered the clinic. Specifically, Lumasiran, an RNA interference (RNAi) therapeutic targeting glycolate oxidase (GO) for the treatment of PH1 is currently being evaluated in a Phase III clinical trail (see, *e.g.,* NCT03681184), and DCR-PHXC, an RNA interference (RNAi) therapeutic targeting LDHA for the treatment of PH1 and PH2 has entered Phase II clinical trials (see, *e.g.,* NCT03847909).

However, there are a significant number of subjects that do not have primary hyperoxaluria, *e.g.,* PH1, PH2, or PH3, and yet still would benefit from reduction in oxalate, for example, subjects having a non-primary hyperoxaluria disease or disorder, for which no effective treatments currently exist. For example, as indicated above, CaOx crystals can form and be deposited in renal tissue or collecting system, even in the presence of normal levels of oxalate and contribute to the formation of diffuse renal calcifications (nephrocalcinosis) and stones (nephrolithiasis). In the presence of other comorbidities, such as a metabolic disorder, *e.g.,* diabetes, Crohn's disease, or bariatric surgery, subjects having such comorbidities may be at risk of developing, *e.g.,* obstructing stones, progressive inflammation of the kidney, decreased renal function and end-stage renal failure.

Accordingly, there is a need in the art for methods to treat subjects having, or at risk of developing, a non-primary hyperoxaluria that would benefit from treatment with agents that reduce oxalate, such as a nucleic acid inhibitor of lactate dehydrogenase A (LDHA), a nucleic acid inhibitor of proline dehydrogenase 2 (PRODH2) and/or a nucleic acid inhibitor of hydroxyacid oxidase (HAO1).

SUMMARY OF THE INVENTION

The present invention is based, at least in part, on the discovery that agents that reduce oxalate levels, such as a nucleic acid inhibitor of lactate dehydrogenase A (LDHA), a nucleic acid inhibitor of hydroxyacid oxidase (HAO1) and/or a nucleic acid inhibitor of proline dehydrogenase 2 (PRODH2), can be used to treat subjects having or at risk of developing a non-primary hyperoxaluria disease or disorder, such as a subject having normal urinary oxlate levels, *e.g.,* normal urinary calcium oxlatae levels, or elevated urinary oxalate levels, *e.g.,* elevated urinary calcium oxalate levels, *e.g.,* supersaturated urinary calcium oxlalate levels, *e.g.*, a subject having a kidney stone disease, *e.g.,* calcium oxalate kidney stone disease, such as recurrent calcium oxalate kidney stone disease.

Accordingly, the present invention provides methods for inhibiting the expression of hydroxyacid oxidase (HAO1) in a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate, methods for reducing urinary oxalate levels in a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate, and methods for treating a subject having having or at risk of developing a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate, and compositions comprising nucleic acid inhibitors, *e.g.,* double stranded ribonucleic acid (dsRNA)

agents or single stranded antisense polynucleotide agents targeting lactate dehydrogenase A (LDHA), hydroxyacid oxidase (HAO1) and/or proline dehydrogenase 2 (PRODH2).

In one aspect, the present invention provides a method for inhibiting the expression of hydroxyacid oxidase (HAO1) in a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate, comprising administering to the subject a fixed dose of about 200 mg to about 600 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1, thereby inhibiting the expression of HAO1 in the subject.

In another aspect, the present invention provides a method for reducing urinary oxalate levels in a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate, comprising administering to the subject a fixed dose of about 200 mg to about 600 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1, thereby reducing urinary oxalate levels in the subject.

In one embodiment, the urinary oxalate is urinary calcium oxalate.

In one embodiment, the reduction in urinary calcium oxalate is reduction in urinary calcium oxalate supersaturation.

In one aspect, the present invention provides a method for treating a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate, comprising administering to the subject a fixed dose of about 200 mg to about 600 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1, thereby treating the subject having the non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate.

In one embodiment, the non-primary hyperoxaluria disease or disorder is selected from the group consisting of secondary hyperolxaluria, a kidney stone disease, chronic kidney disease (CKD), end-stage renal disease (ESRD), coronary artery disease, cutaneous oxalate deposition, ethylene glycol poisoning, planned kidney transplantation, and previous kidney transplantation.

In one embodiment, the non-primary hyperoxaluria disease or disorder is a kidney stone disease.

In one embodiment, the kidney stone disease is calcium oxalate kidney stone disease.

In one embodiment, the calcium oxalate kidney stone disease is recurrent calcium oxalate kidney stone disease.

In one embodiment, administration of the dsRNA agent, or salt thereof, to the subject reduces urinary oxalate levels.

In one embodiment, the urinary oxalate is urinary calcium oxalate.

In one embodiment, the reduction in urinary calcium oxalate is reduction in urinary calcium oxalate supersaturation.

In one embodiment, administration of the dsRNA agent, or salt thereof, to the subject reduces clinical and radiographic kidney stone events.

In one embodiment, the subject is a human.

In one embodiment, the dsRNA agent, or salt thereof, is administered to the subject at an interval of once every six months.

In one embodiment, the dsRNA agent, or salt thereof, is administered to the subject initially, at three months, and every six months thereafter.

In one embodiment, the fixed dose of the dsRNA agent, or salt thereof, is about 284 mg.

In one embodiment, the fixed dose of the dsRNA agent, or salt thereof, is about 567 mg.

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

In one embodiment, the subcutaneous administration is subcutaneous injection.

In one embodiment, the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a portion of the nucleotide sequence of SEQ ID NO: 21 and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the corresponding portion of nucleotide sequence of SEQ ID NO: 22 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

In one embodiment, the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 4-14.

In one embodiment, the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises a nucleotide sequence differing by no more than 3 nucleotides from the nucleotide sequence 5'-GACUUUCAUCCUGGAAAUAUA -3' (SEQ ID NO:33) and the antisense strand comprises a nucleotide sequence differing by no more than 3 nucleotides from the nucleotide sequence 5'-UAUAUUUCCAGGAUGAAAGUCCA -3' (SEQ ID NO:34).

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

In one embodiment, no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand are unmodified nucleotides.

In one embodiment, 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 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 a deoxy-nucleotide, a 3'-terminal deoxy-thymine (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 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S-Isomer, a nucleotide comprising 2-hydroxymethyl-tetrahydrofurane-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, and a terminal nucleotide linked to a cholesteryl derivative and a dodecanoic acid bisdecylamide group; and combinations thereof.

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

In one embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3′-terminus of one strand.

In one embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5′-terminus of one 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 dsRNA agent, or salt thereof, comprises 6-8 phosphorothioate internucleotide linkages.

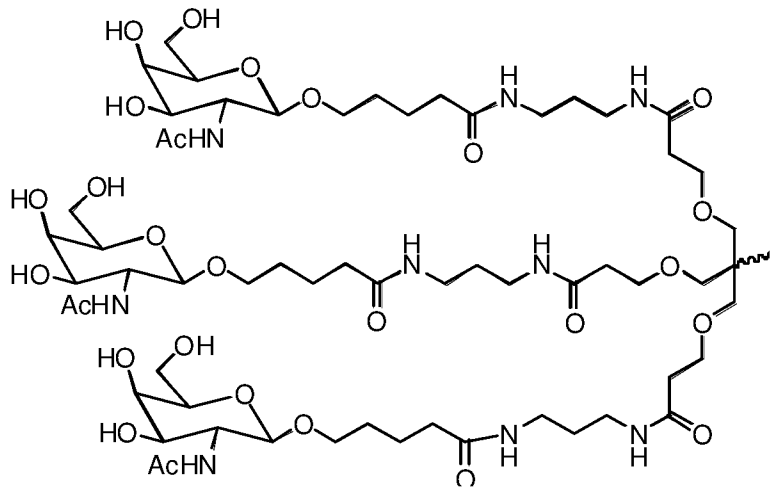
In one embodiment, at least one strand of the dsRNA agent, or salt thereof, further comprises a ligand.

In one embodiment, the ligand is attached to the 3′ end of the sense strand.

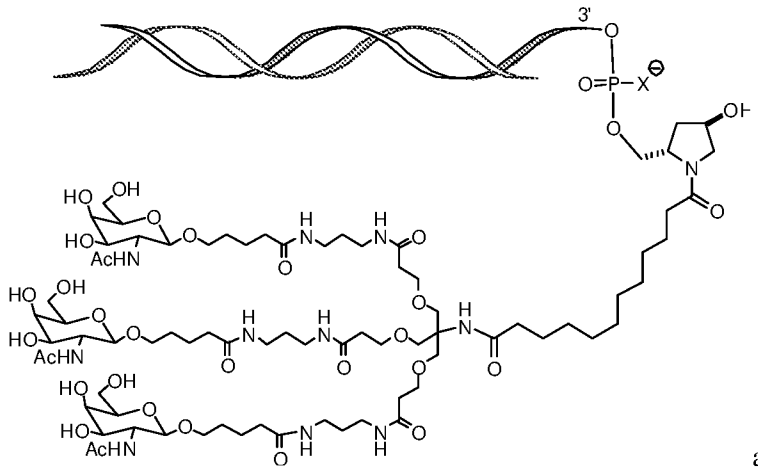
In one embodiment, the ligand is one or more N-acetylgalactosamine (GalNAc) derivatives.

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

In one embodiment, the ligand is



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



and, wherein X is O or S.

In one embodiment, the X is O.

In one embodiment, the nucleotide sequence of the sense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36),

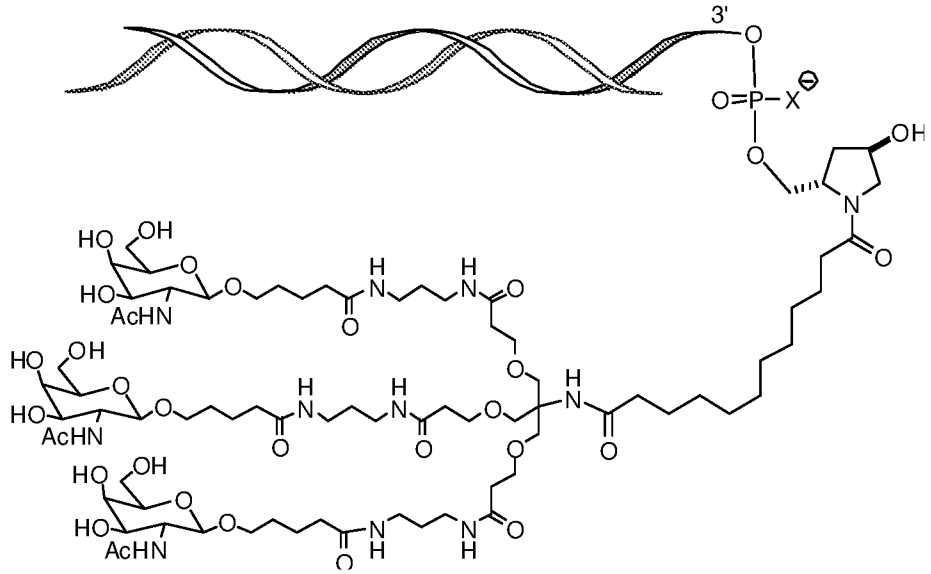
wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; uis a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage.

In one embodiment, the nucleotide sequence of the sense strand differs by no more than 2 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 2 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

In one embodiment, the nucleotide sequence of the sense strand differs by no more than 1 nucleotide from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 1 nucleotide from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

In one embodiment, the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

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



and, wherein X is O or S.

In one aspect, the present invention provides a method for inhibiting the expression of hydroxyacid oxidase (HAO1) in a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate, comprising administering to the subject a fixed dose of about 200 mg to about 600 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1, wherein the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double-stranded region, wherein the nucleotide sequence of the sense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36), wherein Af is a 2'-fluoroadenosine-3'-phosphate; Afs is 2'-fluoroadenosine-3'-phosphorothioate; Cf is a 2'-fluorocytidine-3'-phosphate; U is a Uridine-3'-phosphate; Uf is a 2'-fluorouridine-3'-phosphate; a is a 2'-O-methyladenosine-3'-phosphate; as is a 2'-O-methyladenosine-3'-phosphorothioate; c is a 2'-O-methylcytidine-3'-phosphate; cs is a 2'-O-methylcytidine-3'-phosphorothioate; g is a 2'-O-methylguanosine-3'-phosphate; gs is a 2'-O-methylguanosine-3'-phosphorothioate; uis a 2'-O-methyluridine-3'-phosphate;

us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage, thereby inhibiting the expression of HAO1 in the subject.

In another aspect, the present invention provides a method for reducing urinary oxalate levels in a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate, comprising administering to the subject a fixed dose of about 200 mg to about 600 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1, wherein the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double-stranded region, wherein the nucleotide sequence of the sense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36), wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; uis a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage, thereby reducing urinary oxalate levels in the subject.

In one embodiment, the urinary oxalate is urinary calcium oxalate.

In one embodiment, the reduction in urinary calcium oxalate is reduction in urinary calcium oxalate supersaturation.

In one embodiment, the present invention provides a method for treating a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate, comprising administering to the subject a fixed dose of about 200 mg to about 600 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1, wherein the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double-stranded region, wherein the nucleotide sequence of the sense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36), wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; uis a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a

phosphorothioate linkage, thereby treating the subject having the non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate.

In one embodiment, the non-primary hyperoxaluria disease or disorder is selected from the group consisting of secondary hyperolxaluria, a kidney stone disease, chronic kidney disease (CKD), end-stage renal disease (ESRD), coronary artery disease, cutaneous oxalate deposition, ethylene glycol poisoning, planned kidney transplantation, and previous kidney transplantation.

In one embodiment, the non-primary hyperoxaluria disease or disorder is a kidney stone disease.

In one embodiment, the kidney stone disease is calcium oxalate kidney stone disease.

In one embodiment, the calcium oxalate kidney stone disease is recurrent calcium oxalate kidney stone disease.

In one embodiment, administration of the dsRNA agent, or salt thereof, to the subject reduces urinary oxalate levels.

In one embodiment, the urinary oxalate is urinary calcium oxalate.

In one embodiment, the reduction in urinary calcium oxalate is reduction in urinary calcium oxalate supersaturation.

In one embodiment, administration of the dsRNA agent, or salt thereof, to the subject reduces clinical and radiographic kidney stone events.

In one embodiment, the subject is a human.

In one embodiment, the dsRNA agent, or salt thereof, is administered to the subject at an interval of once every six months.

In one embodiment, the dsRNA agent, or salt thereof, is administered to the subject initially, at three months, and every six months thereafter.

In one embodiment, the fixed dose of the dsRNA agent, or salt thereof, is about 284 mg.

In one embodiment, the fixed dose of the dsRNA agent, or salt thereof, is about 567 mg.

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

In one embodiment, the subcutaneous administration is subcutaneous injection.

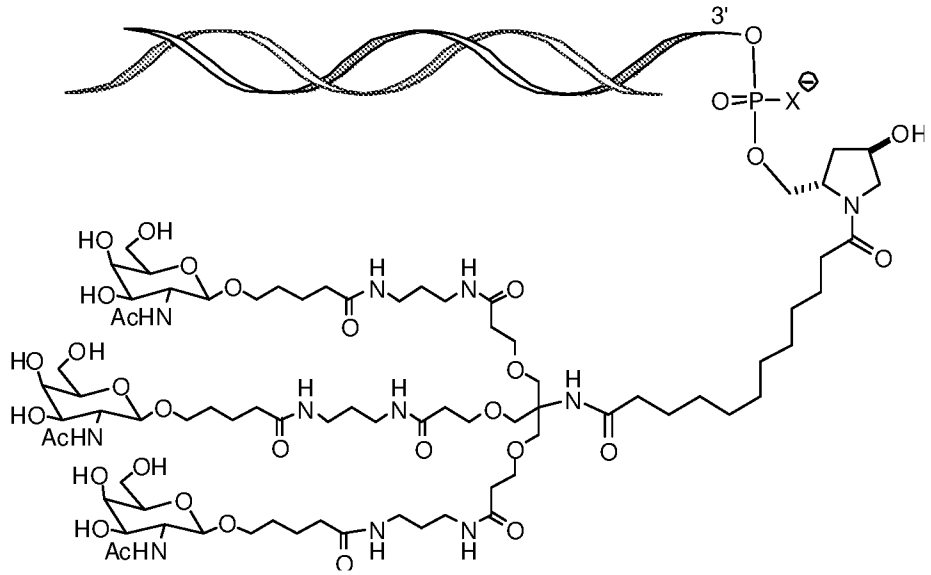
In one embodiment, the nucleotide sequence of the sense strand differs by no more than 2 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 2 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

In one embodiment, the nucleotide sequence of the sense strand differs by no more than 1 nucleotide from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 1 nucleotide from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

In one embodiment, the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the

antisense strand comprises the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

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



and, wherein X is O or S.

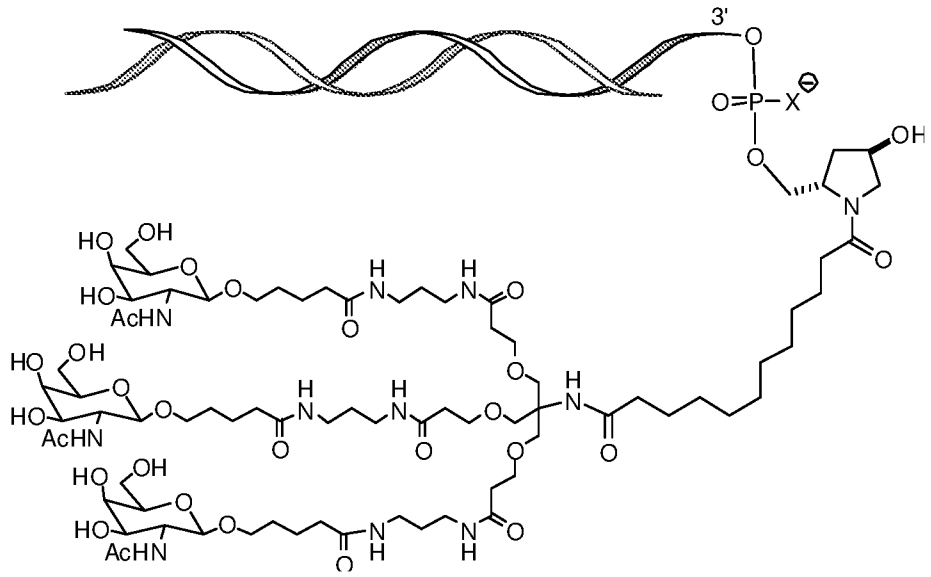
In one embodiment, the X is O.

In one embodiment, the dsRNA agent is in salt form.

In one embodiment, the dsRNA agent, or salt thereof, is administered to the subject in a pharmaceutical formulation.

In one embodiment, the method of the invention further comprise administering an additional therapeutic to the subject.

In one aspect, the present invention provides a method for reducing calcium oxalate kidney stone incidence in a subject, the method comprising subcutaneously administering to the subject a fixed dose of about 284 mg or about 567 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, comprising a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the antisense strand comprises the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36), wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; u is a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage, and wherein the sense strand is conjuaged to a ligand as shown in the following schematic



and, wherein X is O, thereby reducing calcium oxalate kidney stone incidence in the subject.

In one embodiment, the subject has suffered 2 or more oxalate stone events.

In one embodiment, the subject has elevated urinary oxalate levels.

In one embodiment, the subject has suffered 2 or more oxalate stone events and has elevated urinary oxalate levels.

In one embodiment, the dsRNA agent, or salt thereof, is administered to the subject once every six months.

In one embodiment, the dsRNA agent, or salt thereof, is administered to the subject initially, at three months, and every six months thereafter.

In one aspect, the present invention provides a method for treating a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate, the method comprising administering to the subject a therapeutically effective amount of a nucleic acid inhibitor of hydroxyacid oxidase (HAO1) and/or a nucleic acid inhibitor of Proline Dehydrogenase 2 (PRODH2), thereby treating the subject having the non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate.

In some embodiments, the non-primary hyperoxaluria disease or disorder is selected from the group consisting of a secondary hyperolxaluria, a kidney stone disease, chronic kidney disease (CKD), end-stage renal disease (ESRD), coronary artery disease, cutaneous oxalate deposition, ethylene glycol poisoning, planned kidney transplantation, and previous kidney transplantation.

In another aspect, the present invention provides a method of treating a subject at risk of developing a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate, the method comprising administering to the subject a therapeutically effective amount of a nucleic acid inhibitor of lactate dehydrogenase A (LDHA), a nucleic acid inhibitor of hydroxyacid oxidase (HAO1), and/or a nucleic acid inhibitor of Proline Dehydrogenase 2 (PRODH2), thereby treating the subject at risk of developing the non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate.

In some embodiments, subject at risk of developing a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate suffers from Crohn's disease, inflammatory bowel disease, a bariatric surgery, fibromyalgia, an autoimmune disease, coronary artery disease, a kidney stone disease, end-stage renal disease (ESRD), diabetes, obesity, HIV, or ethylene glycol poisoning.

In one embodiment, the subject is a human.

In one embodiment, the nucleic acid inhibitor is a double stranded ribonucleic acid (dsRNA) agent that inhibits the expression of HAO1.

In one embodiment, the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a portion of the nucleotide sequence of SEQ ID NO: 21 and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the corresponding portion of nucleotide sequence of SEQ ID NO: 22 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

In one embodiment, the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 4-14.

In one embodiment, the dsRNA agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises the nucleotide sequence 5'-GACUUUCAUCCUGGAAAUAUA -3' (SEQ ID NO:33) and the antisense strand comprises the nucleotide sequence 5'-UAUAUUUCCAGGAUGAAAGUCCA -3' (SEQ ID NO:34).

In one embodiment, the nucleic acid inhibitor is a double stranded ribonucleic acid (dsRNA) agent that inhibits the expression of LDHA.

In one embodiment, the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a portion of the nucleotide sequence of SEQ ID NO: 1 and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the corresponding portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

In one embodiment, the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 2-3.

In one embodiment, the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence

comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5'-AUGUUGUCCUUUUUAUCUGAGCAGCCGAAAGGCUGC -3' (SEQ ID NO:31), and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence 5'-UCAGAUAAAAAGGACAACAUGG -3' (SEQ ID NO: 32).

one embodiment, the nucleic acid inhibitor is a double stranded ribonucleic acid (dsRNA) agent that inhibits the expression of PRODH2.

In one embodiment, the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a portion of the nucleotide sequence of SEQ ID NO: 4641 and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the corresponding portion of nucleotide sequence of SEQ ID NO: 4642 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

In one embodiment, the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 15-16.

In one embodiment, the nucleic acid inhibitor is a dual targeting double stranded ribonucleic acid (dsRNA) agent that inhibits the expression of LDHA and HAO1.

In one embodiment, the dual targeting dsRNA agent comprises a first double stranded ribonucleic acid (dsRNA) agent that inhibits expression of lactic dehydrogenase A (LDHA) comprising a sense strand and an antisense strand; and a second double stranded ribonucleic acid (dsRNA) agent that inhibits expression of hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) comprising a sense strand and an antisense strand, wherein the first dsRNA agent and the second dsRNA agent are covalently attached, wherein the sense strand of the first dsRNA agent comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and the antisense strand of the first dsRNA agent comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein the sense strand of the second dsRNA agent comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:21, and said antisense strand of the second dsRNA agent comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:22.

In one embodiment, the dual targeting dsRNA agent comprises a first double stranded ribonucleic acid (dsRNA) agent that inhibits expression of lactic dehydrogenase A (LDHA) comprising a sense strand and an antisense strand; and a second double stranded ribonucleic acid (dsRNA) agent that inhibits expression of hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) comprising a sense strand and an antisense strand, wherein the first dsRNA agent and the second

dsRNA agent are covalently attached, wherein the antisense strand of the first dsRNA agent comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 2-3, and wherein the antisense strand of the second dsRNA agent comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 4-14.

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

In one embodiment, no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand are unmodified nucleotides.

In one embodiment, 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 a deoxy-nucleotide, a 3'-terminal deoxythimidine (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 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S-Isomer, a nucleotide comprising 2-hydroxymethyl-tetrahydrofurane-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, and a terminal nucleotide linked to a cholesteryl derivative and a dodecanoic acid bisdecylamide group; and combinations thereof.

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

In one embodiment, the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages.

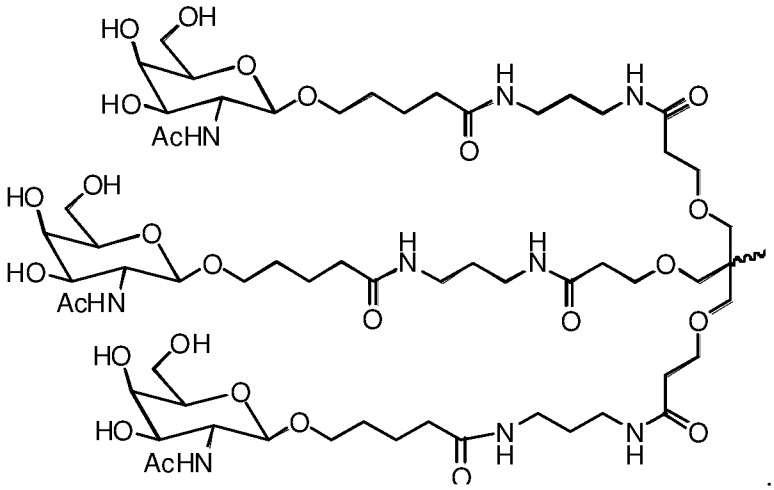
In one embodiment, at least one strand of the dsRNA agent further comprises a ligand.

In one embodiment, the ligand is attached to the 3′ end of the sense strand.

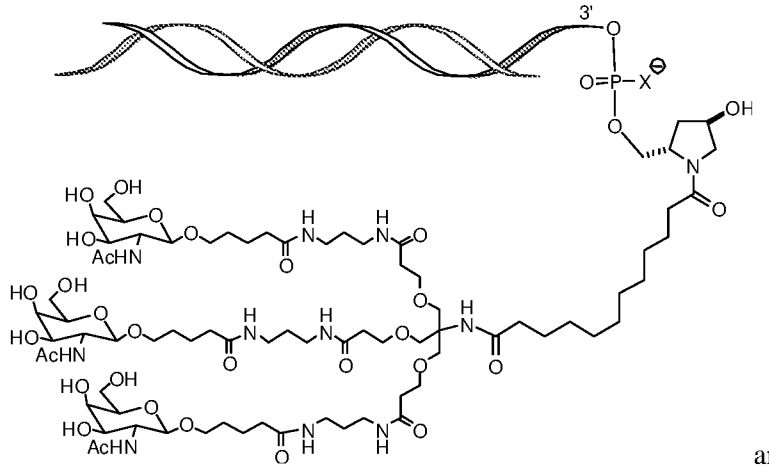
In one embodiment, the ligand is one or more N-acetylgalactosamine (GalNAc) derivatives.

In one embodiment, the one or more GalNAc derivatives is 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

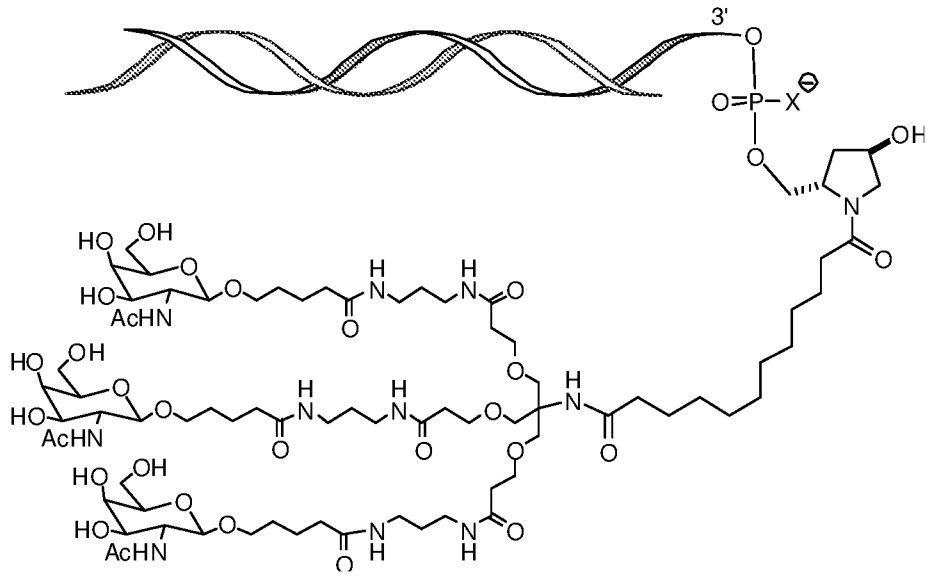


and, wherein X is O or S.

In one embodiment, the X is O.

In one embodiment, the sense strand comprises the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the antisense strand comprises the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36), wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; uis a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage.

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



and, wherein X is O or S.

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

In one embodiment, all of the nucleotides of the dsRNA agent are modified nucleotides.

In one embodiment, the modified nucleotide comprises a 2'- modification.

In one embodiment, the 2 '-modification is a 2'-fluoro or 2'-O- methyl modification.

In one embodiment, one or more of the following positions are modified with a 2'-O-methyl: positions 1, 2, 4, 6, 7, 12, 14, 16, 18-26, or 31-36 of the sense strand and/or positions 1, 6, 8, 11-13, 15, 17, or 19-22 of the antisense strand.

In one embodiment, all of positions 1, 2, 4, 6, 7, 12, 14, 16, 18-26, and 31-36 of the sense strand and all of the positions 1, 6, 8, 11-13, 15, 17, and 19-22 of the antisense strand are modified with a 2'-O-methyl.

In one embodiment, one or more of the following positions are modified with a 2'-fluoro: positions 3, 5, 8-11, 13, 15, or 17 of the sense strand and/or positions 2-5, 7, 9, 10, 14, 16, or 18 of the antisense strand.

In one embodiment, all of positions 3, 5, 8-11, 13, 15, or 17 of the sense strand and all of positions 2-5, 7, 9, 10, 14, 16, and 18 of the antisense strand are modified with a 2'-fluoro.

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

In one embodiment, the at least one modified internucleotide linkage is a phosphorothioate linkage.

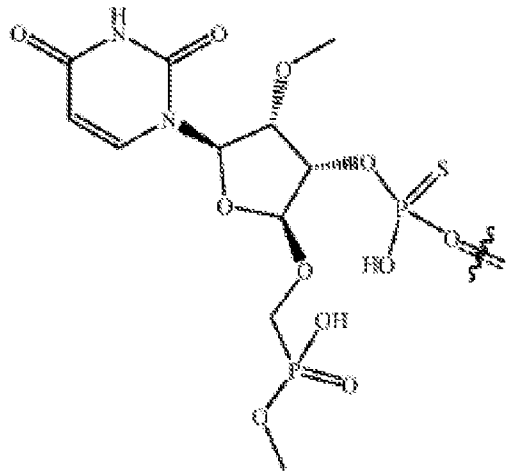
In one embodiment, the dsRNA agent has a phosphorothioate linkage between one or more of: positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

In one embodiment, the dsRNA agent has a phosphorothioate linkage between each of: positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the

antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

In one embodiment, the uridine at the first position of the antisense strand comprises a phosphate analog.

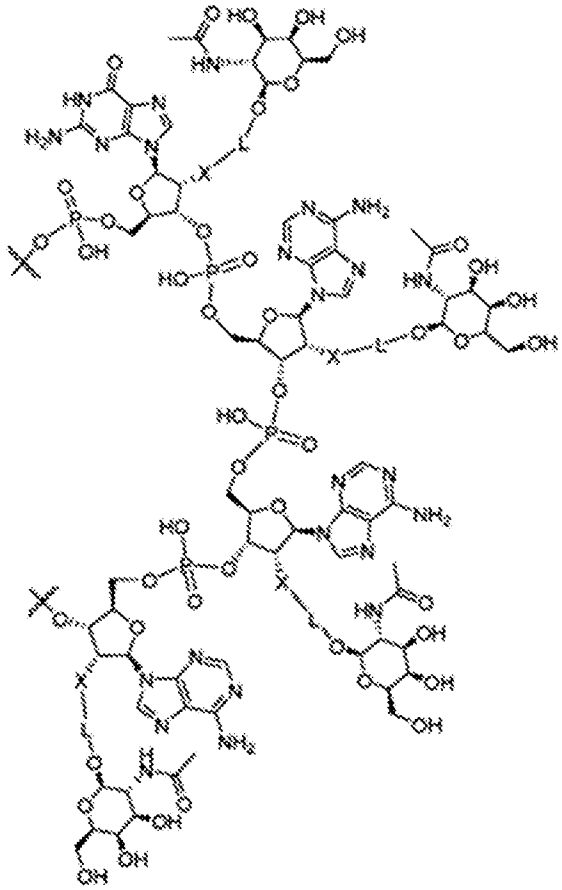
In one embodiment, the dsRNA comprises the following structure at position 1 of the antisense strand:



In one embodiment, one or more of the nucleotides of the -GAAA- sequence on the sense strand is conjugated to a monovalent GalNac moiety.

In one embodiment, each of the nucleotides of the -GAAA- sequence on the sense strand is conjugated to a monovalent GalNac moiety.

In one embodiment, the -GAAA- motif comprises the structure:



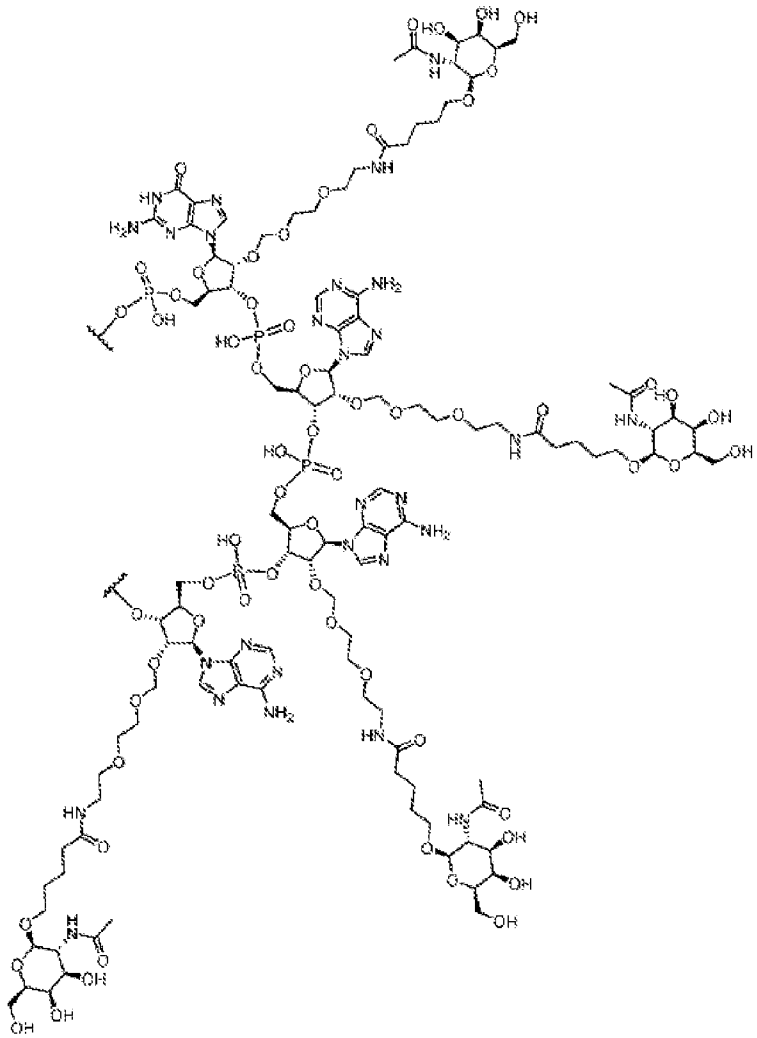
wherein: L represents a bond, click chemistry handle, or a linker of 1 to 20, inclusive, consecutive, covalently bonded atoms in length, selected from the group consisting of substituted and unsubstituted alkylene, substituted and unsubstituted alkenylene, substituted and unsubstituted alkynylene, substituted and unsubstituted heteroalkylene, substituted and unsubstituted heteroalkenylene, substituted and unsubstituted heteroalkynylene, and combinations thereof; and

X is a O, S, or N.

In one embodiment, L is an acetal linker.

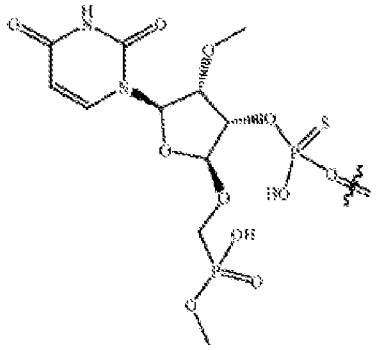
In one embodiment, X is O.

In one embodiment, the -G AAA- sequence comprises the structure:

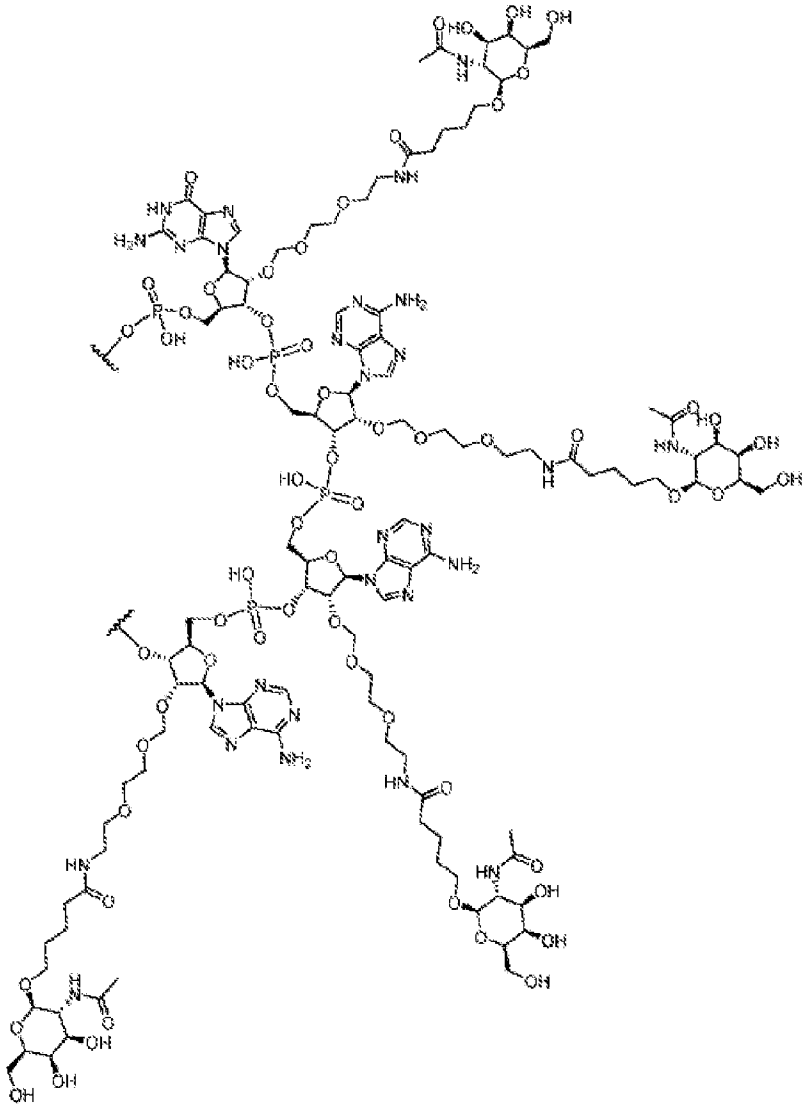


In one embodiment, the dsRNA comprises an antisense strand having a sequence set forth as UCAGAUAAAAAGGACAACAUGG (SEQ ID NO: 32) and a sense strand having a sequence set forth as AUGUUGUCCUUUUUAUCUGAGCAGCCGAAAGGCUGC (SEQ ID NO: 31), wherein all of positions 1, 2, 4, 6, 7, 12, 14, 16, 18-26, and 31-36 of the sense strand and all of positions 1, 6, 8, 11-13, 15, 17, and 19-22 of the antisense strand are modified with a 2'-O- methyl, and all of positions 3, 5, 8-11, 13, 15, or 17 of the sense strand and all of positions 2-5, 7, 9, 10, 14, 16, and 18 of the antisense strand are modified with a 2'-fluoro; wherein the oligonucleotide has a phosphorothioate linkage between each of: positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand;

wherein the dsRNA agent comprises the following structure at position 1 of the antisense strand:



wherein each of the nucleotides of the -GAAA- sequence on the sense strand is conjugated to a monovalent GalNac moiety comprising the structure:



In one embodiment, the dsRNA agent is present in a composition comprising the dsRNA agent and Na+ counterions.

In one embodiment, the nucleic acid inhibitor is a single stranded antisense polynucleotide agent that inhibits the expression of LDHA.

In one embodiment, the single stranded antisense polynucleotide agent comprises at least 15 contiguous nucleotide differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-3.

In one embodiment, the nucleic acid inhibitor is a single stranded antisense polynucleotide agent that inhibits the expression of PRODH2.

In one embodiment, the single stranded antisense polynucleotide agent comprises at least 15 contiguous nucleotide differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 15-16.

In one embodiment, the single stranded antisense polynucleotide agent is about 8 to about 50 nucleotides in length.

In one embodiment, substantially all of the nucleotides of the single stranded antisense polynucleotide agent are modified nucleotides.

In one embodiment, all of the nucleotides of the single stranded antisense polynucleotide agent are modified nucleotides.

In one embodiment, the modified nucleotide comprises a modified sugar moiety selected from the group consisting of: a 2′-O-methoxyethyl modified sugar moiety, a 2′-O-alkyl modified sugar moiety, and a bicyclic sugar moiety.

In one embodiment, the bicyclic sugar moiety has a (—CRH—)n group forming a bridge between the 2′ oxygen and the 4′ carbon atoms of the sugar ring, wherein n is 1 or 2 and wherein R is H, CH_3 or CH_3OCH_3.

In one embodiment, n is 1 and R is CH_3.

In one embodiment, the modified nucleotide is a 5-methylcytosine.

In one embodiment, the single stranded antisense polynucleotide agent comprises a modified internucleoside linkage.

In one embodiment, the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

In one embodiment, the single stranded antisense polynucleotide agent comprises a plurality of 2′-deoxynucleotides flanked on each side by at least one nucleotide having a modified sugar moiety.

In one embodiment, the single stranded antisense polynucleotide agent is a gapmer comprising a gap segment comprised of linked 2′-deoxynucleotides positioned between a 5′ and a 3′ wing segment.

In one embodiment, the modified sugar moiety is selected from the group consisting of a 2′-O-methoxyethyl modified sugar moiety, a 2′-methoxy modified sugar moiety, a 2′-O-alkyl modified sugar moiety, and a bicyclic sugar moiety.

In one embodiment, the nucleic acid inhibitor is present in a pharmaceutical formulation.

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

In one embodiment, the nucleic acid inhibitor is administered to the subject at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

In one embodiment, the nucleic acid inihibitor is administered to the subject subcutaneously.

The present invention also provides methods for treating a subject having chronic kidney disease (CKD). The methods include administering to the subject a weight-based dose of a dsRNA agent, or salt thereof, which inhibits the expression of HAO1 in a doing regimen which includes a loading phase of closely spaced administrations that may be followed by a maintenance phase, in which the the dsRNA agent, or salt thereof, is administred at longer spaced intervals.

Accordingly, in one aspect, the present invention provides a method for inhibiting the expression of hydroxyacid oxidase (HAO1) in a subject having chronic kidney disease (CKD), comprising administering to the subject a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1 in a dosing regimen that includes a loading phase followed by a maintenance phase, wherein the subject has a body weight of less than about 10 kilograms (kg) and the loading phase comprises administering a dose of about 6 milligram per kilogram (mg/kg) of the double stranded RNAi agent, or salt thereof, to the subject about once a month for about three months, and the maintenance phase comprises administering a dose of about 3 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once a month; or wherein the subject has a body weight of between about 10 kg to about less than 20 kg and the loading phase comprises administering a dose of about 6 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once a month for about three months, and the maintenance phase comprises administering a dose of about 6 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once every three months; or wherein the subject has a body weight of greater than about 20 kg and the loading phase comprises administering a dose of about 3 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once a month for about three months, and the maintenance phase comprises administering a dose of about 3 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once every three months, wherein the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double-stranded region, wherein the nucleotide sequence of the sense strand differs by no more than 3 nucleotides from the nucleotide sequence 5’-gsascuuuCfaUfCfCfuggaaauaua-3’ (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 3 nucleotides from the nucleotide sequence 5’-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3’ (SEQ ID NO:36), wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is

a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; uis a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage, thereby inhibiting the expression of HAO1 in the subject.

In another aspect, the present invention provides a method for reducing urinary oxalate levels in a subject having chronic kidney disease, comprising administering to the subject a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1 in a dosing regimen that includes a loading phase followed by a maintenance phase, wherein the subject has a body weight of less than about 10 kilograms (kg) and the loading phase comprises administering a dose of about 6 milligram per kilogram (mg/kg) of the double stranded RNAi agent, or salt thereof, to the subject about once a month for about three months, and the maintenance phase comprises administering a dose of about 3 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once a month; or wherein the subject has a body weight of between about 10 kg to about less than 20 kg and the loading phase comprises administering a dose of about 6 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once a month for about three months, and the maintenance phase comprises administering a dose of about 6 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once every three months; or wherein the subject has a body weight of greater than about 20 kg and the loading phase comprises administering a dose of about 3 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once a month for about three months, and the maintenance phase comprises administering a dose of about 3 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once every three months, wherein the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double-stranded region, wherein the nucleotide sequence of the sense strand differs by no more than 3 nucleotides from the nucleotide sequence 5’-gsascuuuCfaUfCfCfuggaaauaua-3’ (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 3 nucleotides from the nucleotide sequence 5’-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3’ (SEQ ID NO:36), wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; uis a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage, thereby reducing urinary oxalate levels in the subject.

In one aspect, the present invention provides a method for treating a subject having chronic kidney disease, comprising administering to the subject a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1 in a dosing regimen that includes a

loading phase followed by a maintenance phase, wherein the subject has a body weight of less than about 10 kilograms (kg) and the loading phase comprises administering a dose of about 6 milligram per kilogram (mg/kg) of the double stranded RNAi agent, or salt thereof, to the subject about once a month for about three months, and the maintenance phase comprises administering a dose of about 3 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once a month; or wherein the subject has a body weight of between about 10 kg to about less than 20 kg and the loading phase comprises administering a dose of about 6 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once a month for about three months, and the maintenance phase comprises administering a dose of about 6 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once every three months; or wherein the subject has a body weight of greater than about 20 kg and the loading phase comprises administering a dose of about 3 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once a month for about three months, and the maintenance phase comprises administering a dose of about 3 mg/kg of the double stranded RNAi agent, or salt thereof, to the subject about once every three months, wherein the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double-stranded region, wherein the nucleotide sequence of the sense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36), wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; uis a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage, thereby treating the subject.

In one embodiment, the subject is a human.

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

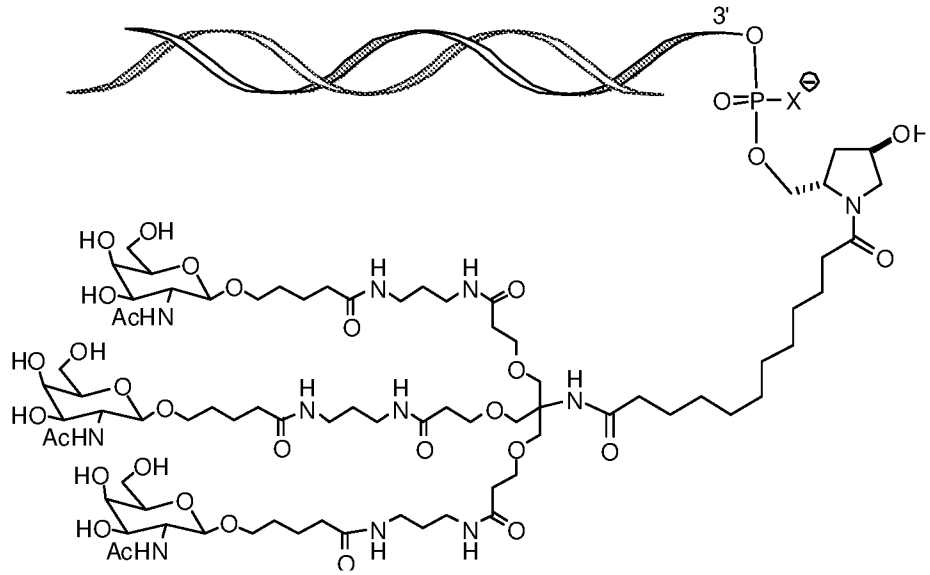
In one embodiment, the subcutaneous administration is subcutaneous injection.

In one embodiment, the nucleotide sequence of the sense strand differs by no more than 2 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 2 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

In one embodiment, the nucleotide sequence of the sense strand differs by no more than 1 nucleotide from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 1 nucleotide from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

In one embodiment, the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

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



and, wherein X is O or S.

In one embodiment, the X is O.

In one embodiment, the dsRNA agent is in salt form.

In one embodiment, the dsRNA agent, or salt thereof, is administered to the subject in a pharmaceutical formulation.

In one embodiment,the nmethods further comprise administering an additional therapeutic to the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic of the endogenous pathways for oxalate synthesis.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based, at least in part, on the discovery that agents that reduce oxalate levels, such as a nucleic acid inhibitor of lactate dehydrogenase A (LDHA), a nucleic acid inhibitor of hydroxyacid oxidase (HAO1) and/or a nucleic acid inhibitor of proline dehydrogenase 2 (PRODH2), can be used to treat subjects having or at risk of developing a non-primary hyperoxaluria disease or disorder, such as a subject having normal urinary oxlate levels, *e.g.*, normal urinary calcium oxlatae levels, or elevated urinary oxalate levels, *e.g.*, elevated urinary calcium oxalate levels, *e.g.*, supersaturated urinary calcium oxlalate levels, *e.g.*, a subject having a kidney stone disease, *e.g.*, calcium oxalate kidney stone disease, such as recurrent calcium oxalate kidney stone disease.

Accordingly, the present invention provides methods for inhibiting the expression of hydroxyacid oxidase (HAO1) in a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate, methods for reducing urinary oxalate levels in a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate, and methods for treating a subject having having or at risk of developing a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate, and compositions comprising nucleic acid inhibitors, *e.g.,* double stranded ribonucleic acid (dsRNA) agents or single stranded antisense polynucleotide agents targeting lactate dehydrogenase A (LDHA), hydroxyacid oxidase (HAO1) and/or proline dehydrogenase 2 (PRODH2).

The following detailed description discloses how to make and use compositions containing iRNAs to inhibit the expression of an HAO1gene, an LDHA gene, a PRODH2 gene, and/or both an LDHA gene and an HAO1 gene, as well as compositions and methods for treating subjects having diseases and disorders that would benefit from inhibition and/or reduction of the expression of these genes.

I. Definitions

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

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

The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to". The term "or" is used herein to mean, and is used interchangeably with, the term "and/or," unless context clearly indicates otherwise.

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 ±10%. In certain embodiments, about means ±5%. When about is present before a series of numbers or a range, it is understood that “about” can modify each of the numbers in the series or range.

The term “at least”, “no less than” or “or more” prior to a number or series of numbers is understood to include the number adjacent to the term “at least”, and all subsequent numbers or integers that could logically be included, as clear from context. For example, the number of nucleotides in a nucleic acid molecule must be an integer. For example, “at least 18 nucleotides of a 21 nucleotide nucleic acid molecule” means that 18, 19, 20, or 21 nucleotides have the indicated

property. When at least is present before a series of numbers or a range, it is understood that "at least" can modify each of the numbers in the series or range.

As used herein, "no more than" or "or less" is understood as the value adjacent to the phrase and logical lower values or intergers, 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.

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 chemical structure and a chemical name, the chemical structure takes precedence.

The term "hyperoxaluria", as used herein, refers to a condition characterized by increased urinary excretion of oxalate. Generally, hyperoxaluria can be divided into two categories: primary and secondary hyperoxaluria.

Primary hyperoxaluria, as used herein, refers to autosomal recessive disorders of glyoxylate metabolism. Primary hyperoxaluria is the result of inherited enzyme deficiencies leading to increased endogenous oxalate synthesis. Primary hyperoxaluria can be divided into primary hyperoxaluria Type 1 (PH1); primary hyperoxaluria Type 2 (PH2); primary hyperoxaluria Type 3 (PH3); or primary hyperoxaluria Non-Type 1, Non-Type 2, Non-Type 3 (PH-Non-Type 1, Non-Type 2, Non-Type 3). PH1 is a hereditary disorder caused by mutations in alanine glyoxylate aminotransferase (AGT). PH2 is due to mutations in glyoxylate reductase/hydroxypyruvate reductase (GRHPR). PH3 is caused by mutations in HOGA1 (formerly DHDPSL). Subjects having PH-Non-Type 1, Non-Type 2, Non-Type 3 have clinical characteristics indistinguishable from type 1, 2, and 3, but with normal AGT, GRHPR, and HOGA1 liver enzyme activity, yet the etiology of the marked hyperoxaluria in such subjects remains to be elucidated.

A deficiency in either AGT or GRHPR activities results in an excess of glyoxylate and oxalate (see, *e.g.*, Knight *et al.*, (2011) Am J Physiol Renal Physiol 302(6): F688-F693). Therefore, inhibition of glycolate oxidase (HAO1) and proline dehydrogenase 2 (PRODH2) will reduce the level of glyoxylate. In addition, inhibition of LDHA expression and/or activity will decrease the level of excess oxalate. The buildup of oxalate in subjects having PH causes increased excretion of oxalate, which in turn results in renal and bladder stones. Stones cause urinary obstruction (often with severe and acute pain), secondary infection of urine and eventually kidney damage. Oxalate stones tend to be severe, resulting in relatively early kidney damage (*e.g.*, onset in teenage years to early adulthood), which impairs the excretion of oxalate, leading to a further acceleration in accumulation of oxalate in the body. After the development of renal failure, patients may get deposits of oxalate in the bones, joints and bone marrow. Severe cases may develop hematological problems such as anaemia and thrombocytopaenia. The deposition of oxalate in the body is sometimes called "oxalosis" to be distinguished from "oxaluria" which refers to oxalate in the urine. Renal failure is a serious

complication requiring treatment in its own right. Dialysis can control renal failure but tends to be inadequate to dispose of excess oxalate. Renal transplant is more effective and this is the primary treatment of severe hyperoxaluria. Liver transplantation (often in addition to renal transplant) may be able to control the disease by correcting the metabolic defect. In a proportion of patients with primary hyperoxaluria type 1, pyridoxine treatment (vitamin B6) may also decrease oxalate excretion and prevent kidney stone formation.

The term "a non-primary hyperoxaluria disease or disorder", as used herein, refers to a disease, disorder or condition thereof, that is associated with oxalate metabolism, and would benefit from reduction in oxalate and/or from a decrease in the gene expression, replication, or protein activity of lactate dehydrogenase A (LDHA), hydroxyacid oxidase (HAO1) and/or proline dehydrogenase 2 (PRODH2).

The term "a non-primary hyperoxaluria disease or disorder," as used herein, does not include primary hyperoxaluria, *e.g.*, primary hyperoxaluria 1 (PH1), primary hyperoxaluria 2 (PH2), or primary hyperoxaluria 3 (PH3).

Subjects having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate include subjects having an elevated level of oxalate, *e.g.,* a mild hyperoxaluria condition, *i.e.,* a urinary calcium oxalate excretion level of about 40 to about 60 mg/day, or a high hyperoxaluria condition, *i.e.,* a urinary calcium oxalate excretion level of greater than about 60 mg/day. In one embodiment, subjects having a high hyperoxaluria condition have a supersaturation level of calcium oxalate, *e.g.,* calcium oxalate (*i.e.,* the concentration in urine is above the solubility of oxalate that drives crystallization and kidney stone formation). In other embodiments, subjects having a high hyperoxaluria condition do not have a supersaturation level of calcium oxalate, *e.g.,* calcium oxalate. In some embodiments, subjects at risk of develoiong a non-primary hyperoxaluria disease or disorder, are subjects having a normal level of urinary oxalate excretion, *i.e.*, a urinary oxalate excretion level of <40mg/day and would still benefit from a reduction in oxalate.

Such subjects include those who suffer from a secondary hyperolxaluria, *e.g.,* enteric hyperoxaluria, dietary hyperoxaluria, or idiopathic hyperoxaluria, a kidney stone disease, chronic kidney disease (CKD), end-stage renal disease (ESRD), coronary artery disease, cutaneous oxalate deposition, or ethylene glycol poisoning. Such subjects also include those who are planning to undergo kidney trasnplanation or have undergone kidney transplantation. In one embodiment, the subject suffers from a kidney stone disease, *e.g.,* a calcium oxalate kidney stone disease, *e.g.,* recurrent calcium oxalate kidney stone disease.

In certain embodiments, the methods of the invention reduce the level of urinary oxalate, *e.g.,* urinary calcium oxalate, by about ≥20% from baseline as assessed in a 24-hour urinary oxalate analysis.

In certain embodiments, the methods of the invention reduce the level of urinary oxalate, *e.g.,* urinary calcium oxalate, supersaturation from baseline as assessed in a 24-hour urinary oxalate analysis.

As used herein, the term "kidney stone disease" refers to a disease in which kidney stones (also called renal stones or urinary stones) form in one or both kidneys of the subject. Kidney stones are small, hard deposits which are made up of minerals or other compounds found in urine. Kidney stones vary in size, shape, and color. To be cleared from the body (or "passed"), the stones need to travel through ducts that carry urine from the kidneys to the bladder (ureters) and be excreted. Depending on their size, kidney stones generally take days to weeks to pass out of the body. There are four main types of kidney stones which are classified by the material they are made of. Up to 75 percent of all kidney stones are composed primarily of calcium. Stones can also be made up of uric acid (a normal waste product), cystine (a protein building block), or struvite (a phosphate mineral). Stones form when there is more of the compound in the urine than can be dissolved. This imbalance can occur when there is an increased amount of the material in the urine, a reduced amount of liquid urine, or a combination of both. People are most likely to develop kidney stones between ages 40 and 60, though the stones can appear at any age. Research shows that 35 to 50 percent of people who have one kidney stone will develop additional stones, usually within 10 years of the first stone.

In one embodiment, the kidney stone disease is a calcium oxalate kidney stone disease. In another embodiment, the kidney stone disease is a non-calcium oxalate kidney stone disease.

In some embodiments, the kidney stone disease (either calcium oxalate kidney stone disease or non-calcium oxalate kidney stone disease) is non-recurrent kidney stone disease. In other embodiments, the kidney stone disease (either calcium oxalate kidney stone disease or non-calcium oxalate kidney stone disease) is recurrent kidney stone disease.

As used herein, the term "non-recurrent kidney stone disease" refers to kidney stone disease newly diagnosed in a subject, *i.e.,* the subject was not previously diagnosed as having had kidney stone disease.

As used herein, the term "recurrent kidney stone disease" refers to kidney stone disease that returns in a subject that previously had kidney stone disease and was successfully treated for the disease (*e.g.,* surgically treated to remove the kidney stone) or passed a kidney stone. Recurrent kidney stone disease may return at any time interval following treatment of the subject for kidney stone disease. In one embodiment, recurrent kidney stone disease is ≥2 stone events within a 5 year period.

"Chronic kidney disease" ("CKD") or "chronic renal failure" ("CRF"), as defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation and the international guideline group Kidney Disease Improving Global Outcomes (KDIGO), is either kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m2 for at least 3 months.

The different stages of CKD form a continuum. The stages of CKD are classified as: Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m^2); Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m^2); Stage 3a: Moderate reduction in GFR (45-59 mL/min/1.73 m^2); Stage

3b: Moderate reduction in GFR (30-44 mL/min/1.73 m^2); Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m^2); Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m^2 or dialysis).

By itself, measurement of GFR may not be sufficient for identifying stage 1 and stage 2 CKD, because in those patients the GFR may in fact be normal or borderline normal. In such cases, the presence of one or more of the following markers of kidney damage can establish the diagnosis: Albuminuria (albumin excretion > 30 mg/24 hr or albumin:creatinine ratio > 30 mg/g [> 3 mg/mmol]); Urine sediment abnormalities; Electrolyte and other abnormalities due to tubular disorders; Histologic abnormalities; Structural abnormalities detected by imaging; History of kidney transplantation in such cases

"End-stage renal disease" is the last stage of chronic kidney disease. Patients with end-stage renal disease will need dialysis or a kidney transplant in order to survive. In most cases, kidney failure is caused by other health problems, *e.g.,* diabetes, or high blood pressure, that have done permanent damage to the kidneys over time.

"Secondary hyperoxaluria" results from over absorption of oxalate from the diet and is further characterized either as enteric, resulting from a chronic and unremediable underlying GI disorder associated with malabsorption, such as bariatric surgery complications or Crohn's disease, which predisposes patients to excess oxalate absorption, or idiopathic, meaning the underlying cause is unknown. Enteric hyperoxaluria is the more severe type of secondary hyperoxaluria. Secondary hyperoxaluria may also result from conditions underlying increased intestinal oxalate absorption, such as alterations in intestinal oxalate-degrading microorganisms, and genetic variations of intestinal oxalate transporters. Furthermore, hyperoxaluria may also occur following renal transplantation because of rapid clearance of accumulated oxalate.

In some embodiments, a non-primary hyperoxaluria disease or disorder is enteric hyperoxaluria. Enteric hyperoxaluria is the formation of calcium oxalate calculi in the urinary tract due to excessive absorption of oxalate from the colon, occurring as a result of intestinal bacterial overgrowth syndromes, fat malabsorption, chronic biliary or pancreatic disease, various intestinal surgical procedures, gastric bypass surgery, inflammatory bowel disease, or any medical condition that causes chronic diarrhea, *e.g.*, Crohn's disease or ulcerative colitis).

In some embodiments, a non-primary hyperoxaluria disease or disorder is dietary hyperoxaluria, *e.g.*, hyperoxaluria as a result of too much oxalate in the diet, *e.g.*, from too much spinach, rhubarb, almonds, bulgur, millet, corn grits, soy flour, cornmeal, navy beans, etc.

In some embodiments, a non-primary hyperoxaluria disease or disorder is idiopathic hyperoxaluria. Subjects having idiopathic hyperoxaluria have above normal levels of urinary oxalate of unknown cause, but still develop stones.

In some embodiments, a non-primary hyperoxaluria disease or disorder is a calcium oxalate tissue deposition disease. For example, when glomerular filtration rate (GFR) drops below about 30-40 mL/min per 1.73 m^2, renal capacity to excrete calcium oxalate is significantly impaired. At this stage, calcium oxalate starts to deposit in extrarenal tissues. Calcium oxalate deposits may occur in

the thyroid, breasts, kidneys, bones, bone marrow, myocardium, or cardiac conduction system. This leads to cardiomyopathy, heart block and other cardiac conduction defects, vascular diseases, retinopathy, synovitis, oxalate osteopathy and anemia that is noted to be resistant to treatment. The deposition of calcium oxalate mat be systemic or tissue specific.

Subjects having arthritis, sarcoidosis, end-stage renal disease are at risk of developing systemic calcium oxalate tissue deposition disease. Subjects at risk of developing tissue specific depositions in the kidney, for example, include subjects having medullary sponge kidney, nephrocalcinosis, renal tubular acidosis (RTA), and transplant recipients, *e.g.*, kidney transplant receipients. In some embodiments, subjects at risk of developing tissue specific depositions include subjects having coronary artery disease or other vascular diseases, especially in patients with end-stage renal disease, HIV and other conditions where oxalate deposition occurs in plaques or in the vasculature.

In some embodiments, a non-primary hyperoxaluria disease or disorder is cutaneous oxalate deposition. Oxalate deposition in the skin can contribute to livedo reticularis, ulceration, and distal ischemia. In contrast to patients with primary hyperoxalria, wherein oxalosis rarely occurs in the skin, patients with systemic oxalosis of chronic renal failure are more likely to present with extravascular calcified deposits of the skin, including dermal and subcutaneous nodules, tender subungual nodules, and skin-colored to yellow macules and papules usually in an acral distribution or on the face. In some embodiments, the non-primary hyperoxaluria disease or disorder is cutaneous oxalate deposition in the setting of dialysis.

In some embodiments, a non-primary hyperoxaluria disease or disorder is ethylene glycol poisoning. Ethylene glycol is an important cause of metabolic acidosis and subsequent acute renal failure, and the toxicity results from the depressant effects of ethylene glycol on the central nervous system. Specifically, metabolic acidosis and renal failure are caused by the conversion of ethylene glycol to noxious metabolites. Oxidative reactions convert ethylene glycol to glycoaldehyde, and then to glycolic acid, which is the major cause of metabolic acidosis. Both of these steps promote the production of lactate from pyruvate. The conversion of glycolic acid to glyoxylic acid proceeds slowly, further increasing the serum concentration of glycolic acid. Glyoxylic acid is eventually converted to oxalic acid and glycine. Oxalic acid does not contribute to the metabolic acidosis, but it is deposited as calcium oxalate crystals in many tissues.

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 camel, a llama, a horse, a goat, a rabbit, a sheep, a hamster, a guinea pig, a cat, a dog, a rat, a mouse, a horse, and a whale), or a bird (*e.g.*, a duck or a goose). In one embodiment, a subject is a human subject

As used herein, the terms "treating" or "treatment" refer to a beneficial or desired result, such as inhibiting oxalate accumulation and/or lowering urinary excretion levels of oxalate in a subject. The terms "treating" or "treatment" also include, but are not limited to, alleviation or amelioration of

one or more symptoms of a non-primary hyperoxaluria disease or disorder, such as, *e.g.*, slowing the course of the disease; reducing the severity of later-developing disease; and/or preventing further oxalate tissue deposition. "Treatment" can also mean prolonging survival as compared to expected survival in the absence of treatment.

The term "lower" in the context of a disease marker or symptom refers to a statistically significant decrease in such level. The decrease can be, for example, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or more and is a decrease to a level accepted as within the range of normal for an individual without such disorder.

As used herein, "prevention" or "preventing," when used in reference to a disease refers to a reduction in the likelihood that a subject will develop a symptom associated with such disease, disorder, or condition, *e.g.,* oxalate accumulation or stone formation. The likelihood of, *e.g.,* oxalate accumulation or stone formation, is reduced, for example, when an individual having one or more risk factors for stone formation either fails to develop stones or develops stones with less severity relative to a population having the same risk factors and not receiving treatment as described herein. The failure to develop a disease, or the reduction in the development of a symptom associated with such a disease, disorder or condition (*e.g.*, by at least about 10% on a clinically accepted scale for that disease or disorder), or the exhibition of delayed symptoms delayed (*e.g.*, by days, weeks, months or years) is considered effective prevention.

"Therapeutically effective amount," as used herein, is intended to include the amount of an inhibitor that, when administered to a subject having a non-primary hyperoxaluria disease, 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 inhibitor, how the inhibitor 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 inhibitor that, when administered to a subject having a non-primary hyperoxaluria disease, is sufficient to prevent or ameliorate the disease or one or more symptoms of the disease. 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 inhibitor, how the inhibitor 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 "prophylacticaly effective amount" also includes an amount of an inhibitor that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. Inhibitors 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.

In the methods of the invention which include administering to a subject a pharmaceutical composition comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, the therapeutically effective amount of the first dsRNA agent may be the same or different than the therapeutically effective amount of the second dsRNA agent. Similarly, in the methods of the invention which include administering to a subject a pharmaceutical composition comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, the prophylacticly effective amountof the first dsRNA agent may be the same or different than the prophylacticaly effective amount of the second dsRNA agent.

In addition, in the methods of the invention which include administering to a subject a pharmaceutical composition comprising a first single stranded antisense polynucleotide agent targeting LDHA and a second single stranded antisense polynucleotide agent targeting HAO1, the therapeutically effective amount of the first single stranded antisense polynucleotide agent may be the same or different than the therapeutically effective amount of the second single stranded antisense polynucleotide agent. Similarly, in the methods of the invention which include administering to a subject a pharmaceutical composition comprising a first single stranded antisense polynucleotide agent targeting LDHA and a second single stranded antisense polynucleotide agent targeting HAO1, the prophylacticly effective amountof the first single stranded antisense polynucleotide agent may be the same or different than the prophylacticaly effective amount of the second single stranded antisense polynucleotide agent.

As used herein, the term a "nucleic acid inhibitor" includes iRNA agents and antisense polynucleotide agents.

The terms "iRNA", "RNAi agent," "iRNA agent," "RNA interference agent" as used interchangeably herein, refer to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript *via* an RNA-induced silencing complex (RISC) pathway. RNA interference (RNAi) is a process that directs the sequence-specific degradation of mRNA. RNAi modulates, *e.g.,* inhibits, the expression of LDHA, PRODH2 and/or HAO1 in a cell, *e.g.,* a cell within a subject, such as a subject suffering from a non-primary hyperoxaluria disease or disorder.

In one embodiment, an RNAi agent of the disclosure includes a single stranded RNAi that interacts with a target RNA sequence, *e.g.,* an LDHA, PRODH2, and/or HAO1 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 double-stranded short interfering RNAs (siRNAs) comprising a sense strand and an antisense strand by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) *Genes Dev.* 15:485). Dicer, a ribonuclease-III-like enzyme, processes these dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409:363). These 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 disclosure relates to a single stranded RNA (ssRNA) (the antisense strand of a siRNA duplex) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.,* an LDHA, PRODH2 and/or HAO1 gene. Accordingly, the term "siRNA" is also used herein to refer to an RNAi as described above.

In another embodiment, the RNAi agent may be a single-stranded RNA 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 RNAs 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 another embodiment, a "RNAi agent" for use in the compositions and methods of the disclosure is a double stranded RNA and is referred to herein as a "double stranded RNAi 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 LDHA, PRODH2 and/or HAO1 gene. In some embodiments of the disclosure, 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 yet another embodiment, an "iRNA" for use in the compositions and methods of the invention is a "dual targeting RNAi agent." The term "dual targeting RNAi agent" refers to a molecule comprising a first dsRNA agent comprising 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 first target RNA, *i.e.,* an LDHA gene, covalently attached to a molecule comprising a second dsRNA agent comprising 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 second target RNA, *i.e.,* an HAO1 gene. In some embodiments of the invention, a dual targeting RNAi agent triggers the degradation of the first and the second target RNAs, *e.g.*, mRNAs, through a post-transcriptional gene-silencing mechanism referred to herein as RNA interference or RNAi.

The terms "polynucleotide agent," "antisense polynucleotide agent" "antisense compound", and "agent" as used interchangeably herein, refer to an agent comprising a single-stranded oligonucleotide that contains RNA as that term is defined herein, and which targets nucleic acid molecules encoding LDHA, PRODH2 and/or HAO1 (*e.g.,* mRNA encoding LDHA, PRODH2 and/or HAO1). The antisense polynucleotide agents specifically bind to the target nucleic acid molecules *via* hydrogen bonding (*e.g.*, Watson-Crick, Hoogsteen, or reversed Hoogsteen hydrogen bonding) and interfere with the normal function of the targeted nucleic acid (*e.g.*, by an antisense mechanism of action). This interference with or modulation of the function of a target nucleic acid by the polynucleotide agents of the present invention is referred to as "antisense inhibition." The functions of the target nucleic acid molecule to be interfered with may include functions such as, for example, translocation of the RNA to the site of protein translation, translation of protein from the RNA, splicing of the RNA to yield one or more mRNA species, and catalytic activity which may be engaged in or facilitated by the RNA.

As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of an LDHA gene, a PRODH2 gene, or an HAO1 gene, including mRNA that is a product of RNA processing of a primary transcription product.

In one embodment, the target portion of the sequence will be at least long enough to serve as a substrate for iRNA-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during the transcription of an LDHA gene. In another embodment, the target portion of the sequence will be at least long enough to serve as a substrate for iRNA-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a PRODH2 gene. In another embodment, the target portion of the sequence will be at least long enough to serve as a substrate for iRNA-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during the transcription of an HAO1 gene.

The target sequence of an LDHA gene, a PRODH2 gene or an HAO1 gene may be from about 19-36 nucleotides in length, *e.g.*, about 19-30 nucleotides in length. For example, the target sequence can be about 19-30 nucleotides, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length. In certain embodiments, the target sequence is 19-23 nucleotides in length, optionally 21-23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

In aspects in which a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1 are covalently attached (*i.e.,* a dual targeting RNAi agent), the length of the LDHA target sequence may be the same as the HAO1 target sequence or different.

A target sequence may be from about 4-50 nucleotides in length, *e.g.*, 8-45, 10-45, 10-40, 10-35, 10-30, 10-20, 11-45, 11-40, 11-35, 11-30, 11-20, 12-45, 12-40, 12-35, 12-30, 12-25, 12-20, 13-45, 13-40, 13-35, 13-30, 13-25, 13-20, 14-45, 14-40, 14-35, 14-30, 14-25, 14-20, 15-45, 15-40, 15-35, 15-

30, 15-25, 15-20, 16-45, 16-40, 16-35, 16-30, 16-25, 16-20, 17-45, 17-40, 17-35, 17-30, 17-25, 17-20, 18-45, 18-40, 18-35, 18-30, 18-25, 18-20, 19-45, 19-40, 19-35, 19-30, 19-25, 19-20, *e.g.,* 4, 5, 6, 7, 8, 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, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 contiguous nucleotides of the nucleotide sequence of an mRNA molecule formed during the transcription of an LDHA gene and/or an HAO1 gene. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

The terms "complementary," "fully complementary" and "substantially complementary" are used herein with respect to the base matching between a nucleic acid inhibitor and a target sequence. The term"complementarity" refers to the capacity for pairing between nucleobases of a first nucleic acid and a second nucleic acid.

As used herein, a nucleic acid inhibitor that is "substantially complementary to at least part of" a messenger RNA (mRNA) refers to a nucleic acid inhibitor that is substantially complementary to a contiguous portion of the mRNA of interest (*e.g.*, an mRNA encoding LDHA, an mRNA encoding PRODH2, and/or an mRNA encoding HAO1). For example, a polynucleotide is complementary to at least a part of an HAO1 mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding HAO1.

As used herein, the term "region of complementarity" refers to the region of the nucleic acid inhibito that is substantially complementary to a sequence, for example a target sequence, *e.g.,* an LDHA nucleotide sequence, a PRODH2 nucleotide sequence and/or an HAO1 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, 3, or 2 nucleotides of the 5'- and/or 3'-terminus of the polynucleotide.

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

Complementary sequences include those nucleotide sequences of a nucleic acid inhibitor of the invention that base-pair to 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 target gene expression.

"Complementary" sequences, as used herein, can also include, or be formed entirely from, non-Watson-Crick base pairs and/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. As used herein, the term "strand comprising a sequence" refers to an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature.

"G," "C," "A," "T" and "U" each generally stand for a nucleotide that contains guanine, cytosine, adenine, thymidine and uracil as a base, respectively. However, it will be understood that the terms "deoxyribonucleotide", "ribonucleotide" and "nucleotide" can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety (see, *e.g.*, Table 1). The skilled person is well aware that guanine, cytosine, adenine, and uracil can be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base can base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine can be replaced in the nucleotide sequences of the agents 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.

A "nucleoside" is a base-sugar combination. The "nucleobase" (also known as "base") portion of the nucleoside is normally a heterocyclic base moiety. "Nucleotides" are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to the 2′, 3′ or 5′ hydroxyl moiety of the sugar. "Polynucleotides," also referred to as "oligonucleotides," are formed through the covalent linkage of adjacent nucleosides to one another, to form a linear polymeric oligonucleotide. Within the polynucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside linkages of the polynucleotide.

In general, the majority of nucleotides of the nucleic acid inhibitors are ribonucleotides, but as described in detail herein, the inhibitors may also include one or more non-ribonucleotides, *e.g.*, a deoxyribonucleotide. In addition, as used in this specification, a "nucleic acid inhibitor" may include nucleotides (*e.g.*, ribonucleotides or deoxyribonucleotides) with chemical modifications; a nucleic acid inhibitor 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, and/or modified nucleobase. 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 nucleic acid inhibitors of the invention include all types of modifications disclosed herein or known in the art. Any such modifications, as used in nucleotides, are encompassed by "nucleic acid inhibitor" for the purposes of this specification and claims.

The term "LDHA" (used interchangeable herein with the term "Ldha"), also known as Cell Proliferation-Inducing Gene 19 Protein, Renal Carcinoma Antigen NY-REN-59, LDH Muscle Subunit, EC 1.1.1.27 4 61, LDH-A, LDH-M,Epididymis Secretory Sperm Binding Protein Li 133P, L-Lactate Dehydrogenase A Chain, Proliferation-Inducing Gene 19, Lactate Dehydrogenase M, HEL-S-133P, EC 1.1.1, GSD11, PIG19, and LDHM, refers to the well known gene encoding a lactate dehydrogenase A from any vertebrate or mammalian source, including, but not limited to, human, bovine, chicken, rodent, mouse, rat, porcine, ovine, primate, monkey, and guinea pig, unless specified otherwise.

The term also refers to fragments and variants of native LDHA that maintain at least one *in vivo* or *in vitro* activity of a native LDHA. The term encompasses full-length unprocessed precursor forms of LDHA as well as mature forms resulting from post-translational cleavage of the signal peptide and forms resulting from proteolytic processing.

The sequence of a human LDHA mRNA transcript can be found at, for example, GenBank Accession No. GI: 207028493 (NM_001135239.1; SEQ ID NO:1), GenBank Accession No. GI: 260099722 (NM_001165414.1; SEQ ID NO:3), GenBank Accession No. GI: 260099724 (NM_001165415.1; SEQ ID NO:5), GenBank Accession No. GI: 260099726 (NM_001165416.1; SEQ ID NO:7), GenBank Accession No. GI: 207028465 (NM_005566.3; SEQ ID NO:9); the sequence of a mouse LDHA mRNA transcript can be found at, for example, GenBank Accession No. GI: 257743038 (NM_001136069.2; SEQ ID NO:11), GenBank Accession No. GI: 257743036(NM_010699.2; SEQ ID NO:13); the sequence of a rat LDHA mRNA transcript can be found at, for example, GenBank Accession No. GI: 8393705 (NM_017025.1; SEQ ID NO:15); and the sequence of a monkey LDHA mRNA transcript can be found at, for example, GenBank Accession No. GI: 402766306 (NM_001257735.2; SEQ ID NO:17), GenBank Accession No. GI: 545687102 (NM_001283551.1; SEQ ID NO:19).

Additional examples of LDHA mRNA sequences are readily available using publicly available databases, *e.g.*, GenBank, UniProt, and OMIM.

The term"LDHA" as used herein also refers to a particular polypeptide expressed in a cell by naturally occurring DNA sequence variations of the LDHA gene, such as a single nucleotide polymorphism in the LDHA gene. Numerous SNPs within the LDHA gene have been identified and may be found at, for example, NCBI dbSNP (see, *e.g.,* www.ncbi.nlm.nih.gov/snp).

As used herein, the term "HAO1" refers to the well known gene encoding the enzyme hydroxyacid oxidase 1 from any vertebrate or mammalian source, including, but not limited to, human, bovine, chicken, rodent, mouse, rat, porcine, ovine, primate, monkey, and guinea pig, unless specified otherwise. Other gene names include GO, GOX, GOX1, HAO, and HAOX1. The protein is also known as glycolate oxidase and (S)-2-hydroxy-acid oxidase.

The term also refers to fragments and variants of native HAO1 that maintain at least one *in vivo* or *in vitro* activity of a native HAO1. The term encompasses full-length unprocessed precursor forms of HAO1 as well as mature forms resulting from post-translational cleavage of the signal peptide and forms resulting from proteolytic processing. The sequence of a human HAO1 mRNA transcript can be found at, for example, GenBank Accession No. GI:11184232 (NM_017545.2; SEQ ID NO:21); the sequence of a monkey HAO1 mRNA transcript can be found at, for example, GenBank Accession No. GI:544464345 (XM_005568381.1; SEQ I DNO:23); the sequence of a mouse HAO1 mRNA transcript can be found at, for example, GenBank Accession No. GI:133893166 (NM_010403.2; SEQ ID NO:25); and the sequence of a rat HAO1 mRNA transcript can be found at, for example, GenBank Accession No. GI: 166157785 (NM_001107780.2; SEQ ID NO:27).

The term"HAO1," as used herein, also refers to naturally occurring DNA sequence variations of the HAO1 gene, such as a single nucleotide polymorphism (SNP) in the HAO1 gene. Exemplary SNPs may be found in the NCBI dbSNP Short Genetic Variations database available at www.ncbi.nlm.nih.gov/projects/SNP.

As used herein, "proline dehydrogenase 2," used interchangeably with the term "PRODH2," refers to the enzyme which catalyzes the first step in the catabolism of trans-4-hydroxy-L-proline, an amino acid derivative obtained through food intake and collagen turnover. Glyoxylate is one of the downstream products of hydroxyproline catabolism, which in people with disorders of glyoxalate metabolism can lead to an increase in oxalate levels and the formation of calcium-oxalate kidney stones. PRODH2 is also known as proline dehydrogenase, HYPDH, HSPOX1, and hydroxyproline dehydrogenase.

The sequence of a human PRODH2 mRNA transcript can be found at, for example, GenBank Accession No. GI: 1818882103 (NM_021232.2; SEQ ID NO:4641; reverse complement, SEQ ID NO: 4642). The sequence of mouse PRODH2 mRNA can be found at, for example, GenBank Accession No. GI: 142372879 (NM_019546.5; SEQ ID NO:4643; reverse complement, SEQ ID NO: 4644). The sequence of rat PRODH2 mRNA can be found at, for example, GenBank Accession No. GI: 198278487 (NM_001038588.1; SEQ ID NO:4645; reverse complement, SEQ ID NO: 4646). The sequence of Macaca fascicularis PRODH2 mRNA can be found at, for example, GenBank Accession No. GI: 982316449 (XM_005588902.2; SEQ ID NO: 4647; reverse complement, SEQ ID NO: 4648). The sequence of Macaca mulatta PRODH2 mRNA can be found at, for example, GenBank Accession No. GI: 1622893613 (XM_015123711.2; SEQ ID NO: 4649; reverse complement, SEQ ID NO: 4650).

Additional examples of PRODH2 mRNA sequences are readily available through publicly available databases, *e.g.*, GenBank, UniProt, OMIM, and the *Macaca* genome project web site.

Further information on PRODH2 can be found, for example, at www.ncbi.nlm.nih.gov/gene/?term=PRODH2.

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 PRODH2, as used herein, also refers to variations of the PRODH2 gene including variants provided in the SNP database. Numerous seuqnce variations within the PRODH2 gene have been identified and may be found at, for example, NCBI dbSNP and UniProt (see, *e.g.*, www.ncbi.nlm.nih.gov/snp/?term=PRODH2, the entire contents of which is incorporated herein by reference as of the date of filing this application.

II. Methods of the Invention

The present invention provides a method for inhibiting the expression of hydroxyacid oxidase (HAO1) in a subject, *e.g.*, a human subject, having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate. The present invention also provides a method for reducing urinary oxalate levels, *e.g.*, urinary oxalate is urinary calcium oxalate, *e.g.*, urinary calcium oxalate supersaturation in a subject, *e.g.*, a human subject, having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate. In addition, the present invention provides a method for treating a subject, *e.g.*, a human subject, having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate. The methods include administering, *e.g.*, subcutaneously administering, *e.g.*, subcutaneous injection, to the subject a fixed dose of about 200 mg to about 600 mg, *e.g.*, about 284 mg or about 567 mg, of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1, thereby inhibiting the expression of HAO1 in the subject.

In other aspects, the present invention also provides a method for treating a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate. The method includes administering to the subject a therapeutically effective amount of a nucleic acid inhibitor of hydroxyacid oxidase (HAO1) and/or a nucleic acid inhibitor of Proline Dehydrogenase 2 (PRODH2), thereby treating the subject having the non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate.

In addition, the present invention also provides a method of treating a subject at risk of developing a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate. The method includes administering to the subject a therapeutically effective amount of a nucleic acid inhibitor of lactate dehydrogenase A (LDHA), a nucleic acid inhibitor of hydroxyacid oxidase (HAO1), and/or a nucleic acid inhibitor of Proline Dehydrogenase 2 (PRODH2), thereby treating the subject at risk of developing the non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate.

Subjects having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate include subjects having an elevated level of oxalate, *e.g.,* a mild hyperoxaluria condition, *i.e.,* a urinary calcium oxalate excretion level of about 40 to about 60 mg/day, or a high hyperoxaluria condition, *i.e.,* a urinary calcium oxalate excretion level of greater than about 60 mg/day. In one embodiment, subjects having a high hyperoxaluria condition have a supersaturation level of calcium oxalate, *e.g.,* calcium oxalate (*i.e.,* the concentration in urine is above the solubility of oxalate that drives crystallization and kidney stone formation). In other embodiments, subjects having a high hyperoxaluria condition do not have a supersaturation level of calcium oxalate, *e.g.,* calcium oxalate. In some embodiments, subjects at risk of develoiong a non-primary hyperoxaluria disease or disorder, are subjects having a normal level of urinary oxalate excretion, *i.e.*, a urinary oxalate excretion level of <40mg/day and would still benefit from a reduction in oxalate.

Such subjects include those who suffer from a secondary hyperolxaluria, *e.g.,* enteric hyperoxaluria, dietary hyperoxaluria, or idiopathic hyperoxaluria, a kidney stone disease, chronic kidney disease (CKD), end-stage renal disease (ESRD), coronary artery disease, cutaneous oxalate deposition, or ethylene glycol poisoning. Such subjects also include those who are planning to undergo kidney trasnplanation or have undergone kidney transplantation.

In the methods of the present invention, suubjects having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate do not have primary hyperoxaluria (PH), *i.e.*, PH1, PH2, or PH3.

In some embodiments, the non-primary hyperoxaluria disease or disorder is a kidney stone disease, *e.g.,* calcium oxalate kidney stone disease, *e.g.,* recurrent calcium oxalate kidney stone disease.

Administration of the dsRNA agent, or salt thereof, is to a subject may be repeated on a regular basis, for example, at an interval of once every three months, or once every six monthes.

In one embodiment, the dsRNA agent, or salt thereof, is administered to the subject at an interval of once every six months.

In other embodiment, the dsRNA agent, or salt thereof, is administered to the subject initially, at three months, and every six months thereafter.

Administration of the dsRNA, or salt thereof, to the subject may, *e.g.,* reduce urinary oxalate levels, *e.g.,* urinary calcium oxalate, urinary calcium oxalate supersaturation, *e.g.,* by about ≥20% from baseline as assessed in a 24-hour urinary oxalate analysis, and/or reduce clinical and radiographic kidney stone events.

When the subject to be treated is a mammal such as a human, the nucleic acid inhibitor can be administered by any means known in the art including, but not limited to oral, intraperitoneal, or parenteral routes, including intracranial (*e.g.*, intraventricular, intraparenchymal and intrathecal), intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), nasal, rectal, 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 some embodiments, the administration is *via* a depot injection. A depot injection may release the nucleic acid inhibitor in a consistent way over a prolonged time period. Thus, a depot injection may reduce the frequency of dosing needed to obtain a desired effect, *e.g.*, a desired inhibition of LDHA or HAO1 or PRODH2, or a desired inhibition of both LDHA and HAO1, or a therapeutic or prophylactic effect. A depot injection may also provide more consistent serum concentrations. Depot injections may include subcutaneous injections or intramuscular injections. In certain embodiments, the depot injection is a subcutaneous injection.

In some embodiments, the administration is *via* a pump. The pump may be an external pump or a surgically implanted pump. In certain embodiments, the pump is a subcutaneously implanted osmotic pump. In other embodiments, the pump is an infusion pump. An infusion pump may be used for intravenous, subcutaneous, arterial, or epidural infusions. In certain embodiments, the infusion pump is a subcutaneous infusion pump. In other embodiments, the pump is a surgically implanted pump that delivers the nucleic acid inhibitor to the liver.

A nucleic acid inhibitor of the invention, *e.g.,* the dsRNA agent, or salt thereof, may be present in a pharmaceutical composition, such as in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolarity of the buffer solution containing the iRNA can be adjusted such that it is suitable for administering to a subject.

Alternatively, a nucleic acid inhibitor of the invention may be administered as a pharmaceutical composition, such as a dsRNA liposomal formulation.

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.

The methods (and uses) of the invention include administering to the subject, *e.g.,* a human, a therapeutically effective amount of a nucleic acid inhibitor, *e.g..,* a dsRNA agent, a dual targeting iRNA agent, a single stranded antisense polynucleotide agent, or a pharmaceutical composition comprising a nucleic acid inhibitor, *e.g..,* a dsRNA, a pharmaceutical composition comprising a dual targeting RNAi agent, a pharmaceutical composition of the invention comprising a first dsRNA agent that inhibits expression of LDHA and a second dsRNA agent that inhibits expression of HAO1, or a pharmaceutical composition of the invention comprising a single stranded antisense polynucleotide agent.

Subjects that would benefit from the methods of the invention include subjects having or at risk of developing a non-primary hyperoxaluria disease.

In the methods (and uses) of the invention which comprise administering to a subject a first nucleic acid inhibitor, such as a dsRNA agent targeting LDHA and a second dsRNA agent targeting

HAO1, the first and second nucleic acid inhibitor may be formulated in the same composition or different compositions and may administered to the subject in the same composition or in separate compositions.

The nucleic acid inhibitor may be administered to the subject at a dose of about 0.1 mg/kg to about 50 mg/kg. Typically, a suitable dose 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.

In the methods (and uses) of the invention which comprise administering to a subject a first nucleic acid inhibitor, *e.g.,* dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, the first and second nucleic acid inhibitor may be administered to a subject at the same dose or different doses.

The nucleic acid inhibitor can be administered by intravenous infusion over a period of time, on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis.

Administration of a nucleic acid inhibitor can reduce LDHA levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least about 5%, 6, 7, 8, 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, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 39, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or at least about 99% or more. In one embodiment, administration of the nucleic acid inhibitor can reduce LDHA levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least 20%.

Administration of a nucleic acid inhibitor can reduce HAO1 levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least about 5%, 6, 7, 8, 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, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 39, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or at least about 99% or more. In one embodiment, administration of the nucleic acid inhibitor can reduce HAO1 levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least 20%.

Administration of a nucleic acid inhibitor can reduce PRODH2 levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least about 5%, 6, 7, 8, 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, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 39, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or at least about 99% or more. In one embodiment, administration of the nucleic acid inhibitor can reduce PRODH2 levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least 20%.

In the methods (and uses) of the invention which comprise administering to a subject a first nucleic acid inhibitor, *e.g.,* a dsRNA agent targeting LDHA and a second nucleic acid inhibitor, *e.g.,* a dsRNA agent targeting HAO1, the level of inhibition of LDHA may be the same or different that the level of inhibition of HAO1.

In the methods (and uses) of the invention which comprise administering to a subject a dual targeting RNAi agent, the dual targeting RNAi agent may inhibit expression of the LDHA gene and the HAO1 gene to a level substantially the same as the level of inhibition of expression obtained by the contacting of a cell with both dsRNA agents individually, or the dual targeting RNAi agent may inhibit expression of the LDHA gene and the HAO1 gene to a level higher than the level of inhibition of expression obtained by the contacting of a cell with both dsRNA agents individually.

Before administration of a full dose of the nucleic acid inhibitor, patients can be administered a smaller dose, such as a 5% infusion reaction, and monitored for adverse effects, such as an allergic reaction. In another example, the patient can be monitored for unwanted immunostimulatory effects, such as increased cytokine (*e.g.*, TNF-alpha or INF-alpha) levels.

Alternatively, the nucleic acid inhibitor can be administered subcutaneously, *i.e.*, by subcutaneous injection. One or more injections may be used to deliver the desired dose of nucleic acid inhibitor to a subject. The injections may be repeated over a period of time. The administration may be repeated on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. A repeat-dose regimine may include administration of a therapeutic amount of nucleic acid inhibitor on a regular basis, such as every other day, on a monthly basis, or once a year. In certain embodiments, thenucleic acid inhibitor is administered about once per month to about once per quarter (*i.e.*, about once every three months).

In one embodiment, the method includes administering a composition featured herein such that expression of the target LDHA gene, the target PRODH2 gene and/or the target HAO1 gene is decreased, such as for about 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 18, 24 hours, 28, 32, or abour 36 hours. In one embodiment, expression of the target LDHA gene, the target PRODH2 gene and/or the HAO1 gene is decreased for an extended duration, *e.g.*, at least about two, three, four days or more, *e.g.*, about one week, two weeks, three weeks, or four weeks or longer.

In some embodiments, the nucleic acid inhibitors useful for the methods and compositions featured herein specifically target RNAs (primary or processed) of the target LDHA, PRODH2 and/or HAO1 genes. Compositions and methods for inhibiting the expression of these genes using iRNAs can be prepared and performed as described herein.

Administration of the nucleic acid inhibitors according to the methods of the invention may result in a reduction of the severity, signs, symptoms, and/or markers of such diseases or disorders in a patient with a kidney stone disease. By "reduction" in this context is meant a statistically significant decrease in such level. The reduction can be, for example, at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or about 100%.

Efficacy of treatment or prevention of kidney stone disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. Comparisons of the later readings with the initial readings provide a physician an indication of whether the treatment is effective. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of a nucleic acid inhibitor or pharmaceutical composition thereof, "effective against" indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as a improvement of symptoms, a cure, a reduction in disease, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating a kidney stone disease and the related causes.

A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of disease, and such as, at least 20%, 30%, 40%, 50% or more can be indicative of effective treatment. Efficacy for a given nucleic acid inhibitor or formulation of that nucleic acid inhibitor can also be judged using an experimental animal model for the given disease as known in the art, such as alanine-glyoxylate amino trasferase deficient (Agxt knockout) mice (see, *e.g.,* Salido, *et al.* (2006) *Proc Natl Acad Sci USA* 103:18249) and/or glyoxylate reductase/hydroxypyruvate reductase deficient (Grhpr knockout) mice (see, *e.g.,* Knight, *et al.* (2011) *Am J Physiol Renal Physiol* 302:F688).

The invention further provides methods for the use of a nucleic acid inhibitor or a pharmaceutical composition of the invention, *e.g.*, for treating a subject having or at risk of developing a non-primary hyperoxaluria disease that would benefit from reduction in oxalate, 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. For example, in certain embodiments, a nucleic acid inhibitor or pharmaceutical composition of the invention is administered in combination with, *e.g.*, pyridoxine, an ACE inhibitor (angiotensin converting enzyme inhibitors), *e.g.*, benazepril (Lotensin); an angiotensin II receptor antagonist (ARB) (*e.g.*, losartan potassium, such as Merck & Co. 's Cozaar®), *e.g.*, Candesartan (Atacand); an HMG-CoA reductase inhibitor (*e.g.*, a statin); dietary oxalate degrading compounds, *e.g.*, Oxalate decarboxylase (Oxazyme); calcium binding agents, *e.g.*, Sodium cellulose phosphate (Calcibind); diuretics, *e.g.*, thiazide diuretics, such as hydrochlorothiazide (Microzide); phosphate binders, *e.g.*, Sevelamer (Renagel); magnesium and Vitamin B6 supplements;

potassium citrate; orthophosphates, bisphosphonates; oral phosphate and citrate solutions; high fluid intake, urinary tract endoscopy; extracorporeal shock wave lithotripsy; kidney dialysis; kidney stone removal (*e.g.,* surgery); and kidney/liver transplant; or a combination of any of the foregoing.

III. Nucleic Acid Inhibitors for Use in the Methods of the Invention

A. Double Stranded Ribonucleic Acid Agents of the Invention

In one embodiment, a nucleic acid inhibitor for use in the methods of the invention is a dsRNA agent. In one embodiment, the dsRNA agent targets an LDHA gene. In one embodiment, the dsRNA agent targets a PRODH2 gene. In another embodiment, the dsRNA agent targets an HAO1 gene. In one embodiment, the dsRNA agent is a dual targeting dsRNA agent targeting an LDHA gene and an HAO1 gene.

Suitable dsRNA agents for use in the methods of the invention are known in the art and described in, for example, U.S. Patent Publication No. 20200113927 (Alnylam Pharmaceuticals, Inc.); U.S. Patent Publication Nos. 2017/0304446 (Lumasiran) (Alnylam Pharmaceuticals, Inc.), 2017/0306332 (Dicerna Pharmaceuticals), and 2019/0323014 (Dicerna Pharmaceuticals); U.S. Patent Nos. 10,478,500 (Lumasiran) (Alnylam Pharmaceuticals, Inc.) and 10,351,854 (Dicerna Pharmaceuticals); and PCT Publication Nos. WO 2019/014530 (Attorney Docket No.: 121301-07520) and WO 2019/075419 (Dicerna Pharmaceuticals), the entire contents of each of which are incorporated herein by reference. Any of these agents may further comprise a ligand. In one embodiment, a suitable dsRNA agent is nedosiran (formerly referred to as DCR-PHXC) (Dicerna Pharmaceuticals).

In certain specific embodiments, a nucleic acid inhibitor of the present invention is a dsRNA agent which inhibits the expression of an LDHA gene and is selected from the group of agents listed in any one of Tables 2-3. In other embodiments, a nucleic acid inhibitor of the present invention is a dsRNA agent which inhibits the expression of an HAO1 gene and is selected from the group of agents listed in any one of Tables 4-12. In other embodiments, a nucleic acid inhibitor of the present invention is a dsRNA agent which inhibits the expression of a PRODH2 gene and is selected from the group of agents listed in any one of Tables 15-16. In yet other embodiments, nucleic acid inhibitor of the present invention is an dual targeting iRNA agent that inhibits the expression of an LDHA gene and an HAO1 gene, wherein the first dsRNA inhibits expression of an LDHA gene and is selected from the group of agents listed in any one of Tables 2-3, and the first dsRNA inhibits expression of an HAO1 gene and is selected from the group of agents listed in any one of Tables 4-12.

The dsRNAs of the invention targeting LDHA may include an RNA strand (the antisense strand) having a region which is about 30 nucleotides or less in length, *e.g.*, 15-30, 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, which region is substantially complementary to at least part of an mRNA transcript of an LDHA gene.

The dsRNAs of the invention targeting HAO1 may include an RNA strand (the antisense strand) having a region which is about 30 nucleotides or less in length, *e.g.*, 15-30, 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, which region is substantially complementary to at least part of an mRNA transcript of an HAO1 gene.

The dsRNAs of the invention targeting PRODH2 may include an RNA strand (the antisense strand) having a region which is about 30 nucleotides or less in length, *e.g.*, 15-30, 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, which region is substantially complementary to at least part of an mRNA transcript of a PRODH2 gene.

When the dsRNA agent is a dual targeting agent, as described herein, the agent targeting LDHA may include an antisense strand comprising a region of complementarity to LDHA which is the same length or a different length from the region of complementarity of the antisense strand of the agent targeting HAO1.

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

In other embodiments, one or both of the strands of the double stranded RNAi agents of the invention is up to 66 nucleotides in length, *e.g.*, 36-66, 26-36, 25-36, 31-60, 22-43, 27-53 nucleotides in length, with a region of at least 19 contiguous nucleotides that is substantially complementary to at least a part of an mRNA transcript of an HAO1 gene. In some embodiments, such dsRNA agents having longer length antisense strands may include a second RNA strand (the sense strand) of 20-60 nucleotides in length wherein the sense and antisense strands form a duplex of 18-30 contiguous nucleotides.

In embodiments in which a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1 are covalently attached, the duplex lengths of the first agent and the second agent may be the same or different.

The use of these dsRNA agents described herein enables the targeted degradation of mRNAs of an LDHA gene, a PRODH2 gene and/or an HAO1 gene in mammals.

The dsRNA 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 LDHA gene or an HAO1 gene or a PRODH2 gene. The region of complementarity is about 30 nucleotides or less in length (*e.g.,* about 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, or 18 nucleotides or less in length). Upon contact with a cell expressing the target gene, the iRNA inhibits the expression of the target gene (*e.g.,* a human, a primate, a non-primate, or a bird target gene) by at least about 10% 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 flowcytometric techniques.

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 LDHA gene or an HAO1 gene or a PRODH2 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 between 15 and 30 base pairs in length, *e.g.,* between, 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. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

Similarly, the region of complementarity to the target sequence is between 15 and 30 nucleotides in length, *e.g.,* between 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. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

In some embodiments, the dsRNA is between about 15 and about 23 nucleotides in length, or between about 25 and 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 can 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 9 to 36 base pairs, *e.g.*, about 10-36, 11-36, 12-36, 13-36, 14-36, 15-36, 9-35, 10-35, 11-35, 12-35, 13-35, 14-35, 15-35, 9-34, 10-34, 11-34, 12-34, 13-34, 14-34, 15-34, 9-33, 10-33, 11-33, 12-33, 13-33, 14-33, 15-33, 9-32, 10-32, 11-32, 12-32, 13-32, 14-32, 15-32, 9-31, 10-31, 11-31, 12-31, 13-32, 14-31, 15-31, 15-30, 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. 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 LDHA or HAO1 or PRODH2 expression or LDHA and HAO1 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, 2, 3, or 4 nucleotides. dsRNAs having at least one nucleotide overhang can have unexpectedly 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 either an antisense or sense strand of a dsRNA.

A dsRNA can be synthesized by standard methods known in the art as further discussed below, *e.g.*, by use of an automated DNA synthesizer, such as are commercially available from, for example, Biosearch, Applied Biosystems, Inc.

A dsRNA 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. Single-stranded oligonucleotides of the invention can be prepared using solution-phase or solid-phase organic synthesis or both.

In one aspect, a dsRNA of the invention targets an LDHA gene and includes at least two nucleotide sequences, a sense sequence and an anti-sense sequence. The sense strand sequence is

selected from the group of sequences provided in any one of Tables 2-3 and the corresponding nucleotide sequence of the antisense strand is selected from the group of sequences of any one of Tables 2-3. 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 LDHA gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand (passenger strand) in any one of Tables 2-3 and the second oligonucleotide is described as the corresponding antisense strand (guide strand) of the sense strand in any one of Tables 2-3. In one embodiment, the substantially complementary sequences of the dsRNA are contained on separate oligonucleotides. In another embodiment, the substantially complementary sequences of the dsRNA are contained on a single oligonucleotide.

In another aspect, a dsRNA of the invention targets an HAO1 gene and includes at least two nucleotide sequences, a sense sequence and an anti-sense sequence. The sense strand sequence is selected from the group of sequences provided in any one of Tables 4-14 and the corresponding nucleotide sequence of the antisense strand of the sense strand is selected from the group of sequences of any one of Tables 4-14. 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 HAO1 gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand (passenger strand) in any one of Tables 4-14 and the second oligonucleotide is described as the corresponding antisense strand (guide strand) of the sense strand in any one of Tables 4-14. In one embodiment, the substantially complementary sequences of the dsRNA are contained on separate oligonucleotides. In another embodiment, the substantially complementary sequences of the dsRNA are contained on a single oligonucleotide.

In yet another aspect, a dsRNA of the invention targets a PRODH2 gene and includes at least two nucleotide sequences, a sense sequence and an anti-sense sequence. The sense strand sequence is selected from the group of sequences provided in any one of Tables 15-16 and the corresponding nucleotide sequence of the antisense strand of the sense strand is selected from the group of sequences of any one of Tables 15-16. 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 a PRODH2 gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand (passenger strand) in any one of Tables 15-16 and the second oligonucleotide is described as the corresponding antisense strand (guide strand) of the sense strand in any one of Tables 15-16. In one embodiment, the substantially complementary sequences of the dsRNA are contained on separate oligonucleotides. In another embodiment, the substantially complementary sequences of the dsRNA are contained on a single oligonucleotide.

It will be understood that, although the sequences in Tables 2-16 are described as modified, unmodified, unconjugated. and/or conjugated sequences, the RNA of the dsRNA of the invention *e.g.*, a dsRNA of the invention, may comprise any one of the sequences set forth in any one of Table 2-16 that is un-modified, un-conjugated, and/or modified and/or conjugated differently than described therein.

The skilled person is well aware that dsRNAs having a duplex structure of between about 20 and 23 base pairs, *e.g.,* 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir *et al.*, (2001) *EMBO J.*, 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 herein, dsRNAs described herein can include at least one strand of a length of minimally 21 nucleotides. It can be reasonably expected that shorter duplexes 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 15, 16, 17, 18, 19, 20, or more contiguous nucleotides derived from one of the sequences provided herein, and differing in their ability to inhibit the expression of an LDHA gene or an HAO1 gene or a PRODH2 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 described in any one of Tables 2-3 identify a site(s) in an LDHA transcript that is susceptible to RISC-mediated cleavage, the RNAs described in any one of Tables 4-14 identify a site(s) in an HAO1 transcript that is susceptible to RISC-mediated cleavage, and those RNAs described in any one of Tables 15-16 identify a site(s) in a PRODH2 transcript that is susceptible to RISC-mediated cleavage. As such, the present invention further features iRNAs that target within this site(s). 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 15 contiguous nucleotides from one of the sequences provided herein coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in the gene.

While a target sequence is generally about 15-30 nucleotides in length, there is wide variation in the suitability of particular sequences in this range for directing cleavage of any given target RNA. Various software packages and the guidelines set out herein provide guidance for the identification of optimal target sequences for any given gene target, but an empirical approach can also be taken in which a "window" or "mask" of a given size (as a non-limiting example, 21 nucleotides) is literally or figuratively (including, *e.g.*, in silico) placed on the target RNA sequence to identify sequences in the size range that can serve as target sequences. By moving the sequence "window" progressively one nucleotide upstream or downstream of an initial target sequence location, the next potential target sequence can be identified, until the complete set of possible sequences is identified for any given target size selected. This process, coupled with systematic synthesis and testing of the identified

sequences (using assays as described herein or as known in the art) to identify those sequences that perform optimally can identify those RNA sequences that, when targeted with an iRNA agent, mediate the best inhibition of target gene expression. Thus, while the sequences identified herein represent effective target sequences, it is contemplated that further optimization of inhibition efficiency can be achieved by progressively "walking the window" one nucleotide upstream or downstream of the given sequences to identify sequences with equal or better inhibition characteristics.

Further, it is contemplated that for any sequence identified herein, further optimization could be achieved by systematically either adding or removing nucleotides to generate longer or shorter sequences and testing those sequences generated by walking a window of the longer or shorter size up or down the target RNA from that point. Again, coupling this approach to generating new candidate targets with testing for effectiveness of iRNAs based on those target sequences in an inhibition assay as known in the art and/or as described herein can lead to further improvements in the efficiency of inhibition. Further still, such optimized sequences can be adjusted by, *e.g.*, the introduction of modified nucleotides as described herein or as known in the art, addition or changes in overhang, or other modifications as known in the art and/or discussed herein to further optimize the molecule (*e.g.*, increasing serum stability or circulating half-life, increasing thermal stability, enhancing transmembrane delivery, targeting to a particular location or cell type, increasing interaction with silencing pathway enzymes, increasing release from endosomes) as an expression inhibitor.

A dsRNA agent as described herein can contain one or more mismatches to the target sequence. In one embodiment, an iRNA as described herein contains no more than 3 mismatches. If the antisense strand of the iRNA contains mismatches to a target sequence, it is preferable that the area of mismatch is not located in the center of the region of complementarity. If the antisense strand of the iRNA contains mismatches to the target sequence, it is preferable that the mismatch be restricted to be within the last 5 nucleotides from either the 5'- or 3'-end of the region of complementarity. For example, for a 23 nucleotide iRNA agent the strand which is complementary to a region of an LDHA gene or an HAO1 gene or a PRODH2 gene, generally does not contain any mismatch within the central 13 nucleotides. The methods described herein or methods known in the art can be used to determine whether an iRNA containing a mismatch to a target sequence is effective in inhibiting the expression of an LDHA gene, a PRODH2 gene and/or an HAO1 gene. Consideration of the efficacy of iRNAs with mismatches in inhibiting expression of an LDHA gene, a PRODH2 gene and/or an HAO1 gene is important, especially if the particular region of complementarity in an LDHA gene, a PRODH2 gene and/or HAO1 gene is known to have polymorphic sequence variation within the population.

The dual targeting RNAi agents of the invention, which include two dsRNA agents, are covalently attached via, *e.g.,* a covalent linker. Covalent linkers are well known in the art and include, *e.g.*, nucleic acid linkers, peptide linkers, carbohydrate linkers, and the like. The covalent linker can include RNA and/or DNA and/or a peptide. The linker can be single stranded, double

stranded, partially single strands, or partially double stranded. Modified nucleotides or a mixture of nucleotides can also be present in a nucleic acid linker.

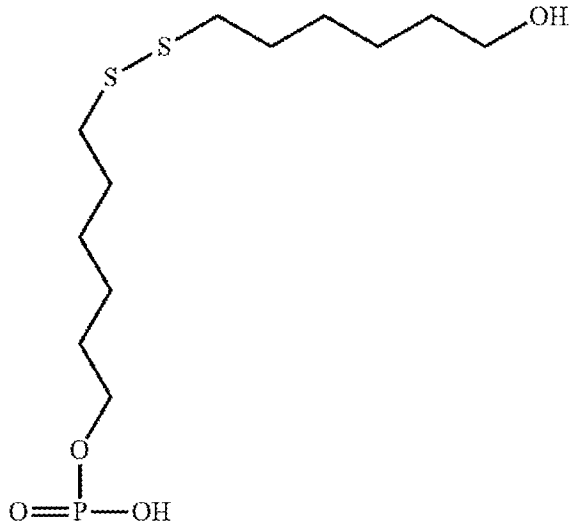
Suitable linkers for use in the dual targeting agent of the invention include those described in U.S. Patent No, 9,187,746, the entire contents of which are incorporated herein by reference.

In some embodiments the linker includes a disulfide bond. The linker can be cleavable or non-cleavable.

The linker can be, *e.g.*, dTsdTuu=(5′-2′deoxythymidyl-3′-thiophosphate-5′-2′deoxythymidyl-3′-phosphate-5′-uridyl-3′-phosphate-5′-uridyl-3′-phosphate); rUsrU (a thiophosphate linker: 5′-uridyl-3′-thiophosphate-5′-uridyl-3′-phosphate); an rUrU linker; dTsdTaa (aadTsdT, 5′-2′deoxythymidyl-3′-thiophosphate-5′-2′deoxythymidyl-3′-phosphate-5′-adenyl-3′-phosphate-5′-adenyl-3′-phosphate); dTsdT (5′-2′deoxythymidyl-3′-thiophosphate-5′-2′ deoxythymidyl-3′-phosphate); dTsdTuu=uudTsdT=5′-2′deoxythymidyl-3′-thiophosphate-5′-2′deoxythymidyl-3′-phosphate-5′-uridyl-3′-phosphate-5′-uridyl-3′-phosphate.

The linker can be a polyRNA, such as poly(5′-adenyl-3′-phosphate-AAAAAAAA) or poly(5′-cytidyl-3′-phosphate-5′-uridyl-3′-phosphate—CUCUCUCU)), *e.g.*, Xn single stranded poly RNA linker wherein n is an integer from 2-50 inclusive, such as, 4-15 inclusive, or 7-8 inclusive. Modified nucleotides or a mixture of nucleotides can also be present in said polyRNA linker. The covalent linker can be a polyDNA, such as poly(5′-2′deoxythymidyl-3′-phosphate-TTTTTTTT), *e.g.*, wherein n is an integer from 2-50 inclusive, such as 4-15 inclusive, or 7-8 inclusive. Modified nucleotides or a mixture of nucleotides can also be present in said polyDNA linker, a single stranded polyDNA linker wherein n is an integer from 2-50 inclusive, such as 4-15 inclusive, or 7-8 inclusive. Modified nucleotides or a mixture of nucleotides can also be present in said polyDNA linker.

The linker can include a disulfide bond, optionally a bis-hexyl-disulfide linker. In one embodiment, the disulfide linker is



$C_{12}H_{26}O_4PS_2$
Exact Mass: 329.1010
Mol. Wt.: 329.4362

The linker can include a peptide bond, *e.g.*, include amino acids. In one embodiment, the covalent linker is a 1-10 amino acid long linker, such as, comprising 4-5 amino acids, optionally X-Gly-Phe-Gly-Y wherein X and Y represent any amino acid.

The linker can include HEG, a hexaethylenglycol linker.

The covalent linker can attach the sense strand of the first dsRNA agent to the sense strand of the second dsRNA agent; the antisense strand of the first dsRNA agent to the antisense strand of the second dsRNA agent; the sense strand of the first dsRNA agent to the antisense strand of the second dsRNA agent; or the antisense strand of the first dsRNA agent to the sense strand of the second dsRNA agent.

In some embodiments, the covalent linker further comprises at least one ligand, described below.

i. Modified dsRNA Agent of the Invention

In one embodiment, the nucleic acid, *e.g.*, RNA, of a nucleic acid inhibitor of the invention is un-modified, and does not comprise, *e.g.*, chemical modifications and/or conjugations known in the art and described herein. In another embodiment, the nucleic acid, *e.g.*, RNA, of a nucleic acid inhibitor of the invention is chemically modified to enhance stability or other beneficial characteristics. In certain embodiments of the invention, substantially all of the nucleotides of a nucleic acid inhibitor of the invention are modified. In other embodiments of the invention, all of the nucleotides of a nucleic acid inhibitor of the invention are modified. Nucleic acid inhibitors of the invention in which "substantially all of the nucleotides are modified" are largely but not wholly modified and can include not more than 5, 4, 3, 2, or 1 unmodified nucleotides.

In embodiments in which a first nucleic acid inhibitor, *e.g.*, dsRNA agent targeting LDHA, and a second nucleic acid inhibitor, *e.g.*, dsRNA agent targeting HAO1, are covalently attached (*i.e.*, a dual targeting RNAi agent), substantially all of the nucleotides of the first agent and substantially all

of the nucleotides of the second agent may be independently modified; all of the nucleotides of the first agent may be modified and all of the nucleotides of the second agent may be independently modified; substantially all of the nucleotides of the first agent and all of the nucleotides of the second agent may be independently modified; or all of the nucleotides of the first agent may be modified and substantially all of the nucleotides of the second agent may be independently modified.

In some aspects of the invention, substantially all of the nucleotides of a nucleic acid inhibitor of the invention are modified and the nucleic acid inhibitors comprise no more than 10 nucleotides comprising 2'-fluoro modifications (*e.g.,* no more than 9 2′-fluoro modifications, no more than 8 2′-fluoro modifications, no more than 7 2′-fluoro modifications, no more than 6 2′-fluoro modifications, no more than 5 2′-fluoro modifications, no more than 4 2′-fluoro modifications, no more than 5 2′-fluoro modifications, no more than 4 2′-fluoro modifications, no more than 3 2′-fluoro modifications, or no more than 2 2′-fluoro modifications). For example, in some embodiments, the sense strand comprises no more than 4 nucleotides comprising 2′-fluoro modifications (*e.g.,* no more than 3 2′-fluoro modifications, or no more than 2 2′-fluoro modifications). In other embodiments, the antisense strand comprises no more than 6 nucleotides comprising 2′-fluoro modifications (*e.g.,* no more than 5 2′-fluoro modifications, no more than 4 2′-fluoro modifications, no more than 4 2′-fluoro modifications, or no more than 2 2′-fluoro modifications).

In embodiments in which a first nucleic acid inhibitor, *e.g.,* dsRNA agent targeting LDHA, and a second nucleic acid inhibitor, *e.g.,* dsRNA agent targeting HAO1, are covalently attached (*i.e.,* a dual targeting RNAi agent), substantially all of the nucleotides of the first agent and/or substantially all of the nucleotides of the second agent may be independently modified and the first and second agents may independently comprise no more than 10 nucleotides comprising 2'-fluoro modifications.

In other aspects of the invention, all of the nucleotides of a nucleic acid inhibitor of the invention are modified and the nucleic acid inhibitors comprise no more than 10 nucleotides comprising 2'-fluoro modifications (*e.g.,* no more than 9 2′-fluoro modifications, no more than 8 2′-fluoro modifications, no more than 7 2′-fluoro modifications, no more than 6 2′-fluoro modifications, no more than 5 2′-fluoro modifications, no more than 4 2′-fluoro modifications, no more than 5 2′-fluoro modifications, no more than 4 2′-fluoro modifications, no more than 3 2′-fluoro modifications, or no more than 2 2′-fluoro modifications).

In embodiments in which a first nucleic acid inhibitor, *e.g.,* dsRNA agent targeting LDHA, and a second nucleic acid inhibitor, *e.g.,* dsRNA agent targeting HAO1, are covalently attached (*i.e.,* a dual targeting RNAi agent), all of the nucleotides of the first agent and/or all of the nucleotides of the second agent may be independently modified and the first and second agents may independently comprise no more than 10 nucleotides comprising 2'-fluoro modifications.

In one embodiment, a nucleic acid inhibitor of the invention further comprises a 5'-phosphate or a 5'-phosphate mimic at the 5' nucleotide of the antisense strand. In another embodiment, the double stranded RNAi agent further comprises a 5'-phosphate mimic at the 5' nucleotide of the

antisense strand. In a specific embodiment, the 5'-phosphate mimic is a 5'-vinyl phosphonate (5'-VP).

In embodiments in which a first nucleic acid inhibitor, *e.g.,* dsRNA agent targeting LDHA, and a second nucleic acid inhibitor, *e.g.,* dsRNA agent targeting HAO1, are covalently attached (*i.e.,* a dual targeting RNAi agent), the first agent may further comprise a 5'-phosphate or a 5'-phosphate mimic at the 5' nucleotide of the antisense strand; the second agent may further comprise a 5'-phosphate or a 5'-phosphate mimic at the 5' nucleotide of the antisense strand; or the first agent and the second agent may further independently comprise a 5'-phosphate or a 5'-phosphate mimic at the 5' nucleotide of the antisense strand.

The nucleic acids featured in the invention can be synthesized and/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; and/or backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of nucleic acid inhibitor compounds useful in the embodiments described herein include, but are not limited to nucleic acid inhibitors containing modified backbones or no natural internucleoside linkages. Nucleic acid inhibitors 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 nucleic acid inhibitors that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In some embodiments, a modified nucleic acid inhibitor will have a phosphorus atom in its internucleoside backbone.

Modified nucleic acid inhibitor backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5'-linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included.

Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Patent Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253;

5,571,799; 5,587,361; 5,625,050; 6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6, 239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and US Pat RE39464, the entire contents of each of which are hereby incorporated herein by reference.

Modified nucleic acid inhibitor 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 CH_2 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.

In other embodiments, suitable RNA mimetics are contemplated for use in nucleic acid inhibitors, 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, 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 U.S. 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 nucleic acid inhibitors, *e.g.,* RNAs, with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular --CH_2--NH--CH_2-, --CH_2--N(CH_3)--O--CH_2--[known as a methylene (methylimino) or MMI backbone], --CH_2--O--N(CH_3)--CH_2--, --CH_2--N(CH_3)--N(CH_3)--CH_2-- and --N(CH_3)--CH_2--CH_2-- 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 nucleic acid inhibitors can also contain one or more substituted sugar moieties. The nucleic acid inhibitors, *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 C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nOCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an iRNA, or a group for improving the pharmacodynamic properties of a nucleic acid inhibitor, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--$CH_2CH_2OCH_3$, 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'-dimethylaminooxyethoxy, *i.e.*, a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH_2--O--CH_2--$N(CH_3)_2$. Further exemplary modifications include : 5'-Me-2'-F nucleotides, 5'-Me-2'-OMe nucleotides, 5'-Me-2'-deoxynucleotides, (both R and S isomers in these three families); 2'-alkoxyalkyl; and 2'-NMA (N-methylacetamide).

Other modifications include 2'-methoxy (2'-OCH_3), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$) and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of a nucleic acid inhibitor, 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. Nucleic acid inhibitors can also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. 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.

Additional nucleotides having modified or substituted sugar moieties for use in the nucleic acid inhibitors of the invention include nucleotides comprising a bicyclic sugar. A "bicyclic sugar" is a furanosyl ring modified by the bridging of two atoms. A"bicyclic nucleoside" ("BNA") is a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring,

thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4′-carbon and the 2′-carbon of the sugar ring. Thus, in some embodiments a nucleic acid inhibitor may include one or more locked nucleic acids. A "locked nucleic acid" ("LNA") 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'-CH_2-O-2' bridge. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to polynucleotide agents has been shown to increase polynucleotide agent 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 nucleic acid inhibitors of the invention include without limitation nucleosides comprising a bridge between the 4′ and the 2′ ribosyl ring atoms. In certain embodiments, the nucleic acid inhibitors of the invention include one or more bicyclic nucleosides comprising a 4′ to 2′ bridge. 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. Pat. No. 7,399,845); 4′-C(CH3)(CH3)—O-2′ (and analogs thereof; see *e.g.,* US Patent No. 8,278,283); 4′-CH2—N(OCH3)-2′ (and analogs thereof; see *e.g.,* US 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 protecting group (see, *e.g.,* U.S. Pat. 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.,* US Patent No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein by reference.

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

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

In one particular embodiment of the invention, a nucleic acid inhibitor can 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'-$CH(CH_3)$-O-2' bridge. In one embodiment, a constrained ethyl nucleotide is in an S conformation and is referred to as an "*S*-constrained ethyl nucleotide" or "*S*-cEt."

Modified nucleotides included in the nucleic acid inhibitors of the invention can also contain one or more sugar mimetics. For example, the nucleic acid inhibitor may include a "modified tetrahydropyran nucleotide" or "modified THP nucleotide." A "modified tetrahydropyran nucleotide" has a six-membered tetrahydropyran "sugar" substituted in for the pentofuranosyl residue in normal nucleotides (a sugar surrogate). Modified THP nucleotides include, but are not limited to, what is referred to in the art as hexitol nucleic acid (HNA), anitol nucleic acid (ANA), manitol nucleic acid (MNA) (see, *e.g.,* Leumann, *Bioorg. Med. Chem.*, 2002, 10, 841-854), or fluoro HNA (F-HNA). In some embodiments of the invention, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example nucleotides comprising morpholino sugar moieties and their use in oligomeric compounds has been reported (see for example: Braasch *et al., Biochemistry*, 2002, 41, 4503-4510; and U.S. Patent Nos. 5,698,685; 5,166,315; 5,185,444; and 5,034,506). Morpholinos may be modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are referred to herein as "modified morpholinos."

Combinations of modifications are also provided without limitation, such as 2′-F-5′-methyl substituted nucleosides (see PCT International Application WO 2008/101157 published on Aug. 21, 2008 for other disclosed 5′, 2′-bis substituted nucleosides) and replacement of the ribosyl ring oxygen atom with S and further substitution at the 2′-position (see published U.S. Patent Application US2005-0130923, published on Jun. 16, 2005) or alternatively 5′-substitution of a bicyclic nucleic acid (see PCT International Application WO 2007/134181, published on 11/22/07 wherein a 4′-CH2-0-2′ bicyclic nucleoside is further substituted at the 5′ position with a 5′-methyl or a 5′-vinyl group). The synthesis and preparation of carbocyclic bicyclic nucleosides along with their oligomerization and biochemical studies have also been described (see, *e.g.*, Srivastava *et al.*, J. Am. Chem. Soc. 2007, 129(26), 8362-8379).

In certain embodiments, a nucleic acid inhibitor comprises one or more modified cyclohexenyl nucleosides, which is a nucleoside having a six-membered cyclohexenyl in place of the pentofuranosyl residue in naturally occurring nucleosides. Modified cyclohexenyl nucleosides include, but are not limited to those described in the art (see for example commonly owned, published PCT Application WO 2010/036696, published on Apr. 10, 2010, Robeyns *et al.*, J. Am. Chem. Soc., 2008, 130(6), 1979-1984; Horvath *et al.*, Tetrahedron Letters, 2007, 48, 3621-3623; Nauwelaerts *et al.*, J. Am. Chem. Soc., 2007, 129(30), 9340-9348; Gu *et al.*, Nucleosides, Nucleotides & Nucleic Acids, 2005, 24(5-7), 993-998; Nauwelaerts *et al.*, Nucleic Acids Research, 2005, 33(8), 2452-2463; Robeyns *et al.*, Acta Crystallographica, Section F: Structural Biology and Crystallization Communications, 2005, F61(6), 585-586; Gu *et al.*, Tetrahedron, 2004, 60(9), 2111-2123; Gu *et al.*, Oligonucleotides, 2003, 13(6), 479-489; Wang *et al.*, J. Org. Chem., 2003, 68, 4499-4505; Verbeure *et al.*, Nucleic Acids Research, 2001, 29(24), 4941-4947; Wang *et al.*, J. Org. Chem., 2001, 66, 8478-82; Wang *et al.*, Nucleosides, Nucleotides & Nucleic Acids, 2001, 20(4-7), 785-788; Wang *et al.*, J. Am. Chem., 2000, 122, 8595-8602; Published PCT application, WO 06/047842; and Published PCT Application WO 01/049687; the text of each is incorporated by reference herein, in their entirety).

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

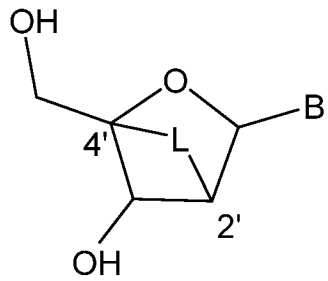
Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Patent Nos. 3,687,808, 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255;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

A nucleic acid inhibitor of the invention can also be modified to 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. 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).

A nucleic acid inhibitor of the invention can also be modified to include one or more bicyclic sugar moities. A "bicyclic sugar" is a furanosyl ring modified by a aring 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 bridgeing two carbon, whether adjacent or non-adjacent,of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4′-carbon and the 2′-carbon of the sugar ring, optionally, via the 2'-acyclic oxygen atom. Thus, in some embodiments an agent of the invention may include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. In other words, an LNA is a nucleotide comprising a bicyclic sugar moiety comprising a 4'-CH2-O-2' bridge. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193). Examples of bicyclic nucleosides for use in the polynucleotides of the invention include without limitation nucleosides comprising a bridge between the 4′ and the 2′ ribosyl ring atoms. In certain embodiments, the antisense polynucleotide agents of the invention include one or more bicyclic nucleosides comprising a 4′ to 2′ bridge.

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



wherein B is a nucleobase or modified nucleobase and L is the linking group that joins the 2'-carbon to the 4'-carbon of the ribose ring. Examples of such 4′ to 2′ bridged bicyclic nucleosides, include but are not limited to 4′-(CH2)—O-2′ (LNA); 4′-(CH2)—S-2′; 4′-(CH2)2—O-2′ (ENA); 4′-CH(CH3)—O-2′ (also referred to as "constrained ethyl" or "cEt") and 4′-CH(CH2OCH3)—O-2′ (and analogs thereof; see, *e.g.*, U.S. Pat. No. 7,399,845); 4′-C(CH3)(CH3)—O-2′ (and analogs thereof; see *e.g.*, US Patent No. 8,278,283); 4′-CH2—N(OCH3)-2′ (and analogs thereof; see *e.g.*, US 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. Pat. 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.*, US Patent No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein by reference.

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

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

A nucleic acid inhibitor of the invention 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)-0-2' bridge (*i.e.*, L in the preceding structure). In one embodiment, a constrained ethyl nucleotide is in the S conformation referred to herein as "S-cEt."

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

Representative U.S. publications that teach the preparation of UNA include, but are not limited to, US Patent No. 8,314,227; and US 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 nucleic acid inhibitors can include N-(acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-0-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"- phosphate, inverted

base dT(idT) and others. Disclosure of this modification can be found in PCT Publication No. WO 2011/005861.

Other modifications of a nucleic acid inhibitor 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 a nucleic acid inhibitor. Suitable phosphate mimics are disclosed in, for example US Patent Publication No. 2012/0157511, the entire contents of which are incorporated herein by reference.

Any of the nucleic acid inhibitors of the invention may be optionally conjugated with a ligand, such as a GalNAc derivative ligand, as described below.

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

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

The nucleic acid inhibitors may be conjugated to a ligand *via* a carrier, wherein the carrier can be cyclic group or acyclic group; in some embodiments, the cyclic group is selected from pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl,

tetrahydrofuryl and and decalin; in some embodiments, the acyclic group is selected from serinol backbone or diethanolamine backbone.

ii. Modified dsRNA Agents Comprising Motifs of the Invention

In certain aspects of the invention, the double stranded RNAi agents of the invention include agents with chemical modifications as disclosed, for example, in WO 2013/075035, filed on November 16, 2012, the entire contents of which are incorporated herein by reference.

It is to be understood that, in embodiments in which a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1 are covalently attached (*i.e.*, a dual targeting RNAi agent), the first agent may comprise any one or more of the motifs described below, the second agent may comprise any one or more of the motifs described below, or both the first agent and the second agent may independently comprise any one or more of the motifs described below.

Accordingly, the invention provides double stranded RNAi agents capable of inhibiting the expression of a target gene (*i.e.*, an LDHA gene, an HAO1 gene, a PRODH2 gene, or both an LDHA gene and an HAO1 gene) *in vivo*. The RNAi agent comprises a sense strand and an antisense strand. Each strand of the RNAi agent may range from 12-30 nucleotides in length. For example, each strand may be between 14-30 nucleotides in length, 17-30 nucleotides in length, 25-30 nucleotides in length, 27-30 nucleotides in length, 17-23 nucleotides in length, 17-21 nucleotides in length, 17-19 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 an "RNAi agent." The duplex region of an RNAi agent may be 12-30 nucleotide pairs in length. For example, the duplex region can be between 14-30 nucleotide pairs in length, 17-30 nucleotide pairs in length, 27-30 nucleotide pairs in length, 17 - 23 nucleotide pairs in length, 17-21 nucleotide pairs in length, 17-19 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 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, and 27 nucleotides in length.

In one embodiment, the RNAi agent may contain one or more overhang regions and/or capping groups at the 3'-end, 5'-end, or both ends of one or both strands. The overhang can be 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. 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 linkers.

In one embodiment, the nucleotides in the overhang region of the RNAi agent can each independently be a modified or unmodified nucleotide including, but no limited to 2'-sugar modified,

such as, 2-F, 2'-Omethyl, thymidine (T), 2`-O-methoxyethyl-5-methyluridine (Teo), 2`-O-methoxyethyladenosine (Aeo), 2`-O-methoxyethyl-5-methylcytidine (m5Ceo), and any combinations 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 RNAi 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 one embodiment, the overhang is present at the 3'-end of the sense strand, antisense strand, or both strands. In one embodiment, this 3'-overhang is present in the antisense strand. In one embodiment, this 3'-overhang is present in the sense strand.

The RNAi 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'-terminal end of the sense strand or, alternatively, at the 3'-terminal end of the antisense strand. The RNAi may also have a blunt end, located at the 5'-end of the antisense strand (or the 3'-end of the sense strand) or *vice versa*. Generally, the antisense strand of the RNAi 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 one embodiment, the RNAi 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, and 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 another embodiment, the RNAi 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 another embodiment, the RNAi 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 one embodiment, the RNAi 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. For example, 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 one embodiment, every nucleotide in the sense strand and the antisense strand of the RNAi agent, including the nucleotides that are part of the motifs are modified nucleotides. In one embodiment each residue is independently modified with a 2'-O-methyl or 2'-fluoro, *e.g.,* in an alternating motif. Optionally, the RNAi agent further comprises a ligand (such as $GalNAc_3$).

In one embodiment, the RNAi 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 one embodiment, the RNAi agent comprises sense and antisense strands, wherein the RNAi 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, and 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 region which is at least 25 nucleotides in length, and the second strand is sufficiently complemenatary

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 RNAi 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 RNAi agent further comprises a ligand.

In one embodiment, the sense strand of the RNAi 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 one embodiment, the antisense strand of the RNAi 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 an RNAi agent having a duplex region of 17-23 nucleotide 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, and 11 positions; 10, 11, and 12 positions; 11, 12, and 13 positions; 12, 13, and 14 positions; or 13, 14, and 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 RNAi from the 5'-end.

The sense strand of the RNAi 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 one embodiment, the sense strand of the RNAi 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 adajacent 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 chemistry of the motifs are distinct from each other and when the motifs are separated by one or more nucleotide than 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 RNAi agent may contain more than one motifs 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 one embodiment, the wing modification on the sense strand or antisense strand of the RNAi 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 another embodiment, the wing modification on the sense strand or antisense strand of the RNAi 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 RNAi 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 RNAi 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 one embodiment, every nucleotide in the sense strand and antisense strand of the RNAi 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 and/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 a 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 one embodiment, 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 one embodiment, the N_a and/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…," "AAABAAABAAAB…," "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 one embodiment, the RNAi 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'-3' of the strand and the alternating motif in the antisense strand may start with "BABABA" from 5'-3'of the strand within the duplex region. As another example, the alternating motif in the sense strand may start with

"AABBAABB" from 5'-3' of the strand and the alternating motif in the antisenese strand may start with "BBAABBAA" from 5'-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 embodiment, the RNAi 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 and/or antisense strand interrupts the initial modification pattern present in the sense strand and/or antisense strand. This interruption of the modification pattern of the sense and/or antisense strand by introducing one or more motifs of three identical modifications on three consecutive nucleotides to the sense and/or antisense strand surprisingly enhances the gene silencing acitivty to the target gene.

In one embodiment, 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. Altnernatively, N_a and/or N_b may be present or absent when there is a wing modification present.

The RNAi agent 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 or 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 and/or antisense strand; each internucleotide linkage modification may occur in an alternating pattern on the sense strand and/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-standed RNAi agent comprises 6-8phosphorothioate internucleotide linkages. In one embodiment, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two

phosphorothioate internucleotide linkages at the 3'-terminus, and the sense strand comprises at least two phosphorothioate internucleotide linkages at either the 5'-terminus or the 3'-terminus.

In one embodiment, the RNAi 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, and/or the 5'end of the antisense strand.

In one embodiment, 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 RNAi 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 RNAi agent comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mistmatch 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 one embodiment, the RNAi 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 one embodiment, the nucleotide at the 1 position within the duplex region from the 5'-end in the antisense strand is selected from the group consisting of 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 another embodiment, the nucleotide at the 3'-end of the sense strand is deoxythimidine (dT). In another embodiment, the nucleotide at the 3'-end of the antisense strand is deoxythimidine (dT). In one embodiment, there is a short sequence of deoxy-thymine nucleotides, for example, two dT nucleotides on the 3'-end of the sense and/or antisense strand.

In one embodiment, the sense strand sequence may be represented by formula (I):

5' n_p-N_a-(X X X)$_i$-N_b-Y Y Y -N_b-(Z Z Z)$_j$-N_a-n_q 3' (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 Nb 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 some embodiments, YYY is all 2'-F modified nucleotides. In one embodiment, the N_a and/or N_b comprise modifications of alternating pattern.

In one embodiment, the YYY motif occurs at or near the cleavage site of the sense strand. For example, when the RNAi 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 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st 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:

5' n_p-N_a-YYY-N_b-ZZZ-N_a-n_q 3' (Ib);

5' n_p-N_a-XXX-N_b-YYY-N_a-n_q 3' (Ic); or

5' n_p-N_a-XXX-N_b-YYY-N_b-ZZZ-N_a-n_q 3' (Id).

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 some 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 one embodiment, the N_a' and/or N_b' comprise modifications of alternating pattern.

The Y'Y'Y' motif occurs at or near the cleavage site of the antisense strand. For example, when the RNAi agent has a duplex region of 17-23nucleotidein 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 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end. In some embodiments, the Y'Y'Y' motif occurs at positions 11, 12, 13.

In one embodiment, Y'Y'Y' motif is all 2'-OMe modified nucleotides.

In one embodiment, k is 1 and l is 0, or k is 0 and l is 1, or both k and l are 1.

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).

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.

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.

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 some embodiments, 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).

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.

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.

In one embodiment, the sense strand of the RNAi 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 1st nucleotide from the 5'-end, or optionally, the count starting at the 1st 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 one embodiment the antisense strand may contain Y′Y′Y′ motif occurring at positions 11, 12, 13 of the strand, the count starting from the 1st nucleotide from the 5' end, or optionally, the count starting at the 1st 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 a antisense strand being represented by any one of formulas (IIa), (IIb), (IIc), and (IId), respectively.

Accordingly, the RNAi 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 RNAi duplex represented by formula (III):

sense: 5' np -Na-(X X X)i -Nb- Y Y Y -Nb -(Z Z Z)j-Na-nq 3'

antisense: 3' np'-Na'-(X'X'X')k-Nb'-Y'Y'Y'-Nb'-(Z'Z'Z')l-Na'-nq' 5'

(III)

wherein:

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

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

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

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

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

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

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

Exemplary combinations of the sense strand and antisense strand forming a RNAi duplex include the formulas below:

5' np - Na -Y Y Y -Na-nq 3'

3' np'-Na'-Y'Y'Y' -Na'nq' 5'

(IIIa)

5' np -Na -Y Y Y -Nb -Z Z Z -Na-nq 3'

3' np'-Na'-Y'Y'Y'-Nb'-Z'Z'Z'-Na'nq' 5'

(IIIb)

5' np-Na- X X X -Nb -Y Y Y - Na-nq 3'

3' np'-Na'-X'X'X'-Nb'-Y'Y'Y'-Na'-nq' 5'

(IIIc)

5' np -Na -X X X -Nb-Y Y Y -Nb- Z Z Z -Na-nq 3'

3' np'-Na'-X'X'X'-Nb'-Y'Y'Y'-Nb'-Z'Z'Z'-Na-nq' 5'

(IIId)

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

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

When the RNAi agent is represented as formula (IIIc), each Nb, Nb' 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 Na independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented as formula (IIId), each Nb, Nb' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0modified nucleotides. Each Na, Na' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Each of Na, Na', Nb and Nb' 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 RNAi 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 RNAi 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 RNAi 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 one embodiment, 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, and/or the modification on the X nucleotide is different than the modification on the X' nucleotide.

In one embodiment, when the RNAi agent is represented by formula (IIId), the Na modifications are 2′-O-methyl or 2′–fluoro modifications. In another embodiment, when the RNAi agent is represented by formula (IIId), the Na modifications are 2′-O-methyl or 2′-fluoro modifications and np′ >0 and at least one np′ is linked to a neighboring nucleotide a via phosphorothioate linkage. In yet another embodiment, when the RNAi agent is represented by formula (IIId), the Na modifications are 2′-O-methyl or 2′-fluoro modifications , np′ >0 and at least one np′ 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 another embodiment, when the RNAi agent is represented by formula (IIId), the Na modifications are 2′-O-methyl or 2′-fluoro modifications , np′ >0 and at least one np′ 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.

In one embodiment, when the RNAi agent is represented by formula (IIIa), the Na modifications are 2′-O-methyl or 2′-fluoro modifications , np′ >0 and at least one np′ 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.

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

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

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

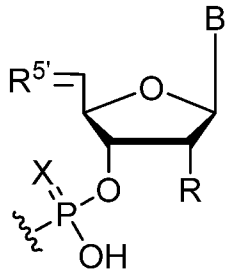
In certain embodiments, an RNAi agent of the invention may contain a low number of nucleotides containing a 2'-fluoro modification, *e.g.*, 10 or fewer nucleotides with 2'-fluoro modification. For example, the RNAi agent may contain 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0 nucleotides with a 2'-fluoro modification.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

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

modification, *e.g.*, 0 nucleotides with a 2-fluoro modification in the sense strand and 2 nucleotides with a 2'-fluoro modification in the antisense strand.

Various publications describe multimeric RNAi agents that can be used in the methods of the invention. Such publications include WO2007/091269, US Patent No. 7858769, WO2010/141511, WO2007/117686, WO2009/014887 and WO2011/031520 the entire contents of each of which are hereby incorporated herein by reference.

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



wherein X is O or S;

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

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

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

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

Vinyl phosphonate modifications are also contemplated for the compositions and methods of the instant disclosure. An exemplary vinyl phosphonate structure includes the preceding structure, where $R^{5'}$ is =C(H)-OP(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).

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

may be a monocyclic ring system, or may contain two or more rings, *e.g.* fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds.

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

The RNAi agents may be conjugated to a ligand *via* a carrier, wherein the carrier can be cyclic group or acyclic group; in some embodiments, the cyclic group is selected from pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl and and decalin; in some embodiments, the acyclic group is selected from serinol backbone or diethanolamine backbone.

iii. Thermally Destabilizing Modifications

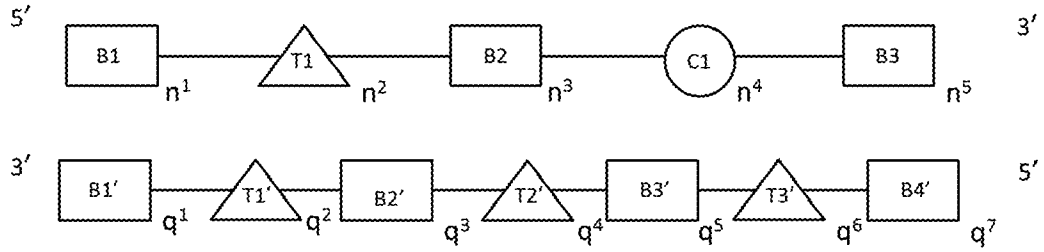
In certain embodiments, a nucleic acid inhibitor molecule can be optimized for RNA interference by incorporating thermally destabilizing modifications in the seed region of the antisense strand. As used herein "seed region" means at positions 2-9 of the 5'-end of the referenced strand. For example, thermally 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.

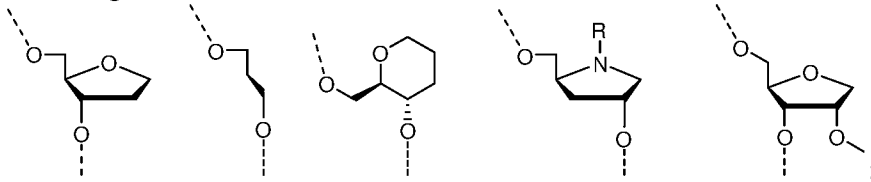
In another embodiment of the invention, an iRNA agent comprises a sense strand and an antisense strand, each strand having 14 to 40 nucleotides. The RNAi agent may be represented by formula (L):



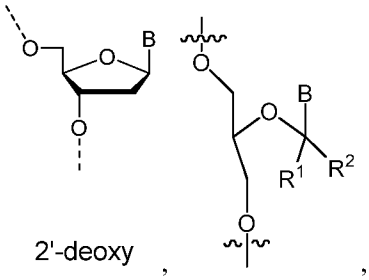
(L),

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) 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). 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) or glycerol nucleic acid (GNA). 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:



; and iii) sugar modification selected from the group consisting of:



2'-deoxy

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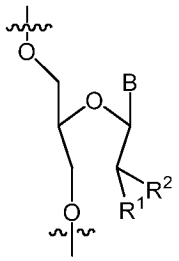

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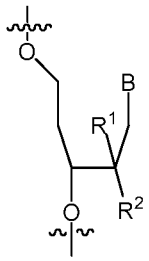

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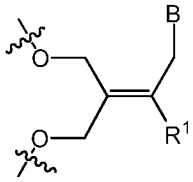
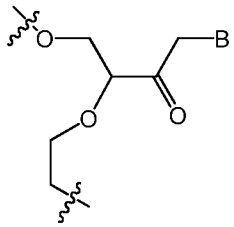


, and



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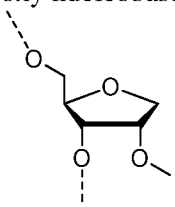
wherein B is a modified or unmodified nucleobase, R^1 and R^2 independently are H, halogen, OR_3, or alkyl; and R_3 is H, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar. In one embodiment, the thermally destabilizing modification in C1 is a mismatch selected from the group consisting of G:G, G:A, 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 

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In an exemplary embodiment, T1 is at the cleavage site of the sense strand, for instance, at position 11 from the 5' end of the sense strand, when the sense strand is 19-22 nucleotides in length, and n^2 is 1; T1' is at position 14 from the 5' end of the antisense strand, and q^2 is equal to 1, and the

modification to T1' is at the 2' position of a ribose sugar or at positions in a non-ribose, acyclic or backbone that provide less steric bulk than a 2'-OMe ribose; T2' is at positions 6-10 from the 5' end of the antisense strand, and q^4 is 1; and T3' is at position 2 from the 5' end of the antisense strand, and q^6 is equal to 1, and the modification to T3' is at the 2' position or at positions in a non-ribose, acyclic or backbone that provide less than or equal to steric bulk than a 2'-OMe ribose.

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

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

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

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

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

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

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

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

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

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

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

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

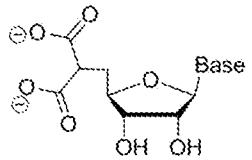
In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 5, T2' is 2'-F, q^4 is 1, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4'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

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

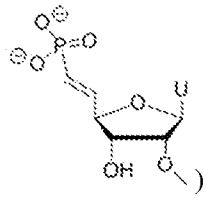
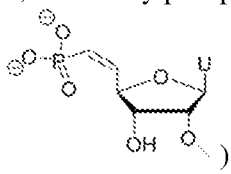
In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and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

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

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, 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 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 dsRNA 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'-PS_2), 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.

In one embodiment, the RNAi agent comprises a 5'-PS_2. In one embodiment, the RNAi agent comprises a 5'-PS_2 in the antisense strand.

In one embodiment, the RNAi agent comprises a 5'-PS_2. In one embodiment, the RNAi agent comprises a 5'-deoxy-5'-*C*-malonyl in the antisense strand.

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

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

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

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

q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'- PS_2.

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

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

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

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

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

modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'- PS_2.

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

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

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

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

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1. The RNAi agent also comprises a 5'- PS_2.

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

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

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

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

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'- PS_2.

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'- PS_2.

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

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

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

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

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'- PS_2.

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.

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.

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'- PS_2.

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'-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.

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.

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

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'- PS_2.

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

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

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

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

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'- PS_2 and a targeting ligand. In one embodiment, the 5'- PS_2 is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

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

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

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

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

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-PS_2 and a targeting ligand. In one embodiment, the 5'-PS_2 is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-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, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-P 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'-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, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-VP (*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'-PS_2 and a targeting ligand. In one embodiment, the 5'-PS_2 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'- PS_2 and a targeting ligand. In one embodiment, the 5'-PS_2 is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

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

(a) a sense strand having:
  (i) a length of 21 nucleotides;
  (ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;
  (iii) 2'-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
  (iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);
  and
(b) an antisense strand having:
  (i) a length of 23 nucleotides;
  (ii) 2'-OMe modifications at positions 1, 3, 5 to 7, 9, 11 to 13, 15, 17 to 19, and 21 to 23, and 2'-F modifications at positions 2, 4, 8, 10, 14, 16, and 20 (counting from the 5' end); and

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 25 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 19 nucleotides;

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

(iii) 2'-OMe modifications at positions 1 to 4, 6, and 10 to 19, and 2'-F modifications at positions 5, and 7 to 9; and

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

and

(b) an antisense strand having:

(i) a length of 21 nucleotides;

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

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 19 and 20, and between nucleotide positions 20 and 21 (counting from the 5' end);

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

B. Single Stranded Antisense Polynucleotide Agents of the Invention

In one embodiment, a nucleic acid inhibitor for use in the methods of the invention is a single stranded antisense polynucleotide agent that targets LDHA, a single stranded antisense polynucleotide agent that targets PRODH2, and/or a single stranded antisense polynucleotide agent that targets HAO1.

Suitable antisense polynucleotide agent for use in the methods of the invention are known in the art and described in, for example, U.S. Patent Publication No. 2018/0092990 (Attorney Docket No. 121301-03602), the entire contents of which are incorporated herein by reference.

In certain specific embodiments, a nucleic acid inhibitor of the present invention is a single stranded antisense polynucleotide agent which inhibits the expression of an LDHA gene and is selected from the group of antisense sequence listed in any one of Tables 2-3. In some embodiments, a nucleic acid inhibitor of the present invention is a single stranded antisense polynucleotide agent which inhibits the expression of an HAO1 gene and is selected from the group of antisense sequence listed in any one of Tables 4-14. In some embodiments, a nucleic acid inhibitor of the present invention is a single stranded antisense polynucleotide agent which inhibits the expression of a PRODH2 gene and is selected from the group of antisense sequence listed in any one of Tables 15-16. Any of these agents may further comprise a ligand.

The polynucleotide agents of the invention include a nucleotide sequence which is about 4 to about 50 nucleotides or less in length and which is about 80% complementary to at least part of an mRNA transcript of an LDHA gene, a PRODH2 gene and/or HAO1 gene. The use of these polynucleotide agents enables the targeted inhibition of RNA expression and/or activity of a corresponding gene in subjects, such as human subjects.

The polynucleotide agents, *e.g.,* antisense polynucleotide agents, and compositions comprising such agents, of the invention target an LDHA gene, a PRODH2 gene and/or an HAO1 gene and inhibit the expression of the gene. In one embodiment, the polynucleotide agents inhibit the expression of the gene in a cell, such as a cell within a subject, *e.g.,* a mammal, such as a human having or at risk of developing a non-primary hyperoxaluria disease or disorder.

The polynucleotide agents of the invention include a region of complementarity which is complementary to at least a part of an mRNA formed in the expression of an LDHA gene, a PRODH2 gene and/or an HAO1 gene. The region of complementarity may be about 50 nucleotides or less in

length (*e.g.*, about 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, or 4 nucleotides or less in length). Upon contact with a cell expressing the gene, the polynucleotide agent inhibits the expression of the gene (*e.g.*, a human, a primate, a non-primate, or a bird LDHA gene, PRODH2 gene and/or HAO1 gene) by at least about 10% 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.

The region of complementarity between a polynucleotide agent and a target sequence may be substantially complementary (*e.g.*, there is a sufficient degree of complementarity between the polynucleotide agent and a target nucleic acid to so that they specifically hybridize and induce a desired effect), but is generally fully complementary to the target sequence. The target sequence can be derived from the sequence of an mRNA formed during the expression of an LDHA gene, a PRODH2 gene and/or an HAO1 gene.

In one aspect, an antisense polynucleotide agent, specifically hybridizes to a target nucleic acid molecule, such as the mRNA encoding LDHA, and comprises a contiguous nucleotide sequence which corresponds to the reverse complement of a nucleotide sequence of SEQ ID NOs:1, 3, 5, 7, or 9, or a fragment of SEQ ID NOs:1, 3, 5, 7, or 9.

In one aspect, an antisense polynucleotide agent, specifically hybridizes to a target nucleic acid molecule, such as the mRNA encoding HAO1, and comprises a contiguous nucleotide sequence which corresponds to the reverse complement of a nucleotide sequence of SEQ ID NO:21, or a fragment of SEQ ID NO:21.

In another aspect, an antisense polynucleotide agent, specifically hybridizes to a target nucleic acid molecule, such as the mRNA encoding PRODH2, and comprises a contiguous nucleotide sequence which corresponds to the reverse complement of a nucleotide sequence of SEQ ID NO:4641, or a fragment of SEQ ID NO:4641.

In some embodiments, the polynucleotide agents of the invention may be substantially complementary to the target sequence. For example, a polynucleotide agent that is substantially complementary to the target sequence may include a contiguous nucleotide sequence comprising no more than 5 mismatches (*e.g.*, no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches) when hybridizing to a target sequence, such as to the corresponding region of a nucleic acid which encodes a mammalian LDHA mRNA, a mammalian PRODH2 mRNA, and/or a mammalian HAO1 mRNA. In some embodiments, the contiguous nucleotide sequence comprises no more than a single mismatch when hybridizing to the target sequence, such as the corresponding region of a nucleic acid which encodes a mammalian LDHA mRNA, a mammalian PRODH2 mRNA, and/or a mammalian HAO1 mRNA.

In some embodiments, the polynucleotide agents of the invention that are substantially complementary to the target sequence comprise 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:1, 3, 5, 7, or 9, or a fragment of SEQ ID NOs:1, 3, 5, 7, or 9, such as about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about % 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In some embodiments, a polynucleotide agent comprises a contiguous nucleotide sequence which is fully complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs:1, 3, 5, 7, or 9 (or a fragment of SEQ ID NOs:1, 3, 5, 7, or 9).

In some embodiments, the polynucleotide agents of the invention that are substantially complementary to the target sequence comprise 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 NO:21, or a fragment of SEQ ID NO:21, such as about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about % 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In some embodiments, a polynucleotide agent comprises a contiguous nucleotide sequence which is fully complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NO:21(or a fragment of SEQ ID NO:21).

In some embodiments, the polynucleotide agents of the invention that are substantially complementary to the target sequence comprise 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 NO:4641, or a fragment of SEQ ID NO:4641, such as about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about % 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In some embodiments, a polynucleotide agent comprises a contiguous nucleotide sequence which is fully complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NO:4641 (or a fragment of SEQ ID NO:4641).

A polynucleotide agent may comprise a contiguous nucleotide sequence of about 4 to about 50 nucleotides in length, *e.g.*, 4, 5, 6, 7, 8, 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, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides in length.

In some embodiments, a polynucleotide agent may comprise a contiguous nucleotide sequence of no more than 22 nucleotides, such as no more than 21 nucleotides, 20 nucleotides, 19 nucleotides, or no more than 18 nucleotides. In some embodiments the polynucleotide agenst of the invention comprises less than 20 nucleotides. In other embodiments, the polynucleotide agents of the invention comprise 20 nucleotides.

In certain aspects, a polynucleotide agent of the invention targeting LDHA includes a sequence selected from the group of antisense sequences provided in any one of Tables 2-3.

In certain aspects, a polynucleotide agent of the invention targeting HAO1 includes a sequence selected from the group of antisense sequences provided inany one of Tables 4-14.

In certain aspects, a polynucleotide agent of the invention targeting PRODH2 includes a sequence selected from the group of antisense sequences provided in any one of Tables 15-16.

It will be understood that, although some of the antisense sequences in Tables 2-16 are described as modified and/or conjugated sequences, a polynucleotide agent of the invention, may also comprise any one of the sequences set forth in Tables 2-16 that is un-modified, un-conjugated, and/or modified and/or conjugated differently than described therein.

By virtue of the nature of the nucleotide sequences provided in Tables 2-16, polynucleotide agents of the invention may include one of the sequences of Tables 2-16 minus only a few nucleotides on one or both ends and yet remain similarly effective as compared to the polynucleotide agents described above. Hence, polynucleotide agents having a sequence of at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,15, 16, 17, 18, 19, 20, or more contiguous nucleotides derived from one of the sequences of Tables 2-14 and differing in their ability to inhibit the expression of the corresponding gene by not more than about 5, 10, 15, 20, 25, or 30% inhibition from an polynucleotide agent comprising the full sequence, are contemplated to be within the scope of the present invention.

In addition, the polynucleotide agents provided in Tables 2 -16 identify a region(s) in an LDHA transcript, a PRODH2 transcript and/or an HAO1 transcript that is susceptible to antisense inhibition (*e.g.,* the regions in SEQ ID NO: 1 or SEQ ID NO:21 or SEQ ID NO: 4641 which the polynucleitde agents may target). As such, the present invention further features polynucleotide agents that target within one of these sites. As used herein, a polynucleotide agent is said to target within a particular site of an RNA transcript if the polynucleotide agent promotes antisense inhibition of the target at that site. Such a polynucleotide agent will generally include at least about 15 contiguous nucleotides from one of the sequences provided in Tables 2-16 coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in the target gene.

While a target sequence is generally about 4-50 nucleotides in length, there is wide variation in the suitability of particular sequences in this range for directing antisense inhibition of any given target RNA. Various software packages and the guidelines set out herein provide guidance for the identification of optimal target sequences for any given gene target, but an empirical approach can also be taken in which a "window" or "mask" of a given size (as a non-limiting example, 20 nucleotides) is literally or figuratively (including, *e.g.*, *in silico*) placed on the target RNA sequence to identify sequences in the size range that can serve as target sequences. By moving the sequence "window" progressively one nucleotide upstream or downstream of an initial target sequence location, the next potential target sequence can be identified, until the complete set of possible sequences is identified for any given target size selected. This process, coupled with systematic synthesis and testing of the identified sequences (using assays as described herein or as known in the art) to identify those sequences that perform optimally can identify those RNA sequences that, when targeted with a polynucleotide agent, mediate the best inhibition of target gene expression. Thus, while the sequences identified, for example, in Tables 2-16, represent effective target sequences, it is contemplated that further optimization of antisense inhibition efficiency can be achieved by progressively "walking the

window" one nucleotide upstream or downstream of the given sequences to identify sequences with equal or better inhibition characteristics.

Further, it is contemplated that for any sequence identified, *e.g.*, in Tables 2-16, further optimization could be achieved by systematically either adding or removing nucleotides to generate longer or shorter sequences and testing those sequences generated by walking a window of the longer or shorter size up or down the target RNA from that point. Again, coupling this approach to generating new candidate targets with testing for effectiveness of polynucleotide agents based on those target sequences in an inhibition assay as known in the art and/or as described herein can lead to further improvements in the efficiency of inhibition. Further still, such optimized sequences can be adjusted by, *e.g.*, the introduction of modified nucleotides as described herein or as known in the art, addition or changes in length, or other modifications as known in the art and/or discussed herein to further optimize the molecule (*e.g.*, increasing serum stability or circulating half-life, increasing thermal stability, enhancing transmembrane delivery, targeting to a particular location or cell type, increasing interaction with silencing pathway enzymes, increasing release from endosomes) as an expression inhibitor.

i. Single Stranded Polynucleotide Agents Comprising Motifs

In certain embodiments of the invention, at least one of the contiguous nucleotides of the antisense polynucleotide agents of the invention may be a modified nucleotide. Suitable nucleotide modifications for use in the single stranded antisense polynucletiude agents of the invention are described in Section A(ii), above. In one embodiment, the modified nucleotide comprises one or more modified sugars. In other embodiments, the modified nucleotide comprises one or more modified nucleobases. In yet other embodiments, the modified nucleotide comprises one or more modified internucleoside linkages. In some embodiments, the modifications (sugar modifications, nucleobase modifications, and/or linkage modifications) define a pattern or motif. In one embodiment, the patterns of modifications of sugar moieties, internucleoside linkages, and nucleobases are each independent of one another.

Polynucleotide agents having modified oligonucleotides arranged in patterns, or motifs may, for example, confer to the agents properties such as enhanced inhibitory activity, increased binding affinity for a target nucleic acid, or resistance to degradation by *in vivo* nucleases. For example, such agents may contain at least one region modified so as to confer increased resistance to nuclease degradation, increased cellular uptake, increased binding affinity for the target nucleic acid, and/or increased inhibitory activity. A second region of such agents may optionally serve as a substrate for the cellular endonuclease RNase H, which cleaves the RNA strand of an RNA:DNA duplex.

An exemplary polynucleotide agent having modified oligonucleotides arranged in patterns, or motifs is a gapmer. In a "gapmer", an internal region or "gap" having a plurality of linked nucleotides that supports RNaseH cleavage is positioned between two external flanking regions or "wings" having a plurality of linked nucleotides that are chemically distinct from the linked nucleotides of the internal

region. The gap segment generally serves as the substrate for endonuclease cleavage, while the wing segments comprise modified nucleotides.

The three regions of a gapmer motif (the 5 '-wing, the gap, and the 3 '-wing) form a contiguous sequence of nucleotides and may be described as "X-Y-Z", wherein "X" represents the length of the 5-wing, "Y" represents the length of the gap, and "Z" represents the length of the 3'-wing. In one embodiment, a gapmer described as "X-Y-Z" has a configuration such that the gap segment is positioned immediately adjacent to each of the 5′ wing segment and the 3′ wing segment. Thus, no intervening nucleotides exist between the 5′ wing segment and gap segment, or the gap segment and the 3′ wing segment. Any of the compounds, *e.g.,* antisense compounds, described herein can have a gapmer motif. In some embodiments, X and Z are the same, in other embodiments they are different.

In certain embodiments, the regions of a gapmer are differentiated by the types of modified nucleotides in the region. The types of modified nucleotides that may be used to differentiate the regions of a gapmer, in some embodiments, include β-D-ribonucleotides, β-D-deoxyribonucleotides, 2′-modified nucleotides, *e.g.,* 2′-modified nucleotides (*e.g.,* 2′-MOE, and 2′-O—CH3), and bicyclic sugar modified nucleotides (*e.g.,* those having a 4′-(CH2)n-O-2′ bridge, where n=1 or n=2).
In one embodiment, at least some of the modified nucleotides of each of the wings may differ from at least some of the modified nucleotides of the gap. For example, at least some of the modified nucleotides of each wing that are closest to the gap (the 3 '-most nucleotide of the 5'-wing and the 5'-most nucleotide of the 3 -wing) differ from the modified nucleotides of the neighboring gap nucleotides, thus defining the boundary between the wings and the gap. In certain embodiments, the modified nucleotides within the gap are the same as one another. In certain embodiments, the gap includes one or more modified nucleotides that differ from the modified nucleotides of one or more other nucleotides of the gap.

The length of the 5'- wing (X) of a gapmer may be 1 to 6 nucleotides in length, *e.g.,* 2 to 6, 2 to 5, 3 to 6, 3 to 5, 1 to 5, 1 to 4, 1 to 3, 2 to 4 nucleotides in length, *e.g.,* 1, 2, 3, 4, 5, or 6 nucleotides in length.

The length of the 3'- wing (Z) of a gapmer may be 1 to 6 nucleotides in length, *e.g.,* 2 to 6, 2-5, 3 to 6, 3 to 5, 1 to 5, 1 to 4, 1 to 3, 2 to 4 nucleotides in length, *e.g.,* 1, 2, 3, 4, 5, or 6 nucleotides in length.

The length of the gap (Y) of a gapmer may be 5 to 14 nucleotides in length, *e.g.,* 5 to 13, 5 to 12, 5 to 11, 5 to 10, 5 to 9, 5 to 8, 5 to 7, 5 to 6, 6 to 14, 6 to 13, 6 to 12, 6 to 11, 6 to 10, 6 to 9, 6 to 8, 6 to 7, 7 to 14, 7 to 13, 7 to 12, 7 to 11, 7 to 10, 7 to 9, 7 to 8, 8 to 14, 8 to 13, 8 to 12, 8 to 11, 8 to 10, 8 to 9, 9 to 14, 9 to 13, 9 to 12, 9 to 11, 9 to 10, 10 to 14, 10 to 13, 10 to 12, 10 to 11, 11 to 14, 11 to 13, 11 to 12, 12 to 14, 12 to 13, or 13 to 14 nucleotides in length, *e.g.,* 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 nucleotides in length.

In some embodiments of the invention X consists of 2, 3, 4, 5 or 6 nucleotides, Y consists of 7, 8, 9, 10, 11, or 12 nucleotides, and Z consists of 2, 3, 4, 5 or 6 nucleotides. Such gapmers include

(X-Y-Z) 2-7-2, 2-7-3, 2-7-4, 2-7-5, 2-7-6, 3-7-2, 3-7-3, 3-7-4, 3-7-5, 3-7-6, 4-7-3, 4-7-4, 4-7-5, 4-7-6, 5-7-3, 5-7-4, 5-7-5, 5-7-6, 6-7-3, 6-7-4, 6-7-5, 6-7-6, 3-7-3, 3-7-4, 3-7-5, 3-7-6, 4-7-3, 4-7-4, 4-7-5, 4-7-6, 5-7-3, 5-7-4, 5-7-5, 5-7-6, 6-7-3, 6-7-4, 6-7-5, 6-7-6, 2-8-2, 2-8-3, 2-8-4, 2-8-5, 2-8-6, 3-8-2, 3-8-3, 3-8-4, 3-8-5, 3-8-6, 4-8-3, 4-8-4, 4-8-5, 4-8-6, 5-8-3, 5-8-4, 5-8-5, 5-8-6, 6-8-3, 6-8-4, 6-8-5, 6-8-6, 2-9-2, 2-9-3, 2-9-4, 2-9-5, 2-9-6, 3-9-2, 3-9-3, 3-9-4, 3-9-5, 3-9-6, 4-9-3, 4-9-4, 4-9-5, 4-9-6, 5-9-3, 5-9-4, 5-9-5, 5-9-6, 6-9-3, 6-9-4, 6-9-5, 6-9-6, 2-10-2, 2-10-3, 2-10-4, 2-10-5, 2-10-6, 3-10-2, 3-10-3, 3-10-4, 3-10-5, 3-10-6, 4-10-3, 4-10-4, 4-10-5, 4-10-6, 5-10-3, 5-10-4, 5-10-5, 5-10-6, 6-10-3, 6-10-4, 6-10-5, 6-10-6, 2-11-2, 2-11-3, 2-11-4, 2-11-5, 2-11-6, 3-11-2, 3-11-3, 3-11-4, 3-11-5, 3-11-6, 4-11-3, 4-11-4, 4-11-5, 4-11-6, 5-11-3, 5-11-4, 5-11-5, 5-11-6, 6-11-3, 6-11-4, 6-11-5, 6-11-6, 2-12-2, 2-12-3, 2-12-4, 2-12-5, 2-12-6, 3-12-2, 3-12-3, 3-12-4, 3-12-5, 3-12-6, 4-12-3, 4-12-4, 4-12-5, 4-12-6, 5-12-3, 5-12-4, 5-12-5, 5-12-6, 6-12-3, 6-12-4, 6-12-5, or 6-12-6.

In some embodiments of the invention, polynucleotide agents of the inventioninclude a 5-10-5 gapmer motif. In other embodiments of the invention, polynucleotide agents of the invention include a 4-10-4 gapmer motif. In another embodiment of the invention, polynucleotide agents of the invention include a 3-10-3 gapmer motif. In yet other embodiments of the invention, polynucleotide agents of the invention include a 2-10-2 gapmer motif.

The 5'- wing and/or 3'-wing of a gapmer may independently include 1-6 modified nucleotides, *e.g.,* 1, 2, 3, 4, 5, or 6 modified nucleotides.

In some embodiment, the 5'-wing of a gapmer includes at least one modified nucleotide. In one embodiment, the 5'- wing of a gapmer comprises at least two modified nucleotides. In another embodiment, the 5'- wing of a gapmer comprises at least three modified nucleotides. In yet another embodiment, the 5'- wing of a gapmer comprises at least four modified nucleotides. In another embodiment, the 5'- wing of a gapmer comprises at least five modified nucleotides. In certain embodiments, each nucleotide of the 5'-wing of a gapmer is a modified nucleotide.

In some embodiments, the 3'-wing of a gapmer includes at least one modified nucleotide. In one embodiment, the 3'- wing of a gapmer comprises at least two modified nucleotides. In another embodiment, the 3'- wing of a gapmer comprises at least three modified nucleotides. In yet another embodiment, the 3'- wing of a gapmer comprises at least four modified nucleotides. In another embodiment, the 3'- wing of a gapmer comprises at least five modified nucleotides. In certain embodiments, each nucleotide of the 3'-wing of a gapmer is a modified nucleotide.

In certain embodiments, the regions of a gapmer are differentiated by the types of sugar moieties of the nucleotides. In one embodiment, the nucleotides of each distinct region comprise uniform sugar moieties. In other embodiments, the nucleotides of each distinct region comprise different sugar moieties. In certain embodiments, the sugar nucleotide modification motifs of the two wings are the same as one another. In certain embodiments, the sugar nucleotide modification motifs of the 5'-wing differs from the sugar nucleotide modification motif of the 3'-wing.

The 5'-wing of a gapmer may include 1-6 modified nucleotides, *e.g.,* 1, 2, 3, 4, 5, or 6 modified nucleotides.

In one embodiment, at least one modified nucleotide of the 5'-wing of a gapmer is a bicyclic nucleotide, such as a constrained ethyl nucleotide, or an LNA. In another embodiment, the 5'-wing of a gapmer includes 2, 3, 4, or 5 bicyclic nucleotides. In some embodiments, each nucleotide of the 5'- wing of a gapmer is a bicyclic nucleotide.

In one embodiment, the 5'-wing of a gapmer includes at least 1, 2, 3, 4, or 5 constrained ethyl nucleotides. In some embodiments, each nucleotide of the 5'- wing of a gapmer is a constrained ethyl nucleotide.

In one embodiment, the 5'-wing of a gapmer comprises at least one LNA nucleotide. In another embodiment, the 5'-wing of a gapmer includes 2, 3, 4, or 5 LNA nucleotides. In other embodiments, each nucleotide of the 5'- wing of a gapmer is an LNA nucleotide.

In certain embodiments, at least one modified nucleotide of the 5'- wing of a gapmer is a non-bicyclic modified nucleotide, *e.g.,* a 2 '-substituted nucleotide. A "2 '-substituted nucleotide" is a nucleotide comprising a modification at the 2'-position which is other than H or OH, such as a 2'-OMe nucleotide, or a 2'-MOE nucleotide. In one embodiment, the 5'-wing of a gapmer comprises 2, 3, 4, or 5 2 '-substituted nucleotides. In one embodiment, each nucleotide of the 5'-wing of a gapmer is a 2 '-substituted nucleotide.

In one embodiment, the 5'- wing of a gapmer comprises at least one 2'-OMe nucleotide. In one embodiment, the 5'- wing of a gapmer comprises at least 2, 3, 4, or 5 2'-OMe nucleotides. In one embodiment, each of the nucleotides of the 5'- wing of a gapmer comprises a 2'-OMe nucleotide.

In one embodiment, the 5'- wing of a gapmer comprises at least one 2'- MOE nucleotide. In one embodiment, the 5'- wing of a gapmer comprises at least 2, 3, 4, or 5 2'- MOE nucleotides. In one embodiment, each of the nucleotides of the 5'- wing of a gapmer comprises a 2'- MOE nucleotide.

In certain embodiments, the 5'- wing of a gapmer comprises at least one 2'-deoxynucleotide. In certain embodiments, each nucleotide of the 5'- wing of a gapmer is a 2'-deoxynucleotide. In a certain embodiments, the 5'- wing of a gapmer comprises at least one ribonucleotide. In certain embodiments, each nucleotide of the 5'- wing of a gapmer is a ribonucleotide.

The 3'-wing of a gapmer may include 1-6 modified nucleotides, *e.g.,* 1, 2, 3, 4, 5, or 6 modified nucleotides.

In one embodiment, at least one modified nucleotide of the 3'-wing of a gapmer is a bicyclic nucleotide, such as a constrained ethyl nucleotide, or an LNA. In another embodiment, the 3'-wing of a gapmer includes 2, 3, 4, or 5 bicyclic nucleotides. In some embodiments, each nucleotide of the 3'-wing of a gapmer is a bicyclic nucleotide.

In one embodiment, the 3'-wing of a gapmer includes at least one constrained ethyl nucleotide. In another embodiment, the 3'-wing of a gapmer includes 2, 3, 4, or 5 constrained ethyl nucleotides. In some embodiments, each nucleotide of the 3'-wing of a gapmer is a constrained ethyl nucleotide.

In one embodiment, the 3'-wing of a gapmer comprises at least one LNA nucleotide. In another embodiment, the 3'-wing of a gapmer includes 2, 3, 4, or 5 LNA nucleotides. In other embodiments, each nucleotide of the 3'-wing of a gapmer is an LNA nucleotide.

In certain embodiments, at least one modified nucleotide of the 3'-wing of a gapmer is a non-bicyclic modified nucleotide, *e.g.*, a 2 '-substituted nucleotide. In one embodiment, the 3'-wing of a gapmer comprises 2, 3, 4, or 5 2 '-substituted nucleotides. In one embodiment, each nucleotide of the 3'-wing of a gapmer is a 2 '-substituted nucleotide.

In one embodiment, the 3'-wing of a gapmer comprises at least one 2'-OMe nucleotide. In one embodiment, the 3'-wing of a gapmer comprises at least 2, 3, 4, or 5 2'-OMe nucleotides. In one embodiment, each of the nucleotides of the 3'-wing of a gapmer comprises a 2'-OMe nucleotide. In one embodiment, the 3'-wing of a gapmer comprises at least one 2'- MOE nucleotide. In one embodiment, the 3'-wing of a gapmer comprises at least 2, 3, 4, or 5 2'- MOE nucleotides. In one embodiment, each of the nucleotides of the 3'-wing of a gapmer comprises a 2'- MOE nucleotide. In certain embodiments, the 3'-wing of a gapmer comprises at least one 2'-deoxynucleotide. In certain embodiments, each nucleotide of the 3'-wing of a gapmer is a 2'-deoxynucleotide. In a certain embodiments, the 3'-wing of a gapmer comprises at least one ribonucleotide. In certain embodiments, each nucleotide of the 3'-wing of a gapmer is a ribonucleotide.

The gap of a gapmer may include 5-14 modified nucleotides, *e.g.*, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 modified nucleotides.

In one embodiment, the gap of a gapmer comprises at least one 5-methylcytosine. In one embodiment, the gap of a gapmer comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 5-methylcytosines. In one embodiment, all of the nucleotides of the the gap of a gapmer are 5-methylcytosines.

In one embodiment, the gap of a gapmer comprises at least one 2'-deoxynucleotide. In one embodiment, the gap of a gapmer comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 2'-deoxynucleotides. In one embodiment, all of the nucleotides of the the gap of a gapmer are 2'-deoxynucleotides.

A gapmer may include one or more modified internucleotide linkages. In some embodiments, a gapmer includes one or more phosphodiester internucleotide linkages. In other embodiments, a gapmer includes one or more phosphorothioate internucleotide linkages.

In one embodiment, each nucleotide of a 5'-wing of a gapmer are linked *via* a phosphorothioate internucleotide linkage. In another embodiment, each nucleotide of a 3'-wing of a gapmer are linked *via* a phosphorothioate internucleotide linkage. In yet another embodiment, each nucleotide of a gap segment of a gapmer is linked *via* a phosphorothioate internucleotide linkage. In one embodiment, all of the nucleotides in a gapmer are linked *via* phosphorothioate internucleotide linkages.

In one embodiment, a polynucleotide agent comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising five nucleotides and a 3’-wing segment comprising 5 nucleotides.

In another embodiment, a polynucleotide agent comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising four nucleotides and a 3’-wing segment comprising four nucleotides.

In another embodiment, a polynucleotide agent comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising three nucleotides and a 3’-wing segment comprising three nucleotides.

In another embodiment, a polynucleotide agent comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising two nucleotides and a 3’-wing segment comprising two nucleotides.

In one embodiment, each nucleotide of a 5-wing flanking a gap segment of 10 2′-deoxyribonucleotides comprises a modified nucleotide. In another embodiment, each nucleotide of a 3-wing flanking a gap segment of 10 2′-deoxyribonucleotides comprises a modified nucleotide. In one embodiment, each of the modified 5’-wing nucleotides and each of the modified 3’-wing nucleotides comprise a 2′-sugar modification. In one embodiment, the 2′-sugar modification is a 2’-OMe modification. In another embodiment, the 2′-sugar modification is a 2’-MOE modification. In one embodiment, each of the modified 5’-wing nucleotides and each of the modified 3’-wing nucleotides comprise a bicyclic nucleotide. In one embodiment, the bicyclic nucleotide is a constrained ethyl nucleotide. In another embodiment, the bicyclic nucleotide is an LNA nucleotide.

In one embodiment, each cytosine in a polynucleotide agent is a 5-methylcytosine.

In one embodiment, a polynucleotide agent comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising five nucleotides comprising a 2’OMe modification and a 3’-wing segment comprising five nucleotides comprising a 2’OMe modification, wherein each internucleotde linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine. In one embodiment, the agent further comprises a ligand.

In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising five nucleotides comprising a 2’MOE modification and a 3’-wing segment comprising five nucleotides comprising a 2’MOE modification, wherein each internucleotide linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine. In one embodiment, the agent further comprises a ligand.

In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising five constrained ethyl nucleotides and a 3’-wing segment comprising five constrained

ethyl nucleotides, wherein each internucleoitde linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine.

In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising five LNA nucleotides and a 3’-wing segment comprising five LNA nucleotides, wherein each internucleotide linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine.

In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising four nucleotides comprising a 2’OMe modification and a 3’-wing segment comprising four nucleotides comprising a 2’OMe modification, wherein each internucleotde linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine. In one embodiment, a polynucleotide agent tof the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising four nucleotides comprising a 2’MOE modification and a 3’-wing segment comprising four nucleotides comprising a 2’MOE modification, wherein each internucleotide linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine. In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising four constrained ethyl nucleotides and a 3’-wing segment comprising four constrained ethyl nucleotides, wherein each internucleoitde linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine.

In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising four LNA nucleotides and a 3’-wing segment comprising four LNA nucleotides, wherein each internucleotide linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine.

In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising three nucleotides comprising a 2’OMe modification and a 3’-wing segment comprising three nucleotides comprising a 2’OMe modification, wherein each internucleotde linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine.

In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5’-wing segment comprising three nucleotides comprising a 2’MOE modification and a 3’-wing segment comprising three nucleotides comprising a 2’MOE modification, wherein each internucleotide linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine.

In one embodiment, a polynucleotide agent of the inventioncomprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5'-wing segment comprising three constrained ethyl nucleotides and a 3'-wing segment comprising three constrained ethyl nucleotides, wherein each internucleoitde linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine.

In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5'-wing segment comprising three LNA nucleotides and a 3'-wing segment comprising three LNA nucleotides, wherein each internucleotide linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine.

In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5'-wing segment comprising two nucleotides comprising a 2'OMe modification and a 3'-wing segment comprising two nucleotides comprising a 2'OMe modification, wherein each internucleotde linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine. In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5'-wing segment comprising two nucleotides comprising a 2'MOE modification and a 3'-wing segment comprising two nucleotides comprising a 2'MOE modification, wherein each internucleotide linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine.

In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5'-wing segment comprising two constrained ethyl nucleotides and a 3'-wing segment comprising two constrained ethyl nucleotides, wherein each internucleoitde linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine.

In one embodiment, a polynucleotide agent of the invention comprises a gap segment of ten 2′-deoxyribonucleotides positioned immediately adjacent to and between a 5'-wing segment comprising two LNA nucleotides and a 3'-wing segment comprising two LNA nucleotides, wherein each internucleotide linkage of the agent is a phosphorothioate linkage. In one embodiment, each cytosine of the agent is a 5-methylcytosine.

Further gapmer designs suitable for use in the agents, compositions, and methods of the invention are disclosed in, for example, U.S. Patent Nos. 7,687,617 and 8,580,756; U.S. Patent Publication Nos. 20060128646, 20090209748, 20140128586, 20140128591, 20100210712, and 20080015162A1; and International Publication No. WO 2013/159108, the entire content of each of which are incorporated herein by reference.

C. Nucleic Acid Inhibitors Conjugated to Ligands

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

In embodiments in which a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1 are covalently attached (*i.e.*, a dual targeting RNAi agent described herein), one or both of the dsRNA agents may independently comprise one or more ligands.

In one embodiment, a ligand alters the distribution, targeting or lifetime of a nucleic acid inhibitor into which it is incorporated. In certain 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 will not take part in duplex pairing in a duplexed nucleic acid.

Ligands can include a naturally occurring substance, such as a protein (*e.g.*, human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (*e.g.*, a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin, N-acetylglucosamine, N-acetylgalactosamine or hyaluronic acid); or a lipid. The ligand can also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.*, a synthetic polyamino acid. Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine,

arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

Ligands can also include targeting groups, *e.g.*, a cell or tissue targeting agent, *e.g.*, a lectin, glycoprotein, lipid or protein, *e.g.*, an antibody, that binds to a specified cell type such as a kidney cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine 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.

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-gulucosamine 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 nucleic acid inhibitor into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.*, by disrupting the cell's microtubules, microfilaments, and/or intermediate filaments. The drug can be, for example, taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin.

In some embodiments, a ligand attached to a nucleic acid inhibitor as described herein acts as a pharmacokinetic modulator (PK modulator). PK modulators include lipophiles, bile acids, steroids, phospholipid analogues, peptides, protein binding agents, PEG, vitamins *etc.* Exemplary PK modulators include, but are not limited to, cholesterol, fatty acids, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, phospholipids, sphingolipids, naproxen, ibuprofen, vitamin E,

biotin *etc*. Oligonucleotides that comprise a number of phosphorothioate linkages are also known to bind to serum protein, thus short oligonucleotides, *e.g.*, oligonucleotides of about 5 bases, 10 bases, 15 bases or 20 bases, comprising multiple of phosphorothioate linkages in the backbone are also amenable to the present invention as ligands (*e.g.* as PK modulating ligands). In addition, aptamers that bind serum components (*e.g.* serum proteins) are also suitable for use as PK modulating ligands in the embodiments described herein.

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

The oligonucleotides used in the conjugates of the present invention may be conveniently and routinely made through the well-known technique of solid-phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). Any other means 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 oligonucleotides and ligand-molecule bearing sequence-specific linked nucleosides of the present invention, the oligonucleotides and oligonucleosides may be assembled on a suitable DNA synthesizer utilizing standard nucleotide or nucleoside precursors, or nucleotide or nucleoside conjugate precursors that already bear the linking moiety, ligand-nucleotide or nucleoside-conjugate precursors that already bear the ligand molecule, or non-nucleoside ligand-bearing building blocks.

When using nucleotide-conjugate precursors that already bear a linking moiety, the synthesis of the sequence-specific linked nucleosides is typically completed, and the ligand molecule is then reacted with the linking moiety to form the ligand-conjugated oligonucleotide. In some embodiments, the oligonucleotides or linked nucleosides of the present invention are synthesized by an automated synthesizer using phosphoramidites derived from ligand-nucleoside conjugates in addition to the standard phosphoramidites and non-standard phosphoramidites that are commercially available and routinely used in oligonucleotide synthesis.

i. Lipid Conujugates

In one embodiment, the ligand or conjugate is a lipid or lipid-based molecule. In one embodiment, such a lipid or lipid-based molecule binds a serum protein, *e.g.*, human serum albumin (HSA). An HSA binding ligand allows for distribution of the conjugate to a target tissue, *e.g.*, a non-kidney target tissue of the body. For example, the target tissue can be the liver, including parenchymal cells of the liver. Other molecules that can bind HSA can also be used as ligands. For example, neproxin 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, and/or (c) can be used to adjust binding to a serum protein, *e.g.*, HSA.

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

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

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

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

ii. 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 antennopedia. 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 some embodiments, the helical agent is an alpha-helical agent, which may have 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 nucleic acid inhibitors can affect pharmacokinetic distribution of the nucleic acid inhibitor, 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.

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 AAVALLPAVLLALLAP (SEQ ID NO: 4154). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO: 4151) 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: 4152) and the Drosophila Antennapedia protein (RQIKIWFQNRRMKWKK (SEQ ID NO: 4153) 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 nucleic acid inhibitor via an incorporated monomer unit for cell targeting purposes is an arginine-glycine-aspartic acid (RGD)-peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.

An RGD peptide for use in the compositions and methods of the invention may be linear or cyclic, and may be modified, *e.g.,* glyciosylated or methylated, to facilitate targeting to a specific tissue(s). RGD-containing peptides and peptidiomimemtics 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. Exemplary conjugates of this ligand target PECAM-1 or VEGF.

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, a 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 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).

iii. Carbohydrate Conjugates

In some embodiments of the compositions and methods of the invention, a nucleic acid inhibitor further comprises a carbohydrate. The carbohydrate conjugated nucleic acid inhibitors are 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 embodiments in which a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1 are covalently attached (*i.e.*, a dual targetingRNAi agent), one or both of the dsRNA agents may independently comprise one or more carbohydrate ligands.

In one embodiment, a carbohydrate conjugate for use in the compositions and In certain embodiments, a carbohydrate conjugate comprises 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 nucleic acid inhibitor to particular cells. In some embodiments, the GalNAc conjugate targets the nucleic acid inhibitor 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 nucleic acid inhibitor (*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 nucleic acid inhibitor (*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 a nucleic acid inhibitor of the invention via a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to a nucleic acid inhibitor of the invention via a bivalent linker. In yet other embodiments of the invention, the GalNAc or GalNAc derivative is attached to a nucleic acid inhibitor of the invention via a trivalent linker. In other embodiments of the invention, the GalNAc or GalNAc derivative is attached to a nucleic acid inhibitor of the invention via a tetravalent linker.

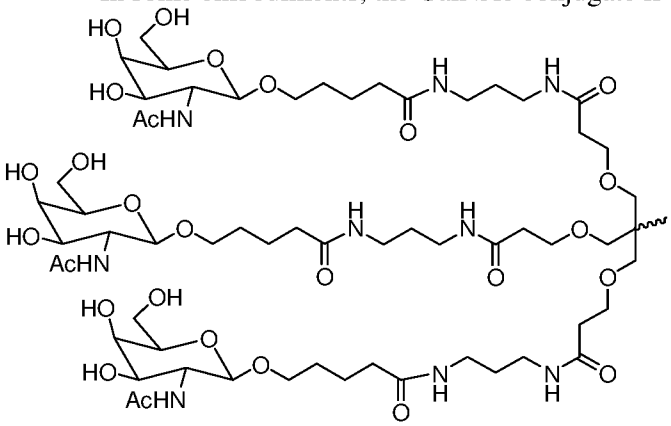
In certain embodiments, the nucleic acid inhibitors of the invention comprise one GalNAc or GalNAc derivative attached to the nucleic acid inhibitor. In certain embodiments, the nucleic acid inhibitors of the invention comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently attached to a plurality of nucleotides of the nucleic acid inhibitor through a plurality of monovalent linkers.

In some embodiments, for example, when two strands of a nucleic acid inhibitor 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.

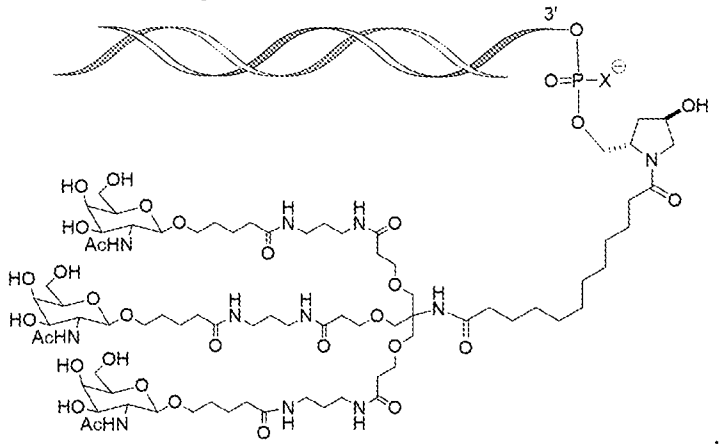
In some embodiments, for example, when the two strands of a nucleic acid inhibitor of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality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

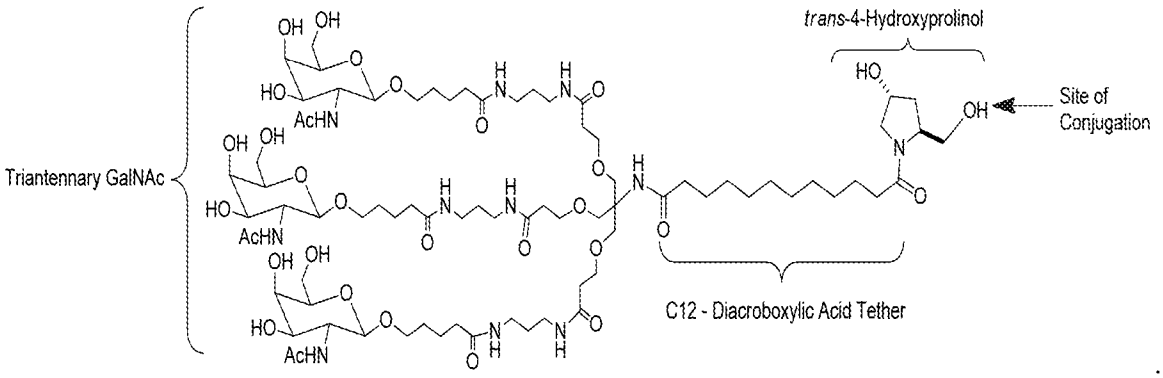


Formula II.

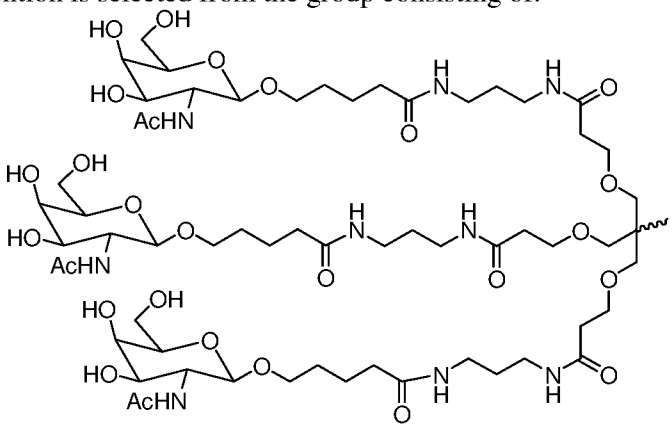
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate via a linker as shown in the following schematic, wherein X is O or S



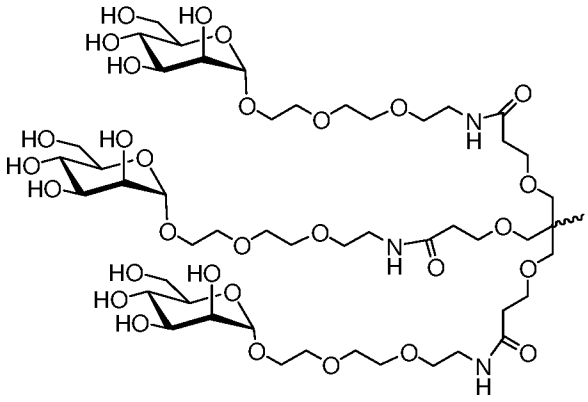
In some embodiments, the RNAi agent is conjugated to L96 as defined in Table 1 and shown below:



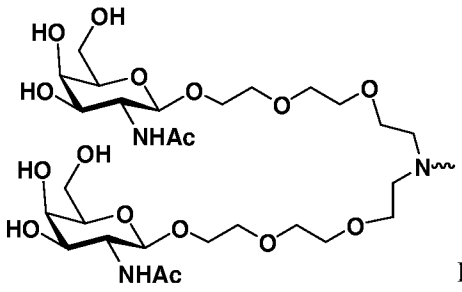
In certain embodiments, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



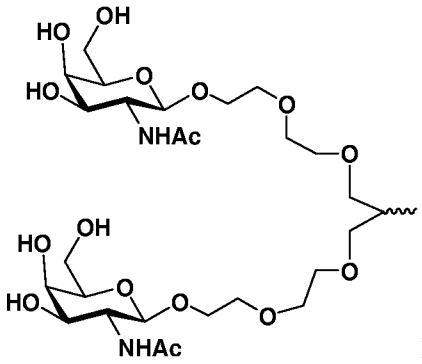
Formula II,



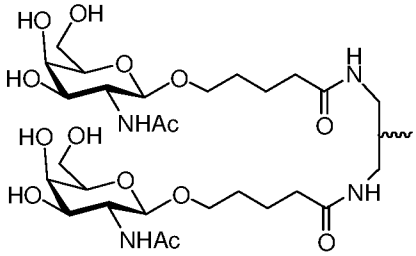
Formula III,



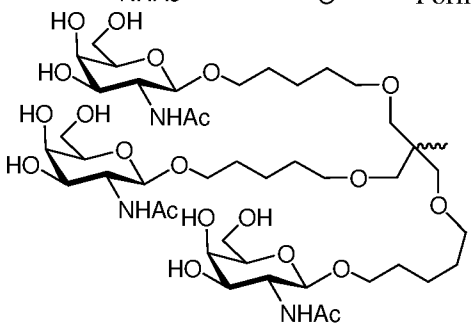
Formula IV,



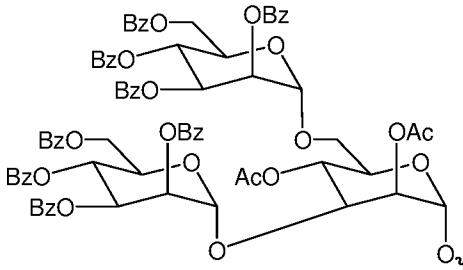
Formula V,



Formula VI,



Formula VII,



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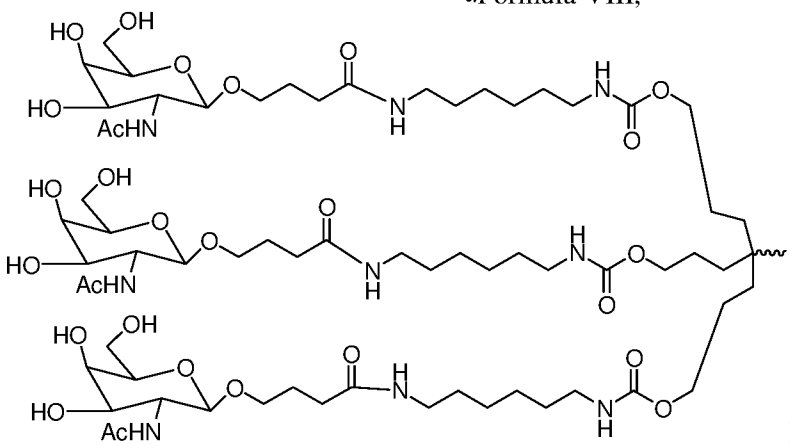

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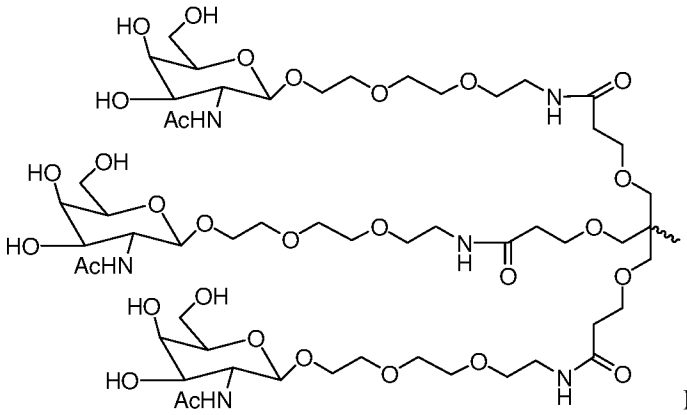
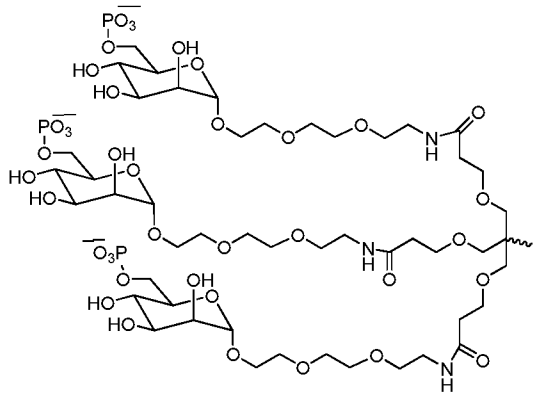


Formula X,



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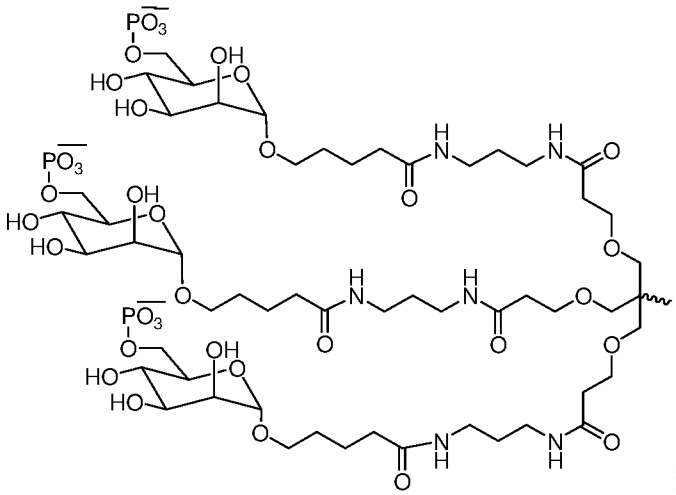

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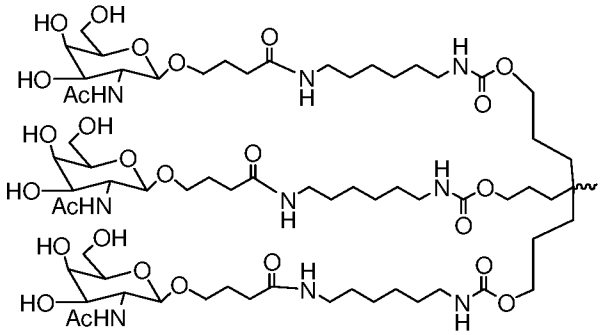

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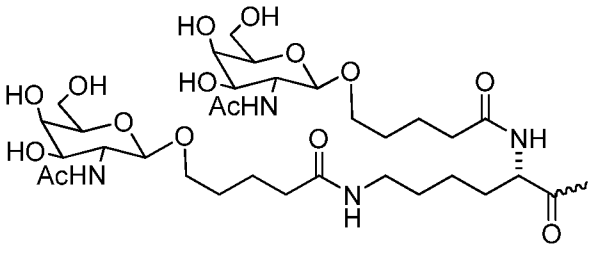

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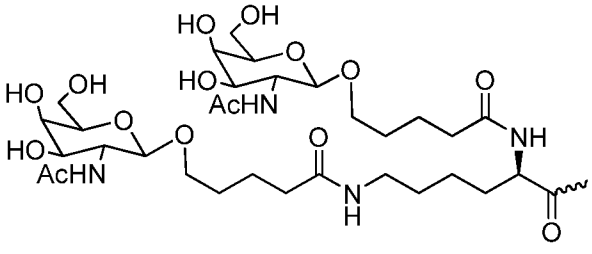

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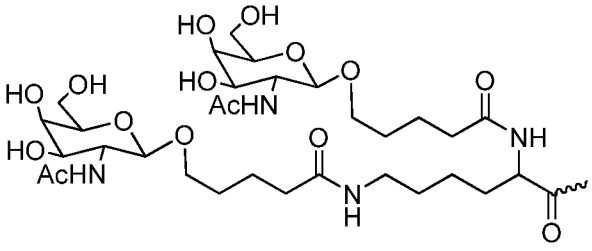
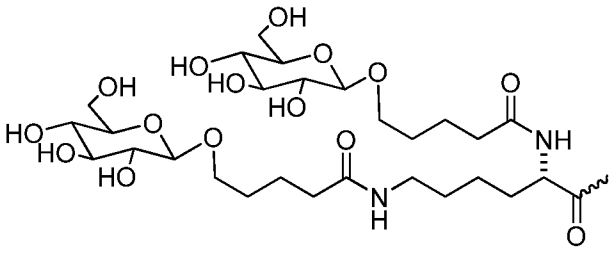
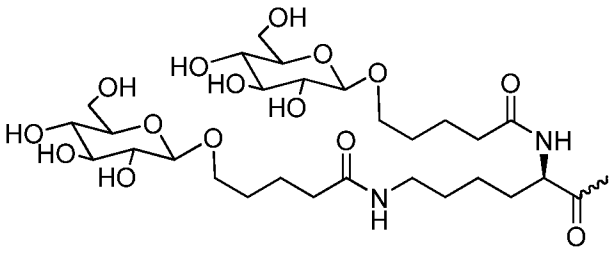


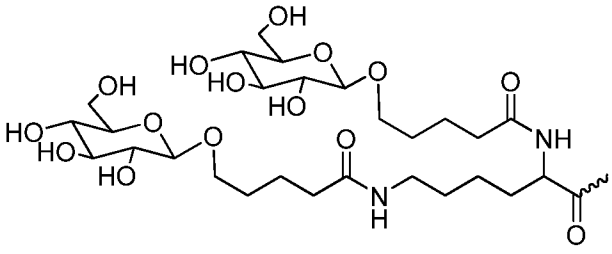
Formula XVI,



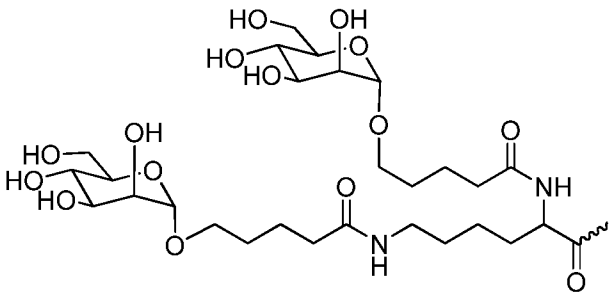
Formula XVII,



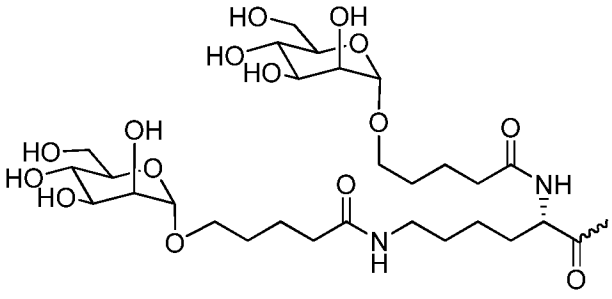
Formula XVIII,



Formula XIX,



Formula XX,



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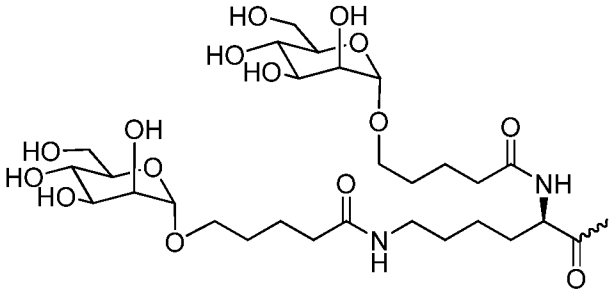
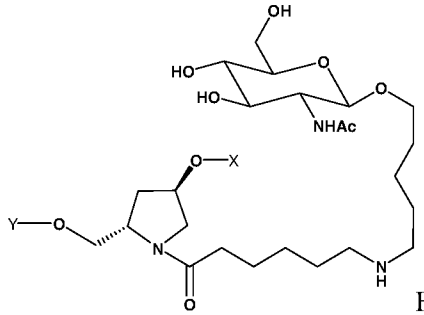
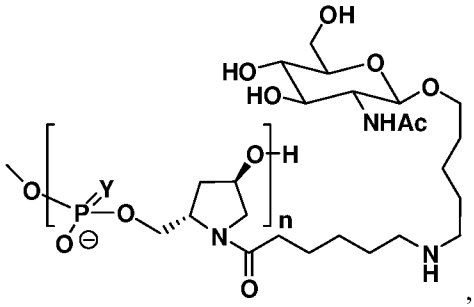


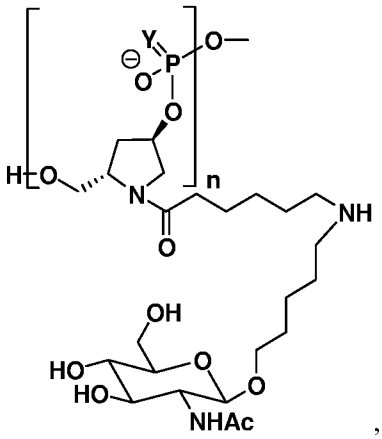
Formula XXII,



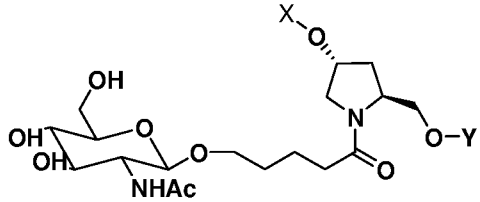
Formula XXIII;



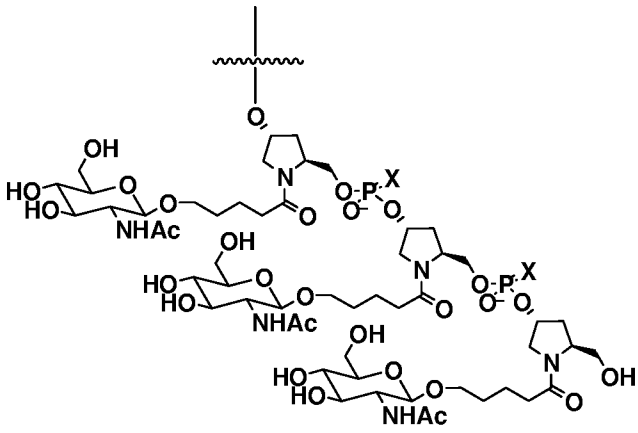
, wherein Y is O or S and n is 3 -6 (Formula XXIV);



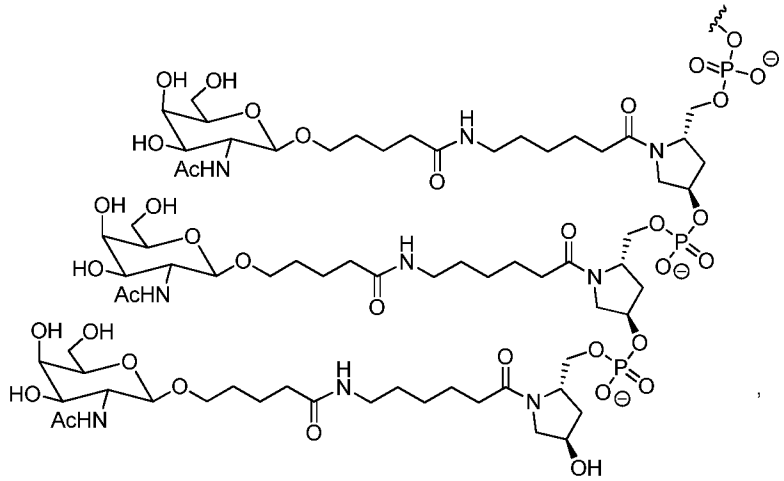
, wherein Y is O or S and n is 3-6 (Formula XXV);



Formula XXVI;



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



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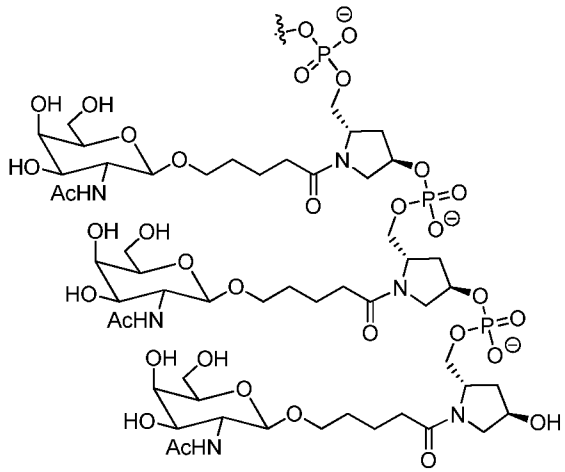
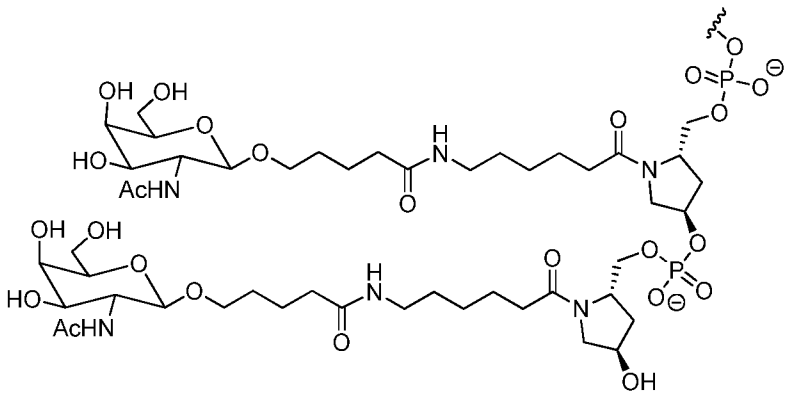


Formula XXVII; Formula XXIX;



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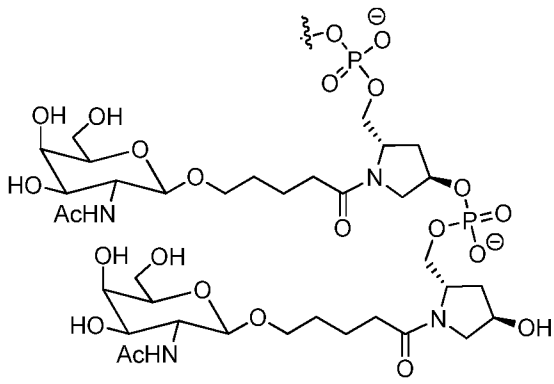
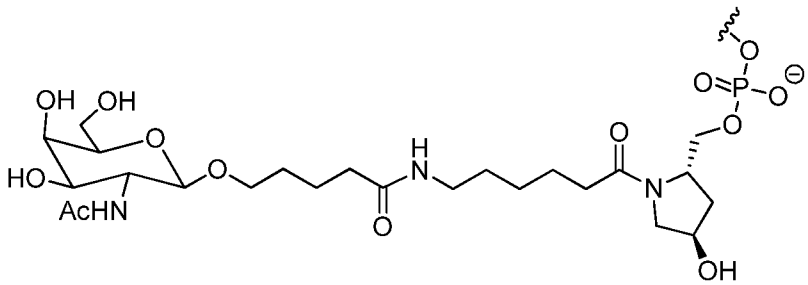


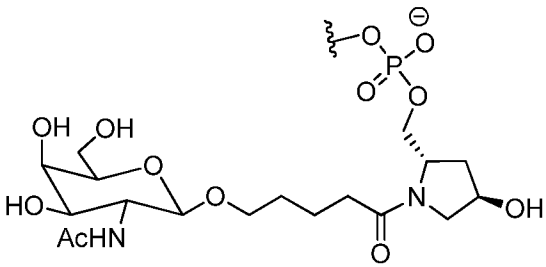
,

Formula XXX;

Formula XXXI;



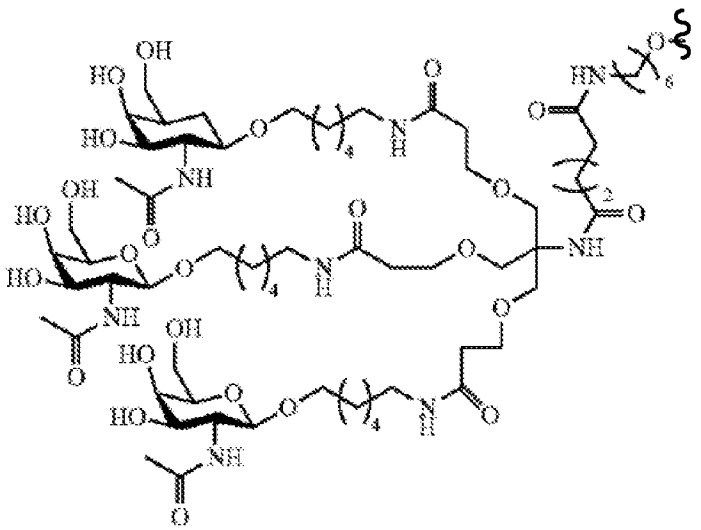
, and



.

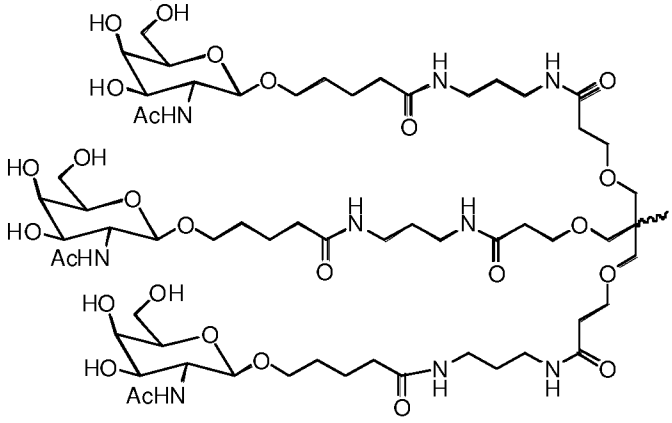
Formula XXXII;

Formula XXXIII.



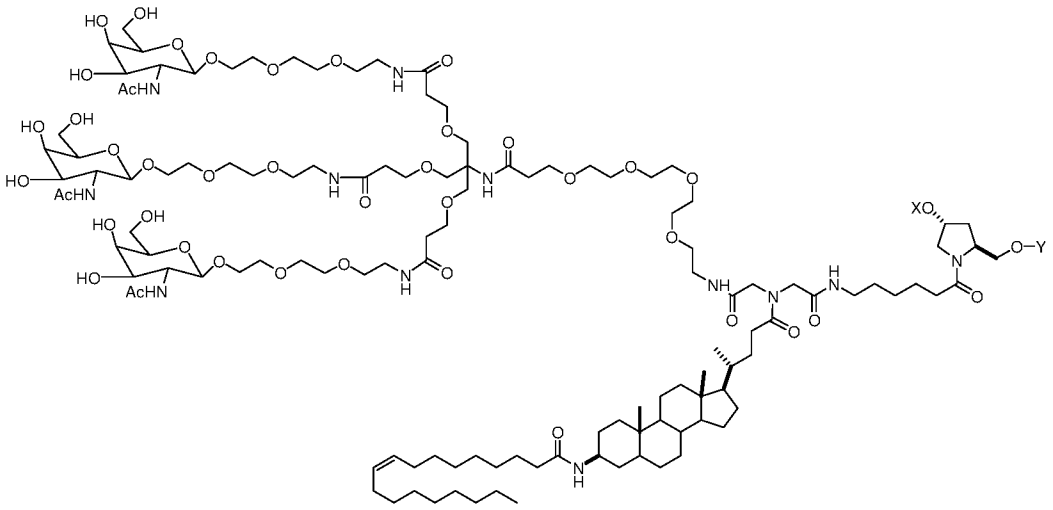
Formula XXXIV.

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, such as



Formula II.

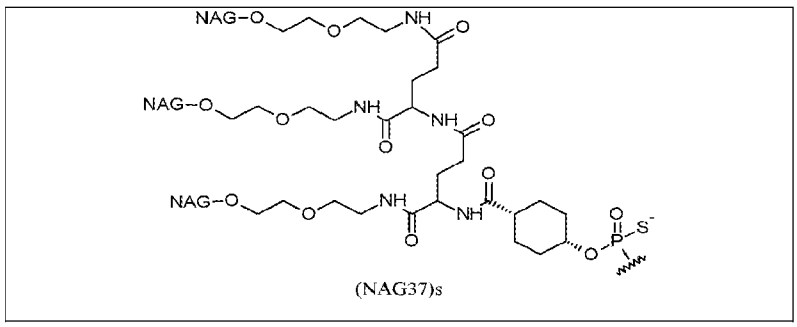
Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,



(Formula XXXVI),

when one of X or Y is an oligonucleotide, the other is a hydrogen.

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



In certain embodiments, the nucleic acid inhibitors of the disclosure may include GalNAc ligands, even if such GalNAc ligands are currently projected to be of limited value for the intrathecal/CNS delivery route(s) of the instant disclosure.

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 WO 2014/179620 and WO 2014/179627, the entire contents of each of which are incorporated herein by reference.

In embodiments in which a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1 are covalently attached (*i.e.*, a dual targetingRNAi agent), one or both of the dsRNA agents may independently comprise a GalNAc or GalNAc derivative ligand.

iv. Linkers

In some embodiments, the conjugate or ligand described herein can be attached to a nucleic acid inhibitor with various linkers that can be cleavable or non cleavable.

The term "linker" or “linking group” means an organic moiety that connects two parts of a compound, *e.g.,* covalently attaches two parts of a compound. Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR8, C(O), C(O)NH, SO, SO_2, SO_2NH 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, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclylalkyl, alkylheterocyclylalkenyl, alkylhererocyclylalkynyl, alkenylheterocyclylalkyl, alkenylheterocyclylalkenyl, alkenylheterocyclylalkynyl, alkynylheterocyclylalkyl, alkynylheterocyclylalkenyl, alkynylheterocyclylalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylhereroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO_2, N(R8), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R8 is hydrogen, acyl, aliphatic or substituted aliphatic. In one embodiment, the linker is between about 1-24 atoms, 2-24, 3-24, 4-24, 5-24, 6-24, 6-18, 7-18, 8-18 atoms, 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 one embodiment, the cleavable linking group is cleaved at least about 10 times, 20, times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times or more, or at least about 100 times faster in a target cell or under a first reference condition (which can, *e.g.*, be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, *e.g.*, be selected to mimic or represent conditions found in the blood or serum).

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

A cleavable linkage group, such as a disulfide bond can be susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic

pH at around 5.0. Some linkers will have a cleavable linking group that is cleaved at a certain 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 about 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).

a. Redox cleavable linking groups

In one embodment, 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 nucleic acid inhibitor 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 know 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.

b. 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.

c. Acid cleavable linking groups

In another embodiment, a cleavable linker comprises an acid cleavable linking group. An *a*cid cleavable linking group is a linking group that is cleaved under acidic conditions. In one 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, 5.75, 5.5, 5.25, 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.

d. Ester-based linking groups

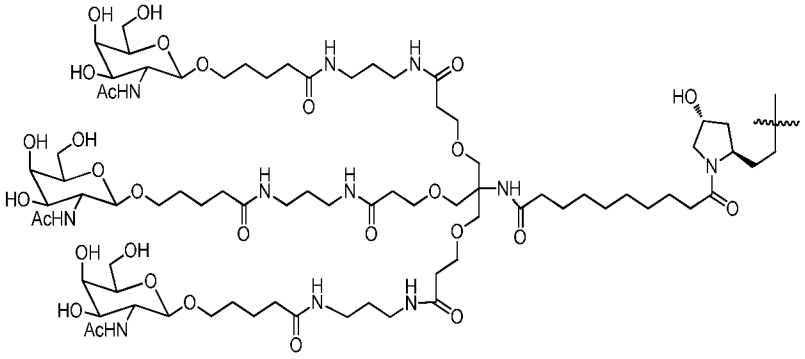
In another embodiment, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include but are not limited to esters of alkylene, alkenylene 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.

e. Peptide-based cleaving groups

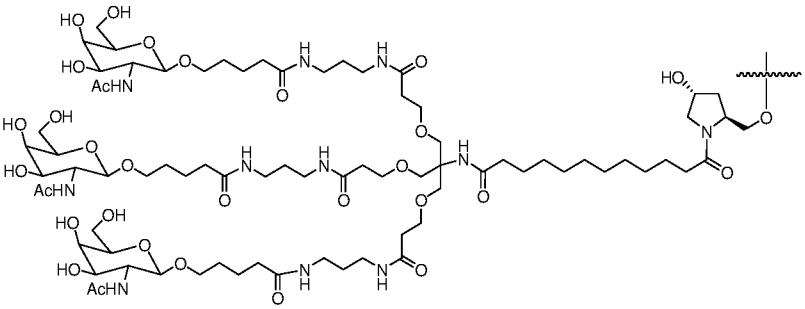
In yet another embodiment, a cleavable linker comprises a peptide-based cleavable linking group. A peptide-based cleavable linking group is cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (*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 alkynelene. 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.

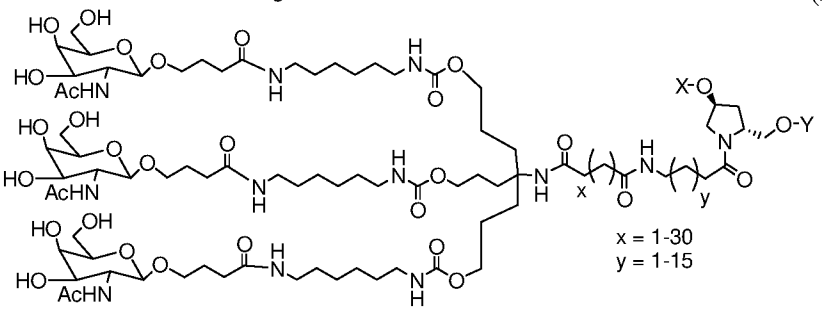
In one embodiment, a nucleic acid inhibitor of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



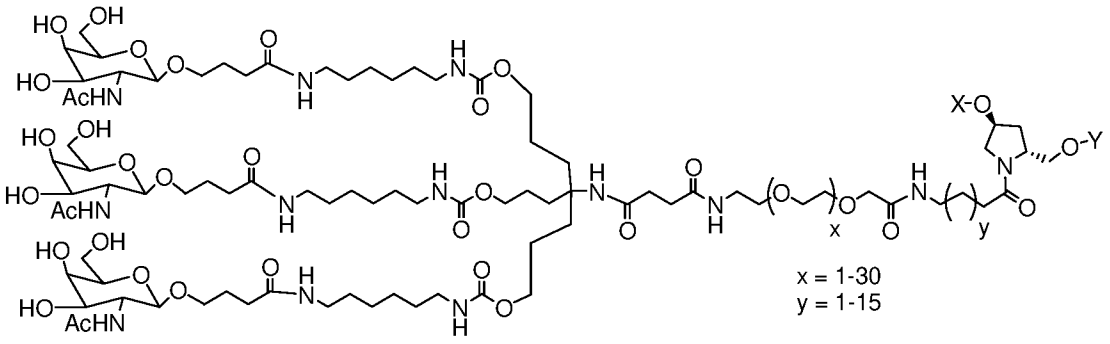
(Formula XXXVII),



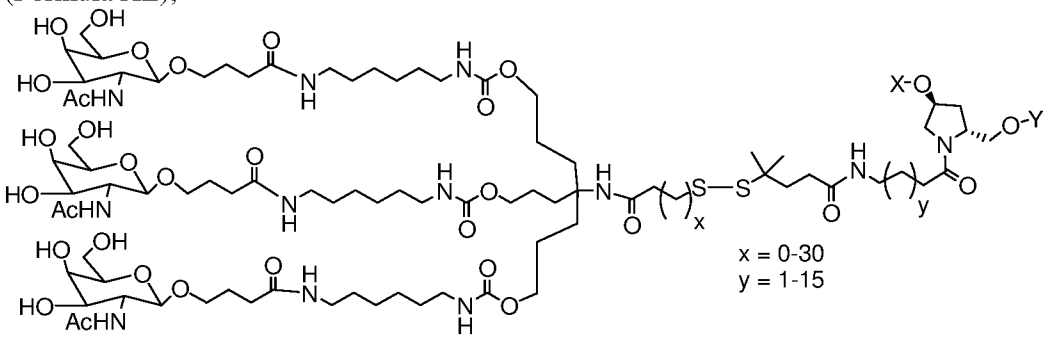
(Formula XXXVIII),



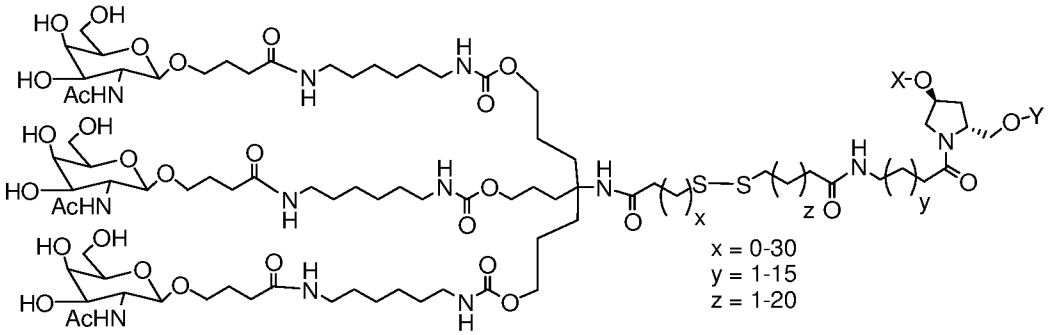
(Formula XXXIX),



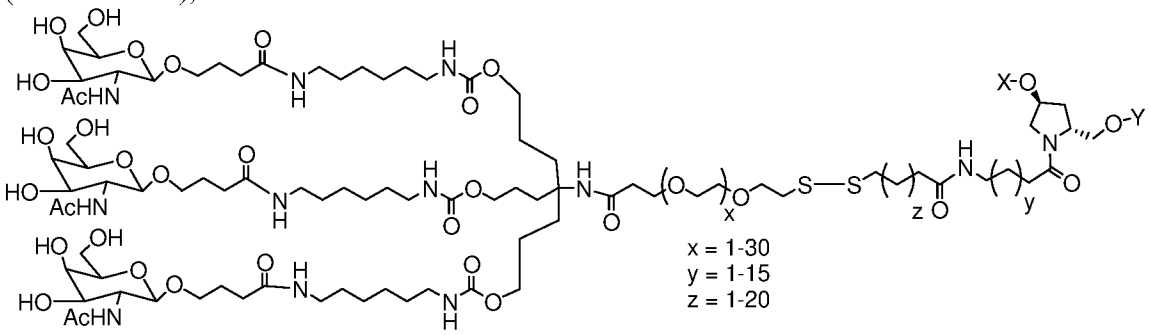
(Formula XL),



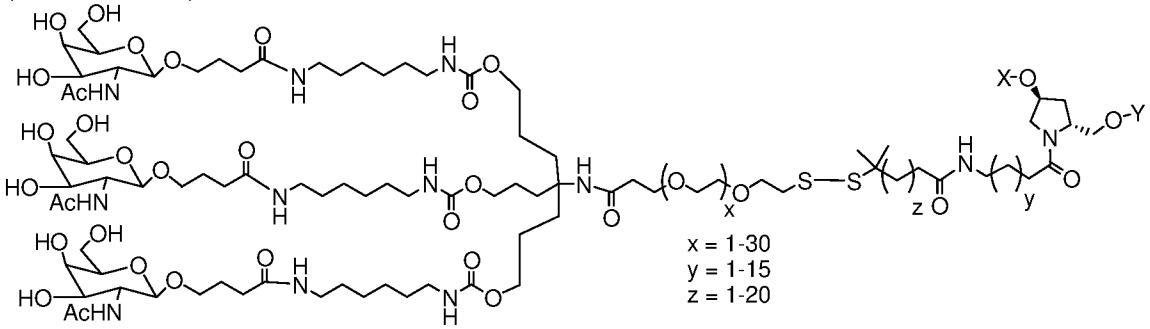
(Formula XLI),



(Formula XLII),



(Formula XLIII), and



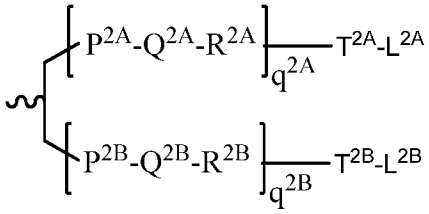
(Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

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.

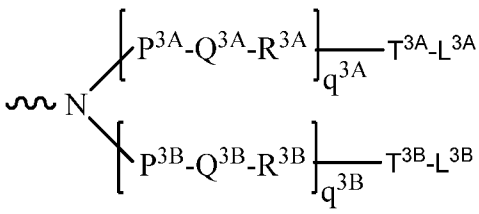
In embodiments in which a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1 are covalently attached (*i.e.*, a dual targetingRNAi agent), one or both of the dsRNA agents may independently a ligand comprising one or more GalNAc (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

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

Formula XLV



Formula XLVI



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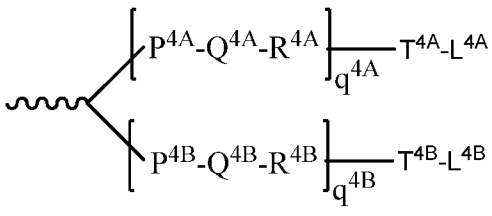
Formula XLVII



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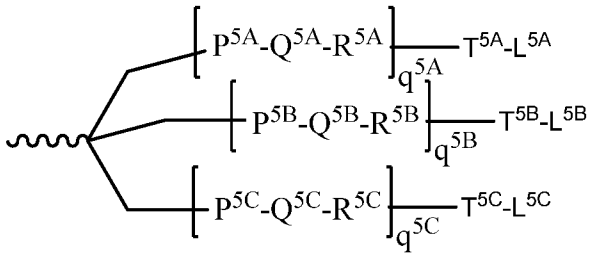
Formula XLVIII



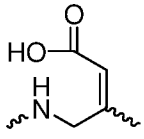
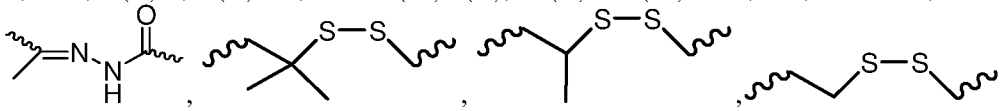
;

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;

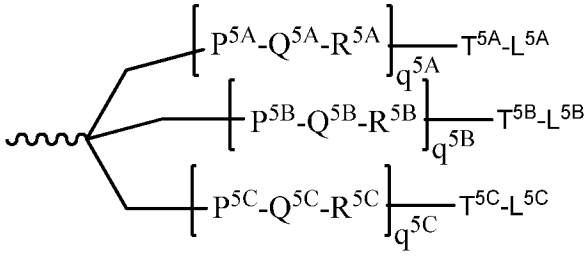
P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{4A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2, CH_2NH or CH_2O;

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 wherin one or more methylenes can be interrupted or terminated by one or more of O, S, S(O), SO_2, $N(R^N)$, 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, S, CH_2, C(O)O, C(O)NH, NHCH(R^a)C(O), -C(O)-CH(R^a)-NH-, CO, CH=N-O,  ,  , or heterocyclyl;

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; andR^a is H or amino acid side chain.Trivalent conjugating GalNAc derivatives are particularly useful for use with RNAi agents for inhibiting the expression of a target gene, such as those of formula (XLIX):

Formula XLIX



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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.

Representative U.S. patents that teach the preparation of conjugates include, but are not limited to, U.S. Pat. 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 and 5,688,941; 6,294,664; 6,320,017; 6,576,752; 6,783,931; 6,900,297; 7,037,646; 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 a nucleic acid inhibitor. The present invention also includesnucleic acid inhibitors that are chimeric compounds.

"Chimeric" iRNA compounds or "chimeras," in the context of this invention, are nucleic acid inhibitors which 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 nucleic acid inhibitors typically contain at least one region wherein the RNA is modified so as to confer upon the nucleic acid inhibitor increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. An additional region of the nucleic acid inhibitor 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 a nucleic acid inhibitor 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. Let., 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 an 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.

III. Delivery of a Nucleic Acid Inhibitor of the Invention

The delivery of a nucleic acid inhibitor 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 having or at risk of developing a non-primary hyperoxaluria disease or disorder) can be achieved in a number of different ways. For example, delivery may be performed by contacting a cell with a nucleic acid inhibitor of the invention either *in vitro* or *in vivo*. *In vivo* delivery may also be performed directly by administering a composition comprising a nucleic acid inhibitor, *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 nucleic acid inhibitor. These alternatives are discussed further below.

In the methods of the invention which include a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1 which are covalently attached (*i.e.*, a dual targeting RNAi agent), the delivery of the first agent may be the same or different than the delivery of the second agent.

In general, any method of delivering a nucleic acid molecule (*in vitro* or *in vivo*) can be adapted for use with a nucleic acid inhibitor 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 a nucleic acid inhibitor include, for example, biological stability of the delivered molecule, prevention of non-specific effects, and accumulation of the delivered molecule in the target tissue. The non-specific effects of a nucleic acid inhibitor can be minimized by local administration, for example, by direct injection or implantation into a tissue or topically administering the preparation. Local administration to a treatment site maximizes local concentration of the agent, limits the exposure of the agent to systemic tissues that can otherwise be harmed by the agent or that can degrade the agent, and permits a lower total dose of then ucleic acid inhibitor to be administered. Several studies have shown successful knockdown of gene products when a nucleic acid inhibitor is administered locally. For example, intraocular delivery of a VEGF dsRNA by intravitreal injection in cynomolgus monkeys (Tolentino, MJ. *et al.*, (2004) *Retina* 24:132-138) and subretinal injections in mice (Reich, SJ. *et al.* (2003) *Mol. Vis.* 9:210-216) were both shown to prevent neovascularization in an experimental model of age-related macular degeneration. In addition, direct intratumoral injection of a dsRNA in mice reduces tumor volume (Pille, J. *et al.* (2005) *Mol. Ther.* 11:267-274) and can prolong survival of tumor-bearing mice (Kim, WJ. *et al.*, (2006) *Mol. Ther.* 14:343-350; Li, S. *et al.*, (2007) *Mol. Ther.* 15:515-523). 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 a.l* (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) and to the lungs by intranasal administration (Howard, KA. *et al.*, (2006) *Mol. Ther.* 14:476-484; Zhang, X. *et al.*, (2004) *J. Biol. Chem.* 279:10677-10684; Bitko, V. *et al.*, (2005) *Nat. Med.* 11:50-55). For administering a nucleic acid inhibitor systemically for the treatment of a disease, the nucleic acid inhibitor can be modified or alternatively delivered using a drug delivery system; both methods act to prevent the rapid degradation of the nucleic acid inhibitor by endo- and exo-nucleases in vivo. Modification of the nucleic acid inhibitor or the pharmaceutical carrier can also permit targeting of the nucleic acid inhibitor to the target tissue and avoid undesirable off-target effects. Nucleic acid inhibitors can be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For example, a nucleic acid inhibitor 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). Conjugation of an nucleic acid inhibitor to an aptamer has been shown to inhibit tumor growth and mediate tumor regression in a mouse model of prostate cancer (McNamara, JO. *et al.*, (2006) *Nat. Biotechnol.* 24:1005-1015). In an alternative embodiment, the nucleic acid inhibitor 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 a nucleic acid inhibitor (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of a nucleic acid inhibitor by the cell. Cationic lipids, dendrimers, or polymers can either be bound to a nucleic acid inhibitor, 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 a nucleic acid inhibitor. The formation of vesicles or micelles further prevents degradation of the iRNA when administered systemically. Methods for making and administering cationic-nucleic acid inhibitor 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 nucleic acid inhibitors include DOTAP (Sorensen, DR., *et al* (2003), supra; Verma, UN. *et al.*, (2003), supra), Oligofectamine, "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, a nucleic acid inhibitor forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of nucleic acid inhibitors and cyclodextrins can be found in U.S. Patent No. 7, 427, 605, which is herein incorporated by reference in its entirety.

A. Vector encoded iRNAs of the Invention

Nucleic acid inhibitors targeting the LDHA gene, nucleic acid inhibitor targeting the HAO1 gene, nucleic acid inhibitor targeting the PRODH2 gene, and nucleic acid inhibitors targeting LDHA and HAO1 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. Pat. 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.*, (1995) *Proc. Natl. Acad. Sci. USA* 92:1292).

The individual strand or strands of a nucleic acid inhibitor can be transcribed from a promoter on an expression vector. Where two separate strands are to be expressed to generate, for example, a dsRNA, two separate expression vectors can be co-introduced (*e.g.*, by transfection or infection) into a target cell. Alternatively each individual strand of a nucleic acid inhibitor can be transcribed by promoters both of which are located on the same expression plasmid. In one embodiment, a dsRNA is expressed as inverted repeat polynucleotides joined by a linker polynucleotide sequence such that the dsRNA has a stem and loop structure.

Nucleic acid inhibitor expression vectors are generally DNA plasmids or viral vectors. Expression vectors compatible with eukaryotic cells, such as those compatible with vertebrate cells, can be used to produce recombinant constructs for the expression of a nucleic acid inhibitor as described herein. Eukaryotic cell expression vectors are well known in the art and are available from a number of commercial sources. Typically, such vectors are provided containing convenient restriction sites for insertion of the desired nucleic acid segment. Delivery of nucleic acid inhibitor expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that allows for introduction into a desired target cell.

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.

IV. Pharmaceutical Compositions of the Invention

The present invention also includes pharmaceutical compositions and formulations which include the nucleic acid inhibitors of the invention. Accordingly, in one embodiment, provided herein are pharmaceutical compositions comprising a nucleic acid inhibitor, such as a double stranded ribonucleic acid (dsRNA) agent or a single stranded antisense polynucleotide agent that inhibits expression of LDHA1 in a cell, such as a liver cell; and a pharmaceutically acceptable carrier.

In another embodiment, provided herein are pharmaceutical compositions comprising a nucleic acid inhibitor, such as a double stranded ribonucleic acid (dsRNA) agent or a single stranded antisense polynucleotide agent that inhibits expression of HAO1 in a cell, such as a liver cell; and a pharmaceutically acceptable carrier.

In another embodiment, provided herein are pharmaceutical compositions comprising a nucleic acid inhibitor, such as a double stranded ribonucleic acid (dsRNA) agent or a single stranded antisense polynucleotide agent that inhibits expression of PRODH2 in a cell, such as a liver cell; and a pharmaceutically acceptable carrier.

In one embodiment, provided herein are pharmaceutical compositions comprising a first nucleic acid inhibitor, such as a double stranded ribonucleic acid (dsRNA) agent or a single stranded antisense polynucleotide agent, that inhibits expression of lactic acid dehydrogenase A (LDHA) in a cell, such as a liver cell, and a second nucleic acid inhibitor, such as a double stranded ribonucleic acid (dsRNA) agent or a single stranded antisense polynucleotide agent, that inhibits expression of hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) in a cell, such as a liver cell; and a pharmaceutically acceptable carrier.

In yet another embodiment, the present invention provides pharmaceutical compositions and formulations comprising a nucleic acid inhibitor, such as a dual targeting RNAi agent of the invention, and a pharmaceutically acceptable carrier.

The pharmaceutical compositions containing the iRNA of the invention are useful for treating a subject having or at risk of developing a non-primary hyperoxaluria disease or disorder.

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 intravenous (IV) or for subcutaneous delivery. Another example is compositions that are formulated for direct delivery into the liver, *e.g.*, by infusion into the liver, such as by continuous pump infusion.

The pharmaceutical compositions of the invention may be administered in dosages sufficient to inhibit expression of an LDHA gene, an HAO1 gene, a PRODH2 gene, or both an LDHA gene and an HAO1 gene. In general, a suitable dose of a nucleic acid inhibitor 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 a nucleic acid inhibitor 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.

In the methods of the invention which include a first nucleic acid inhibitor targeting LDHA and a second nucleic acid inhibitor targeting HAO1, the first inhibitor and the second inhibitor may be present in the same pharmaceutical formulation or separate pharmaceutical formulations.

A repeat-dose regimine may include administration of a therapeutic amount of nucleic acid inhibitor on a regular basis, such as every other day to once a year. In certain embodiments, the

nucleic acid inhibitor is administered about once per month to about once per quarter (*i.e.*, about once every three months).

After an initial treatment regimen, the treatments can be administered on a less frequent basis. 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 the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a composition can include a single treatment or a series of treatments. Estimates of effective dosages and *in vivo* half-lives for the individual nucleic acid inhibitors encompassed by the invention can be made using conventional methodologies or on the basis of *in vivo* testing using an appropriate animal model.

The pharmaceutical compositions of the present invention 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 can be topical (*e.g.*, by a transdermal patch), pulmonary, *e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and 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 nucleic acid inhibitor can be delivered in a manner to target a particular cell or tissue, such as the liver (*e.g.*, the hepatocytes of 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 iRNAs featured in the invention 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, distearolyphosphatidyl choline) negative (*e.g.*, dimyristoylphosphatidyl glycerol DMPG) and cationic (*e.g.*, dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). Nucleic acid inhibitors featured in the invention can be encapsulated within liposomes or can form complexes thereto, in particular to cationic liposomes. Alternatively, nucleic acid inhibitors 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, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C_{1-20} alkyl ester (*e.g.*, isopropylmyristate IPM), monoglyceride, diglyceride or pharmaceutically acceptable salt thereof. Topical formulations are described in detail in U.S. Patent No. 6,747,014, which is incorporated herein by reference.

Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitablets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders can be desirable. In some embodiments, oral formulations are those in which nucleic acid inhibitors featured in the invention are administered in conjunction with one or more penetration enhancer surfactants and chelators. Suitable surfactants include fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. Suitable bile acids/salts include chenodeoxycholic acid (CDCA) and ursodeoxychenodeoxycholic acid (UDCA), cholic acid, dehydrocholic acid, deoxycholic acid, glucholic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate and sodium glycodihydrofusidate. Suitable fatty acids include arachidonic acid, undecanoic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof (*e.g.,* sodium). In some embodiments, combinations of penetration enhancers are used, for example, fatty acids/salts in combination with bile acids/salts. One exemplary combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. DsRNAs featured in the invention can be delivered orally, in granular form including sprayed dried particles, or complexed to form micro or nanoparticles. DsRNA complexing agents include poly-amino acids; polyimines; polyacrylates; polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates; cationized gelatins, albumins, starches, acrylates, polyethyleneglycols (PEG) and starches; polyalkylcyanoacrylates; DEAE-derivatized polyimines, pollulans, celluloses and starches. Suitable complexing agents include chitosan, N-trimethylchitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines, protamine, polyvinylpyridine, polythiodiethylaminomethylethylene P(TDAE), polyaminostyrene (*e.g.,* p-amino), poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcynaoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, DEAE-acrylamide, DEAE-albumin and DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), alginate, and polyethyleneglycol (PEG). Oral formulations for dsRNAs and their preparation are described in detail in U.S. Patent 6,887,906, US Publn. No. 20030027780, and U.S. Patent No. 6,747,014, each of which is incorporated herein by reference.

Compositions and formulations for parenteral, intraparenchymal (into the brain), intrathecal, intraventricular or intrahepatic administration can include sterile aqueous solutions which can also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

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.

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 or finely divided solid carriers or both, and then, if necessary, shaping the product.

The compositions of the present invention can be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present invention can also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions can further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension can also contain stabilizers.

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 0.1μm 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 in either 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. Either of the phases of the emulsion can be a semisolid or a solid, as is the case of emulsion-style ointment bases and creams. 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).

Naturally occurring emulsifiers used in emulsion formulations include lanolin, beeswax, phosphatides, lecithin and acacia. Absorption bases possess hydrophilic properties such that they can soak up water to form w/o emulsions yet retain their semisolid consistencies, such as anhydrous lanolin and hydrophilic petrolatum. Finely divided solids have also been used as good emulsifiers especially in combination with surfactants and in viscous preparations. These include polar inorganic solids, such as heavy metal hydroxides, nonswelling clays such as bentonite, attapulgite, hectorite, kaolin, montmorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

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).

Hydrophilic colloids or hydrocolloids include naturally occurring gums and synthetic polymers such as polysaccharides (for example, acacia, agar, alginic acid, carrageenan, guar gum, karaya gum, and tragacanth), cellulose derivatives (for example, carboxymethylcellulose and carboxypropylcellulose), and synthetic polymers (for example, carbomers, cellulose ethers, and carboxyvinyl polymers). These disperse or swell in water to form colloidal solutions that stabilize emulsions by forming strong interfacial films around the dispersed-phase droplets and by increasing the viscosity of the external phase.

Since emulsions often contain a number of ingredients such as carbohydrates, proteins, sterols and phosphatides that can readily support the growth of microbes, these formulations often incorporate preservatives. Commonly used preservatives included in emulsion formulations include methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, and boric acid. Antioxidants are also commonly added to emulsion formulations to prevent deterioration of the formulation. Antioxidants used can be free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

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). Emulsion formulations for oral delivery have been very widely used because of ease of formulation, as well as efficacy from an absorption and bioavailability standpoint (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 Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Mineral-oil base laxatives, oil-soluble vitamins and high fat nutritive preparations are among the materials that have commonly been administered orally as o/w emulsions.

ii. Microemulsions

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 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 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). Microemulsions commonly are prepared via a combination of three to five components that include oil, water, surfactant, cosurfactant and electrolyte. Whether the microemulsion is of the water-in-oil (w/o) or an oil-in-water (o/w) type is dependent on the properties of the oil and surfactant used and on the structure and geometric packing of the polar heads and hydrocarbon tails of the surfactant molecules (Schott, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 271).

The phenomenological approach utilizing phase diagrams has been extensively studied and has yielded a comprehensive knowledge, to one skilled in the art, of how to formulate microemulsions (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 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 1, p. 335). Compared to conventional emulsions, microemulsions offer the advantage of solubilizing water-insoluble drugs in a formulation of thermodynamically stable droplets that are formed spontaneously.

Surfactants used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (SO750), decaglycerol decaoleate (DAO750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules. Microemulsions can, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase can

typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase can include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C8-C12) mono, di, and tri-glycerides, polyoxyethylated glyceryl fatty acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C8-C10 glycerides, vegetable oils and silicone oil.

Microemulsions are particularly of interest from the standpoint of drug solubilization and the enhanced absorption of drugs. Lipid based microemulsions (both o/w and w/o) have been proposed to enhance the oral bioavailability of drugs, including peptides (see *e.g.*, U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al.*, Pharmaceutical Research, 1994, 11, 1385-1390; Ritschel, Meth. Find. Exp. Clin. Pharmacol., 1993, 13, 205). Microemulsions afford advantages of improved drug solubilization, protection of drug from enzymatic hydrolysis, possible enhancement of drug absorption due to surfactant-induced alterations in membrane fluidity and permeability, ease of preparation, ease of oral administration over solid dosage forms, improved clinical potency, and decreased toxicity (see *e.g.*, U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al.*, Pharmaceutical Research, 1994, 11, 1385; Ho *et al.*, J. Pharm. Sci., 1996, 85, 138-143). Often microemulsions can form spontaneously when their components are brought together at ambient temperature. This can be particularly advantageous when formulating thermolabile drugs, peptides or iRNAs. Microemulsions have also been effective in the transdermal delivery of active components in both cosmetic and pharmaceutical applications. It is expected that the microemulsion compositions and formulations of the present invention will facilitate the increased systemic absorption of iRNAs and nucleic acids from the gastrointestinal tract, as well as improve the local cellular uptake of iRNAs and nucleic acids.

Microemulsions of the present invention can also contain additional components and additives such as sorbitan monostearate (Grill 3), Labrasol, and penetration enhancers to improve the properties of the formulation and to enhance the absorption of the iRNAs and nucleic acids of the present invention. Penetration enhancers used in the microemulsions of the present invention can be classified as belonging to one of five broad categories--surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p. 92). Each of these classes has been discussed above.

iii. Microparticles

A nucleic acid inhibitor 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.

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 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.*, 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 are described below in greater detail.

Surfactants (or "surface-active agents") are chemical entities which, when dissolved in an aqueous solution, reduce the surface tension of the solution or the interfacial tension between the aqueous solution and another liquid, with the result that absorption of iRNAs through the mucosa is enhanced. In addition to bile salts and fatty acids, these penetration enhancers include, for example, sodium lauryl sulfate, polyoxyethylene-9-lauryl ether and polyoxyethylene-20-cetyl ether) (see *e.g.*, 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); and perfluorochemical emulsions, such as FC-43. Takahashi *et al.*, J. Pharm. Pharmacol., 1988, 40, 252).

Various fatty acids and their derivatives which act as penetration enhancers include, for example, oleic acid, lauric acid, capric acid (n-decanoic acid), myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein (1-monooleoyl-rac-glycerol), dilaurin, caprylic acid, arachidonic acid, glycerol 1-monocaprate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, C_{1-20} alkyl esters thereof (*e.g.*, methyl, isopropyl and t-butyl), and mono- and di-glycerides thereof (*i.e.*, oleate, laurate, caprate, myristate, palmitate, stearate, linoleate, *etc.*) (see *e.g.*, Touitou, E., *et al.* Enhancement in Drug Delivery, CRC Press, Danvers, MA, 2006; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; El Hariri *et al.*, J. Pharm. Pharmacol., 1992, 44, 651-654).

The physiological role of bile includes the facilitation of dispersion and absorption of lipids and fat-soluble vitamins (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Brunton, Chapter 38 in: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., Hardman *et al.* Eds., McGraw-Hill, New York, 1996, pp. 934-935). Various natural bile salts, and their synthetic derivatives, act as penetration enhancers. Thus the term "bile salts" includes any of the naturally occurring components of bile as well as any of their synthetic derivatives. Suitable bile salts include, for example, cholic acid (or its pharmaceutically acceptable sodium salt, sodium cholate), dehydrocholic acid (sodium dehydrocholate), deoxycholic acid (sodium deoxycholate), glucholic acid (sodium glucholate), glycholic acid (sodium glycocholate), glycodeoxycholic acid (sodium glycodeoxycholate),

taurocholic acid (sodium taurocholate), taurodeoxycholic acid (sodium taurodeoxycholate), chenodeoxycholic acid (sodium chenodeoxycholate), ursodeoxycholic acid (UDCA), sodium tauro-24,25-dihydro-fusidate (STDHF), sodium glycodihydrofusidate and polyoxyethylene-9-lauryl ether (POE) (see *e.g.*, 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, page 92; Swinyard, Chapter 39 In: Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, Pa., 1990, pages 782-783; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; Yamamoto *et al.*, J. Pharm. Exp. Ther., 1992, 263, 25; Yamashita *et al.*, J. Pharm. Sci., 1990, 79, 579-583).

Chelating agents, as used in connection with the present invention, can be defined as compounds that remove metallic ions from solution by forming complexes therewith, with the result that absorption of nucleic acid inhibitors s through the mucosa is enhanced. With regards to their use as penetration enhancers in the present invention, chelating agents have the added advantage of also serving as DNase inhibitors, as most characterized DNA nucleases require a divalent metal ion for catalysis and are thus inhibited by chelating agents (Jarrett, J. Chromatogr., 1993, 618, 315-339). Suitable chelating agents include but are not limited to disodium ethylenediaminetetraacetate (EDTA), citric acid, salicylates (*e.g.*, sodium salicylate, 5-methoxysalicylate and homovanilate), N-acyl derivatives of collagen, laureth-9 and N-amino acyl derivatives of beta-diketones (enamines)(see *e.g.*, Katdare, A. *et al.*, Excipient development for pharmaceutical, biotechnology, and drug delivery, CRC Press, Danvers, MA, 2006; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; Buur *et al.*, J. Control Rel., 1990, 14, 43-51).

As used herein, non-chelating non-surfactant penetration enhancing compounds can be defined as compounds that demonstrate insignificant activity as chelating agents or as surfactants but that nonetheless enhance absorption of iRNAs through the alimentary mucosa (see *e.g.*, Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). This class of penetration enhancers includes, for example, unsaturated cyclic ureas, 1-alkyl- and 1-alkenylazacyclo-alkanone derivatives (Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92); and non-steroidal anti-inflammatory agents such as diclofenac sodium, indomethacin and phenylbutazone (Yamashita *et al.*, J. Pharm. Pharmacol., 1987, 39, 621-626).

Agents that enhance uptake of nucleic acid inhibitors at the cellular level can also be added to the pharmaceutical and other compositions of the present invention. For example, cationic lipids, such as lipofectin (Junichi *et al*, U.S. Pat. No. 5,705,188), cationic glycerol derivatives, and polycationic molecules, such as polylysine (Lollo *et al.*, PCT Application WO 97/30731), are also known to enhance the cellular uptake of dsRNAs. Examples of commercially available transfection reagents include, for example Lipofectamine™ (Invitrogen; Carlsbad, CA), Lipofectamine 2000™ (Invitrogen; Carlsbad, CA), 293fectin™ (Invitrogen; Carlsbad, CA), Cellfectin™ (Invitrogen; Carlsbad, CA), DMRIE-C™ (Invitrogen; Carlsbad, CA), FreeStyle™ MAX (Invitrogen; Carlsbad,

CA), Lipofectamine™ 2000 CD (Invitrogen; Carlsbad, CA), Lipofectamine™ (Invitrogen; Carlsbad, CA), RNAiMAX (Invitrogen; Carlsbad, CA), Oligofectamine™ (Invitrogen; Carlsbad, CA), Optifect™ (Invitrogen; Carlsbad, CA), X-tremeGENE Q2 Transfection Reagent (Roche; Grenzacherstrasse, Switzerland), DOTAP Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), DOSPER Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), or Fugene (Grenzacherstrasse, Switzerland), Transfectam® Reagent (Promega; Madison, WI), TransFast™ Transfection Reagent (Promega; Madison, WI), Tfx™-20 Reagent (Promega; Madison, WI), Tfx™-50 Reagent (Promega; Madison, WI), DreamFect™ (OZ Biosciences; Marseille, France), EcoTransfect (OZ Biosciences; Marseille, France), TransPass[a] D1 Transfection Reagent (New England Biolabs; Ipswich, MA, USA), LyoVec™/LipoGen™ (Invitrogen; San Diego, CA, USA), PerFectin Transfection Reagent (Genlantis; San Diego, CA, USA), NeuroPORTER Transfection Reagent (Genlantis; San Diego, CA, USA), GenePORTER Transfection reagent (Genlantis; San Diego, CA, USA), GenePORTER 2 Transfection reagent (Genlantis; San Diego, CA, USA), Cytofectin Transfection Reagent (Genlantis; San Diego, CA, USA), BaculoPORTER Transfection Reagent (Genlantis; San Diego, CA, USA), TroganPORTER™ transfection Reagent (Genlantis; San Diego, CA, USA), RiboFect (Bioline; Taunton, MA, USA), PlasFect (Bioline; Taunton, MA, USA), UniFECTOR (B-Bridge International; Mountain View, CA, USA), SureFECTOR (B-Bridge International; Mountain View, CA, USA), or HiFect™ (B-Bridge International, Mountain View, CA, USA), among others.

Other agents can be utilized to enhance the penetration of the administered nucleic acids, including glycols such as ethylene glycol and propylene glycol, pyrrols such as 2-pyrrol, azones, and terpenes such as limonene and menthone.

v. Carriers

Certain compositions of the present invention also incorporate carrier compounds in the formulation. As used herein, "carrier compound" or "carrier" can refer to a nucleic acid, or analog thereof, which is inert (*i.e.*, does not possess biological activity per se) but is recognized as a nucleic acid by *in vivo* processes that reduce the bioavailability of a nucleic acid having biological activity by, for example, degrading the biologically active nucleic acid or promoting its removal from circulation. The coadministration of a nucleic acid and a carrier compound, typically with an excess of the latter substance, can result in a substantial reduction of the amount of nucleic acid recovered in the liver, kidney or other extracirculatory reservoirs, presumably due to competition between the carrier compound and the nucleic acid for a common receptor. For example, the recovery of a partially phosphorothioate dsRNA in hepatic tissue can be reduced when it is coadministered with polyinosinic acid, dextran sulfate, polycytidic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid (Miyao *et al.*, DsRNA Res. Dev., 1995, 5, 115-121; Takakura *et al.*, DsRNA & Nucl. Acid Drug Dev., 1996, 6, 177-183.

vi. Excipients

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 pharmaceutical composition. Typical pharmaceutical carriers include, but are not limited to, binding agents (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, *etc.*); fillers (*e.g.*, lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, *etc.*); lubricants (*e.g.*, magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, *etc.*); disintegrants (*e.g.*, starch, sodium starch glycolate, *etc.*); and wetting agents (*e.g.*, sodium lauryl sulphate, *etc*). Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can also be used to formulate the compositions of the present invention. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

Formulations for topical administration of nucleic acid inhibitors can include sterile and non-sterile aqueous solutions, non-aqueous solutions in common solvents such as alcohols, or solutions of the nucleic acids in liquid or solid oil bases. The solutions can also contain buffers, diluents and other suitable additives. Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can be used. Suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

vii. 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 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 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 and/or aromatic substances and the like which do not deleteriously interact with the nucleic acid(s) of the formulation.

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

In some embodiments, pharmaceutical compositions featured in the invention include (a) one or more nucleic acid inhibitors and (b) one or more agents which function by a non-RNAi mechanism and which are useful in treating a kidney stone disease. Examples of such agents include, but are not lmited to pyridoxine, an ACE inhibitor (angiotensin converting enzyme inhibitors), *e.g.*, benazepril (Lotensin); an angiotensin II receptor antagonist (ARB) (*e.g.*, losartan potassium, such as Merck & Co. 's Cozaar®), *e.g.*, Candesartan (Atacand); an HMG-CoA reductase inhibitor (*e.g.*, a statin); dietary oxalate degrading compounds, *e.g.*, Oxalate decarboxylase (Oxazyme); calcium binding agents, *e.g.*, Sodium cellulose phosphate (Calcibind); diuretics, *e.g.*, thiazide diuretics, such as hydrochlorothiazide (Microzide); phosphate binders, *e.g.*, Sevelamer (Renagel); magnesium and Vitamin B6 supplements; potassium citrate; orthophosphates, bisphosphonates; oral phosphate and citrate solutions; high fluid intake, urinary tract endoscopy; extracorporeal shock wave lithotripsy; kidney dialysis; kidney stone removal (*e.g.*, surgery); and kidney/liver transplant; or a combination of any of the foregoing.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. 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 ED_{50} 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 therapeutically 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 IC_{50} (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) 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.

VII. Kits of the Invention

In certain aspects, the instant disclosure provides kits that include a suitable container containing a pharmaceutical formulation of a nucleic acid inhibitor. In certain embodiments the individual components of the pharmaceutical formulation may be provided in one container. 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 nucleic acid inhibitor 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.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the RNAi agents and methods featured in the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

A Sequence Listing is filed herewith and forms part of the specification as filed. A supplemental informal sequence listing is also included as part of the specification.

EXAMPLES

Example 1. Treating Subjects Having or at Risk of Developing a Non-Primary Hyperoxaluria Disease with a Nucleic Acid Inhibitor of LDHA, a nucleic acid inhibitor of PRODH2 and/or a Nucleic Acid Inhibitor of HAO1

Primary hyperoxaluria is a well-known disease associated with high levels of oxalate. Specifically, primary hyperoxaluria is characterized by impaired glyoxylate metabolism resulting in overproduction and accumulation of oxalate throughout the body, typically manifesting as kidney and bladder stones. There are three major types of primary hyperoxaluria that differ in their severity and genetic cause. Autosomal recessive mutations in the AGXT gene cause primary hyperoxaluria type 1 (PH1); autosomal recessive mutations in the GRHPR gene cause primary hyperoxaluria type 2 (PH2); and autosomal recessive mutations in the HOGA1 gene cause primary hyperoxaluria type 3 (PH3) (see, Figure 1).

Therapeutics that reduce oxalate levels have entered the clinic for the treatment of subjects having PH1 and PH2. Specifically, Lumasiran, an RNA interference (RNAi) therapeutic targeting glycolate oxidase (GO) for treatment of PH1 is currently being evaluated in a Phase III clinical trail (see, *e.g.,* NCT03681184), and DCR-PHXC, an RNA interference (RNAi) therapeutic targeting LDHA for the treatment of PH1 and PH2 has entered Phase II clinical trials (see, *e.g.,* NCT03847909).

However, there are also a significant number of subjects that do not have primary hyperoxaluria, *e.g.,* PH1, PH2, or PH3, but yet still would benefit from treatement with agents that reduce oxalate. For example, subjects having or at risk of developing a non-primary hyperoxaluria disease or disorder, as described herein, would benefit from treatment with agents that reduce oxlate.

Specifically, subjects having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate include subjects having elevated levels of oxalate who suffer from enteric hyperoxaluria, dietary hyperoxaluria, idiopathic hyperoxaluria, a kidney stone disease, chronic kidney disease (CKD), end-stage renal disease (ESRD), coronary artery disease, cutaneous oxalate deposition, or ethylene glycol poisoning, or those who are planning to undergo kidney transplantation or have undergone kidney transplantation. Subjects having a non-primary hyperoxaluria disease or disorder do not have primary hyperoxaluria (PH), *i.e.*, PH1, PH2, or PH3.

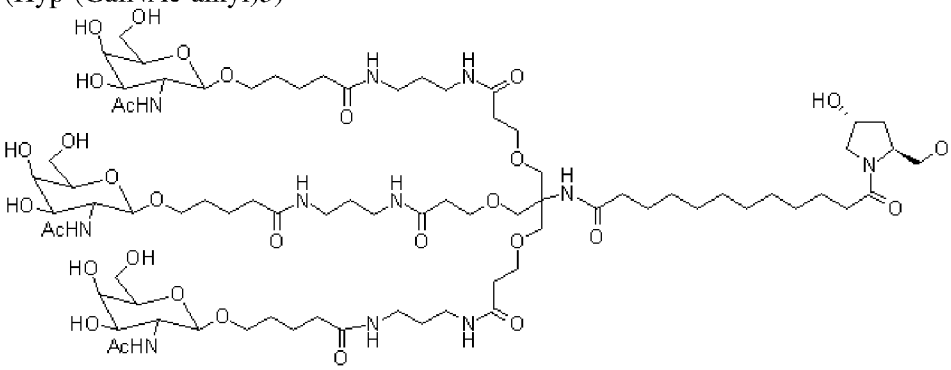
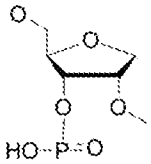
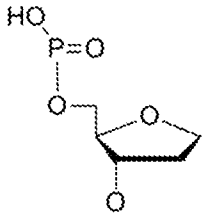
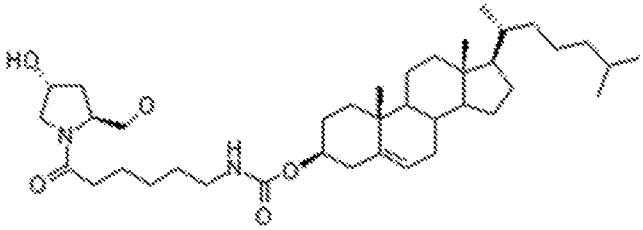
Subjects at risk of developing a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate include subjects having normal levels of oxalate who suffer from a kidney stone disease, end-stage renal disease (ESRD), coronary artery disease, diabetes, cutaneous oxalate deposition, or ethylene glycol poisoning. Subjects at risk of developing a non-primary hyperoxaluria disease or disorder do not have primary hyperoxaluria (PH), *i.e.*, PH1, PH2, or PH3.

Accordingly, the present invention provides methods for treating subjects having or at risk of developing a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate using nucleic acid inhibitors, *e.g.,* double stranded ribonucleic acid (dsRNA) agents or single stranded antisense polynucleotide agents targeting lactate dehydrogenase A (LDHA), hydroxyacid oxidase (HAO1) and/or proline dehydrogenase 2 (PRODH2), as described herein.

Tables 2-16 provide exemplary nucleic acid inhibitors for LDHA, HAO1 and/or PRODH2 for use in the methods of the present invention.

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
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

Abbreviation	Nucleotide(s)
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol (Hyp-(GalNAc-alkyl)3) 
Y34	2-hydroxymethyl-tetrahydrofurane-4-methoxy-3-phosphate (abasic 2'-OMe furanose) 
Y44	inverted abasic DNA (2-hydroxymethyl-tetrahydrofurane-5-phosphate) 
L10	N-(cholesterylcarboxamidocaproyl)-4-hydroxyprolinol (Hyp-C6-Chol) 
(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
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

Abbreviation	Nucleotide(s)
(G2p)	guanosine-2`-phosphate
(U2p)	uridine-2`-phosphate
(A2p)	adenosine-2`-phosphate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(Ahds)	2'-O-hexadecyl-adenosine-3'-phosphorothioate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Chds)	2'-O-hexadecyl-cytidine-3'-phosphorothioate
(Ghd)	2'-O-hexadecyl-guanosine-3'-phosphate
(Ghds)	2'-O-hexadecyl-guanosine-3'-phosphorothioate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
(Uhds)	2'-O-hexadecyl-uridine-3'-phosphorothioate
s	phosphorothioate

TABLE 2. UNMODIFIED HUMAN/CYNOMOLGUS CROSS-REACTIVE LDHA iRNA SEQUENCES

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3	Antisense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3
AD-159469	UUUAUCUGAUCUGUGAUUAAA	3210	1347-1367	UUUAAUCACAGAUCAGAUAAAAA	3396	1345-1367
AD-159607	ACUGGUUAGUGUGAAAUAGUU	3211	1489-1509	AACUAUUUCACACUAACCAGUUG	3397	1487-1509
AD-159713	AACAUGCCUAGUCCAACAUUU	3212	1615-1635	AAAUGUUGGACUAGGCAUGUUCA	3398	1613-1635
AD-158504	CAAGUCCAAUAUGGCAACUCU	3213	263-283	AGAGUUGCCAUAUUGGACUUGGA	3399	261-283
AD-159233	UCCACCAUGAUUAAGGGUCUU	3214	1092-1112	AAGACCCUUAAUCAUGGUGGAAA	3400	1090-1112
AD-159411	UCAUUUCACUGUCUAGGCUAA	3215	1289-1309	UUAGCCUAGACAGUGAAAUGAUA	3401	1287-1309
AD-159462	UGUCCUUUUUAUCUGAUCUGU	3216	1340-1360	ACAGAUCAGAUAAAAAGGACAAC	3402	1338-1360
AD-159742	CCAGUGUAUAAAUCCAAUAUA	3217	1662-1682	UAUAUUGGAUUUAUACACUGGAU	3403	1660-1682
AD-159863	UCCAAGUGUUAUACCAACUAA	3218	1791-1811	UUAGUUGGUAUAACACUUGGAUA	3404	1789-1811
AD-158626	GUCAUCGAAGACAAAUUGAAA	3219	429-449	UUUCAAUUUGUCUUCGAUGACAU	3405	427-449
AD-158687	GAACACCAAAGAUUGUCUCUA	3220	490-510	UAGAGACAAUCUUUGGUGUUCUA	3406	488-510
AD-158688	AACACCAAAGAUUGUCUCUGA	3221	491-511	UCAGAGACAAUCUUUGGUGUUCU	3407	489-511
AD-159458	AUGUUGUCCUUUUUAUCUGAU	3222	1336-1356	AUCAGAUAAAAAGGACAACAUGC	3408	1334-1356
AD-159519	UCAACUCCUGAAGUUAGAAAU	3223	1401-1421	AUUUCUAACUUCAGGAGUUGAUG	3409	1399-1421
AD-159858	AACUAUCCAAGUGUUAUACCA	3224	1786-1806	UGGUAUAACACUUGGAUAGUUGG	3410	1784-1806
AD-158681	UCCUUAGAACACCAAAGAUUA	3225	484-504	UAAUCUUUGGUGUUCUAAGGAAA	3411	482-504
AD-159583	GGUAUUAAUCUUGUGUAGUCU	3226	1465-1485	AGACUACACAAGAUUAAUACCAU	3412	1463-1485
AD-159700	GGCUCCUUCACUGAACAUGCA	3227	1602-1622	UGCAUGUUCAGUGAAGGAGCCAG	3413	1600-1622
AD-159807	UAUCAGUAGUGUACAUUACCA	3228	1728-1748	UGGUAAUGUACACUACUGAUAUA	3414	1726-1748
AD-158673	CAGCCUUUUCCUUAGAACACA	3229	476-496	UGUGUUCUAAGGAAAAGGCUGCC	3415	474-496
AD-159608	CUGGUUAGUGUGAAAUAGUUA	3230	1490-1510	UAACUAUUUCACACUAACCAGUU	3416	1488-1510
AD-159803	ACUAUAUCAGUAGUGUACAUU	3231	1724-1744	AAUGUACACUACUGAUAUAGUUC	3417	1722-1744
AD-159805	UAUAUCAGUAGUGUACAUUAA	3232	1726-1746	UUAAUGUACACUACUGAUAUAGU	3418	1724-1746

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3	Antisense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3
AD-159489	GUAAUAUUUUAAGAUGGACUA	3233	1371-1391	UAGUCCAUCUUAAAAUAUUACUG	3419	1369-1391
AD-159495	UUUUAAGAUGGACUGGGAAAA	3234	1377-1397	UUUUCCCAGUCCAUCUUAAAAUA	3420	1375-1397
AD-159609	UGGUUAGUGUGAAAUAGUUCU	3235	1491-1511	AGAACUAUUUCACACUAACCAGU	3421	1489-1511
AD-159706	UUCACUGAACAUGCCUAGUCA	3236	1608-1628	UGACUAGGCAUGUUCAGUGAAGG	3422	1606-1628
AD-159855	ACCAACUAUCCAAGUGUUAUA	3237	1783-1803	UAUAACACUUGGAUAGUUGGUUG	3423	1781-1803
AD-159864	CCAAGUGUUAUACCAACUAAA	3238	1792-1812	UUUAGUUGGUAUAACACUUGGAU	3424	1790-1812
AD-158491	UUCCUUUUGGUUCCAAGUCCA	3239	250-270	UGGACUUGGAACCAAAAGGAAUC	3425	248-270
AD-158672	GCAGCCUUUUCCUUAGAACAA	3240	475-495	UUGUUCUAAGGAAAAGGCUGCCA	3426	473-495
AD-159488	AGUAAUAUUUUAAGAUGGACU	3241	1370-1390	AGUCCAUCUUAAAAUAUUACUGC	3427	1368-1390
AD-159553	AAAAUCCACAGCUAUAUCCUA	3242	1435-1455	UAGGAUAUAGCUGUGGAUUUUAC	3428	1433-1455
AD-159703	UCCUUCACUGAACAUGCCUAA	3243	1605-1625	UUAGGCAUGUUCAGUGAAGGAGC	3429	1603-1625
AD-159708	CACUGAACAUGCCUAGUCCAA	3244	1610-1630	UUGGACUAGGCAUGUUCAGUGAA	3430	1608-1630
AD-159866	AAGUGUUAUACCAACUAAAAC	3245	1794-1814	GUUUUAGUUGGUAUAACACUUGG	3431	1792-1814
AD-159232	UUCCACCAUGAUUAAGGGUCU	3246	1091-1111	AGACCCUUAAUCAUGGUGGAAAC	3432	1089-1111
AD-159712	GAACAUGCCUAGUCCAACAUU	3247	1614-1634	AAUGUUGGACUAGGCAUGUUCAG	3433	1612-1634
AD-159808	AUCAGUAGUGUACAUUACCAU	3248	1729-1749	AUGGUAAUGUACACUACUGAUAU	3434	1727-1749
AD-159862	AUCCAAGUGUUAUACCAACUA	3249	1790-1810	UAGUUGGUAUAACACUUGGAUAG	3435	1788-1810
AD-158503	CCAAGUCCAAUAUGGCAACUA	3250	262-282	UAGUUGCCAUAUUGGACUUGGAA	3436	260-282
AD-159311	AUCUCAGACCUUGUGAAGGUA	3251	1170-1190	UACCUUCACAAGGUCUGAGAUUC	3437	1168-1190
AD-159412	CAUUUCACUGUCUAGGCUACA	3252	1290-1310	UGUAGCCUAGACAGUGAAAUGAU	3438	1288-1310
AD-159558	CCACAGCUAUAUCCUGAUGCU	3253	1440-1460	AGCAUCAGGAUAUAGCUGUGGAU	3439	1438-1460
AD-159705	CUUCACUGAACAUGCCUAGUA	3254	1607-1627	UACUAGGCAUGUUCAGUGAAGGA	3440	1605-1627
AD-159113	GUGGUUGAGAGUGCUUAUGAA	3255	972-992	UUCAUAAGCACUCUCAACCACCU	3441	970-992
AD-159139	CAAACUCAAAGGCUACACAUA	3256	998-1018	UAUGUGUAGCCUUUGAGUUUGAU	3442	996-1018
AD-159806	AUAUCAGUAGUGUACAUUACA	3257	1727-1747	UGUAAUGUACACUACUGAUAUAG	3443	1725-1747

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3	Antisense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3
AD-159853	CAACCAACUAUCCAAGUGUUA	3258	1781-1801	UAACACUUGGAUAGUUGGUUGCA	3444	1779-1801
AD-158627	UCAUCGAAGACAAAUUGAAGA	3259	430-450	UCUUCAAUUUGUCUUCGAUGACA	3445	428-450
AD-159182	GCAGAUUUGGCAGAGAGUAUA	3260	1041-1061	UAUACUCUCUGCCAAAUCUGCUA	3446	1039-1061
AD-159702	CUCCUUCACUGAACAUGCCUA	3261	1604-1624	UAGGCAUGUUCAGUGAAGGAGCC	3447	1602-1624
AD-159715	CAUGCCUAGUCCAACAUUUUU	3262	1617-1637	AAAAAUGUUGGACUAGGCAUGUU	3448	1615-1637
AD-158575	UGCCAUCAGUAUCUUAAUGAA	3263	377-397	UUCAUUAAGAUACUGAUGGCACA	3449	375-397
AD-158576	GCCAUCAGUAUCUUAAUGAAA	3264	378-398	UUUCAUUAAGAUACUGAUGGCAC	3450	376-398
AD-158684	UUAGAACACCAAAGAUUGUCU	3265	487-507	AGACAAUCUUUGGUGUUCUAAGG	3451	485-507
AD-159410	AUCAUUUCACUGUCUAGGCUA	3266	1288-1308	UAGCCUAGACAGUGAAAUGAUAU	3452	1286-1308
AD-159416	UCACUGUCUAGGCUACAACAA	3267	1294-1314	UUGUUGUAGCCUAGACAGUGAAA	3453	1292-1314
AD-159738	GGAUCCAGUGUAUAAAUCCAA	3268	1658-1678	UUGGAUUUAUACACUGGAUCCCA	3454	1656-1678
AD-159857	CAACUAUCCAAGUGUUAUACA	3269	1785-1805	UGUAUAACACUUGGAUAGUUGGU	3455	1783-1805
AD-158497	UUGGUUCCAAGUCCAAUAUGA	3270	256-276	UCAUAUUGGACUUGGAACCAAAA	3456	254-276
AD-159124	UGCUUAUGAGGUGAUCAAACU	3271	983-1003	AGUUUGAUCACCUCAUAAGCACU	3457	981-1003
AD-159140	AAACUCAAAGGCUACACAUCA	3272	999-1019	UGAUGUGUAGCCUUUGAGUUUGA	3458	997-1019
AD-159312	UCUCAGACCUUGUGAAGGUGA	3273	1171-1191	UCACCUUCACAAGGUCUGAGAUU	3459	1169-1191
AD-159552	UAAAAUCCACAGCUAUAUCCU	3274	1434-1454	AGGAUAUAGCUGUGGAUUUUACA	3460	1432-1454
AD-159704	CCUUCACUGAACAUGCCUAGU	3275	1606-1626	ACUAGGCAUGUUCAGUGAAGGAG	3461	1604-1626
AD-159737	GGGAUCCAGUGUAUAAAUCCA	3276	1657-1677	UGGAUUUAUACACUGGAUCCCAG	3462	1655-1677
AD-159869	CAAUAAACCUUGAACAGUGAA	3277	1818-1838	UUCACUGUUCAAGGUUUAUUGGG	3463	1816-1838
AD-158570	GGCCUGUGCCAUCAGUAUCUU	3278	371-391	AAGAUACUGAUGGCACAGGCCAU	3464	369-391
AD-158618	UUGUUGAUGUCAUCGAAGACA	3279	421-441	UGUCUUCGAUGACAUCAACAAGA	3465	419-441
AD-159788	GGAUCUUAUUUUGUGAACUAU	3280	1708-1728	AUAGUUCACAAAAUAAGAUCCUU	3466	1706-1728
AD-159786	AAGGAUCUUAUUUUGUGAACU	3281	1706-1726	AGUUCACAAAAUAAGAUCCUUUG	3467	1704-1726
AD-159760	AUCAUGUCUUGUGCAUAAUUA	3282	1680-1700	UAAUUAUGCACAAGACAUGAUAU	3468	1678-1700

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3	Antisense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3
AD-159404	UGUCAUAUCAUUUCACUGUCU	3283	1282-1302	AGACAGUGAAAUGAUAUGACAUC	3469	1280-1302
AD-159406	UCAUAUCAUUUCACUGUCUAA	3284	1284-1304	UUAGACAGUGAAAUGAUAUGACA	3470	1282-1304
AD-158536	AUUUAUAAUCUUCUAAAGGAA	3285	297-317	UUCCUUUAGAAGAUUAUAAAUCA	3471	295-317
AD-159545	UGGUUUGUAAAAUCCACAGCU	3286	1427-1447	AGCUGUGGAUUUUACAAACCAUU	3472	1425-1447
AD-159574	AUGCUGGAUGGUAUUAAUCUU	3287	1456-1476	AAGAUUAAUACCAUCCAGCAUCA	3473	1454-1476
AD-159802	AACUAUAUCAGUAGUGUACAU	3288	1723-1743	AUGUACACUACUGAUAUAGUUCA	3474	1721-1743
AD-159518	AUCAACUCCUGAAGUUAGAAA	3289	1400-1420	UUUCUAACUUCAGGAGUUGAUGU	3475	1398-1420
AD-159577	CUGGAUGGUAUUAAUCUUGUA	3290	1459-1479	UACAAGAUUAAUACCAUCCAGCA	3476	1457-1479
AD-159409	UAUCAUUUCACUGUCUAGGCU	3291	1287-1307	AGCCUAGACAGUGAAAUGAUAUG	3477	1285-1307
AD-159551	GUAAAAUCCACAGCUAUAUCA	3292	1433-1453	UGAUAUAGCUGUGGAUUUUACAA	3478	1431-1453
AD-159276	UCCUUAGUGUUCCUUGCAUUU	3293	1135-1155	AAAUGCAAGGAACACUAAGGAAG	3479	1133-1155
AD-159407	CAUAUCAUUUCACUGUCUAGA	3294	1285-1305	UCUAGACAGUGAAAUGAUAUGAC	3480	1283-1305
AD-159515	AACAUCAACUCCUGAAGUUAA	3295	1397-1417	UUAACUUCAGGAGUUGAUGUUUU	3481	1395-1417
AD-159570	CCUGAUGCUGGAUGGUAUUAA	3296	1452-1472	UUAAUACCAUCCAGCAUCAGGAU	3482	1450-1472
AD-159849	AAUGCAACCAACUAUCCAAGU	3297	1777-1797	ACUUGGAUAGUUGGUUGCAUUGU	3483	1775-1797
AD-159252	UUUACGGAAUAAAGGAUGAUA	3298	1111-1131	UAUCAUCCUUUAUUCCGUAAAGA	3484	1109-1131
AD-159275	UUCCUUAGUGUUCCUUGCAUU	3299	1134-1154	AAUGCAAGGAACACUAAGGAAGA	3485	1132-1154
AD-159848	CAAUGCAACCAACUAUCCAAA	3300	1776-1796	UUUGGAUAGUUGGUUGCAUUGUU	3486	1774-1796
AD-159184	AGAUUUGGCAGAGAGUAUAAU	3301	1043-1063	AUUAUACUCUCUGCCAAAUCUGC	3487	1041-1063
AD-159231	UUUCCACCAUGAUUAAGGGUA	3302	1090-1110	UACCCUUAAUCAUGGUGGAAACU	3488	1088-1110
AD-159607	ACUGGUUAGUGUGAAAUAGUU	3303	1489-1509	AACUAUUUCACACUAACCAGUUG	3489	1487-1509
AD-158504	CAAGUCCAAUAUGGCAACUCU	3304	263-283	AGAGUUGCCAUAUUGGACUUGGA	3490	261-283
AD-159233	UCCACCAUGAUUAAGGGUCUU	3305	1092-1112	AAGACCCUUAAUCAUGGUGGAAA	3491	1090-1112
AD-159411	UCAUUUCACUGUCUAGGCUAA	3306	1289-1309	UUAGCCUAGACAGUGAAAUGAUA	3492	1287-1309
AD-159462	UGUCCUUUUUAUCUGAUCUGU	3307	1340-1360	ACAGAUCAGAUAAAAAGGACAAC	3493	1338-1360

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3	Antisense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3
AD-159742	CCAGUGUAUAAAUCCAAUAUA	3308	1662-1682	UAUAUUGGAUUUAUACACUGGAU	3494	1660-1682
AD-159863	UCCAAGUGUUAUACCAACUAA	3309	1791-1811	UUAGUUGGUAUAACACUUGGAUA	3495	1789-1811
AD-158687	GAACACCAAAGAUUGUCUCUA	3310	490-510	UAGAGACAAUCUUUGGUGUUCUA	3496	488-510
AD-158688	AACACCAAAGAUUGUCUCUGA	3311	491-511	UCAGAGACAAUCUUUGGUGUUCU	3497	489-511
AD-159458	AUGUUGUCCUUUUUAUCUGAU	3312	1336-1356	AUCAGAUAAAAAGGACAACAUGC	3498	1334-1356
AD-159519	UCAACUCCUGAAGUUAGAAAU	3313	1401-1421	AUUUCUAACUUCAGGAGUUGAUG	3499	1399-1421
AD-159858	AACUAUCCAAGUGUUAUACCA	3314	1786-1806	UGGUAUAACACUUGGAUAGUUGG	3500	1784-1806
AD-159583	GGUAUUAAUCUUGUGUAGUCU	3315	1465-1485	AGACUACACAAGAUUAAUACCAU	3501	1463-1485
AD-159700	GGCUCCUUCACUGAACAUGCA	3316	1602-1622	UGCAUGUUCAGUGAAGGAGCCAG	3502	1600-1622
AD-159807	UAUCAGUAGUGUACAUUACCA	3317	1728-1748	UGGUAAUGUACACUACUGAUAUA	3503	1726-1748
AD-158673	CAGCCUUUUCCUUAGAACACA	3318	476-496	UGUGUUCUAAGGAAAAGGCUGCC	3504	474-496
AD-159608	CUGGUUAGUGUGAAAUAGUUA	3319	1490-1510	UAACUAUUUCACACUAACCAGUU	3505	1488-1510
AD-159803	ACUAUAUCAGUAGUGUACAUU	3320	1724-1744	AAUGUACACUACUGAUAUAGUUC	3506	1722-1744
AD-159805	UAUAUCAGUAGUGUACAUUAA	3321	1726-1746	UUAAUGUACACUACUGAUAUAGU	3507	1724-1746
AD-159489	GUAAUAUUUUAAGAUGGACUA	3322	1371-1391	UAGUCCAUCUUAAAAUAUUACUG	3508	1369-1391
AD-159495	UUUUAAGAUGGACUGGGAAAA	3323	1377-1397	UUUUCCCAGUCCAUCUUAAAAUA	3509	1375-1397
AD-159706	UUCACUGAACAUGCCUAGUCA	3324	1608-1628	UGACUAGGCAUGUUCAGUGAAGG	3510	1606-1628
AD-159855	ACCAACUAUCCAAGUGUUAUA	3325	1783-1803	UAUAACACUUGGAUAGUUGGUUG	3511	1781-1803
AD-159864	CCAAGUGUUAUACCAACUAAA	3326	1792-1812	UUUAGUUGGUAUAACACUUGGAU	3512	1790-1812
AD-159488	AGUAAUAUUUUAAGAUGGACU	3327	1370-1390	AGUCCAUCUUAAAAUAUUACUGC	3513	1368-1390
AD-159553	AAAAUCCACAGCUAUAUCCUA	3328	1435-1455	UAGGAUAUAGCUGUGGAUUUUAC	3514	1433-1455
AD-159703	UCCUUCACUGAACAUGCCUAA	3329	1605-1625	UUAGGCAUGUUCAGUGAAGGAGC	3515	1603-1625
AD-159708	CACUGAACAUGCCUAGUCCAA	3330	1610-1630	UUGGACUAGGCAUGUUCAGUGAA	3516	1608-1630
AD-159866	AAGUGUUAUACCAACUAAAAC	3331	1794-1814	GUUUUAGUUGGUAUAACACUUGG	3517	1792-1814
AD-159232	UUCCACCAUGAUUAAGGGUCU	3332	1091-1111	AGACCCUUAAUCAUGGUGGAAAC	3518	1089-1111

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3	Antisense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3
AD-159712	GAACAUGCCUAGUCCAACAUU	3333	1614-1634	AAUGUUGGACUAGGCAUGUUCAG	3519	1612-1634
AD-159808	AUCAGUAGUGUACAUUACCAU	3334	1729-1749	AUGGUAAUGUACACUACUGAUAU	3520	1727-1749
AD-159862	AUCCAAGUGUUAUACCAACUA	3335	1790-1810	UAGUUGGUAUAACACUUGGAUAG	3521	1788-1810
AD-158503	CCAAGUCCAAUAUGGCAACUA	3336	262-282	UAGUUGCCAUAUUGGACUUGGAA	3522	260-282
AD-159412	CAUUUCACUGUCUAGGCUACA	3337	1290-1310	UGUAGCCUAGACAGUGAAAUGAU	3523	1288-1310
AD-159558	CCACAGCUAUAUCCUGAUGCU	3338	1440-1460	AGCAUCAGGAUAUAGCUGUGGAU	3524	1438-1460
AD-159705	CUUCACUGAACAUGCCUAGUA	3339	1607-1627	UACUAGGCAUGUUCAGUGAAGGA	3525	1605-1627
AD-159113	GUGGUUGAGAGUGCUUAUGAA	3340	972-992	UUCAUAAGCACUCUCAACCACCU	3526	970-992
AD-159806	AUAUCAGUAGUGUACAUUACA	3341	1727-1747	UGUAAUGUACACUACUGAUAUAG	3527	1725-1747
AD-159853	CAACCAACUAUCCAAGUGUUA	3342	1781-1801	UAACACUUGGAUAGUUGGUUGCA	3528	1779-1801
AD-159182	GCAGAUUUGGCAGAGAGUAUA	3343	1041-1061	UAUACUCUCUGCCAAAUCUGCUA	3529	1039-1061
AD-159702	CUCCUUCACUGAACAUGCCUA	3344	1604-1624	UAGGCAUGUUCAGUGAAGGAGCC	3530	1602-1624
AD-159715	CAUGCCUAGUCCAACAUUUUU	3345	1617-1637	AAAAAUGUUGGACUAGGCAUGUU	3531	1615-1637
AD-158575	UGCCAUCAGUAUCUUAAUGAA	3346	377-397	UUCAUUAAGAUACUGAUGGCACA	3532	375-397
AD-158576	GCCAUCAGUAUCUUAAUGAAA	3347	378-398	UUUCAUUAAGAUACUGAUGGCAC	3533	376-398
AD-158684	UUAGAACACCAAAGAUUGUCU	3348	487-507	AGACAAUCUUUGGUGUUCUAAGG	3534	485-507
AD-159410	AUCAUUUCACUGUCUAGGCUA	3349	1288-1308	UAGCCUAGACAGUGAAAUGAUAU	3535	1286-1308
AD-159416	UCACUGUCUAGGCUACAACAA	3350	1294-1314	UUGUUGUAGCCUAGACAGUGAAA	3536	1292-1314
AD-159857	CAACUAUCCAAGUGUUAUACA	3351	1785-1805	UGUAUAACACUUGGAUAGUUGGU	3537	1783-1805
AD-158497	UUGGUUCCAAGUCCAAUAUGA	3352	256-276	UCAUAUUGGACUUGGAACCAAAA	3538	254-276
AD-159124	UGCUUAUGAGGUGAUCAAACU	3353	983-1003	AGUUUGAUCACCUCAUAAGCACU	3539	981-1003
AD-159312	UCUCAGACCUUGUGAAGGUGA	3354	1171-1191	UCACCUUCACAAGGUCUGAGAUU	3540	1169-1191
AD-159552	UAAAAUCCACAGCUAUAUCCU	3355	1434-1454	AGGAUAUAGCUGUGGAUUUUACA	3541	1432-1454
AD-159704	CCUUCACUGAACAUGCCUAGU	3356	1606-1626	ACUAGGCAUGUUCAGUGAAGGAG	3542	1604-1626
AD-159737	GGGAUCCAGUGUAUAAAUCCA	3357	1657-1677	UGGAUUUAUACACUGGAUCCCAG	3543	1655-1677

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3	Antisense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3
AD-159869	CAAUAAACCUUGAACAGUGAA	3358	1818-1838	UUCACUGUUCAAGGUUUAUUGGG	3544	1816-1838
AD-158570	GGCCUGUGCCAUCAGUAUCUU	3359	371-391	AAGAUACUGAUGGCACAGGCCAU	3545	369-391
AD-158618	UUGUUGAUGUCAUCGAAGACA	3360	421-441	UGUCUUCGAUGACAUCAACAAGA	3546	419-441
AD-159184	AGAUUUGGCAGAGAGUAUAAU	3361	1043-1063	AUUAUACUCUCUGCCAAAUCUGC	3547	1041-1063
AD-159231	UUUCCACCAUGAUUAAGGGUA	3362	1090-1110	UACCCUUAAUCAUGGUGGAAACU	3548	1088-1110
AD-159423	CUAGGCUACAACAGGAUUCUA	3363	1301-1321	UAGAAUCCUGUUGUAGCCUAGAC	3549	1299-1321
AD-159446	UGGAGGUUGUGCAUGUUGUCA	3364	1324-1344	UGACAACAUGCACAACCUCCACC	3550	1322-1344
AD-159701	GCUCCUUCACUGAACAUGCCU	3365	1603-1623	AGGCAUGUUCAGUGAAGGAGCCA	3551	1601-1623
AD-158494	CUUUUGGUUCCAAGUCCAAUA	3366	253-273	UAUUGGACUUGGAACCAAAAGGA	3552	251-273
AD-158571	GCCUGUGCCAUCAGUAUCUUA	3367	372-392	UAAGAUACUGAUGGCACAGGCCA	3553	370-392
AD-159125	GCUUAUGAGGUGAUCAAACUA	3368	984-1004	UAGUUUGAUCACCUCAUAAGCAC	3554	982-1004
AD-159126	CUUAUGAGGUGAUCAAACUCA	3369	985-1005	UGAGUUUGAUCACCUCAUAAGCA	3555	983-1005
AD-159287	CCUUGCAUUUUGGGACAGAAU	3370	1146-1166	AUUCUGUCCCAAAAUGCAAGGAA	3556	1144-1166
AD-158499	GGUUCCAAGUCCAAUAUGGCA	3371	258-278	UGCCAUAUUGGACUUGGAACCAA	3557	256-278
AD-159417	CACUGUCUAGGCUACAACAGA	3372	1295-1315	UCUGUUGUAGCCUAGACAGUGAA	3558	1293-1315
AD-159418	ACUGUCUAGGCUACAACAGGA	3373	1296-1316	UCCUGUUGUAGCCUAGACAGUGA	3559	1294-1316
AD-158550	AAUAAGAUUACAGUUGUUGGA	3374	333-353	UCCAACAACUGUAAUCUUAUUCU	3560	331-353
AD-159116	GUUGAGAGUGCUUAUGAGGUA	3375	975-995	UACCUCAUAAGCACUCUCAACCA	3561	973-995
AD-159421	GUCUAGGCUACAACAGGAUUA	3376	1299-1319	UAAUCCUGUUGUAGCCUAGACAG	3562	1297-1319
AD-159422	UCUAGGCUACAACAGGAUUCU	3377	1300-1320	AGAAUCCUGUUGUAGCCUAGACA	3563	1298-1320
AD-159445	GUGGAGGUUGUGCAUGUUGUA	3378	1323-1343	UACAACAUGCACAACCUCCACCU	3564	1321-1343
AD-159130	UGAGGUGAUCAAACUCAAAGA	3379	989-1009	UCUUUGAGUUUGAUCACCUCAUA	3565	987-1009
AD-159134	GUGAUCAAACUCAAAGGCUAA	3380	993-1013	UUAGCCUUUGAGUUUGAUCACCU	3566	991-1013
AD-159343	UGAGGAAGAGGCCCGUUUGAA	3381	1202-1222	UUCAAACGGGCCUCUUCCUCAGA	3567	1200-1222
AD-159105	ACAAGCAGGUGGUUGAGAGUA	3382	964-984	UACUCUCAACCACCUGCUUGUGA	3568	962-984

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3	Antisense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3
AD-159183	CAGAUUUGGCAGAGAGUAUAA	3383	1042-1062	UUAUACUCUCUGCCAAAUCUGCU	3569	1040-1062
AD-159123	GUGCUUAUGAGGUGAUCAAAC	3384	982-1002	GUUUGAUCACCUCAUAAGCACUC	3570	980-1002
AD-159181	AGCAGAUUUGGCAGAGAGUAU	3385	1040-1060	AUACUCUCUGCCAAAUCUGCUAC	3571	1038-1060
AD-159186	AUUUGGCAGAGAGUAUAAUGA	3386	1045-1065	UCAUUAUACUCUCUGCCAAAUCU	3572	1043-1065
AD-159187	UUUGGCAGAGAGUAUAAUGAA	3387	1046-1066	UUCAUUAUACUCUCUGCCAAAUC	3573	1044-1066
AD-159288	CUUGCAUUUUGGGACAGAAUA	3388	1147-1167	UAUUCUGUCCCAAAAUGCAAGGA	3574	1145-1167
AD-159306	AUGGAAUCUCAGACCUUGUGA	3389	1165-1185	UCACAAGGUCUGAGAUUCCAUUC	3575	1163-1185
AD-159559	CACAGCUAUAUCCUGAUGCUA	3390	1441-1461	UAGCAUCAGGAUAUAGCUGUGGA	3576	1439-1461
AD-159344	GAGGAAGAGGCCCGUUUGAAA	3391	1203-1223	UUUCAAACGGGCCUCUUCCUCAG	3577	1201-1223
AD-159341	UCUGAGGAAGAGGCCCGUUUA	3392	1200-1220	UAAACGGGCCUCUUCCUCAGAAG	3578	1198-1220
AD-159729	CACAUCCUGGGAUCCAGUGUA	3393	1649-1669	UACACUGGAUCCCAGGAUGUGAC	3579	1647-1669
AD-158674	AGCCUUUUCCUUAGAACACCA	3394	477-497	UGGUGUUCUAAGGAAAAGGCUGC	3580	475-497
AD-159604	UCAACUGGUUAGUGUGAAAUA	3395	1486-1506	UAUUUCACACUAACCAGUUGAAG	3581	1484-1506

TABLE 3. MODIFIED HUMAN/CYNOMOLGUS CROSS-REACTIVE LDHA iRNA SEQUENCES

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-159469	ususuaucUfgAfUfCfugugauuaaaL96	3582	usUfsuaaUfcAfCfagauCfaGfauaaasasa	3768	UUUUUAUCUGAUCUGUGAUUAAA	3954
AD-159607	ascsugguUfaGfUfGfugaaauaguuL96	3583	asAfscuaUfuUfCfacacUfaAfccagususg	3769	CAACUGGUUAGUGUGAAAUAGUU	3955
AD-159713	asascaugCfcUfAfGfuccaacauuuL96	3584	asAfsaugUfuGfGfacuaGfgCfauguuscsa	3770	UGAACAUGCCUAGUCCAACAUUU	3956
AD-158504	csasagucCfaAfUfAfuggcaacucuL96	3585	asGfsaguUfgCfCfauauUfgGfacuugsgsa	3771	UCCAAGUCCAAUAUGGCAACUCU	3957
AD-159233	uscscaccAfuGfAfUfuaagggucuuL96	3586	asAfsgacCfcUfUfaaucAfuGfguggasasa	3772	UUUCCACCAUGAUUAAGGGUCUU	3958
AD-159411	uscsauuuCfaCfUfGfucuaggcuaaL96	3587	usUfsagcCfuAfGfacagUfgAfaaugasusa	3773	UAUCAUUUCACUGUCUAGGCUAC	3959
AD-159462	usgsuccuUfuUfUfAfucugaucuguL96	3588	asCfsagaUfcAfGfauaaAfaAfggacasasc	3774	GUUGUCCUUUUUAUCUGAUCUGU	3960
AD-159742	cscsagugUfaUfAfAfauccaauauaL96	3589	usAfsuauUfgGfAfuuuaUfaCfacuggsasu	3775	AUCCAGUGUAUAAAUCCAAUAUC	3961
AD-159863	uscscaagUfgUfUfAfuaccaacuaaL96	3590	usUfsaguUfgGfUfauaaCfaCfuuggasusa	3776	UAUCCAAGUGUUAUACCAACUAA	3962

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-158626	gsuscaucGfaAfGfAfcaaauugaaaL96	3591	usUfsucaAfuUfUfgucuUfcGfaugacsasu	3777	AUGUCAUCGAAGACAAAUUGAAG	3963
AD-158687	gsasacacCfaAfAfGfauugucucuaL96	3592	usAfsgagAfcAfAfucuuUfgGfuguucsusa	3778	UAGAACACCAAAGAUUGUCUCUG	3964
AD-158688	asascaccAfaAfGfAfuugucucugaL96	3593	usCfsagaGfaCfAfaucuUfuGfguguuscsu	3779	AGAACACCAAAGAUUGUCUCUGG	3965
AD-159458	asusguugUfcCfUfUfuuuaucugauL96	3594	asUfscagAfuAfAfaaagGfaCfaacausgsc	3780	GCAUGUUGUCCUUUUUAUCUGAU	3966
AD-159519	uscsaacuCfcUfGfAfaguuagaaauL96	3595	asUfsuucUfaAfCfuucaGfgAfguugasusg	3781	CAUCAACUCCUGAAGUUAGAAAU	3967
AD-159858	asascuauCfcAfAfGfuguuauaccaL96	3596	usGfsguaUfaAfCfacuuGfgAfuaguusgsg	3782	CCAACUAUCCAAGUGUUAUACCA	3968
AD-158681	uscscuuaGfaAfCfAfccaaagauuaL96	3597	usAfsaucUfuUfGfguguUfcUfaaggasasa	3783	UUUCCUUAGAACACCAAAGAUUG	3969
AD-159583	gsgsuauuAfaUfCfUfuguguagucuL96	3598	asGfsacuAfcAfCfaagaUfuAfauaccsasu	3784	AUGGUAUUAAUCUUGUGUAGUCU	3970
AD-159700	gsgscuccUfuCfAfCfugaacaugcaL96	3599	usGfscauGfuUfCfagugAfaGfgagccsasg	3785	CUGGCUCCUUCACUGAACAUGCC	3971
AD-159807	usasucagUfaGfUfGfuacauuaccaL96	3600	usGfsguaAfuGfUfacacUfaCfugauasusa	3786	UAUAUCAGUAGUGUACAUUACCA	3972
AD-158673	csasgccuUfuUfCfCfuuagaacacaL96	3601	usGfsuguUfcUfAfaggaAfaAfggcugscsc	3787	GGCAGCCUUUUCCUUAGAACACC	3973
AD-159608	csusgguuAfgUfGfUfgaaauaguuaL96	3602	usAfsacuAfuUfUfcacaCfuAfaccagsusu	3788	AACUGGUUAGUGUGAAAUAGUUC	3974
AD-159803	ascsuauaUfcAfGfUfaguguacauuL96	3603	asAfsuguAfcAfCfuacuGfaUfauagususc	3789	GAACUAUAUCAGUAGUGUACAUU	3975
AD-159805	usasuaucAfgUfAfGfuguacauuaaL96	3604	usUfsaauGfuAfCfacuaCfuGfauauasgsu	3790	ACUAUAUCAGUAGUGUACAUUAC	3976
AD-159489	gsusaauaUfuUfUfAfagauggacuaL96	3605	usAfsgucCfaUfCfuuaaAfaUfauuacsusg	3791	CAGUAAUAUUUUAAGAUGGACUG	3977
AD-159495	ususuuaaGfaUfGfGfacugggaaaaL96	3606	usUfsuucCfcAfGfuccaUfcUfuaaaasusa	3792	UAUUUUAAGAUGGACUGGGAAAA	3978
AD-159609	usgsguuaGfuGfUfGfaaauaguucuL96	3607	asGfsaacUfaUfUfucacAfcUfaaccasgsu	3793	ACUGGUUAGUGUGAAAUAGUUCU	3979
AD-159706	ususcacuGfaAfCfAfugccuagucaL96	3608	usGfsacuAfgGfCfauguUfcAfgugaasgsg	3794	CCUUCACUGAACAUGCCUAGUCC	3980
AD-159855	ascscaacUfaUfCfCfaaguguuauaL96	3609	usAfsuaaCfaCfUfuggaUfaGfuuggususg	3795	CAACCAACUAUCCAAGUGUUAUA	3981
AD-159864	cscsaaguGfuUfAfUfaccaacuaaaL96	3610	usUfsuagUfuGfGfuauaAfcAfcuuggsasu	3796	AUCCAAGUGUUAUACCAACUAAA	3982
AD-158491	ususccuuUfuGfGfUfuccaaguccaL96	3611	usGfsgacUfuGfGfaaccAfaAfaggaasusc	3797	GAUUCCUUUUGGUUCCAAGUCCA	3983
AD-158672	gscsagccUfuUfUfCfcuuagaacaaL96	3612	usUfsguuCfuAfAfggaaAfaGfgcugcscsa	3798	UGGCAGCCUUUUCCUUAGAACAC	3984
AD-159488	asgsuaauAfuUfUfUfaagauggacuL96	3613	asGfsuccAfuCfUfuaaaAfuAfuuacusgsc	3799	GCAGUAAUAUUUUAAGAUGGACU	3985
AD-159553	asasaaucCfaCfAfGfcuauauccuaL96	3614	usAfsggaUfaUfAfgcugUfgGfauuuusasc	3800	GUAAAAUCCACAGCUAUAUCCUG	3986
AD-159703	uscscuucAfcUfGfAfacaugccuaaL96	3615	usUfsaggCfaUfGfuucaGfuGfaaggasgsc	3801	GCUCCUUCACUGAACAUGCCUAG	3987
AD-159708	csascugaAfcAfUfGfccuaguccaaL96	3616	usUfsggaCfuAfGfgcauGfuUfcagugsasa	3802	UUCACUGAACAUGCCUAGUCCAA	3988
AD-159866	asasguguUfaUfAfCfcaacuaaaacL96	3617	gsUfsuuuAfgUfUfgguaUfaAfcacuusgsg	3803	CCAAGUGUUAUACCAACUAAAAC	3989
AD-159232	ususccacCfaUfGfAfuuaagggucuL96	3618	asGfsaccCfuUfAfaucaUfgGfuggaasasc	3804	GUUUCCACCAUGAUUAAGGGUCU	3990
AD-159712	gsasacauGfcCfUfAfguccaacauuL96	3619	asAfsuguUfgGfAfcuagGfcAfuguucsasg	3805	CUGAACAUGCCUAGUCCAACAUU	3991
AD-159808	asuscaguAfgUfGfUfacauuaccauL96	3620	asUfsgguAfaUfGfuacaCfuAfcugausasu	3806	AUAUCAGUAGUGUACAUUACCAU	3992
AD-159862	asusccaaGfuGfUfUfauaccaacuaL96	3621	usAfsguuGfgUfAfuaacAfcUfuggausasg	3807	CUAUCCAAGUGUUAUACCAACUA	3993
AD-158503	cscsaaguCfcAfAfUfauggcaacuaL96	3622	usAfsguuGfcCfAfuauuGfgAfcuuggsasa	3808	UUCCAAGUCCAAUAUGGCAACUC	3994
AD-159311	asuscucaGfaCfCfUfugugaagguaL96	3623	usAfsccuUfcAfCfaaggUfcUfgagaususc	3809	GAAUCUCAGACCUUGUGAAGGUG	3995
AD-159412	csasuuucAfcUfGfUfcuaggcuacaL96	3624	usGfsuagCfcUfAfgacaGfuGfaaaugsasu	3810	AUCAUUUCACUGUCUAGGCUACA	3996

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-159558	cscsacagCfuAfUfAfuccugaugcuL96	3625	asGfscauCfaGfGfauauAfgCfuguggsasu	3811	AUCCACAGCUAUAUCCUGAUGCU	3997
AD-159705	csusucacUfgAfAfCfaugccuaguaL96	3626	usAfscuaGfgCfAfuguuCfaGfugaagsgsa	3812	UCCUUCACUGAACAUGCCUAGUC	3998
AD-159113	gsusgguuGfaGfAfGfugcuuaugaaL96	3627	usUfscauAfaGfCfacucUfcAfaccacscsu	3813	AGGUGGUUGAGAGUGCUUAUGAG	3999
AD-159139	csasaacuCfaAfAfGfgcuacacauaL96	3628	usAfsuguGfuAfGfccuuUfgAfguuugsasu	3814	AUCAAACUCAAAGGCUACACAUC	4000
AD-159806	asusaucaGfuAfGfUfguacauuacaL96	3629	usGfsuaaUfgUfAfcacuAfcUfgauausasg	3815	CUAUAUCAGUAGUGUACAUUACC	4001
AD-159853	csasaccaAfcUfAfUfccaaguguuaL96	3630	usAfsacaCfuUfGfgauaGfuUfgguugscsa	3816	UGCAACCAACUAUCCAAGUGUUA	4002
AD-158627	uscsaucgAfaGfAfCfaaauugaagaL96	3631	usCfsuucAfaUfUfugucUfuCfgaugascsa	3817	UGUCAUCGAAGACAAAUUGAAGG	4003
AD-159182	gscsagauUfuGfGfCfagagaguauaL96	3632	usAfsuacUfcUfCfugccAfaAfucugcsusa	3818	UAGCAGAUUUGGCAGAGAGUAUA	4004
AD-159702	csusccuuCfaCfUfGfaacaugccuaL96	3633	usAfsggcAfuGfUfucagUfgAfaggagscsc	3819	GGCUCCUUCACUGAACAUGCCUA	4005
AD-159715	csasugccUfaGfUfCfcaacauuuuuL96	3634	asAfsaaaUfgUfUfggacUfaGfgcaugsusu	3820	AACAUGCCUAGUCCAACAUUUUU	4006
AD-158575	usgsccauCfaGfUfAfucuuaaugaaL96	3635	usUfscauUfaAfGfauacUfgAfuggcascsa	3821	UGUGCCAUCAGUAUCUUAAUGAA	4007
AD-158576	gscscaucAfgUfAfUfcuuaaugaaaL96	3636	usUfsucaUfuAfAfgauaCfuGfauggcsasc	3822	GUGCCAUCAGUAUCUUAAUGAAG	4008
AD-158684	ususagaaCfaCfCfAfaagauugucuL96	3637	asGfsacaAfuCfUfuuggUfgUfucuaasgsg	3823	CCUUAGAACACCAAAGAUUGUCU	4009
AD-159410	asuscauuUfcAfCfUfgucuaggcuaL96	3638	usAfsgccUfaGfAfcaguGfaAfaugausasu	3824	AUAUCAUUUCACUGUCUAGGCUA	4010
AD-159416	uscsacugUfcUfAfGfgcuacaacaaL96	3639	usUfsguuGfuAfGfccuaGfaCfagugasasa	3825	UUUCACUGUCUAGGCUACAACAG	4011
AD-159738	gsgsauccAfgUfGfUfauaaauccaaL96	3640	usUfsggaUfuUfAfuacaCfuGfgauccscsa	3826	UGGGAUCCAGUGUAUAAAUCCAA	4012
AD-159857	csasacuaUfcCfAfAfguguuauacaL96	3641	usGfsuauAfaCfAfcuugGfaUfaguugsgsu	3827	ACCAACUAUCCAAGUGUUAUACC	4013
AD-158497	ususgguuCfcAfAfGfuccaauaugaL96	3642	usCfsauaUfuGfGfacuuGfgAfaccaasasa	3828	UUUUGGUUCCAAGUCCAAUAUGG	4014
AD-159124	usgscuuaUfgAfGfGfugaucaaacuL96	3643	asGfsuuuGfaUfCfaccuCfaUfaagcascsu	3829	AGUGCUUAUGAGGUGAUCAAACU	4015
AD-159140	asasacucAfaAfGfGfcuacacaucaL96	3644	usGfsaugUfgUfAfgccuUfuGfaguuusgsa	3830	UCAAACUCAAAGGCUACACAUCC	4016
AD-159312	uscsucagAfcCfUfUfgugaaggugaL96	3645	usCfsaccUfuCfAfcaagGfuCfugagasusu	3831	AAUCUCAGACCUUGUGAAGGUGA	4017
AD-159552	usasaaauCfcAfCfAfgcuauauccuL96	3646	asGfsgauAfuAfGfcuguGfgAfuuuuascsa	3832	UGUAAAAUCCACAGCUAUAUCCU	4018
AD-159704	cscsuucaCfuGfAfAfcaugccuaguL96	3647	asCfsuagGfcAfUfguucAfgUfgaaggsasg	3833	CUCCUUCACUGAACAUGCCUAGU	4019
AD-159737	gsgsgaucCfaGfUfGfuauaaauccaL96	3648	usGfsgauUfuAfUfacacUfgGfaucccsasg	3834	CUGGGAUCCAGUGUAUAAAUCCA	4020
AD-159869	csasauaaAfcCfUfUfgaacagugaaL96	3649	usUfscacUfgUfUfcaagGfuUfuauugsgsg	3835	CCCAAUAAACCUUGAACAGUGAC	4021
AD-158570	gsgsccugUfgCfCfAfucaguaucuuL96	3650	asAfsgauAfcUfGfauggCfaCfaggccsasu	3836	AUGGCCUGUGCCAUCAGUAUCUU	4022
AD-158618	ususguugAfuGfUfCfaucgaagacaL96	3651	usGfsucuUfcGfAfugacAfuCfaacaasgsa	3837	UCUUGUUGAUGUCAUCGAAGACA	4023
AD-159788	gsgsaucuUfaUfUfUfugugaacuauL96	3652	asUfsaguUfcAfCfaaaaUfaAfgauccsusu	3838	AAGGAUCUUAUUUUGUGAACUAU	4024
AD-159786	asasggauCfuUfAfUfuuugugaacuL96	3653	asGfsuucAfcAfAfaauaAfgAfuccuususg	3839	CAAAGGAUCUUAUUUUGUGAACU	4025
AD-159760	asuscaugUfcUfUfGfugcauaauuaL96	3654	usAfsauuAfuGfCfacaaGfaCfaugausasu	3840	AUAUCAUGUCUUGUGCAUAAUUC	4026
AD-159404	usgsucauAfuCfAfUfuucacugucuL96	3655	asGfsacaGfuGfAfaaugAfuAfugacasusc	3841	GAUGUCAUAUCAUUUCACUGUCU	4027
AD-159406	uscsauauCfaUfUfUfcacugucuaaL96	3656	usUfsagaCfaGfUfgaaaUfgAfuaugascsa	3842	UGUCAUAUCAUUUCACUGUCUAG	4028
AD-158536	asusuuauAfaUfCfUfucuaaaggaaL96	3657	usUfsccuUfuAfGfaagaUfuAfuaaauscsa	3843	UGAUUUAUAAUCUUCUAAAGGAA	4029
AD-159545	usgsguuuGfuAfAfAfauccacagcuL96	3658	asGfscugUfgGfAfuuuuAfcAfaaccasusu	3844	AAUGGUUUGUAAAAUCCACAGCU	4030

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-159574	asusgcugGfaUfGfGfuauuaaucuuL96	3659	asAfsgauUfaAfUfaccaUfcCfagcauscsa	3845	UGAUGCUGGAUGGUAUUAAUCUU	4031
AD-159802	asascuauAfuCfAfGfuaguguacauL96	3660	asUfsguaCfaCfUfacugAfuAfuaguuscsa	3846	UGAACUAUAUCAGUAGUGUACAU	4032
AD-159518	asuscaacUfcCfUfGfaaguuagaaaL96	3661	usUfsucuAfaCfUfucagGfaGfuugausgsu	3847	ACAUCAACUCCUGAAGUUAGAAA	4033
AD-159577	csusggauGfgUfAfUfuaaucuuguaL96	3662	usAfscaaGfaUfUfaauaCfcAfuccagscsa	3848	UGCUGGAUGGUAUUAAUCUUGUG	4034
AD-159409	usasucauUfuCfAfCfugucuaggcuL96	3663	asGfsccuAfgAfCfagugAfaAfugauasusg	3849	CAUAUCAUUUCACUGUCUAGGCU	4035
AD-159551	gsusaaaaUfcCfAfCfagcuauaucaL96	3664	usGfsauaUfaGfCfugugGfaUfuuuacsasa	3850	UUGUAAAAUCCACAGCUAUAUCC	4036
AD-159276	uscscuuaGfuGfUfUfccuugcauuuL96	3665	asAfsaugCfaAfGfgaacAfcUfaaggasasg	3851	CUUCCUUAGUGUUCCUUGCAUUU	4037
AD-159407	csasuaucAfuUfUfCfacugucuagaL96	3666	usCfsuagAfcAfGfugaaAfuGfauaugsasc	3852	GUCAUAUCAUUUCACUGUCUAGG	4038
AD-159515	asascaucAfaCfUfCfcugaaguuaaL96	3667	usUfsaacUfuCfAfggagUfuGfauguususu	3853	AAAACAUCAACUCCUGAAGUUAG	4039
AD-159570	cscsugauGfcUfGfGfaugguauuaaL96	3668	usUfsaauAfcCfAfuccaGfcAfucaggsasu	3854	AUCCUGAUGCUGGAUGGUAUUAA	4040
AD-159849	asasugcaAfcCfAfAfcuauccaaguL96	3669	asCfsuugGfaUfAfguugGfuUfgcauusgsu	3855	ACAAUGCAACCAACUAUCCAAGU	4041
AD-159252	ususuacgGfaAfUfAfaaggaugauaL96	3670	usAfsucaUfcCfUfuuauUfcCfguaaasgsa	3856	UCUUUACGGAAUAAAGGAUGAUG	4042
AD-159275	ususccuuAfgUfGfUfuccuugcauuL96	3671	asAfsugcAfaGfGfaacaCfuAfaggaasgsa	3857	UCUUCCUUAGUGUUCCUUGCAUU	4043
AD-159848	csasaugcAfaCfCfAfacuauccaaaL96	3672	usUfsuggAfuAfGfuuggUfuGfcauugsusu	3858	AACAAUGCAACCAACUAUCCAAG	4044
AD-159184	asgsauuuGfgCfAfGfagaguauaauL96	3673	asUfsuauAfcUfCfucugCfcAfaaucusgsc	3859	GCAGAUUUGGCAGAGAGUAUAAU	4045
AD-159231	ususuccaCfcAfUfGfauuaaggguaL96	3674	usAfscccUfuAfAfucauGfgUfggaaascsu	3860	AGUUUCCACCAUGAUUAAGGGUC	4046
AD-159607	ascsugguUfaGfUfGfugaaauaguuL96	3675	asAfscuaUfuUfCfacacUfaAfccagususg	3861	CAACUGGUUAGUGUGAAAUAGUU	4047
AD-158504	csasagucCfaAfUfAfuggcaacucuL96	3676	asGfsaguUfgCfCfauauUfgGfacuugsgsa	3862	UCCAAGUCCAAUAUGGCAACUCU	4048
AD-159233	uscscaccAfuGfAfUfuaagggucuuL96	3677	asAfsgacCfcUfUfaaucAfuGfguggasasa	3863	UUUCCACCAUGAUUAAGGGUCUU	4049
AD-159411	uscsauuuCfaCfUfGfucuaggcuaaL96	3678	usUfsagcCfuAfGfacagUfgAfaaugasusa	3864	UAUCAUUUCACUGUCUAGGCUAC	4050
AD-159462	usgsuccuUfuUfUfAfucugaucuguL96	3679	asCfsagaUfcAfGfauaaAfaAfggacasasc	3865	GUUGUCCUUUUUAUCUGAUCUGU	4051
AD-159742	cscsagugUfaUfAfAfauccaauauaL96	3680	usAfsuauUfgGfAfuuuaUfaCfacuggsasu	3866	AUCCAGUGUAUAAAUCCAAUAUC	4052
AD-159863	uscscaagUfgUfUfAfuaccaacuaaL96	3681	usUfsaguUfgGfUfauaaCfaCfuuggasusa	3867	UAUCCAAGUGUUAUACCAACUAA	4053
AD-158687	gsasacacCfaAfAfGfauugucucuaL96	3682	usAfsgagAfcAfAfucuuUfgGfuguucsusa	3868	UAGAACACCAAAGAUUGUCUCUG	4054
AD-158688	asascaccAfaAfGfAfuugucucugaL96	3683	usCfsagaGfaCfAfaucuUfuGfguguuscsu	3869	AGAACACCAAAGAUUGUCUCUGG	4055
AD-159458	asusguugUfcCfUfUfuuuaucugauL96	3684	asUfscagAfuAfAfaaagGfaCfaacausgsc	3870	GCAUGUUGUCCUUUUUAUCUGAU	4056
AD-159519	uscsaacuCfcUfGfAfaguuagaaauL96	3685	asUfsuucUfaAfCfuucaGfgAfguugasusg	3871	CAUCAACUCCUGAAGUUAGAAAU	4057
AD-159858	asascuauCfcAfAfGfuguuauaccaL96	3686	usGfsguaUfaAfCfacuuGfgAfuaguusgsg	3872	CCAACUAUCCAAGUGUUAUACCA	4058
AD-159583	gsgsuauuAfaUfCfUfuguguagucuL96	3687	asGfsacuAfcAfCfaagaUfuAfauaccsasu	3873	AUGGUAUUAAUCUUGUGUAGUCU	4059
AD-159700	gsgscuccUfuCfAfCfugaacaugcaL96	3688	usGfscauGfuUfCfagugAfaGfgagccsasg	3874	CUGGCUCCUUCACUGAACAUGCC	4060
AD-159807	usasucagUfaGfUfGfuacauuaccaL96	3689	usGfsguaAfuGfUfacacUfaCfugauasusa	3875	UAUAUCAGUAGUGUACAUUACCA	4061
AD-158673	csasgccuUfuUfCfCfuuagaacacaL96	3690	usGfsuguUfcUfAfaggaAfaAfggcugscsc	3876	GGCAGCCUUUUCCUUAGAACACC	4062
AD-159608	csusgguuAfgUfGfUfgaaauaguuaL96	3691	usAfsacuAfuUfUfcacaCfuAfaccagsusu	3877	AACUGGUUAGUGUGAAAUAGUUC	4063
AD-159803	ascsuauaUfcAfGfUfaguguacauuL96	3692	asAfsuguAfcAfCfuacuGfaUfauagususc	3878	GAACUAUAUCAGUAGUGUACAUU	4064

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-159805	usasuaucAfgUfAfGfuguacauuaaL96	3693	usUfsaauGfuAfCfacuaCfuGfauauasgsu	3879	ACUAUAUCAGUAGUGUACAUUAC	4065
AD-159489	gsusaauaUfuUfUfAfagauggacuaL96	3694	usAfsgucCfaUfCfuuaaAfaUfauuacsusg	3880	CAGUAAUAUUUUAAGAUGGACUG	4066
AD-159495	ususuuaaGfaUfGfGfacugggaaaaL96	3695	usUfsuucCfcAfGfuccaUfcUfuaaaasusa	3881	UAUUUUAAGAUGGACUGGGAAAA	4067
AD-159706	ususcacuGfaAfCfAfugccuagucaL96	3696	usGfsacuAfgGfCfauguUfcAfgugaasgsg	3882	CCUUCACUGAACAUGCCUAGUCC	4068
AD-159855	ascscaacUfaUfCfCfaaguguuauaL96	3697	usAfsuaaCfaCfUfuggaUfaGfuuggususg	3883	CAACCAACUAUCCAAGUGUUAUA	4069
AD-159864	cscsaaguGfuUfAfUfaccaacuaaaL96	3698	usUfsuagUfuGfGfuauaAfcAfcuuggsasu	3884	AUCCAAGUGUUAUACCAACUAAA	4070
AD-159488	asgsuaauAfuUfUfUfaagauggacuL96	3699	asGfsuccAfuCfUfuaaaAfuAfuuacusgsc	3885	GCAGUAAUAUUUUAAGAUGGACU	4071
AD-159553	asasaaucCfaCfAfGfcuauauccuaL96	3700	usAfsggaUfaUfAfgcugUfgGfauuuusasc	3886	GUAAAAUCCACAGCUAUAUCCUG	4072
AD-159703	uscscuucAfcUfGfAfacaugccuaaL96	3701	usUfsaggCfaUfGfuucaGfuGfaaggasgsc	3887	GCUCCUUCACUGAACAUGCCUAG	4073
AD-159708	csascugaAfcAfUfGfccuaguccaaL96	3702	usUfsggaCfuAfGfgcauGfuUfcagugsasa	3888	UUCACUGAACAUGCCUAGUCCAA	4074
AD-159866	asasguguUfaUfAfCfcaacuaaaacL96	3703	gsUfsuuuAfgUfUfgguaUfaAfcacuusgsg	3889	CCAAGUGUUAUACCAACUAAAAC	4075
AD-159232	ususccacCfaUfGfAfuuaaggucuL96	3704	asGfsaccCfuUfAfaucaUfgGfuggaasasc	3890	GUUUCCACCAUGAUUAAGGGUCU	4076
AD-159712	gsasacauGfcCfUfAfguccaacauuL96	3705	asAfsuguUfgGfAfcuagGfcAfuguucsasg	3891	CUGAACAUGCCUAGUCCAACAUU	4077
AD-159808	asuscaguAfgUfGfUfacauuaccauL96	3706	asUfsgguAfaUfGfuacaCfuAfcugausasu	3892	AUAUCAGUAGUGUACAUUACCAU	4078
AD-159862	asusccaaGfuGfUfUfauaccaacuaL96	3707	usAfsguuGfgUfAfuaacAfcUfuggausasg	3893	CUAUCCAAGUGUUAUACCAACUA	4079
AD-158503	cscsaaguCfcAfAfUfauggcaacuaL96	3708	usAfsguuGfcCfAfuauuGfgAfcuuggsasa	3894	UUCCAAGUCCAAUAUGGCAACUC	4080
AD-159412	csasuuucAfcUfGfUfcuaggcuacaL96	3709	usGfsuagCfcUfAfgacaGfuGfaaaugsasu	3895	AUCAUUUCACUGUCUAGGCUACA	4081
AD-159558	cscsacagCfuAfUfAfuccugaugcuL96	3710	asGfscauCfaGfGfauauAfgCfuguggsasu	3896	AUCCACAGCUAUAUCCUGAUGCU	4082
AD-159705	csusucacUfgAfAfCfaugccuaguaL96	3711	usAfscuaGfgCfAfuguuCfaGfugaagsgsa	3897	UCCUUCACUGAACAUGCCUAGUC	4083
AD-159113	gsusgguuGfaGfAfGfugcuuaugaaL96	3712	usUfscauAfaGfCfacucUfcAfaccacscsu	3898	AGGUGGUUGAGAGUGCUUAUGAG	4084
AD-159806	asusaucaGfuAfGfUfguacauuacaL96	3713	usGfsuaaUfgUfAfcacuAfcUfgauausasg	3899	CUAUAUCAGUAGUGUACAUUACC	4085
AD-159853	csasaccaAfcUfAfUfccaaguguuaL96	3714	usAfsacaCfuUfGfgauaGfuUfgguugscsa	3900	UGCAACCAACUAUCCAAGUGUUA	4086
AD-159182	gscsagauUfuGfGfCfagagaguauaL96	3715	usAfsuacUfcUfCfugccAfaAfucugcsusa	3901	UAGCAGAUUUGGCAGAGAGUAUA	4087
AD-159702	csuscuuCfaCfUfGfaacaugccuaL96	3716	usAfsggcAfuGfUfucagUfgAfaggagscsc	3902	GGCUCCUUCACUGAACAUGCCUA	4088
AD-159715	csasugccUfaGfUfCfcaacauuuuuL96	3717	asAfsaaaUfgUfUfggacUfaGfgcaugsusu	3903	AACAUGCCUAGUCCAACAUUUUU	4089
AD-158575	usgsccauCfaGfUfAfucuuaaugaaL96	3718	usUfscauUfaAfGfauacUfgAfuggcascsa	3904	UGUGCCAUCAGUAUCUUAAUGAA	4090
AD-158576	gscscaucAfgUfAfUfcuuaaugaaaL96	3719	usUfsucaUfuAfAfgauaCfuGfauggcsasc	3905	GUGCCAUCAGUAUCUUAAUGAAG	4091
AD-158684	ususagaaCfaCfCfAfaagauugucuL96	3720	asGfsacaAfuCfUfuuggUfgUfucuaasgsg	3906	CCUUAGAACACCAAAGAUUGUCU	4092
AD-159410	asuscauuUfcAfCfUfgucuaggcuaL96	3721	usAfsgccUfaGfAfcaguGfaAfaugausasu	3907	AUAUCAUUUCACUGUCUAGGCUA	4093
AD-159416	uscsacugUfcUfAfGfgcuacaacaaL96	3722	usUfsguuGfuAfGfccuaGfaCfagugasasa	3908	UUUCACUGUCUAGGCUACAACAG	4094
AD-159857	csasacuaUfcCfAfAfguguuauacaL96	3723	usGfsuauAfaCfAfcuugGfaUfaguugsgsu	3909	ACCAACUAUCCAAGUGUUAUACC	4095
AD-158497	ususgguuCfcAfAfGfuccaauaugaL96	3724	usCfsauaUfuGfGfacuuGfgAfaccaasasa	3910	UUUUGGUUCCAAGUCCAAUAUGG	4096
AD-159124	usgscuuaUfgAfGfGfugaucaaacuL96	3725	asGfsuuuGfaUfCfaccuCfaUfaagcascsu	3911	AGUGCUUAUGAGGUGAUCAAACU	4097
AD-159312	uscsucagAfcCfUfUfgugaaggugaL96	3726	usCfsaccUfuCfAfcaagGfuCfugagasusu	3912	AAUCUCAGACCUUGUGAAGGUGA	4098

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-159552	usasaaauCfcAfCfAfgcuauauccuL96	3727	asGfsgauAfuAfGfcuguGfgAfuuuuascsa	3913	UGUAAAAUCCACAGCUAUAUCCU	4099
AD-159704	cscsuucaCfuGfAfAfcaugccuaguL96	3728	asCfsuagGfcAfUfguucAfgUfgaaggsasg	3914	CUCCUUCACUGAACAUGCCUAGU	4100
AD-159737	gsgsgaucCfaGfUfGfuauaaauccaL96	3729	usGfsgauUfuAfUfacacUfgGfaucccsasg	3915	CUGGGAUCCAGUGUAUAAAUCCA	4101
AD-159869	csasauaaAfcCfUfUfgaacagugaaL96	3730	usUfscacUfgUfUfcaagGfuUfuauugsgsg	3916	CCCAAUAAACCUUGAACAGUGAC	4102
AD-158570	gsgsccugUfgCfCfAfucaguaucuuL96	3731	asAfsgauAfcUfGfauggCfaCfaggccsasu	3917	AUGGCCUGUGCCAUCAGUAUCUU	4103
AD-158618	ususguugAfuGfUfCfaucgaagacaL96	3732	usGfsucuUfcGfAfugacAfuCfaacaasgsa	3918	UCUUGUUGAUGUCAUCGAAGACA	4104
AD-159184	asgsauuuGfgCfAfGfagaguauaauL96	3733	asUfsuauAfcUfCfucugCfcAfaaucusgsc	3919	GCAGAUUUGGCAGAGAGUAUAAU	4105
AD-159231	ususuccaCfcAfUfGfauuaaggguaL96	3734	usAfscccUfuAfAfucauGfgUfggaaascsu	3920	AGUUUCCACCAUGAUUAAGGGUC	4106
AD-159423	csusaggcUfaCfAfAfcaggauucuaL96	3735	usAfsgaaUfcCfUfguugUfaGfccuagsasc	3921	GUCUAGGCUACAACAGGAUUCUA	4107
AD-159446	usgsgaggUfuGfUfGfcauguugucaL96	3736	usGfsacaAfcAfUfgcacAfaCfcuccascsc	3922	GGUGGAGGUUGUGCAUGUUGUCC	4108
AD-159701	gscsuccuUfcAfCfUfgaacaugccuL96	3737	asGfsgcaUfgUfUfcaguGfaAfggagcscsa	3923	UGGCUCCUUCACUGAACAUGCCU	4109
AD-158494	csusuuugGfuUfCfCfaaguccaauaL96	3738	usAfsuugGfaCfUfuggaAfcCfaaaagsgsa	3924	UCCUUUUGGUUCCAAGUCCAAUA	4110
AD-158571	gscscuguGfcCfAfUfcaguaucuuaL96	3739	usAfsagaUfaCfUfgaugGfcAfcaggcscsa	3925	UGGCCUGUGCCAUCAGUAUCUUA	4111
AD-159125	gscsuuauGfaGfGfUfgaucaaacuaL96	3740	usAfsguuUfgAfUfcaccUfcAfuaagcsasc	3926	GUGCUUAUGAGGUGAUCAAACUC	4112
AD-159126	csusuaugAfgGfUfGfaucaaacucaL96	3741	usGfsaguUfuGfAfucacCfuCfauaagscsa	3927	UGCUUAUGAGGUGAUCAAACUCA	4113
AD-159287	cscsuugcAfuUfUfUfgggacagaauL96	3742	asUfsucuGfuCfCfcaaaAfuGfcaaggsasa	3928	UUCCUUGCAUUUUGGGACAGAAU	4114
AD-158499	gsgsuuccAfaGfUfCfcaauauggcaL96	3743	usGfsccaUfaUfUfggacUfuGfgaaccsasa	3929	UUGGUUCCAAGUCCAAUAUGGCA	4115
AD-159417	csascuguCfuAfGfGfcuacaacagaL96	3744	usCfsuguUfgUfAfgccuAfgAfcagugsasa	3930	UUCACUGUCUAGGCUACAACAGG	4116
AD-159418	ascsugucUfaGfGfCfuacaacaggaL96	3745	usCfscugUfuGfUfagccUfaGfacagusgsa	3931	UCACUGUCUAGGCUACAACAGGA	4117
AD-158550	asasuaagAfuUfAfCfaguuguuggaL96	3746	usCfscaaCfaAfCfuguaAfuCfuuauuscsu	3932	AGAAUAAGAUUACAGUUGUUGGG	4118
AD-159116	gsusugagAfgUfGfCfuuaugagguaL96	3747	usAfsccuCfaUfAfagcaCfuCfucaacscsa	3933	UGGUUGAGAGUGCUUAUGAGGUG	4119
AD-159421	gsuscuagGfcUfAfCfaacaggauuaL96	3748	usAfsaucCfuGfUfuguaGfcCfuagacsasg	3934	CUGUCUAGGCUACAACAGGAUUC	4120
AD-159422	uscsuaggCfuAfCfAfacaggauucuL96	3749	asGfsaauCfcUfGfuuguAfgCfcuagascsa	3935	UGUCUAGGCUACAACAGGAUUCU	4121
AD-159445	gsusggagGfuUfGfUfgcauguuguaL96	3750	usAfscaaCfaUfGfcacaAfcCfuccacscsu	3936	AGGUGGAGGUUGUGCAUGUUGUC	4122
AD-159130	usgsagguGfaUfCfAfaacucaaagaL96	3751	usCfsuuuGfaGfUfuugaUfcAfccucasusa	3937	UAUGAGGUGAUCAAACUCAAAGG	4123
AD-159134	gsusgaucAfaAfCfUfcaaaggcuaaL96	3752	usUfsagcCfuUfUfgaguUfuGfaucacscsu	3938	AGGUGAUCAAACUCAAAGGCUAC	4124
AD-159343	usgsaggaAfgAfGfGfcccguuugaaL96	3753	usUfscaaAfcGfGfgccuCfuUfccucasgsa	3939	UCUGAGGAAGAGGCCCGUUUGAA	4125
AD-159105	ascsaagcAfgGfUfGfguugagaguaL96	3754	usAfscucUfcAfAfccacCfuGfcuugusgsa	3940	UCACAAGCAGGUGGUUGAGAGUG	4126
AD-159183	csasgauuUfgGfCfAfgagaguauaaL96	3755	usUfsauaCfuCfUfcugcCfaAfaucugscsu	3941	AGCAGAUUUGGCAGAGAGUAUAA	4127
AD-159123	gsusgcuuAfuGfAfGfgugaucaaacL96	3756	gsUfsuugAfuCfAfccucAfuAfagcacsusc	3942	GAGUGCUUAUGAGGUGAUCAAAC	4128
AD-159181	asgscagaUfuUfGfGfcagagaguauL96	3757	asUfsacuCfuCfUfgccaAfaUfcugcusasc	3943	GUAGCAGAUUUGGCAGAGAGUAU	4129
AD-159186	asususuggCfaGfAfGfaguauaaugaL96	3758	usCfsauuAfuAfCfucucUfgCfcaaauscsu	3944	AGAUUUGGCAGAGAGUAUAAUGA	4130
AD-159187	ususuggcAfgAfGfAfguauaaugaaL96	3759	usUfscauUfaUfAfcucuCfuGfccaaasusc	3945	GAUUUGGCAGAGAGUAUAAUGAA	4131
AD-159288	csusugcaUfuUfUfGfggacagaauaL96	3760	usAfsuucUfgUfCfccaaAfaUfgcaagsgsa	3946	UCCUUGCAUUUUGGGACAGAAUG	4132

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-159306	asusggaaUfcUfCfAfgaccuugugaL96	3761	usCfsacaAfgGfUfcugaGfaUfuccaususc	3947	GAAUGGAAUCUCAGACCUUGUGA	4133
AD-159559	csascagcUfaUfAfUfccugaugcuaL96	3762	usAfsgcaUfcAfGfgauaUfaGfcugugsgsa	3948	UCCACAGCUAUAUCCUGAUGCUG	4134
AD-159344	gsasggaaGfaGfGfCfccguuugaaaL96	3763	usUfsucaAfaCfGfggccUfcUfuccucsasg	3949	CUGAGGAAGAGGCCCGUUUGAAG	4135
AD-159341	uscsugagGfaAfGfAfggcccguuuaL96	3764	usAfsaacGfgGfCfcucuUfcCfucagasasg	3950	CUUCUGAGGAAGAGGCCCGUUUG	4136
AD-159729	csascaucCfuGfGfGfauccaguguaL96	3765	usAfscacUfgGfAfucccAfgGfaugugsasc	3951	GUCACAUCCUGGGAUCCAGUGUA	4137
AD-158674	asgsccuuUfuCfCfUfuagaacaccaL96	3766	usGfsgugUfuCfUfaaggAfaAfaggcusgsc	3952	GCAGCCUUUUCCUUAGAACACCA	4138
AD-159604	uscsaacuGfgUfUfAfgugugaaauaL96	3767	usAfsuuuCfaCfAfcuaaCfcAfguugasasg	3953	CUUCAACUGGUUAGUGUGAAAUA	4139

Table 4. Modified Human/Mouse/Cyno/Rat, Mouse, Mouse/Rat, and Human/Cyno Cross-Reactive HAO1 iRNA Sequences

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Species
AD-62933	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	4140	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	89	Hs/Mm
AD-62939	UfsusUfuCfaAfuGfGfGfuGfuCfcUfaGfgAfL96	4141	usCfscUfaGfgAfcAfcccAfuUfgAfaAfasgsu	90	Hs/Mm
AD-62944	GfsasAfaGfuCfaUfCfGfaCfaAfgAfcAfuUfL96	4142	asAfsuGfuCfuUfgUfcgaUfgAfcUfuUfcsasc	91	Hs/Mm
AD-62949	UfscsAfuCfgAfcAfAfGfaCfaUfuGfgUfgAfL96	4143	usCfsaCfcAfaUfgUfcuuGfuCfgAfuGfascsu	92	Hs/Mm
AD-62954	UfsusUfcAfaUfgGfGfUfgUfcCfuAfgGfaAfL96	4144	usUfscCfuAfgGfaCfaccCfaUfuGfaAfasasg	93	Hs/Mm
AD-62959	AfsasUfgGfgUfgUfCfCfuAfgGfaAfcCfuUfL96	4145	asAfsgGfuUfcCfuAfggaCfaCfcCfaUfusgsa	94	Hs/Mm
AD-62964	GfsasCfaGfuGfcAfCfAfaUfaUfuUfuCfcAfL96	4146	usGfsgAfaAfaUfaUfuguGfcAfcUfgUfcsasg	95	Hs/Mm
AD-62969	AfscsUfuUfuCfaAfUfGfgGfuGfuCfcUfaAfL96	4147	usUfsaGfgAfcAfcCfcauUfgAfaAfaGfuscsa	96	Hs/Mm
AD-62934	AfsasGfuCfaUfcGfAfCfaAfgAfcAfuUfgAfL96	4148	usCfsaAfuGfuCfuUfgucGfaUfgAfcUfususc	97	Hs/Mm
AD-62940	AfsusCfgAfcAfaGfAfCfaUfuGfgUfgAfgAfL96	4149	usCfsuCfaCfcAfaUfgucUfuGfuCfgAfusgsa	98	Hs/Mm
AD-62945	GfsgsGfaGfaAfaGfGfUfgUfuCfaAfgAfuAfL96	4150	usAfsuCfuUfgAfaCfaccUfuUfcUfcCfcscsc	99	Hs/Mm
AD-62950	CfsusUfuUfcAfaUfGfGfgUfgUfcCfuAfgAfL96	4311	usCfsuAfgGfaCfaCfccaUfuGfaAfaAfgsusc	100	Hs/Mm
AD-62955	UfscsAfaUfgGfgUfGfUfcCfuAfgGfaAfcAfL96	4312	usGfsuUfcCfuAfgGfacaCfcCfaUfuGfasasa	101	Hs/Mm
AD-62960	UfsusGfaCfuUfuUfCfAfaUfgGfgUfgUfcAfL96	4313	usGfsaCfaCfcCfaUfugaAfaAfgUfcAfasasa	102	Hs/Mm
AD-62965	AfsasAfgUfcAfuCfGfAfcAfaGfaCfaUfuAfL96	4314	usAfsaUfgUfcUfuGfucgAfuGfaCfuUfuscsa	103	Hs/Mm

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Species
AD-62970	CfsasGfgGfgGfaGfAfAfaGfgUfgUfuCfaAfL96	4315	usUfsgAfaCfaCfcUfuucUfcCfcCfcUfgsgsa	104	Hs/Mm
AD-62935	CfsasUfuGfgUfgAfGfGfaAfaAfaUfcCfuUfL96	4316	asAfsgGfaUfuUfuUfccuCfaCfcAfaUfgsusc	105	Hs/Mm
AD-62941	AfscsAfuUfgGfuGfAfGfgAfaAfaAfuCfcUfL96	4317	asGfsgAfuUfuUfuCfcucAfcCfaAfuGfuscsu	106	Hs/Mm
AD-62946	AfsgsGfgGfgAfgAfAfAfgGfuGfuUfcAfaAfL96	4318	usUfsuGfaAfcAfcCfuuuCfuCfcCfcCfusgsg	107	Hs/Mm
AD-62951	AfsusGfgUfgGfuAfAfUfuUfgUfgAfuUfuUfL96	37	asAfsaAfuCfaCfaAfauuAfcCfaCfcAfuscsc	108	Hs
AD-62956	GfsasCfuUfgCfaUfCfCfuGfgAfaAfuAfuAfL96	38	usAfsuAfuUfuCfcAfggaUfgCfaAfgUfcscsa	109	Hs
AD-62961	GfsgsAfaGfgGfaAfGfGfuAfgAfaGfuCfuUfL96	39	asAfsgAfcUfuCfuAfccuUfcCfcUfuCfcsasc	110	Hs
AD-62966	UfsgsUfcUfuCfuGfUfUfuAfgAfuUfuCfcUfL96	40	asGfsgAfaAfuCfuAfaacAfgAfaGfaCfasgsg	111	Hs
AD-62971	CfsusUfuGfgCfuGfUfUfuCfcAfaGfaUfcUfL96	41	asGfsaUfcUfuGfgAfaacAfgCfcAfaAfgsgsa	112	Hs
AD-62936	AfsasUfgUfgUfuUfGfGfgCfaAfcGfuCfaUfL96	42	asUfsgAfcGfuUfgCfccaAfaCfaCfaUfususu	113	Hs
AD-62942	UfsgsUfgAfcUfgUfGfGfaCfaCfcCfcUfuAfL96	43	usAfsaGfgGfgUfgUfccaCfaGfuCfaCfasasa	114	Hs
AD-62947	GfsasUfgGfgGfuGfCfCfaGfcUfaCfuAfuUfL96	44	asAfsuAfgUfaGfcUfggcAfcCfcCfaUfcscsa	115	Hs
AD-62952	GfsasAfaAfuGfuGfUfUfuGfgGfcAfaCfgUfL96	45	asCfsgUfuGfcCfcAfaacAfcAfuUfuUfcsasa	116	Hs
AD-62957	GfsgsCfuGfuUfuCfCfAfaGfaUfcUfgAfcAfL96	46	usGfsuCfaGfaUfcUfuggAfaAfcAfgCfcsasa	117	Hs
AD-62962	UfscsCfaAfcAfaAfAfUfaGfcCfaCfcCfcUfL96	47	asGfsgGfgUfgGfcUfauuUfuGfuUfgGfasasa	118	Hs
AD-62967	GfsusCfuUfcUfgUfUfUfaGfaUfuUfcCfuUfL96	48	asAfsgGfaAfaUfcUfaaaCfaGfaAfgAfcsasg	119	Hs
AD-62972	UfsgsGfaAfgGfgAfAfGfgUfaGfaAfgUfcUfL96	49	asGfsaCfuUfcUfaCfcuuCfcCfuUfcCfascsa	120	Hs
AD-62937	UfscsCfuUfuGfgCfUfGfuUfuCfcAfaGfaUfL96	50	asUfscUfuGfgAfaAfcagCfcAfaAfgGfasusu	121	Hs
AD-62943	CfsasUfcUfcUfcAfGfCfuGfgGfaUfgAfuAfL96	51	usAfsuCfaUfcCfcAfgcuGfaGfaGfaUfgsgsg	122	Hs
AD-62948	GfsgsGfgUfgCfcAfGfCfuAfcUfaUfuGfaUfL96	52	asUfscAfaUfaGfuAfgcuGfgCfaCfcCfcsasu	123	Hs
AD-62953	AfsusGfuGfuUfuGfGfGfcAfaCfgUfcAfuAfL96	53	usAfsuGfaCfgUfuGfcccAfaAfcAfcAfususu	124	Hs
AD-62958	CfsusGfuUfuAfgAfUfUfuCfcUfuAfaGfaAfL96	54	usUfscUfuAfaGfgAfaauCfuAfaAfcAfgsasa	125	Hs
AD-62963	AfsgsAfaAfgAfaAfUfGfgAfcUfuGfcAfuAfL96	55	usAfsuGfcAfaGfuCfcauUfuCfuUfuCfusasg	126	Hs
AD-62968	GfscsAfuCfcUfgGfAfAfaUfaUfaUfuAfaAfL96	56	usUfsuAfaUfaUfaUfuucCfaGfgAfuGfcsasa	127	Hs
AD-62973	CfscsUfgUfcAfgAfCfCfaUfgGfgAfaCfuAfL96	57	usAfsgUfuCfcCfaUfgguCfuGfaCfaGfgscsu	128	Hs
AD-62938	AfsasAfcAfuGfgUfGfUfgGfaUfgGfgAfuAfL96	58	usAfsuCfcCfaUfcCfacaCfcAfuGfuUfusasa	129	Hs

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Species
AD-62974	CfsusCfaGfgAfuGfAfAfaAfaUfuUfuGfaAfL96	59	usUfscAfaAfaUfuUfuucAfuCfcUfgAfgsusu	130	Hs
AD-62978	CfsasGfcAfuGfuAfUfUfaCfuUfgAfcAfaAfL96	60	usUfsuGfuCfaAfgUfaauAfcAfuGfcUfgsasa	131	Hs
AD-62982	UfsasUfgAfaCfaAfCfAfuGfcUfaAfaUfcAfL96	61	usGfsaUfuUfaGfcAfuguUfgUfuCfaUfasasu	132	Hs
AD-62986	AfsusAfuAfuCfcAfAfAfuGfuUfuUfaGfgAfL96	62	usCfscUfaAfaAfcAfuuuGfgAfuAfuAfususc	133	Hs
AD-62990	CfscsAfgAfuGfgAfAfGfcUfgUfaUfcCfaAfL96	63	usUfsgGfaUfaCfaGfcuuCfcAfuCfuGfgsasa	134	Hs
AD-62994	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	64	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	135	Hs
AD-62998	CfscsCfcGfgCfuAfAfUfuUfgUfaUfcAfaUfL96	65	asUfsuGfaUfaCfaAfauuAfgCfcGfgGfgsgsa	136	Hs
AD-63002	UfsusAfaAfcAfuGfGfCfuUfgAfaUfgGfgAfL96	66	usCfscCfaUfuCfaAfgccAfuGfuUfuAfascsa	137	Hs
AD-62975	AfsasUfgUfgUfuUfAfGfaCfaAfcGfuCfaUfL96	67	asUfsgAfcGfuUfgUfcuaAfaCfaCfaUfususu	138	Mm
AD-62979	AfscsUfaAfaGfgAfAfGfaAfuUfcCfgGfuUfL96	68	asAfscCfgGfaAfuUfcuuCfcUfuUfaGfusasu	139	Mm
AD-62983	UfsasUfaUfcCfaAfAfUfgUfuUfuAfgGfaUfL96	69	asUfscCfuAfaAfaCfauuUfgGfaUfaUfasusu	140	Mm
AD-62987	GfsusGfcGfgAfaAfGfGfcAfcUfgAfuGfuUfL96	70	asAfscAfuCfaGfuGfccuUfuCfcGfcAfcsasc	141	Mm
AD-62991	UfsasAfaAfcAfgUfGfGfuUfcUfuAfaAfuUfL96	71	asAfsuUfuAfaGfaAfccaCfuGfuUfuUfasasa	142	Mm
AD-62995	AfsusGfaAfaAfaUfUfUfuGfaAfaCfcAfgUfL96	72	asCfsuGfgUfuUfcAfaaaUfuUfuUfcAfuscsc	143	Mm
AD-62999	AfsasCfaAfaAfuAfGfCfaAfuCfcCfuUfuUfL96	73	asAfsaAfgGfgAfuUfgcuAfuUfuUfgUfusgsg	144	Mm
AD-63003	CfsusGfaAfaCfaGfAfUfcUfgUfcGfaCfuUfL96	74	asAfsgUfcGfaCfaGfaucUfgUfuUfcAfgscsa	145	Mm
AD-62976	UfsusGfuUfgCfaAfAfGfgGfcAfuUfuUfgAfL96	75	usCfsaAfaAfuGfcCfcuuUfgCfaAfcAfasusu	146	Mm
AD-62980	CfsusCfaUfuGfuUfUfAfuUfaAfcCfuGfuAfL96	76	usAfscAfgGfuUfaAfuaaAfcAfaUfgAfgsasu	147	Mm
AD-62984	CfsasAfcAfaAfaUfAfGfcAfaUfcCfcUfuUfL96	77	asAfsaGfgGfaUfuGfcuaUfuUfuGfuUfgsgsa	148	Mm
AD-62992	CfsasUfuGfuUfuAfUfUfaAfcCfuGfuAfuUfL96	78	asAfsuAfcAfgGfuUfaauAfaAfcAfaUfgsasg	149	Mm
AD-62996	UfsasUfcAfgCfuGfGfGfaAfgAfuAfuCfaAfL96	79	usUfsgAfuAfuCfuUfcccAfgCfuGfaUfasgsa	150	Mm
AD-63000	UfsgsUfcCfuAfgGfAfAfcCfuUfuUfaGfaAfL96	80	usUfscUfaAfaAfgGfuucCfuAfgGfaCfascsc	151	Mm
AD-63004	UfscsCfaAfcAfaAfAfUfaGfcAfaUfcCfcUfL96	81	asGfsgGfaUfuGfcUfauuUfuGfuUfgGfasasa	152	Mm
AD-62977	GfsgsUfgUfgCfgGfAfAfaGfgCfaCfuGfaUfL96	82	asUfscAfgUfgCfcUfuucCfgCfaCfaCfcscsc	153	Mm
AD-62981	UfsusGfaAfaCfcAfGfUfaCfuUfuAfuCfaUfL96	83	asUfsgAfuAfaAfgUfacuGfgUfuUfcAfasasa	154	Mm
AD-62985	UfsasCfuUfcCfaAfAfGfuCfuAfuAfuAfuAfL96	84	usAfsuAfuAfuAfgAfcuuUfgGfaAfgUfascsu	155	Mm

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Species
AD-62989	UfscsCfuAfgGfaAfCfCfuUfuUfaGfaAfaUfL96	85	asUfsuUfcUfaAfaAfgguUfcCfuAfgGfascsa	156	Mm
AD-62993	CfsusCfcUfgAfgGfAfAfaAfuUfuUfgGfaAfL96	86	usUfscCfaAfaAfuUfuucCfuCfaGfgAfgsasa	157	Mm
AD-62997	GfscsUfcCfgGfaAfUfGfuUfgCfuGfaAfaUfL96	87	asUfsuUfcAfgCfaAfcauUfcCfgGfaGfcsasu	158	Mm
AD-63001	GfsusGfuUfuGfuGfGfGfgAfgAfcCfaAfuAfL96	88	usAfsuUfgGfuCfuCfcccAfcAfaAfcAfcsasg	159	Mm

Table 5. Additional Modified Human/Mouse/Cyno/Rat, Human/Mouse/Rat, Human/Mouse/Cyno, Mouse, Mouse/Rat, and Human/Cyno Cross-Reactive HAO1 iRNA Sequences

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Species
AD-62933.2	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	4140	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	89	Hs/Mm
AD-62939.2	UfsusUfuCfaAfuGfGfGfuGfuCfcUfaGfgAfL96	4141	usCfscUfaGfgAfcAfcccAfuUfgAfaAfasgsu	90	Hs/Mm
AD-62944.2	GfsasAfaGfuCfaUfCfGfaCfaAfgAfcAfuUfL96	4142	asAfsuGfuCfuUfgUfcgaUfgAfcUfuUfcsasc	91	Hs/Mm
AD-62949.2	UfscsAfuCfgAfcAfAfGfaCfaUfuGfgUfgAfL96	4143	usCfsaCfcAfaUfgUfcuuGfuCfgAfuGfascsu	92	Hs/Mm
AD-62954.2	UfsusUfcAfaUfgGfGfUfgUfcCfuAfgGfaAfL96	4144	usUfscCfuAfgGfaCfaccCfaUfuGfaAfasasg	93	Hs/Mm
AD-62959.2	AfsasUfgGfgUfgUfCfCfuAfgGfaAfcCfuUfL96	4145	asAfsgGfuUfcCfuAfggaCfaCfcCfaUfusgsa	94	Hs/Mm
AD-62964.2	GfsasCfaGfuGfcAfCfAfaUfaUfuUfuCfcAfL96	4146	usGfsgAfaAfaUfaUfuguGfcAfcUfgUfcsasg	95	Hs/Mm
AD-62969.2	AfscsUfuUfuCfaAfUfGfgGfuGfuCfcUfaAfL96	4147	usUfsaGfgAfcAfcCfcauUfgAfaAfaGfuscsa	96	Hs/Mm
AD-62934.2	AfsasGfuCfaUfcGfAfCfaAfgAfcAfuUfgAfL96	4148	usCfsaAfuGfuCfuUfgucGfaUfgAfcUfususc	97	Hs/Mm
AD-62940.2	AfsusCfgAfcAfaGfAfCfaUfuGfgUfgAfgAfL96	4149	usCfsuCfaCfcAfaUfgucUfuGfuCfgAfusgsa	98	Hs/Mm
AD-62945.2	GfsgsGfaGfaAfaGfGfUfgUfuCfaAfgAfuAfL96	4150	usAfsuCfuUfgAfaCfaccUfuUfcUfcCfcscsc	99	Hs/Mm
AD-62950.2	CfsusUfuUfcAfaUfGfGfgUfgUfcCfuAfgAfL96	4311	usCfsuAfgGfaCfaCfccaUfuGfaAfaAfgsusc	100	Hs/Mm
AD-62955.2	UfscsAfaUfgGfgUfGfUfcCfuAfgGfaAfcAfL96	4312	usGfsuUfcCfuAfgGfacaCfcCfaUfuGfasasa	101	Hs/Mm
AD-62960.2	UfsusGfaCfuUfuUfCfAfaUfgGfgUfgUfcAfL96	4313	usGfsaCfaCfcCfaUfugaAfaAfgUfcAfasasa	102	Hs/Mm
AD-62965.2	AfsasAfgUfcAfuCfGfAfcAfaGfaCfaUfuAfL96	4314	usAfsaUfgUfcUfuGfucgAfuGfaCfuUfuscsa	103	Hs/Mm
AD-62970.2	CfsasGfgGfgGfaGfAfAfaGfgUfgUfuCfaAfL96	4315	usUfsgAfaCfaCfcUfuucUfcCfcCfcUfgsgsa	104	Hs/Mm

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AD-62935.2	CfsasUfuGfgUfgAfGfGfaAfaAfaUfcCfuUfL96	4316	asAfsgGfaUfuUfuUfccuCfaCfcAfaUfgsusc	105	Hs/Mm
AD-62941.2	AfscsAfuUfgGfuGfAfGfgAfaAfaAfuCfcUfL96	4317	asGfsgAfuUfuUfuCfcucAfcCfaAfuGfuscsu	106	Hs/Mm
AD-62946.2	AfsgsGfgGfgAfgAfAfAfgGfuGfuUfcAfaAfL96	4318	usUfsuGfaAfcAfcCfuuuCfuCfcCfcCfusgsg	107	Hs/Mm
AD-62951.2	AfsusGfgUfgGfuAfAfUfuUfgUfgAfuUfuUfL96	37	asAfsaAfuCfaCfaAfauuAfcCfaCfcAfuscsc	108	Hs
AD-62956.2	GfsasCfuUfgCfaUfCfCfuGfgAfaAfuAfuAfL96	38	usAfsuAfuUfuCfcAfggaUfgCfaAfgUfcscsa	109	Hs
AD-62961.2	GfsgsAfaGfgGfaAfGfGfuAfgAfaGfuCfuUfL96	39	asAfsgAfcUfuCfuAfccuUfcCfcUfuCfcsasc	110	Hs
AD-62966.2	UfsgsUfcUfuCfuGfUfUfuAfgAfuUfuCfcUfL96	40	asGfsgAfaAfuCfuAfaacAfgAfaGfaCfasgsg	111	Hs
AD-62971.2	CfsusUfuGfgCfuGfUfUfuCfcAfaGfaUfcUfL96	41	asGfsaUfcUfuGfgAfaacAfgCfcAfaAfgsgsa	112	Hs
AD-62936.2	AfsasUfgUfgUfuUfGfGfgCfaAfcGfuCfaUfL96	42	asUfsgAfcGfuUfgCfccaAfaCfaCfaUfususu	113	Hs
AD-62942.2	UfsgsUfgAfcUfgUfGfGfaCfaCfcCfcUfuAfL96	43	usAfsaGfgGfgUfgUfccaCfaGfuCfaCfasasa	114	Hs
AD-62947.2	GfsasUfgGfgGfuGfCfCfaGfcUfaCfuAfuUfL96	44	asAfsuAfgUfaGfcUfggcAfcCfcCfaUfcscsa	115	Hs
AD-62952.2	GfsasAfaAfuGfuGfUfUfuGfgGfcAfaCfgUfL96	45	asCfsgUfuGfcCfcAfaacAfcAfuUfuUfcsasa	116	Hs
AD-62957.2	GfsgsCfuGfuUfuCfCfAfaGfaUfcUfgAfcAfL96	46	usGfsuCfaGfaUfcUfuggAfaAfcAfgCfcsasa	117	Hs
AD-62962.2	UfscsCfaAfcAfaAfAfUfaGfcCfaCfcCfcUfL96	47	asGfsgGfgUfgGfcUfauuUfuGfuUfgGfasasa	118	Hs
AD-62967.2	GfsusCfuUfcUfgUfUfUfaGfaUfuUfcCfuUfL96	48	asAfsgGfaAfaUfcUfaaaCfaGfaAfgAfcsasg	119	Hs
AD-62972.2	UfsgsGfaAfgGfgAfAfGfgUfaGfaAfgUfcUfL96	49	asGfsaCfuUfcUfaCfcuuCfcCfuUfcCfascsa	120	Hs
AD-62937.2	UfscsCfuUfuGfgCfUfGfuUfuCfcAfaGfaUfL96	50	asUfscUfuGfgAfaAfcagCfcAfaAfgGfasusu	121	Hs
AD-62943.2	CfsasUfcUfcUfcAfGfCfuGfgGfaUfgAfuAfL96	51	usAfsuCfaUfcCfcAfgcuGfaGfaGfaUfgsgsg	122	Hs
AD-62948.2	GfsgsGfgUfgCfcAfGfCfuAfcUfaUfuGfaUfL96	52	asUfscAfaUfaGfuAfgcuGfgCfaCfcCfcsasu	123	Hs
AD-62953.2	AfsusGfuGfuUfuGfGfGfcAfaCfgUfcAfuAfL96	53	usAfsuGfaCfgUfuGfcccAfaAfcAfcAfususu	124	Hs
AD-62958.2	CfsusGfuUfuAfgAfUfUfuCfcUfuAfaGfaAfL96	54	usUfscUfuAfaGfgAfaauCfuAfaAfcAfgsasa	125	Hs
AD-62963.2	AfsgsAfaAfgAfaAfUfGfgAfcUfuGfcAfuAfL96	55	usAfsuGfcAfaGfuCfcauUfuCfuUfuCfusasg	126	Hs
AD-62968.2	GfscsAfuCfcUfgGfAfAfaUfaUfaUfuAfaAfL96	56	usUfsuAfaUfaUfaUfuucCfaGfgAfuGfcsasa	127	Hs
AD-62973.2	CfscsUfgUfcAfgAfCfCfaUfgGfgAfaCfuAfL96	57	usAfsgUfuCfcCfaUfgguCfuGfaCfaGfgscsu	128	Hs
AD-62938.2	AfsasAfcAfuGfgUfGfUfgGfaUfgGfgAfuAfL96	58	usAfsuCfcCfaUfcCfacaCfcAfuGfuUfusasa	129	Hs
AD-62974.2	CfsusCfaGfgAfuGfAfAfaAfaUfuUfuGfaAfL96	59	usUfscAfaAfaUfuUfuucAfuCfcUfgAfgsusu	130	Hs

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AD-62978.2	CfsasGfcAfuGfuAfUfUfaCfuUfgAfcAfaAfL96	60	usUfsuGfuCfaAfgUfaauAfcAfuGfcUfgsasa	131	Hs
AD-62982.2	UfsasUfgAfaCfaAfCfAfuGfcUfaAfaUfcAfL96	61	usGfsaUfuUfaGfcAfuguUfgUfuCfaUfasasu	132	Hs
AD-62986.2	AfsusAfuAfuCfcAfAfAfuGfuUfuUfaGfgAfL96	62	usCfscUfaAfaAfcAfuuuGfgAfuAfuAfususc	133	Hs
AD-62990.2	CfscsAfgAfuGfgAfAfGfcUfgUfaUfcCfaAfL96	63	usUfsgGfaUfaCfaGfcuuCfcAfuCfuGfgsasa	134	Hs
AD-62994.2	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	64	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	135	Hs
AD-62998.2	CfscsCfcGfgCfuAfAfUfuUfgUfaUfcAfaUfL96	65	asUfsuGfaUfaCfaAfauuAfgCfcGfgGfgsgsa	136	Hs
AD-63002.2	UfsusAfaAfcAfuGfGfCfuUfgAfaUfgGfgAfL96	66	usCfscCfaUfuCfaAfgccAfuGfuUfuAfascsa	137	Hs
AD-62975.2	AfsasUfgUfgUfuUfAfGfaCfaAfcGfuCfaUfL96	67	asUfsgAfcGfuUfgUfcuaAfaCfaCfaUfususu	138	Mm
AD-62979.2	AfscsUfaAfaGfgAfAfGfaAfuUfcCfgGfuUfL96	68	asAfscCfgGfaAfuUfcuuCfcUfuUfaGfusasu	139	Mm
AD-62983.2	UfsasUfaUfcCfaAfAfUfgUfuUfuAfgGfaUfL96	69	asUfscCfuAfaAfaCfauuUfgGfaUfaUfasusu	140	Mm
AD-62987.2	GfsusGfcGfgAfaAfGfGfcAfcUfgAfuGfuUfL96	70	asAfscAfuCfaGfuGfccuUfuCfcGfcAfcsasc	141	Mm
AD-62991.2	UfsasAfaAfcAfgUfGfGfuUfcUfuAfaAfuUfL96	71	asAfsuUfuAfaGfaAfccaCfuGfuUfuUfasasa	142	Mm
AD-62995.2	AfsusGfaAfaAfaUfUfUfuGfaAfaCfcAfgUfL96	72	asCfsuGfgUfuUfcAfaaaUfuUfuUfcAfuscsc	143	Mm
AD-62999.2	AfsasCfaAfaAfuAfGfCfaAfuCfcCfuUfuUfL96	73	asAfsaAfgGfgAfuUfgcuAfuUfuUfgUfusgsg	144	Mm
AD-63003.2	CfsusGfaAfaCfaGfAfUfcUfgUfcGfaCfuUfL96	74	asAfsgUfcGfaCfaGfaucUfgUfuUfcAfgscsa	145	Mm
AD-62976.2	UfsusGfuUfgCfaAfAfGfgGfcAfuUfuUfgAfL96	75	usCfsaAfaAfuGfcCfcuuUfgCfaAfcAfasusu	146	Mm
AD-62980.2	CfsusCfaUfuGfuUfUfAfuUfaAfcCfuGfuAfL96	76	usAfscAfgGfuUfaAfuaaAfcAfaUfgAfgsasu	147	Mm
AD-62984.2	CfsasAfcAfaAfaUfAfGfcAfaUfcCfcUfuUfL96	77	asAfsaGfgGfaUfuGfcuaUfuUfuGfuUfgsgsa	148	Mm
AD-62992.2	CfsasUfuGfuUfuAfUfUfaAfcCfuGfuAfuUfL96	78	asAfsuAfcAfgGfuUfaauAfaAfcAfaUfgsasg	149	Mm
AD-62996.2	UfsasUfcAfgCfuGfGfGfaAfgAfuAfuCfaAfL96	79	usUfsgAfuAfuCfuUfcccAfgCfuGfaUfasgsa	150	Mm
AD-63000.2	UfsgsUfcCfuAfgGfAfAfcCfuUfuUfaGfaAfL96	80	usUfscUfaAfaAfgGfuucCfuAfgGfaCfascsc	151	Mm
AD-63004.2	UfscsCfaAfcAfaAfAfUfaGfcAfaUfcCfcUfL96	81	asGfsgGfaUfuGfcUfauuUfuGfuUfgGfasasa	152	Mm
AD-62977.2	GfsgsUfgUfgCfgGfAfAfaGfgCfaCfuGfaUfL96	82	asUfscAfgUfgCfcUfuucCfgCfaCfaCfcscsc	153	Mm
AD-62981.2	UfsusGfaAfaCfcAfGfUfaCfuUfuAfuCfaUfL96	83	asUfsgAfuAfaAfgUfacuGfgUfuUfcAfasasa	154	Mm
AD-62985.2	UfsasCfuUfcCfaAfAfGfuCfuAfuAfuAfuAfL96	84	usAfsuAfuAfuAfgAfcuuUfgGfaAfgUfascsu	155	Mm
AD-62989.2	UfscsCfuAfgGfaAfCfCfuUfuUfaGfaAfaUfL96	85	asUfsuUfcUfaAfaAfgguUfcCfuAfgGfascsa	156	Mm

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AD-62993.2	CfsusCfcUfgAfgGfAfAfaAfuUfuUfgGfaAfL96	86	usUfscCfaAfaAfuUfuucCfuCfaGfgAfgsasa	157	Mm
AD-62997.2	GfscsUfcCfgGfaAfUfGfuUfgCfuGfaAfaUfL96	87	asUfsuUfcAfgCfaAfcauUfcCfgGfaGfcsasu	158	Mm
AD-63001.2	GfsusGfuUfuGfuGfGfGfgAfgAfcCfaAfuAfL96	88	usAfsuUfgGfuCfuCfcccAfcAfaAfcAfcsasg	159	Mm
AD-62933.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	160	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	277	
AD-65630.1	Y44gsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	161	PusUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	278	
AD-65636.1	gsasauguGfaAfAfGfucauCfgacaaL96	162	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	279	
AD-65642.1	gsasauguGfaAfAfGfucaucgacaaL96	163	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	280	
AD-65647.1	gsasauguGfaaAfGfucaucgacaaL96	164	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	281	
AD-65652.1	gsasauguGfaaaGfucaucGfacaaL96	165	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	282	
AD-65657.1	gsasaugugaaaGfucaucGfacaaL96	166	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	283	
AD-65662.1	gsasauguGfaaaGfucaucgacaaL96	167	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	284	
AD-65625.1	AfsusGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	168	usUfsgUfcGfaUfgAfcuuUfcAfcAfususc	285	
AD-65631.1	asusguGfaAfAfGfucaucgacaaL96	169	usUfsgucGfaugacuuUfcAfcaususc	286	
AD-65637.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	170	usUfsgucGfaUfgAfcuuUfcAfcauucsusg	287	
AD-65643.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	171	usUfsgucGfaUfGfacuuUfcAfcauucsusg	288	
AD-65648.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	172	usUfsgucGfaugacuuUfcAfcauucsusg	289	
AD-65653.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	173	usUfsgucGfaugacuuUfcacauucsusg	290	
AD-65658.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	174	usUfsgucgaugacuuUfcacauucsusg	291	
AD-65663.1	gsasauguGfaAfAfGfucaucgacaaL96	175	usUfsgucGfaUfgAfcuuUfcAfcauucsusg	292	
AD-65626.1	gsasauguGfaAfAfGfucaucgacaaL96	176	usUfsgucGfaUfGfacuuUfcAfcauucsusg	293	
AD-65638.1	gsasauguGfaaAfGfucaucgacaaL96	177	usUfsgucGfaUfgAfcuuUfcAfcauucsusg	294	
AD-65644.1	gsasauguGfaaAfGfucaucgacaaL96	178	usUfsgucGfaUfGfacuuUfcAfcauucsusg	295	
AD-65649.1	gsasauguGfaaAfGfucaucgacaaL96	179	usUfsgucGfaugacuuUfcAfcauucsusg	296	
AD-65654.1	gsasaugugaaagucau(Cgn)gacaaL96	180	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	297	
AD-65659.1	gsasaugdTgaaagucau(Cgn)gacaaL96	181	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	298	
AD-65627.1	gsasaudGugaaadGucau(Cgn)gacaaL96	182	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	299	

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AD-65633.1	gsasaugdTgaaadGucau(Cgn)gacaaL96	183	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	300	
AD-65639.1	gsasaugudGaaadGucau(Cgn)gacaaL96	184	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	301	
AD-65645.1	gsasaugugaaadGucaucdGacaaL96	185	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	302	
AD-65650.1	gsasaugugaaadGucaucdTacaaL96	186	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	303	
AD-65655.1	gsasaugugaaadGucaucY34acaaL96	187	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	304	
AD-65660.1	gsasaugugaaadGucadTcdTacaaL96	188	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	305	
AD-65665.1	gsasaugugaaadGucaucdGadCaaL96	189	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	306	
AD-65628.1	gsasaugugaaadGucaucdTadCaaL96	190	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	307	
AD-65634.1	gsasaugugaaadGucaucY34adCaaL96	191	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	308	
AD-65646.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	192	usdTsgucgaugdAcuudTcacauucsusg	309	
AD-65656.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	193	usUsgucgaugacuudTcacauucsusg	310	
AD-65661.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	194	usdTsgucdGaugacuudTcacauucsusg	311	
AD-65666.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	195	usUsgucdGaugacuudTcacauucsusg	312	
AD-65629.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	196	usdTsgucgaugacuudTcdAcauucsusg	313	
AD-65635.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	197	usdTsgucdGaugacuudTcdAcauucsusg	314	
AD-65641.1	gsasaugugaaadGucau(Cgn)gacaaL96	198	usdTsgucgaugdAcuudTcacauucsusg	315	
AD-62994.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	199	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	316	
AD-65595.1	gsascuuuCfaUfCfCfuggaAfauauaL96	200	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	317	
AD-65600.1	gsascuuuCfaUfCfCfuggaaauauaL96	201	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	318	
AD-65610.1	gsascuuuCfaucCfuggaaAfuauaL96	202	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	319	
AD-65615.1	gsascuuucaucCfuggaaAfuauaL96	203	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	320	
AD-65620.1	gsascuuuCfaucCfuggaaauauaL96	204	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	321	
AD-65584.1	CfsusUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	205	usAfsuAfuUfuCfcAfggaUfgAfaAfgsusc	322	
AD-65590.1	csusuuCfaUfCfCfuggaaauauaL96	206	usAfsuauUfuccaggaUfgAfaagsusc	323	
AD-65596.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	207	usAfsuauUfuCfcAfggaUfgAfaagucscsa	324	
AD-65601.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	208	usAfsuauUfuCfCfaggaUfgAfaagucscsa	325	

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AD-65606.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	209	usAfsuauUfuccaggaUfgAfaagucscsa	326	
AD-65611.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	210	usAfsuauUfuccaggaUfgaaagucscsa	327	
AD-65616.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	211	usAfsuauuuccaggaUfgaaagucscsa	328	
AD-65621.1	gsascuuuCfaUfCfCfuggaaauauaL96	212	usAfsuauUfuCfcAfggaUfgAfaagucscsa	329	
AD-65585.1	gsascuuuCfaUfCfCfuggaaauauaL96	213	usAfsuauUfuCfCfaggaUfgAfaagucscsa	330	
AD-65591.1	gsascuuuCfaUfCfCfuggaaauauaL96	214	usAfsuauUfuccaggaUfgAfaagucscsa	331	
AD-65597.1	gsascuuuCfauCfCfuggaaauauaL96	215	usAfsuauUfuCfcAfggaUfgAfaagucscsa	332	
AD-65602.1	gsascuuuCfauCfCfuggaaauauaL96	216	usAfsuauUfuCfCfaggaUfgAfaagucscsa	333	
AD-65607.1	gsascuuuCfauCfCfuggaaauauaL96	217	usAfsuauUfuccaggaUfgAfaagucscsa	334	
AD-65612.1	gsascuuucauccuggaa(Agn)uauaL96	218	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	335	
AD-65622.1	gsascuuucaucdCuggaa(Agn)uauaL96	219	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	336	
AD-65586.1	gsascudTucaucdCuggaa(Agn)uauaL96	220	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	337	
AD-65592.1	gsascuudTcaucdCuggaa(Agn)uauaL96	221	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	338	
AD-65598.1	gsascuuudCaucdCuggaa(Agn)uauaL96	222	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	339	
AD-65603.1	gsascuuucaucdCuggaadAuauaL96	223	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	340	
AD-65608.1	gsascuuucaucdCuggaadTuauaL96	224	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	341	
AD-65613.1	gsascuuucaucdCuggaaY34uauaL96	225	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	342	
AD-65618.1	gsascuuucaucdCuggdAadTuauaL96	226	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	343	
AD-65623.1	gsascuuucaucdCuggaadTudAuaL96	227	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	344	
AD-65587.1	gsascuuucaucdCuggaa(Agn)udAuaL96	228	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	345	
AD-65593.1	gsascuudTcaucdCuggaadAudAuaL96	229	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	346	
AD-65599.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	230	usdAsuauuuccdAggadTgaaagucscsa	347	
AD-65604.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	231	usdAsuauuuccaggadTgaaagucscsa	348	
AD-65609.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	232	usAsuauuuccaggadTgaaagucscsa	349	
AD-65614.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	233	usdAsuaudTuccaggadTgaaagucscsa	350	
AD-65619.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	234	usAsuaudTuccaggadTgaaagucscsa	351	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Species
AD-65624.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	235	usdAsuauuuccaggadTgdAaagucscsa	352	
AD-65588.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	236	usdAsuaudTuccaggadTgdAaagucscsa	353	
AD-65594.1	gsascuuucaucdCuggaa(Agn)uauaL96	237	usdAsuauuuccdAggadTgaaagucscsa	354	
AD-68309.1	asgsaaagGfuGfUfUfcaagaugucaL96	238	usGfsacaUfcUfUfgaacAfcCfuuucuscsc	355	
AD-68303.1	csasuccuGfgAfAfAfuauauuaacuL96	239	asGfsuuaAfuAfUfauuuCfcAfggaugsasa	356	
AD-65626.5	gsasauguGfaAfAfGfucaucgacaaL96	240	usUfsgucGfaUfGfacuuUfcAfcauucsusg	357	
AD-68295.1	asgsugcaCfaAfUfAfuuuucccauaL96	241	usAfsuggGfaAfAfauauUfgUfgcacusgsu	358	
AD-68273.1	gsasaaguCfaUfCfGfacaagacauuL96	242	asAfsuguCfuUfGfucgaUfgAfcuuucsasc	359	
AD-68297.1	asasugugAfaAfGfUfcaucgacaaaL96	243	usUfsuguCfgAfUfgacuUfuCfacauuscsu	360	
AD-68287.1	csusggaaAfuAfUfAfuuaacuguuaL96	244	usAfsacaGfuUfAfauauAfuUfuccagsgsa	361	
AD-68300.1	asusuuucCfcAfUfCfuguauuauuuL96	245	asAfsauaAfuAfCfagauGfgGfaaaausasu	362	
AD-68306.1	usgsucguUfcUfUfUfuccaacaaaaL96	246	usUfsuugUfuGfGfaaaaGfaAfcgacascsc	363	
AD-68292.1	asusccugGfaAfAfUfauauuaacuaL96	247	usAfsguuAfaUfAfuauuUfcCfaggausgsa	364	
AD-68298.1	gscsauuuUfgAfGfAfggugaugauaL96	248	usAfsucaUfcAfCfcucuCfaAfaaugcscsc	365	
AD-68277.1	csasggggGfaGfAfAfagguguucaaL96	249	usUfsgaaCfaCfCfuuucUfcCfcccugsgsa	366	
AD-68289.1	gsgsaaauAfuAfUfUfaacuguuaaaL96	250	usUfsuaaCfaGfUfuaauAfuAfuuuccsasg	367	
AD-68272.1	csasuuggUfgAfGfGfaaaaauccuuL96	251	asAfsggaUfuUfUfuccuCfaCfcaaugsusc	368	
AD-68282.1	gsgsgagaAfaGfGfUfguucaagauaL96	252	usAfsucuUfgAfAfcaccUfuUfcucccscsc	369	
AD-68285.1	gsgscauuUfuGfAfGfaggugaugauL96	253	asUfscauCfaCfCfucucAfaAfaugccscsu	370	
AD-68290.1	usascaaaGfgGfUfGfucguucuuuuL96	254	asAfsaagAfaCfGfacacCfcUfuuguasusu	371	
AD-68296.1	usgsggauCfuUfGfGfugucgaaucaL96	255	usGfsauuCfgAfCfaccaAfgAfucccasusu	372	
AD-68288.1	csusgacaGfuGfCfAfcaauauuuuaL96	256	usAfsaaaUfaUfUfgugcAfcUfgucagsasu	373	
AD-68299.1	csasgugcAfcAfAfUfauuuucccauL96	257	asUfsgggAfaAfAfuauuGfuGfcacugsusc	374	
AD-68275.1	ascsuuuuCfaAfUfGfgguguccuaaL96	258	usUfsaggAfcAfCfccauUfgAfaaaguscsa	375	
AD-68274.1	ascsauugGfuGfAfGfgaaaaauccuL96	259	asGfsgauUfuUfUfccucAfcCfaauguscsu	376	
AD-68294.1	ususgcuuUfuGfAfCfuuuucaaugaL96	260	usCfsauuGfaAfAfagucAfaAfagcaasusg	377	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	Species
AD-68302.1	csasuuuuGfaGfAfGfgugaugaugaL96	261	usCfsaucAfuCfAfccucUfcAfaaaugscsc	378	
AD-68279.1	ususgacuUfuUfCfAfaugggugucaL96	262	usGfsacaCfcCfAfuugaAfaAfgucaasasa	379	
AD-68304.1	csgsacuuCfuGfUfUfuuaggacagaL96	263	usCfsuguCfcUfAfaaacAfgAfagucgsasc	380	
AD-68286.1	csuscugaGfuGfGfGfugccagaauaL96	264	usAfsuucUfgGfCfacccAfcUfcagagscsc	381	
AD-68291.1	gsgsgugcCfaGfAfAfugugaaaguaL96	265	usAfscuuUfcAfCfauucUfgGfcacccsasc	382	
AD-68283.1	uscsaaugGfgUfGfUfccuaggaacaL96	266	usGfsuucCfuAfGfgacaCfcCfauugasasa	383	
AD-68280.1	asasagucAfuCfGfAfcaagacauuaL96	267	usAfsaugUfcUfUfgucgAfuGfacuuuscsa	384	
AD-68293.1	asusuuugAfgAfGfGfugaugaugcaL96	268	usGfscauCfaUfCfaccuCfuCfaaaausgsc	385	
AD-68276.1	asuscgacAfaGfAfCfauuggugagaL96	269	usCfsucaCfcAfAfugucUfuGfucgausgsa	386	
AD-68308.1	gsgsugccAfgAfAfUfgugaaagucaL96	270	usGfsacuUfuCfAfcauuCfuGfgcaccscsa	387	
AD-68278.1	gsascaguGfcAfCfCfAfauauuuuccaL96	271	usGfsgaaAfaUfAfuuguGfcAfcugucsasg	388	
AD-68307.1	ascsaaagAfgAfCfAfcugugcagaaL96	272	usUfscugCfaCfAfguguCfuCfuuuguscsa	389	
AD-68284.1	ususuucaAfuGfGfGfuguccuaggaL96	273	usCfscuaGfgAfCfacccAfuUfgaaaasgsu	390	
AD-68301.1	cscsguuuCfcAfAfGfaucugacaguL96	274	asCfsuguCfaGfAfucuuGfgAfaacggscsc	391	
AD-68281.1	asgsggggAfgAfAfAfgguguucaaaL96	275	usUfsugaAfcAfCfcuuuCfuCfccccusgsg	392	
AD-68305.1	asgsucauCfgAfCfAfagacauugguL96	276	asCfscaaUfgUfCfuuguCfgAfugacususu	393	

Table 6. Unmodified Human/Mouse/Cyno/Rat, Human/Mouse/Cyno, andHuman/Cyno Cross-Reactive HAO1 iRNA Sequences

Duplex Name	SEQ ID NO:	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Position in NM_017545.2
AD-62933	394	GAAUGUGAAAGUCAUCGACAA	443	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-62939	395	UUUUCAAUGGGUGUCCUAGGA	444	UCCUAGGACACCCAUUGAAAAGU	1302-1324
AD-62944	396	GAAAGUCAUCGACAAGACAUU	445	AAUGUCUUGUCGAUGACUUUCAC	1078-1100
AD-62949	397	UCAUCGACAAGACAUUGGUGA	446	UCACCAAUGUCUUGUCGAUGACU	1083-1105
AD-62954	398	UUUCAAUGGGUGUCCUAGGAA	447	UUCCUAGGACACCCAUUGAAAAG	1303-1325
AD-62959	399	AAUGGGUGUCCUAGGAACCUU	448	AAGGUUCCUAGGACACCCAUUGA	1307-1329

Duplex Name	SEQ ID NO:	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Position in NM_017545.2
AD-62964	400	GACAGUGCACAAUAUUUUCCA	449	UGGAAAAUAUUGUGCACUGUCAG	1134-1156_C21A
AD-62969	401	ACUUUUCAAUGGGUGUCCUAA	450	UUAGGACACCCAUUGAAAAGUCA	1300-1322_G21A
AD-62934	402	AAGUCAUCGACAAGACAUUGA	451	UCAAUGUCUUGUCGAUGACUUUC	1080-1102_G21A
AD-62940	403	AUCGACAAGACAUUGGUGAGA	452	UCUCACCAAUGUCUUGUCGAUGA	1085-1107_G21A
AD-62945	404	GGGAGAAAGGUGUUCAAGAUA	453	UAUCUUGAACACCUUUCUCCCCC	996-1018_G21A
AD-62950	405	CUUUUCAAUGGGUGUCCUAGA	454	UCUAGGACACCCAUUGAAAAGUC	1301-1323_G21A
AD-62955	406	UCAAUGGGUGUCCUAGGAACA	455	UGUUCCUAGGACACCCAUUGAAA	1305-1327_C21A
AD-62960	407	UUGACUUUUCAAUGGGUGUCA	456	UGACACCCAUUGAAAAGUCAAAA	1297-1319_C21A
AD-62965	408	AAAGUCAUCGACAAGACAUUA	457	UAAUGUCUUGUCGAUGACUUUCA	1079-1101_G21A
AD-62970	409	CAGGGGGAGAAAGGUGUUCAA	458	UUGAACACCUUUCUCCCCCUGGA	992-1014
AD-62935	410	CAUUGGUGAGGAAAAAUCCUU	459	AAGGAUUUUUCCUCACCAAUGUC	1095-1117
AD-62941	411	ACAUUGGUGAGGAAAAAUCCU	460	AGGAUUUUUCCUCACCAAUGUCU	1094-1116
AD-62946	412	AGGGGGAGAAAGGUGUUCAAA	461	UUUGAACACCUUUCUCCCCCUGG	993-1015_G21A
AD-62974	413	CUCAGGAUGAAAAAUUUUGAA	462	UUCAAAAUUUUUCAUCCUGAGUU	563-585
AD-62978	414	CAGCAUGUAUUACUUGACAAA	463	UUUGUCAAGUAAUACAUGCUGAA	1173-1195
AD-62982	415	UAUGAACAACAUGCUAAAUCA	464	UGAUUUAGCAUGUUGUUCAUAAU	53-75
AD-62986	416	AUAUAUCCAAAUGUUUUAGGA	465	UCCUAAAACAUUUGGAUAUAUUC	1679-1701
AD-62990	417	CCAGAUGGAAGCUGUAUCCAA	466	UUGGAUACAGCUUCCAUCUGGAA	156-178
AD-62994	418	GACUUUCAUCCUGGAAAUAUA	467	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-62998	419	CCCCGGCUAAUUUGUAUCAAU	468	AUUGAUACAAAUUAGCCGGGGGA	29-51
AD-63002	420	UUAAACAUGGCUUGAAUGGGA	469	UCCCAUUCAAGCCAUGUUUAACA	765-787
AD-62975	421	AAUGUGUUUAGACAACGUCAU	470	AUGACGUUGUCUAAACACAUUUU	1388-1410
AD-62979	422	ACUAAAGGAAGAAUUCCGGUU	471	AACCGGAAUUCUUCCUUUAGUAU	1027-1049
AD-62983	423	UAUAUCCAAAUGUUUUAGGAU	472	AUCCUAAAACAUUUGGAUAUAUU	1680-1702
AD-62987	424	GUGCGGAAAGGCACUGAUGUU	473	AACAUCAGUGCCUUUCCGCACAC	902-924
AD-62991	425	UAAAACAGUGGUUCUUAAAUU	474	AAUUUAAGAACCACUGUUUUAAA	1521-1543
AD-62995	426	AUGAAAAAUUUUGAAACCAGU	475	ACUGGUUUCAAAAUUUUUCAUCC	569-591
AD-62999	427	AACAAAAUAGCAAUCCCUUUU	476	AAAAGGGAUUGCUAUUUUGUUGG	1264-1286
AD-63003	428	CUGAAACAGAUCUGUCGACUU	477	AAGUCGACAGAUCUGUUUCAGCA	195-217
AD-62976	429	UUGUUGCAAAGGGCAUUUUGA	478	UCAAAAUGCCCUUUGCAACAAUU	720-742
AD-62980	430	CUCAUUGUUUAUUAACCUGUA	479	UACAGGUUAAUAAACAAUGAGAU	1483-1505

Duplex Name	SEQ ID NO:	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Position in NM_017545.2
AD-62984	431	CAACAAAAUAGCAAUCCCUUU	480	AAAGGGAUUGCUAUUUUGUUGGA	1263-1285
AD-62992	432	CAUUGUUUAUUAACCUGUAUU	481	AAUACAGGUUAAUAAACAAUGAG	1485-1507
AD-62996	433	UAUCAGCUGGGAAGAUAUCAA	482	UUGAUAUCUUCCCAGCUGAUAGA	670-692
AD-63000	434	UGUCCUAGGAACCUUUUAGAA	483	UUCUAAAAGGUUCCUAGGACACC	1313-1335
AD-63004	435	UCCAACAAAAUAGCAAUCCCU	484	AGGGAUUGCUAUUUUGUUGGAAA	1261-1283
AD-62977	436	GGUGUGCGGAAAGGCACUGAU	485	AUCAGUGCCUUUCCGCACACCCC	899-921
AD-62981	437	UUGAAACCAGUACUUUAUCAU	486	AUGAUAAAGUACUGGUUUCAAAA	579-601
AD-62985	438	UACUUCCAAAGUCUAUAUAUA	487	UAUAUAUAGACUUUGGAAGUACU	75-97_G21A
AD-62989	439	UCCUAGGAACCUUUUAGAAAU	488	AUUUCUAAAAGGUUCCUAGGACA	1315-1337_G21U
AD-62993	440	CUCCUGAGGAAAAUUUUGGAA	489	UUCCAAAAUUUUCCUCAGGAGAA	603-625_G21A
AD-62997	441	GCUCCGGAAUGUUGCUGAAAU	490	AUUUCAGCAACAUUCCGGAGCAU	181-203_C21U
AD-63001	442	GUGUUUGUGGGGAGACCAAUA	491	UAUUGGUCUCCCCACAAACACAG	953-975_C21A

Table 7. Additional Unmodified Human/Cyno/Mouse/Rat, Human/Mouse/Cyno, Human/Cyno, and Mouse/Rat HAO1 iRNA Sequences

Duplex Name	SEQ ID NO:	Sense strand sequence 5' to 3'	SEQ ID NO:	Antisense strand sequence 5' to 3'	Position in NM_017545.2
AD-62933.2	394	GAAUGUGAAAGUCAUCGACAA	443	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-62939.2	395	UUUUCAAUGGGUGUCCUAGGA	444	UCCUAGGACACCCAUUGAAAAGU	1302-1324
AD-62944.2	396	GAAAGUCAUCGACAAGACAUU	445	AAUGUCUUGUCGAUGACUUUCAC	1078-1100
AD-62949.2	397	UCAUCGACAAGACAUUGGUGA	446	UCACCAAUGUCUUGUCGAUGACU	1083-1105
AD-62954.2	398	UUUCAAUGGGUGUCCUAGGAA	447	UUCCUAGGACACCCAUUGAAAAG	1303-1325
AD-62959.2	399	AAUGGGUGUCCUAGGAACCUU	448	AAGGUUCCUAGGACACCCAUUGA	1307-1329
AD-62964.2	400	GACAGUGCACAAUAUUUUCCA	449	UGGAAAAUAUUGUGCACUGUCAG	1134-1156_C21A
AD-62969.2	401	ACUUUUCAAUGGGUGUCCUAA	450	UUAGGACACCCAUUGAAAAGUCA	1300-1322_G21A
AD-62934.2	402	AAGUCAUCGACAAGACAUUGA	451	UCAAUGUCUUGUCGAUGACUUUC	1080-1102_G21A
AD-62940.2	403	AUCGACAAGACAUUGGUGAGA	452	UCUCACCAAUGUCUUGUCGAUGA	1085-1107_G21A
AD-62945.2	404	GGGAGAAAGGUGUUCAAGAUA	453	UAUCUUGAACACCUUUCUCCCCC	996-1018_G21A
AD-62950.2	405	CUUUUCAAUGGGUGUCCUAGA	454	UCUAGGACACCCAUUGAAAAGUC	1301-1323_G21A

Duplex Name	SEQ ID NO:	Sense strand sequence 5' to 3'	SEQ ID NO:	Antisense strand sequence 5' to 3'	Position in NM_017545.2
AD-62955.2	406	UCAAUGGGUGUCCUAGGAACA	455	UGUUCCUAGGACACCCAUUGAAA	1305-1327_C21A
AD-62960.2	407	UUGACUUUUCAAUGGGUGUCA	456	UGACACCCAUUGAAAAGUCAAAA	1297-1319_C21A
AD-62965.2	408	AAAGUCAUCGACAAGACAUUA	457	UAAUGUCUUGUCGAUGACUUUCA	1079-1101_G21A
AD-62970.2	409	CAGGGGGAGAAAGGUGUUCAA	458	UUGAACACCUUUCUCCCCCUGGA	992-1014
AD-62935.2	410	CAUUGGUGAGGAAAAAUCCUU	459	AAGGAUUUUUCCUCACCAAUGUC	1095-1117
AD-62941.2	411	ACAUUGGUGAGGAAAAAUCCU	460	AGGAUUUUUCCUCACCAAUGUCU	1094-1116
AD-62946.2	412	AGGGGGAGAAAGGUGUUCAAA	461	UUUGAACACCUUUCUCCCCCUGG	993-1015_G21A
AD-62974.2	413	CUCAGGAUGAAAAAUUUUGAA	462	UUCAAAAUUUUUCAUCCUGAGUU	563-585
AD-62978.2	414	CAGCAUGUAUUACUUGACAAA	463	UUUGUCAAGUAAUACAUGCUGAA	1173-1195
AD-62982.2	415	UAUGAACAACAUGCUAAAUCA	464	UGAUUUAGCAUGUUGUUCAUAAU	53-75
AD-62986.2	416	AUAUAUCCAAAUGUUUUAGGA	465	UCCUAAAACAUUUGGAUAUAUUC	1679-1701
AD-62990.2	417	CCAGAUGGAAGCUGUAUCCAA	466	UUGGAUACAGCUUCCAUCUGGAA	156-178
AD-62994.2	418	GACUUUCAUCCUGGAAAUAUA	467	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-62998.2	419	CCCCGGCUAAUUUGUAUCAAU	468	AUUGAUACAAAUUAGCCGGGGGA	29-51
AD-63002.2	420	UUAAACAUGGCUUGAAUGGGA	469	UCCCAUUCAAGCCAUGUUUAACA	765-787
AD-62975.2	421	AAUGUGUUUAGACAACGUCAU	470	AUGACGUUGUCUAAACACAUUUU	1388-1410
AD-62979.2	422	ACUAAAGGAAGAAUUCCGGUU	471	AACCGGAAUUCUUCCUUUAGUAU	1027-1049
AD-62983.2	423	UAUAUCCAAAUGUUUUAGGAU	472	AUCCUAAAACAUUUGGAUAUAUU	1680-1702
AD-62987.2	424	GUGCGGAAAGGCACUGAUGUU	473	AACAUCAGUGCCUUUCCGCACAC	902-924
AD-62991.2	425	UAAAACAGUGGUUCUUAAAUU	474	AAUUUAAGAACCACUGUUUUAAA	1521-1543
AD-62995.2	426	AUGAAAAAUUUUGAAACCAGU	475	ACUGGUUUCAAAAUUUUUCAUCC	569-591
AD-62999.2	427	AACAAAAUAGCAAUCCCUUUU	476	AAAAGGGAUUGCUAUUUUGUUGG	1264-1286
AD-63003.2	428	CUGAAACAGAUCUGUCGACUU	477	AAGUCGACAGAUCUGUUUCAGCA	195-217
AD-62976.2	429	UUGUUGCAAAGGGCAUUUUGA	478	UCAAAAUGCCCUUUGCAACAAUU	720-742
AD-62980.2	430	CUCAUUGUUUAUUAACCUGUA	479	UACAGGUUAAUAAACAAUGAGAU	1483-1505
AD-62984.2	431	CAACAAAAUAGCAAUCCCUUU	480	AAAGGGAUUGCUAUUUUGUUGGA	1263-1285
AD-62992.2	432	CAUUGUUUAUUAACCUGUAUU	481	AAUACAGGUUAAUAAACAAUGAG	1485-1507

Duplex Name	SEQ ID NO:	Sense strand sequence 5' to 3'	SEQ ID NO:	Antisense strand sequence 5' to 3'	Position in NM_017545.2
AD-62996.2	433	UAUCAGCUGGGAAGAUAUCAA	482	UUGAUAUCUUCCCAGCUGAUAGA	670-692
AD-63000.2	434	UGUCCUAGGAACCUUUUAGAA	483	UUCUAAAAGGUUCCUAGGACACC	1313-1335
AD-63004.2	435	UCCAACAAAAUAGCAAUCCCU	484	AGGGAUUGCUAUUUUGUUGGAAA	1261-1283
AD-62977.2	436	GGUGUGCGGAAAGGCACUGAU	485	AUCAGUGCCUUUCCGCACACCCC	899-921
AD-62981.2	437	UUGAAACCAGUACUUUAUCAU	486	AUGAUAAAGUACUGGUUUCAAAA	579-601
AD-62985.2	438	UACUUCCAAAGUCUAUAUAUA	487	UAUAUAUAGACUUUGGAAGUACU	75-97_G21A
AD-62989.2	439	UCCUAGGAACCUUUUAGAAAU	488	AUUUCUAAAAGGUUCCUAGGACA	1315-1337_G21U
AD-62993.2	440	CUCCUGAGGAAAAUUUUGGAA	489	UUCCAAAAUUUUCCUCAGGAGAA	603-625_G21A
AD-62997.2	441	GCUCCGGAAUGUUGCUGAAAU	490	AUUUCAGCAACAUUCCGGAGCAU	181-203_C21U
AD-63001.2	442	GUGUUUGUGGGGAGACCAAUA	491	UAUUGGUCUCCCCACAAACACAG	953-975_C21A
AD-62951.2	492	AUGGUGGUAAUUUGUGAUUUU	514	AAAAUCACAAAUUACCACCAUCC	1642-1664
AD-62956.2	493	GACUUGCAUCCUGGAAAUAUA	515	UAUAUUUCCAGGAUGCAAGUCCA	1338-1360
AD-62961.2	494	GGAAGGGAAGGUAGAAGUCUU	516	AAGACUUCUACCUUCCCUUCCAC	864-886
AD-62966.2	495	UGUCUUCUGUUUAGAUUUCCU	517	AGGAAAUCUAAACAGAAGACAGG	1506-1528
AD-62971.2	496	CUUUGGCUGUUUCCAAGAUCU	518	AGAUCUUGGAAACAGCCAAAGGA	1109-1131
AD-62936.2	497	AAUGUGUUUGGGCAACGUCAU	519	AUGACGUUGCCCAAACACAUUUU	1385-1407
AD-62942.2	498	UGUGACUGUGGACACCCCUUA	520	UAAGGGGUGUCCACAGUCACAAA	486-508
AD-62947.2	499	GAUGGGGUGCCAGCUACUAUU	521	AAUAGUAGCUGGCACCCCAUCCA	814-836
AD-62952.2	500	GAAAAUGUGUUUGGGCAACGU	522	ACGUUGCCCAAACACAUUUUCAA	1382-1404
AD-62957.2	501	GGCUGUUUCCAAGAUCUGACA	523	UGUCAGAUCUUGGAAACAGCCAA	1113-1135
AD-62962.2	502	UCCAACAAAAUAGCCACCCCU	524	AGGGGUGGCUAUUUUGUUGGAAA	1258-1280
AD-62967.2	503	GUCUUCUGUUUAGAUUUCCUU	525	AAGGAAAUCUAAACAGAAGACAG	1507-1529
AD-62972.2	504	UGGAAGGGAAGGUAGAAGUCU	526	AGACUUCUACCUUCCCUUCCACA	863-885
AD-62937.2	505	UCCUUUGGCUGUUUCCAAGAU	527	AUCUUGGAAACAGCCAAAGGAUU	1107-1129
AD-62943.2	506	CAUCUCUCAGCUGGGAUGAUA	528	UAUCAUCCCAGCUGAGAGAUGGG	662-684
AD-62948.2	507	GGGGUGCCAGCUACUAUUGAU	529	AUCAAUAGUAGCUGGCACCCCAU	817-839
AD-62953.2	508	AUGUGUUUGGGCAACGUCAUA	530	UAUGACGUUGCCCAAACACAUUU	1386-1408_C21A

Duplex Name	SEQ ID NO:	Sense strand sequence 5' to 3'	SEQ ID NO:	Antisense strand sequence 5' to 3'	Position in NM_017545.2
AD-62958.2	509	CUGUUUAGAUUUCCUUAAGAA	531	UUCUUAAGGAAAUCUAAACAGAA	1512-1534_C21A
AD-62963.2	510	AGAAAGAAAUGGACUUGCAUA	532	UAUGCAAGUCCAUUUCUUUCUAG	1327-1349_C21A
AD-62968.2	511	GCAUCCUGGAAAUAUAUUAAA	533	UUUAAUAUAUUUCCAGGAUGCAA	1343-1365_C21A
AD-62973.2	512	CCUGUCAGACCAUGGGAACUA	534	UAGUUCCCAUGGUCUGACAGGCU	308-330_G21A
AD-62938.2	513	AAACAUGGUGUGGAUGGGAUA	535	UAUCCCAUCCACACCAUGUUUAA	763-785_C21A
AD-62933.1	536	GAAUGUGAAAGUCAUCGACAA	653	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65630.1	537	GAAUGUGAAAGUCAUCGACAA	654	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65636.1	538	GAAUGUGAAAGUCAUCGACAA	655	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65642.1	539	GAAUGUGAAAGUCAUCGACAA	656	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65647.1	540	GAAUGUGAAAGUCAUCGACAA	657	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65652.1	541	GAAUGUGAAAGUCAUCGACAA	658	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65657.1	542	GAAUGUGAAAGUCAUCGACAA	659	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65662.1	543	GAAUGUGAAAGUCAUCGACAA	660	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65625.1	544	AUGUGAAAGUCAUCGACAA	661	UUGUCGAUGACUUUCACAUUC	1072-1094
AD-65631.1	545	AUGUGAAAGUCAUCGACAA	662	UUGUCGAUGACUUUCACAUUC	1072-1094
AD-65637.1	546	GAAUGUGAAAGUCAUCGACAA	663	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65643.1	547	GAAUGUGAAAGUCAUCGACAA	664	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65648.1	548	GAAUGUGAAAGUCAUCGACAA	665	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65653.1	549	GAAUGUGAAAGUCAUCGACAA	666	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65658.1	550	GAAUGUGAAAGUCAUCGACAA	667	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65663.1	551	GAAUGUGAAAGUCAUCGACAA	668	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65626.1	552	GAAUGUGAAAGUCAUCGACAA	669	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65638.1	553	GAAUGUGAAAGUCAUCGACAA	670	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65644.1	554	GAAUGUGAAAGUCAUCGACAA	671	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65649.1	555	GAAUGUGAAAGUCAUCGACAA	672	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65654.1	556	GAAUGUGAAAGUCAUCGACAA	673	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65659.1	557	GAAUGTGAAAGUCAUCGACAA	674	UUGUCGAUGACUUUCACAUUCUG	1072-1094

Duplex Name	SEQ ID NO:	Sense strand sequence 5' to 3'	SEQ ID NO:	Antisense strand sequence 5' to 3'	Position in NM_017545.2
AD-65627.1	558	GAAUGUGAAAGUCAUCGACAA	675	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65633.1	559	GAAUGTGAAAGUCAUCGACAA	676	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65639.1	560	GAAUGUGAAAGUCAUCGACAA	677	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65645.1	561	GAAUGUGAAAGUCAUCGACAA	678	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65650.1	562	GAAUGUGAAAGUCAUCTACAA	679	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65655.1	563	GAAUGUGAAAGUCAUCACAA	680	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65660.1	564	GAAUGUGAAAGUCATCTACAA	681	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65665.1	565	GAAUGUGAAAGUCAUCGACAA	682	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65628.1	566	GAAUGUGAAAGUCAUCTACAA	683	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65634.1	567	GAAUGUGAAAGUCAUCACAA	684	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65646.1	568	GAAUGUGAAAGUCAUCGACAA	685	UTGUCGAUGACUUTCACAUUCUG	1072-1094
AD-65656.1	569	GAAUGUGAAAGUCAUCGACAA	686	UUGUCGAUGACUUTCACAUUCUG	1072-1094
AD-65661.1	570	GAAUGUGAAAGUCAUCGACAA	687	UTGUCGAUGACUUTCACAUUCUG	1072-1094
AD-65666.1	571	GAAUGUGAAAGUCAUCGACAA	688	UUGUCGAUGACUUTCACAUUCUG	1072-1094
AD-65629.1	572	GAAUGUGAAAGUCAUCGACAA	689	UTGUCGAUGACUUTCACAUUCUG	1072-1094
AD-65635.1	573	GAAUGUGAAAGUCAUCGACAA	690	UTGUCGAUGACUUTCACAUUCUG	1072-1094
AD-65641.1	574	GAAUGUGAAAGUCAUCGACAA	691	UTGUCGAUGACUUTCACAUUCUG	1072-1094
AD-62994.1	575	GACUUUCAUCCUGGAAAUAUA	692	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65595.1	576	GACUUUCAUCCUGGAAAUAUA	693	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65600.1	577	GACUUUCAUCCUGGAAAUAUA	694	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65610.1	578	GACUUUCAUCCUGGAAAUAUA	695	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65615.1	579	GACUUUCAUCCUGGAAAUAUA	696	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65620.1	580	GACUUUCAUCCUGGAAAUAUA	697	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65584.1	581	CUUUCAUCCUGGAAAUAUA	698	UAUAUUUCCAGGAUGAAAGUC	1341-1361
AD-65590.1	582	CUUUCAUCCUGGAAAUAUA	699	UAUAUUUCCAGGAUGAAAGUC	1341-1361
AD-65596.1	583	GACUUUCAUCCUGGAAAUAUA	700	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65601.1	584	GACUUUCAUCCUGGAAAUAUA	701	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363

Duplex Name	SEQ ID NO:	Sense strand sequence 5' to 3'	SEQ ID NO:	Antisense strand sequence 5' to 3'	Position in NM_017545.2
AD-65606.1	585	GACUUUCAUCCUGGAAAUAUA	702	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65611.1	586	GACUUUCAUCCUGGAAAUAUA	703	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65616.1	587	GACUUUCAUCCUGGAAAUAUA	704	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65621.1	588	GACUUUCAUCCUGGAAAUAUA	705	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65585.1	589	GACUUUCAUCCUGGAAAUAUA	706	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65591.1	590	GACUUUCAUCCUGGAAAUAUA	707	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65597.1	591	GACUUUCAUCCUGGAAAUAUA	708	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65602.1	592	GACUUUCAUCCUGGAAAUAUA	709	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65607.1	593	GACUUUCAUCCUGGAAAUAUA	710	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65612.1	594	GACUUUCAUCCUGGAAAUAUA	711	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65622.1	595	GACUUUCAUCCUGGAAAUAUA	712	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65586.1	596	GACUTUCAUCCUGGAAAUAUA	713	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65592.1	597	GACUUTCAUCCUGGAAAUAUA	714	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65598.1	598	GACUUUCAUCCUGGAAAUAUA	715	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65603.1	599	GACUUUCAUCCUGGAAAUAUA	716	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65608.1	600	GACUUUCAUCCUGGAATUAUA	717	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65613.1	601	GACUUUCAUCCUGGAAUAUA	718	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65618.1	602	GACUUUCAUCCUGGAATUAUA	719	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65623.1	603	GACUUUCAUCCUGGAATUAUA	720	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65587.1	604	GACUUUCAUCCUGGAAAUAUA	721	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65593.1	605	GACUUTCAUCCUGGAAAUAUA	722	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65599.1	606	GACUUUCAUCCUGGAAAUAUA	723	UAUAUUUCCAGGATGAAAGUCCA	1341-1363
AD-65604.1	607	GACUUUCAUCCUGGAAAUAUA	724	UAUAUUUCCAGGATGAAAGUCCA	1341-1363
AD-65609.1	608	GACUUUCAUCCUGGAAAUAUA	725	UAUAUUUCCAGGATGAAAGUCCA	1341-1363
AD-65614.1	609	GACUUUCAUCCUGGAAAUAUA	726	UAUAUTUCCAGGATGAAAGUCCA	1341-1363
AD-65619.1	610	GACUUUCAUCCUGGAAAUAUA	727	UAUAUTUCCAGGATGAAAGUCCA	1341-1363
AD-65624.1	611	GACUUUCAUCCUGGAAAUAUA	728	UAUAUUUCCAGGATGAAAGUCCA	1341-1363

Duplex Name	SEQ ID NO:	Sense strand sequence 5' to 3'	SEQ ID NO:	Antisense strand sequence 5' to 3'	Position in NM_017545.2
AD-65588.1	612	GACUUUCAUCCUGGAAAUAUA	729	UAUAUTUCCAGGATGAAAGUCCA	1341-1363
AD-65594.1	613	GACUUUCAUCCUGGAAAUAUA	730	UAUAUUUCCAGGATGAAAGUCCA	1341-1363
AD-68309.1	614	AGAAAGGUGUUCAAGAUGUCA	731	UGACAUCUUGAACACCUUUCUCC	1001-1022_C21A
AD-68303.1	615	CAUCCUGGAAAUAUAUUAACU	732	AGUUAAUAUAUUUCCAGGAUGAA	1349-1370
AD-65626.5	616	GAAUGUGAAAGUCAUCGACAA	733	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-68295.1	617	AGUGCACAAUAUUUUCCCAUA	734	UAUGGGAAAAUAUUGUGCACUGU	1139-1160_C21A
AD-68273.1	618	GAAAGUCAUCGACAAGACAUU	735	AAUGUCUUGUCGAUGACUUUCAC	1080-1100
AD-68297.1	619	AAUGUGAAAGUCAUCGACAAA	736	UUUGUCGAUGACUUUCACAUUCU	1075-1096_G21A
AD-68287.1	620	CUGGAAAUAUAUUAACUGUUA	737	UAACAGUUAAUAUAUUUCCAGGA	1353-1374
AD-68300.1	621	AUUUUCCCAUCUGUAUUAUUU	738	AAAUAAUACAGAUGGGAAAAUAU	1149-1170
AD-68306.1	622	UGUCGUUCUUUUCCAACAAAA	739	UUUUGUUGGAAAAGAACGACACC	1252-1273
AD-68292.1	623	AUCCUGGAAAUAUAUUAACUA	740	UAGUUAAUAUAUUUCCAGGAUGA	1350-1371_G21A
AD-68298.1	624	GCAUUUUGAGAGGUGAUGAUA	741	UAUCAUCACCUCUCAAAAUGCCC	734-755_G21A
AD-68277.1	625	CAGGGGGAGAAAGGUGUUCAA	742	UUGAACACCUUUCUCCCCCUGGA	994-1014
AD-68289.1	626	GGAAAUAUAUUAACUGUUAAA	743	UUUAACAGUUAAUAUAUUUCCAG	1355-1376
AD-68272.1	627	CAUUGGUGAGGAAAAAUCCUU	744	AAGGAUUUUUCCUCACCAAUGUC	1097-1117
AD-68282.1	628	GGGAGAAAGGUGUUCAAGAUA	745	UAUCUUGAACACCUUUCUCCCCC	998-1018_G21A
AD-68285.1	629	GGCAUUUUGAGAGGUGAUGAU	746	AUCAUCACCUCUCAAAAUGCCCU	733-754
AD-68290.1	630	UACAAAGGGUGUCGUUCUUUU	747	AAAAGAACGACACCCUUUGUAUU	1243-1264
AD-68296.1	631	UGGGAUCUUGGUGUCGAAUCA	748	UGAUUCGACACCAAGAUCCCAUU	783-804
AD-68288.1	632	CUGACAGUGCACAAUAUUUUA	749	UAAAAUAUUGUGCACUGUCAGAU	1134-1155_C21A
AD-68299.1	633	CAGUGCACAAUAUUUUCCCAU	750	AUGGGAAAAUAUUGUGCACUGUC	1138-1159
AD-68275.1	634	ACUUUUCAAUGGGUGUCCUAA	751	UUAGGACACCCAUUGAAAAGUCA	1302-1322_G21A
AD-68274.1	635	ACAUUGGUGAGGAAAAAUCCU	752	AGGAUUUUUCCUCACCAAUGUCU	1096-1116
AD-68294.1	636	UUGCUUUUGACUUUUCAAUGA	753	UCAUUGAAAAGUCAAAAGCAAUG	1293-1314_G21A
AD-68302.1	637	CAUUUUGAGAGGUGAUGAUGA	754	UCAUCAUCACCUCUCAAAAUGCC	735-756_C21A
AD-68279.1	638	UUGACUUUUCAAUGGGUGUCA	755	UGACACCCAUUGAAAAGUCAAAA	1299-1319_C21A

Duplex Name	SEQ ID NO:	Sense strand sequence 5' to 3'	SEQ ID NO:	Antisense strand sequence 5' to 3'	Position in NM_017545.2
AD-68304.1	639	CGACUUCUGUUUUAGGACAGA	756	UCUGUCCUAAAACAGAAGUCGAC	212-233
AD-68286.1	640	CUCUGAGUGGGUGCCAGAAUA	757	UAUUCUGGCACCCACUCAGAGCC	1058-1079_G21A
AD-68291.1	641	GGGUGCCAGAAUGUGAAAGUA	758	UACUUUCACAUUCUGGCACCCAC	1066-1087_C21A
AD-68283.1	642	UCAAUGGGUGUCCUAGGAACA	759	UGUUCCUAGGACACCCAUUGAAA	1307-1327_C21A
AD-68280.1	643	AAAGUCAUCGACAAGACAUUA	760	UAAUGUCUUGUCGAUGACUUUCA	1081-1101_G21A
AD-68293.1	644	AUUUUGAGAGGUGAUGAUGCA	761	UGCAUCAUCACCUCUCAAAAUGC	736-757_C21A
AD-68276.1	645	AUCGACAAGACAUUGGUGAGA	762	UCUCACCAAUGUCUUGUCGAUGA	1087-1107_G21A
AD-68308.1	646	GGUGCCAGAAUGUGAAAGUCA	763	UGACUUUCACAUUCUGGCACCCA	1067-1088
AD-68278.1	647	GACAGUGCACAAUAUUUUCCA	764	UGGAAAAUAUUGUGCACUGUCAG	1136-1156_C21A
AD-68307.1	648	ACAAAGAGACACUGUGCAGAA	765	UUCUGCACAGUGUCUCUUUGUCA	1191-1212_G21A
AD-68284.1	649	UUUUCAAUGGGUGUCCUAGGA	766	UCCUAGGACACCCAUUGAAAAGU	1304-1324
AD-68301.1	650	CCGUUUCCAAGAUCUGACAGU	767	ACUGUCAGAUCUUGGAAACGGCC	1121-1142
AD-68281.1	651	AGGGGGAGAAAGGUGUUCAAA	768	UUUGAACACCUUUCUCCCCCUGG	995-1015_G21A
AD-68305.1	652	AGUCAUCGACAAGACAUUGGU	769	ACCAAUGUCUUGUCGAUGACUUU	1083-1104

Table 8. Additional Human/Mouse/Cyno HAO1 Modified and Unmodified Sense Strand iRNA Sequences

Duplex Name	Modified sense strand sequence 5' to 3'	Unmodified sense strand sequence 5' to 3'	SEQ ID NO:
AD-40257.1	uucAAuGGGuGuccuAGGAdTsdT	UUCAAUGGGUGUCCUAGGA	770 & 771
AD-40257.2	uucAAuGGGuGuccuAGGAdTsdT	UUCAAUGGGUGUCCUAGGA	770 & 771
AD-63102.1	AcAAcuGGAGGGAcAucGudTsdT	ACAACUGGAGGGACAUCGU	772 & 773
AD-63102.2	AcAAcuGGAGGGAcAucGudTsdT	ACAACUGGAGGGACAUCGU	772 & 773
AD-63102.3	AcAAcuGGAGGGAcAucGudTsdT	ACAACUGGAGGGACAUCGU	772 & 773

Table 9. Additional Human/Mouse/Cyno HAO1 Modified and Unmodified Antisense Strand iRNA Sequences

Duplex Name	Modified antisense strand sequence 5' to 3'	Unmodified antisense strand sequence 5' to 3'	SEQ ID NO:

AD-40257.1	UCCuAGGAcACCcAUUGAAdTsdT	UCCUAGGACACCCAUUGAA	774 & 775
AD-40257.2	UCCuAGGAcACCcAUUGAAdTsdT	UCCUAGGACACCCAUUGAA	774 & 775
AD-63102.1	ACGAUGUCCCUCcAGUUGUdTsdT	ACGAUGUCCCUCCAGUUGU	776 & 777
AD-63102.2	ACGAUGUCCCUCcAGUUGUdTsdT	ACGAUGUCCCUCCAGUUGU	776 & 777
AD-63102.3	ACGAUGUCCCUCcAGUUGUdTsdT	ACGAUGUCCCUCCAGUUGU	776 & 777

Table 10. Additional Human/Cyno/Mouse/Rat and Human/Cyno/Rat HAO1 Modified Sense Strand iRNA Sequences

Duplex Name	Modified sense strand sequence	SEQ ID NO:
AD-62989.2	UfscsCfuAfgGfaAfCfCfuUfuUfaGfaAfaUfL96	778
AD-62994.2	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfL96	779
AD-62933.2	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfL96	780
AD-62935.2	CfsasUfuGfgUfgAfGfGfaAfaAfaUfcCfuUfL96	781
AD-62940.2	AfsusCfgAfcAfaGfAfCfaUfuGfgUfgAfgAfL96	782
AD-62941.2	AfscsAfuUfgGfuGfAfGfgAfaAfaAfuCfcUfL96	783
AD-62944.2	GfsasAfaGfuCfaUfCfGfaCfaAfgAfcAfuUfL96	784
AD-62965.2	AfsasAfgUfcAfuCfGfAfcAfaGfaCfaUfuAfL96	785

Table 11. Additional Human/Cyno/Mouse/Rat and Human/Cyno/Rat HAO1 Modified Antisense Strand iRNA Sequences

Duplex Name	Modified antisense strand	SEQ ID NO:
AD-62989.2	asUfsuUfcUfaAfaAfgguUfcCfuAfgGfascsa	786
AD-62994.2	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcscsa	787
AD-62933.2	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	788
AD-62935.2	asAfsgGfaUfuUfuUfccuCfaCfcAfaUfgsusc	789
AD-62940.2	usCfsuCfaCfcAfaUfgucUfuGfuCfgAfusgsa	790
AD-62941.2	asGfsgAfuUfuUfuCfcucAfcCfaAfuGfuscsu	791
AD-62944.2	asAfsuGfuCfuUfgUfcgaUfgAfcUfuUfcsasc	792
AD-62965.2	usAfsaUfgUfcUfuGfucgAfuGfaCfuUfuscsa	793

Table 12. Additional Human Unmodified and Modifieded Sense and Antisense Strand HAO1 iRNA Sequences Targeting NM_017545.2

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
AUGUAUGUUACUUCUUAGAGA	794	asusguauGfuUfAfCfuucuuagagaL96	1890	sense	21
UCUCUAAGAAGUAACAUACAUCC	795	usCfsucuAfaGfAfaguaAfcAfuacauscsc	1891	antisense	23
UGUAUGUUACUUCUUAGAGAG	796	usgsuaugUfuAfCfUfucuuagagagL96	1892	sense	21
CUCUCUAAGAAGUAACAUACAUC	797	csUfscucUfaAfGfaaguAfaCfauacasusc	1893	antisense	23
UAGGAUGUAUGUUACUUCUUA	798	usasggauGfuAfUfGfuuacuucuuaL96	1894	sense	21
UAAGAAGUAACAUACAUCCUAAA	799	usAfsagaAfgUfAfacauAfcAfuccuasasa	1895	antisense	23
UUAGGAUGUAUGUUACUUCUU	800	ususaggaUfgUfAfUfguuacuucuuL96	1896	sense	21
AAGAAGUAACAUACAUCCUAAAA	801	asAfsgaaGfuAfAfcauaCfaUfccuaasasa	1897	antisense	23
AGAAAGGUGUUCAAGAUGUCC	802	asgsaaagGfuGfUfUfcaagauguccL96	1898	sense	21
GGACAUCUUGAACACCUUUCUCC	803	gsGfsacaUfcUfUfgaacAfcCfuuucuscsc	1899	antisense	23
GAAAGGUGUUCAAGAUGUCCU	804	gsasaaggUfgUfUfCfaagauguccuL96	1900	sense	21
AGGACAUCUUGAACACCUUUCUC	805	asGfsgacAfuCfUfugaaCfaCfcuuucsusc	1901	antisense	23
GGGGAGAAAGGUGUUCAAGAU	806	gsgsggagAfaAfGfGfuguucaagauL96	1902	sense	21
AUCUUGAACACCUUUCUCCCCCU	807	asUfscuuGfaAfCfaccuUfuCfucccccscsu	1903	antisense	23
GGGGGAGAAAGGUGUUCAAGA	808	gsgsgggaGfaAfAfGfguguucaagaL96	1904	sense	21
UCUUGAACACCUUUCUCCCCCUG	809	usCfsuugAfaCfAfccuuUfcUfcccccsusg	1905	antisense	23
AGAAACUUUGGCUGAUAAUAU	810	asgsaaacUfuUfGfGfcugauaauauL96	1906	sense	21
AUAUUAUCAGCCAAAGUUUCUUC	811	asUfsauuAfuCfAfgccaAfaGfuuucususc	1907	antisense	23
GAAACUUUGGCUGAUAAUAUU	812	gsasaacuUfuGfGfCfugauaauauuL96	1908	sense	21
AAUAUUAUCAGCCAAAGUUUCUU	813	asAfsuauUfaUfCfagccAfaAfguuucsusu	1909	antisense	23
AUGAAGAAACUUUGGCUGAUA	814	asusgaagAfaAfCfUfuuggcugauaL96	1910	sense	21
UAUCAGCCAAAGUUUCUUCAUCA	815	usAfsucaGfcCfAfaaguUfuCfuucauscsa	1911	antisense	23
GAUGAAGAAACUUUGGCUGAU	816	gsasugaaGfaAfAfCfuuuggcugauL96	1912	sense	21
AUCAGCCAAAGUUUCUUCAUCAU	817	asUfscagCfcAfAfaguuUfcUfucaucsasu	1913	antisense	23
AAGGCACUGAUGUUCUGAAAG	818	asasggcaCfuGfAfUfguucugaaagL96	1914	sense	21
CUUUCAGAACAUCAGUGCCUUUC	819	csUfsuucAfgAfAfcaucAfgUfgccuususc	1915	antisense	23
AGGCACUGAUGUUCUGAAAGC	820	asgsgcacUfgAfUfGfuucugaaagcL96	1916	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
GCUUUCAGAACAUCAGUGCCUUU	821	gsCfsuuuCfaGfAfacauCfaGfugccususu	1917	antisense	23
CGGAAAGGCACUGAUGUUCUG	822	csgsgaaaGfgCfAfCfugauguucugL96	1918	sense	21
CAGAACAUCAGUGCCUUUCCGCA	823	csAfsgaaCfaUfCfagugCfcUfuuccgscsa	1919	antisense	23
GCGGAAAGGCACUGAUGUUCU	824	gscsggaaAfgGfCfAfcugauguucuL96	1920	sense	21
AGAACAUCAGUGCCUUUCCGCAC	825	asGfsaacAfuCfAfgugcCfuUfuccgcsasc	1921	antisense	23
AGAAGACUGACAUCAUUGCCA	826	asgsaagaCfuGfAfCfaucauugccaL96	1922	sense	21
UGGCAAUGAUGUCAGUCUUCUCA	827	usGfsgcaAfuGfAfugucAfgUfcuucuscsa	1923	antisense	23
GAAGACUGACAUCAUUGCCAA	828	gsasagacUfgAfCfAfucauugccaaL96	1924	sense	21
UUGGCAAUGAUGUCAGUCUUCUC	829	usUfsggcAfaUfGfauguCfaGfucuucsusc	1925	antisense	23
GCUGAGAAGACUGACAUCAUU	830	gscsugagAfaGfAfCfugacaucauuL96	1926	sense	21
AAUGAUGUCAGUCUUCUCAGCCA	831	asAfsugaUfgUfCfagucUfuCfucagcscsa	1927	antisense	23
GGCUGAGAAGACUGACAUCAU	832	gsgscugaGfaAfGfAfcugacaucauL96	1928	sense	21
AUGAUGUCAGUCUUCUCAGCCAU	833	asUfsgauGfuCfAfgucuUfcUfcagccsasu	1929	antisense	23
UAAUGCCUGAUUCACAACUUU	834	usasaugcCfuGfAfUfucacaacuuuL96	1930	sense	21
AAAGUUGUGAAUCAGGCAUUACC	835	asAfsaguUfgUfGfaaucAfgGfcauuascsc	1931	antisense	23
AAUGCCUGAUUCACAACUUUG	836	asasugccUfgAfUfUfcacaacuuugL96	1932	sense	21
CAAAGUUGUGAAUCAGGCAUUAC	837	csAfsaagUfuGfUfgaauCfaGfgcauusasc	1933	antisense	23
UUGGUAAUGCCUGAUUCACAA	838	ususgguaAfuGfCfCfugauucacaaL96	1934	sense	21
UUGUGAAUCAGGCAUUACCAACA	839	usUfsgugAfaUfCfaggcAfuUfaccaascsa	1935	antisense	23
GUUGGUAAUGCCUGAUUCACA	840	gsusugguAfaUfGfCfcugauucacaL96	1936	sense	21
UGUGAAUCAGGCAUUACCAACAC	841	usGfsugaAfuCfAfggcaUfuAfccaacsasc	1937	antisense	23
UAUCAAAUGGCUGAGAAGACU	842	usasucaaAfuGfGfCfugagaagacuL96	1938	sense	21
AGUCUUCUCAGCCAUUUGAUAUC	843	asGfsucuUfcUfCfagccAfuUfugauasusc	1939	antisense	23
AUCAAAUGGCUGAGAAGACUG	844	asuscaaaUfgGfCfUfgagaagacugL96	1940	sense	21
CAGUCUUCUCAGCCAUUUGAUAU	845	csAfsgucUfuCfUfcagcCfaUfuugausasu	1941	antisense	23
AAGAUAUCAAAUGGCUGAGAA	846	asasgauaUfcAfAfAfuggcugagaaL96	1942	sense	21
UUCUCAGCCAUUUGAUAUCUUCC	847	usUfscucAfgCfCfauuuGfaUfaucuuscsc	1943	antisense	23
GAAGAUAUCAAAUGGCUGAGA	848	gsasagauAfuCfAfAfauggcugagaL96	1944	sense	21
UCUCAGCCAUUUGAUAUCUUCCC	849	usCfsucaGfcCfAfuuugAfuAfucuucscsc	1945	antisense	23
UCUGACAGUGCACAAUAUUUU	850	uscsugacAfgUfGfCfacaauauuuuL96	1946	sense	21
AAAAUAUUGUGCACUGUCAGAUC	851	asAfsaauAfuUfGfugcaCfuGfucagasusc	1947	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
CUGACAGUGCACAAUAUUUUC	852	csusgacaGfuGfCfAfcaauauuuucL96	1948	sense	21
GAAAAUAUUGUGCACUGUCAGAU	853	gsAfsaaaUfaUfUfgugcAfcUfgucagsasu	1949	antisense	23
AAGAUCUGACAGUGCACAAUA	854	asasgaucUfgAfCfAfgugcacaauaL96	1950	sense	21
UAUUGUGCACUGUCAGAUCUUGG	855	usAfsuugUfgCfAfcuguCfaGfaucuusgsg	1951	antisense	23
CAAGAUCUGACAGUGCACAAU	856	csasagauCfuGfAfCfagugcacaauL96	1952	sense	21
AUUGUGCACUGUCAGAUCUUGGA	857	asUfsuguGfcAfCfugucAfgAfucuugsgsa	1953	antisense	23
ACUGAUGUUCUGAAAGCUCUG	858	ascsugauGfuUfCfUfgaaagcucugL96	1954	sense	21
CAGAGCUUUCAGAACAUCAGUGC	859	csAfsgagCfuUfUfcagaAfcAfucagusgsc	1955	antisense	23
CUGAUGUUCUGAAAGCUCUGG	860	csusgaugUfuCfUfGfaaagcucuggL96	1956	sense	21
CCAGAGCUUUCAGAACAUCAGUG	861	csCfsagaGfcUfUfucagAfaCfaucagsusg	1957	antisense	23
AGGCACUGAUGUUCUGAAAGC	862	asgsgcacUfgAfUfGfuucugaaagcL96	1958	sense	21
GCUUUCAGAACAUCAGUGCCUUU	863	gsCfsuuuCfaGfAfacauCfaGfugccususu	1959	antisense	23
AAGGCACUGAUGUUCUGAAAG	864	asasggcaCfuGfAfUfguucugaaagL96	1960	sense	21
CUUUCAGAACAUCAGUGCCUUUC	865	csUfsuucAfgAfAfcaucAfgUfgccuususc	1961	antisense	23
AACAACAUGCUAAAUCAGUAC	866	asascaacAfuGfCfUfaaaucaguacL96	1962	sense	21
GUACUGAUUUAGCAUGUUGUUCA	867	gsUfsacuGfaUfUfuagcAfuGfuuguuccsa	1963	antisense	23
ACAACAUGCUAAAUCAGUACU	868	ascsaacaUfgCfUfAfaaucaguacuL96	1964	sense	21
AGUACUGAUUUAGCAUGUUGUUC	869	asGfsuacUfgAfUfuuagCfaUfguugususc	1965	antisense	23
UAUGAACAACAUGCUAAAUCA	870	usasugaaCfaAfCfAfugcuaaaucaL96	1966	sense	21
UGAUUUAGCAUGUUGUUCAUAAU	871	usGfsauuUfaGfCfauguUfgUfucauasasu	1967	antisense	23
UUAUGAACAACAUGCUAAAUC	872	ususaugaAfcAfAfCfaugcuaaaucL96	1968	sense	21
GAUUUAGCAUGUUGUUCAUAAUC	873	gsAfsuuuAfgCfAfuguuGfuUfcauaasusc	1969	antisense	23
UCUUUAGUGUCUGAAUAUAUC	874	uscsuuuaGfuGfUfCfugaauauaucL96	1970	sense	21
GAUAUAUUCAGACACUAAAGAUG	875	gsAfsuauAfuUfCfagacAfcUfaaagasusg	1971	antisense	23
CUUUAGUGUCUGAAUAUAUCC	876	csusuuagUfgUfCfUfgaauauauccL96	1972	sense	21
GGAUAUAUUCAGACACUAAAGAU	877	gsGfsauaUfaUfUfcagaCfaCfuaaagsasu	1973	antisense	23
CACAUCUUUAGUGUCUGAAUA	878	csascaucUfuUfAfGfugucugaauaL96	1974	sense	21
UAUUCAGACACUAAAGAUGUGAU	879	usAfsuucAfgAfCfacuaAfaGfaugugsasu	1975	antisense	23
UCACAUCUUUAGUGUCUGAAU	880	uscsacauCfuUfUfAfgugucugaauL96	1976	sense	21
AUUCAGACACUAAAGAUGUGAUU	881	asUfsucaGfaCfAfcuaaAfgAfugugasusu	1977	antisense	23
UGAUACUUCUUUGAAUGUAGA	882	usgsauacUfuCfUfUfugaauguagaL96	1978	sense	21

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Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
UCUACAUUCAAAGAAGUAUCACC	883	usCfsuacAfuUfCfaaagAfaGfuaucascsc	1979	antisense	23
GAUACUUCUUUGAAUGUAGAU	884	gsasuacuUfcUfUfUfgaauguagauL96	1980	sense	21
AUCUACAUUCAAAGAAGUAUCAC	885	asUfscuaCfaUfUfcaaaGfaAfguaucsasc	1981	antisense	23
UUGGUGAUACUUCUUUGAAUG	886	ususggugAfuAfCfUfucuuugaaugL96	1982	sense	21
CAUUCAAAGAAGUAUCACCAAUU	887	csAfsuucAfaAfGfaaguAfuCfaccaasusu	1983	antisense	23
AUUGGUGAUACUUCUUUGAAU	888	asusugguGfaUfAfCfuucuuugaauL96	1984	sense	21
AUUCAAAGAAGUAUCACCAAUUA	889	asUfsucaAfaGfAfaguaUfcAfccaaususa	1985	antisense	23
AAUAACCUGUGAAAAUGCUCC	890	asasuaacCfuGfUfGfaaaaugcuccL96	1986	sense	21
GGAGCAUUUUCACAGGUUAUUGC	891	gsGfsagcAfuUfUfucacAfgGfuuauusgsc	1987	antisense	23
AUAACCUGUGAAAAUGCUCCC	892	asusaaccUfgUfGfAfaaaugcucccL96	1988	sense	21
GGGAGCAUUUUCACAGGUUAUUG	893	gsGfsgagCfaUfUfuucaCfaGfguuaususg	1989	antisense	23
UAGCAAUAACCUGUGAAAAUG	894	usasgcaaUfaAfCfCfugugaaaaugL96	1990	sense	21
CAUUUUCACAGGUUAUUGCUAUC	895	csAfsuuuUfcAfCfagguUfaUfugcuasusc	1991	antisense	23
AUAGCAAUAACCUGUGAAAAU	896	asusagcaAfuAfAfCfcugugaaaauL96	1992	sense	21
AUUUUCACAGGUUAUUGCUAUCC	897	asUfsuuuCfaCfAfgguuAfuUfgcuauscsc	1993	antisense	23
AAUCACAUCUUUAGUGUCUGA	898	asasucacAfuCfUfUfuagugucugaL96	1994	sense	21
UCAGACACUAAAGAUGUGAUUGG	899	usCfsagaCfaCfUfaaagAfuGfugauusgsg	1995	antisense	23
AUCACAUCUUUAGUGUCUGAA	900	asuscacaUfcUfUfUfagugucugaaL96	1996	sense	21
UUCAGACACUAAAGAUGUGAUUG	901	usUfscagAfcAfCfuaaaGfaUfgugaususg	1997	antisense	23
UUCCAAUCACAUCUUUAGUGU	902	ususccaaUfcAfCfAfucuuuaguguL96	1998	sense	21
ACACUAAAGAUGUGAUUGGAAAU	903	asCfsacuAfaAfGfauguGfaUfuggaasasu	1999	antisense	23
UUUCCAAUCACAUCUUUAGUG	904	ususuccaAfuCfAfCfaucuuuagugL96	2000	sense	21
CACUAAAGAUGUGAUUGGAAAUC	905	csAfscuaAfaGfAfugugAfuUfggaaasusc	2001	antisense	23
ACGGGCAUGAUGUUGAGUUCC	906	ascsgggcAfuGfAfUfguugaguuccL96	2002	sense	21
GGAACUCAACAUCAUGCCCGUUC	907	gsGfsaacUfcAfAfcaucAfuGfcccgususc	2003	antisense	23
CGGGCAUGAUGUUGAGUUCCU	908	csgsggcaUfgAfUfGfuugaguuccuL96	2004	sense	21
AGGAACUCAACAUCAUGCCCGUU	909	asGfsgaaCfuCfAfacauCfaUfgcccgsusu	2005	antisense	23
GGGAACGGGCAUGAUGUUGAG	910	gsgsgaacGfgGfCfAfugauguugagL96	2006	sense	21
CUCAACAUCAUGCCCGUUCCCAG	911	csUfscaaCfaUfCfaugcCfcGfuucccsasg	2007	antisense	23
UGGGAACGGGCAUGAUGUUGA	912	usgsggaaCfgGfGfCfaugauguugaL96	2008	sense	21
UCAACAUCAUGCCCGUUCCCAGG	913	usCfsaacAfuCfAfugccCfgUfucccasgsg	2009	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
ACUAAGGUGAAAAGAUAAUGA	914	ascsuaagGfuGfAfAfaagauaaugaL96	2010	sense	21
UCAUUAUCUUUUCACCUUAGUGU	915	usCfsauuAfuCfUfuuucAfcCfuuagusgsu	2011	antisense	23
CUAAGGUGAAAAGAUAAUGAU	916	csusaaggUfgAfAfAfagauaaugauL96	2012	sense	21
AUCAUUAUCUUUUCACCUUAGUG	917	asUfscauUfaUfCfuuuuCfaCfcuuagsusg	2013	antisense	23
AAACACUAAGGUGAAAAGAUA	918	asasacacUfaAfGfGfugaaaagauaL96	2014	sense	21
UAUCUUUUCACCUUAGUGUUUGC	919	usAfsucuUfuUfCfaccuUfaGfuguuusgsc	2015	antisense	23
CAAACACUAAGGUGAAAAGAU	920	csasaacaCfuAfAfGfgugaaaagauL96	2016	sense	21
AUCUUUUCACCUUAGUGUUUGCU	921	asUfscuuUfuCfAfccuuAfgUfguuugscsu	2017	antisense	23
AGGUAGCACUGGAGAGAAUUG	922	asgsguagCfaCfUfGfgagagaauugL96	2018	sense	21
CAAUUCUCUCCAGUGCUACCUUC	923	csAfsauuCfuCfUfccagUfgCfuaccususc	2019	antisense	23
GGUAGCACUGGAGAGAAUUGG	924	gsgsuagcAfcUfGfGfagagaauuggL96	2020	sense	21
CCAAUUCUCUCCAGUGCUACCUU	925	csCfsaauUfcUfCfuccaGfuGfcuaccsusu	2021	antisense	23
GAGAAGGUAGCACUGGAGAGA	926	gsasgaagGfuAfGfCfacuggagagaL96	2022	sense	21
UCUCUCCAGUGCUACCUUCUCAA	927	usCfsucuCfcAfGfugcuAfcCfuucucsasa	2023	antisense	23
UGAGAAGGUAGCACUGGAGAG	928	usgsagaaGfgUfAfGfcacuggagagL96	2024	sense	21
CUCUCCAGUGCUACCUUCUCAAA	929	csUfscucCfaGfUfgcuaCfcUfucucasasa	2025	antisense	23
AGUGGACUUGCUGCAUAUGUG	930	asgsuggaCfuUfGfCfugcauaugugL96	2026	sense	21
CACAUAUGCAGCAAGUCCACUGU	931	csAfscauAfuGfCfagcaAfgUfccacusgsu	2027	antisense	23
GUGGACUUGCUGCAUAUGUGG	932	gsusggacUfuGfCfUfgcauauguggL96	2028	sense	21
CCACAUAUGCAGCAAGUCCACUG	933	csCfsacaUfaUfGfcagcAfaGfuccacsusg	2029	antisense	23
CGACAGUGGACUUGCUGCAUA	934	csgsacagUfgGfAfCfuugcugcauaL96	2030	sense	21
UAUGCAGCAAGUCCACUGUCGUC	935	usAfsugcAfgCfAfagucCfaCfugucgsusc	2031	antisense	23
ACGACAGUGGACUUGCUGCAU	936	ascsgacaGfuGfGfAfcuugcugcauL96	2032	sense	21
AUGCAGCAAGUCCACUGUCGUCU	937	asUfsgcaGfcAfAfguccAfcUfgucguscsu	2033	antisense	23
AAGGUGUUCAAGAUGUCCUCG	938	asasggugUfuCfAfAfgauguccucgL96	2034	sense	21
CGAGGACAUCUUGAACACCUUUC	939	csGfsaggAfcAfUfcuugAfaCfaccuususc	2035	antisense	23
AGGUGUUCAAGAUGUCCUCGA	940	asgsguguUfcAfAfGfauguccucgaL96	2036	sense	21
UCGAGGACAUCUUGAACACCUUU	941	usCfsgagGfaCfAfucuuGfaAfcaccususu	2037	antisense	23
GAGAAAGGUGUUCAAGAUGUC	942	gsasgaaaGfgUfGfUfucaagaugucL96	2038	sense	21
GACAUCUUGAACACCUUUCUCCC	943	gsAfscauCfuUfGfaacaCfcUfuucucscsc	2039	antisense	23
GGAGAAAGGUGUUCAAGAUGU	944	gsgsagaaAfgGfUfGfuucaagauguL96	2040	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
ACAUCUUGAACACCUUUCUCCCC	945	asCfsaucUfuGfAfacacCfuUfucuccscsc	2041	antisense	23
AACCGUCUGGAUGAUGUGCGU	946	asasccguCfuGfGfAfugaugugcguL96	2042	sense	21
ACGCACAUCAUCCAGACGGUUGC	947	asCfsgcaCfaUfCfauccAfgAfcgguusgsc	2043	antisense	23
ACCGUCUGGAUGAUGUGCGUA	948	ascscgucUfgGfAfUfgaugugcguaL96	2044	sense	21
UACGCACAUCAUCCAGACGGUUG	949	usAfscgcAfcAfUfcaucCfaGfacggususg	2045	antisense	23
GGGCAACCGUCUGGAUGAUGU	950	gsgsgcaaCfcGfUfCfuggaugauguL96	2046	sense	21
ACAUCAUCCAGACGGUUGCCCAG	951	asCfsaucAfuCfCfagacGfgUfugcccsasg	2047	antisense	23
UGGGCAACCGUCUGGAUGAUG	952	usgsggcaAfcCfGfUfcuggaugaugL96	2048	sense	21
CAUCAUCCAGACGGUUGCCCAGG	953	csAfsucaUfcCfAfgacgGfuUfgcccasgsg	2049	antisense	23
GAAACUUUGGCUGAUAAUAUU	954	gsasaacuUfuGfGfCfugauaauauuL96	2050	sense	21
AAUAUUAUCAGCCAAAGUUUCUU	955	asAfsuauUfaUfCfagccAfaAfguuucsusu	2051	antisense	23
AAACUUUGGCUGAUAAUAUUG	956	asasacuuUfgGfCfUfgauaauauugL96	2052	sense	21
CAAUAUUAUCAGCCAAAGUUUCU	957	csAfsauaUfuAfUfcagcCfaAfaguuuscsu	2053	antisense	23
UGAAGAAACUUUGGCUGAUAA	958	usgsaagaAfaCfUfUfuggcugauaaL96	2054	sense	21
UUAUCAGCCAAAGUUUCUUCAUC	959	usUfsaucAfgCfCfaaagUfuUfcuucasusc	2055	antisense	23
AUGAAGAAACUUUGGCUGAUA	960	asusgaagAfaAfCfUfuuggcugauaL96	2056	sense	21
UAUCAGCCAAAGUUUCUUCAUCA	961	usAfsucaGfcCfAfaaguUfuCfuucauscsa	2057	antisense	23
AAAGGUGUUCAAGAUGUCCUC	962	asasagguGfuUfCfAfagauguccucL96	2058	sense	21
GAGGACAUCUUGAACACCUUUCU	963	gsAfsggaCfaUfCfuugaAfcAfccuuuscsu	2059	antisense	23
AAGGUGUUCAAGAUGUCCUCG	964	asasggugUfuCfAfAfgauguccucgL96	2060	sense	21
CGAGGACAUCUUGAACACCUUUC	965	csGfsaggAfcAfUfcuugAfaCfaccuususc	2061	antisense	23
GGAGAAAGGUGUUCAAGAUGU	966	gsgsagaaAfgGfUfGfuucaagauguL96	2062	sense	21
ACAUCUUGAACACCUUUCUCCCC	967	asCfsaucUfuGfAfacacCfuUfucuccscsc	2063	antisense	23
GGGAGAAAGGUGUUCAAGAUG	968	gsgsgagaAfaGfGfUfguucaagaugL96	2064	sense	21
CAUCUUGAACACCUUUCUCCCCC	969	csAfsucuUfgAfAfcaccUfuUfcucccscsc	2065	antisense	23
AAAUCAGUACUUCCAAAGUCU	970	asasaucaGfuAfCfUfuccaaagucuL96	2066	sense	21
AGACUUUGGAAGUACUGAUUUAG	971	asGfsacuUfuGfGfaaguAfcUfgauuusasg	2067	antisense	23
AAUCAGUACUUCCAAAGUCUA	972	asasucagUfaCfUfUfccaaagucuaL96	2068	sense	21
UAGACUUUGGAAGUACUGAUUUA	973	usAfsgacUfuUfGfgaagUfaCfugauususa	2069	antisense	23
UGCUAAAUCAGUACUUCCAAA	974	usgscuaaAfuCfAfGfuacuuccaaaL96	2070	sense	21
UUUGGAAGUACUGAUUUAGCAUG	975	usUfsuggAfaGfUfacugAfuUfuagcasusg	2071	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
AUGCUAAAUCAGUACUUCCAA	976	asusgcuaAfaUfCfAfguacuuccaaL96	2072	sense	21
UUGGAAGUACUGAUUUAGCAUGU	977	usUfsggaAfgUfAfcugaUfuUfagcausgsu	2073	antisense	23
ACAUCUUUAGUGUCUGAAUAU	978	ascsaucuUfuAfGfUfgucugaauauL96	2074	sense	21
AUAUUCAGACACUAAAGAUGUGA	979	asUfsauuCfaGfAfcacuAfaAfgaugusgsa	2075	antisense	23
CAUCUUUAGUGUCUGAAUAUA	980	csasucuuUfaGfUfGfucugaauauaL96	2076	sense	21
UAUAUUCAGACACUAAAGAUGUG	981	usAfsuauUfcAfGfacacUfaAfagaugsusg	2077	antisense	23
AAUCACAUCUUUAGUGUCUGA	982	asasucacAfuCfUfUfuagugucugaL96	2078	sense	21
UCAGACACUAAAGAUGUGAUUGG	983	usCfsagaCfaCfUfaaagAfuGfugauusgsg	2079	antisense	23
CAAUCACAUCUUUAGUGUCUG	984	csasaucaCfaUfCfUfuuagugucugL96	2080	sense	21
CAGACACUAAAGAUGUGAUUGGA	985	csAfsgacAfcUfAfaagaUfgUfgauugsgsa	2081	antisense	23
GCAUGUAUUACUUGACAAAGA	986	gscsauguAfuUfAfCfuugacaaagaL96	2082	sense	21
UCUUUGUCAAGUAAUACAUGCUG	987	usCfsuuuGfuCfAfaguaAfuAfcaugcsusg	2083	antisense	23
CAUGUAUUACUUGACAAAGAG	988	csasuguaUfuAfCfUfugacaaagagL96	2084	sense	21
CUCUUUGUCAAGUAAUACAUGCU	989	csUfscuuUfgUfCfaaguAfaUfacaugscsu	2085	antisense	23
UUCAGCAUGUAUUACUUGACA	990	ususcagcAfuGfUfAfuuacuugacaL96	2086	sense	21
UGUCAAGUAAUACAUGCUGAAAA	991	usGfsucaAfgUfAfauacAfuGfcugaasasa	2087	antisense	23
UUUCAGCAUGUAUUACUUGAC	992	ususucagCfaUfGfUfauuacuugacL96	2088	sense	21
GUCAAGUAAUACAUGCUGAAAAA	993	gsUfscaaGfuAfAfuacaUfgCfugaaasasa	2089	antisense	23
AUGUUACUUCUUAGAGAGAAA	994	asusguuaCfuUfCfUfuagagagaaaL96	2090	sense	21
UUUCUCUCUAAGAAGUAACAUAC	995	usUfsucuCfuCfUfaagaAfgUfaacausasc	2091	antisense	23
UGUUACUUCUUAGAGAGAAAU	996	usgsuuacUfuCfUfUfagagagaaauL96	2092	sense	21
AUUUCUCUCUAAGAAGUAACAUA	997	asUfsuucUfcUfCfuaagAfaGfuaacasusa	2093	antisense	23
AUGUAUGUUACUUCUUAGAGA	998	asusguauGfuUfAfCfuucuuagagaL96	2094	sense	21
UCUCUAAGAAGUAACAUACAUCC	999	usCfsucuAfaGfAfaguaAfcAfuacauscsc	2095	antisense	23
GAUGUAUGUUACUUCUUAGAG	1000	gsasuguaUfgUfUfAfcuucuuagagL96	2096	sense	21
CUCUAAGAAGUAACAUACAUCCU	1001	csUfscuaAfgAfAfguaaCfaUfacaucscsu	2097	antisense	23
ACAACUUUGAGAAGGUAGCAC	1002	ascsaacuUfuGfAfGfaagguagcacL96	2098	sense	21
GUGCUACCUUCUCAAAGUUGUGA	1003	gsUfsgcuAfcCfUfucucAfaAfguugusgsa	2099	antisense	23
CAACUUUGAGAAGGUAGCACU	1004	csasacuuUfgAfGfAfagguagcacuL96	2100	sense	21
AGUGCUACCUUCUCAAAGUUGUG	1005	asGfsugcUfaCfCfuucuCfaAfaguugsusg	2101	antisense	23
AUUCACAACUUUGAGAAGGUA	1006	asusucacAfaCfUfUfugagaagguaL96	2102	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
UACCUUCUCAAAGUUGUGAAUCA	1007	usAfsccuUfcUfCfaaagUfuGfugaauscsa	2103	antisense	23
GAUUCACAACUUUGAGAAGGU	1008	gsasuucaCfaAfCfUfuugagaagguL96	2104	sense	21
ACCUUCUCAAAGUUGUGAAUCAG	1009	asCfscuuCfuCfAfaaguUfgUfgaaucsasg	2105	antisense	23
AACAUGCUAAAUCAGUACUUC	1010	asascaugCfuAfAfAfucaguacuucL96	2106	sense	21
GAAGUACUGAUUUAGCAUGUUGU	1011	gsAfsaguAfcUfGfauuuAfgCfauguusgsu	2107	antisense	23
ACAUGCUAAAUCAGUACUUCC	1012	ascsaugcUfaAfAfUfcaguacuuccL96	2108	sense	21
GGAAGUACUGAUUUAGCAUGUUG	1013	gsGfsaagUfaCfUfgauuUfaGfcaugususg	2109	antisense	23
GAACAACAUGCUAAAUCAGUA	1014	gsasacaaCfaUfGfCfuaaaucaguaL96	2110	sense	21
UACUGAUUUAGCAUGUUGUUCAU	1015	usAfscugAfuUfUfagcaUfgUfuguucsasu	2111	antisense	23
UGAACAACAUGCUAAAUCAGU	1016	usgsaacaAfcAfUfGfcuaaaucaguL96	2112	sense	21
ACUGAUUUAGCAUGUUGUUCAUA	1017	asCfsugaUfuUfAfgcauGfuUfguucasusa	2113	antisense	23
AAACCAGUACUUUAUCAUUUU	1018	asasaccaGfuAfCfUfuuaucauuuuL96	2114	sense	21
AAAAUGAUAAAGUACUGGUUUCA	1019	asAfsaauGfaUfAfaaguAfcUfgguuuscsa	2115	antisense	23
AACCAGUACUUUAUCAUUUUC	1020	asasccagUfaCfUfUfuaucauuuucL96	2116	sense	21
GAAAAUGAUAAAGUACUGGUUUC	1021	gsAfsaaaUfgAfUfaaagUfaCfugguususc	2117	antisense	23
UUUGAAACCAGUACUUUAUCA	1022	ususugaaAfcCfAfGfuacuuuaucaL96	2118	sense	21
UGAUAAAGUACUGGUUUCAAAAU	1023	usGfsauaAfaGfUfacugGfuUfucaaasasu	2119	antisense	23
UUUUGAAACCAGUACUUUAUC	1024	ususuugaAfaCfCfAfguacuuuaucL96	2120	sense	21
GAUAAAGUACUGGUUUCAAAAUU	1025	gsAfsuaaAfgUfAfcuggUfuUfcaaaasusu	2121	antisense	23
GAGAAGAUGGGCUACAAGGCC	1026	gsasgaagAfuGfGfGfcuacaaggccL96	2122	sense	21
GGCCUUGUAGCCCAUCUUCUCUG	1027	gsGfsccuUfgUfAfgcccAfuCfuucucsusg	2123	antisense	23
AGAAGAUGGGCUACAAGGCCA	1028	asgsaagaUfgGfGfCfuacaaggccaL96	2124	sense	21
UGGCCUUGUAGCCCAUCUUCUCU	1029	usGfsgccUfuGfUfagccCfaUfcuucuscsu	2125	antisense	23
GGCAGAGAAGAUGGGCUACAA	1030	gsgscagaGfaAfGfAfugggcuacaaL96	2126	sense	21
UUGUAGCCCAUCUUCUCUGCCUG	1031	usUfsguaGfcCfCfaucuUfcUfcugccsusg	2127	antisense	23
AGGCAGAGAAGAUGGGCUACA	1032	asgsgcagAfgAfAfGfaugggcuacaL96	2128	sense	21
UGUAGCCCAUCUUCUCUGCCUGC	1033	usGfsuagCfcCfAfucuuCfuCfugccusgsc	2129	antisense	23
AACGGGCAUGAUGUUGAGUUC	1034	asascgggCfaUfGfAfuguugaguucL96	2130	sense	21
GAACUCAACAUCAUGCCCGUUCC	1035	gsAfsacuCfaAfCfaucaUfgCfccguuscsc	2131	antisense	23
ACGGGCAUGAUGUUGAGUUCC	1036	ascsgggcAfuGfAfUfguugaguuccL96	2132	sense	21
GGAACUCAACAUCAUGCCCGUUC	1037	gsGfsaacUfcAfAfcaucAfuGfcccgususc	2133	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
UGGGAACGGGCAUGAUGUUGA	1038	usgsggaaCfgGfGfCfaugauguugaL96	2134	sense	21
UCAACAUCAUGCCCGUUCCCAGG	1039	usCfsaacAfuCfAfugccCfgUfucccasgsg	2135	antisense	23
CUGGGAACGGGCAUGAUGUUG	1040	csusgggaAfcGfGfGfcaugauguugL96	2136	sense	21
CAACAUCAUGCCCGUUCCCAGGG	1041	csAfsacaUfcAfUfgcccGfuUfcccagsgsg	2137	antisense	23
AUGUGGCUAAAGCAAUAGACC	1042	asusguggCfuAfAfAfgcaauagaccL96	2138	sense	21
GGUCUAUUGCUUUAGCCACAUAU	1043	gsGfsucuAfuUfGfcuuuAfgCfcacausasu	2139	antisense	23
UGUGGCUAAAGCAAUAGACCC	1044	usgsuggcUfaAfAfGfcaauagacccL96	2140	sense	21
GGGUCUAUUGCUUUAGCCACAUA	1045	gsGfsgucUfaUfUfgcuuUfaGfccacasusa	2141	antisense	23
GCAUAUGUGGCUAAAGCAAUA	1046	gscsauauGfuGfGfCfuaaagcaauaL96	2142	sense	21
UAUUGCUUUAGCCACAUAUGCAG	1047	usAfsuugCfuUfUfagccAfcAfuaugcsasg	2143	antisense	23
UGCAUAUGUGGCUAAAGCAAU	1048	usgscauaUfgUfGfGfcuaaagcaauL96	2144	sense	21
AUUGCUUUAGCCACAUAUGCAGC	1049	asUfsugcUfuUfAfgccaCfaUfaugcasgsc	2145	antisense	23
AGGAUGCUCCGGAAUGUUGCU	1050	asgsgaugCfuCfCfGfgaauguugcuL96	2146	sense	21
AGCAACAUUCCGGAGCAUCCUUG	1051	asGfscaaCfaUfUfccggAfgCfauccususg	2147	antisense	23
GGAUGCUCCGGAAUGUUGCUG	1052	gsgsaugcUfcCfGfGfaauguugcugL96	2148	sense	21
CAGCAACAUUCCGGAGCAUCCUU	1053	csAfsgcaAfcAfUfuccgGfaGfcauccsusu	2149	antisense	23
UCCAAGGAUGCUCCGGAAUGU	1054	uscscaagGfaUfGfCfuccggaauguL96	2150	sense	21
ACAUUCCGGAGCAUCCUUGGAUA	1055	asCfsauuCfcGfGfagcaUfcCfuuggasusa	2151	antisense	23
AUCCAAGGAUGCUCCGGAAUG	1056	asusccaaGfgAfUfGfcuccggaaugL96	2152	sense	21
CAUUCCGGAGCAUCCUUGGAUAC	1057	csAfsuucCfgGfAfgcauCfcUfuggausasc	2153	antisense	23
UCACAUCUUUAGUGUCUGAAU	1058	uscsacauCfuUfUfAfgugucugaauL96	2154	sense	21
AUUCAGACACUAAAGAUGUGAUU	1059	asUfsucaGfaCfAfcuaaAfgAfugugasusu	2155	antisense	23
CACAUCUUUAGUGUCUGAAUA	1060	csascaucUfuUfAfGfugucugaauaL96	2156	sense	21
UAUUCAGACACUAAAGAUGUGAU	1061	usAfsuucAfgAfCfacuaAfaGfaugugsasu	2157	antisense	23
CCAAUCACAUCUUUAGUGUCU	1062	cscsaaucAfcAfUfCfuuuagugucuL96	2158	sense	21
AGACACUAAAGAUGUGAUUGGAA	1063	asGfsacaCfuAfAfagauGfuGfauuggsasa	2159	antisense	23
UCCAAUCACAUCUUUAGUGUC	1064	uscscaauCfaCfAfUfcuuuagugucL96	2160	sense	21
GACACUAAAGAUGUGAUUGGAAA	1065	gsAfscacUfaAfAfgaugUfgAfuuggasasa	2161	antisense	23
AAAUGUGUUUAGACAACGUCA	1066	asasauguGfuUfUfAfgacaacgucaL96	2162	sense	21
UGACGUUGUCUAAACACAUUUUC	1067	usGfsacgUfuGfUfcuaaAfcAfcauuususc	2163	antisense	23
AAUGUGUUUAGACAACGUCAU	1068	asasugugUfuUfAfGfacaacgucauL96	2164	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
AUGACGUUGUCUAAACACAUUUU	1069	asUfsgacGfuUfGfucuaAfaCfacauususu	2165	antisense	23
UUGAAAAUGUGUUUAGACAAC	1070	ususgaaaAfuGfUfGfuuuagacaacL96	2166	sense	21
GUUGUCUAAACACAUUUUCAAUG	1071	gsUfsuguCfuAfAfacacAfuUfuucaasusg	2167	antisense	23
AUUGAAAAUGUGUUUAGACAA	1072	asusugaaAfaUfGfUfguuuagacaaL96	2168	sense	21
UUGUCUAAACACAUUUUCAAUGU	1073	usUfsgucUfaAfAfcacaUfuUfucaausgsu	2169	antisense	23
UACUAAAGGAAGAAUUCCGGU	1074	usascuaaAfgGfAfAfgaauuccgguL96	2170	sense	21
ACCGGAAUUCUUCCUUUAGUAUC	1075	asCfscggAfaUfUfcuucCfuUfuaguasusc	2171	antisense	23
ACUAAAGGAAGAAUUCCGGUU	1076	ascsuaaaGfgAfAfGfaauuccgguuL96	2172	sense	21
AACCGGAAUUCUUCCUUUAGUAU	1077	asAfsccgGfaAfUfucuuCfcUfuuagusasu	2173	antisense	23
GAGAUACUAAAGGAAGAAUUC	1078	gsasgauaCfuAfAfAfggaagaauucL96	2174	sense	21
GAAUUCUUCCUUUAGUAUCUCGA	1079	gsAfsauuCfuUfCfcuuuAfgUfaucucsgsa	2175	antisense	23
CGAGAUACUAAAGGAAGAAUU	1080	csgsagauAfcUfAfAfaggaagaauuL96	2176	sense	21
AAUUCUUCCUUUAGUAUCUCGAG	1081	asAfsuucUfuCfCfuuuaGfuAfucucgsasg	2177	antisense	23
AACUUUGGCUGAUAAUAUUGC	1082	asascuuuGfgCfUfGfauaauauugcL96	2178	sense	21
GCAAUAUUAUCAGCCAAAGUUUC	1083	gsCfsaauAfuUfAfucagCfcAfaaguususc	2179	antisense	23
ACUUUGGCUGAUAAUAUUGCA	1084	ascsuuugGfcUfGfAfuaauauugcaL96	2180	sense	21
UGCAAUAUUAUCAGCCAAAGUUU	1085	usGfscaaUfaUfUfaucaGfcCfaaagususu	2181	antisense	23
AAGAAACUUUGGCUGAUAAUA	1086	asasgaaaCfuUfUfGfgcugauaauaL96	2182	sense	21
UAUUAUCAGCCAAAGUUUCUUCA	1087	usAfsuuaUfcAfGfccaaAfgUfuucuuscsa	2183	antisense	23
GAAGAAACUUUGGCUGAUAAU	1088	gsasagaaAfcUfUfUfggcugauaauL96	2184	sense	21
AUUAUCAGCCAAAGUUUCUUCAU	1089	asUfsuauCfaGfCfcaaaGfuUfucuucsasu	2185	antisense	23
AAAUGGCUGAGAAGACUGACA	1090	asasauggCfuGfAfGfaagacugacaL96	2186	sense	21
UGUCAGUCUUCUCAGCCAUUUGA	1091	usGfsucaGfuCfUfucucAfgCfcauuusgsa	2187	antisense	23
AAUGGCUGAGAAGACUGACAU	1092	asasuggcUfgAfGfAfagacugacauL96	2188	sense	21
AUGUCAGUCUUCUCAGCCAUUUG	1093	asUfsgucAfgUfCfuucuCfaGfccauususg	2189	antisense	23
UAUCAAAUGGCUGAGAAGACU	1094	usasucaaAfuGfGfCfugagaagacuL96	2190	sense	21
AGUCUUCUCAGCCAUUUGAUAUC	1095	asGfsucuUfcUfCfagccAfuUfugauasusc	2191	antisense	23
AUAUCAAAUGGCUGAGAAGAC	1096	asusaucaAfaUfGfGfcugagaagacL96	2192	sense	21
GUCUUCUCAGCCAUUUGAUAUCU	1097	gsUfscuuCfuCfAfgccaUfuUfgauauscsu	2193	antisense	23
GUGGUUCUUAAAUUGUAAGCU	1098	gsusgguuCfuUfAfAfauuguaagcuL96	2194	sense	21
AGCUUACAAUUUAAGAACCACUG	1099	asGfscuuAfcAfAfuuuaAfgAfaccacsusg	2195	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
UGGUUCUUAAAUUGUAAGCUC	1100	usgsguucUfuAfAfAfuuguaagcucL96	2196	sense	21
GAGCUUACAAUUUAAGAACCACU	1101	gsAfsgcuUfaCfAfauuuAfaGfaaccascsu	2197	antisense	23
AACAGUGGUUCUUAAAUUGUA	1102	asascaguGfgUfUfCfuuaaauuguaL96	2198	sense	21
UACAAUUUAAGAACCACUGUUUU	1103	usAfscaaUfuUfAfagaaCfcAfcuguususu	2199	antisense	23
AAACAGUGGUUCUUAAAUUGU	1104	asasacagUfgGfUfUfcuuaaauuguL96	2200	sense	21
ACAAUUUAAGAACCACUGUUUUA	1105	asCfsaauUfuAfAfgaacCfaCfuguuususa	2201	antisense	23
AAGUCAUCGACAAGACAUUGG	1106	asasgucaUfcGfAfCfaagacauuggL96	2202	sense	21
CCAAUGUCUUGUCGAUGACUUUC	1107	csCfsaauGfuCfUfugucGfaUfgacuususc	2203	antisense	23
AGUCAUCGACAAGACAUUGGU	1108	asgsucauCfgAfCfAfagacauugguL96	2204	sense	21
ACCAAUGUCUUGUCGAUGACUUU	1109	asCfscaaUfgUfCfuuguCfgAfugacususu	2205	antisense	23
GUGAAAGUCAUCGACAAGACA	1110	gsusgaaaGfuCfAfUfcgacaagacaL96	2206	sense	21
UGUCUUGUCGAUGACUUUCACAU	1111	usGfsucuUfgUfCfgaugAfcUfuucacsasu	2207	antisense	23
UGUGAAAGUCAUCGACAAGAC	1112	usgsugaaAfgUfCfAfucgacaagacL96	2208	sense	21
GUCUUGUCGAUGACUUUCACAUU	1113	gsUfscuuGfuCfGfaugaCfuUfucacasusu	2209	antisense	23
GAUAAUAUUGCAGCAUUUUCC	1114	gsasuaauAfuUfGfCfagcauuuuccL96	2210	sense	21
GGAAAAUGCUGCAAUAUUAUCAG	1115	gsGfsaaaAfuGfCfugcaAfuAfuuaucsasg	2211	antisense	23
AUAAUAUUGCAGCAUUUUCCA	1116	asusaauaUfuGfCfAfgcauuuuccaL96	2212	sense	21
UGGAAAAUGCUGCAAUAUUAUCA	1117	usGfsgaaAfaUfGfcugcAfaUfauuauscsa	2213	antisense	23
GGCUGAUAAUAUUGCAGCAUU	1118	gsgscugaUfaAfUfAfuugcagcauuL96	2214	sense	21
AAUGCUGCAAUAUUAUCAGCCAA	1119	asAfsugcUfgCfAfauauUfaUfcagccsasa	2215	antisense	23
UGGCUGAUAAUAUUGCAGCAU	1120	usgsgcugAfuAfAfUfauugcagcauL96	2216	sense	21
AUGCUGCAAUAUUAUCAGCCAAA	1121	asUfsgcuGfcAfAfuauuAfuCfagccasasa	2217	antisense	23
GCUAAUUUGUAUCAAUGAUUA	1122	gscsuaauUfuGfUfAfucaaugauuaL96	2218	sense	21
UAAUCAUUGAUACAAAUUAGCCG	1123	usAfsaucAfuUfGfauacAfaAfuuagcscsg	2219	antisense	23
CUAAUUUGUAUCAAUGAUUAU	1124	csusaauuUfgUfAfUfcaaugauuauL96	2220	sense	21
AUAAUCAUUGAUACAAAUUAGCC	1125	asUfsaauCfaUfUfgauaCfaAfauuagscsc	2221	antisense	23
CCCGGCUAAUUUGUAUCAAUG	1126	cscscggcUfaAfUfUfuguaucaaugL96	2222	sense	21
CAUUGAUACAAAUUAGCCGGGGG	1127	csAfsuugAfuAfCfaaauUfaGfccgggsgsg	2223	antisense	23
CCCCGGCUAAUUUGUAUCAAU	1128	cscsccggCfuAfAfUfuuguaucaauL96	2224	sense	21
AUUGAUACAAAUUAGCCGGGGGA	1129	asUfsugaUfaCfAfaauuAfgCfcggggsgsa	2225	antisense	23
UAAUUGGUGAUACUUCUUUGA	1130	usasauugGfuGfAfUfacuucuuugaL96	2226	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
UCAAAGAAGUAUCACCAAUUACC	1131	usCfsaaaGfaAfGfuaucAfcCfaauuascsc	2227	antisense	23
AAUUGGUGAUACUUCUUUGAA	1132	asasuuggUfgAfUfAfcuucuuugaaL96	2228	sense	21
UUCAAAGAAGUAUCACCAAUUAC	1133	usUfscaaAfgAfAfguauCfaCfcaauusasc	2229	antisense	23
GCGGUAAUUGGUGAUACUUCU	1134	gscsgguaAfuUfGfGfugauacuucuL96	2230	sense	21
AGAAGUAUCACCAAUUACCGCCA	1135	asGfsaagUfaUfCfaccaAfuUfaccgcscsa	2231	antisense	23
GGCGGUAAUUGGUGAUACUUC	1136	gsgscgguAfaUfUfGfgugauacuucL96	2232	sense	21
GAAGUAUCACCAAUUACCGCCAC	1137	gsAfsaguAfuCfAfccaaUfuAfccgccsasc	2233	antisense	23
CAGUGGUUCUUAAAUUGUAAG	1138	csasguggUfuCfUfUfaaauuguaagL96	2234	sense	21
CUUACAAUUUAAGAACCACUGUU	1139	csUfsuacAfaUfUfuaagAfaCfcacugsusu	2235	antisense	23
AGUGGUUCUUAAAUUGUAAGC	1140	asgsugguUfcUfUfAfaauuguaagcL96	2236	sense	21
GCUUACAAUUUAAGAACCACUGU	1141	gsCfsuuaCfaAfUfuuaaGfaAfccacusgsu	2237	antisense	23
AAAACAGUGGUUCUUAAAUUG	1142	asasaacaGfuGfGfUfucuuaaauugL96	2238	sense	21
CAAUUUAAGAACCACUGUUUUAA	1143	csAfsauuUfaAfGfaaccAfcUfguuuusasa	2239	antisense	23
UAAAACAGUGGUUCUUAAAUU	1144	usasaaacAfgUfGfGfuucuuaaauuL96	2240	sense	21
AAUUUAAGAACCACUGUUUUAAA	1145	asAfsuuuAfaGfAfaccaCfuGfuuuuasasa	2241	antisense	23
ACCUGUAUUCUGUUUACAUGU	1146	ascscuguAfuUfCfUfguuuacauguL96	2242	sense	21
ACAUGUAAACAGAAUACAGGUUA	1147	asCfsaugUfaAfAfcagaAfuAfcaggususa	2243	antisense	23
CCUGUAUUCUGUUUACAUGUC	1148	cscsuguaUfuCfUfGfuuuacaugucL96	2244	sense	21
GACAUGUAAACAGAAUACAGGUU	1149	gsAfscauGfuAfAfacagAfaUfacaggsusu	2245	antisense	23
AUUAACCUGUAUUCUGUUUAC	1150	asusuaacCfuGfUfAfuucuguuuacL96	2246	sense	21
GUAAACAGAAUACAGGUUAAUAA	1151	gsUfsaaaCfaGfAfauacAfgGfuuaausasa	2247	antisense	23
UAUUAACCUGUAUUCUGUUUA	1152	usasuuaaCfcUfGfUfauucuguuuaL96	2248	sense	21
UAAACAGAAUACAGGUUAAUAAA	1153	usAfsaacAfgAfAfuacaGfgUfuaauasasa	2249	antisense	23
AAGAAACUUUGGCUGAUAAUA	1154	asasgaaaCfuUfUfGfgcugauaauaL96	2250	sense	21
UAUUAUCAGCCAAAGUUUCUUCA	1155	usAfsuuaUfcAfGfccaaAfgUfuucuuscsa	2251	antisense	23
AGAAACUUUGGCUGAUAAUAU	1156	asgsaaacUfuUfGfGfcugauaauauL96	2252	sense	21
AUAUUAUCAGCCAAAGUUUCUUC	1157	asUfsauuAfuCfAfgccaAfaGfuuucususc	2253	antisense	23
GAUGAAGAAACUUUGGCUGAU	1158	gsasugaaGfaAfAfCfuuuggcugauL96	2254	sense	21
AUCAGCCAAAGUUUCUUCAUCAU	1159	asUfscagCfcAfAfaguuUfcUfucaucsasu	2255	antisense	23
UGAUGAAGAAACUUUGGCUGA	1160	usgsaugaAfgAfAfAfcuuuggcugaL96	2256	sense	21
UCAGCCAAAGUUUCUUCAUCAUU	1161	usCfsagcCfaAfAfguuuCfuUfcaucasusu	2257	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
GAAAGGUGUUCAAGAUGUCCU	1162	gsasaaggUfgUfUfCfaagauguccuL96	2258	sense	21
AGGACAUCUUGAACACCUUUCUC	1163	asGfsgacAfuCfUfugaaCfaCfcuuucsusc	2259	antisense	23
AAAGGUGUUCAAGAUGUCCUC	1164	asasagguGfuUfCfAfagauguccucL96	2260	sense	21
GAGGACAUCUUGAACACCUUUCU	1165	gsAfsggaCfaUfCfuugaAfcAfccuuuscsu	2261	antisense	23
GGGAGAAAGGUGUUCAAGAUG	1166	gsgsgagaAfaGfGfUfguucaagaugL96	2262	sense	21
CAUCUUGAACACCUUUCUCCCCC	1167	csAfsucuUfgAfAfcaccUfuUfcucccscsc	2263	antisense	23
GGGGAGAAAGGUGUUCAAGAU	1168	gsgsggagAfaAfGfGfuguucaagauL96	2264	sense	21
AUCUUGAACACCUUUCUCCCCCU	1169	asUfscuuGfaAfCfaccuUfuCfucccscsu	2265	antisense	23
AUCUUGGUGUCGAAUCAUGGG	1170	asuscuugGfuGfUfCfgaaucaugggL96	2266	sense	21
CCCAUGAUUCGACACCAAGAUCC	1171	csCfscauGfaUfUfcgacAfcCfaagauscsc	2267	antisense	23
UCUUGGUGUCGAAUCAUGGGG	1172	uscsuuggUfgUfCfGfaaucaggggL96	2268	sense	21
CCCCAUGAUUCGACACCAAGAUC	1173	csCfsccaUfgAfUfucgaCfaCfcaagasusc	2269	antisense	23
UGGGAUCUUGGUGUCGAAUCA	1174	usgsggauCfuUfGfGfugucgaaucaL96	2270	sense	21
UGAUUCGACACCAAGAUCCCAUU	1175	usGfsauuCfgAfCfaccaAfgAfucccasusu	2271	antisense	23
AUGGGAUCUUGGUGUCGAAUC	1176	asusgggaUfcUfUfGfgugucgaaucL96	2272	sense	21
GAUUCGACACCAAGAUCCCAUUC	1177	gsAfsuucGfaCfAfccaaGfaUfcccaususc	2273	antisense	23
GCUACAAGGCCAUAUUUGUGA	1178	gscsuacaAfgGfCfCfauauuugugaL96	2274	sense	21
UCACAAAUAUGGCCUUGUAGCCC	1179	usCfsacaAfaUfAfuggcCfuUfguagcscsc	2275	antisense	23
CUACAAGGCCAUAUUUGUGAC	1180	csusacaaGfgCfCfAfuauuugugacL96	2276	sense	21
GUCACAAAUAUGGCCUUGUAGCC	1181	gsUfscacAfaAfUfauggCfcUfuguagscsc	2277	antisense	23
AUGGGCUACAAGGCCAUAUUU	1182	asusgggcUfaCfAfAfggccauauuuL96	2278	sense	21
AAAUAUGGCCUUGUAGCCCAUCU	1183	asAfsauaUfgGfCfcuugUfaGfcccauscsu	2279	antisense	23
GAUGGGCUACAAGGCCAUAUU	1184	gsasugggCfuAfCfAfaggccauauuL96	2280	sense	21
AAUAUGGCCUUGUAGCCCAUCUU	1185	asAfsuauGfgCfCfuuguAfgCfccaucsusu	2281	antisense	23
ACUGGAGAGAAUUGGAAUGGG	1186	ascsuggaGfaGfAfAfuuggaaugggL96	2282	sense	21
CCCAUUCCAAUUCUCUCCAGUGC	1187	csCfscauUfcCfAfauucUfcUfccagusgsc	2283	antisense	23
CUGGAGAGAAUUGGAAUGGGU	1188	csusggagAfgAfAfUfuggaauggguL96	2284	sense	21
ACCCAUUCCAAUUCUCUCCAGUG	1189	asCfsccaUfuCfCfaauuCfuCfuccagsusg	2285	antisense	23
UAGCACUGGAGAGAAUUGGAA	1190	usasgcacUfgGfAfGfagaauuggaaL96	2286	sense	21
UUCCAAUUCUCUCCAGUGCUACC	1191	usUfsccaAfuUfCfucucCfaGfugcuascsc	2287	antisense	23
GUAGCACUGGAGAGAAUUGGA	1192	gsusagcaCfuGfGfAfgagaauuggaL96	2288	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
UCCAAUUCUCUCCAGUGCUACCU	1193	usCfscaaUfuCfUfcuccAfgUfgcuacscsu	2289	antisense	23
ACAGUGGACACACCUUACCUG	1194	ascsagugGfaCfAfCfaccuuaccugL96	2290	sense	21
CAGGUAAGGUGUGUCCACUGUCA	1195	csAfsgguAfaGfGfugugUfcCfacuguscsa	2291	antisense	23
CAGUGGACACACCUUACCUGG	1196	csasguggAfcAfCfAfccuuaccuggL96	2292	sense	21
CCAGGUAAGGUGUGUCCACUGUC	1197	csCfsaggUfaAfGfguguGfuCfcacugsusc	2293	antisense	23
UGUGACAGUGGACACACCUUA	1198	usgsugacAfgUfGfGfacacaccuuaL96	2294	sense	21
UAAGGUGUGUCCACUGUCACAAA	1199	usAfsaggUfgUfGfuccaCfuGfucacasasa	2295	antisense	23
UUGUGACAGUGGACACACCUU	1200	ususgugaCfaGfUfGfgacacaccuuL96	2296	sense	21
AAGGUGUGUCCACUGUCACAAAU	1201	asAfsgguGfuGfUfccacUfgUfcacaasasu	2297	antisense	23
GAAGACUGACAUCAUUGCCAA	1202	gsasagacUfgAfCfAfucauugccaaL96	2298	sense	21
UUGGCAAUGAUGUCAGUCUUCUC	1203	usUfsggcAfaUfGfauguCfaGfucuucsusc	2299	antisense	23
AAGACUGACAUCAUUGCCAAU	1204	asasgacuGfaCfAfUfcauugccaauL96	2300	sense	21
AUUGGCAAUGAUGUCAGUCUUCU	1205	asUfsuggCfaAfUfgaugUfcAfgucuuscsu	2301	antisense	23
CUGAGAAGACUGACAUCAUUG	1206	csusgagaAfgAfCfUfgacaucauugL96	2302	sense	21
CAAUGAUGUCAGUCUUCUCAGCC	1207	csAfsaugAfuGfUfcaguCfuUfcucagscsc	2303	antisense	23
GCUGAGAAGACUGACAUCAUU	1208	gscsugagAfaGfAfCfugacaucauuL96	2304	sense	21
AAUGAUGUCAGUCUUCUCAGCCA	1209	asAfsugaUfgUfCfagucUfuCfucagcscsa	2305	antisense	23
GCUCAGGUUCAAAGUGUUGGU	1210	gscsucagGfuUfCfAfaaguguugguL96	2306	sense	21
ACCAACACUUUGAACCUGAGCUU	1211	asCfscaaCfaCfUfuugaAfcCfugagcsusu	2307	antisense	23
CUCAGGUUCAAAGUGUUGGUA	1212	csuscaggUfuCfAfAfaguguugguaL96	2308	sense	21
UACCAACACUUUGAACCUGAGCU	1213	usAfsccaAfcAfCfuuugAfaCfcugagscsu	2309	antisense	23
GUAAGCUCAGGUUCAAAGUGU	1214	gsusaagcUfcAfGfGfuucaaaguguL96	2310	sense	21
ACACUUUGAACCUGAGCUUACAA	1215	asCfsacuUfuGfAfaccuGfaGfcuuacsasa	2311	antisense	23
UGUAAGCUCAGGUUCAAAGUG	1216	usgsuaagCfuCfAfGfguucaaagugL96	2312	sense	21
CACUUUGAACCUGAGCUUACAAU	1217	csAfscuuUfgAfAfccugAfgCfuuacasasu	2313	antisense	23
AUGUAUUACUUGACAAAGAGA	1218	asusguauUfaCfUfUfgacaaagagaL96	2314	sense	21
UCUCUUUGUCAAGUAAUACAUGC	1219	usCfsucuUfuGfUfcaagUfaAfuacausgsc	2315	antisense	23
UGUAUUACUUGACAAAGAGAC	1220	usgsuauuAfcUfUfGfacaaagagacL96	2316	sense	21
GUCUCUUUGUCAAGUAAUACAUG	1221	gsUfscucUfuUfGfucaaGfuAfauacasusg	2317	antisense	23
CAGCAUGUAUUACUUGACAAA	1222	csasgcauGfuAfUfUfacuugacaaaL96	2318	sense	21
UUUGUCAAGUAAUACAUGCUGAA	1223	usUfsuguCfaAfGfuaauAfcAfugcugsasa	2319	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
UCAGCAUGUAUUACUUGACAA	1224	uscsagcaUfgUfAfUfuacuugacaaL96	2320	sense	21
UUGUCAAGUAAUACAUGCUGAAA	1225	usUfsgucAfaGfUfaauaCfaUfgcugasasa	2321	antisense	23
CUGCAACUGUAUAUCUACAAG	1226	csusgcaaCfuGfUfAfuaucuacaagL96	2322	sense	21
CUUGUAGAUAUACAGUUGCAGCC	1227	csUfsuguAfgAfUfauacAfgUfugcagscsc	2323	antisense	23
UGCAACUGUAUAUCUACAAGG	1228	usgscaacUfgUfAfUfaucuacaaggL96	2324	sense	21
CCUUGUAGAUAUACAGUUGCAGC	1229	csCfsuugUfaGfAfuauaCfaGfuugcasgsc	2325	antisense	23
UUGGCUGCAACUGUAUAUCUA	1230	ususggcuGfcAfAfCfuguauaucuaL96	2326	sense	21
UAGAUAUACAGUUGCAGCCAACG	1231	usAfsgauAfuAfCfaguuGfcAfgccaascsg	2327	antisense	23
GUUGGCUGCAACUGUAUAUCU	1232	gsusuggcUfgCfAfAfcuguauaucuL96	2328	sense	21
AGAUAUACAGUUGCAGCCAACGA	1233	asGfsauaUfaCfAfguugCfaGfccaacsgsa	2329	antisense	23
CAAAUGAUGAAGAAACUUUGG	1234	csasaaugAfuGfAfAfgaaacuuuggL96	2330	sense	21
CCAAAGUUUCUUCAUCAUUUGCC	1235	csCfsaaaGfuUfUfcuucAfuCfauuugscsc	2331	antisense	23
AAAUGAUGAAGAAACUUUGGC	1236	asasaugaUfgAfAfGfaaacuuuggcL96	2332	sense	21
GCCAAAGUUUCUUCAUCAUUUGC	1237	gsCfscaaAfgUfUfucuuCfaUfcauuusgsc	2333	antisense	23
GGGGCAAAUGAUGAAGAAACU	1238	gsgsggcaAfaUfGfAfugaagaaacuL96	2334	sense	21
AGUUUCUUCAUCAUUUGCCCCAG	1239	asGfsuuuCfuUfCfaucaUfuUfgccccsasg	2335	antisense	23
UGGGGCAAAUGAUGAAGAAAC	1240	usgsgggcAfaAfUfGfaugaagaaacL96	2336	sense	21
GUUUCUUCAUCAUUUGCCCCAGA	1241	gsUfsuucUfuCfAfucauUfuGfccccasgsa	2337	antisense	23
CAAAGGGUGUCGUUCUUUUCC	1242	csasaaggGfuGfUfCfguucuuuuccL96	2338	sense	21
GGAAAAGAACGACACCCUUUGUA	1243	gsGfsaaaAfgAfAfcgacAfcCfcuuugsusa	2339	antisense	23
AAAGGGUGUCGUUCUUUUCCA	1244	asasagggUfgUfCfGfuucuuuuccaL96	2340	sense	21
UGGAAAAGAACGACACCCUUUGU	1245	usGfsgaaAfaGfAfacgaCfaCfccuuusgsu	2341	antisense	23
AAUACAAAGGGUGUCGUUCUU	1246	asasuacaAfaGfGfGfugucguucuuL96	2342	sense	21
AAGAACGACACCCUUUGUAUUGA	1247	asAfsgaaCfgAfCfacccUfuUfguauusgsa	2343	antisense	23
CAAUACAAAGGGUGUCGUUCU	1248	csasauacAfaAfGfGfgugucguucuL96	2344	sense	21
AGAACGACACCCUUUGUAUUGAA	1249	asGfsaacGfaCfAfcccuUfuGfuauugsasa	2345	antisense	23
AAAGGCACUGAUGUUCUGAAA	1250	asasaggcAfcUfGfAfuguucugaaaL96	2346	sense	21
UUUCAGAACAUCAGUGCCUUUCC	1251	usUfsucaGfaAfCfaucaGfuGfccuuuscsc	2347	antisense	23
AAGGCACUGAUGUUCUGAAAG	1252	asasggcaCfuGfAfUfguucugaaagL96	2348	sense	21
CUUUCAGAACAUCAGUGCCUUUC	1253	csUfsuucAfgAfAfcaucAfgUfgccuususc	2349	antisense	23
GCGGAAAGGCACUGAUGUUCU	1254	gscsggaaAfgGfCfAfcugauguucuL96	2350	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
AGAACAUCAGUGCCUUUCCGCAC	1255	asGfsaacAfuCfAfgugcCfuUfuccgcsasc	2351	antisense	23
UGCGGAAAGGCACUGAUGUUC	1256	usgscggaAfaGfGfCfacugauguucL96	2352	sense	21
GAACAUCAGUGCCUUUCCGCACA	1257	gsAfsacaUfcAfGfugccUfuUfccgcascsa	2353	antisense	23
AAGGAUGCUCCGGAAUGUUGC	1258	asasggauGfcUfCfCfggaauguugcL96	2354	sense	21
GCAACAUUCCGGAGCAUCCUUGG	1259	gsCfsaacAfuUfCfcggaGfcAfuccuusgsg	2355	antisense	23
AGGAUGCUCCGGAAUGUUGCU	1260	asgsgaugCfuCfCfGfgaauguugcuL96	2356	sense	21
AGCAACAUUCCGGAGCAUCCUUG	1261	asGfscaaCfaUfUfccggAfgCfauccususg	2357	antisense	23
AUCCAAGGAUGCUCCGGAAUG	1262	asusccaaGfgAfUfGfcuccggaaugL96	2358	sense	21
CAUUCCGGAGCAUCCUUGGAUAC	1263	csAfsuucCfgGfAfgcauCfcUfuggausasc	2359	antisense	23
UAUCCAAGGAUGCUCCGGAAU	1264	usasuccaAfgGfAfUfgcuccggaauL96	2360	sense	21
AUUCCGGAGCAUCCUUGGAUACA	1265	asUfsuccGfgAfGfcaucCfuUfggauascsa	2361	antisense	23
AAUGGGUGGCGGUAAUUGGUG	1266	asasugggUfgGfCfGfguaauuggugL96	2362	sense	21
CACCAAUUACCGCCACCCAUUCC	1267	csAfsccaAfuUfAfccgcCfaCfccauuscsc	2363	antisense	23
AUGGGUGGCGGUAAUUGGUGA	1268	asusggguGfgCfGfGfuaauuggugaL96	2364	sense	21
UCACCAAUUACCGCCACCCAUUC	1269	usCfsaccAfaUfUfaccgCfcAfcccaususc	2365	antisense	23
UUGGAAUGGGUGGCGGUAAUU	1270	ususggaaUfgGfGfUfggcgguaauuL96	2366	sense	21
AAUUACCGCCACCCAUUCCAAUU	1271	asAfsuuaCfcGfCfcaccCfaUfuccaasusu	2367	antisense	23
AUUGGAAUGGGUGGCGGUAAU	1272	asusuggaAfuGfGfGfuggcgguaauL96	2368	sense	21
AUUACCGCCACCCAUUCCAAUUC	1273	asUfsuacCfgCfCfacccAfuUfccaaususc	2369	antisense	23
GGAAAGGCACUGAUGUUCUGA	1274	gsgsaaagGfcAfCfUfgauguucugaL96	2370	sense	21
UCAGAACAUCAGUGCCUUUCCGC	1275	usCfsagaAfcAfUfcaguGfcCfuuuccsgsc	2371	antisense	23
GAAAGGCACUGAUGUUCUGAA	1276	gsasaaggCfaCfUfGfauguucugaaL96	2372	sense	21
UUCAGAACAUCAGUGCCUUUCCG	1277	usUfscagAfaCfAfucagUfgCfcuuucscsg	2373	antisense	23
GUGCGGAAAGGCACUGAUGUU	1278	gsusgcggAfaAfGfGfcacugauguuL96	2374	sense	21
AACAUCAGUGCCUUUCCGCACAC	1279	asAfscauCfaGfUfgccuUfuCfcgcacsasc	2375	antisense	23
UGUGCGGAAAGGCACUGAUGU	1280	usgsugcgGfaAfAfGfgcacugauguL96	2376	sense	21
ACAUCAGUGCCUUUCCGCACACC	1281	asCfsaucAfgUfGfccuuUfcCfgcacascsc	2377	antisense	23
AAUUGUAAGCUCAGGUUCAAA	1282	asasuuguAfaGfCfUfcagguucaaaL96	2378	sense	21
UUUGAACCUGAGCUUACAAUUUA	1283	usUfsugaAfcCfUfgagcUfuAfcaauususa	2379	antisense	23
AUUGUAAGCUCAGGUUCAAAG	1284	asusuguaAfgCfUfCfagguucaaagL96	2380	sense	21
CUUUGAACCUGAGCUUACAAUUU	1285	csUfsuugAfaCfCfugagCfuUfacaaususu	2381	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
CUUAAAUUGUAAGCUCAGGUU	1286	csusuaaaUfuGfUfAfagcucagguuL96	2382	sense	21
AACCUGAGCUUACAAUUUAAGAA	1287	asAfsccuGfaGfCfuuacAfaUfuuaagsasa	2383	antisense	23
UCUUAAAUUGUAAGCUCAGGU	1288	uscsuuaaAfuUfGfUfaagcucagguL96	2384	sense	21
ACCUGAGCUUACAAUUUAAGAAC	1289	asCfscugAfgCfUfuacaAfuUfuaagasasc	2385	antisense	23
GCAAACACUAAGGUGAAAAGA	1290	gscsaaacAfcUfAfAfggugaaaagaL96	2386	sense	21
UCUUUUCACCUUAGUGUUUGCUA	1291	usCfsuuuUfcAfCfcuuaGfuGfuuugcsusa	2387	antisense	23
CAAACACUAAGGUGAAAAGAU	1292	csasaacaCfuAfAfGfgugaaaagauL96	2388	sense	21
AUCUUUUCACCUUAGUGUUUGCU	1293	asUfscuuUfuCfAfccuuAfgUfguuugscsu	2389	antisense	23
GGUAGCAAACACUAAGGUGAA	1294	gsgsuagcAfaAfCfAfcuaaggugaaL96	2390	sense	21
UUCACCUUAGUGUUUGCUACCUC	1295	usUfscacCfuUfAfguguUfuGfcuaccsusc	2391	antisense	23
AGGUAGCAAACACUAAGGUGA	1296	asgsguagCfaAfAfCfacuaaggugaL96	2392	sense	21
UCACCUUAGUGUUUGCUACCUCC	1297	usCfsaccUfuAfGfuguuUfgCfuaccuscsc	2393	antisense	23
AGGUAGCAAACACUAAGGUGA	1298	asgsguagCfaAfAfCfacuaaggugaL96	2394	sense	21
UCACCUUAGUGUUUGCUACCUCC	1299	usCfsaccUfuAfGfuguuUfgCfuaccuscsc	2395	antisense	23
GGUAGCAAACACUAAGGUGAA	1300	gsgsuagcAfaAfCfAfcuaaggugaaL96	2396	sense	21
UUCACCUUAGUGUUUGCUACCUC	1301	usUfscacCfuUfAfguguUfuGfcuaccsusc	2397	antisense	23
UUGGAGGUAGCAAACACUAAG	1302	ususggagGfuAfGfCfaaacacuaagL96	2398	sense	21
CUUAGUGUUUGCUACCUCCAAUU	1303	csUfsuagUfgUfUfugcuAfcCfuccaasusu	2399	antisense	23
AUUGGAGGUAGCAAACACUAA	1304	asusuggaGfgUfAfGfcaaacacuaaL96	2400	sense	21
UUAGUGUUUGCUACCUCCAAUUU	1305	usUfsaguGfuUfUfgcuaCfcUfccaaususu	2401	antisense	23
UAAAGUGCUGUAUCCUUUAGU	1306	usasaaguGfcUfGfUfauccuuuaguL96	2402	sense	21
ACUAAAGGAUACAGCACUUUAGC	1307	asCfsuaaAfgGfAfuacaGfcAfcuuuasgsc	2403	antisense	23
AAAGUGCUGUAUCCUUUAGUA	1308	asasagugCfuGfUfAfuccuuuaguaL96	2404	sense	21
UACUAAAGGAUACAGCACUUUAG	1309	usAfscuaAfaGfGfauacAfgCfacuuusasg	2405	antisense	23
AGGCUAAAGUGCUGUAUCCUU	1310	asgsgcuaAfaGfUfGfcuguauccuuL96	2406	sense	21
AAGGAUACAGCACUUUAGCCUGC	1311	asAfsggaUfaCfAfgcacUfuUfagccusgsc	2407	antisense	23
CAGGCUAAAGUGCUGUAUCCU	1312	csasggcuAfaAfGfUfgcuguauccuL96	2408	sense	21
AGGAUACAGCACUUUAGCCUGCC	1313	asGfsgauAfcAfGfcacuUfuAfgccugscsc	2409	antisense	23
AAGACAUUGGUGAGGAAAAAU	1314	asasgacaUfuGfGfUfgaggaaaaauL96	2410	sense	21
AUUUUUCCUCACCAAUGUCUUGU	1315	asUfsuuuUfcCfUfcaccAfaUfgucuusgsu	2411	antisense	23
AGACAUUGGUGAGGAAAAAUC	1316	asgsacauUfgGfUfGfaggaaaaaucL96	2412	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
GAUUUUUCCUCACCAAUGUCUUG	1317	gsAfsuuuUfuCfCfucacCfaAfugucususg	2413	antisense	23
CGACAAGACAUUGGUGAGGAA	1318	csgsacaaGfaCfAfUfuggugaggaaL96	2414	sense	21
UUCCUCACCAAUGUCUUGUCGAU	1319	usUfsccuCfaCfCfaaugUfcUfugucgsasu	2415	antisense	23
UCGACAAGACAUUGGUGAGGA	1320	uscsgacaAfgAfCfAfuuggugaggaL96	2416	sense	21
UCCUCACCAAUGUCUUGUCGAUG	1321	usCfscucAfcCfAfauguCfuUfgucgasusg	2417	antisense	23
AAGAUGUCCUCGAGAUACUAA	1322	asasgaugUfcCfUfCfgagauacuaaL96	2418	sense	21
UUAGUAUCUCGAGGACAUCUUGA	1323	usUfsaguAfuCfUfcgagGfaCfaucuusgsa	2419	antisense	23
AGAUGUCCUCGAGAUACUAAA	1324	asgsauguCfcUfCfGfagauacuaaaL96	2420	sense	21
UUUAGUAUCUCGAGGACAUCUUG	1325	usUfsuagUfaUfCfucgaGfgAfcaucususg	2421	antisense	23
GUUCAAGAUGUCCUCGAGAUA	1326	gsusucaaGfaUfGfUfccucgagauaL96	2422	sense	21
UAUCUCGAGGACAUCUUGAACAC	1327	usAfsucuCfgAfGfgacaUfcUfugaacsasc	2423	antisense	23
UGUUCAAGAUGUCCUCGAGAU	1328	usgsuucaAfgAfUfGfuccucgagauL96	2424	sense	21
AUCUCGAGGACAUCUUGAACACC	1329	asUfscucGfaGfGfacauCfuUfgaacascsc	2425	antisense	23
GAGAAAGGUGUUCAAGAUGUC	1330	gsasgaaaGfgUfGfUfucaagaugucL96	2426	sense	21
GACAUCUUGAACACCUUUCUCCC	1331	gsAfscauCfuUfGfaacaCfcUfuucucscsc	2427	antisense	23
AGAAAGGUGUUCAAGAUGUCC	1332	asgsaaagGfuGfUfUfcaagauguccL96	2428	sense	21
GGACAUCUUGAACACCUUUCUCC	1333	gsGfsacaUfcUfUfgaacAfcCfuuucuscsc	2429	antisense	23
GGGGGAGAAAGGUGUUCAAGA	1334	gsgsgggaGfaAfAfGfguguucaagaL96	2430	sense	21
UCUUGAACACCUUUCUCCCCCUG	1335	usCfsuugAfaCfAfccuuUfcUfcccccsusg	2431	antisense	23
AGGGGGAGAAAGGUGUUCAAG	1336	asgsggggAfgAfAfAfgguguucaagL96	2432	sense	21
CUUGAACACCUUUCUCCCCCUGG	1337	csUfsugaAfcAfCfcuuuCfuCfccccusgsg	2433	antisense	23
GCUGGGAAGAUAUCAAAUGGC	1338	gscsugggAfaGfAfUfaucaaauggcL96	2434	sense	21
GCCAUUUGAUAUCUUCCCAGCUG	1339	gsCfscauUfuGfAfuaucUfuCfccagcsusg	2435	antisense	23
CUGGGAAGAUAUCAAAUGGCU	1340	csusgggaAfgAfUfAfucaaauggcuL96	2436	sense	21
AGCCAUUUGAUAUCUUCCCAGCU	1341	asGfsccaUfuUfGfauauCfuUfcccagscsu	2437	antisense	23
AUCAGCUGGGAAGAUAUCAAA	1342	asuscagcUfgGfGfAfagauaucaaaL96	2438	sense	21
UUUGAUAUCUUCCCAGCUGAUAG	1343	usUfsugaUfaUfCfuuccCfaGfcugausasg	2439	antisense	23
UAUCAGCUGGGAAGAUAUCAA	1344	usasucagCfuGfGfGfaagauaucaaL96	2440	sense	21
UUGAUAUCUUCCCAGCUGAUAGA	1345	usUfsgauAfuCfUfucccAfgCfugauasgsa	2441	antisense	23
UCUGUCGACUUCUGUUUUAGG	1346	uscsugucGfaCfUfUfcuguuuuaggL96	2442	sense	21
CCUAAAACAGAAGUCGACAGAUC	1347	csCfsuaaAfaCfAfgaagUfcGfacagasusc	2443	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
CUGUCGACUUCUGUUUUAGGA	1348	csusgucgAfcUfUfCfuguuuuaggaL96	2444	sense	21
UCCUAAAACAGAAGUCGACAGAU	1349	usCfscuaAfaAfCfagaaGfuCfgacagsasu	2445	antisense	23
CAGAUCUGUCGACUUCUGUUU	1350	csasgaucUfgUfCfGfacuucuguuuL96	2446	sense	21
AAACAGAAGUCGACAGAUCUGUU	1351	asAfsacaGfaAfGfucgaCfaGfaucugsusu	2447	antisense	23
ACAGAUCUGUCGACUUCUGUU	1352	ascsagauCfuGfUfCfgacuucuguuL96	2448	sense	21
AACAGAAGUCGACAGAUCUGUUU	1353	asAfscagAfaGfUfcgacAfgAfucugususu	2449	antisense	23
UACUUCUUUGAAUGUAGAUUU	1354	usascuucUfuUfGfAfauguagauuuL96	2450	sense	21
AAAUCUACAUUCAAAGAAGUAUC	1355	asAfsaucUfaCfAfuucaAfaGfaaguasusc	2451	antisense	23
ACUUCUUUGAAUGUAGAUUUC	1356	ascsuucuUfuGfAfAfuguagauuucL96	2452	sense	21
GAAAUCUACAUUCAAAGAAGUAU	1357	gsAfsaauCfuAfCfauucAfaAfgaagusasu	2453	antisense	23
GUGAUACUUCUUUGAAUGUAG	1358	gsusgauaCfuUfCfUfuugaauguagL96	2454	sense	21
CUACAUUCAAAGAAGUAUCACCA	1359	csUfsacaUfuCfAfaagaAfgUfaucacscsa	2455	antisense	23
GGUGAUACUUCUUUGAAUGUA	1360	gsgsugauAfcUfUfCfuuugaauguaL96	2456	sense	21
UACAUUCAAAGAAGUAUCACCAA	1361	usAfscauUfcAfAfagaaGfuAfucaccsasa	2457	antisense	23
UGGGAAGAUAUCAAAUGGCUG	1362	usgsggaaGfaUfAfUfcaaauggcugL96	2458	sense	21
CAGCCAUUUGAUAUCUUCCCAGC	1363	csAfsgccAfuUfUfgauaUfcUfucccasgsc	2459	antisense	23
GGGAAGAUAUCAAAUGGCUGA	1364	gsgsgaagAfuAfUfCfaaauggcugaL96	2460	sense	21
UCAGCCAUUUGAUAUCUUCCCAG	1365	usCfsagcCfaUfUfugauAfuCfuucccsasg	2461	antisense	23
CAGCUGGGAAGAUAUCAAAUG	1366	csasgcugGfgAfAfGfauaucaaaugL96	2462	sense	21
CAUUUGAUAUCUUCCCAGCUGAU	1367	csAfsuuuGfaUfAfucuuCfcCfagcugsasu	2463	antisense	23
UCAGCUGGGAAGAUAUCAAAU	1368	uscsagcuGfgGfAfAfgauaucaaauL96	2464	sense	21
AUUUGAUAUCUUCCCAGCUGAUA	1369	asUfsuugAfuAfUfcuucCfcAfgcugasusa	2465	antisense	23
UCCAAAGUCUAUAUAUGACUA	1370	uscscaaaGfuCfUfAfuauaugacuaL96	2466	sense	21
UAGUCAUAUAUAGACUUUGGAAG	1371	usAfsgucAfuAfUfauagAfcUfuuggasasg	2467	antisense	23
CCAAAGUCUAUAUAUGACUAU	1372	cscsaaagUfcUfAfUfauaugacuauL96	2468	sense	21
AUAGUCAUAUAUAGACUUUGGAA	1373	asUfsaguCfaUfAfuauaGfaCfuuuggsasa	2469	antisense	23
UACUUCCAAAGUCUAUAUAUG	1374	usascuucCfaAfAfGfucuauauaugL96	2470	sense	21
CAUAUAUAGACUUUGGAAGUACU	1375	csAfsuauAfuAfGfacuuUfgGfaaguascsu	2471	antisense	23
GUACUUCCAAAGUCUAUAUAU	1376	gsusacuuCfcAfAfAfgucuauauauL96	2472	sense	21
AUAUAUAGACUUUGGAAGUACUG	1377	asUfsauaUfaGfAfcuuuGfgAfaguacsusg	2473	antisense	23
UUAUGAACAACAUGCUAAAUC	1378	ususaugaAfcAfAfCfaugcuaaaucL96	2474	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
GAUUUAGCAUGUUGUUCAUAAUC	1379	gsAfsuuuAfgCfAfuguuGfuUfcauaasusc	2475	antisense	23
UAUGAACAACAUGCUAAAUCA	1380	usasugaaCfaAfCfAfugcuaaaucaL96	2476	sense	21
UGAUUUAGCAUGUUGUUCAUAAU	1381	usGfsauuUfaGfCfauguUfgUfucauasasu	2477	antisense	23
AUGAUUAUGAACAACAUGCUA	1382	asusgauuAfuGfAfAfcaacaugcuaL96	2478	sense	21
UAGCAUGUUGUUCAUAAUCAUUG	1383	usAfsgcaUfgUfUfguucAfuAfaucaususg	2479	antisense	23
AAUGAUUAUGAACAACAUGCU	1384	asasugauUfaUfGfAfacaacaugcuL96	2480	sense	21
AGCAUGUUGUUCAUAAUCAUUGA	1385	asGfscauGfuUfGfuucaUfaAfucauusgsa	2481	antisense	23
AAUUCCCCACUUCAAUACAAA	1386	asasuuccCfcAfCfUfucaauacaaaL96	2482	sense	21
UUUGUAUUGAAGUGGGGAAUUAC	1387	usUfsuguAfuUfGfaaguGfgGfgaauusasc	2483	antisense	23
AUUCCCCACUUCAAUACAAAG	1388	asusucccCfaCfUfUfcaauacaaagL96	2484	sense	21
CUUUGUAUUGAAGUGGGGAAUUA	1389	csUfsuugUfaUfUfgaagUfgGfggaaususa	2485	antisense	23
CUGUAAUUCCCCACUUCAAUA	1390	csusguaaUfuCfCfCfcacuucaauaL96	2486	sense	21
UAUUGAAGUGGGGAAUUACAGAC	1391	usAfsuugAfaGfUfggggAfaUfuacagsasc	2487	antisense	23
UCUGUAAUUCCCCACUUCAAU	1392	uscsuguaAfuUfCfCfccacuucaauL96	2488	sense	21
AUUGAAGUGGGGAAUUACAGACU	1393	asUfsugaAfgUfGfgggaAfuUfacagascsu	2489	antisense	23
UGAUGUGCGUAACAGAUUCAA	1394	usgsauguGfcGfUfAfacagauucaaL96	2490	sense	21
UUGAAUCUGUUACGCACAUCAUC	1395	usUfsgaaUfcUfGfuuacGfcAfcaucasusc	2491	antisense	23
GAUGUGCGUAACAGAUUCAAA	1396	gsasugugCfgUfAfAfcagauucaaaL96	2492	sense	21
UUUGAAUCUGUUACGCACAUCAU	1397	usUfsugaAfuCfUfguuaCfgCfacaucsasu	2493	antisense	23
UGGAUGAUGUGCGUAACAGAU	1398	usgsgaugAfuGfUfGfcguaacagauL96	2494	sense	21
AUCUGUUACGCACAUCAUCCAGA	1399	asUfscugUfuAfCfgcacAfuCfauccasgsa	2495	antisense	23
CUGGAUGAUGUGCGUAACAGA	1400	csusggauGfaUfGfUfgcguaacagaL96	2496	sense	21
UCUGUUACGCACAUCAUCCAGAC	1401	usCfsuguUfaCfGfcacaUfcAfuccagsasc	2497	antisense	23
GAAUGGGUGGCGGUAAUUGGU	1402	gsasauggGfuGfGfCfgguaauugguL96	2498	sense	21
ACCAAUUACCGCCACCCAUUCCA	1403	asCfscaaUfuAfCfcgccAfcCfcauucscsa	2499	antisense	23
AAUGGGUGGCGGUAAUUGGUG	1404	asasugggUfgGfCfGfguaauuggugL96	2500	sense	21
CACCAAUUACCGCCACCCAUUCC	1405	csAfsccaAfuUfAfccgcCfaCfccauuscsc	2501	antisense	23
AUUGGAAUGGGUGGCGGUAAU	1406	asusuggaAfuGfGfGfuggcgguaauL96	2502	sense	21
AUUACCGCCACCCAUUCCAAUUC	1407	asUfsuacCfgCfCfacccAfuUfccaaususc	2503	antisense	23
AAUUGGAAUGGGUGGCGGUAA	1408	asasuuggAfaUfGfGfguggcgguaaL96	2504	sense	21
UUACCGCCACCCAUUCCAAUUCU	1409	usUfsaccGfcCfAfcccaUfuCfcaauuscsu	2505	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
UCCGGAAUGUUGCUGAAACAG	1410	uscscggaAfuGfUfUfgcugaaacagL96	2506	sense	21
CUGUUUCAGCAACAUUCCGGAGC	1411	csUfsguuUfcAfGfcaacAfuUfccggasgsc	2507	antisense	23
CCGGAAUGUUGCUGAAACAGA	1412	cscsggaaUfgUfUfGfcugaaacagaL96	2508	sense	21
UCUGUUUCAGCAACAUUCCGGAG	1413	usCfsuguUfuCfAfgcaaCfaUfuccggsasg	2509	antisense	23
AUGCUCCGGAAUGUUGCUGAA	1414	asusgcucCfgGfAfAfuguugcugaaL96	2510	sense	21
UUCAGCAACAUUCCGGAGCAUCC	1415	usUfscagCfaAfCfauucCfgGfagcauscsc	2511	antisense	23
GAUGCUCCGGAAUGUUGCUGA	1416	gsasugcuCfcGfGfAfauguugcugaL96	2512	sense	21
UCAGCAACAUUCCGGAGCAUCCU	1417	usCfsagcAfaCfAfuuccGfgAfgcaucscsu	2513	antisense	23
UGUCCUCGAGAUACUAAAGGA	1418	usgsuccuCfgAfGfAfuacuaaaggaL96	2514	sense	21
UCCUUUAGUAUCUCGAGGACAUC	1419	usCfscuuUfaGfUfaucuCfgAfggacasusc	2515	antisense	23
GUCCUCGAGAUACUAAAGGAA	1420	gsusccucGfaGfAfUfacuaaaggaaL96	2516	sense	21
UUCCUUUAGUAUCUCGAGGACAU	1421	usUfsccuUfuAfGfuaucUfcGfaggacsasu	2517	antisense	23
AAGAUGUCCUCGAGAUACUAA	1422	asasgaugUfcCfUfCfgagauacuaaL96	2518	sense	21
UUAGUAUCUCGAGGACAUCUUGA	1423	usUfsaguAfuCfUfcgagGfaCfaucuusgsa	2519	antisense	23
CAAGAUGUCCUCGAGAUACUA	1424	csasagauGfuCfCfUfcgagauacuaL96	2520	sense	21
UAGUAUCUCGAGGACAUCUUGAA	1425	usAfsguaUfcUfCfgaggAfcAfucuugsasa	2521	antisense	23
ACAACAUGCUAAAUCAGUACU	1426	ascsaacaUfgCfUfAfaaucaguacuL96	2522	sense	21
AGUACUGAUUUAGCAUGUUGUUC	1427	asGfsuacUfgAfUfuuagCfaUfguugususc	2523	antisense	23
CAACAUGCUAAAUCAGUACUU	1428	csasacauGfcUfAfAfaucaguacuuL96	2524	sense	21
AAGUACUGAUUUAGCAUGUUGUU	1429	asAfsguaCfuGfAfuuuaGfcAfuguugsusu	2525	antisense	23
AUGAACAACAUGCUAAAUCAG	1430	asusgaacAfaCfAfUfgcuaaaucagL96	2526	sense	21
CUGAUUUAGCAUGUUGUUCAUAA	1431	csUfsgauUfuAfGfcaugUfuGfuucausasa	2527	antisense	23
UAUGAACAACAUGCUAAAUCA	1432	usasugaaCfaAfCfAfugcuaaaucaL96	2528	sense	21
UGAUUUAGCAUGUUGUUCAUAAU	1433	usGfsauuUfaGfCfauguUfgUfucauasasu	2529	antisense	23
GCCAAGGCUGUGUUUGUGGGG	1434	gscscaagGfcUfGfUfguuugggggL96	2530	sense	21
CCCCACAAACACAGCCUUGGCGC	1435	csCfsccaCfaAfAfcacaGfcCfuuggcsgsc	2531	antisense	23
CCAAGGCUGUGUUUGUGGGGA	1436	cscsaaggCfuGfUfGfuuugggggaL96	2532	sense	21
UCCCCACAAACACAGCCUUGGCG	1437	usCfscccAfcAfAfacacAfgCfcuuggscsg	2533	antisense	23
UGGCGCCAAGGCUGUGUUUGU	1438	usgsgcgcCfaAfGfGfcuguguuuguL96	2534	sense	21
ACAAACACAGCCUUGGCGCCAAG	1439	asCfsaaaCfaCfAfgccuUfgGfcgccasasg	2535	antisense	23
UUGGCGCCAAGGCUGUGUUUG	1440	ususggcgCfcAfAfGfgcuguguuugL96	2536	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
CAAACACAGCCUUGGCGCCAAGA	1441	csAfsaacAfcAfGfccuuGfgCfgccaasgsa	2537	antisense	23
UGAAAGCUCUGGCUCUUGGCG	1442	usgsaaagCfuCfUfGfgcucuuggcgL96	2538	sense	21
CGCCAAGAGCCAGAGCUUUCAGA	1443	csGfsccaAfgAfGfccagAfgCfuuucasgsa	2539	antisense	23
GAAAGCUCUGGCUCUUGGCGC	1444	gsasaagcUfcUfGfGfcucuuggcgcL96	2540	sense	21
GCGCCAAGAGCCAGAGCUUUCAG	1445	gsCfsgccAfaGfAfgccaGfaGfcuuucsasg	2541	antisense	23
GUUCUGAAAGCUCUGGCUCUU	1446	gsusucugAfaAfGfCfucuggcucuuL96	2542	sense	21
AAGAGCCAGAGCUUUCAGAACAU	1447	asAfsgagCfcAfGfagcuUfuCfagaacsasu	2543	antisense	23
UGUUCUGAAAGCUCUGGCUCU	1448	usgsuucuGfaAfAfGfcucuggcucuL96	2544	sense	21
AGAGCCAGAGCUUUCAGAACAUC	1449	asGfsagcCfaGfAfgcuuUfcAfgaacasusc	2545	antisense	23
CAGCCACUAUUGAUGUUCUGC	1450	csasgccaCfuAfUfUfgauguucugcL96	2546	sense	21
GCAGAACAUCAAUAGUGGCUGGC	1451	gsCfsagaAfcAfUfcaauAfgUfggcugsgsc	2547	antisense	23
AGCCACUAUUGAUGUUCUGCC	1452	asgsccacUfaUfUfGfauguucugccL96	2548	sense	21
GGCAGAACAUCAAUAGUGGCUGG	1453	gsGfscagAfaCfAfucaaUfaGfuggcusgsg	2549	antisense	23
GUGCCAGCCACUAUUGAUGUU	1454	gsusgccaGfcCfAfCfuauugauguuL96	2550	sense	21
AACAUCAAUAGUGGCUGGCACCC	1455	asAfscauCfaAfUfagugGfcUfggcacscsc	2551	antisense	23
GGUGCCAGCCACUAUUGAUGU	1456	gsgsugccAfgCfCfAfcuauugauguL96	2552	sense	21
ACAUCAAUAGUGGCUGGCACCCC	1457	asCfsaucAfaUfAfguggCfuGfgcaccscsc	2553	antisense	23
ACAAGGACCGAGAAGUCACCA	1458	ascsaaggAfcCfGfAfgaagucaccaL96	2554	sense	21
UGGUGACUUCUCGGUCCUUGUAG	1459	usGfsgugAfcUfUfcucgGfuCfcuugusasg	2555	antisense	23
CAAGGACCGAGAAGUCACCAA	1460	csasaggaCfcGfAfGfaagucaccaaL96	2556	sense	21
UUGGUGACUUCUCGGUCCUUGUA	1461	usUfsgguGfaCfUfucucGfgUfccuugsusa	2557	antisense	23
AUCUACAAGGACCGAGAAGUC	1462	asuscuacAfaGfGfAfccgagaagucL96	2558	sense	21
GACUUCUCGGUCCUUGUAGAUAU	1463	gsAfscuuCfuCfGfguccUfuGfuagausasu	2559	antisense	23
UAUCUACAAGGACCGAGAAGU	1464	usasucuaCfaAfGfGfaccgagaaguL96	2560	sense	21
ACUUCUCGGUCCUUGUAGAUAUA	1465	asCfsuucUfcGfGfuccuUfgUfagauasusa	2561	antisense	23
CAGAAUGUGAAAGUCAUCGAC	1466	csasgaauGfuGfAfAfagucaucgacL96	2562	sense	21
GUCGAUGACUUUCACAUUCUGGC	1467	gsUfscgaUfgAfCfuuucAfcAfuucugsgsc	2563	antisense	23
AGAAUGUGAAAGUCAUCGACA	1468	asgsaaugUfgAfAfAfgucaucgacaL96	2564	sense	21
UGUCGAUGACUUUCACAUUCUGG	1469	usGfsucgAfuGfAfcuuuCfaCfauucusgsg	2565	antisense	23
GUGCCAGAAUGUGAAAGUCAU	1470	gsusgccaGfaAfUfGfugaaagucauL96	2566	sense	21
AUGACUUUCACAUUCUGGCACCC	1471	asUfsgacUfuUfCfacauUfcUfggcacscsc	2567	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
GGUGCCAGAAUGUGAAAGUCA	1472	gsgsugccAfgAfAfUfgugaaagucaL96	2568	sense	21
UGACUUUCACAUUCUGGCACCCA	1473	usGfsacuUfuCfAfcauuCfuGfgcaccscsa	2569	antisense	23
AGAUGUCCUCGAGAUACUAAA	1474	asgsauguCfcUfCfGfagauacuaaaL96	2570	sense	21
UUUAGUAUCUCGAGGACAUCUUG	1475	usUfsuagUfaUfCfucgaGfgAfcaucususg	2571	antisense	23
GAUGUCCUCGAGAUACUAAAG	1476	gsasugucCfuCfGfAfgauacuaaagL96	2572	sense	21
CUUUAGUAUCUCGAGGACAUCUU	1477	csUfsuuaGfuAfUfcucgAfgGfacaucsusu	2573	antisense	23
UUCAAGAUGUCCUCGAGAUAC	1478	ususcaagAfuGfUfCfcucgagauacL96	2574	sense	21
GUAUCUCGAGGACAUCUUGAACA	1479	gsUfsaucUfcGfAfggacAfuCfuugaascsa	2575	antisense	23
GUUCAAGAUGUCCUCGAGAUA	1480	gsusucaaGfaUfGfUfccucgagauaL96	2576	sense	21
UAUCUCGAGGACAUCUUGAACAC	1481	usAfsucuCfgAfGfgacaUfcUfugaacsasc	2577	antisense	23
GUGGACUUGCUGCAUAUGUGG	1482	gsusggacUfuGfCfUfgcauauguggL96	2578	sense	21
CCACAUAUGCAGCAAGUCCACUG	1483	csCfsacaUfaUfGfcagcAfaGfuccacsusg	2579	antisense	23
UGGACUUGCUGCAUAUGUGGC	1484	usgsgacuUfgCfUfGfcauauguggcL96	2580	sense	21
GCCACAUAUGCAGCAAGUCCACU	1485	gsCfscacAfuAfUfgcagCfaAfguccascsu	2581	antisense	23
GACAGUGGACUUGCUGCAUAU	1486	gsascaguGfgAfCfUfugcugcauauL96	2582	sense	21
AUAUGCAGCAAGUCCACUGUCGU	1487	asUfsaugCfaGfCfaaguCfcAfcugucsgsu	2583	antisense	23
CGACAGUGGACUUGCUGCAUA	1488	csgsacagUfgGfAfCfuugcugcauaL96	2584	sense	21
UAUGCAGCAAGUCCACUGUCGUC	1489	usAfsugcAfgCfAfagucCfaCfugucgsusc	2585	antisense	23
AACCAGUACUUUAUCAUUUUC	1490	asasccagUfaCfUfUfuaucauuuucL96	2586	sense	21
GAAAAUGAUAAAGUACUGGUUUC	1491	gsAfsaaaUfgAfUfaaagUfaCfugguususc	2587	antisense	23
ACCAGUACUUUAUCAUUUUCU	1492	ascscaguAfcUfUfUfaucauuuucuL96	2588	sense	21
AGAAAAUGAUAAAGUACUGGUUU	1493	asGfsaaaAfuGfAfuaaaGfuAfcuggususu	2589	antisense	23
UUGAAACCAGUACUUUAUCAU	1494	ususgaaaCfcAfGfUfacuuuaucauL96	2590	sense	21
AUGAUAAAGUACUGGUUUCAAAA	1495	asUfsgauAfaAfGfuacuGfgUfuucaasasa	2591	antisense	23
UUUGAAACCAGUACUUUAUCA	1496	ususugaaAfcCfAfGfuacuuuaucaL96	2592	sense	21
UGAUAAAGUACUGGUUUCAAAAU	1497	usGfsauaAfaGfUfacugGfuUfucaaasasu	2593	antisense	23
CGAGAAGUCACCAAGAAGCUA	1498	csgsagaaGfuCfAfCfcaagaagcuaL96	2594	sense	21
UAGCUUCUUGGUGACUUCUCGGU	1499	usAfsgcuUfcUfUfggugAfcUfucucgsgsu	2595	antisense	23
GAGAAGUCACCAAGAAGCUAG	1500	gsasgaagUfcAfCfCfaagaagcuagL96	2596	sense	21
CUAGCUUCUUGGUGACUUCUCGG	1501	csUfsagcUfuCfUfugguGfaCfuucucsgsg	2597	antisense	23
GGACCGAGAAGUCACCAAGAA	1502	gsgsaccgAfgAfAfGfucaccaagaaL96	2598	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
UUCUUGGUGACUUCUCGGUCCUU	1503	usUfscuuGfgUfGfacuuCfuCfgguccsusu	2599	antisense	23
AGGACCGAGAAGUCACCAAGA	1504	asgsgaccGfaGfAfAfgucaccaagaL96	2600	sense	21
UCUUGGUGACUUCUCGGUCCUUG	1505	usCfsuugGfuGfAfcuucUfcGfguccususg	2601	antisense	23
UCAAAGUGUUGGUAAUGCCUG	1506	uscsaaagUfgUfUfGfguaaugccugL96	2602	sense	21
CAGGCAUUACCAACACUUUGAAC	1507	csAfsggcAfuUfAfccaaCfaCfuuugasasc	2603	antisense	23
CAAAGUGUUGGUAAUGCCUGA	1508	csasaaguGfuUfGfGfuaaugccugaL96	2604	sense	21
UCAGGCAUUACCAACACUUUGAA	1509	usCfsaggCfaUfUfaccaAfcAfcuuugsasa	2605	antisense	23
AGGUUCAAAGUGUUGGUAAUG	1510	asgsguucAfaAfGfUfguugguaaugL96	2606	sense	21
CAUUACCAACACUUUGAACCUGA	1511	csAfsuuaCfcAfAfcacuUfuGfaaccusgsa	2607	antisense	23
CAGGUUCAAAGUGUUGGUAAU	1512	csasgguuCfaAfAfGfuguugguaauL96	2608	sense	21
AUUACCAACACUUUGAACCUGAG	1513	asUfsuacCfaAfCfacuuUfgAfaccugsasg	2609	antisense	23
UAUUACUUGACAAAGAGACAC	1514	usasuuacUfuGfAfCfaaagagacacL96	2610	sense	21
GUGUCUCUUUGUCAAGUAAUACA	1515	gsUfsgucUfcUfUfugucAfaGfuaauascsa	2611	antisense	23
AUUACUUGACAAAGAGACACU	1516	asusuacuUfgAfCfAfaagagacacuL96	2612	sense	21
AGUGUCUCUUUGUCAAGUAAUAC	1517	asGfsuguCfuCfUfuuguCfaAfguaausasc	2613	antisense	23
CAUGUAUUACUUGACAAAGAG	1518	csasuguaUfuAfCfUfugacaaagagL96	2614	sense	21
CUCUUUGUCAAGUAAUACAUGCU	1519	csUfscuuUfgUfCfaaguAfaUfacaugscsu	2615	antisense	23
GCAUGUAUUACUUGACAAAGA	1520	gscsauguAfuUfAfCfuugacaaagaL96	2616	sense	21
UCUUUGUCAAGUAAUACAUGCUG	1521	usCfsuuuGfuCfAfaguaAfuAfcaugcsusg	2617	antisense	23
AAAGUCAUCGACAAGACAUUG	1522	asasagucAfuCfGfAfcaagacauugL96	2618	sense	21
CAAUGUCUUGUCGAUGACUUUCA	1523	csAfsaugUfcUfUfgucgAfuGfacuuuscsa	2619	antisense	23
AAGUCAUCGACAAGACAUUGG	1524	asasgucaUfcGfAfCfaagacauuggL96	2620	sense	21
CCAAUGUCUUGUCGAUGACUUUC	1525	csCfsaauGfuCfUfugucGfaUfgacuususc	2621	antisense	23
UGUGAAAGUCAUCGACAAGAC	1526	usgsugaaAfgUfCfAfucgacaagacL96	2622	sense	21
GUCUUGUCGAUGACUUUCACAUU	1527	gsUfscuuGfuCfGfaugaCfuUfucacasusu	2623	antisense	23
AUGUGAAAGUCAUCGACAAGA	1528	asusgugaAfaGfUfCfaucgacaagaL96	2624	sense	21
UCUUGUCGAUGACUUUCACAUUC	1529	usCfsuugUfcGfAfugacUfuUfcacaususc	2625	antisense	23
AUAUGUGGCUAAAGCAAUAGA	1530	asusauguGfgCfUfAfaagcaauagaL96	2626	sense	21
UCUAUUGCUUUAGCCACAUAUGC	1531	usCfsuauUfgCfUfuuagCfcAfcauausgsc	2627	antisense	23
UAUGUGGCUAAAGCAAUAGAC	1532	usasugugGfcUfAfAfagcaauagacL96	2628	sense	21
GUCUAUUGCUUUAGCCACAUAUG	1533	gsUfscuaUfuGfCfuuuaGfcCfacauasusg	2629	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
CUGCAUAUGUGGCUAAAGCAA	1534	csusgcauAfuGfUfGfgcuaaagcaaL96	2630	sense	21
UUGCUUUAGCCACAUAUGCAGCA	1535	usUfsgcuUfuAfGfccacAfuAfugcagscsa	2631	antisense	23
GCUGCAUAUGUGGCUAAAGCA	1536	gscsugcaUfaUfGfUfggcuaaagcaL96	2632	sense	21
UGCUUUAGCCACAUAUGCAGCAA	1537	usGfscuuUfaGfCfcacaUfaUfgcagcsasa	2633	antisense	23
AGACGACAGUGGACUUGCUGC	1538	asgsacgaCfaGfUfGfgacuugcugcL96	2634	sense	21
GCAGCAAGUCCACUGUCGUCUCC	1539	gsCfsagcAfaGfUfccacUfgUfcgucuscsc	2635	antisense	23
GACGACAGUGGACUUGCUGCA	1540	gsascgacAfgUfGfGfacuugcugcaL96	2636	sense	21
UGCAGCAAGUCCACUGUCGUCUC	1541	usGfscagCfaAfGfuccaCfuGfucgucsusc	2637	antisense	23
UUGGAGACGACAGUGGACUUG	1542	ususggagAfcGfAfCfaguggacuugL96	2638	sense	21
CAAGUCCACUGUCGUCUCCAAAA	1543	csAfsaguCfcAfCfugucGfuCfuccaasasa	2639	antisense	23
UUUGGAGACGACAGUGGACUU	1544	ususuggaGfaCfGfAfcaguggacuuL96	2640	sense	21
AAGUCCACUGUCGUCUCCAAAAU	1545	asAfsgucCfaCfUfgucgUfcUfccaaasasu	2641	antisense	23
GGCCACCUCCUCAAUUGAAGA	1546	gsgsccacCfuCfCfUfcaauugaagaL96	2642	sense	21
UCUUCAAUUGAGGAGGUGGCCCA	1547	usCfsuucAfaUfUfgaggAfgGfuggccscsa	2643	antisense	23
GCCACCUCCUCAAUUGAAGAA	1548	gscscaccUfcCfUfCfaauugaagaaL96	2644	sense	21
UUCUUCAAUUGAGGAGGUGGCCC	1549	usUfscuuCfaAfUfugagGfaGfguggcscsc	2645	antisense	23
CCUGGGCCACCUCCUCAAUUG	1550	cscsugggCfcAfCfCfuccucaauugL96	2646	sense	21
CAAUUGAGGAGGUGGCCCAGGAA	1551	csAfsauuGfaGfGfagguGfgCfccaggsasa	2647	antisense	23
UCCUGGGCCACCUCCUCAAUU	1552	uscscuggGfcCfAfCfcuccucaauuL96	2648	sense	21
AAUUGAGGAGGUGGCCCAGGAAC	1553	asAfsuugAfgGfAfggugGfcCfcaggasasc	2649	antisense	23
UGUAUGUUACUUCUUAGAGAG	1554	usgsuaugUfuAfCfUfucuuagagagL96	2650	sense	21
CUCUCUAAGAAGUAACAUACAUC	1555	csUfscucUfaAfGfaaguAfaCfauacasusc	2651	antisense	23
GUAUGUUACUUCUUAGAGAGA	1556	gsusauguUfaCfUfUfcuuagagagaL96	2652	sense	21
UCUCUCUAAGAAGUAACAUACAU	1557	usCfsucuCfuAfAfgaagUfaAfcauacsasu	2653	antisense	23
AGGAUGUAUGUUACUUCUUAG	1558	asgsgaugUfaUfGfUfuacuucuuagL96	2654	sense	21
CUAAGAAGUAACAUACAUCCUAA	1559	csUfsaagAfaGfUfaacaUfaCfauccusasa	2655	antisense	23
UAGGAUGUAUGUUACUUCUUA	1560	usasggauGfuAfUfGfuuacuucuuaL96	2656	sense	21
UAAGAAGUAACAUACAUCCUAAA	1561	usAfsagaAfgUfAfacauAfcAfuccuasasa	2657	antisense	23
AAAUGUUUUAGGAUGUAUGUU	1562	asasauguUfuUfAfGfgauguauguuL96	2658	sense	21
AACAUACAUCCUAAAACAUUUGG	1563	asAfscauAfcAfUfccuaAfaAfcauuusgsg	2659	antisense	23
AAUGUUUUAGGAUGUAUGUUA	1564	asasuguuUfuAfGfGfauguauguuaL96	2660	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
UAACAUACAUCCUAAAACAUUUG	1565	usAfsacaUfaCfAfuccuAfaAfacauususg	2661	antisense	23
AUCCAAAUGUUUUAGGAUGUA	1566	asusccaaAfuGfUfUfuuaggauguaL96	2662	sense	21
UACAUCCUAAAACAUUUGGAUAU	1567	usAfscauCfcUfAfaaacAfuUfuggausasu	2663	antisense	23
UAUCCAAAUGUUUUAGGAUGU	1568	usasuccaAfaUfGfUfuuuaggauguL96	2664	sense	21
ACAUCCUAAAACAUUUGGAUAUA	1569	asCfsaucCfuAfAfaacaUfuUfggauasusa	2665	antisense	23
AUGGGUGGCGGUAAUUGGUGA	1570	asusggguGfgCfGfGfuaauuggugaL96	2666	sense	21
UCACCAAUUACCGCCACCCAUUC	1571	usCfsaccAfaUfUfaccgCfcAfcccaususc	2667	antisense	23
UGGGUGGCGGUAAUUGGUGAU	1572	usgsggugGfcGfGfUfaauuggugauL96	2668	sense	21
AUCACCAAUUACCGCCACCCAUU	1573	asUfscacCfaAfUfuaccGfcCfacccasusu	2669	antisense	23
UGGAAUGGGUGGCGGUAAUUG	1574	usgsgaauGfgGfUfGfgcgguaauugL96	2670	sense	21
CAAUUACCGCCACCCAUUCCAAU	1575	csAfsauuAfcCfGfccacCfcAfuuccasasu	2671	antisense	23
UUGGAAUGGGUGGCGGUAAUU	1576	ususggaaUfgGfGfUfggcgguaauuL96	2672	sense	21
AAUUACCGCCACCCAUUCCAAUU	1577	asAfsuuaCfcGfCfcaccCfaUfuccaasusu	2673	antisense	23
UUCAAAGUGUUGGUAAUGCCU	1578	ususcaaaGfuGfUfUfgguaaugccuL96	2674	sense	21
AGGCAUUACCAACACUUUGAACC	1579	asGfsgcaUfuAfCfcaacAfcUfuugaascsc	2675	antisense	23
UCAAAGUGUUGGUAAUGCCUG	1580	uscsaaagUfgUfUfGfguaaugccugL96	2676	sense	21
CAGGCAUUACCAACACUUUGAAC	1581	csAfsggcAfuUfAfccaaCfaCfuuugasasc	2677	antisense	23
CAGGUUCAAAGUGUUGGUAAU	1582	csasgguuCfaAfAfGfuguugguaauL96	2678	sense	21
AUUACCAACACUUUGAACCUGAG	1583	asUfsuacCfaAfCfacuuUfgAfaccugsasg	2679	antisense	23
UCAGGUUCAAAGUGUUGGUAA	1584	uscsagguUfcAfAfAfguguugguaaL96	2680	sense	21
UUACCAACACUUUGAACCUGAGC	1585	usUfsaccAfaCfAfcuuuGfaAfccugasgsc	2681	antisense	23
CCACCUCCUCAAUUGAAGAAG	1586	cscsaccuCfcUfCfAfauugaagaagL96	2682	sense	21
CUUCUUCAAUUGAGGAGGUGGCC	1587	csUfsucuUfcAfAfuugaGfgAfgguggscsc	2683	antisense	23
CACCUCCUCAAUUGAAGAAGU	1588	csasccucCfuCfAfAfuugaagaaguL96	2684	sense	21
ACUUCUUCAAUUGAGGAGGUGGC	1589	asCfsuucUfuCfAfauugAfgGfaggugsgsc	2685	antisense	23
UGGGCCACCUCCUCAAUUGAA	1590	usgsggccAfcCfUfCfcucaauugaaL96	2686	sense	21
UUCAAUUGAGGAGGUGGCCCAGG	1591	usUfscaaUfuGfAfggagGfuGfgcccasgsg	2687	antisense	23
CUGGGCCACCUCCUCAAUUGA	1592	csusgggcCfaCfCfUfccucaauugaL96	2688	sense	21
UCAAUUGAGGAGGUGGCCCAGGA	1593	usCfsaauUfgAfGfgaggUfgGfcccagsgsa	2689	antisense	23
GAGUGGGUGCCAGAAUGUGAA	1594	gsasguggGfuGfCfCfagaaugugaaL96	2690	sense	21
UUCACAUUCUGGCACCCACUCAG	1595	usUfscacAfuUfCfuggcAfcCfcacucsasg	2691	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
AGUGGGUGCCAGAAUGUGAAA	1596	asgsugggUfgCfCfAfgaaugugaaaL96	2692	sense	21
UUUCACAUUCUGGCACCCACUCA	1597	usUfsucaCfaUfUfcuggCfaCfccacuscsa	2693	antisense	23
CUCUGAGUGGGUGCCAGAAUG	1598	csuscugaGfuGfGfGfugccagaaugL96	2694	sense	21
CAUUCUGGCACCCACUCAGAGCC	1599	csAfsuucUfgGfCfacccAfcUfcagagscsc	2695	antisense	23
GCUCUGAGUGGGUGCCAGAAU	1600	gscsucugAfgUfGfGfgugccagaauL96	2696	sense	21
AUUCUGGCACCCACUCAGAGCCA	1601	asUfsucuGfgCfAfcccaCfuCfagagcscsa	2697	antisense	23
GCACUGAUGUUCUGAAAGCUC	1602	gscsacugAfuGfUfUfcugaaagcucL96	2698	sense	21
GAGCUUUCAGAACAUCAGUGCCU	1603	gsAfsgcuUfuCfAfgaacAfuCfagugcscsu	2699	antisense	23
CACUGAUGUUCUGAAAGCUCU	1604	csascugaUfgUfUfCfugaaagcucuL96	2700	sense	21
AGAGCUUUCAGAACAUCAGUGCC	1605	asGfsagcUfuUfCfagaaCfaUfcagugscsc	2701	antisense	23
AAAGGCACUGAUGUUCUGAAA	1606	asasaggcAfcUfGfAfuguucugaaaL96	2702	sense	21
UUUCAGAACAUCAGUGCCUUUCC	1607	usUfsucaGfaAfCfaucaGfuGfccuuuscsc	2703	antisense	23
GAAAGGCACUGAUGUUCUGAA	1608	gsasaaggCfaCfUfGfauguucugaaL96	2704	sense	21
UUCAGAACAUCAGUGCCUUUCCG	1609	usUfscagAfaCfAfucagUfgCfcuuucscsg	2705	antisense	23
GGGAAGGUGGAAGUCUUCCUG	1610	gsgsgaagGfuGfGfAfagucuuccugL96	2706	sense	21
CAGGAAGACUUCCACCUUCCCUU	1611	csAfsggaAfgAfCfuuccAfcCfuucccsusu	2707	antisense	23
GGAAGGUGGAAGUCUUCCUGG	1612	gsgsaaggUfgGfAfAfgucuuccuggL96	2708	sense	21
CCAGGAAGACUUCCACCUUCCCU	1613	csCfsaggAfaGfAfcuucCfaCfcuuccscsu	2709	antisense	23
GGAAGGGAAGGUGGAAGUCUU	1614	gsgsaaggGfaAfGfGfuggaagucuuL96	2710	sense	21
AAGACUUCCACCUUCCCUUCCAC	1615	asAfsgacUfuCfCfaccuUfcCfcuuccsasc	2711	antisense	23
UGGAAGGGAAGGUGGAAGUCU	1616	usgsgaagGfgAfAfGfguggaagucuL96	2712	sense	21
AGACUUCCACCUUCCCUUCCACA	1617	asGfsacuUfcCfAfccuuCfcCfuuccascsa	2713	antisense	23
UGCUAAAUCAGUACUUCCAAA	1618	usgscuaaAfuCfAfGfuacuuccaaaL96	2714	sense	21
UUUGGAAGUACUGAUUUAGCAUG	1619	usUfsuggAfaGfUfacugAfuUfuagcasusg	2715	antisense	23
GCUAAAUCAGUACUUCCAAAG	1620	gscsuaaaUfcAfGfUfacuuccaaagL96	2716	sense	21
CUUUGGAAGUACUGAUUUAGCAU	1621	csUfsuugGfaAfGfuacuGfaUfuuagcsasu	2717	antisense	23
AACAUGCUAAAUCAGUACUUC	1622	asascaugCfuAfAfAfucaguacuucL96	2718	sense	21
GAAGUACUGAUUUAGCAUGUUGU	1623	gsAfsaguAfcUfGfauuuAfgCfauguusgsu	2719	antisense	23
CAACAUGCUAAAUCAGUACUU	1624	csasacauGfcUfAfAfaucaguacuuL96	2720	sense	21
AAGUACUGAUUUAGCAUGUUGUU	1625	asAfsguaCfuGfAfuuuaGfcAfuguugsusu	2721	antisense	23
CCACAACUCAGGAUGAAAAAU	1626	cscsacaaCfuCfAfGfgaugaaaaauL96	2722	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
AUUUUUCAUCCUGAGUUGUGGCG	1627	asUfsuuuUfcAfUfccugAfgUfuguggscsg	2723	antisense	23
CACAACUCAGGAUGAAAAAUU	1628	csascaacUfcAfGfGfaugaaaaauuL96	2724	sense	21
AAUUUUUCAUCCUGAGUUGUGGC	1629	asAfsuuuUfuCfAfuccuGfaGfuugugsgsc	2725	antisense	23
GCCGCCACAACUCAGGAUGAA	1630	gscscgccAfcAfAfCfucaggaugaaL96	2726	sense	21
UUCAUCCUGAGUUGUGGCGGCAG	1631	usUfscauCfcUfGfaguuGfuGfgcggcsasg	2727	antisense	23
UGCCGCCACAACUCAGGAUGA	1632	usgsccgcCfaCfAfAfcucaggaugaL96	2728	sense	21
UCAUCCUGAGUUGUGGCGGCAGU	1633	usCfsaucCfuGfAfguugUfgGfcggcasgsu	2729	antisense	23
GCAACCGUCUGGAUGAUGUGC	1634	gscsaaccGfuCfUfGfgaugaugugcL96	2730	sense	21
GCACAUCAUCCAGACGGUUGCCC	1635	gsCfsacaUfcAfUfccagAfcGfguugcscsc	2731	antisense	23
CAACCGUCUGGAUGAUGUGCG	1636	csasaccgUfcUfGfGfaugaugugcgL96	2732	sense	21
CGCACAUCAUCCAGACGGUUGCC	1637	csGfscacAfuCfAfuccaGfaCfgguugscsc	2733	antisense	23
CUGGGCAACCGUCUGGAUGAU	1638	csusgggcAfaCfCfGfucuggaugauL96	2734	sense	21
AUCAUCCAGACGGUUGCCCAGGU	1639	asUfscauCfcAfGfacggUfuGfcccagsgsu	2735	antisense	23
CCUGGGCAACCGUCUGGAUGA	1640	cscsugggCfaAfCfCfgucuggaugaL96	2736	sense	21
UCAUCCAGACGGUUGCCCAGGUA	1641	usCfsaucCfaGfAfcgguUfgCfccaggsusa	2737	antisense	23
GCAAAUGAUGAAGAAACUUUG	1642	gscsaaauGfaUfGfAfagaaacuuugL96	2738	sense	21
CAAAGUUUCUUCAUCAUUUGCCC	1643	csAfsaagUfuUfCfuucaUfcAfuuugcscsc	2739	antisense	23
CAAAUGAUGAAGAAACUUUGG	1644	csasaaugAfuGfAfAfgaaacuuuggL96	2740	sense	21
CCAAAGUUUCUUCAUCAUUUGCC	1645	csCfsaaaGfuUfUfcuucAfuCfauuugscsc	2741	antisense	23
UGGGGCAAAUGAUGAAGAAAC	1646	usgsgggcAfaAfUfGfaugaagaaacL96	2742	sense	21
GUUUCUUCAUCAUUUGCCCCAGA	1647	gsUfsuucUfuCfAfucauUfuGfccccasgsa	2743	antisense	23
CUGGGGCAAAUGAUGAAGAAA	1648	csusggggCfaAfAfUfgaugaagaaaL96	2744	sense	21
UUUCUUCAUCAUUUGCCCCAGAC	1649	usUfsucuUfcAfUfcauuUfgCfcccagsasc	2745	antisense	23
CCAAGGCUGUGUUUGUGGGGA	1650	cscsaaggCfuGfUfGfuuuguggggaL96	2746	sense	21
UCCCCACAAACACAGCCUUGGCG	1651	usCfscccAfcAfAfacacAfgCfcuuggscsg	2747	antisense	23
CAAGGCUGUGUUUGUGGGGAG	1652	csasaggcUfgUfGfUfuuguggggagL96	2748	sense	21
CUCCCCACAAACACAGCCUUGGC	1653	csUfscccCfaCfAfaacaCfaGfccuugsgsc	2749	antisense	23
GGCGCCAAGGCUGUGUUUGUG	1654	gsgscgccAfaGfGfCfuguguuugugL96	2750	sense	21
CACAAACACAGCCUUGGCGCCAA	1655	csAfscaaAfcAfCfagccUfuGfgcgccsasa	2751	antisense	23
UGGCGCCAAGGCUGUGUUUGU	1656	usgsgcgcCfaAfGfGfcuguguuuguL96	2752	sense	21
ACAAACACAGCCUUGGCGCCAAG	1657	asCfsaaaCfaCfAfgccuUfgGfcgccasasg	2753	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
ACUGCCGCCACAACUCAGGAU	1658	ascsugccGfcCfAfCfaacucaggauL96	2754	sense	21
AUCCUGAGUUGUGGCGGCAGUUU	1659	asUfsccuGfaGfUfugugGfcGfgcagususu	2755	antisense	23
CUGCCGCCACAACUCAGGAUG	1660	csusgccgCfcAfCfAfacucaggaugL96	2756	sense	21
CAUCCUGAGUUGUGGCGGCAGUU	1661	csAfsuccUfgAfGfuuguGfgCfggcagsusu	2757	antisense	23
UCAAACUGCCGCCACAACUCA	1662	uscsaaacUfgCfCfGfccacaacucaL96	2758	sense	21
UGAGUUGUGGCGGCAGUUUGAAU	1663	usGfsaguUfgUfGfgcggCfaGfuuugasasu	2759	antisense	23
UUCAAACUGCCGCCACAACUC	1664	ususcaaaCfuGfCfCfgccacaacucL96	2760	sense	21
GAGUUGUGGCGGCAGUUUGAAUC	1665	gsAfsguuGfuGfGfcggcAfgUfuugaasusc	2761	antisense	23
GGGAAGAUAUCAAAUGGCUGA	1666	gsgsgaagAfuAfUfCfaaauggcugaL96	2762	sense	21
UCAGCCAUUUGAUAUCUUCCCAG	1667	usCfsagcCfaUfUfugauAfuCfuucccsasg	2763	antisense	23
GGAAGAUAUCAAAUGGCUGAG	1668	gsgsaagaUfaUfCfAfaauggcugagL96	2764	sense	21
CUCAGCCAUUUGAUAUCUUCCCA	1669	csUfscagCfcAfUfuugaUfaUfcuuccscsa	2765	antisense	23
AGCUGGGAAGAUAUCAAAUGG	1670	asgscuggGfaAfGfAfuaucaaauggL96	2766	sense	21
CCAUUUGAUAUCUUCCCAGCUGA	1671	csCfsauuUfgAfUfaucuUfcCfcagcusgsa	2767	antisense	23
CAGCUGGGAAGAUAUCAAAUG	1672	csasgcugGfgAfAfGfauaucaaaugL96	2768	sense	21
CAUUUGAUAUCUUCCCAGCUGAU	1673	csAfsuuuGfaUfAfucuuCfcCfagcugsasu	2769	antisense	23
AAUCAGUACUUCCAAAGUCUA	1674	asasucagUfaCfUfUfccaaagucuaL96	2770	sense	21
UAGACUUUGGAAGUACUGAUUUA	1675	usAfsgacUfuUfGfgaagUfaCfugauususa	2771	antisense	23
AUCAGUACUUCCAAAGUCUAU	1676	asuscaguAfcUfUfCfcaaagucuauL96	2772	sense	21
AUAGACUUUGGAAGUACUGAUUU	1677	asUfsagaCfuUfUfggaaGfuAfcugaususu	2773	antisense	23
GCUAAAUCAGUACUUCCAAAG	1678	gscsuaaaUfcAfGfUfacuuccaaagL96	2774	sense	21
CUUUGGAAGUACUGAUUUAGCAU	1679	csUfsuugGfaAfGfuacuGfaUfuuagcsasu	2775	antisense	23
UGCUAAAUCAGUACUUCCAAA	1680	usgscuaaAfuCfAfGfuacuuccaaaL96	2776	sense	21
UUUGGAAGUACUGAUUUAGCAUG	1681	usUfsuggAfaGfUfacugAfuUfuagcasusg	2777	antisense	23
UCAGCAUGCCAAUAUGUGUGG	1682	uscsagcaUfgCfCfAfauaugugguggL96	2778	sense	21
CCACACAUAUUGGCAUGCUGACC	1683	csCfsacaCfaUfAfuuggCfaUfgcugascsc	2779	antisense	23
CAGCAUGCCAAUAUGUGUGGG	1684	csasgcauGfcCfAfAfuaugugugggL96	2780	sense	21
CCCACACAUAUUGGCAUGCUGAC	1685	csCfscacAfcAfUfauugGfcAfugcugsasc	2781	antisense	23
AGGGUCAGCAUGCCAAUAUGU	1686	asgsggucAfgCfAfUfgccaauauguL96	2782	sense	21
ACAUAUUGGCAUGCUGACCCUCU	1687	asCfsauaUfuGfGfcaugCfuGfacccuscsu	2783	antisense	23
GAGGGUCAGCAUGCCAAUAUG	1688	gsasggguCfaGfCfAfugccaauaugL96	2784	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
CAUAUUGGCAUGCUGACCCUCUG	1689	csAfsuauUfgGfCfaugcUfgAfcccucsusg	2785	antisense	23
GCAUAUGUGGCUAAAGCAAUA	1690	gscsauauGfuGfGfCfuaaagcaauaL96	2786	sense	21
UAUUGCUUUAGCCACAUAUGCAG	1691	usAfsuugCfuUfUfagccAfcAfuaugcsasg	2787	antisense	23
CAUAUGUGGCUAAAGCAAUAG	1692	csasuaugUfgGfCfUfaaagcaauagL96	2788	sense	21
CUAUUGCUUUAGCCACAUAUGCA	1693	csUfsauuGfcUfUfuagcCfaCfauaugscsa	2789	antisense	23
UGCUGCAUAUGUGGCUAAAGC	1694	usgscugcAfuAfUfGfuggcuaaagcL96	2790	sense	21
GCUUUAGCCACAUAUGCAGCAAG	1695	gsCfsuuuAfgCfCfacauAfuGfcagcasasg	2791	antisense	23
UUGCUGCAUAUGUGGCUAAAG	1696	ususgcugCfaUfAfUfguggcuaaagL96	2792	sense	21
CUUUAGCCACAUAUGCAGCAAGU	1697	csUfsuuaGfcCfAfcauaUfgCfagcaasgsu	2793	antisense	23
AAAUGAUGAAGAAACUUUGGC	1698	asasaugaUfgAfAfGfaaacuuuggcL96	2794	sense	21
GCCAAAGUUUCUUCAUCAUUUGC	1699	gsCfscaaAfgUfUfucuuCfaUfcauuusgsc	2795	antisense	23
AAUGAUGAAGAAACUUUGGCU	1700	asasugauGfaAfGfAfaacuuuggcuL96	2796	sense	21
AGCCAAAGUUUCUUCAUCAUUUG	1701	asGfsccaAfaGfUfuucuUfcAfucauususg	2797	antisense	23
GGGCAAAUGAUGAAGAAACUU	1702	gsgsgcaaAfuGfAfUfgaagaaacuuL96	2798	sense	21
AAGUUUCUUCAUCAUUUGCCCCA	1703	asAfsguuUfcUfUfcaucAfuUfugcccscsa	2799	antisense	23
GGGGCAAAUGAUGAAGAAACU	1704	gsgsggcaAfaUfGfAfugaagaaacuL96	2800	sense	21
AGUUUCUUCAUCAUUUGCCCCAG	1705	asGfsuuuCfuUfCfaucaUfuUfgccccsasg	2801	antisense	23
GAGAUACUAAAGGAAGAAUUC	1706	gsasgauaCfuAfAfAfggaagaauucL96	2802	sense	21
GAAUUCUUCCUUUAGUAUCUCGA	1707	gsAfsauuCfuUfCfcuuuAfgUfaucucsgsa	2803	antisense	23
AGAUACUAAAGGAAGAAUUCC	1708	asgsauacUfaAfAfGfgaagaauuccL96	2804	sense	21
GGAAUUCUUCCUUUAGUAUCUCG	1709	gsGfsaauUfcUfUfccuuUfaGfuaucuscsg	2805	antisense	23
CCUCGAGAUACUAAAGGAAGA	1710	cscsucgaGfaUfAfCfuaaaggaagaL96	2806	sense	21
UCUUCCUUUAGUAUCUCGAGGAC	1711	usCfsuucCfuUfUfaguaUfcUfcgaggsasc	2807	antisense	23
UCCUCGAGAUACUAAAGGAAG	1712	uscscucgAfgAfUfAfcuaaaggaagL96	2808	sense	21
CUUCCUUUAGUAUCUCGAGGACA	1713	csUfsuccUfuUfAfguauCfuCfgaggascsa	2809	antisense	23
ACAACUCAGGAUGAAAAAUUU	1714	ascsaacuCfaGfGfAfugaaaaauuuL96	2810	sense	21
AAAUUUUUCAUCCUGAGUUGUGG	1715	asAfsauuUfuUfCfauccUfgAfguugusgsg	2811	antisense	23
CAACUCAGGAUGAAAAAUUUU	1716	csasacucAfgGfAfUfgaaaaauuuuL96	2812	sense	21
AAAAUUUUUCAUCCUGAGUUGUG	1717	asAfsaauUfuUfUfcaucCfuGfaguugsusg	2813	antisense	23
CGCCACAACUCAGGAUGAAAA	1718	csgsccacAfaCfUfCfaggaugaaaaL96	2814	sense	21
UUUUCAUCCUGAGUUGUGGCGGC	1719	usUfsuucAfuCfCfugagUfuGfuggcgsgsc	2815	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
CCGCCACAACUCAGGAUGAAA	1720	cscsgccaCfaAfCfUfcaggaugaaaL96	2816	sense	21
UUUCAUCCUGAGUUGUGGCGGCA	1721	usUfsucaUfcCfUfgaguUfgUfggcggscsa	2817	antisense	23
AGGGAAGGUGGAAGUCUUCCU	1722	asgsggaaGfgUfGfGfaagucuuccuL96	2818	sense	21
AGGAAGACUUCCACCUUCCCUUC	1723	asGfsgaaGfaCfUfuccaCfcUfucccususc	2819	antisense	23
GGGAAGGUGGAAGUCUUCCUG	1724	gsgsgaagGfuGfGfAfagucuuccugL96	2820	sense	21
CAGGAAGACUUCCACCUUCCCUU	1725	csAfsggaAfgAfCfuuccAfcCfuucccsusu	2821	antisense	23
UGGAAGGGAAGGUGGAAGUCU	1726	usgsgaagGfgAfAfGfguggaagucuL96	2822	sense	21
AGACUUCCACCUUCCCUUCCACA	1727	asGfsacuUfcCfAfccuuCfcCfuuccascsa	2823	antisense	23
GUGGAAGGGAAGGUGGAAGUC	1728	gsusggaaGfgGfAfAfgguggaagucL96	2824	sense	21
GACUUCCACCUUCCCUUCCACAG	1729	gsAfscuuCfcAfCfcuucCfcUfuccacsasg	2825	antisense	23
GGCGAGCUUGCCACUGUGAGA	1730	gsgscgagCfuUfGfCfcacugugagaL96	2826	sense	21
UCUCACAGUGGCAAGCUCGCCGU	1731	usCfsucaCfaGfUfggcaAfgCfucgccsgsu	2827	antisense	23
GCGAGCUUGCCACUGUGAGAG	1732	gscsgagcUfuGfCfCfacugugagagL96	2828	sense	21
CUCUCACAGUGGCAAGCUCGCCG	1733	csUfscucAfcAfGfuggcAfaGfcucgcscsg	2829	antisense	23
GGACGGCGAGCUUGCCACUGU	1734	gsgsacggCfgAfGfCfuugccacuguL96	2830	sense	21
ACAGUGGCAAGCUCGCCGUCCAC	1735	asCfsaguGfgCfAfagcuCfgCfcguccsasc	2831	antisense	23
UGGACGGCGAGCUUGCCACUG	1736	usgsgacgGfcGfAfGfcuugccacugL96	2832	sense	21
CAGUGGCAAGCUCGCCGUCCACA	1737	csAfsgugGfcAfAfgcucGfcCfguccascsa	2833	antisense	23
AUGUGCGUAACAGAUUCAAAC	1738	asusgugcGfuAfAfCfagauucaaacL96	2834	sense	21
GUUUGAAUCUGUUACGCACAUCA	1739	gsUfsuugAfaUfCfuguuAfcGfcacauscsa	2835	antisense	23
UGUGCGUAACAGAUUCAAACU	1740	usgsugcgUfaAfCfAfgauucaaacuL96	2836	sense	21
AGUUUGAAUCUGUUACGCACAUC	1741	asGfsuuuGfaAfUfcuguUfaCfgcacasusc	2837	antisense	23
GAUGAUGUGCGUAACAGAUUC	1742	gsasugauGfuGfCfGfuaacagauucL96	2838	sense	21
GAAUCUGUUACGCACAUCAUCCA	1743	gsAfsaucUfgUfUfacgcAfcAfucaucscsa	2839	antisense	23
GGAUGAUGUGCGUAACAGAUU	1744	gsgsaugaUfgUfGfCfguaacagauuL96	2840	sense	21
AAUCUGUUACGCACAUCAUCCAG	1745	asAfsucuGfuUfAfcgcaCfaUfcauccsasg	2841	antisense	23
GGGUCAGCAUGCCAAUAUGUG	1746	gsgsgucaGfcAfUfGfccaauaugugL96	2842	sense	21
CACAUAUUGGCAUGCUGACCCUC	1747	csAfscauAfuUfGfgcauGfcUfgacccsusc	2843	antisense	23
GGUCAGCAUGCCAAUAUGUGU	1748	gsgsucagCfaUfGfCfcaauauguguL96	2844	sense	21
ACACAUAUUGGCAUGCUGACCCU	1749	asCfsacaUfaUfUfggcaUfgCfugaccscsu	2845	antisense	23
CAGAGGGUCAGCAUGCCAAUA	1750	csasgaggGfuCfAfGfcaugccaauaL96	2846	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
UAUUGGCAUGCUGACCCUCUGUC	1751	usAfsuugGfcAfUfgcugAfcCfcucugsusc	2847	antisense	23
ACAGAGGGUCAGCAUGCCAAU	1752	ascsagagGfgUfCfAfgcaugccaauL96	2848	sense	21
AUUGGCAUGCUGACCCUCUGUCC	1753	asUfsuggCfaUfGfcugaCfcCfucuguscsc	2849	antisense	23
GCUUGAAUGGGAUCUUGGUGU	1754	gscsuugaAfuGfGfGfaucuugguguL96	2850	sense	21
ACACCAAGAUCCCAUUCAAGCCA	1755	asCfsaccAfaGfAfucccAfuUfcaagcscsa	2851	antisense	23
CUUGAAUGGGAUCUUGGUGUC	1756	csusugaaUfgGfGfAfucuuggugucL96	2852	sense	21
GACACCAAGAUCCCAUUCAAGCC	1757	gsAfscacCfaAfGfauccCfaUfucaagscsc	2853	antisense	23
CAUGGCUUGAAUGGGAUCUUG	1758	csasuggcUfuGfAfAfugggaucuugL96	2854	sense	21
CAAGAUCCCAUUCAAGCCAUGUU	1759	csAfsagaUfcCfCfauucAfaGfccaugsusu	2855	antisense	23
ACAUGGCUUGAAUGGGAUCUU	1760	ascsauggCfuUfGfAfaugggaucuuL96	2856	sense	21
AAGAUCCCAUUCAAGCCAUGUUU	1761	asAfsgauCfcCfAfuucaAfgCfcaugususu	2857	antisense	23
UCAAAUGGCUGAGAAGACUGA	1762	uscsaaauGfgCfUfGfagaagacugaL96	2858	sense	21
UCAGUCUUCUCAGCCAUUUGAUA	1763	usCfsaguCfuUfCfucagCfcAfuuugasusa	2859	antisense	23
CAAAUGGCUGAGAAGACUGAC	1764	csasaaugGfcUfGfAfgaagacugacL96	2860	sense	21
GUCAGUCUUCUCAGCCAUUUGAU	1765	gsUfscagUfcUfUfcucaGfcCfauuugsasu	2861	antisense	23
GAUAUCAAAUGGCUGAGAAGA	1766	gsasuaucAfaAfUfGfgcugagaagaL96	2862	sense	21
UCUUCUCAGCCAUUUGAUAUCUU	1767	usCfsuucUfcAfGfccauUfuGfauaucsusu	2863	antisense	23
AGAUAUCAAAUGGCUGAGAAG	1768	asgsauauCfaAfAfUfggcugagaagL96	2864	sense	21
CUUCUCAGCCAUUUGAUAUCUUC	1769	csUfsucuCfaGfCfcauuUfgAfuaucususc	2865	antisense	23
GAAAGUCAUCGACAAGACAUU	1770	gsasaaguCfaUfCfGfacaagacauuL96	2866	sense	21
AAUGUCUUGUCGAUGACUUUCAC	1771	asAfsuguCfuUfGfucgaUfgAfcuuucsasc	2867	antisense	23
AAAGUCAUCGACAAGACAUUG	1772	asasagucAfuCfGfAfcaagacauugL96	2868	sense	21
CAAUGUCUUGUCGAUGACUUUCA	1773	csAfsaugUfcUfUfgucgAfuGfacuuuscsa	2869	antisense	23
AUGUGAAAGUCAUCGACAAGA	1774	asusgugaAfaGfUfCfaucgacaagaL96	2870	sense	21
UCUUGUCGAUGACUUUCACAUUC	1775	usCfsuugUfcGfAfugacUfuUfcacaususc	2871	antisense	23
AAUGUGAAAGUCAUCGACAAG	1776	asasugugAfaAfGfUfcaucgacaagL96	2872	sense	21
CUUGUCGAUGACUUUCACAUUCU	1777	csUfsuguCfgAfUfgacuUfuCfacauuscsu	2873	antisense	23
GGCUAAUUUGUAUCAAUGAUU	1778	gsgscuaaUfuUfGfUfaucaaugauuL96	2874	sense	21
AAUCAUUGAUACAAAUUAGCCGG	1779	asAfsucaUfuGfAfuacaAfaUfuagccsgsg	2875	antisense	23
GCUAAUUUGUAUCAAUGAUUA	1780	gscsuaauUfuGfUfAfucaaugauuaL96	2876	sense	21
UAAUCAUUGAUACAAAUUAGCCG	1781	usAfsaucAfuUfGfauacAfaAfuuagcscsg	2877	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
CCCCGGCUAAUUUGUAUCAAU	1782	cscsccggCfuAfAfUfuuguaucaauL96	2878	sense	21
AUUGAUACAAAUUAGCCGGGGGA	1783	asUfsugaUfaCfAfaauuAfgCfcgggggsgsa	2879	antisense	23
CCCCCGGCUAAUUUGUAUCAA	1784	cscscccgGfcUfAfAfuuuguaucaaL96	2880	sense	21
UUGAUACAAAUUAGCCGGGGGAG	1785	usUfsgauAfcAfAfauuaGfcCfgggggsasg	2881	antisense	23
UGUCGACUUCUGUUUUAGGAC	1786	usgsucgaCfuUfCfUfguuuuaggacL96	2882	sense	21
GUCCUAAAACAGAAGUCGACAGA	1787	gsUfsccuAfaAfAfcagaAfgUfcgacasgsa	2883	antisense	23
GUCGACUUCUGUUUUAGGACA	1788	gsuscgacUfuCfUfGfuuuuaggacaL96	2884	sense	21
UGUCCUAAAACAGAAGUCGACAG	1789	usGfsuccUfaAfAfacagAfaGfucgacsasg	2885	antisense	23
GAUCUGUCGACUUCUGUUUUA	1790	gsasucugUfcGfAfCfuucuguuuuaL96	2886	sense	21
UAAAACAGAAGUCGACAGAUCUG	1791	usAfsaaaCfaGfAfagucGfaCfagaucsusg	2887	antisense	23
AGAUCUGUCGACUUCUGUUUU	1792	asgsaucuGfuCfGfAfcuucuguuuuL96	2888	sense	21
AAAACAGAAGUCGACAGAUCUGU	1793	asAfsaacAfgAfAfgucgAfcAfgaucusgsu	2889	antisense	23
CCGAGAAGUCACCAAGAAGCU	1794	cscsgagaAfgUfCfAfccaagaagcuL96	2890	sense	21
AGCUUCUUGGUGACUUCUCGGUC	1795	asGfscuuCfuUfGfgugaCfuUfcucggsusc	2891	antisense	23
CGAGAAGUCACCAAGAAGCUA	1796	csgsagaaGfuCfAfCfcaagaagcuaL96	2892	sense	21
UAGCUUCUUGGUGACUUCUCGGU	1797	usAfsgcuUfcUfUfGfggugAfcUfucucgsgsu	2893	antisense	23
AGGACCGAGAAGUCACCAAGA	1798	asgsgaccGfaGfAfAfgucaccaagaL96	2894	sense	21
UCUUGGUGACUUCUCGGUCCUUG	1799	usCfsuugGfuGfAfcuucUfcGfguccususg	2895	antisense	23
AAGGACCGAGAAGUCACCAAG	1800	asasggacCfgAfGfAfagucaccaagL96	2896	sense	21
CUUGGUGACUUCUCGGUCCUUGU	1801	csUfsuggUfgAfCfuucuCfgGfuccuusgsu	2897	antisense	23
AAACAUGGCUUGAAUGGGAUC	1802	asasacauGfgCfUfUfgaaugggaucL96	2898	sense	21
GAUCCCAUUCAAGCCAUGUUUAA	1803	gsAfsuccCfaUfUfcaagCfcAfuguuusasa	2899	antisense	23
AACAUGGCUUGAAUGGGAUCU	1804	asascaugGfcUfUfGfaaugggaucuL96	2900	sense	21
AGAUCCCAUUCAAGCCAUGUUUA	1805	asGfsaucCfcAfUfucaaGfcCfauguususa	2901	antisense	23
UGUUAAACAUGGCUUGAAUGG	1806	usgsuuaaAfcAfUfGfgcuugaauggL96	2902	sense	21
CCAUUCAAGCCAUGUUUAACAGC	1807	csCfsauuCfaAfGfccauGfuUfuaacasgsc	2903	antisense	23
CUGUUAAACAUGGCUUGAAUG	1808	csusguuaAfaCfAfUfggcuugaaugL96	2904	sense	21
CAUUCAAGCCAUGUUUAACAGCC	1809	csAfsuucAfaGfCfcaugUfuUfaacagscsc	2905	antisense	23
GACUUGCUGCAUAUGUGGCUA	1810	gsascuugCfuGfCfAfuauguggcuaL96	2906	sense	21
UAGCCACAUAUGCAGCAAGUCCA	1811	usAfsgccAfcAfUfaugcAfgCfaagucscsa	2907	antisense	23
ACUUGCUGCAUAUGUGGCUAA	1812	ascsuugcUfgCfAfUfauguggcuaaL96	2908	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
UUAGCCACAUAUGCAGCAAGUCC	1813	usUfsagcCfaCfAfuaugCfaGfcaaguscsc	2909	antisense	23
AGUGGACUUGCUGCAUAUGUG	1814	asgsuggaCfuUfGfCfugcauaugugL96	2910	sense	21
CACAUAUGCAGCAAGUCCACUGU	1815	csAfscauAfuGfCfagcaAfgUfccacusgsu	2911	antisense	23
CAGUGGACUUGCUGCAUAUGU	1816	csasguggAfcUfUfGfcugcauauguL96	2912	sense	21
ACAUAUGCAGCAAGUCCACUGUC	1817	asCfsauaUfgCfAfgcaaGfuCfcacugsusc	2913	antisense	23
UAAAUCAGUACUUCCAAAGUC	1818	usasaaucAfgUfAfCfuuccaaagucL96	2914	sense	21
GACUUUGGAAGUACUGAUUUAGC	1819	gsAfscuuUfgGfAfaguaCfuGfauuuasgsc	2915	antisense	23
AAAUCAGUACUUCCAAAGUCU	1820	asasaucaGfuAfCfUfuccaaagucuL96	2916	sense	21
AGACUUUGGAAGUACUGAUUUAG	1821	asGfsacuUfuGfGfaaguAfcUfgauuusasg	2917	antisense	23
AUGCUAAAUCAGUACUUCCAA	1822	asusgcuaAfaUfCfAfguacuuccaaL96	2918	sense	21
UUGGAAGUACUGAUUUAGCAUGU	1823	usUfsggaAfgUfAfcugaUfuUfagcausgsu	2919	antisense	23
CAUGCUAAAUCAGUACUUCCA	1824	csasugcuAfaAfUfCfaguacuuccaL96	2920	sense	21
UGGAAGUACUGAUUUAGCAUGUU	1825	usGfsgaaGfuAfCfugauUfuAfgcaugsusu	2921	antisense	23
UCCUCAAUUGAAGAAGUGGCG	1826	uscscucaAfuUfGfAfagaaguggcgL96	2922	sense	21
CGCCACUUCUUCAAUUGAGGAGG	1827	csGfsccaCfuUfCfuucaAfuUfgaggasgsg	2923	antisense	23
CCUCAAUUGAAGAAGUGGCGG	1828	cscsucaaUfuGfAfAfgaaguggcggL96	2924	sense	21
CCGCCACUUCUUCAAUUGAGGAG	1829	csCfsgccAfcUfUfcuucAfaUfugaggsasg	2925	antisense	23
CACCUCCUCAAUUGAAGAAGU	1830	csasccucCfuCfAfAfuugaagaaguL96	2926	sense	21
ACUUCUUCAAUUGAGGAGGUGGC	1831	asCfsuucUfuCfAfauugAfgGfaggugsgsc	2927	antisense	23
CCACCUCCUCAAUUGAAGAAG	1832	cscsaccuCfcUfCfAfauugaagaagL96	2928	sense	21
CUUCUUCAAUUGAGGAGGUGGCC	1833	csUfsucuUfcAfAfuugaGfgAfgguggscsc	2929	antisense	23
CAAGAUGUCCUCGAGAUACUA	1834	csasagauGfuCfCfUfcgagauacuaL96	2930	sense	21
UAGUAUCUCGAGGACAUCUUGAA	1835	usAfsguaUfcUfCfgaggAfcAfucuugsasa	2931	antisense	23
AAGAUGUCCUCGAGAUACUAA	1836	asasgaugUfcCfUfCfgagauacuaaL96	2932	sense	21
UUAGUAUCUCGAGGACAUCUUGA	1837	usUfsaguAfuCfUfcgagGfaCfaucuusgsa	2933	antisense	23
UGUUCAAGAUGUCCUCGAGAU	1838	usgsuucaAfgAfUfGfuccucgagauL96	2934	sense	21
AUCUCGAGGACAUCUUGAACACC	1839	asUfscucGfaGfGfacauCfuUfgaacascsc	2935	antisense	23
GUGUUCAAGAUGUCCUCGAGA	1840	gsusguucAfaGfAfUfguccucgagaL96	2936	sense	21
UCUCGAGGACAUCUUGAACACCU	1841	usCfsucgAfgGfAfcaucUfuGfaacacscsu	2937	antisense	23
ACAUGCUAAAUCAGUACUUCC	1842	ascsaugcUfaAfAfUfcaguacuuccL96	2938	sense	21
GGAAGUACUGAUUUAGCAUGUUG	1843	gsGfsaagUfaCfUfgauuUfaGfcaugususg	2939	antisense	23

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
CAUGCUAAAUCAGUACUUCCA	1844	csasugcuAfaAfUfCfaguacuuccaL96	2940	sense	21
UGGAAGUACUGAUUUAGCAUGUU	1845	usGfsgaaGfuAfCfugauUfuAfgcaugsusu	2941	antisense	23
AACAACAUGCUAAAUCAGUAC	1846	asascaacAfuGfCfUfaaaucaguacL96	2942	sense	21
GUACUGAUUUAGCAUGUUGUUCA	1847	gsUfsacuGfaUfUfuagcAfuGfuuguuscsa	2943	antisense	23
GAACAACAUGCUAAAUCAGUA	1848	gsasacaaCfaUfGfCfuaaaucaguaL96	2944	sense	21
UACUGAUUUAGCAUGUUGUUCAU	1849	usAfscugAfuUfUfagcaUfgUfuguucsasu	2945	antisense	23
GAAAGGCACUGAUGUUCUGAA	1850	gsasaaggCfaCfUfGfauguucugaaL96	2946	sense	21
UUCAGAACAUCAGUGCCUUUCCG	1851	usUfscagAfaCfAfucagUfgCfcuuucscsg	2947	antisense	23
AAAGGCACUGAUGUUCUGAAA	1852	asasaggcAfcUfGfAfuguucugaaaL96	2948	sense	21
UUUCAGAACAUCAGUGCCUUUCC	1853	usUfsucaGfaAfCfaucaGfuGfccuuuscsc	2949	antisense	23
UGCGGAAAGGCACUGAUGUUC	1854	usgscggaAfaGfGfCfacugauguucL96	2950	sense	21
GAACAUCAGUGCCUUUCCGCACA	1855	gsAfsacaUfcAfGfugccUfuUfccgcascsa	2951	antisense	23
GUGCGGAAAGGCACUGAUGUU	1856	gsusgcggAfaAfGfGfcacugauguuL96	2952	sense	21
AACAUCAGUGCCUUUCCGCACAC	1857	asAfscauCfaGfUfgccuUfuCfcgcacsasc	2953	antisense	23
GUCAGCAUGCCAAUAUGUGUG	1858	gsuscagcAfuGfCfCfaauaugugugL96	2954	sense	21
CACACAUAUUGGCAUGCUGACCC	1859	csAfscacAfuAfUfuggcAfuGfcugacscsc	2955	antisense	23
UCAGCAUGCCAAUAUGUGUGG	1860	uscsagcaUfgCfCfAfauaugugguggL96	2956	sense	21
CCACACAUAUUGGCAUGCUGACC	1861	csCfsacaCfaUfAfuuggCfaUfgcugascsc	2957	antisense	23
GAGGGUCAGCAUGCCAAUAUG	1862	gsasggguCfaGfCfAfugccaauaugL96	2958	sense	21
CAUAUUGGCAUGCUGACCCUCUG	1863	csAfsuauUfgGfCfaugcUfgAfcccucsusg	2959	antisense	23
AGAGGGUCAGCAUGCCAAUAU	1864	asgsagggUfcAfGfCfaugccaauauL96	2960	sense	21
AUAUUGGCAUGCUGACCCUCUGU	1865	asUfsauuGfgCfAfugcuGfaCfccucusgsu	2961	antisense	23
GAUGCUCCGGAAUGUUGCUGA	1866	gsasugcuCfcGfGfAfauguugcugaL96	2962	sense	21
UCAGCAACAUUCCGGAGCAUCCU	1867	usCfsagcAfaCfAfuuccGfgAfgcaucscsu	2963	antisense	23
AUGCUCCGGAAUGUUGCUGAA	1868	asusgcucCfgGfAfAfuguugcugaaL96	2964	sense	21
UUCAGCAACAUUCCGGAGCAUCC	1869	usUfscagCfaAfCfauucCfgGfagcauscsc	2965	antisense	23
CAAGGAUGCUCCGGAAUGUUG	1870	csasaggaUfgCfUfCfcggaauguugL96	2966	sense	21
CAACAUUCCGGAGCAUCCUUGGA	1871	csAfsacaUfuCfCfggagCfaUfccuugsgsa	2967	antisense	23
CCAAGGAUGCUCCGGAAUGUU	1872	cscsaaggAfuGfCfUfccggaauguuL96	2968	sense	21
AACAUUCCGGAGCAUCCUUGGAU	1873	asAfscauUfcCfGfgagcAfuCfcuuggsasu	2969	antisense	23
GCGUAACAGAUUCAAACUGCC	1874	gscsguaaCfaGfAfUfucaaacugccL96	2970	sense	21

Unmodified sequence 5' to 3'	SEQ ID NO:	Modified sequence 5' to 3'	SEQ ID NO:	Strand	Length
GGCAGUUUGAAUCUGUUACGCAC	1875	gsGfscagUfuUfGfaaucUfgUfuacgcsasc	2971	antisense	23
CGUAACAGAUUCAAACUGCCG	1876	csgsuaacAfgAfUfUfcaaacugccgL96	2972	sense	21
CGGCAGUUUGAAUCUGUUACGCA	1877	csGfsgcaGfuUfUfgaauCfuGfuuacgscsa	2973	antisense	23
AUGUGCGUAACAGAUUCAAAC	1878	asusgugcGfuAfAfCfagauucaaacL96	2974	sense	21
GUUUGAAUCUGUUACGCACAUCA	1879	gsUfsuugAfaUfCfuguuAfcGfcacauscsa	2975	antisense	23
GAUGUGCGUAACAGAUUCAAA	1880	gsasugugCfgUfAfAfcagauucaaaL96	2976	sense	21
UUUGAAUCUGUUACGCACAUCAU	1881	usUfsugaAfuCfUfguuaCfgCfacaucsasu	2977	antisense	23
AGAGAAGAUGGGCUACAAGGC	1882	asgsagaaGfaUfGfGfgcuacaaggcL96	2978	sense	21
GCCUUGUAGCCCAUCUUCUCUGC	1883	gsCfscuuGfuAfGfcccaUfcUfucucusgsc	2979	antisense	23
GAGAAGAUGGGCUACAAGGCC	1884	gsasgaagAfuGfGfGfcuacaaggccL96	2980	sense	21
GGCCUUGUAGCCCAUCUUCUCUG	1885	gsGfsccuUfgUfAfgcccAfuCfuucucsusg	2981	antisense	23
AGGCAGAGAAGAUGGGCUACA	1886	asgsgcagAfgAfAfGfaugggcuacaL96	2982	sense	21
UGUAGCCCAUCUUCUCUGCCUGC	1887	usGfsuagCfcCfAfucuuCfuCfugccusgsc	2983	antisense	23
CAGGCAGAGAAGAUGGGCUAC	1888	csasggcaGfaGfAfAfgaugggcuacL96	2984	sense	21
GUAGCCCAUCUUCUCUGCCUGCC	1889	gsUfsagcCfcAfUfcuucUfcUfgccugscsc	2985	antisense	23

Table 13. Modified antisense polynucleotides targeting HAO1.

Target	Oligo Name	Sequence 5'-3'	SEQ ID NO:
HAO1	A-133284.1	gsgsgsasgs(5MdC)sdAsdTsdTsdTsdTs(5MdC)sdAs(5MdC)sdAsgsgsususa	4155
HAO1	A-133285.1	asasususasdGs(5MdC)s(5MdC)sdGsdGsdGsdGsdGsdAsdGscsasususu	4156
HAO1	A-133286.1	asuscsasusdTsdGsdAsdTsdAs(5MdC)sdAsdAsdAsdTsusasgscsc	4157
HAO1	A-133287.1	gsususgsusdTs(5MdC)sdAsdTsdAsdAsdTs(5MdC)sdAsdTsusgsasusa	4158
HAO1	A-133288.1	gsasususususdAsdGs(5MdC)sdAsdTsdGsdTsdTsdGsdTsuscsasusa	4159
HAO1	A-133289.1	ususgsgsasdAsdGsdTsdAs(5MdC)sdTsdGsdAsdTsdTsusasgscsa	4160
HAO1	A-133290.1	csasusasusdAsdTsdAsdGsdAs(5MdC)sdTsdTsdTsdGsgsasasgsu	4161
HAO1	A-133291.1	csusgsusasdAsdTsdAsdGsdTs(5MdC)sdAsdTsdAsdTsasusasgsa	4162
HAO1	A-133292.1	ususgscscs(5MdC)s(5MdC)sdAsdGsdAs(5MdC)s(5MdC)sdTsdGsdTsasasusasg	4163

Target	Oligo Name	Sequence 5'-3'	SEQ ID NO:
HAO1	A-133293.1	ususcsusus(5MdC)sdAsdTs(5MdC)sdAsdTsdTsdTsdGs(5MdC)scscscsasg	4164
HAO1	A-133294.1	usasuscsasdGs(5MdC)s(5MdC)sdAsdAsdAsdGsdTsdTsdTscsususcsa	4165
HAO1	A-133295.1	gscsusgscsdAsdAsdTsdAsdTsdTsdAsdTs(5MdC)sdAsgscscsasa	4166
HAO1	A-133296.1	asuscsusgsdGsdAsdAsdAsdAsdTsdGs(5MdC)sdTsdGscsasasusa	4167
HAO1	A-133297.1	gsasusascsdAsdGs(5MdC)sdTsdTs(5MdC)s(5MdC)sdAsdTs(5MdC)susgsgsasa	4168
HAO1	A-133298.1	gsasgscsasdTs(5MdC)s(5MdC)sdTsdTsdGsdGsdAsdTsdAscsasgscsu	4169
HAO1	A-133299.1	csasascsasdTsdTs(5MdC)s(5MdC)sdGsdGsdAsdGs(5MdC)sdAsuscscsusu	4170
HAO1	A-133300.1	gsasuscsusdGsdTsdTsdTs(5MdC)sdAsdGs(5MdC)sdAsdAscsasususc	4171
HAO1	A-133301.1	asgsasasgsdTs(5MdC)sdGsdAs(5MdC)sdAsdGsdAsdTs(5MdC)susgsususu	4172
HAO1	A-133302.1	usgsuscscsdTsdAsdAsdAsdAs(5MdC)sdAsdGsdAsdAsgsuscsgsa	4173
HAO1	A-133303.1	usgscsusgsdAs(5MdC)s(5MdC)s(5MdC)sdTs(5MdC)sdTsdGsdTs(5MdC)scsusasasa	4174
HAO1	A-133304.1	csasusasusdTsdGsdGs(5MdC)sdAsdTsdGs(5MdC)sdTsdGsascscscsu	4175
HAO1	A-133305.1	asgscscscs(5MdC)s(5MdC)sdAs(5MdC)sdAs(5MdC)sdAsdTsdAsdTsusgsgscsa	4176
HAO1	A-133306.1	csusgscsasdTsdGsdGs(5MdC)s(5MdC)sdGsdTsdAsdGs(5MdC)scscscscsa	4177
HAO1	A-133307.1	gsasgscscsdAsdTsdGs(5MdC)sdGs(5MdC)sdTsdGs(5MdC)sdAsusgsgscsc	4178
HAO1	A-133308.1	gscscsgsus(5MdC)s(5MdC)sdAs(5MdC)sdAsdTsdGsdAsdGs(5MdC)scsasusgsc	4179
HAO1	A-133309.1	asgsusgsgs(5MdC)sdAsdAsdGs(5MdC)sdTs(5MdC)sdGs(5MdC)s(5MdC)sgsuscscsa	4180
HAO1	A-133310.1	ascsasgsgs(5MdC)sdTs(5MdC)sdTs(5MdC)sdAs(5MdC)sdAsdGsdTsgsgscsasa	4181
HAO1	A-133311.1	csasgsgsgsdAs(5MdC)sdTsdGsdAs(5MdC)sdAsdGsdGs(5MdC)suscsuscsa	4182
HAO1	A-133312.1	asusgscscs(5MdC)sdGsdTsdTs(5MdC)s(5MdC)s(5MdC)sdAsdGsdGsgsascsusg	4183
HAO1	A-133313.1	gsasascsus(5MdC)sdAsdAs(5MdC)sdAsdTs(5MdC)sdAsdTsdGscscscsgsu	4184
HAO1	A-133314.1	gsasgsgsusdGsdGs(5MdC)s(5MdC)s(5MdC)sdAsdGsdGsdAsdAscsuscsasa	4185
HAO1	A-133315.1	uscsasasusdTsdGsdAsdGsdGsdAsdGsdGsdTsdGsgscscscsa	4186
HAO1	A-133316.1	cscsgscscsdAs(5MdC)sdTsdTs(5MdC)sdTsdTs(5MdC)sdAsdAsususgsasg	4187
HAO1	A-133317.1	csasgsgsas(5MdC)s(5MdC)sdAsdGs(5MdC)sdTsdTs(5MdC)s(5MdC)sdGscscsascsu	4188
HAO1	A-133318.1	ascsgsasasdGsdTsdGs(5MdC)s(5MdC)sdTs(5MdC)sdAsdGsdGsascscsasg	4189

Target	Oligo Name	Sequence 5'-3'	SEQ ID NO:
HAO1	A-133319.1	csasgsususdGs(5MdC)sdAsdGs(5MdC)s(5MdC)sdAsdAs(5MdC)sdGsasasgsusg	4190
HAO1	A-133320.1	usgsusasgsdAsdTsdAsdTsdAs(5MdC)sdAsdGsdTsdTsgscsasgsc	4191
HAO1	A-133321.1	uscsuscsgsdGsdTs(5MdC)s(5MdC)sdTsdTsdGsdTsdAsdGsasusasusa	4192
HAO1	A-133322.1	ususcsususdGsdGsdTsdGsdAs(5MdC)sdTsdTs(5MdC)sdTscsgsgsusc	4193
HAO1	A-133323.1	cscsgscsas(5MdC)sdTsdAsdGs(5MdC)sdTsdTs(5MdC)sdTsdTsgsgsusgsa	4194
HAO1	A-133324.1	csususcsus(5MdC)sdTsdGs(5MdC)s(5MdC)sdTsdGs(5MdC)s(5MdC)sdGscsascsusa	4195
HAO1	A-133325.1	csususgsusdAsdGs(5MdC)s(5MdC)s(5MdC)sdAsdTs(5MdC)sdTsdTscsuscsusg	4196
HAO1	A-133326.1	asasasusasdTsdGsdGs(5MdC)s(5MdC)sdTsdTsdGsdTsdAsgscscscsa	4197
HAO1	A-133327.1	usgsuscscsdAs(5MdC)sdTsdGsdTs(5MdC)sdAs(5MdC)sdAsdAsasusasusg	4198
HAO1	A-133328.1	csasgsgsusdAsdAsdGsdGsdTsdGsdTsdGsdTs(5MdC)scsascsusg	4199
HAO1	A-133329.1	gsascsgsgsdTsdTsdGs(5MdC)s(5MdC)s(5MdC)sdAsdGsdGsdTsasasgsgsu	4200
HAO1	A-133330.1	csascsasus(5MdC)sdAsdTs(5MdC)s(5MdC)sdAsdGsdAs(5MdC)sdGsgsususgsc	4201
HAO1	A-133331.1	asasuscsusdGsdTsdTsdAs(5MdC)sdGs(5MdC)sdAs(5MdC)sdAsuscsasusc	4202
HAO1	A-133332.1	gscsgsgscsdAsdGsdTsdTsdTsdGsdAsdAsdTs(5MdC)susgsususa	4203
HAO1	A-133333.1	csusgsasgsdTsdTsdGsdTsdGsdGs(5MdC)sdGsdGs(5MdC)sasgsususu	4204
HAO1	A-133334.1	asasasasusdTsdTsdTsdTs(5MdC)sdAsdTs(5MdC)s(5MdC)sdTsgsasgsusu	4205
HAO1	A-133335.1	usascsusgsdGsdTsdTsdTs(5MdC)sdAsdAsdAsdAsdTsususususc	4206
HAO1	A-133336.1	asasasusgsdAsdTsdAsdAsdAsdGsdTsdAs(5MdC)sdTsgsgsususu	4207
HAO1	A-133337.1	cscsuscsasdGsdGsdAsdGsdAsdAsdAsdAsdTsdGsasusasasa	4208
HAO1	A-133338.1	uscscsasasdAsdAsdTsdTsdTsdTs(5MdC)s(5MdC)sdTs(5MdC)sasgsgsasg	4209
HAO1	A-133339.1	gsuscscsas(5MdC)sdTsdGsdTs(5MdC)sdGsdTs(5MdC)sdTs(5MdC)scsasasasa	4210
HAO1	A-133340.1	asusasusgs(5MdC)sdAsdGs(5MdC)sdAsdAsdGsdTs(5MdC)s(5MdC)sascsusgsu	4211
HAO1	A-133341.1	ususususasgs(5MdC)s(5MdC)sdAs(5MdC)sdAsdTsdAsdTsdGs(5MdC)sasgscsasa	4212
HAO1	A-133342.1	usgsgsgsus(5MdC)sdTsdAsdTsdTsdGs(5MdC)sdTsdTsdTsasgscscsa	4213
HAO1	A-133343.1	asgscsusgsdAsdTsdAsdGsdAsdTsdGsdGsdGsdTscsusasusu	4214
HAO1	A-133344.1	gsasusasus(5MdC)sdTsdTs(5MdC)s(5MdC)s(5MdC)sdAsdGs(5MdC)sdTsgsasusasg	4215

Target	Oligo Name	Sequence 5'-3'	SEQ ID NO:
HAO1	A-133345.1	csuscsasgs(5MdC)s(5MdC)sdAsdTsdTsdTsdGsdAsdTsdAsuscsususc	4216
HAO1	A-133346.1	gsasusgsus(5MdC)sdAsdGsdTs(5MdC)sdTsdTs(5MdC)sdTs(5MdC)sasgscscsa	4217
HAO1	A-133347.1	csasasususdGsdGs(5MdC)sdAsdAsdTsdGsdAsdTsdGsuscsasgsu	4218
HAO1	A-133348.1	cscscsususdTsdGs(5MdC)sdAsdAs(5MdC)sdAsdAsdTsdTsgsgscsasa	4219
HAO1	A-133349.1	csuscsuscsdAsdAsdAsdAsdTsdGs(5MdC)s(5MdC)s(5MdC)sdTsususgscsa	4220
HAO1	A-133350.1	gsgscsasus(5MdC)sdAsdTs(5MdC)sdAs(5MdC)s(5MdC)sdTs(5MdC)sdTscsasasasa	4221
HAO1	A-133351.1	asascsasgs(5MdC)s(5MdC)sdTs(5MdC)s(5MdC)s(5MdC)sdTsdGsdGs(5MdC)sasuscsasu	4222
HAO1	A-133352.1	asasgscscsdAsdTsdGsdTsdTsdTsdAsdAs(5MdC)sdAsgscscsusc	4223
HAO1	A-133353.1	asasgsasus(5MdC)s(5MdC)s(5MdC)sdAsdTsdTs(5MdC)sdAsdAsdGscscsasusg	4224
HAO1	A-133354.1	ususcsgsas(5MdC)sdAs(5MdC)s(5MdC)sdAsdAsdGsdAsdTs(5MdC)scscsasusu	4225
HAO1	A-133355.1	uscsgsasgs(5MdC)s(5MdC)s(5MdC)s(5MdC)sdAsdTsdGsdAsdTsdTscsgsascsa	4226
HAO1	A-133356.1	asuscsgsasdGsdTsdTsdGsdTs(5MdC)sdGsdAsdGs(5MdC)scscscsasu	4227
HAO1	A-133357.1	gsgscsusgsdGs(5MdC)sdAs(5MdC)s(5MdC)s(5MdC)s(5MdC)sdAsdTs(5MdC)sgsasgsusu	4228
HAO1	A-133358.1	asascsasus(5MdC)sdAsdAsdTsdAsdGsdTsdGsdGs(5MdC)susgsgscsa	4229
HAO1	A-133359.1	asusususcsdTsdGsdGs(5MdC)sdAsdGsdAsdAs(5MdC)sdAsuscsasasu	4230
HAO1	A-133360.1	asgscscsus(5MdC)s(5MdC)sdAs(5MdC)sdAsdAsdTsdTsdTs(5MdC)susgsgscsa	4231
HAO1	A-133361.1	csususcscs(5MdC)sdTsdTs(5MdC)s(5MdC)sdAs(5MdC)sdAsdGs(5MdC)scsuscscsa	4232
HAO1	A-133362.1	asasgsascsdTsdTs(5MdC)s(5MdC)sdAs(5MdC)s(5MdC)sdTsdTs(5MdC)scscsususc	4233
HAO1	A-133363.1	cscsgsuscs(5MdC)sdAsdGsdGsdAsdAsdGsdAs(5MdC)sdTsuscscsasc	4234
HAO1	A-133364.1	uscscsgscsdAs(5MdC)sdAs(5MdC)s(5MdC)s(5MdC)s(5MdC)s(5MdC)sdGsdTscscsasgsg	4235
HAO1	A-133365.1	csasuscsasdGsdTsdGs(5MdC)s(5MdC)sdTsdTsdTs(5MdC)s(5MdC)sgscsascsa	4236
HAO1	A-133366.1	asgscsususdTs(5MdC)sdAsdGsdAsdAs(5MdC)sdAsdTs(5MdC)sasgsusgsc	4237
HAO1	A-133367.1	csasasgsasdGs(5MdC)s(5MdC)sdAsdGsdAsdGs(5MdC)sdTsdTsuscsasgsa	4238
HAO1	A-133368.1	ascsasgscs(5MdC)sdTsdTsdGsdGs(5MdC)sdGs(5MdC)s(5MdC)sdAsasgsasgsc	4239
HAO1	A-133369.1	uscscscscsdAs(5MdC)sdAsdAsdAs(5MdC)sdAs(5MdC)sdAsdGscscsususg	4240
HAO1	A-133370.1	ascsgsasusdTsdGsdGsdTs(5MdC)sdTs(5MdC)s(5MdC)s(5MdC)s(5MdC)sascsasasa	4241

Target	Oligo Name	Sequence 5'-3'	SEQ ID NO:
HAO1	A-133371.1	usasasgscs(5MdC)s(5MdC)s(5MdC)sdAsdAsdAs(5MdC)sdGsdAsdTsusgsgsusc	4242
HAO1	A-133372.1	cscscsusgsdGsdAsdAsdAsdGs(5MdC)sdTsdAsdAsdGscscscscsa	4243
HAO1	A-133373.1	csascscsusdTsdTs(5MdC)sdTs(5MdC)s(5MdC)s(5MdC)s(5MdC)s(5MdC)sdTsgsgsasasa	4244
HAO1	A-133374.1	gsascsasus(5MdC)sdTsdTsdGsdAsdAs(5MdC)sdAs(5MdC)s(5MdC)susususcsu	4245
HAO1	A-133375.1	usasgsusasdTs(5MdC)sdTs(5MdC)sdGsdAsdGsdGsdAs(5MdC)sasuscsusu	4246
HAO1	A-133376.1	gsasasusus(5MdC)sdTsdTs(5MdC)s(5MdC)sdTsdTsdTsdAsdGsusasuscsu	4247
HAO1	A-133377.1	gsgscscsasdAs(5MdC)s(5MdC)sdGsdGsdAsdAsdTsdTs(5MdC)sususcscsu	4248
HAO1	A-133378.1	csuscsasgsdAsdGs(5MdC)s(5MdC)sdAsdTsdGsdGs(5MdC)s(5MdC)sasascscsg	4249
HAO1	A-133379.1	asususcsusdGsdGs(5MdC)sdAs(5MdC)s(5MdC)s(5MdC)sdAs(5MdC)sdTscsasgsasg	4250
HAO1	A-133380.1	asusgsascsdTsdTsdTs(5MdC)sdAs(5MdC)sdAsdTsdTs(5MdC)susgsgscsa	4251
HAO1	A-133381.1	gsuscsususdGsdTs(5MdC)sdGsdAsdTsdGsdAs(5MdC)sdTsususcsasc	4252
HAO1	A-133382.1	usususcscsdTs(5MdC)sdAs(5MdC)s(5MdC)sdAsdAsdTsdGsdTscsususgsu	4253
HAO1	A-133383.1	csasasasgsdGsdAsdTsdTsdTsdTs(5MdC)s(5MdC)sdTscsascscsa	4254
HAO1	A-133384.1	ususgsgsasdAsdAs(5MdC)sdGsdGs(5MdC)s(5MdC)sdAsdAsdAsgsgsasusu	4255
HAO1	A-133385.1	gscsascsusdGsdTs(5MdC)sdAsdGsdAsdTs(5MdC)sdTsdTsgsgsasasa	4256
HAO1	A-133386.1	asasasusasdTsdTsdGsdTsdGs(5MdC)sdAs(5MdC)sdTsdGsuscsasgsa	4257
HAO1	A-133387.1	usascsasgsdAsdTsdGsdGsdGsdAsdAsdAsdAsdTsasususgsu	4258
HAO1	A-133388.1	usgsasasasdAsdAsdAsdAsdAsdTsdAsdAsdTsdAscsasgsasu	4259
HAO1	A-133389.1	usasasusas(5MdC)sdAsdTsdGs(5MdC)sdTsdGsdAsdAsdAsasasasasa	4260
HAO1	A-133390.1	csuscsususdTsdGsdTs(5MdC)sdAsdAsdGsdTsdAsdAsusascsasu	4261
HAO1	A-133391.1	gscsascsasdGsdTsdGsdTs(5MdC)sdTs(5MdC)sdTsdTsdTsgsuscsasa	4262
HAO1	A-133392.1	usgsgsuscsdAs(5MdC)s(5MdC)s(5MdC)sdTs(5MdC)sdTsdGs(5MdC)sdAscsasgsusg	4263
HAO1	A-133393.1	ususascsasdGsdAs(5MdC)sdTsdGsdTsdGsdGsdTs(5MdC)sascscscsu	4264
HAO1	A-133394.1	ususgsasasdGsdTsdGsdGsdGsdGsdAsdAsdTsdTsascsasgsa	4265
HAO1	A-133395.1	cscscsususdTsdGsdTsdAsdTsdTsdGsdAsdAsdGsusgsgsgsg	4266
HAO1	A-133396.1	asasasgsasdAs(5MdC)sdGsdAs(5MdC)sdAs(5MdC)s(5MdC)s(5MdC)sdTsususgsusa	4267

Target	Oligo Name	Sequence 5'-3'	SEQ ID NO:
HAO1	A-133397.1	usasususususdTsdGsdTsdTsdGsdGsdAsdAsdAsdAsgsasascsg	4268
HAO1	A-133398.1	asasgsgsgsdAsdTsdTsdGs(5MdC)sdTsdAsdTsdTsdTsusgsususg	4269
HAO1	A-133399.1	gscsasasusdGsdAsdAsdAsdTsdAsdAsdAsdAsdGsgsgsasusu	4270
HAO1	A-133400.1	asasasasgsdTs(5MdC)sdAsdAsdAsdAsdGs(5MdC)sdAsdAsusgsasasa	4271
HAO1	A-133401.1	gsascsascs(5MdC)s(5MdC)sdAsdTsdTsdGsdAsdAsdAsdAsgsuscsasa	4272
HAO1	A-133402.1	asasasgsgsdTsdTs(5MdC)s(5MdC)sdTsdAsdGsdGsdAs(5MdC)sascscscsa	4273
HAO1	A-133403.1	usususcsusdTsdTs(5MdC)sdTsdAsdAsdAsdAsdGsdGsususcscscsu	4274
HAO1	A-133404.1	usgsasasasdGsdTs(5MdC)s(5MdC)sdAsdTsdTsdTs(5MdC)sdTsususcsusa	4275
HAO1	A-133405.1	usasusasusdTsdTs(5MdC)s(5MdC)sdAsdGsdGsdAsdTsdGsasasasgsu	4276
HAO1	A-133406.1	usasascsasdGsdTsdTsdAsdAsdTsdAsdTsdAsdTsususcscsa	4277
HAO1	A-133407.1	gsususususs(5MdC)sdTsdTsdTsdTsdTsdAsdAs(5MdC)sdAsgsususasa	4278
HAO1	A-133408.1	csascsasusdTsdTsdTs(5MdC)sdAsdAsdTsdGsdTsdTsususcsusu	4279
HAO1	A-133409.1	ascsgsususdGsdTs(5MdC)sdTsdAsdAsdAs(5MdC)sdAs(5MdC)sasususususu	4280
HAO1	A-133410.1	csasgsgsgsdGsdAsdTsdGsdAs(5MdC)sdGsdTsdTsdGsuscsusasa	4281
HAO1	A-133411.1	csascsususdTsdAsdGs(5MdC)s(5MdC)sdTsdGs(5MdC)s(5MdC)sdAsgsgsgsgsa	4282
HAO1	A-133412.1	asasasgsgsdAsdTsdAs(5MdC)sdAsdGs(5MdC)sdAs(5MdC)sdTsususasgsc	4283
HAO1	A-133413.1	csasasususdTsdTsdAs(5MdC)sdTsdAsdAsdAsdGsdGsasusascsa	4284
HAO1	A-133414.1	ususgscsusdAs(5MdC)s(5MdC)sdTs(5MdC)s(5MdC)sdAsdAsdTsdTsususascsu	4285
HAO1	A-133415.1	csascscsusdTsdAsdGsdTsdGsdTsdTsdTsdGs(5MdC)susascscsu	4286
HAO1	A-133416.1	uscsasususdAsdTs(5MdC)sdTsdTsdTsdTs(5MdC)sdAs(5MdC)scsususasg	4287
HAO1	A-133417.1	asascsasasdTsdGsdAsdGsdAsdTs(5MdC)sdAsdTsdTsasuscsusu	4288
HAO1	A-133418.1	usascsasgsdGsdTsdTsdAsdAsdTsdAsdAsdAs(5MdC)sasasusgsa	4289
HAO1	A-133419.1	gsusasasas(5MdC)sdAsdGsdAsdAsdTsdAs(5MdC)sdAsdGsgsususasa	4290
HAO1	A-133420.1	ususususasasdAsdGsdAs(5MdC)sdAsdTsdGsdTsdAsdAsascsasgsa	4291
HAO1	A-133421.1	asasgsasas(5MdC)s(5MdC)sdAs(5MdC)sdTsdGsdTsdTsdTsdTsasasasgsa	4292
HAO1	A-133422.1	csususascsdAsdAsdTsdTsdTsdAsdAsdGsdAsdAscscsascsu	4293

Target	Oligo Name	Sequence 5'-3'	SEQ ID NO:
HAO1	A-133423.1	csusususgsdAsdAs(5MdC)s(5MdC)sdTsdGsdAsdGs(5MdC)sdTsusascsasa	4294
HAO1	A-133424.1	asususascs(5MdC)sdAsdAs(5MdC)sdAs(5MdC)sdTsdTsdTsdGsasascscsu	4295
HAO1	A-133425.1	usgsusgsasdAsdTs(5MdC)sdAsdGsdGs(5MdC)sdAsdTsdTsascscsasa	4296
HAO1	A-133426.1	uscsuscsasdAsdAsdGsdTsdTsdGsdTsdGsdAsdAsuscsasggsg	4297
HAO1	A-133427.1	csasgsusgs(5MdC)sdTsdAs(5MdC)s(5MdC)sdTsdTs(5MdC)sdTs(5MdC)sasasasgsu	4298
HAO1	A-133428.1	ususcscsasdAsdTsdTs(5MdC)sdTs(5MdC)sdTs(5MdC)s(5MdC)sdAsgsusgscsu	4299
HAO1	A-133429.1	cscsgscscsdAs(5MdC)s(5MdC)s(5MdC)sdAsdTsdTs(5MdC)s(5MdC)sdAsasususcsu	4300
HAO1	A-133430.1	uscsascscsdAsdAsdTsdTsdAs(5MdC)s(5MdC)sdGs(5MdC)s(5MdC)sascscscsa	4301
HAO1	A-133431.1	asususcsasdAsdAsdGsdAsdAsdGsdTsdAsdTs(5MdC)sascscsasa	4302
HAO1	A-133432.1	usgsgsasasdAsdTs(5MdC)sdTsdAs(5MdC)sdAsdTsdTs(5MdC)sasasasgsa	4303
HAO1	A-133433.1	asasgsasusdGsdTsdGsdAsdTsdTsdGsdGsdAsdAsasususcsusa	4304
HAO1	A-133434.1	ususcsasgsdAs(5MdC)sdAs(5MdC)sdTsdAsdAsdAsdGsdAsusgsusgsa	4305
HAO1	A-133435.1	csasususdGsdGsdAsdTsdAsdTsdTs(5MdC)sasgsascsa	4306
HAO1	A-133436.1	csasuscscsdTsdAsdAsdAsdAs(5MdC)sdAsdTsdTsdTsgsgsasusa	4307
HAO1	A-133437.1	asasgsusasdAs(5MdC)sdAsdTsdAs(5MdC)sdAsdTs(5MdC)s(5MdC)susasasasa	4308
HAO1	A-133438.1	usususcsus(5MdC)sdTs(5MdC)sdTsdAsdAsdGsdAsdAsdGsusasascsa	4309
HAO1	A-133439.1	asasasusgs(5MdC)sdTsdTsdTsdAsdTsdTsdTs(5MdC)sdTscsuscsusa	4310

Table 14. Unmodified antisense polynucleotides targeting HAO1.

Target	Oligo Name	Oligo transSeq	SEQ ID NO:	mRNA Target sequence	SEQ ID NO:	Position
HAO1	A-133284.1	GGGAGCAUUUUCACAGGUUA	4319	UAACCUGUGAAAAUGCUCCC	4475	13
HAO1	A-133285.1	AAUUAGCCGGGGGAGCAUUU	4320	AAAUGCUCCCCCGGCUAAUU	4476	23
HAO1	A-133286.1	AUCAUUGAUACAAAUUAGCC	4321	GGCUAAUUUGUAUCAAUGAU	4477	35
HAO1	A-133287.1	GUUGUUCAUAAUCAUUGAUA	4322	UAUCAAUGAUUAUGAACAAC	4478	45
HAO1	A-133288.1	GAUUUAGCAUGUUGUUCAUA	4323	UAUGAACAACAUGCUAAAUC	4479	55
HAO1	A-133289.1	UUGGAAGUACUGAUUUAGCA	4324	UGCUAAAUCAGUACUUCCAA	4480	66
HAO1	A-133290.1	CAUAUAUAGACUUUGGAAGU	4325	ACUUCCAAAGUCUAUAUAUG	4481	78
HAO1	A-133291.1	CUGUAAUAGUCAUAUAUAGA	4326	UCUAUAUAUGACUAUUACAG	4482	88
HAO1	A-133292.1	UUGCCCCAGACCUGUAAUAG	4327	CUAUUACAGGUCUGGGGCAA	4483	99
HAO1	A-133293.1	UUCUUCAUCAUUUGCCCCAG	4328	CUGGGGCAAAUGAUGAAGAA	4484	110
HAO1	A-133294.1	UAUCAGCCAAAGUUUCUUCA	4329	UGAAGAAACUUUGGCUGAUA	4485	123
HAO1	A-133295.1	GCUGCAAUAUUAUCAGCCAA	4330	UUGGCUGAUAAUAUUGCAGC	4486	133
HAO1	A-133296.1	AUCUGGAAAAUGCUGCAAUA	4331	UAUUGCAGCAUUUUCCAGAU	4487	144
HAO1	A-133297.1	GAUACAGCUUCCAUCUGGAA	4332	UUCCAGAUGGAAGCUGUAUC	4488	156
HAO1	A-133298.1	GAGCAUCCUUGGAUACAGCU	4333	AGCUGUAUCCAAGGAUGCUC	4489	167
HAO1	A-133299.1	CAACAUUCCGGAGCAUCCUU	4334	AAGGAUGCUCCGGAAUGUUG	4490	177
HAO1	A-133300.1	GAUCUGUUUCAGCAACAUUC	4335	GAAUGUUGCUGAAACAGAUC	4491	189
HAO1	A-133301.1	AGAAGUCGACAGAUCUGUUU	4336	AAACAGAUCUGUCGACUUCU	4492	200
HAO1	A-133302.1	UGUCCUAAAACAGAAGUCGA	4337	UCGACUUCUGUUUUAGGACA	4493	211
HAO1	A-133303.1	UGCUGACCCUCUGUCCUAAA	4338	UUUAGGACAGAGGGUCAGCA	4494	222
HAO1	A-133304.1	CAUAUUGGCAUGCUGACCCU	4339	AGGGUCAGCAUGCCAAUAUG	4495	232
HAO1	A-133305.1	AGCCCCCACACAUAUUGGCA	4340	UGCCAAUAUGUGUGGGGGCU	4496	242
HAO1	A-133306.1	CUGCAUGGCCGUAGCCCCCA	4341	UGGGGGCUACGGCCAUGCAG	4497	254
HAO1	A-133307.1	GAGCCAUGCGCUGCAUGGCC	4342	GGCCAUGCAGCGCAUGGCUC	4498	264
HAO1	A-133308.1	GCCGUCCACAUGAGCCAUGC	4343	GCAUGGCUCAUGUGGACGGC	4499	275
HAO1	A-133309.1	AGUGGCAAGCUCGCCGUCCA	4344	UGGACGGCGAGCUUGCCACU	4500	287

Target	Oligo Name	Oligo transSeq	SEQ ID NO:	mRNA Target sequence	SEQ ID NO:	Position
HAO1	A-133310.1	ACAGGCUCUCACAGUGGCAA	4345	UUGCCACUGUGAGAGCCUGU	4501	299
HAO1	A-133311.1	CAGGGACUGACAGGCUCUCA	4346	UGAGAGCCUGUCAGUCCCUG	4502	308
HAO1	A-133312.1	AUGCCCGUUCCCAGGGACUG	4347	CAGUCCCUGGGAACGGGCAU	4503	319
HAO1	A-133313.1	GAACUCAACAUCAUGCCCGU	4348	ACGGGCAUGAUGUUGAGUUC	4504	331
HAO1	A-133314.1	GAGGUGGCCCAGGAACUCAA	4349	UUGAGUUCCUGGGCCACCUC	4505	343
HAO1	A-133315.1	UCAAUUGAGGAGGUGGCCCA	4350	UGGGCCACCUCCUCAAUUGA	4506	352
HAO1	A-133316.1	CCGCCACUUCUUCAAUUGAG	4351	CUCAAUUGAAGAAGUGGCGG	4507	363
HAO1	A-133317.1	CAGGACCAGCUUCCGCCACU	4352	AGUGGCGGAAGCUGGUCCUG	4508	375
HAO1	A-133318.1	ACGAAGUGCCUCAGGACCAG	4353	CUGGUCCUGAGGCACUUCGU	4509	386
HAO1	A-133319.1	CAGUUGCAGCCAACGAAGUG	4354	CACUUCGUUGGCUGCAACUG	4510	398
HAO1	A-133320.1	UGUAGAUAUACAGUUGCAGC	4355	GCUGCAACUGUAUAUCUACA	4511	408
HAO1	A-133321.1	UCUCGGUCCUUGUAGAUAUA	4356	UAUAUCUACAAGGACCGAGA	4512	418
HAO1	A-133322.1	UUCUUGGUGACUUCUCGGUC	4357	GACCGAGAAGUCACCAAGAA	4513	430
HAO1	A-133323.1	CCGCACUAGCUUCUUGGUGA	4358	UCACCAAGAAGCUAGUGCGG	4514	440
HAO1	A-133324.1	CUUCUCUGCCUGCCGCACUA	4359	UAGUGCGGCAGGCAGAGAAG	4515	452
HAO1	A-133325.1	CUUGUAGCCCAUCUUCUCUG	4360	CAGAGAAGAUGGGCUACAAG	4516	464
HAO1	A-133326.1	AAAUAUGGCCUUGUAGCCCA	4361	UGGGCUACAAGGCCAUAUUU	4517	473
HAO1	A-133327.1	UGUCCACUGUCACAAAUAUG	4362	CAUAUUUGUGACAGUGGACA	4518	486
HAO1	A-133328.1	CAGGUAAGGUGUGUCCACUG	4363	CAGUGGACACACCUUACCUG	4519	497
HAO1	A-133329.1	GACGGUUGCCCAGGUAAGGU	4364	ACCUUACCUGGGCAACCGUC	4520	507
HAO1	A-133330.1	CACAUCAUCCAGACGGUUGC	4365	GCAACCGUCUGGAUGAUGUG	4521	518
HAO1	A-133331.1	AAUCUGUUACGCACAUCAUC	4366	GAUGAUGUGCGUAACAGAUU	4522	529
HAO1	A-133332.1	GCGGCAGUUUGAAUCUGUUA	4367	UAACAGAUUCAAACUGCCGC	4523	540
HAO1	A-133333.1	CUGAGUUGUGGCGGCAGUUU	4368	AAACUGCCGCCACAACUCAG	4524	550
HAO1	A-133334.1	AAAAUUUUUCAUCCUGAGUU	4369	AACUCAGGAUGAAAAAAUUUU	4525	563
HAO1	A-133335.1	UACUGGUUUCAAAAUUUUUC	4370	GAAAAAAUUUUUGAAACCAGUA	4526	573
HAO1	A-133336.1	AAAUGAUAAAGUACUGGUUU	4371	AAACCAGUACUUUAUCAUUU	4527	584

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Target	Oligo Name	Oligo transSeq	SEQ ID NO:	mRNA Target sequence	SEQ ID NO:	Position
HAO1	A-133337.1	CCUCAGGAGAAAAUGAUAAA	4372	UUUAUCAUUUUCUCCUGAGG	4528	594
HAO1	A-133338.1	UCCAAAAUUUUCCUCAGGAG	4373	CUCCUGAGGAAAAUUUUGGA	4529	605
HAO1	A-133339.1	GUCCACUGUCGUCUCCAAAA	4374	UUUUGGAGACGACAGUGGAC	4530	618
HAO1	A-133340.1	AUAUGCAGCAAGUCCACUGU	4375	ACAGUGGACUUGCUGCAUAU	4531	629
HAO1	A-133341.1	UUUAGCCACAUAUGCAGCAA	4376	UUGCUGCAUAUGUGGCUAAA	4532	638
HAO1	A-133342.1	UGGGUCUAUUGCUUUAGCCA	4377	UGGCUAAAGCAAUAGACCCA	4533	650
HAO1	A-133343.1	AGCUGAUAGAUGGGUCUAUU	4378	AAUAGACCCAUCUAUCAGCU	4534	660
HAO1	A-133344.1	GAUAUCUUCCCAGCUGAUAG	4379	CUAUCAGCUGGGAAGAUAUC	4535	671
HAO1	A-133345.1	CUCAGCCAUUUGAUAUCUUC	4380	GAAGAUAUCAAAUGGCUGAG	4536	682
HAO1	A-133346.1	GAUGUCAGUCUUCUCAGCCA	4381	UGGCUGAGAAGACUGACAUC	4537	694
HAO1	A-133347.1	CAAUUGGCAAUGAUGUCAGU	4382	ACUGACAUCAUUGCCAAUUG	4538	705
HAO1	A-133348.1	CCCUUUGCAACAAUUGGCAA	4383	UUGCCAAUUGUUGCAAAGGG	4539	715
HAO1	A-133349.1	CUCUCAAAAUGCCCUUUGCA	4384	UGCAAAGGGCAUUUUGAGAG	4540	726
HAO1	A-133350.1	GGCAUCAUCACCUCUCAAAA	4385	UUUUGAGAGGUGAUGAUGCC	4541	737
HAO1	A-133351.1	AACAGCCUCCCUGGCAUCAU	4386	AUGAUGCCAGGGAGGCUGUU	4542	749
HAO1	A-133352.1	AAGCCAUGUUUAACAGCCUC	4387	GAGGCUGUUAAACAUGGCUU	4543	760
HAO1	A-133353.1	AAGAUCCCAUUCAAGCCAUG	4388	CAUGGCUUGAAUGGGAUCUU	4544	772
HAO1	A-133354.1	UUCGACACCAAGAUCCCAUU	4389	AAUGGGAUCUUGGUGUCGAA	4545	781
HAO1	A-133355.1	UCGAGCCCCAUGAUUCGACA	4390	UGUCGAAUCAUGGGGCUCGA	4547	794
HAO1	A-133356.1	AUCGAGUUGUCGAGCCCCAU	4391	AUGGGGCUCGACAACUCGAU	4546	803
HAO1	A-133357.1	GGCUGGCACCCCAUCGAGUU	4392	AACUCGAUGGGGUGCCAGCC	4548	815
HAO1	A-133358.1	AACAUCAAUAGUGGCUGGCA	4393	UGCCAGCCACUAUUGAUGUU	4549	827
HAO1	A-133359.1	AUUUCUGGCAGAACAUCAAU	4394	AUUGAUGUUCUGCCAGAAAU	4550	838
HAO1	A-133360.1	AGCCUCCACAAUUUCUGGCA	4395	UGCCAGAAAUUGUGGAGGCU	4551	848
HAO1	A-133361.1	CUUCCCUUCCACAGCCUCCA	4396	UGGAGGCUGUGGAAGGGAAG	4552	860
HAO1	A-133362.1	AAGACUUCCACCUUCCCUUC	4397	GAAGGGAAGGUGGAAGUCUU	4553	871
HAO1	A-133363.1	CCGUCCAGGAAGACUUCCAC	4398	GUGGAAGUCUUCCUGGACGG	4554	880

Target	Oligo Name	Oligo transSeq	SEQ ID NO:	mRNA Target sequence	SEQ ID NO:	Position
HAO1	A-133364.1	UCCGCACACCCCCGUCCAGG	4399	CCUGGACGGGGGGUGUGCGGA	4555	891
HAO1	A-133365.1	CAUCAGUGCCUUUCCGCACA	4400	UGUGCGGAAAGGCACUGAUG	4556	903
HAO1	A-133366.1	AGCUUUCAGAACAUCAGUGC	4401	GCACUGAUGUUCUGAAAGCU	4557	914
HAO1	A-133367.1	CAAGAGCCAGAGCUUUCAGA	4402	UCUGAAAGCUCUGGCUCUUG	4558	924
HAO1	A-133368.1	ACAGCCUUGGCGCCAAGAGC	4403	GCUCUUGGCGCCAAGGCUGU	4559	937
HAO1	A-133369.1	UCCCCACAAACACAGCCUUG	4404	CAAGGCUGUGUUUGUGGGGA	4560	948
HAO1	A-133370.1	ACGAUUGGUCUCCCCCACAAA	4405	UUUGUGGGGAGACCAAUCGU	4561	958
HAO1	A-133371.1	UAAGCCCCAAACGAUUGGUC	4406	GACCAAUCGUUUGGGGCUUA	4562	968
HAO1	A-133372.1	CCCUGGAAAGCUAAGCCCCA	4407	UGGGGCUUAGCUUUCCAGGG	4563	979
HAO1	A-133373.1	CACCUUUCUCCCCCUGGAAA	4408	UUUCCAGGGGGGAGAAAGGUG	4564	990
HAO1	A-133374.1	GACAUCUUGAACACCUUUCU	4409	AGAAAGGUGUUCAAGAUGUC	4565	1001
HAO1	A-133375.1	UAGUAUCUCGAGGACAUCUU	4410	AAGAUGUCCUCGAGAUACUA	4566	1013
HAO1	A-133376.1	GAAUUCUUCCUUUAGUAUCU	4411	AGAUACUAAAGGAAGAAUUC	4567	1025
HAO1	A-133377.1	GGCCAACCGGAAUUCUUCCU	4412	AGGAAGAAUUCCGGUUGGCC	4568	1034
HAO1	A-133378.1	CUCAGAGCCAUGGCCAACCG	4413	CGGUUGGCCAUGGCUCUGAG	4569	1045
HAO1	A-133379.1	AUUCUGGCACCCACUCAGAG	4414	CUCUGAGUGGGUGCCAGAAU	4570	1058
HAO1	A-133380.1	AUGACUUUCACAUUCUGGCA	4415	UGCCAGAAUGUGAAAGUCAU	4571	1069
HAO1	A-133381.1	GUCUUGUCGAUGACUUUCAC	4416	GUGAAAGUCAUCGACAAGAC	4572	1078
HAO1	A-133382.1	UUUCCUCACCAAUGUCUUGU	4417	ACAAGACAUUGGUGAGGAAA	4573	1091
HAO1	A-133383.1	CAAAGGAUUUUUCCUCACCA	4418	UGGUGAGGAAAAAUCCUUUG	4574	1100
HAO1	A-133384.1	UUGGAAACGGCCAAAGGAUU	4419	AAUCCUUUGGCCGUUUCCAA	4575	1111
HAO1	A-133385.1	GCACUGUCAGAUCUUGGAAA	4420	UUUCCAAGAUCUGACAGUGC	4576	1124
HAO1	A-133386.1	AAAUAUUGUGCACUGUCAGA	4421	UCUGACAGUGCACAAUAUUU	4577	1133
HAO1	A-133387.1	UACAGAUGGGAAAAUAUUGU	4422	ACAAUAUUUUCCCAUCUGUA	4578	1144
HAO1	A-133388.1	UGAAAAAAAAUAAUACAGAU	4423	AUCUGUAUUAUUUUUUUUCA	4579	1157
HAO1	A-133389.1	UAAUACAUGCUGAAAAAAAAA	4424	UUUUUUUUCAGCAUGUAUUA	4580	1167
HAO1	A-133390.1	CUCUUUGUCAAGUAAUACAU	4425	AUGUAUUACUUGACAAAGAG	4581	1179

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Target	Oligo Name	Oligo transSeq	SEQ ID NO:	mRNA Target sequence	SEQ ID NO:	Position
HAO1	A-133391.1	GCACAGUGUCUCUUUGUCAA	4426	UUGACAAAGAGACACUGUGC	4582	1188
HAO1	A-133392.1	UGGUCACCCUCUGCACAGUG	4427	CACUGUGCAGAGGGUGACCA	4583	1200
HAO1	A-133393.1	UUACAGACUGUGGUCACCCU	4428	AGGGUGACCACAGUCUGUAA	4584	1210
HAO1	A-133394.1	UUGAAGUGGGGAAUUACAGA	4429	UCUGUAAUUCCCCACUUCAA	4585	1223
HAO1	A-133395.1	CCCUUUGUAUUGAAGUGGGG	4430	CCCCACUUCAAUACAAAGGG	4586	1232
HAO1	A-133396.1	AAAGAACGACACCCUUUGUA	4431	UACAAAGGGUGUCGUUCUUU	4587	1243
HAO1	A-133397.1	UAUUUUGUUGGAAAAGAACG	4432	CGUUCUUUUCCAACAAAAUA	4588	1255
HAO1	A-133398.1	AAGGGAUUGCUAUUUUGUUG	4433	CAACAAAAUAGCAAUCCCUU	4589	1265
HAO1	A-133399.1	GCAAUGAAAUAAAAGGGAUU	4434	AAUCCCUUUUAUUUCAUUGC	4590	1277
HAO1	A-133400.1	AAAAGUCAAAAGCAAUGAAA	4435	UUUCAUUGCUUUUGACUUUU	4591	1288
HAO1	A-133401.1	GACACCCAUUGAAAAGUCAA	4436	UUGACUUUUCAAUGGGUGUC	4592	1299
HAO1	A-133402.1	AAAGGUUCCUAGGACACCCA	4437	UGGGUGUCCUAGGAACCUUU	4593	1311
HAO1	A-133403.1	UUUCUUUCUAAAAGGUUCCU	4438	AGGAACCUUUUAGAAAGAAA	4594	1321
HAO1	A-133404.1	UGAAAGUCCAUUUCUUUCUA	4439	UAGAAAGAAAUGGACUUUCA	4595	1331
HAO1	A-133405.1	UAUAUUUCCAGGAUGAAAGU	4440	ACUUUCAUCCUGGAAAUAUA	4596	1344
HAO1	A-133406.1	UAACAGUUAAUAUAUUUCCA	4441	UGGAAAUAUAUUAACUGUUA	4597	1354
HAO1	A-133407.1	GUUUUCUUUUUAACAGUUAA	4442	UUAACUGUUAAAAAGAAAAC	4598	1364
HAO1	A-133408.1	CACAUUUUCAAUGUUUUCUU	4443	AAGAAAACAUUGAAAAUGUG	4599	1376
HAO1	A-133409.1	ACGUUGUCUAAACACAUUUU	4444	AAAAUGUGUUUAGACAACGU	4600	1388
HAO1	A-133410.1	CAGGGGAUGACGUUGUCUAA	4445	UUAGACAACGUCAUCCCCUG	4601	1397
HAO1	A-133411.1	CACUUUAGCCUGCCAGGGGA	4446	UCCCCUGGCAGGCUAAAGUG	4602	1410
HAO1	A-133412.1	AAAGGAUACAGCACUUUAGC	4447	GCUAAAGUGCUGUAUCCUUU	4603	1421
HAO1	A-133413.1	CAAUUUUACUAAAGGAUACA	4448	UGUAUCCUUUAGUAAAAUUG	4604	1431
HAO1	A-133414.1	UUGCUACCUCCAAUUUUACU	4449	AGUAAAAUUGGAGGUAGCAA	4605	1441
HAO1	A-133415.1	CACCUUAGUGUUUGCUACCU	4450	AGGUAGCAAACACUAAGGUG	4606	1452
HAO1	A-133416.1	UCAUUAUCUUUUCACCUUAG	4451	CUAAGGUGAAAAGAUAAUGA	4607	1464
HAO1	A-133417.1	AACAAUGAGAUCAUUAUCUU	4452	AAGAUAAUGAUCUCAUUGUU	4608	1474

Target	Oligo Name	Oligo transSeq	SEQ ID NO:	mRNA Target sequence	SEQ ID NO:	Position
HAO1	A-133418.1	UACAGGUUAAUAAACAAUGA	4453	UCAUUGUUUAUUAACCUGUA	4609	1486
HAO1	A-133419.1	GUAAACAGAAUACAGGUUAA	4454	UUAACCUGUAUUCUGUUUAC	4610	1496
HAO1	A-133420.1	UUUAAAGACAUGUAAACAGA	4455	UCUGUUUACAUGUCUUUAAA	4611	1507
HAO1	A-133421.1	AAGAACCACUGUUUUAAAGA	4456	UCUUUAAAACAGUGGUUCUU	4612	1519
HAO1	A-133422.1	CUUACAAUUUAAGAACCACU	4457	AGUGGUUCUUAAAUUGUAAG	4613	1529
HAO1	A-133423.1	CUUUGAACCUGAGCUUACAA	4458	UUGUAAGCUCAGGUUCAAAG	4614	1542
HAO1	A-133424.1	AUUACCAACACUUUGAACCU	4459	AGGUUCAAAGUGUUGGUAAU	4615	1552
HAO1	A-133425.1	UGUGAAUCAGGCAUUACCAA	4460	UUGGUAAUGCCUGAUUCACA	4616	1564
HAO1	A-133426.1	UCUCAAAGUUGUGAAUCAGG	4461	CCUGAUUCACAACUUUGAGA	4617	1573
HAO1	A-133427.1	CAGUGCUACCUUCUCAAAGU	4462	ACUUUGAGAAGGUAGCACUG	4618	1584
HAO1	A-133428.1	UUCCAAUUCUCUCCAGUGCU	4463	AGCACUGGAGAGAAUUGGAA	4619	1597
HAO1	A-133429.1	CCGCCACCCAUUCCAAUUCU	4464	AGAAUUGGAAUGGGUGGCGG	4620	1607
HAO1	A-133430.1	UCACCAAUUACCGCCACCCA	4465	UGGGUGGCGGUAAUUGGUGA	4621	1617
HAO1	A-133431.1	AUUCAAAGAAGUAUCACCAA	4466	UUGGUGAUACUUCUUUGAAU	4622	1630
HAO1	A-133432.1	UGGAAAUCUACAUUCAAAGA	4467	UCUUUGAAUGUAGAUUUCCA	4623	1641
HAO1	A-133433.1	AAGAUGUGAUUGGAAAUCUA	4468	UAGAUUUCCAAUCACAUCUU	4624	1651
HAO1	A-133434.1	UUCAGACACUAAAGAUGUGA	4469	UCACAUCUUUAGUGUCUGAA	4625	1662
HAO1	A-133435.1	CAUUUGGAUAUAUUCAGACA	4470	UGUCUGAAUAUAUCCAAAUG	4626	1674
HAO1	A-133436.1	CAUCCUAAAACAUUUGGAUA	4471	UAUCCAAAUGUUUUAGGAUG	4627	1684
HAO1	A-133437.1	AAGUAACAUACAUCCUAAAA	4472	UUUUAGGAUGUAUGUUACUU	4628	1694
HAO1	A-133438.1	UUUCUCUCUAAGAAGUAACA	4473	UGUUACUUCUUAGAGAGAAA	4629	1706
HAO1	A-133439.1	AAAUGCUUUAUUUCUCUCUA	4474	UAGAGAGAAAUAAAGCAUUU	4630	1716

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TABLE 15. Unmodified Sense and Antisense Strand Sequences of PRODH2 dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_021232.2	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_021232.2
AD-1553630	AGAACCUUCCCUGGUGUGGAU		3-23	AUCCACACCAGGGAAGGUUCUCU		1-23
AD-1553635	CUUCCCUGGUGUGGAGGCAGU		8-28	ACUGCCUCCACACCAGGGAAGGU		86-28
AD-1553662	CAGGAUGCUCCGGACCUGUUU		37-57	AAACAGGUCCGGAGCAUCCUGGG		35-57
AD-1553667	UGCUCCGGACCUGUUACGUGU		42-62	ACACGUAACAGGUCCGGAGCAUC		40-62
AD-1553674	GACCUGUUACGUGCUCUGUUU		49-69	AAACAGAGCACGUAACAGGUCCG		47-69
AD-1553681	UACGUGCUCUGUUCCCAAGCU		56-76	AGCUUGGGAACAGAGCACGUAAC		54-76
AD-1553686	GCUCUGUUCCCAAGCUGGUCU		61-81	AGACCAGCUUGGGAACAGAGCAC		59-81
AD-1553691	CUGGCAGUCCCUGAGCUUUGU		94-114	ACAAAGCUCAGGGACUGCCAGCC		92-114
AD-1553697	GUCCCUGAGCUUUGAUGGCGU		100-120	ACGCCAUCAAAGCUCAGGGACUG		98-120
AD-1553701	GCCUUCCACCUUAAGGGCACU		122-142	AGUGCCCUUAAGGUGGAAGGCCC		120-142
AD-1553707	CACCUUAAGGGCACAGGAGAU		128-148	AUCUCCUGUGCCCUUAAGGUGGA		126-148
AD-1553715	GGGCACAGGAGAGCUGACACU		136-156	AGUGUCAGCUCUCCUGUGCCCUU		134-156
AD-1553722	GGAGAGCUGACACGGGCCUUU		143-163	AAAGGCCCGUGUCAGCUCUCCUG		141-163
AD-1553730	GACACGGGCCUUGCUGGUUCU		151-171	AGAACCAGCAAGGCCCGUGUCAG		149-171
AD-1553739	CUUGCUGGUUCUCCGGCUGUU		160-180	AACAGCCGGAGAACCAGCAAGGC		158-180
AD-1553745	GGUUCUCCGGCUGUGUGCCUU		166-186	AAGGCACACAGCCGGAGAACCAG		164-186
AD-1553751	CUCGUCACUCACGGGCUGUUU		194-214	AAACAGCCCGUGAGUGACGAGUG		192-214
AD-1553758	CUCACGGGCUGUUGCUCCAGU		201-221	ACUGGAGCAACAGCCCGUGAGUG		199-221
AD-1553769	UUGCUCCAGGCCUGGUCUCGU		212-232	ACGAGACCAGGCCUGGAGCAACA		210-232
AD-1553794	GGCUCUCAGGCGCAUUUCUCU		249-269	AGAGAAAUGCGCCUGAGAGCCGG		247-269
AD-1553799	UCAGGCGCAUUUCUCCGAGCU		254-274	AGCUCGGAGAAAUGCGCCUGAGA		252-274
AD-1553804	CGCAUUUCUCCGAGCAUCCGU		259-279	ACGGAUGCUCGGAGAAAUGCGCC		257-279
AD-1553809	UUCUCCGAGCAUCCGUCUAUU		264-284	AAUAGACGGAUGCUCGGAGAAAU		262-284
AD-1553815	GAGCAUCCGUCUAUGGGCAGU		270-290	ACUGCCCAUAGACGGAUGCUCGG		268-290
AD-1553820	UCCGUCUAUGGGCAGUUUGUU		275-295	AACAAACUGCCCAUAGACGGAUG		273-295
AD-1553826	UAUGGGCAGUUUGUGGCUGGU		281-301	ACCAGCCACAAACUGCCCAUAGA		279-301
AD-1553832	CAGUUUGUGGCUGGUGAGACU		287-307	AGUCUCACCAGCCACAAACUGCC		285-307
AD-1553839	UGGCUGGUGAGACAGCAGAGU		294-314	ACUCUGCUGUCUCACCAGCCACA		292-314
AD-1553845	GUGAGACAGCAGAGGAGGUGU		300-320	ACACCUCCUCUGCUGUCUCACCA		298-320
AD-1553852	AGCAGAGGAGGUGAAGGGCUU		307-327	AAGCCCUUCACCUCCUCUGCUGU		305-327
AD-1553859	GAGGUGAAGGGCUGCGUGCAU		314-334	AUGCACGCAGCCCUUCACCUCCU		312-334
AD-1553865	AAGGGCUGCGUGCAGCAGCUU		320-340	AAGCUGCUGCACGCAGCCCUUCA		318-340
AD-1553907	UGCUGGCAGUGCCCACUGAGU		363-383	ACUCAGUGGGCACUGCCAGCAGU		361-383
AD-1553912	GCAGUGCCCACUGAGGAGGAU		368-388	AUCCUCCUCAGUGGGCACUGCCA		366-388

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_021232.2	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_021232.2
AD-1553922	CUGAGGAGGAGCCGGACUCUU		378-398	AAGAGUCCGGCUCCUCCUCAGUG		376-398
AD-1553930	GAGCCGGACUCUGCUGCCAAU		386-406	AUUGGCAGCAGAGUCCGGCUCCU		384-406
AD-1553937	ACUCUGCUGCCAAGAGUGGUU		393-413	AACCACUCUUGGCAGCAGAGUCC		391-413
AD-1553942	GCUGCCAAGAGUGGUGAGGCU		398-418	AGCCUCACCACUCUUGGCAGCAG		396-418
AD-1553951	AGUGGUGAGGCGUGGUAUGAU		407-427	AUCAUACCACGCCUCACCACUCU		405-427
AD-1553957	AACCUCGGUGCUAUGCUGCGU		431-451	ACGCAGCAUAGCACCGAGGUUCC		429-451
AD-1553962	CGGUGCUAUGCUGCGGUGUGU		436-456	ACACACCGCAGCAUAGCACCGAG		434-456
AD-1553967	CUAUGCUGCGGUGUGUGGACU		441-461	AGUCCACACACCGCAGCAUAGCA		439-461
AD-1553975	CGGUGUGUGGACCUGUCACGU		449-469	ACGUGACAGGUCCACACACCGCA		447-469
AD-1553988	GGCCAGCCUCAUGCAGCUGAU		499-519	AUCAGCUGCAUGAGGCUGGCCUC		497-519
AD-1553993	GCCUCAUGCAGCUGAAGGUGU		504-524	ACACCUUCAGCUGCAUGAGGCUG		502-524
AD-1553998	AUGCAGCUGAAGGUGACGGCU		509-529	AGCCGUCACCUUCAGCUGCAUGA		507-529
AD-1554003	GCUGAAGGUGACGGCGCUGAU		514-534	AUCAGCGCCGUCACCUUCAGCUG		512-534
AD-1554009	GGUGACGGCGCUGACCAGUAU		520-540	AUACUGGUCAGCGCCGUCACCUU		518-540
AD-1554018	GCUGACCAGUACUCGGCUCUU		529-549	AAGAGCCGAGUACUGGUCAGCGC		527-549
AD-1554025	AGUACUCGGCUCUGUAAGGAU		536-556	AUCCUUACAGAGCCGAGUACUGG		534-556
AD-1554030	UCGGCUCUGUAAGGAGCUAGU		541-561	ACUAGCUCCUUACAGAGCCGAGU		539-561
AD-1554036	CUGUAAGGAGCUAGCCUCGUU		547-567	AACGAGGCUAGCUCCUUACAGAG		545-567
AD-1554041	AGGAGCUAGCCUCGUGGGUCU		552-572	AGACCCACGAGGCUAGCUCCUUA		550-572
AD-1554048	AGCCUCGUGGGUCAGAAGGCU		559-579	AGCCUUCUGACCCACGAGGCUAG		557-579
AD-1554054	GUGGGUCAGAAGGCCAGGAGU		565-585	ACUCCUGGCCUUCUGACCCACGA		563-585
AD-1554065	GGCCAGGAGCCUCCUUGGAGU		576-596	ACUCCAAGGAGGCUCCUGGCCUU		574-596
AD-1554070	GGAGCCUCCUUGGAGCUGAGU		581-601	ACUCAGCUCCAAGGAGGCUCCUG		579-601
AD-1554074	GAGAGGCUGGCUGAAGCUAUU		605-625	AAUAGCUUCAGCCAGCCUCUCGG		603-625
AD-1554082	GGCUGAAGCUAUGGACUCUGU		613-633	ACAGAGUCCAUAGCUUCAGCCAG		611-633
AD-1554089	GCUAUGGACUCUGGGCAGAAU		620-640	AUUCUGCCCAGAGUCCAUAGCUU		618-640
AD-1554097	CUCUGGGCAGAACCUCCAGGU		628-648	ACCUGGAGGUUCUGCCCAGAGUC		626-648
AD-1554106	GAACCUCCAGGUCUCCUGCCU		637-657	AGGCAGGAGACCUGGAGGUUCUG		635-657
AD-1554111	UCCAGGUCUCCUGCCUCAAUU		642-662	AAUUGAGGCAGGAGACCUGGAGG		640-662
AD-1554119	UCCUGCCUCAAUGCUGAGCAU		650-670	AUGCUCAGCAUUGAGGCAGGAGA		648-670
AD-1554126	UCAAUGCUGAGCAGAACCAGU		657-677	ACUGGUUCUGCUCAGCAUUGAGG		655-677
AD-1554131	GCUGAGCAGAACCAGCACCUU		662-682	AAGGUGCUGGUUCUGCUCAGCAU		660-682
AD-1554156	GCAUCGGGUGGCACAGUAUGU		703-723	ACAUACUGUGCCACCCGAUGCAG		701-723
AD-1554186	CUCCUGGUGGAUGCGGAGUAU		743-763	AUACUCCGCAUCCACCAGGAGCC		741-763
AD-1554193	UGGAUGCGGAGUACACCUCAU		750-770	AUGAGGUGUACUCCGCAUCCACC		748-770

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_021232.2	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_021232.2
AD-1554198	GCGGAGUACACCUCACUGAAU		755-775	AUUCAGUGAGGUGUACUCCGCAU		753-775
AD-1554203	GUACACCUCACUGAACCCUGU		760-780	ACAGGGUUCAGUGAGGUGUACUC		758-780
AD-1554210	UCACUGAACCCUGCGCUCUCU		767-787	AGAGAGCGCAGGGUUCAGUGAGG		765-787
AD-1554216	AACCCUGCGCUCUCGCUGCUU		773-793	AAGCAGCGAGAGCGCAGGGUUCA		771-793
AD-1554263	CCCUGGGUGUGGAACACCUAU		839-859	AUAGGUGUUCCACACCCAGGGCC		837-859
AD-1554268	GGUGUGGAACACCUACCAGGU		844-864	ACCUGGUAGGUGUUCCACACCCA		842-864
AD-1554278	ACCUACCAGGCCUGUCUAAAU		854-874	AUUUAGACAGGCCUGGUAGGUGU		852-874
AD-1554287	GCCUGUCUAAAGGACACAUUU		863-883	AAAUGUGUCCUUUAGACAGGCCU		861-883
AD-1554292	UCUAAAGGACACAUUCGAGCU		868-888	AGCUCGAAUGUGUCCUUUAGACA		866-888
AD-1554298	GGACACAUUCGAGCGGCUGGU		874-894	ACCAGCCGCUCGAAUGUGUCCUU		872-894
AD-1554317	GGCCUUCGGAGUGAAGCUGGU		928-948	ACCAGCUUCACUCCGAAGGCCAG		926-948
AD-1554323	CGGAGUGAAGCUGGUACGAGU		934-954	ACUCGUACCAGCUUCACUCCGAA		932-954
AD-1554328	UGAAGCUGGUACGAGGUGCAU		939-959	AUGCACCUCGUACCAGCUUCACU		937-959
AD-1554333	CUGGUACGAGGUGCAUAUCUU		944-964	AAGAUAUGCACCUCGUACCAGCU		942-964
AD-1554340	GAGGUGCAUAUCUGGACAAGU		951-971	ACUUGUCCAGAUAUGCACCUCGU		949-971
AD-1554346	CAUAUCUGGACAAGGAGAGAU		957-977	AUCUCUCCUUGUCCAGAUAUGCA		955-977
AD-1554351	CUGGACAAGGAGAGAGCGGUU		962-982	AACCGCUCUCUCCUUGUCCAGAU		960-982
AD-1554371	GCCCAGCUCCAUGGGAUGGAU		983-1003	AUCCAUCCCAUGGAGCUGGGCCA		981-1003
AD-1554376	GCUCCAUGGGAUGGAAGACCU		988-1008	AGGUCUUCCAUCCCAUGGAGCUG		986-1008
AD-1554379	CUCAGCCUGACUAUGAGGCCU		1011-1031	AGGCCUCAUAGUCAGGCUGAGUG		1009-1031
AD-1554387	GACUAUGAGGCCACCAGUCAU		1019-1039	AUGACUGGUGGCCUCAUAGUCAG		1017-1039
AD-1554393	GAGGCCACCAGUCAGAGUUAU		1025-1045	AUAACUCUGACUGGUGGCCUCAU		1023-1045
AD-1554399	ACCAGUCAGAGUUACAGCCGU		1031-1051	ACGGCUGUAACUCUGACUGGUGG		1029-1051
AD-1554404	UCAGAGUUACAGCCGCUGCCU		1036-1056	AGGCAGCGGCUGUAACUCUGACU		1034-1056
AD-1554413	CAGCCGCUGCCUGGAACUGAU		1045-1065	AUCAGUUCCAGGCAGCGGCUGUA		1043-1065
AD-1554418	GCUGCCUGGAACUGAUGCUGU		1050-1070	ACAGCAUCAGUUCCAGGCAGCGG		1048-1070
AD-1554425	GGAACUGAUGCUGACGCACGU		1057-1077	ACGUGCGUCAGCAUCAGUUCCAG		1055-1077
AD-1554430	UGAUGCUGACGCACGUGGCCU		1062-1082	AGGCCACGUGCGUCAGCAUCAGU		1060-1082
AD-1554433	CAUGUGCCACCUCAUGGUGGU		1093-1113	ACCACCAUGAGGUGGCACAUGGG		1091-1113
AD-1554443	CUCAUGGUGGCUUCCCACAAU		1103-1123	AUUGUGGGAAGCCACCAUGAGGU		1101-1123
AD-1554451	GGCUUCCCACAAUGAGGAAUU		1111-1131	AAUUCCUCAUUGUGGGAAGCCAC		1109-1131
AD-1554456	CCCACAAUGAGGAAUCUGUUU		1116-1136	AAACAGAUUCCUCAUUGUGGGAA		1114-1136
AD-1554461	AAUGAGGAAUCUGUUCGCCAU		1121-1141	AUGGCGAACAGAUUCCUCAUUGU		1119-1141
AD-1554470	UCUGUUCGCCAGGCAACCAAU		1130-1150	AUUGGUUGCCUGGCGAACAGAUU		1128-1150
AD-1554475	UCGCCAGGCAACCAAGCGCAU		1135-1155	AUGCGCUUGGUUGCCUGGCGAAC		1133-1155

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_021232.2	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_021232.2
AD-1554482	GCAACCAAGrCGCAUGUGGGAU		1142-1162	AUCCCACAUGCGCUUGGUUGrCCU		1140-1162
AD-1554487	CAAGCGCAUGUGGGAGCUGGU		1147-1167	ACCAGCUCCCCACAUGCGCUUGGU		1145-1167
AD-1554492	GCAUGUGGGAGCUGGGCAUUU		1152-1172	AAAUGCCCAGCUCCCCACAUGCGC		1150-1172
AD-1554497	UGGGAGCUGGGCAUUCCUCUU		1157-1177	AAGAGGAAUGCCCAGCUCCCCACA		1155-1177
AD-1554505	GGGCAUUCCUCUGGAUGGGAU		1165-1185	AUCCCAUCCAGAGGAAUGCCCAG		1163-1185
AD-1554510	UUCCUCUGGGAUGGGACUGUCU		1170-1190	AGACAGUCCCCAUCCAGAGGAAUG		1168-1190
AD-1554515	CUGGAUGGGACUGUCUGUUUU		1175-1195	AAAACAGACAGUCCCAUCCAGAG		1173-1195
AD-1554520	UGGGACUGUCUGUUUUCGGACU		1180-1200	AGUCCGAAACAGACAGUCCCAUC		1178-1200
AD-1554525	CUGUCUGUUUUCGGACAACUUU		1185-1205	AAAGUUGUCCGAAACAGACAGUC		1183-1205
AD-1554533	UUCGGACAACUUCUGGGCAUU		1193-1213	AAUGCCCAGAAGUUGUCCGAAAC		1191-1213
AD-1554542	CUUCUGGGCAUGUGUGACCAU		1202-1222	AUGGUCACACAUGCCCAGAAGUU		1200-1222
AD-1554551	AUGUGUGACCACGUCUCUCUU		1211-1231	AAGAGAGACGUGGUCACACAUGC		1209-1231
AD-1554557	GACCACGUCUCUCUAGCACUU		1217-1237	AAGUGCUAGAGAGACGUGGUCAC		1215-1237
AD-1554562	GCAGGCCGGCUAUGUAGUGUU		1240-1260	AACACUACAUAGCCGGCCUGCCC		1238-1260
AD-1554567	CCGGCUAUGUAGUGUAUAAGU		1245-1265	ACUUAUACACUACAUAGCCGGCC		1243-1265
AD-1554573	AUGUAGUGUAUAAGUCCAUUU		1251-1271	AAAUGGACUUAUACACUACAUAG		1249-1271
AD-1554578	GUGUAUAAGUCCAUUCCCUAU		1256-1276	AUAGGGAAUGGACUUAUACACUA		1254-1276
AD-1554584	AAGUCCAUUCCCUAUGGCUCU		1262-1282	AGAGCCAUAGGGAAUGGACUUAU		1260-1282
AD-1554591	UUCCCUAUGGCUCCUUGGAGU		1269-1289	ACUCCAAGGAGCCAUAGGGAAUG		1267-1289
AD-1554599	GGCUCCUUGGAGGAGGUAAUU		1277-1297	AAUUACCUCCUCCAAGGAGCCAU		1275-1297
AD-1554609	AUCCGGAGGGCCCAGGAGAAU		1307-1327	AUUCUCCUGGGCCCUCCGGAUCA		1305-1327
AD-1554626	GAACCGGAGCGUGCUUCAGGU		1324-1344	ACCUGAAGCACGCUCCGGUUCUC		1322-1344
AD-1554642	CAGGGUGCCCGCAGGGAACAU		1340-1360	AUGUUCCCUGCGGGCACCCUGAA		1338-1360
AD-1554653	CAGGGAACAGGAGCUGCUCAU		1351-1371	AUGAGCAGCUCCUGUUCCCUGCG		1349-1371
AD-1554658	AACAGGAGCUGCUCAGCCAAU		1356-1376	AUUGGCUGAGCAGCUCCUGUUCC		1354-1376
AD-1554663	GAGCUGCUCAGCCAAGAACUU		1361-1381	AAGUUCUUGGCUGAGCAGCUCCU		1359-1381
AD-1554668	GCUCAGCCAAGAACUGUGGCU		1366-1386	AGCCACAGUUCUUGGCUGAGCAG		1364-1386
AD-1554690	UGCCAGGAUGCCGAAGGAUAU		1395-1415	AUAUCCUUCGGCAUCCUGGCAGC		1393-1415
AD-1554696	UCAUGUGGUCAAUAAAAGUCU		1438-1458	AGACUUUUAUUGACCACAUGACC		1436-1458
AD-1554704	UCAAUAAAAGUCCUUAGGUGU		1446-1466	ACACCUAAGGACUUUUAUUGACC		1444-1466
AD-1554709	AAAAGUCCUUAGGUGCUGCCU		1451-1471	AGGCAGCACCUAAGGACUUUUAU		1449-1471

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Table 16. Modified Sense and Antisense Strand Sequences of PRODH2 dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Anti sense Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1553630	asgsaaccUfuCfCfCfuggugguggauL96		asUfsccaCfaCfCfagggAfaGfguucuscsu		AGAGAACCUUCCCUGGUGUGGAG	
AD-1553635	csusucccUfgGfUfGfuggaggcaguL96		asCfsugcCfuCfCfacacCfaGfggaagsgsu		ACCUUCCCUGGUGUGGAGGCAGC	
AD-1553662	csasggauGfcUfCfCfggaccuguuuL96		asAfsacaGfgUfCfcggaGfcAfuccugsgsg		CCCAGGAUGCUCCGGACCUGUUA	
AD-1553667	usgscuccGfgAfCfCfuguuacguguL96		asCfsacgUfaAfCfagguCfcGfgagcasusc		GAUGCUCCGGACCUGUUACGUGC	
AD-1553674	gsasccugUfuAfCfGfugcucuguuuL96		asAfsacaGfaGfCfacguAfaCfaggucscsg		CGGACCUGUUACGUGCUCUGUUC	
AD-1553681	usascgugCfuCfUfGfuucccaagcuL96		asGfscuuGfgGfAfacagAfgCfacguasasc		GUUACGUGCUCUGUUCCCAAGCU	
AD-1553686	gscsucugUfuCfCfCfaagcuggucuL96		asGfsaccAfgCfUfugggAfaCfagagcsasc		GUGCUCUGUUCCCAAGCUGGUCC	
AD-1553691	csusggcaGfuCfCfCfugagcuuuguL96		asCfsaaaGfcUfCfagggAfcUfgccagscsc		GGCUGGCAGUCCCUGAGCUUUGA	
AD-1553697	gsuscccuGfaGfCfUfuugauggcguL96		asCfsgccAfuCfAfaagcUfcAfgggacsusg		CAGUCCCUGAGCUUUGAUGGCGG	
AD-1553701	gscscuucCfaCfCfUfuaagggcacuL96		asGfsugcCfcUfUfaaggUfgGfaaggcscsc		GGGCCUUCCACCUUAAGGGCACA	
AD-1553707	csasccuuAfaGfGfGfcacaggagauL96		asUfscucCfuGfUfgcccUfuAfaggugsgsa		UCCACCUUAAGGGCACAGGAGAG	
AD-1553715	gsgsgcacAfgGfAfGfagcugacacuL96		asGfsuguCfaGfCfucucCfuGfugcccsusu		AAGGGCACAGGAGAGCUGACACG	
AD-1553722	gsgsagagCfuGfAfCfacgggccuuuL96		asAfsaggCfcCfGfugucAfgCfucuccsusg		CAGGAGAGCUGACACGGGCCUUG	
AD-1553730	gsascacgGfgCfCfUfugcugguucuL96		asGfsaacCfaGfCfaaggCfcCfgugucsasg		CUGACACGGGCCUUGCUGGUUCU	
AD-1553739	csusugcuGfgUfUfCfuccggcuguuL96		asAfscagCfcGfGfagaaCfcAfgcaagsgsc		GCCUUGCUGGUUCUCCGGCUGUG	
AD-1553745	gsgsuucuCfcGfGfCfugugugccuuL96		asAfsggcAfcAfCfagccGfgAfgaaccsasg		CUGGUUCUCCGGCUGUGUGCCUG	
AD-1553751	csuscgucAfcUfCfAfcgggcuguuuL96		asAfsacaGfcCfCfgugaGfuGfacgagsusg		CACUCGUCACUCACGGGCUGUUG	
AD-1553758	csuscacgGfgCfUfGfuugcuccaguL96		asCfsuggAfgCfAfacagCfcCfgugagsusg		CACUCACGGGCUGUUGCUCCAGG	
AD-1553769	ususgcucCfaGfGfCfcuggucucguL96		asCfsgagAfcCfAfggccUfgGfagcaascsa		UGUUGCUCCAGGCCUGGUCUCGG	
AD-1553794	gsgscucuCfaGfGfCfgcauuucucuL96		asGfsagaAfaUfGfcgccUfgAfgagccsgsg		CCGGCUCUCAGGCGCAUUUCUCC	
AD-1553799	uscsaggcGfcAfUfUfucuccgagcuL96		asGfscucGfgAfGfaaauGfcGfccugasgsa		UCUCAGGCGCAUUUCUCCGAGCA	
AD-1553804	csgscauuUfcUfCfCfgagcauccguL96		asCfsggaUfgCfUfcggaGfaAfaugcgscsc		GGCGCAUUUCUCCGAGCAUCCGU	
AD-1553809	ususcuccGfaGfCfAfuccgucuauuL96		asAfsuagAfcGfGfaugcUfcGfgagaasasu		AUUUCUCCGAGCAUCCGUCUAUG	
AD-1553815	gsasgcauCfcGfUfCfuaugggcaguL96		asCfsugcCfcAfUfagacGfgAfugcucsgsg		CCGAGCAUCCGUCUAUGGGCAGU	
AD-1553820	uscscgucUfaUfGfGfgcaguuuguuL96		asAfscaaAfcUfGfcccaUfaGfacggasusg		CAUCCGUCUAUGGGCAGUUUGUG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Anti sense Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1553826	usasugggCfaGfUfUfuguggcuggguL96		asCfscagCfcAfCfaaacUfgCfccauasgsa		UCUAUGGGCAGUUUGUGGCUGGU	
AD-1553832	csasguuuGfuGfGfCfuggugagacuL96		asGfsucuCfaCfCfagccAfcAfaacugscsc		GGCAGUUUGUGGCUGGUGAGACA	
AD-1553839	usgsgcugGfuGfAfGfacagcagaguL96		asCfsucuGfcUfGfucucAfcCfagccascsa		UGUGGCUGGUGAGACAGCAGAGG	
AD-1553845	gsusgagaCfaGfCfAfgaggagguguL96		asCfsaccUfcCfUfcugcUfgUfcucacscsa		UGGUGAGACAGCAGAGGAGGUGA	
AD-1553852	asgscagaGfgAfGfGfugaagggcuuL96		asAfsgccCfuUfCfaccuCfcUfcugcusgsu		ACAGCAGAGGAGGUGAAGGGCUG	
AD-1553859	gsasggugAfaGfGfGfcugcgugcauL96		asUfsgcaCfgCfAfgcccUfuCfaccucscsu		AGGAGGUGAAGGGCUGCGUGCAG	
AD-1553865	asasgggcUfgCfGfUfgcagcagcuuL96		asAfsgcuGfcUfGfcacgCfaGfcccuuscsa		UGAAGGGCUGCGUGCAGCAGCUG	
AD-1553907	usgscuggCfaGfUfGfcccacugaguL96		asCfsucaGfuGfGfgcacUfgCfcagcasgsu		ACUGCUGGCAGUGCCCACUGAGG	
AD-1553912	gscsagugCfcCfAfCfugaggaggauL96		asUfsccuCfcUfCfagugGfgCfacugcscsa		UGGCAGUGCCCACUGAGGAGGAG	
AD-1553922	csusgaggAfgGfAfGfccggacucuuL96		asAfsgagUfcCfGfgcucCfuCfcucagsusg		CACUGAGGAGGAGCCGGACUCUG	
AD-1553930	gsasgccgGfaCfUfCfugcugccaauL96		asUfsuggCfaGfCfagagUfcCfggcucscsu		AGGAGCCGGACUCUGCUGCCAAG	
AD-1553937	ascsucugCfuGfCfCfaagagugguuL96		asAfsccaCfuCfUfuggcAfgCfagaguscsc		GGACUCUGCUGCCAAGAGUGGUG	
AD-1553942	gscsugccAfaGfAfGfuggugaggcuL96		asGfsccuCfaCfCfacucUfuGfgcagcsasg		CUGCUGCCAAGAGUGGUGAGGCG	
AD-1553951	asgsugguGfaGfGfCfgugguaugauL96		asUfscauAfcCfAfcgccUfcAfccacuscsu		AGAGUGGUGAGGCGUGGUAUGAG	
AD-1553957	asasccucGfgUfGfCfuaugcugcguL96		asCfsgcaGfcAfUfagcaCfcGfagguuscsc		GGAACCUCGGUGCUAUGCUGCGG	
AD-1553962	csgsgugcUfaUfGfCfugcgguguguL96		asCfsacaCfcGfCfagcaUfaGfcaccgsasg		CUCGGUGCUAUGCUGCGGUGUGU	
AD-1553967	csusaugcUfgCfGfGfuguguggacuL96		asGfsuccAfcAfCfaccgCfaGfcauagscsa		UGCUAUGCUGCGGUGUGUGGACC	
AD-1553975	csgsguguGfuGfGfAfccugucacguL96		asCfsgugAfcAfGfguccAfcAfcaccgscsa		UGCGGUGUGUGGACCUGUCACGG	
AD-1553988	gsgsccagCfcUfCfAfugcagcugauL96		asUfscagCfuGfCfaugaGfgCfuggccsusc		GAGGCCAGCCUCAUGCAGCUGAA	
AD-1553993	gscscucaUfgCfAfGfcugaagguguL96		asCfsaccUfuCfAfgcugCfaUfgaggcsusg		CAGCCUCAUGCAGCUGAAGGUGA	
AD-1553998	asusgcagCfuGfAfAfggugacggcuL96		asGfsccgUfcAfCfcuucAfgCfugcausgsa		UCAUGCAGCUGAAGGUGACGGCG	
AD-1554003	gscsugaaGfgUfGfAfcggcgcugauL96		asUfscagCfgCfCfgucaCfcUfucagcsusg		CAGCUGAAGGUGACGGCGCUGAC	
AD-1554009	gsgsugacGfgCfGfCfugaccaguauL96		asUfsacuGfgUfCfagcgCfcGfucaccsusu		AAGGUGACGGCGCUGACCAGUAC	
AD-1554018	gscsugacCfaGfUfAfcucggcucuuL96		asAfsgagCfcGfAfguacUfgGfucagcsgsc		GCGCUGACCAGUACUCGGCUCUG	
AD-1554025	asgsuacuCfgGfCfUfcuguaaggauL96		asUfsccuUfaCfAfgagcCfgAfguacusgsg		CCAGUACUCGGCUCUGUAAGGAG	
AD-1554030	uscsggcuCfuGfUfAfaggagcuaguL96		asCfsuagCfuCfCfuuacAfgAfgccgasgsu		ACUCGGCUCUGUAAGGAGCUAGC	
AD-1554036	csusguaaGfgAfGfCfuagccucguuL96		asAfscgaGfgCfUfagcuCfcUfuacagsasg		CUCUGUAAGGAGCUAGCCUCGUG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Anti sense Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
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AD-1554048	asgsccucGfuGfGfGfucagaaggcuL96		asGfsccuUfcUfGfacccAfcGfaggcusasg		CUAGCCUCGUGGGUCAGAAGGCC	
AD-1554054	gsusggguCfaGfAfAfggccaggaguL96		asCfsuccUfgGfCfcuucUfgAfcccacsgsa		UCGUGGGUCAGAAGGCCAGGAGC	
AD-1554065	gsgsccagGfaGfCfCfuccuuggaguL96		asCfsuccAfaGfGfaggcUfcCfuggccsusu		AAGGCCAGGAGCCUCCUUGGAGC	
AD-1554070	gsgsagccUfcCfUfUfggagcugaguL96		asCfsucaGfcUfCfcaagGfaGfgcuccsusg		CAGGAGCCUCCUUGGAGCUGAGC	
AD-1554074	gsasgaggCfuGfGfCfugaagcuauuL96		asAfsuagCfuUfCfagccAfgCfcucucsgsg		CCGAGAGGCUGGCUGAAGCUAUG	
AD-1554082	gsgscugaAfgCfUfAfuggacucuguL96		asCfsagaGfuCfCfauagCfuUfcagccsasg		CUGGCUGAAGCUAUGGACUCUGG	
AD-1554089	gscsuaugGfaCfUfCfugggcagaauL96		asUfsucuGfcCfCfagagUfcCfauagcsusu		AAGCUAUGGACUCUGGGCAGAAC	
AD-1554097	csuscuggGfcAfGfAfaccuccagguL96		asCfscugGfaGfGfuucuGfcCfcagagsusc		GACUCUGGGCAGAACCUCCAGGU	
AD-1554106	gsasaccuCfcAfGfGfucuccugccuL96		asGfsgcaGfgAfGfaccuGfgAfgguucsusg		CAGAACCUCCAGGUCUCCUGCCU	
AD-1554111	uscscaggUfcUfCfCfugccucaauuL96		asAfsuugAfgGfCfaggaGfaCfcuggasgsg		CCUCCAGGUCUCCUGCCUCAAUG	
AD-1554119	uscscugcCfuCfAfAfugcugagcauL96		asUfsgcuCfaGfCfauugAfgGfcaggasgsa		UCUCCUGCCUCAAUGCUGAGCAG	
AD-1554126	uscsaaugCfuGfAfGfcagaaccaguL96		asCfsuggUfuCfUfgcucAfgCfauugasgsg		CCUCAAUGCUGAGCAGAACCAGC	
AD-1554131	gscsugagCfaGfAfAfccagcaccuuL96		asAfsgguGfcUfGfguucUfgCfucagcsasu		AUGCUGAGCAGAACCAGCACCUC	
AD-1554156	gscsaucgGfgUfGfGfcacaguauguL96		asCfsauaCfuGfUfgccaCfcCfgaugcsasg		CUGCAUCGGGUGGCACAGUAUGC	
AD-1554186	csusccugGfuGfGfAfugcggaguauL96		asUfsacuCfcGfCfauccAfcCfaggagscsc		GGCUCCUGGUGGAUGCGGAGUAC	
AD-1554193	usgsgaugCfgGfAfGfuacaccucauL96		asUfsgagGfuGfUfacucCfgCfauccascsc		GGUGGAUGCGGAGUACACCUCAC	
AD-1554198	gscsggagUfaCfAfCfcucacugaauL96		asUfsucaGfuGfAfggugUfaCfuccgcsasu		AUGCGGAGUACACCUCACUGAAC	
AD-1554203	gsusacacCfuCfAfCfugaacccuguL96		asCfsaggGfuUfCfagugAfgGfuguacsusc		GAGUACACCUCACUGAACCCUGC	
AD-1554210	uscsacugAfaCfCfCfugcgcucucuL96		asGfsagaGfcGfCfagggUfuCfagugasgsg		CCUCACUGAACCCUGCGCUCUCG	
AD-1554216	asascccuGfcGfCfUfcucgcugcuuL96		asAfsgcaGfcGfAfgagcGfcAfggguuscsa		UGAACCCUGCGCUCUCGCUGCUG	
AD-1554263	cscscuggGfuGfUfGfgaacaccuauL96		asUfsaggUfgUfUfccacAfcCfcagggscsc		GGCCCUGGGUGUGGAACACCUAC	
AD-1554268	gsgsugugGfaAfCfAfccuaccagguL96		asCfscugGfuAfGfguguUfcCfacaccscsa		UGGGUGUGGAACACCUACCAGGC	
AD-1554278	ascscuacCfaGfGfCfcugucuaaauL96		asUfsuuaGfaCfAfggccUfgGfuaggusgsu		ACACCUACCAGGCCUGUCUAAAG	
AD-1554287	gscscuguCfuAfAfAfggacacauuuL96		asAfsaugUfgUfCfcuuuAfgAfcaggcscsu		AGGCCUGUCUAAAGGACACAUUC	
AD-1554292	uscsuaaaGfgAfCfAfcauucgagcuL96		asGfscucGfaAfUfguguCfcUfuuagascsa		UGUCUAAAGGACACAUUCGAGCG	
AD-1554298	gsgsacacAfuUfCfGfagcggcugguL96		asCfscagCfcGfCfucgaAfuGfuguccsusu		AAGGACACAUUCGAGCGGCUGGG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Anti sense Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1554317	gsgsccuuCfgGfAfGfugaagcugguL96		asCfscagCfuUfCfacucCfgAfaggccsasg		CUGGCCUUCGGAGUGAAGCUGGU	
AD-1554323	csgsgaguGfaAfGfCfugguacgaguL96		asCfsucgUfaCfCfagcuUfcAfcuccgsasa		UUCGGAGUGAAGCUGGUACGAGG	
AD-1554328	usgsaagcUfgGfUfAfcgaggugcauL96		asUfsgcaCfcUfCfguacCfaGfcuucascsu		AGUGAAGCUGGUACGAGGUGCAU	
AD-1554333	csusgguaCfgAfGfGfugcauaucuuL96		asAfsgauAfuGfCfaccuCfgUfaccagscsu		AGCUGGUACGAGGUGCAUAUCUG	
AD-1554340	gsasggugCfaUfAfUfcuggacaaguL96		asCfsuugUfcCfAfgauaUfgCfaccucsgsu		ACGAGGUGCAUAUCUGGACAAGG	
AD-1554346	csasuaucUfgGfAfCfaaggagagauL96		asUfscucUfcCfUfugucCfaGfauaugscsa		UGCAUAUCUGGACAAGGAGAGAG	
AD-1554351	csusggacAfaGfGfAfgagagcgguuL96		asAfsccgCfuCfUfcuccUfuGfuccagsasu		AUCUGGACAAGGAGAGAGCGGUG	
AD-1554371	gscsccagCfuCfCfAfugggauggauL96		asUfsccaUfcCfCfauggAfgCfugggcscsa		UGGCCCAGCUCCAUGGGAUGGAA	
AD-1554376	gscsuccaUfgGfGfAfuggaagaccuL96		asGfsgucUfuCfCfauccCfaUfggagcsusg		CAGCUCCAUGGGAUGGAAGACCC	
AD-1554379	csuscagcCfuGfAfCfuaugaggccuL96		asGfsgccUfcAfUfagucAfgGfcugagsusg		CACUCAGCCUGACUAUGAGGCCA	
AD-1554387	gsascuauGfaGfGfCfcaccagucauL96		asUfsgacUfgGfUfggccUfcAfuagucsasg		CUGACUAUGAGGCCACCAGUCAG	
AD-1554393	gsasggccAfcCfAfGfucagaguuauL96		asUfsaacUfcUfGfacugGfuGfgccucsasu		AUGAGGCCACCAGUCAGAGUUAC	
AD-1554399	ascscaguCfaGfAfGfuuacagccguL96		asCfsggcUfgUfAfacucUfgAfcuggusgsg		CCACCAGUCAGAGUUACAGCCGC	
AD-1554404	uscsagagUfuAfCfAfgccgcugccuL96		asGfsgcaGfcGfGfcuguAfaCfucugascsu		AGUCAGAGUUACAGCCGCUGCCU	
AD-1554413	csasgccgCfuGfCfCfuggaacugauL96		asUfscagUfuCfCfaggcAfgCfggcugsusa		UACAGCCGCUGCCUGGAACUGAU	
AD-1554418	gscsugccUfgGfAfAfcugaugcuguL96		asCfsagcAfuCfAfguucCfaGfgcagcsgsg		CCGCUGCCUGGAACUGAUGCUGA	
AD-1554425	gsgsaacuGfaUfGfCfugacgcacguL96		asCfsgugCfgUfCfagcaUfcAfguuccsasg		CUGGAACUGAUGCUGACGCACGU	
AD-1554430	usgsaugcUfgAfCfGfcacguggccuL96		asGfsgccAfcGfUfgcguCfaGfcaucasgsu		ACUGAUGCUGACGCACGUGGCCC	
AD-1554433	csasugugCfcAfCfCfcucaugguggguL96		asCfscacCfaUfGfagguGfgCfacaugsgsg		CCCAUGUGCCACCUCAUGGUGGC	
AD-1554443	csuscaugGfuGfGfCfuucccacaauL96		asUfsuguGfgGfAfagccAfcCfaugagsgsu		ACCUCAUGGUGGCUUCCCACAAU	
AD-1554451	gsgscuucCfcAfCfAfaugaggaauuL96		asAfsuucCfuCfAfuuguGfgGfaagccsasc		GUGGCUUCCCACAAUGAGGAAUC	
AD-1554456	cscscacaAfuGfAfGfgaaucuguuuL96		asAfsacaGfaUfUfccucAfuUfgugggsasa		UUCCCACAAUGAGGAAUCUGUUC	
AD-1554461	asasugagGfaAfUfCfuguucgccauL96		asUfsggcGfaAfCfagauUfcCfucauusgsu		ACAAUGAGGAAUCUGUUCGCCAG	
AD-1554470	uscsguuuCfgCfCfAfggcaaccaauL96		asUfsuggUfuGfCfcuggCfgAfacagasusu		AAUCUGUUCGCCAGGCAACCAAG	
AD-1554475	uscsgccaGfgCfAfAfccaagcgcauL96		asUfsgcgCfuUfGfguugCfcUfggcgasasc		GUUCGCCAGGCAACCAAGCGCAU	
AD-1554482	gscsaaccAfaGfCfGfcaugugggauL96		asUfscccAfcAfUfgcgcUfuGfguugcscsu		AGGCAACCAAGCGCAUGUGGGAG	
AD-1554487	csasagcgCfaUfGfUfgggagcugguL96		asCfscagCfuCfCfcacaUfgCfgcuugsgsu		ACCAAGCGCAUGUGGGAGCUGGG	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Anti sense Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
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AD-1554497	usgsggagCfuGfGfGfcauuccucuuL96		asAfsgagGfaAfUfgcccAfgCfucccascsa		UGUGGGAGCUGGGCAUUCCUCUG	
AD-1554505	gsgsgcauUfcCfUfCfuggaugggauL96		asUfscccAfuCfCfagagGfaAfugcccsasg		CUGGGCAUUCCUCUGGAUGGGAC	
AD-1554510	ususccucUfgGfAfUfgggacugucuL96		asGfsacaGfuCfCfcaucCfaGfaggaasusg		CAUUCCUCUGGAUGGGACUGUCU	
AD-1554515	csusggauGfgGfAfCfugucuguuuuL96		asAfsaacAfgAfCfagucCfcAfuccagsasg		CUCUGGAUGGGACUGUCUGUUUC	
AD-1554520	usgsggacUfgUfCfUfguuucggacuL96		asGfsuccGfaAfAfcagaCfaGfucccasusc		GAUGGGACUGUCUGUUUCGGACA	
AD-1554525	csusgucuGfuUfUfCfggacaacuuuL96		asAfsaguUfgUfCfcgaaAfcAfgacagsusc		GACUGUCUGUUUCGGACAACUUC	
AD-1554533	ususcggaCfaAfCfUfucugggcauuL96		asAfsugcCfcAfGfaaguUfgUfccgaasasc		GUUUCGGACAACUUCUGGGCAUG	
AD-1554542	csusucugGfgCfAfUfgugugaccauL96		asUfsgguCfaCfAfcaugCfcCfagaagsusu		AACUUCUGGGCAUGUGUGACCAC	
AD-1554551	asusguguGfaCfCfAfcgucucucuuL96		asAfsgagAfgAfCfguggUfcAfcacausgsc		GCAUGUGUGACCACGUCUCUCUA	
AD-1554557	gsasccacGfuCfUfCfucuagcacuuL96		asAfsgugCfuAfGfagagAfcGfuggucsasc		GUGACCACGUCUCUCUAGCACUG	
AD-1554562	gscsaggcCfgGfCfUfauguaguguuL96		asAfscacUfaCfAfuagcCfgGfccugcscsc		GGGCAGGCCGGCUAUGUAGUGUA	
AD-1554567	cscsggcuAfuGfUfAfguguauaaguL96		asCfsuuaUfaCfAfcuacAfuAfgccggscsc		GGCCGGCUAUGUAGUGUAUAAGU	
AD-1554573	asusguagUfgUfAfUfaaguccauuuL96		asAfsaugGfaCfUfuauaCfaCfuacausasg		CUAUGUAGUGUAUAAGUCCAUUC	
AD-1554578	gsusguauAfaGfUfCfcauucccuauL96		asUfsaggGfaAfUfggacUfuAfuacacsusa		UAGUGUAUAAGUCCAUUCCCUAU	
AD-1554584	asasguccAfuUfCfCfcuauggcucuL96		asGfsagcCfaUfAfgggaAfuGfgacuusasu		AUAAGUCCAUUCCCUAUGGCUCC	
AD-1554591	ususcccuAfuGfGfCfuccuuggaguL96		asCfsuccAfaGfGfagccAfuAfgggaasusg		CAUUCCCUAUGGCUCCUUGGAGG	
AD-1554599	gsgscuccUfuGfGfAfggagguaauuL96		asAfsuuaCfcUfCfcuccAfaGfgagccsasu		AUGGCUCCUUGGAGGAGGUAAUC	
AD-1554609	asusccggAfgGfGfCfccaggagaauL96		asUfsucuCfcUfGfggccCfuCfcggauscsa		UGAUCCGGAGGGCCCAGGAGAAC	
AD-1554626	gsasaccgGfaGfCfGfugcuucagguL96		asCfscugAfaGfCfacgcUfcCfgguucsusc		GAGAACCGGAGCGUGCUUCAGGG	
AD-1554642	csasggguGfcCfCfGfcagggaacauL96		asUfsguuCfcCfUfgcggGfcAfcccugsasa		UUCAGGGUGCCCGCAGGGAACAG	
AD-1554653	csasgggaAfcAfGfGfagcugcucauL96		asUfsgagCfaGfCfuccuGfuUfcccugscsg		CGCAGGGAACAGGAGCUGCUCAG	
AD-1554658	asascaggAfgCfUfGfcucagccaauL96		asUfsuggCfuGfAfgcagCfuCfcuguuscsc		GGAACAGGAGCUGCUCAGCCAAG	
AD-1554663	gsasgcugCfuCfAfGfccaagaacuuL96		asAfsguuCfuUfGfgcugAfgCfagcucscsu		AGGAGCUGCUCAGCCAAGAACUG	
AD-1554668	gscsucagCfcAfAfGfaacuguggcuL96		asGfsccaCfaGfUfucuuGfgCfugagcsasg		CUGCUCAGCCAAGAACUGUGGCG	
AD-1554690	usgsccagGfaUfGfCfcgaaggauauL96		asUfsaucCfuUfCfggcaUfcCfuggcasgsc		GCUGCCAGGAUGCCGAAGGAUAC	
AD-1554696	uscsauguGfgUfCfAfauaaaagucuL96		asGfsacuUfuUfAfuugaCfcAfcaugascsc		GGUCAUGUGGUCAAUAAAAGUCC	

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Anti sense Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1554704	uscsaauaAfaAfGfUfccuuagguguL96		asCfsaccUfaAfGfgacuUfuUfauugascsc		GGUCAAUAAAAAGUCCUUAGGUGC	
AD-1554709	asasaaguCfcUfUfAfggugcugccuL96		asGfsgcaGfcAfCfcuaaGfgAfcuuuusasu		AUAAAAGUCCUUAGGUGCUGCCU	

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Example 2. A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Lumasiran in Patients with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels

Kidney stones are common, affecting approximately 1 in 11 people in the United States, and the prevalence of kidney stone disease has been increasing worldwide over time (Scales, *et al. Eur Urol.* 2012 Jul;62(1):160-5). Approximately 80% of kidney stones in adults are formed from calcium oxalate crystals, with the remainder being predominantly calcium phosphate, uric acid, cystine, or struvite (Worcester EM and Coe FL. *Nephrolithiasis. Prim Care.* 2008 Jun;35(2):369-91; Worcester EM,Coe FL. *N Engl J Med.* 2010 Sep 2;363(10):954-63). Stone formation occurs when a supersaturating level of calcium oxalate is present in the urine, with increasing risk of stone formation as urine oxalate levels increase (Curhan and Taylor *Kidney Int.* 2008 Feb;73(4):489-96). High levels of urinary oxalate may be derived from both endogenous synthesis and diet. More than half of oxalate is endogenous in origin and presumed to come largely from the liver (Mitchell, *et al. Circ Res.* 2018 Feb 16;122(4):555-9). Studies have shown that reduced calcium oxalate supersaturation and urinary oxalate levels are associated with reduced stone formation (Borgh, *et al. N Engl J Med.* 2002 Jan 10;346(2):77-84; Ferrar, *et al. J Urol.* 2018 Nov;200(5):1082-7; Prochaska, *et al. J Urol.* 2018 May;199(5):1262-6].

Kidney stones can develop in patients of all ages; however, the highest incidence rates occur in individuals aged 40 to 66 years (Shin, *et al. World J Nephrol.* 2018 Nov 24;7(7):129-42). There is significant clinical burden associated with the development of kidney stones for patients with recurrent calcium oxalate kidney stone disease, including pain, infection/sepsis, diagnostic and therapeutic procedures, hospitalizations, and a greater risk for developing chronic kidney disease (CKD) and end stage kidney disease (ESKD). For patients with recurrent calcium oxalate stone formation, multiple stone removal procedures may be required. These procedures are invasive and place the patient at risk of complications including bleeding and infection. Patients experiencing obstructive kidney stones can also experience acute kidney injury with permanent loss of renal function. As a result, patients with recurrent kidney stone formation have a higher risk of progression to CKD and ESKD (Dhondup, *et al.* Am J Kidney Dis. 2018 Dec;72(6):790-72018; Rul, *et al.* Clin J Am Soc Nephrol. 2009 Apr;4(4):804-11).

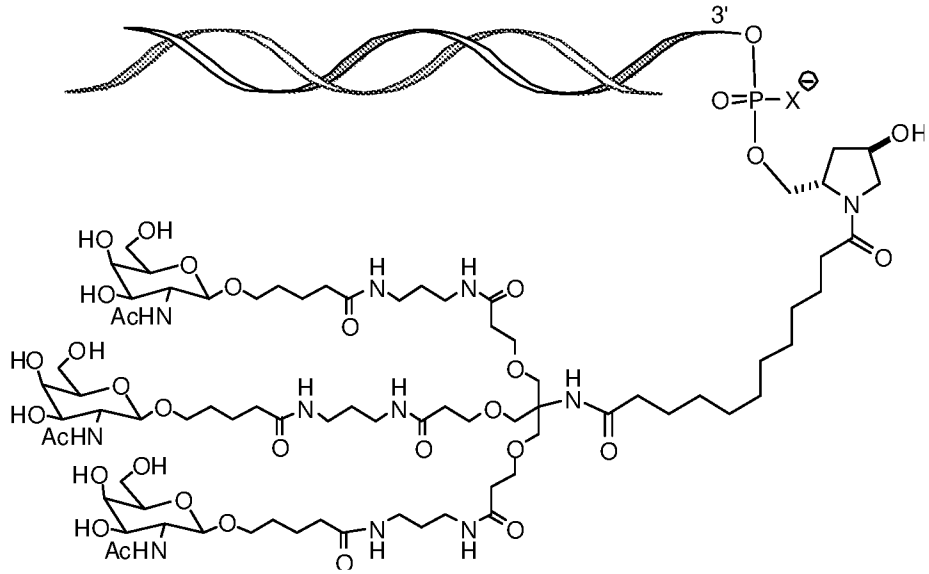
The typical clinical presentation of kidney stones includes sudden onset of lumbar flank pain and hematuria, and may include nausea and vomiting. Evaluation to assess etiology includes assessment of the patient's medical history, medication use, and dietary and lifestyle risk factors. Confirmation of diagnosis may involve renal ultrasound, abdominal x-ray, and/or computed tomography (CT) Heilberg, *et al.* Endocrinol Metabol. 2006 Aug;50(4):823-31). Twenty-four-hour urine collections analyzed for total volume, calcium, oxalate, uric acid, citrate, and other analytes may help to determine the underlying etiology (Pearle, *et al. J Urol.* 2014 Aug;192(2):316-24). Stone composition is generally determined in at least one instance.

There are limited effective treatment options for patients with recurrent calcium oxalate kidney stone disease. Preventive measures in American and European guidelines recommend adequate fluid intake to ensure a urine volume of at least 2 to 2.5 liters daily and provide dietary advice to limit the consumption of oxalate-rich foods, sodium chloride, and animal protein content, while maintaining a normal calcium intake. In some situations, thiazide diuretics, potassium citrate, and/or allopurinol may be considered (Pearle, *supra*; Turk, *et al.* EAU Guidelines on Urolithiasis. EAU Annual Congress; 2021; Milan, Italy: EAU Guidelines Office).

Treatment of pain associated with kidney stone events may involve non-steroidal anti-inflammatory agents and/or opiate pain medications. Depending on the clinical context, medical expulsive therapy, extracorporeal shock-wave lithotripsy, ureteroscopy, stenting, and percutaneous nephrolithotomy are some of the treatment options that may be pursued (Turk, *supra*).

Lumasiran is a ribonucleic acid interference (RNAi) therapeutic that target glycolate oxidase (GO, or HAO1) which reducees hepatic oxalate production. Oxalate produced by the liver is largely excreted in the urine, and lumasiran has been shown to reduce urinary oxalate in patients with PH1. High levels of urinary oxalate increase the risk of stone formation; therefore, lumasiran may have efficacy in patients with recurrent calcium oxalate kidney stone disease who do not have PH1 but who produce high amounts of oxalate endogenously.

The sense strand of lumasiran comprises the nucleotide sequence nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the antisense strand comprises the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36). The sense strand of lumasiran is conjugated to a ligand as shown in the following schematic



and, wherein X is O.

Summary of Study Design

The study is a randomized, placebo-controlled, double-blind, multicenter, multinational, Phase 2 study to evaluate the efficacy, safety, pharmacodynamics (PD), and pharmacokinetics (PK) of lumasiran administered subcutaneously (SC) in patients with recurrent calcium oxalate kidney stone disease and elevated urinary oxalate levels.

The study consists of up to 2 months of screening and 15 months of double-blind treatment (a 6-month Primary Analysis Period followed by a 9-month Treatment Extension Period). Patients were screened from Day -60 to Day -1 to determine eligibility. During screening, patients provided at least two 24-hour urine collections to establish baseline urinary oxalate levels. Consented patients meeting all eligibility criteria were randomized 1:1:1 to receive study drug: lumasiran 567 mg, lumasiran 284 mg, or placebo. Stratification was performed at randomization according to mean baseline urinary oxalate level and the number of kidney stone events in the 12 months prior to screening.

Patients were administered SC injections of lumasiran (284 mg or 567 mg) and/or placebo at the same volume (1.5.mL), on Day 1, Month 3, and Month 9.

Lumasiran 567 mg	**Lumasiran 284 mg**	**Placebo**
1.5 mL lumasiran	1.5 mL lumasiran	1.5 mL placebo
1.5 mL lumasiran	1.5 mL placebo	1.5 mL placebo

During the 6-month Primary Analysis Period, patients were dosed on Day 1 (baseline) and at Month 3. During the Treatment Extension Period, one additional dose will be administered at Month 9; an end of study (EOS) visit will take place at Month 15. Study drug was administered SC. Patients will be assessed for efficacy, safety, PD, and PK. Efficacy assessments will include evaluation of urinary oxalate excretion, urinary calcium oxalate supersaturation, and kidney stone events (including clinical events and low-dose kidney-protocol CT). Safety assessments will include collection of adverse events (AEs), clinical laboratory tests, vital sign assessments, physical examinations, and concomitant medications.

Rationale for Study Design

The primary endpoint for this Phase 2 study is the percent change in 24-hour urinary oxalate excretion. To confirm the optimal dosing regimen, and to facilitate the collection of kidney stone event data (an exploratory endpoint), the study will continue through Month 15. A placebo comparator is included because there is no approved standard of care therapy to decrease urinary oxalate.

A blood DNA sample will be collected as part of standard screening assessments (if testing has not already been performed) to ensure the exclusion of patients with primary hyperoxaluria type 1 (PH1), type 2 (PH2), and type 3 (PH3). Lumasiran is approved in some countries for the treatment of PH1, and patients with PH2 and PH3 are not expected to respond to lumasiran.

Because the primary endpoint will rely on measurements of urinary oxalate, and because some urinary oxalate is diet-derived, diet is an important variable in this study. In a 5-year study of recurrent stone formers published by Borghi *et al.* (*supra*), patients randomized to a normal calcium, low protein/salt diet had lower urinary oxalate levels and a lower cumulative incidence of recurrent kidney stones when compared to a low calcium diet. During the current study, and as of the time of informed consent, patients will be asked to adhere to a diet appropriate for stone formers, including adequate calcium intake and avoidance of spinach and other foods that are high in oxalate.

The secondary endpoint to assess meaningful reduction in 24-hour urinary oxalate from baseline to Month 6 (Months 4 through 6) defines a clinically meaningful reduction as ≥20% in the non-PH1 stone former population, supported by available literature based on stone former populations.

Treatment Groups

Patients were randomized 1:1:1 to receive lumasiran 284 mg, lumasiran 567 mg, or placebo, administered at the same volume, for the duration of the study. Stratification was performed at randomization according to mean baseline urinary oxalate level (>1.25 × ULN vs ≤1.25 × ULN) and the number of historical kidney stone events in the 12 months prior to screening (>1 vs ≤1).

For stratification, a historical kidney stone event is defined as:

- the visible passage of a kidney stone
- a procedural intervention for removal of an asymptomatic or symptomatic stone
  - if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
  - if more than 1 procedure was required to remove a single stone, this counts as 1 event
- a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on CT imaging
  - it must be evident from the CT scans that the new or enlarged kidney stone event occurred during the 12 months prior to screening
  - if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.

Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age

1. Age 18 years or older (or age of legal consent, whichever is older).

Patient and Disease Characteristics

2. Recurrent kidney stone disease, defined as ≥2 stone events within the 5 years prior to screening. For inclusion, a historical kidney stone event is defined as:
   - the visible passage of a kidney stone
   - a procedural intervention for removal of an asymptomatic or symptomatic stone

- if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
- if more than 1 procedure was required to remove a single stone, this counts as 1 event

- a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on CT imaging
  - it must be evident from the CT scans that the new or enlarged kidney stone event occurred during 5 years prior to screening
  - if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.

3. The 2 most recently analyzed kidney stones prior to randomization contained 50% or more of calcium oxalate; if only one stone analysis is available, then it must have contained 50% or more of calcium oxalate.

4. 24-hour urinary oxalate levels from 2 valid 24-hour urine collections obtained during screening are >ULN.

5. Willing to adhere to dietary recommendations appropriate for stone formers including limiting vitamin C supplementation to <200 mg daily.

6. If taking medications and/or hydrating for kidney stone prophylaxis, or taking medications that alter urinary oxalate excretion and/or kidney stone formation, must have been on a stable regimen for at least 60 days before randomization, and willing to remain on this stable regimen for the duration of the study.

7. Body mass index (the weight in kilograms divided by the square of the height in meters) of 20 to <40 kg/m^2.

Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Laboratory Assessments

1. Has any of the following laboratory parameter assessments at screening:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × ULN
   b. Total bilirubin >1.5 × ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2 × ULN
   c. International normalized ratio (INR) >2.0 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed)

2. Has an eGFR of <30 mL/min/1.73m^2 at screening (calculation will be based on the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine formula).

Prior/Concomitant Therapy

3. Received an investigational agent within the last 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug, or are in follow-up of another clinical study prior to study enrollment. Any agent that has received health agency authorization (including for emergency use) by local or regional regulatory authorities is not considered investigational.

Medical Conditions

4. Patients with a known history of secondary causes of elevated urinary oxalate and/or recurrent kidney stones including:

a. Primary hyperoxaluria
b. Severe eating disorders (anorexia or bulimia)
c. Chronic inflammatory bowel disease
d. Intestinal surgery with malabsorption or chronic diarrhea
e. Sarcoidosis
f. Primary hyperparathyroidism
g. Complete distal renal tubular acidosis

5. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation.

6. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.

7. History of intolerance to SC injection(s).

Contraception, Pregnancy, and Breastfeeding

8. Is not willing to comply with the contraceptive requirements during the study period,.

9. Female patient is pregnant, planning a pregnancy, or breast-feeding.

Alcohol Use

10. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).

11. History of alcohol abuse, within the last 12 months before screening, in the opinion of the Investigator.

Efficacy Assessments

24-Hour Urine Collections

Urinary oxalate excretion and calcium oxalate supersaturation (calculated from multiple parameters) will be determined from 24-hour urine sample collections to be completed at the time points specified. The start and stop dates/times of collection, the volume of urine in the collection, whether there were any missed voids, and whether the patient complied with dietary recommendations will be recorded. An aliquot of the 24-hour urine collection will also be used to determine urinary creatinine content and to determine if the 24-hour urine collections need to be repeated.

Validity Criteria for 24-hour Urine Collections

Throughout the study, a urine collection will be considered valid if each of the following criteria are met:

- The collection is between 22 to 26 hours in duration between the initial discarded void and the last void or attempt to void.
- No voids are missed between the start and end time of the collection as indicated by the patient's urine collection diary.
- The 24-hour creatinine content is at least 10 mg/kg as assessed by the central laboratory.
- Patient complied with dietary recommendations appropriate for oxalate stone formers (detailed in the Dietary Reference Sheet) for the 4 days prior to the start of the urine collection and during the collection.

24-hour urine collections that are known to be invalid should still be submitted for analysis.

Variability Criterion for 24-hour Urine Collections at Screening

If the 2 valid 24-hour urine collections from screening meet eligibility requirements (both 24-hour urinary oxalate levels >ULN), the variability between the oxalate levels (in mg/day) should be assessed as follows:

$$Variability = \left|\frac{(Oxalate\ value\ \#1 - Oxalate\ value\ \#2)}{(Average\ of\ oxalate\ values\ \#1\ \&\ \#2)}\right| \times 100\%$$

If the variability is >20%, then a third valid 24-hour urine collection should be obtained. The result of the third sample will not impact the patient's eligibility for the study.

Kidney Stone Events

Since kidney stone events are recorded as an efficacy assessment, these events will not be captured as AEs or serious adverse events (SAEs). However, if a patient experiences other AEs or SAEs during a kidney stone event, they should be reported as an AE.

Kidney stone events will be graded by the Investigator as mild, moderate, or severe:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an AE.

If there are changes in grade during an event, only the highest grade should be reported.

Clinical

All relevant clinical information pertaining to a kidney stone events should be obtained, including laboratory values, medical records, discharge summaries, and medical test results (including stone composition, if available, and radiology reports). A clinical kidney stone event is defined as one of the following:

- Visible passage of a kidney stone
- A procedural intervention for removal of an asymptomatic or symptomatic stone (information on the location, number, and size of stones removed will be collected)
- Or, in the case of potential stone passages without visible stones, it will be up to the Investigator to evaluate patients' symptoms and determine whether a stone passage occurred or the symptoms were due to a different cause.

Radiographic

A non-contrast low-dose kidney-protocol CT scan will be performed for all patients on Day 1 (may be performed up to 3 days prior to Day 1), and at Month 15.

For patients who terminate the study early, a CT scan should be performed at the ET visit only if this visit occurs after Month 6 and at the discretion of the Investigator, and where permitted, following consultation with the Medical Monitor. CT scans will be analyzed centrally.

Spot Urinary Oxalate:Creatinine Ratios

Urine oxalate:creatinine ratios will be calculated from the oxalate and creatinine levels measured in single-void urine collections. Single-void urine collections should be collected as a first morning void when possible; if this is not possible then the reason should be documented.

Estimated Glomerular Filtration Rate

Blood samples for the assessment of eGFR (mL/min/1.73m^2) will be obtained at the time points specified.

eGFR will be calculated based on the CKD-EPI formula:

CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12.

- Conventional units
  - eGFR (mL/min/1.73m^2) = 175 × (SCr [mg/dL])$^{-1.154}$ × (age)$^{-0.203}$ × (0.742, if female), or × (1.212, if African American)
- SI units
  - eGFR (mL/min/1.73m^2) = 175 × (SCr [µmol/L]/88.4)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742, if female), or × (1.212, if African American)

Abbreviations: eGFR= Estimated glomerular filtration rate; SCr=serum creatinine; SI=International System of Units

Pharmacodynamic Assessments

Urine and blood samples will be collected for assessment of PD parameters (plasma oxalate, plasma glycolate, and urinary glycolate) at the time points specified. Urine samples for exploratory analysis will be aliquoted from the samples provided for PD analysis. On dosing days, all blood and urine samples will be collected prior to study drug administration.

All PD assessments will be analyzed centrally. Postdose PD results will not be distributed to the sites until after the last patient completes assessments at the Month 15 visit. Site personnel should refrain from obtaining or viewing local oxalate, calcium oxalate supersaturation, or glycolate assessments, except as medically indicated, due to risk of unblinding.

Where local regulations allow and infrastructure is in place, a healthcare professional may collect urine or blood samples offsite.

Pharmacokinetic Assessments

Blood samples will be collected for the assessment of lumasiran PK parameters at the time points indicated.

The concentration of lumasiran in blood samples will be determined using a validated assay.

Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication and measurements of vital signs, weight and height, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded as either medical history or AEs, as appropriate.

Safety assessments are to be performed as specified. On dosing days and as applicable, assessments of vital signs, weight/height, physical examination, and clinical laboratory assessments are to be completed before study drug administration.

Quality of Life Outcomes

For pain assessments, patients will be asked to assess their "worst daily pain" (0=no pain at all; 10=pain as bad as you can imagine) from Question 3 of the Brief Pain Inventory - Short Form. This will be administered at screening, on Day 1, and daily while experiencing stone-related pain until the conclusion of the associated stone event.

The Wisconsin Stone Quality of Life Questionnaire (WISQOL) will be administered on Day 1 and upon conclusion of each clinical kidney stone event and will assess the degree of kidney stone impacts in terms of:

- Fatigue
- Sleep
- Social function
- Daily activities

- Physical / psychosocial symptoms

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.

Informal Sequence Listing

SEQ ID NO:1
>NM_001135239.1 Homo sapiens lactate dehydrogenase A (LDHA), transcript variant 2, mRNA

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SEQ ID NO:6
Reverse Complement of SEQ ID NO:5
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SEQ ID NO:7
>NM_001165416.1 Homo sapiens lactate dehydrogenase A (LDHA), transcript variant 5, mRNA
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SEQ ID NO:8
Reverse Complement of SEQ ID NO:7
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SEQ ID NO:9
>NM_005566.3 Homo sapiens lactate dehydrogenase A (LDHA), transcript variant 1, mRNA
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SEQ ID NO:10

Reverse Complement of SEQ ID NO:9

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SEQ ID NO:11

>NM_001136069.2 Mus musculus lactate dehydrogenase A (Ldha), transcript variant 2, mRNA

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SEQ ID NO:12
Reverse Complement of SEQ ID NO:11
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SEQ ID NO:13
>NM_010699.2 Mus musculus lactate dehydrogenase A (Ldha), transcript variant 1, mRNA
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SEQ ID NO:14
Reverse Complement of SEQ ID NO:13

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SEQ ID NO:15
>NM_017025.1 Rattus norvegicus lactate dehydrogenase A (Ldha), mRNA
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SEQ ID NO:16
Reverse Complement of SEQ ID NO:15
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SEQ ID NO:17
>NM_001257735.2 Macaca mulatta lactate dehydrogenase A (LDHA), mRNA
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SEQ ID NO:18
Reverse Complement of SEQ ID NO:17
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SEQ ID NO:19
>NM_001283551.1 Macaca fascicularis L-lactate dehydrogenase A chain (LDHA), mRNA
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SEQ ID NO:20
Reverse Complement of SEQ ID NO:19
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SEQ ID NO:21
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SEQ ID NO:22
Reverse Complement of SEQ ID NO:21
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CTTCTCTGCCTGCCGCACTAGCTTCTTGGTGACTTCTCGGTCCTTGTAGATATACAGTTGCAGCCAACGAAGTGC
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SEQ ID NO:23
>gi|544464345|ref|XM_005568381.1| PREDICTED: Macaca fascicularis hydroxyacid oxidase (glycolate oxidase) 1 (HAO1), mRNA
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SEQ ID NO:24
Reverse Complement of SEQ ID NO:23
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C

SEQ ID NO:25
>gi|133893166|ref|NM_010403.2| Mus musculus hydroxyacid oxidase 1, liver (Hao1), mRNA
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SEQ ID NO:26
Reverse Complement of SEQ ID NO:25
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AACC

SEQ ID NO:27
>gi|166157785|ref|NM_001107780.2| Rattus norvegicus hydroxyacid oxidase (glycolate oxidase) 1 (Hao1), mRNA
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SEQ ID NO:28
Reverse Complement of SEQ ID NO:27
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SEQ ID NO:29
>NM_000030.2 Homo sapiens alanine--glyoxylate and serine--pyruvate aminotransferase (AGXT), mRNA

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SEQ ID NO:30
>NP_000021.1 serine--pyruvate aminotransferase [Homo sapiens]
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LNAPPGTSLISFSDKAKKKMYSRKTKPFSFYLDIKWLANFWGCDDQPRMYHHTIPVISLYSLRESLALIA
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SEQ ID NO:31
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SEQ ID NO:32
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SEQ ID NO:34
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SEQ ID NO:35
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SEQ ID NO:36
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SEQ ID NO:4641

>NM_021232.2 Homo sapiens proline dehydrogenase 2 (PRODH2), transcript variant 1, mRNA

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TAA

SEQ ID NO: 4642 Reverse Complement of SEQ ID NO: 4641

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TACCACGCCTCACCACTCTTGGCAGCAGAGTCCGGCTCCTCCTCAGTGGGCACTGCCAGCAGTGGTCGGAGGCTG
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SEQ ID NO: 4643

>NM_019546.5 Mus musculus proline dehydrogenase (oxidase) 2 (Prodh2), mRNA

AGTGTGGTGGTAACCAGGCACTTGCAATGATCTGGACGCGTCTGCCGCTGTATGGCCCCTCCAAGCCCTC
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GGCCGGGGAGACAGCAGAGGAAGTGAGGAACTGTGTCGGGCAGCTGCAGGCCCTGGGACTCCAGCCCCTG
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SEQ ID NO: 4644 Reverse Complement of SEQ ID NO: 4643

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TGAGAGCCGGGATCCCAGGAGTCGCTGAGACCAGGCCTGAAACGCTAGTCCATGAGTGACCAAAGGGGGCCAGGC
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SEQ ID NO: 4645

>NM_001038588.1 Rattus norvegicus proline dehydrogenase 2 (Prodh2), mRNA

GGCACTTACAATGGTCTGGACGCGTCTGCCGCTGTACGGCCACTCCAAGCCCTCTACAGGTGGCTGGCAG
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SEQ ID NO: 4646 Reverse Complement of SEQ ID NO: 4645

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SEQ ID NO: 4647

>XM_005588902.2 PREDICTED: Macaca fascicularis proline dehydrogenase (oxidase) 2 (PRODH2), transcript variant X1, mRNA

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SEQ ID NO: 4648 Reverse Complement of SEQ ID NO: 4647

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SEQ ID NO: 4649

>XM_015123711.2 PREDICTED: Macaca mulatta proline dehydrogenase 2 (PRODH2), transcript variant X1, mRNA

CACGCACCTATAATCCCAGCTACTTGGGAGGGGGAGGAAGCAATTGCCACAAAAGCGGTTAAGTAGCTCG
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SEQ ID NO: 4650 Reverse Complement of SEQ ID NO:4649

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AAGTAGCTGGGATTATAGGTGCGTG

We claim:

1. A method for inhibiting the expression of hydroxyacid oxidase (HAO1) in a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate, comprising

administering to the subject a fixed dose of about 200 mg to about 600 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1,

thereby inhibiting the expression of HAO1 in the subject.

2. A method for reducing urinary oxalate levels in a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate, comprising

administering to the subject a fixed dose of about 200 mg to about 600 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1,

thereby reducing urinary oxalate levels in the subject.

3. The method of claim 2, wherein the urinary oxalate is urinary calcium oxalate.

4. The method of claim 3, wherein the reduction in urinary calcium oxalate is reduction in urinary calcium oxalate supersaturation.

5. A method for treating a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate, comprising

administering to the subject a fixed dose of about 200 mg to about 600 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1,

thereby treating the subject having the non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate.

6. The method of any one of claims 1-5, wherein the non-primary hyperoxaluria disease or disorder is selected from the group consisting of secondary hyperolxaluria, a kidney stone disease, chronic kidney disease (CKD), end-stage renal disease (ESRD), coronary artery disease, cutaneous oxalate deposition, ethylene glycol poisoning, planned kidney transplantation, and previous kidney transplantation.

7. The method of claim 6, wherein the non-primary hyperoxaluria disease or disorder is a kidney stone disease.

8. The method of claim 7, wherein the kidney stone disease is calcium oxalate kidney stone disease.

9. The method of claim 8, wherein the calcium oxalate kidney stone disease is recurrent calcium oxalate kidney stone disease.

10. The method of any one of claims 1 and 5-9, wherein administration of the dsRNA agent, or salt thereof, to the subject reduces urinary oxalate levels.

11. The method of claim 10, wherein the urinary oxalate is urinary calcium oxalate.

12. The method of claim 11, wherein the reduction in urinary calcium oxalate is reduction in urinary calcium oxalate supersaturation.

13. The method of any one of claims 1-12, wherein administration of the dsRNA agent, or salt thereof, to the subject reduces clinical and radiographic kidney stone events.

14. The method of any one of claims 1-13, wherein the subject is a human.

15. The method of any one of claims 1-14, wherein the dsRNA agent, or salt thereof, is administered to the subject at an interval of once every six months.

16. The method of any one of claims 1-14, wherein the dsRNA agent, or salt thereof, is administered to the subject initially, at three months, and every six months thereafter.

17. The method of any one of claims 1-16, wherein the fixed dose of the dsRNA agent, or salt thereof, is about 284 mg.

18. The method of any one of claims 1-16, wherein the fixed dose of the dsRNA agent, or salt thereof, is about 567 mg.

19. The method of any one of claims 1-18, wherein the dsRNA agent, or salt thereof, is administered to the subject subcutaneously.

20. The method of claim 18, wherein the subcutaneous administration is subcutaneous injection.

21. The method of claim any one of claims 1-20, wherein the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a portion of the nucleotide sequence of SEQ ID NO: 21 and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the corresponding portion of nucleotide sequence of SEQ ID NO: 22 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

22. The method of any one of claims 1-21, wherein the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 4-14.

23. The method of any one of claims 1-22, wherein the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises a nucleotide sequence differing by no more than 3 nucleotides from the nucleotide sequence 5'-GACUUUCAUCCUGGAAAUAUA -3' (SEQ ID NO:33) and the antisense strand comprises a nucleotide sequence differing by no more than 3 nucleotides from the nucleotide sequence 5'-UAUAUUUCCAGGAUGAAAGUCCA -3' (SEQ ID NO:34).

24. The method of any one of claims 1-23, wherein the dsRNA agent comprises at least one modified nucleotide.

25. The method of any one of claims 1-24, wherein no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand are unmodified nucleotides.

26. The method of any one of claims 1-25, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides.

27. The method of any one of claims 1-26, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

28. The method of any one of claims 24-27, wherein at least one of the modified nucleotides is selected from the group a deoxy-nucleotide, a 3'-terminal deoxy-thymine (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 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S-Isomer, a nucleotide comprising 2-hydroxymethyl-tetrahydrofurane-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, and a terminal nucleotide linked to a cholesteryl derivative and a dodecanoic acid bisdecylamide group; and combinations thereof.

29. The method of any one of claims 24-28, wherein the dsRNA agent, or salt thereof, further comprises at least one phosphorothioate internucleotide linkage.

30. The dsRNA agent, or salt thereof, of claim 29, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3′-terminus of one strand.

31. The dsRNA agent, or salt thereof, of claim 29, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5′-terminus of one strand.

32. The dsRNA agent, or salt thereof, of claim 29, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5′- and 3′-terminus of one strand

33. The method of any one of claims 24-32, wherein the dsRNA agent, or salt thereof, comprises 6-8 phosphorothioate internucleotide linkages.

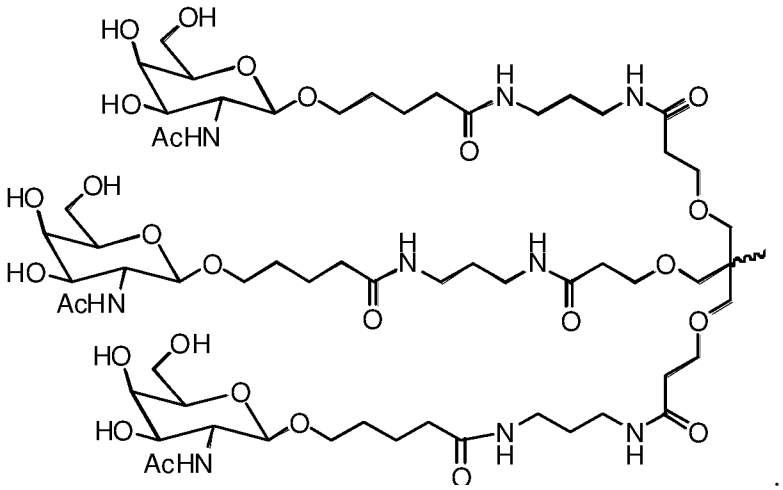
34. The method of any one of claims 1-33, wherein at least one strand of the dsRNA agent, or salt thereof, further comprises a ligand.

35. The method of claim 34, wherein the ligand is attached to the 3′ end of the sense strand.

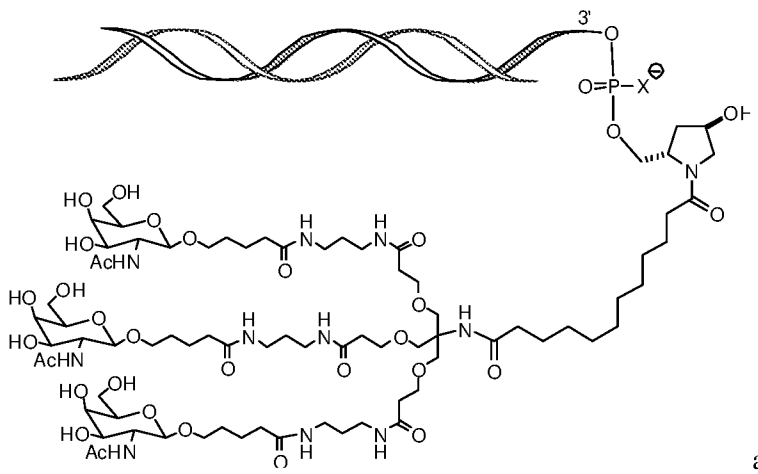
36. The method of claim 34 or 35, wherein the ligand is one or more N-acetylgalactosamine (GalNAc) derivatives.

37. The method of claim 36, wherein the one or more GalNAc derivatives is attached through a monovalent, bivalent, or trivalent branched linker.

38. The method of claim 37, wherein the ligand is



39. The method of 37 or 38, wherein the dsRNA agent, or salt thereof, is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

40. The method of claim 39, wherein the X is O.

41. The method of any one of claims 23-40, wherein the nucleotide sequence of the sense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense

strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36),

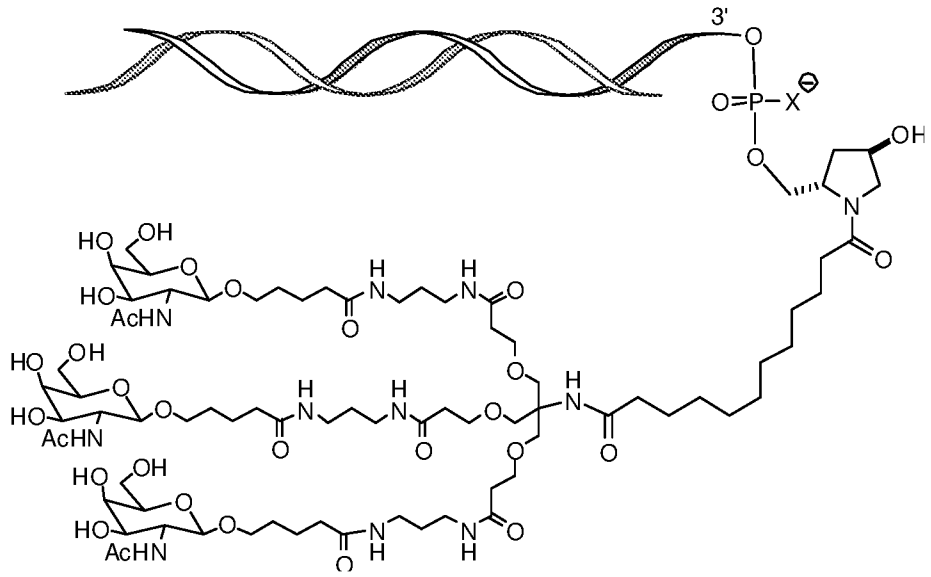
wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; uis a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage.

42. The method of claim 41, wherein the nucleotide sequence of the sense strand differs by no more than 2 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 2 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

43. The method of claim 41, wherein the nucleotide sequence of the sense strand differs by no more than 1 nucleotide from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 1 nucleotide from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

44. The method of claim 41, wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

45. The method of any one of claims 42-44, wherein the dsRNA agent, or salt thereof, is conjugated to a ligand as shown in the following schematic



and, wherein X is O or S.

46. A method for inhibiting the expression of hydroxyacid oxidase (HAO1) in a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate, comprising

administering to the subject a fixed dose of about 200 mg to about 600 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1,

wherein the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double-stranded region,

wherein the nucleotide sequence of the sense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36),

wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; uis a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage,

thereby inhibiting the expression of HAO1 in the subject.

47. A method for reducing urinary oxalate levels in a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in urinary oxalate, comprising

administering to the subject a fixed dose of about 200 mg to about 600 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1,

wherein the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double-stranded region,

wherein the nucleotide sequence of the sense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36),

wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; uis a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage,

thereby reducing urinary oxalate levels in the subject.

48. The method of claim 47, wherein the urinary oxalate is urinary calcium oxalate.

49. The method of claim 48, wherein the reduction in urinary calcium oxalate is reduction in urinary calcium oxalate supersaturation.

50. A method for treating a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate, comprising

administering to the subject a fixed dose of about 200 mg to about 600 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, which inhibits the expression of of HAO1,

wherein the dsRNA agent, or salt thereof, comprises a sense strand and an antisense strand forming a double-stranded region,

wherein the nucleotide sequence of the sense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 3 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36),

wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-

phosphorothioate; uis a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage,

thereby treating the subject having the non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate.

51. The method of any one of claims 46-50, wherein the non-primary hyperoxaluria disease or disorder is selected from the group consisting of secondary hyperolxaluria, a kidney stone disease, chronic kidney disease, end-stage renal disease (ESRD), coronary artery disease, cutaneous oxalate deposition, and ethylene glycol poisoning, or a planned or previous kidney transplantation.

52. The method of claim 51, wherein the non-primary hyperoxaluria disease or disorder is a kidney stone disease.

53. The method of claim 52, wherein the kidney stone disease is calcium oxalate kidney stone disease.

54. The method of claim 53, wherein the calcium oxalate kidney stone disease is recurrent calcium oxalate kidney stone disease.

55. The method of any one of claims 46 and 50-54, wherein administration of the dsRNA agent, or salt thereof, to the subject reduces urinary oxalate levels.

56. The method of claim 55, wherein the urinary oxalate is urinary calcium oxalate.

57. The method of claim 56, wherein the reduction in urinary calcium oxalate is reduction in urinary calcium oxalate supersaturation.

58. The method of any one of claims 46-57, wherein administration of the dsRNA agent, or salt thereof, to the subject reduces clinical and radiographic kidney stone events.

59. The method of any one of claims 46-58, wherein the subject is a human.

60. The method of any one of claims 45-59, wherein the dsRNA agent, or salt thereof, is administered to the subject at an interval of once every six months.

61. The method of any one of claims 45-59, wherein the dsRNA agent, or salt thereof, is administered to the subject initially, at three months, and every six months thereafter.

62. The method of any one of claims 45-61 wherein the fixed dose of the dsRNA agent, or salt thereof, is about 284 mg.

63. The method of any one of claims 45-61, wherein the fixed dose of the dsRNA agent, or salt thereof, is about 567 mg.

64. The method of any one of claims 45-63, wherein the dsRNA agent, or salt thereof, is administered to the subject subcutaneously.

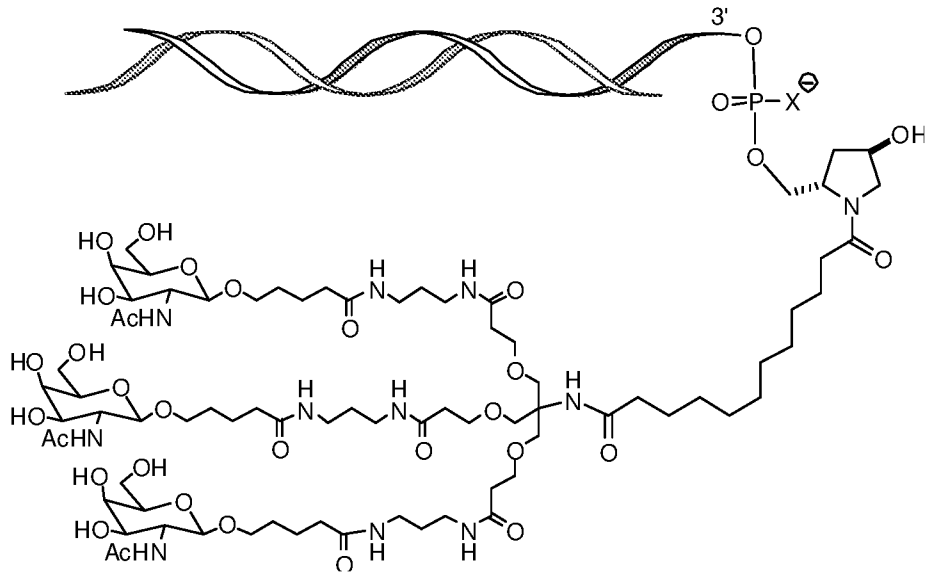
65. The method of claim 64, wherein the subcutaneous administration is subcutaneous injection.

66. The method of any one of claims 45-65, wherein the nucleotide sequence of the sense strand differs by no more than 2 nucleotides from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 2 nucleotides from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

67. The method of any one of claims 45-65, wherein the nucleotide sequence of the sense strand differs by no more than 1 nucleotide from the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand differs by no more than 1 nucleotide from the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

68. The method of any one of claims 45-65, wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36).

69. The method of any one of claims 45-68, wherein the dsRNA agent, or salt thereof, is conjugated to a ligand as shown in the following schematic



and, wherein X is O or S.

70. The method of claim 69, wherein the X is O.

71. The method of any one of claims 1-70, wherein the dsRNA agent is in salt form.

72. The method of any one of claims 1-71, wherein the dsRNA agent, or salt thereof, is administered to the subject in a pharmaceutical formulation.

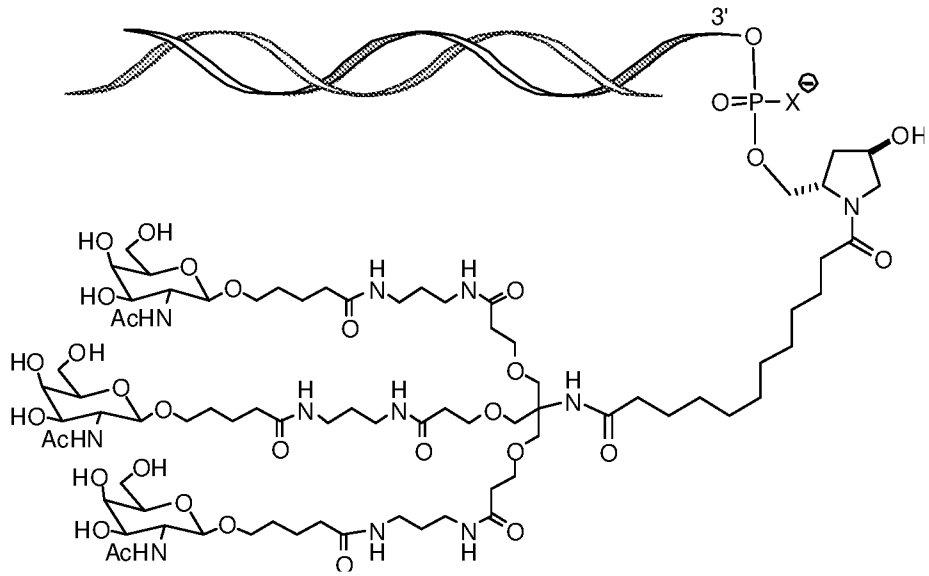
73. The method of any one of claims 1-72, further comprising administering an additional therapeutic to the subject.

74. A method for reducing calcium oxalate kidney stone incidence in a subject, the method comprising subcutaneously administering to the subject a fixed dose of about 284 mg or about 567 mg of a double stranded ribonucleic acid (dsRNA) agent, or salt thereof, comprising a sense strand and an antisense strand forming a double-stranded region,

wherein the sense strand comprises the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the antisense strand comprises the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36),

wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; u is a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-

phosphorothioate; and s is a phosphorothioate linkage, and wherein the sense strand is conjuaged to a ligand as shown in the following schematic



and, wherein X is O, thereby reducing calcium oxalate kidney stone incidence in the subject.

75. The method of claim 74, wherein the subject has suffered 2 or more oxalate stone events.

76. The method of claim 74, wherein the subject has elevated urinary oxalate levels.

77. The method of claim 74, wherein the subject has suffered 2 or more oxalate stone events and has elevated urinary oxalate levels.

78. The method of any one of claims 74-77, wherein the dsRNA agent, or salt thereof, is administered to the subject once every six months.

79. The method of any one of claims 74-78, wherein the dsRNA agent, or salt thereof, is administered to the subject initially, at three months, and every six months thereafter.

80. A method for treating a subject having a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate, the method comprising

administering to the subject a therapeutically effective amount of a nucleic acid inhibitor of hydroxyacid oxidase (HAO1) and/or a nucleic acid inhibitor of Proline Dehydrogenase 2 (PRODH2),

thereby treating the subject having the non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate.

81. The method of claim 80, wherein the non-primary hyperoxaluria disease or disorder is selected from the group consisting of secondary hyperolxaluria, a kidney stone disease, chronic kidney disease (CKD), end-stage renal disease (ESRD), coronary artery disease, cutaneous oxalate deposition, ethylene glycol poisoning, planned kidney transplantation, and previous kidney transplantation.

82. A method for treating a subject at risk of developing a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate, the method comprising

administering to the subject a therapeutically effective amount of a nucleic acid inhibitor of lactate dehydrogenase A (LDHA), a nucleic acid inhibitor of hydroxyacid oxidase (HAO1), and/or a nucleic acid inhibitor of Proline Dehydrogenase 2 (PRODH2),

thereby treating the subject at risk of developing the non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate.

83. The method of claim 82, wherein the subject at risk of developing a non-primary hyperoxaluria disease or disorder that would benefit from reduction in oxalate suffers from Crohn's disease, inflammatory bowel disease a bariatric surgery, fibromyalgia, an autoimmune disease, coronary artery disease, a kidney stone disease, chronic kidney disease (CKD), end-stage renal disease (ESRD), diabetes, obesity, HIV, or ethylene glycol poisoning, or is planning to undergo kidney trasnplanation or has undergone kidney transplantation.

84. The method of any one of claims 80-83, wherein the subject is a human.

85. The method of any one of claims 80-84, wherein the nucleic acid inhibitor is a double stranded ribonucleic acid (dsRNA) agent that inhibits the expression of HAO1.

86. The method of claim 85, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a portion of the nucleotide sequence of SEQ ID NO: 21 and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the corresponding portion of nucleotide sequence of SEQ ID NO: 22 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

87. The method of claim 85, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15

contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 4-14.

88. The method of claim 79, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises the nucleotide sequence 5'-GACUUUCAUCCUGGAAAUAUA -3' (SEQ ID NO:33) and the antisense strand comprises the nucleotide sequence 5'-UAUAUUUCCAGGAUGAAAGUCCA -3' (SEQ ID NO:34).

89. The method of any one of claims 82-84, wherein the nucleic acid inhibitor is a double stranded ribonucleic acid (dsRNA) agent that inhibits the expression of LDHA.

90. The method of claim 89, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a portion of the nucleotide sequence of SEQ ID NO: 1 and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the corresponding portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

91. The method of claim 89, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 2-3.

92. The method of claim 89, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5'-AUGUUGUCCUUUUUAUCUGAGCAGCCGAAAGGCUGC -3' (SEQ ID NO:31), and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence 5'-UCAGAUAAAAAGGACAACAUGG -3' (SEQ ID NO: 32).

93. The method of any one of claims 80-84, wherein the nucleic acid inhibitor is a double stranded ribonucleic acid (dsRNA) agent that inhibits the expression of Proline Dehydrogenase 2 (PRODH2).

94. The method of claim 93, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a portion of the nucleotide sequence of SEQ ID NO: 4641 and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the corresponding portion of nucleotide sequence of SEQ ID NO: 4642 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

95. The method of claim 93, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 15-16.

96. The method of any one of claims 82-84, wherein the nucleic acid inhibitor is a dual targeting double stranded ribonucleic acid (dsRNA) agent that inhibits the expression of LDHA and HAO1.

97. The method of claim 96, wherein the dual targeting dsRNA agent comprises a first double stranded ribonucleic acid (dsRNA) agent that inhibits expression of lactic dehydrogenase A (LDHA) comprising a sense strand and an antisense strand; and a second double stranded ribonucleic acid (dsRNA) agent that inhibits expression of hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) comprising a sense strand and an antisense strand, wherein the first dsRNA agent and the second dsRNA agent are covalently attached, wherein the sense strand of the first dsRNA agent comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and the antisense strand of the first dsRNA agent comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein the sense strand of the second dsRNA agent comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:21, and said antisense strand of the second dsRNA agent comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:22.

98. The method of claim 96, wherein the dual targeting dsRNA agent comprises a first double stranded ribonucleic acid (dsRNA) agent that inhibits expression of lactic dehydrogenase A (LDHA) comprising a sense strand and an antisense strand; and a second double stranded ribonucleic acid (dsRNA) agent that inhibits expression of hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) comprising a sense strand and an antisense strand, wherein the first dsRNA agent and the second dsRNA agent are covalently attached, wherein the antisense strand of the first dsRNA agent

comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 2-3, and wherein the antisense strand of the second dsRNA agent comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in any one of Tables 4-14.

99. The method of any one of claims 80-98, wherein the dsRNA agent comprises at least one modified nucleotide.

100. The method of any one of claims 80-99, wherein no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand are unmodified nucleotides.

101. The method of any one of claims 80-100, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

102. The method of any one of claims 99-101, wherein at least one of the modified nucleotides is selected from the group a deoxy-nucleotide, a 3'-terminal deoxy-thymine (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 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S-Isomer, a nucleotide comprising 2-hydroxymethyl-tetrahydrofurane-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, and a terminal nucleotide linked to a cholesteryl derivative and a dodecanoic acid bisdecylamide group; and combinations thereof.

103. The method of any one of claims 85-102, wherein the dsRNA agent further comprises at least one phosphorothioate internucleotide linkage.

104. The method of any one of claims 85-103, wherein the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages.

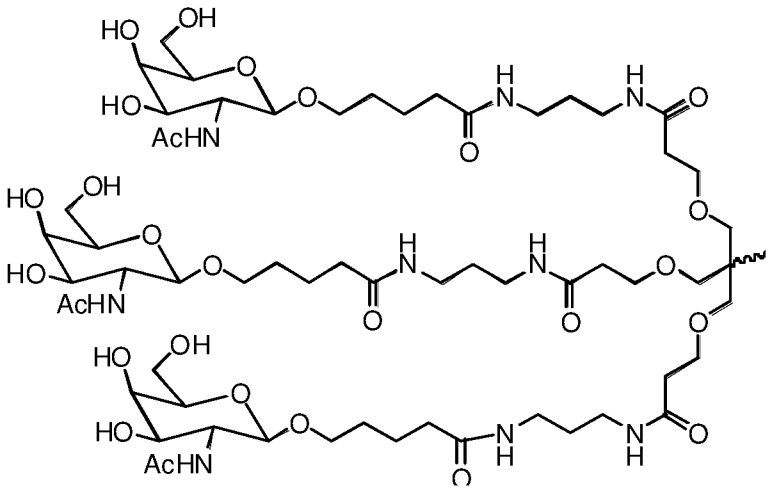
105. The method of any one of claims 85-104, wherein at least one strand of the dsRNA agent further comprises a ligand.

106. The method of claim 105, wherein the ligand is attached to the 3′ end of the sense strand.

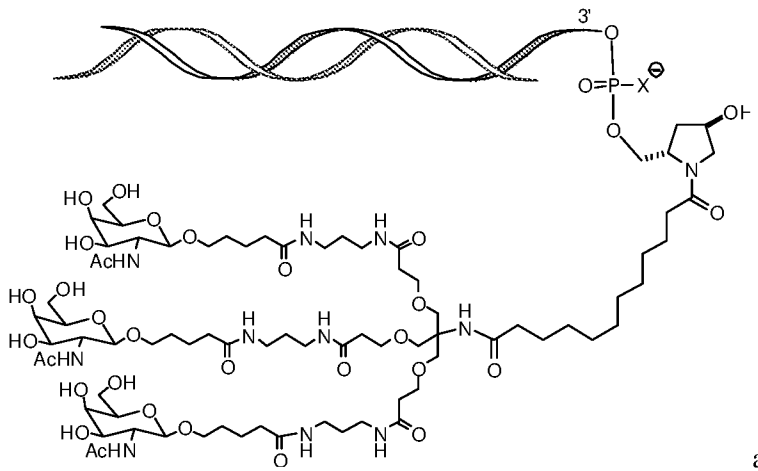
107. The method of claim 105 or 106, wherein the ligand is one or more N-acetylgalactosamine (GalNAc) derivatives.

108. The method of claim 107, wherein the one or more GalNAc derivatives is attached through a monovalent, bivalent, or trivalent branched linker.

109. The method of claim 108, wherein the ligand is



110. The method of claim 108 or 109, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



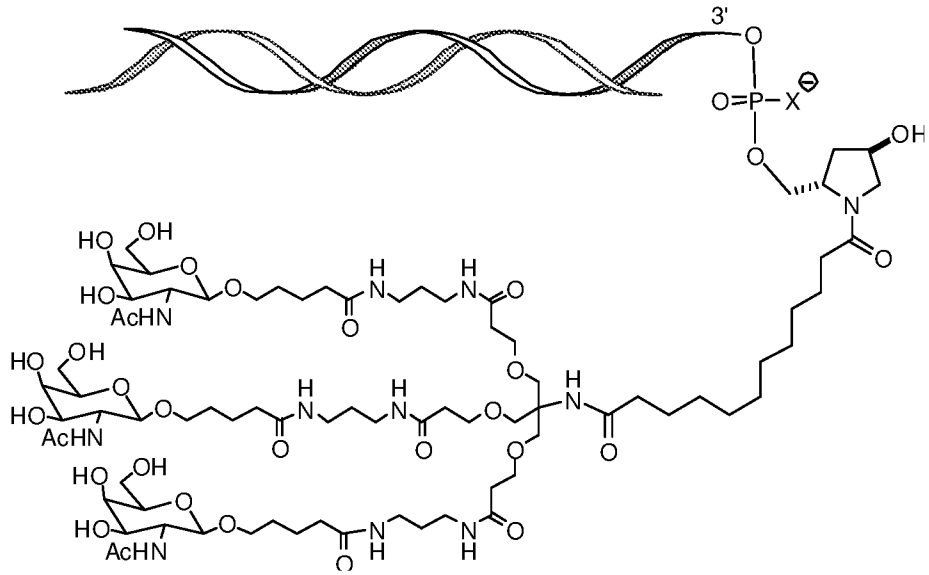
and, wherein X is O or S.

111. The method of claim 110, wherein the X is O.

112. The method of claim 88, wherein the sense strand comprises the nucleotide sequence 5'-gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:35) and the antisense strand comprises the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:36),

wherein Af is a 2′-fluoroadenosine-3′-phosphate; Afs is 2′-fluoroadenosine-3′-phosphorothioate; Cf is a 2′-fluorocytidine-3′-phosphate; U is a Uridine-3′-phosphate; Uf is a 2′-fluorouridine-3′-phosphate; a is a 2′-O-methyladenosine-3′-phosphate; as is a 2′-O-methyladenosine-3′-phosphorothioate; c is a 2′-O-methylcytidine-3′-phosphate; cs is a 2′-O-methylcytidine-3′-phosphorothioate; g is a 2′-O-methylguanosine-3′-phosphate; gs is a 2′-O-methylguanosine-3′-phosphorothioate; uis a 2′-O-methyluridine-3′-phosphate; us is a 2′-O-methyluridine-3′-phosphorothioate; and s is a phosphorothioate linkage.

113. The method of claim 112, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

114. The method of claim 92, wherein the dsRNA agent comprises at least one modified nucleotide.

115. The method of claim 92 or 114, wherein all of the nucleotides of the dsRNA agent are modified nucleotides.

116. The method of claim 115, wherein the modified nucleotide comprises a 2'-modification.

117. The method of claim 116, wherein the 2 '-modification is a 2'-fluoro or 2'-O- methyl modification.

118. The method of any one of claims 115-117, wherein one or more of the following positions are modified with a 2'-O-methyl: positions 1, 2, 4, 6, 7, 12, 14, 16, 18-26, or 31-36 of the sense strand and/or positions 1, 6, 8, 11-13, 15, 17, or 19-22 of the antisense strand.

119. The method of claim 118, wherein all of positions 1, 2, 4, 6, 7, 12, 14, 16, 18-26, and 31-36 of the sense strand and all of the positions 1, 6, 8, 11-13, 15, 17, and 19-22 of the antisense strand are modified with a 2'-O-methyl.

120. The method of any one of claims 114-119, wherein one or more of the following positions are modified with a 2'-fluoro: positions 3, 5, 8-11, 13, 15, or 17 of the sense strand and/or positions 2-5, 7, 9, 10, 14, 16, or 18 of the antisense strand.

121. The method of claim 114, wherein all of positions 3, 5, 8-11, 13, 15, or 17 of the sense strand and all of positions 2-5, 7, 9, 10, 14, 16, and 18 of the antisense strand are modified with a 2'-fluoro.

122. The method of any one of claims 93 and 116-121, wherein the dsRNA agent comprises at least one modified internucleotide linkage.

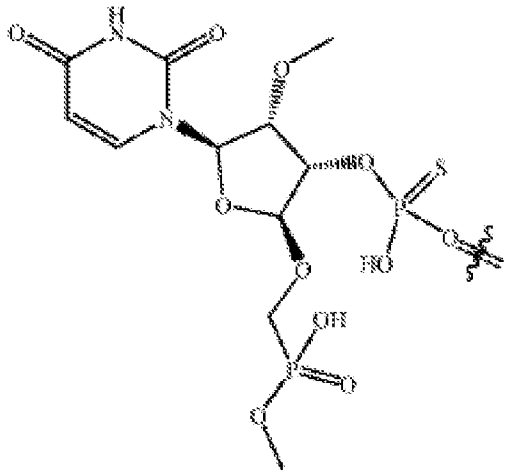
123. The method of claim 122, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

124. The method of claim 122 or claim 123, wherein the dsRNA agent has a phosphorothioate linkage between one or more of: positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

125. The method of any one of claims 122-124, wherein the dsRNA agent has a phosphorothioate linkage between each of: positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

126. The method of any one of claims 92 and 114-125, wherein the uridine at the first position of the antisense strand comprises a phosphate analog.

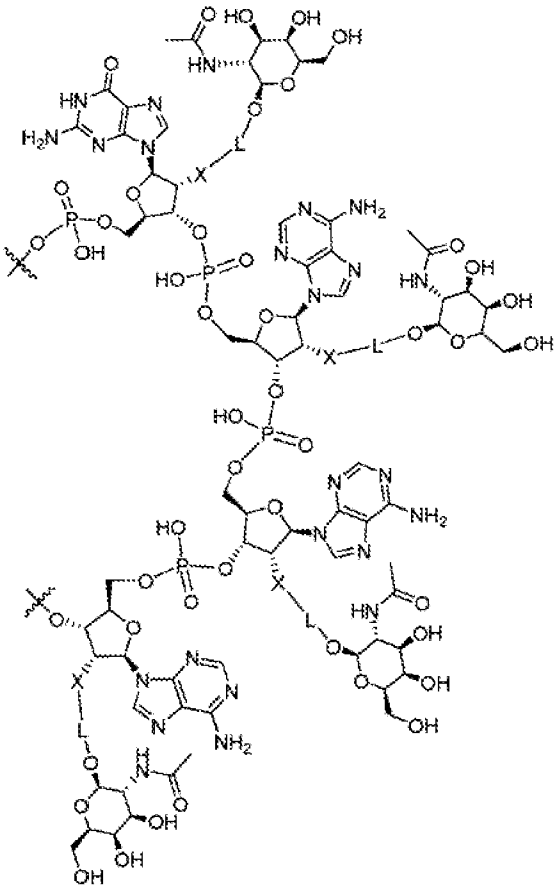
127. The method of claim 126, wherein the dsRNA comprises the following structure at position 1 of the antisense strand:



128. The method of any one of claims 92 and 114-127, wherein one or more of the nucleotides of the -GAAA- sequence on the sense strand is conjugated to a monovalent GalNac moiety.

129. The method of any one of claims 92 and 114-128, wherein each of the nucleotides of the -GAAA- sequence on the sense strand is conjugated to a monovalent GalNac moiety.

130. The method of any one of claims 92 and 114-129, wherein the -GAAA- motif comprises the structure:



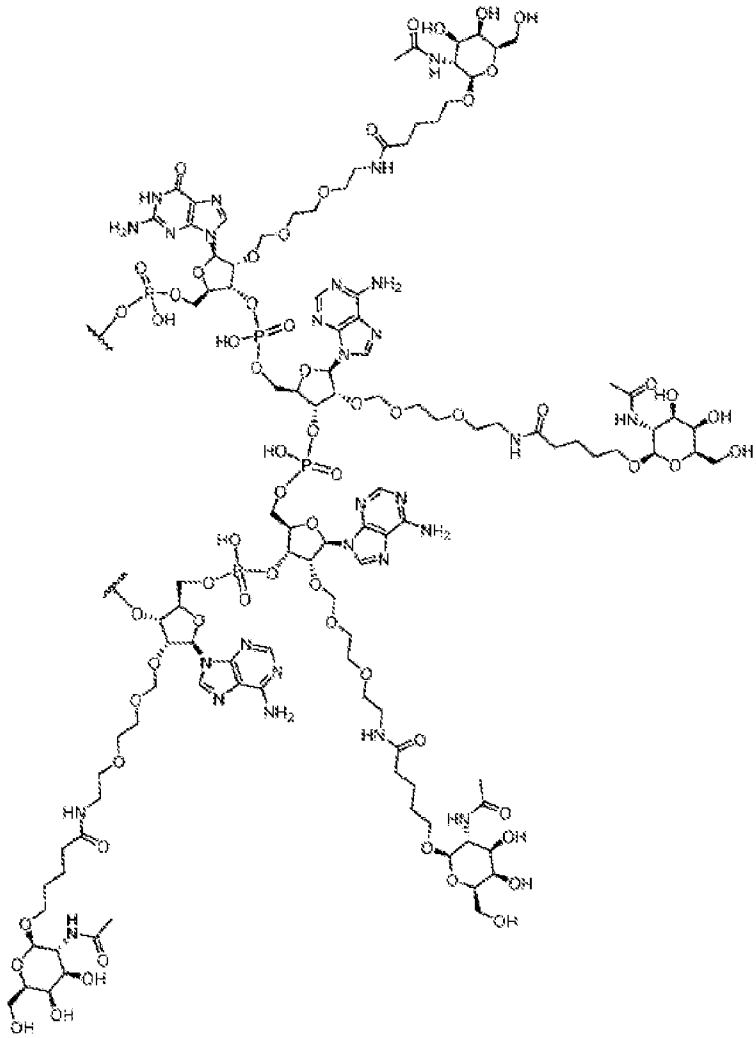
wherein: L represents a bond, click chemistry handle, or a linker of 1 to 20, inclusive, consecutive, covalently bonded atoms in length, selected from the group consisting of substituted and unsubstituted alkylene, substituted and unsubstituted alkenylene, substituted and unsubstituted alkynylene, substituted and unsubstituted heteroalkylene, substituted and unsubstituted heteroalkenylene, substituted and unsubstituted heteroalkynylene, and combinations thereof; and

X is a O, S, or N.

131. The method of claim 124, wherein L is an acetal linker.

132. The method of claim 130 or 131, wherein X is O.

133. The method of any one of claims 92 and 114-132, wherein the -G AAA- sequence comprises the structure:



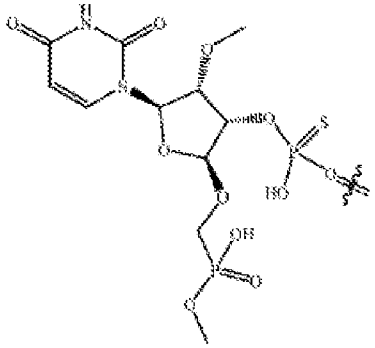
134. The method of any one of claims 92 and 114-133, wherein the dsRNA comprises an antisense strand having a sequence set forth as UCAGAUAAAAAGGACAACAUGG (SEQ ID NO: 32) and a sense strand having a sequence set forth as

AUGUUGUCCUUUUUAUCUGAGCAGCCGAAAGGCUGC (SEQ ID NO: 31),

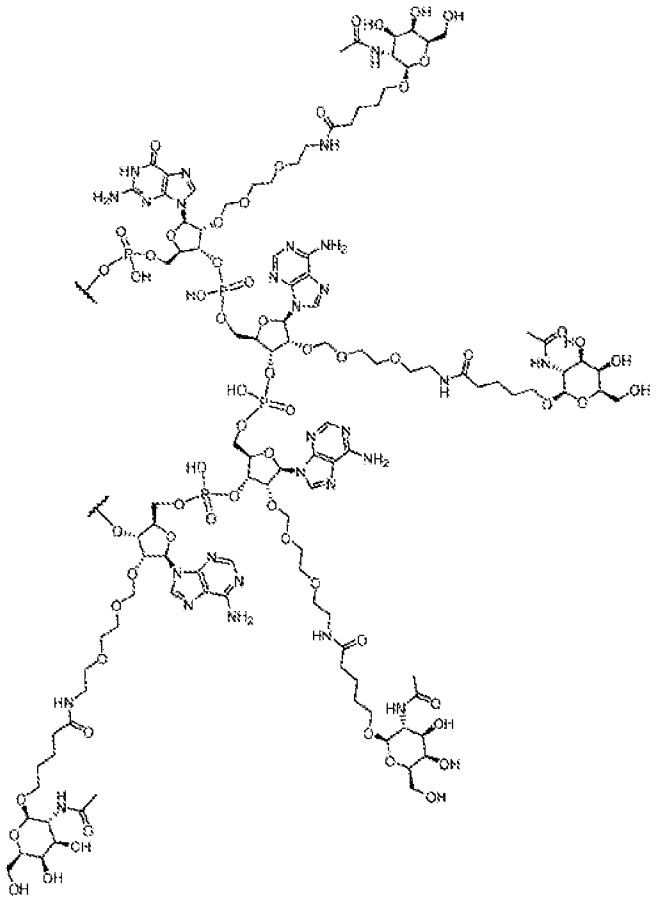
wherein all of positions 1, 2, 4, 6, 7, 12, 14, 16, 18-26, and 31-36 of the sense strand and all of positions 1, 6, 8, 11-13, 15, 17, and 19-22 of the antisense strand are modified with a 2'-O- methyl, and all of positions 3, 5, 8-11, 13, 15, or 17 of the sense strand and all of positions 2-5, 7, 9, 10, 14, 16, and 18 of the antisense strand are modified with a 2'-fluoro;

wherein the oligonucleotide has a phosphorothioate linkage between each of: positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand;

wherein the dsRNA agent comprises the following structure at position 1 of the antisense strand:



wherein each of the nucleotides of the -GAAA- sequence on the sense strand is conjugated to a monovalent GalNac moiety comprising the structure:



135. The method of any one of claims 85-134, wherein the dsRNA agent is present in a composition comprising the dsRNA agent and Na+ counterions.

136. The method of any one of claims 82-84, wherein the nucleic acid inhibitor is a single stranded antisense polynucleotide agent that inhibits the expression of LDHA.

137. The method of claim 136, wherein the single stranded antisense polynucleotide agent comprises at least 15 contiguous nucleotide differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-3.

138. The method of any one of claims 80-84, wherein the nucleic acid inhibitor is a single stranded antisense polynucleotide agent that inhibits the expression of LDHA.

139. The method of claim 138, wherein the single stranded antisense polynucleotide agent comprises at least 15 contiguous nucleotide differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-3.

140. The method of any one of claims 80-84, wherein the nucleic acid inhibitor is a single stranded antisense polynucleotide agent that inhibits the expression of PRODH2.

141. The method of claim 140 wherein the single stranded antisense polynucleotide agent comprises at least 15 contiguous nucleotide differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 15-16.

142. The method of any one of claims 136-141, wherein the single stranded antisense polynucleotide agent is about 8 to about 50 nucleotides in length.

143. The method of any one of claims 136-142, wherein substantially all of the nucleotides of the single stranded antisense polynucleotide agent are modified nucleotides.

144. The method of any one of claims 136-143, wherein all of the nucleotides of the single stranded antisense polynucleotide agent are modified nucleotides.

145. The method of claim 143 or 144, wherein the modified nucleotide comprises a modified sugar moiety selected from the group consisting of: a 2′-O-methoxyethyl modified sugar moiety, a 2′-O-alkyl modified sugar moiety, and a bicyclic sugar moiety.

146. The method of claim 145, wherein the bicyclic sugar moiety has a (—CRH—)n group forming a bridge between the 2′ oxygen and the 4′ carbon atoms of the sugar ring, wherein n is 1 or 2 and wherein R is H, CH3 or CH3OCH3.

147. The method of claim 146, wherein n is 1 and R is CH3.

148. The method of claim 143 or 144, wherein the modified nucleotide is a 5'-methylcytosine.

149. The method of claim 143 or 144, wherein the single stranded antisense polynucleotide agent comprises a modified internucleoside linkage.

150. The method of claim 149, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

151. The method of any one of claims 136-150, wherein the single stranded antisense polynucleotide agent comprises a plurality of 2′-deoxynucleotides flanked on each side by at least one nucleotide having a modified sugar moiety.

152. The method of claim 151, wherein the single stranded antisense polynucleotide agent is a gapmer comprising a gap segment comprised of linked 2′-deoxynucleotides positioned between a 5′ and a 3′ wing segment.

153. The method of claim 151, wherein the modified sugar moiety is selected from the group consisting of a 2′-O-methoxyethyl modified sugar moiety, a 2′-methoxy modified sugar moiety, a 2′-O-alkyl modified sugar moiety, and a bicyclic sugar moiety.

154. The method of any one of claims 80-153, wherein the nucleic acid inhibitor is administered to the subject in a pharmaceutical formulation.

155. The method of any one of claims 80-154, further comprising administering an additional therapeutic to the subject.

156. The method of any one of claims 80-155, wherein the nucleic acid inhibitor is administered to the subject at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

157. The method of any one of claims 80-156, wherein the nucleic acid inhibitor is administered to the subject subcutaneously.

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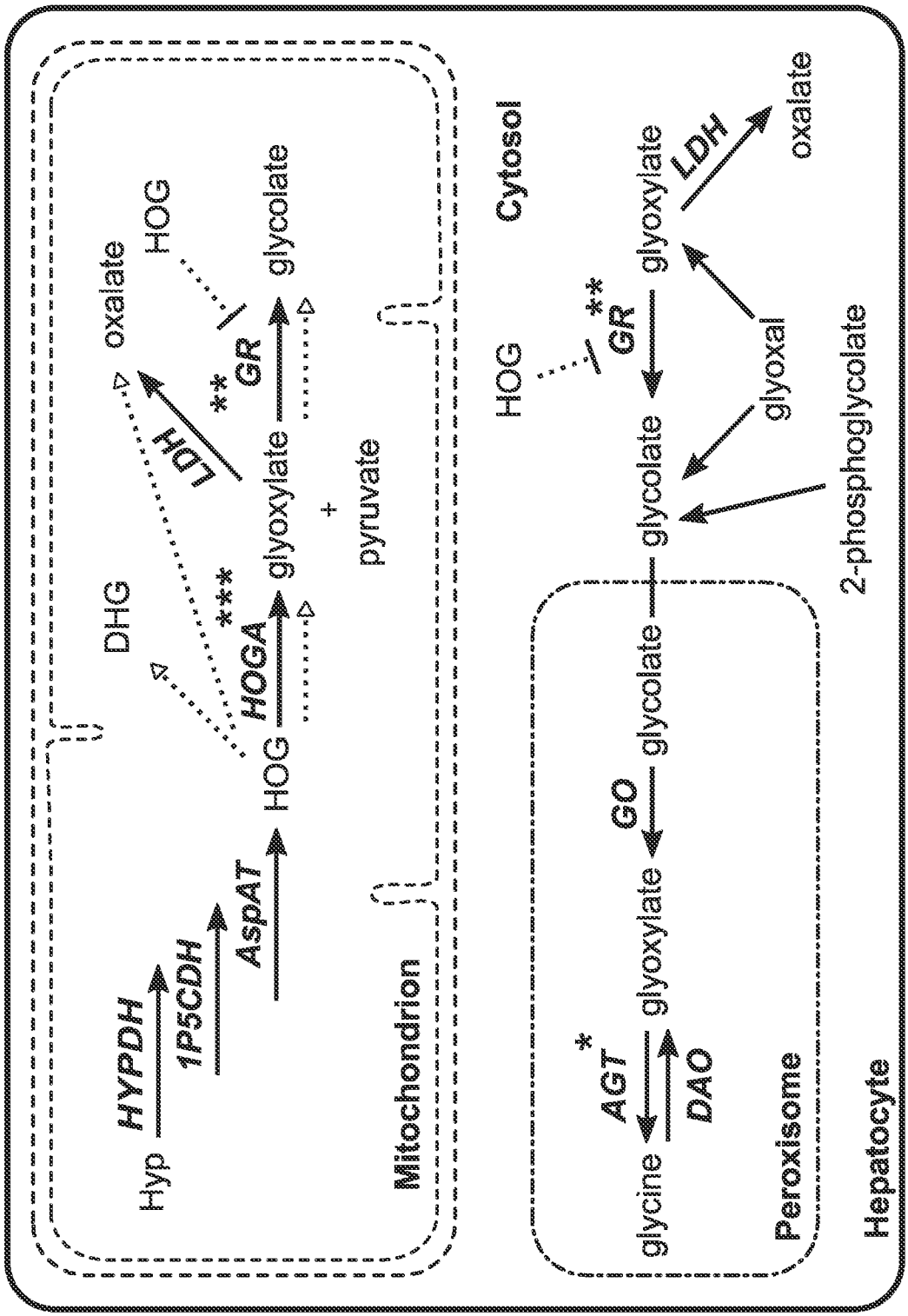

FIG. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/037453

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113 A61K31/713
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, Sequence Search, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2019/014530 A1 (ALNYLAM PHARMACEUTICALS INC [US]; UAB RES FOUND [US]) 17 January 2019 (2019-01-17) cited in the application the whole document	1-88, 96-113, 135, 154-157
X	WO 2016/205323 A1 (ALNYLAM PHARMACEUTICALS INC [US]) 22 December 2016 (2016-12-22)	1-32, 34-87
Y	the whole document	1-79, 96-113, 135, 154-157

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 2022	04/01/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Andres, Serge

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LI XINGSHENG ET AL: "Metabolism of13C5-hydroxyproline in mouse models of Primary Hyperoxaluria and its inhibition by RNAi therapeutics targeting liver glycolate oxidase and hydroxyproline dehydrogenase", BIOCHIMICA ET BIOPHYSICA ACTA. MOLECULAR BASIS OF DISEASE, vol. 1862, no. 2, 2 December 2015 (2015-12-02), pages 233-239, XP029375493, ISSN: 0925-4439, DOI: 10.1016/J.BBADIS.2015.12.001	80-88
A	the whole document	1-79, 96-113, 135, 154-157

A	ABIGAIL LIEBOW ET AL: "An Investigational RNAi Therapeutic Targeting Glycolate Oxidase Reduces Oxalate Production in Models of Primary Hyperoxaluria", JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, vol. 28, no. 2, 18 July 2016 (2016-07-18), pages 494-503, XP055633228, US ISSN: 1046-6673, DOI: 10.1681/ASN.2016030338 the whole document	1-88, 96-113, 135, 154-157

A	WO 2015/100436 A1 (DICERNA PHARMACEUTICALS INC [US]) 2 July 2015 (2015-07-02) the whole document	1-88, 96-113, 135, 154-157

A	WO 2019/014491 A1 (ALNYLAM PHARMACEUTICALS INC [US]) 17 January 2019 (2019-01-17) the whole document	1-88, 96-113, 135, 154-157

A	BELOSTOTSKY RUTH ET AL: "Novel therapeutic approaches for the primary hyperoxalurias", PEDIATRIC NEPHROLOGY, vol. 36, no. 9, 6 November 2020 (2020-11-06), pages 2593-2606, XP037540811, ISSN: 0931-041X, DOI: 10.1007/S00467-020-04817-8 [retrieved on 2020-11-06] the whole document	1-88, 96-113, 135, 154-157

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/037453

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2019/055633 A1 (ARROWHEAD PHARMACEUTICALS INC [US]) 21 March 2019 (2019-03-21) cited in the application the whole document	1-88, 96-113, 135, 154-157
X,P	WO 2022/119873 A1 (ALNYLAM PHARMACEUTICALS INC [US]) 9 June 2022 (2022-06-09) the whole document	1-88, 135, 154-157

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/037453

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

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed.

   b. ☒ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      ☒ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/037453

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

1-79, 85-88, 96-113(completely); 80-84, 135, 154-157(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-79, 85-88, 96-113(completely); 80-84, 135, 154-157(partially)

Inhibition of HAO1 expression in a subject having non-primary polyoxaluria with a dsRNA administered subcutaneously. Combination therapies with nucleic acid inhibitors of PRODH2 and/or LDHA.

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2. claims: 93-95, 140, 141(completely); 80-84, 122-133, 135, 142-157(partially)

Treating a non-primary hyperoxaluria by inhibiting expression of PRODH2 (as far as not covered by subject 1.).

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3. claims: 89-92, 114-121, 134, 136-139(completely); 82-84, 122-133, 135, 142-157(partially)

Treating a non-primary hyperoxaluria by inhibiting expression of LDH2 (as far as not covered by subjects 1. or 2.).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2022/037453

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2022/037453

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