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(54) Titre : COMPOSITIONS D'ARNI DE LACTATE DESHYDROGENASE A (LDHA) ET LEURS PROCEDES
D'UTILISATION
(54) Title: LACTATE DEHYDROGENASE A (LDHA) IRNA COMPOSITIONS AND METHODS OF USE THEREOF

(57) **Abrégé/Abstract:**

The invention relates to double-stranded ribonucleic acid (dsRNA) compositions targeting the LDHA gene, as well as methods of inhibiting expression of LDHA, methods of inhibiting LDHA and HAO1, and methods of treating subjects that would benefit from reduction in expression of LDHA, such as subjects having an oxalate pathway-associated disease, disorder, or condition, using such dsRNA compositions.

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(54) Title: LACTATE DEHYDROGENASE A (LDHA) IRNA COMPOSITIONS AND METHODS OF USE THEREOF

(57) **Abstract:** The invention relates to double-stranded ribonucleic acid (dsRNA) compositions targeting the LDHA gene, as well as methods of inhibiting expression of LDHA, methods of inhibiting LDHA and HAO1, and methods of treating subjects that would benefit from reduction in expression of LDHA, such as subjects having an oxalate pathway-associated disease, disorder, or condition, using such dsRNA compositions.

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CONTENANT LES PAGES 1 À 213

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JUMBO APPLICATIONS/PATENTS

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

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 213

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LACTATE DEHYDROGENASE A (LDHA) iRNA COMPOSITIONS AND METHODS OF USE THEREOF

Related Applications

5 The present application claims the benefit of priority to U.S. Provisional Application No. 62/576,783, filed on October 25, 2017 and U.S. Provisional Application No. 62/532,020, filed on July 13, 2017. The entire contents of each of the foregoing applications are incorporated herein by reference.

10 Sequence Listing

 The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on July 12, 2018, is named 121301-07520_SL.TXT and is 1,154,808 bytes in size.

15 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
20 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. Transamination of glyoxylate with alanine by the enzyme alanine/glyoxylate
25 aminotransferase (AGT) results in the formation of pyruvate and glycine. Excess glyoxylate is converted to oxalate by lactate dehydrogenase A (referred to herein as LDHA). The endogenous pathway for oxalate metabolism is illustrated in Figure 1A.

 Lactate dehydrogenase is a protein found in all tissues. It is composed of four subunits with the two most common subunits being the LDH-M and LDH-H proteins. These proteins are encoded by the LDHA and LDHB genes, respectively. Various combinations of the LDH-M and
30 LDH-H proteins result in five distinct isoforms of LDH. LDHA is the most important gene involved in the liver lactate dehydrogenase isoform. Specifically, within the liver, LDHA is important as the final step in the endogenous production of oxalate, by converting the precursor glyoxylate to oxalate. It also serves an important role in the Cori Cycle and in the anaerobic phase of glycolysis where it converts lactate to pyruvate and *vice versa*.

35 Oxalic acid may form oxalate salts with various cations, such as sodium, potassium, magnesium, and calcium. Although sodium oxalate, potassium oxalate, and magnesium oxalate are water soluble, calcium oxalate (CaOx) is nearly insoluble. Excretion of oxalate occurs primarily by the kidneys *via* glomerular filtration and tubular secretion.

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. These CaOx crystals contribute to the formation of diffuse renal calcifications (nephrocalcinosis) and stones (nephrolithiasis). Subjects having diffuse renal calcifications or nonobstructing 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. Furthermore, systemic deposition of CaOx (systemic oxalosis) may occur in extrarenal tissues, including soft tissues (such as thyroid and breast), heart, nerves, joints, skin, and retina, which can lead to early death if left untreated.

Among the most well-known oxalate pathway-associated diseases, *e.g.*, kidney stone formation diseases, are the primary hyperoxalurias which are inherited diseases characterized by increased endogenous oxalate synthesis with variable clinical phenotypes. Therapies that modulate oxalate synthesis are currently not available and there are only a few treatment options that exist for subjects having a hereditary hyperoxaluria. Ultimately, some subjects with hereditary hyperoxaluria require kidney/liver transplants. Other oxalate pathway-associated diseases, disorders, and conditions include calcium oxalate tissue deposition diseases, disorders, and conditions.

Currently, the primary treatment for many of these oxalate pathway-associated diseases, disorders, and conditions (*e.g.*, with kidney stone disease) is increased fluid intake and dietary alterations (*e.g.*, decreased protein intake, decreased sodium intake, decreased ascorbic acid intake, moderate calcium intake, phosphate or magnesium supplementation, and pyridoxine treatment). However, subjects often fail to adhere to such life-style changes or experience no significant benefit. Treatment for some of the other oxalate pathway-associated diseases, disorders, and conditions, such as chronic kidney disease, include the use of ACE inhibitors (angiotensin converting enzyme inhibitors) and ARBs (angiotensin II antagonists) which may slow the progression of disease. Nonetheless, subjects having chronic kidney disease progressively lose kidney function and progress to the need for dialysis or a kidney transplant. Most of these oxalate pathway-associated diseases are without treatments, and none currently have oxalate reduction treatments available.

Further, there are oxalate pathway-associated diseases, disorders, and conditions include lactate dehydrogenase-associated diseases, disorders, and conditions. For example, the role of lactate dehydrogenase is well known in cancer (hepatocellular), and inhibition has been shown to reduce cancer growth. Other lactate dehydrogenase-associated diseases, disorders and conditions include fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis of the liver, accumulation of fat in the liver, inflammation of the liver, hepatocellular necrosis, liver fibrosis, and nonalcoholic fatty liver disease (NAFLD). Given the essential role of LDH in glycolysis, however, treatment options have been limited.

Accordingly, there is a need in the art for alternative treatments for subjects having an oxalate pathway-associated disease, disorder, and condition.

Summary of the Invention

5 The present invention is based, at least in part, on the discovery that, by targeting LDHA with the iRNA agents, compositions comprising such agents, and methods disclosed herein, a liver specific and superior LDHA and urinary oxalate lowering effect is achieved.

Accordingly, the present invention provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an LDHA gene.

10 The LDHA gene may be within a cell, *e.g.*, a cell within a subject, such as a human. The present invention also provides methods of using the iRNA compositions of the invention for inhibiting the expression of an LDHA gene for treating a subject who would benefit from inhibiting or reducing the expression of an LDHA gene, *e.g.*, a subject that would benefit from a reduction or inhibition in urinary oxalate production, *e.g.*, a subject suffering or prone to suffering from an oxalate pathway-associated disease disorder, or condition, such as a subject suffering or prone to suffering from an oxalate-associated disease, disorder, or condition, *e.g.*, a kidney stone formation disease, disorder, or condition or a calcium oxalate tissue deposition disease, disorder, or condition; or an LDHA-associated disease, disorder, or condition.

20 The present invention also provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an LDHA gene and an HAO1 gene. The LDHA gene and the HAO1 gene may be within a cell, *e.g.*, a cell within a subject, such as a human. The present invention also provides methods of using the iRNA compositions of the invention for inhibiting the expression of an LDHA gene and an HAO1 gene for treating a subject who would benefit from inhibiting or reducing the expression of an LDHA gene and an HAO1 gene, *e.g.*, a subject that would benefit from a reduction or inhibition in urinary oxalate production, *e.g.*, a subject suffering or prone to suffering from an oxalate-associated disease, disorder, or condition, *e.g.*, a kidney stone formation disease, disorder, or condition or a calcium oxalate tissue deposition disease, disorder, or condition; or an LDH-associated disease, disorder, or condition.

30 Accordingly, in one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of lactic acid dehydrogenase A (LDHA) in a cell, wherein said dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which 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 2-5.

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

In other embodiments, substantially all of the nucleotides of the sense strand comprise a modification; substantially all of the nucleotides of the antisense strand comprise a modification;

or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification.

In yet other embodiments, all of the nucleotides of the sense strand comprise a modification; all of the nucleotides of the antisense strand comprise a modification; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In one embodiment, at least one of said modified nucleotides is selected from the group consisting of 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'-hydroxyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a glycol modified nucleotide, and a 2-O-(N-methylacetamide) modified nucleotide, and combinations thereof.

The region of complementarity may be at least 17 nucleotides in length; 19 to 30 nucleotides in length; 19-25 nucleotides in length; or 21 to 23 nucleotides in length.

Each strand of the dsRNA agent may be no more than 30 nucleotides in length. Each strand of the dsRNA agent may be independently 19-30 nucleotides in length; independently 19-25 nucleotides in length; or independently 21-23 nucleotides in length.

At least one strand of the dsRNA agent may comprise a 3' overhang of at least 1 nucleotide; or at least one strand may comprise a 3' overhang of at least 2 nucleotides.

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

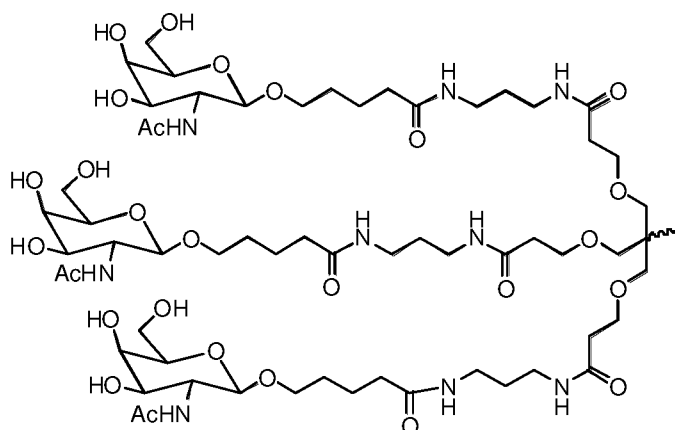
The phosphorothioate or methylphosphonate internucleotide linkage may be at the 3'-terminus of one strand (*e.g.*, the antisense strand; or the sense strand); or the phosphorothioate or methylphosphonate internucleotide linkage may be at the 5'-terminus of one strand (*e.g.*, the antisense strand; or the sense strand); or the phosphorothioate or methylphosphonate internucleotide linkage may be at the both the 5'- and 3'-terminus of one strand.

The dsRNA agent may further comprise a ligand.

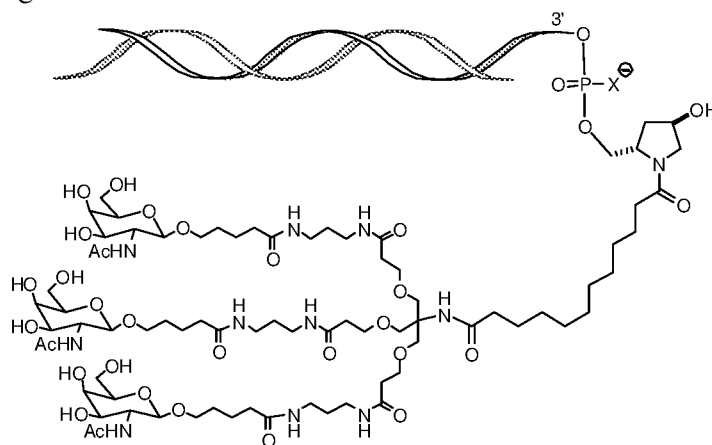
In one embodiment, the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

In one embodiment, the ligand is one or more N-acetylgalactosamine (GalNAc) derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In another embodiment, the ligand is



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



5 and, wherein X is O or S.

In one embodiment, the X is O.

In one embodiment, the region of complementarity consists of one of the antisense sequences listed in any one of Tables 2-5.

10 In one embodiment, the sense strand and the antisense strand comprise nucleotide sequences selected from the group consisting of the nucleotide sequences of any one of the agents listed in any one of Tables 2-5.

15 In another aspect, the present invention provides a dual targeting RNAi agent, comprising 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.

20 In one embodiment, 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.

In another embodiment, the antisense strand of the first dsRNA agent comprises a region of complementarity which 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 2-5.

In one embodiment, 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 another embodiment, the antisense strand of the second dsRNA agent comprises a region of complementarity which 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 7-14.

In one embodiment, the first dsRNA agent and the second dsRNA agent each independently comprise at least one modified nucleotide.

In another embodiment, substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand of the first dsRNA agent and substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand of the second dsRNA agent are modified nucleotides.

In one embodiment, at least one of the modified nucleotides of the first dsRNA agent and at least one of the modified nucleotides of the second dsRNA agent are each independently selected from the group consisting of 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 phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

In another embodiment, at least one of the modified nucleotides of the first dsRNA agent and at least one of the modified nucleotides of the second dsRNA agent are each independently selected from the group consisting of 2'-O-methyl and 2'-fluoro modifications.

The region of complementarity of the first dsRNA agent and /or the region of complementarity of the second dsRNA agent may each independently be 19 to 30 nucleotides in length.

Each strand of the first dsRNA agent and each strand of the second dsRNA agent may each independently be 19-30 nucleotides in length.

In one embodiment, at least one strand of the first dsRNA agent and/or at least one strand of the second dsRNA agent each independently comprise a 3' overhang of at least 1 nucleotide.

In one embodiment, the first dsRNA agent and/or the second dsRNA agent each independently further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage.

In one embodiment, the first dsRNA agent and/or the second dsRNA agent each independently further comprise at least one ligand.

In another embodiment, the at least one ligand is conjugated to the sense strand of the first dsRNA agent and/or the second dsRNA agent.

In one embodiment, the at least one ligand is conjugated to the 3'-end, 5'-end, or an internal position of one of the sense strands.

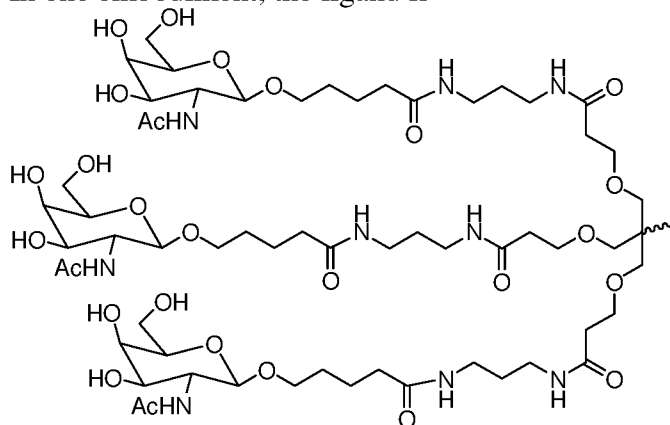
In another embodiment, the at least one ligand is conjugated to the antisense strand of the first dsRNA agent and/or the second dsRNA agent.

In one embodiment, the at least one ligand is conjugated to the 3'-end, 5'-end, or an internal position of one of the antisense strands.

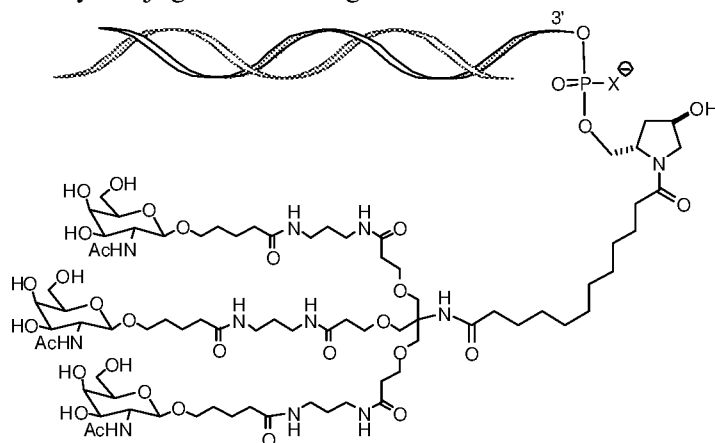
In one embodiment, the ligand is an N-acetylgalactosamine (GalNAc) derivative.

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

In one embodiment, the ligand is



In one embodiment, the first dsRNA agent and the second dsRNA agent are each independently 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 first dsRNA agent and the second dsRNA agent are covalently attached via a covalent linker.

5 In one embodiment, the covalent linker is selected from the group consisting of a single stranded nucleic acid linker, a double stranded nucleic acid linker, a partially single stranded nucleic acid linker, a partially double stranded nucleic acid linker, a carbohydrate moiety linker, and a peptide linker. In another embodiment, the covalent linker is a cleavable linker or a non-cleavable linker. In one embodiment, the covalent linker attaches the sense strand of the first dsRNA agent to the sense strand of the second dsRNA agent. In another embodiment, the
10 covalent linker attaches the antisense strand of the first dsRNA agent to the antisense strand of the second dsRNA agent.

In one embodiment, the covalent linker further comprises at least one ligand.

In one embodiment, contacting a cell with the dual targeting RNAi agent of the invention inhibits expression of the LDHA gene and the HAO1 gene to a level substantially the
15 same as the level of inhibition of expression obtained by the contacting of a cell with both dsRNA agents individually. In another embodiment, contacting a cell with the dual targeting RNAi agent inhibits 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.

20 In one embodiment, the level of inhibition of LDHA expression is at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or about 100% higher than the level of inhibition of expression obtained by the contacting of a cell with both dsRNA agents individually.

25 In one embodiment, the level of inhibition of HAO1 expression is at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or about 100% higher than the level of inhibition of expression obtained by the contacting of a cell with both dsRNA agents individually.

30 In one embodiment, contacting a cell with the dual targeting RNAi agent inhibits oxalate and/or glyoxylate protein production to a level lower than the level of protein production obtained by the contacting of a cell with both dsRNA agents individually. In another embodiment, contacting a cell with the dual targeting RNAi agent inhibits oxalate and/or glyoxylate protein production to a level lower than the level of protein production obtained by
35 the contacting of a cell with both dsRNA agents individually.

The present invention also provides cells containing a dsRNA agent or a dual targeting RNAi agent of the invention; and vectors encoding at least one strand of a dsRNA agent or a dual targeting RNAi agent of the invention.

Further, the the present invention provides apharmaceutical composition for inhibiting expression of a lactic acid dehydrogenase A (LDHA) gene comprising a dsRNA agent of the invention; or a pharmaceutical composition for inhibiting expression of a lactic acid dehydrogenase A (LDHA) gene and an hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) gene comprising a dual targeting RNAi agent of the invention.

In one aspect, the present invention provides a pharmaceutical composition, comprising a first double stranded ribonucleic acid (dsRNA) agent that inhibits expression of lactic acid dehydrogenase A (LDHA) comprising a sense strand and an antisense strand, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2; 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 said sense strand 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 comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:22.

In another aspect, the present invention provides a pharmaceutical composition, comprising a first double stranded ribonucleic acid (dsRNA) agent that inhibits expression of lactic acid dehydrogenase A (LDHA) comprising a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which 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 2-5; 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, the antisense strand comprising a region of complementarity which 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 7-14.

The agent may be formulated in an unbuffered solution, such as saline or water; or the agent may be formulated with a buffered solution, such as a solution comprising acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof; or phosphate buffered saline (PBS).

The present invention provides a method of inhibiting lactic acid dehydrogenase A (LDHA) expression in a cell. The methods include contacting the cell with an agent or a pharmaceutical composition of the invention, thereby inhibiting expression of LDHA in the cell.

The present invention also provides a method of inhibiting lactic acid dehydrogenase A (LDHA) expression and hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) expression in a cell. The method includes contacting the cell with a dual targeting RNAi agent of the invention or a pharmaceutical composition comprising a dual targeting agent of the invention, thereby inhibiting expression of LDHA and HAO1 in the cell.

In one embodiment, the cell is within a subject, such as a human.

In one embodiment, the LDHA expression is inhibited by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or to below the level of detection of LDHA expression.

In one embodiment, the HAO1 expression is inhibited by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or to below the level of detection of HAO1 expression.

In one embodiment, the human subject suffers from an oxalate pathway-associated disease, disorder, or condition.

In one embodiment, the oxalate pathway-associated disease, disorder, or condition is an oxalate-associated disease, disorder, or condition, or a lactate dehydrogenase-associated disease, disorder, or condition.

In one embodiment, the oxalate-associated disease, disorder, or condition is a kidney stone formation disease, disorder, or condition, or a calcium oxalate tissue deposition disease, disorder, or condition.

In one embodiment, the kidney stone formation disease, disorder, or condition is a calcium oxalate stone formation disease, disorder, or condition or a non-calcium oxalate stone formation disease, disorder, or condition.

In one embodiment, the calcium oxalate stone formation disease, disorder, or condition is a hyperoxaluria disease, disorder, or condition or a non-hyperoxaluria disease, disorder, or condition.

In one embodiment, the hyperoxaluria disease, disorder, or condition is selected from the group consisting of primary hyperoxaluria, enteric hyperoxaluria, dietary hyperoxaluria, and idiopathic hyperoxaluria.

In one embodiment, the non-hyperoxaluria stone formation disease, disorder, or condition is hypercalciuria and/or hypocitraturia.

In one embodiment, the non-hyperoxaluria stone formation disease, disorder, or condition is calcium oxalate or non-calcium oxalate kidney stone formation disease.

In one embodiment, the calcium oxalate tissue deposition disease, disorder, or condition is selected from the group consisting of systemic calcium oxalate tissue deposition disease, disorder, or condition or tissue specific calcium oxalate tissue deposition disease, disorder, or condition.

In one embodiment, the lactate dehydrogenase-associated disease, disorder, or condition is selected from the group consisting of cancer, fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis of the liver, accumulation of fat in the liver, inflammation of the liver, hepatocellular necrosis, liver fibrosis, and nonalcoholic fatty liver disease (NAFLD).

In one embodiment, the cell is a liver cell.

In one aspect, the present invention provides a method of inhibiting the expression of LDHA in a subject. The method includes administering to the subject a therapeutically effective amount of the agent or a pharmaceutical composition of the invention, thereby inhibiting the expression of LDHA in the subject.

In another aspect, the present invention provides a method of inhibiting lactic acid dehydrogenase A (LDHA) expression and hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) expression in a subject. The methods include administering to the subject a therapeutically effective amount of dual targeting RNAi agent of the invention, or a pharmaceutical composition comprising a dual targeting RNAi agent of the invention, thereby inhibiting expression of LDHA and HAO1 in the subject.

In one aspect, the present invention provides a method of treating a subject having a disorder that would benefit from a reduction in LDHA expression. The method includes administering to the subject a therapeutically effective amount of the agent or a pharmaceutical composition of the invention, thereby treating said subject.

In another aspect, the present invention provides a method of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in expression of an LDHA gene. The methods include administering to the subject a prophylactically effective amount of an agent or a pharmaceutical composition of the invention, thereby preventing at least one symptom in the subject.

In one embodiment, the disorder is an oxalate pathway-associated disease, disorder, or condition.

In one aspect, the present invention provides a method of treating a subject having an oxalate pathway-associated disease, disorder, or condition. The method includes administering to the subject a therapeutically effective amount of an agent or a pharmaceutical composition of the invention, thereby treating the subject.

In another aspect, the present invention provides a method of preventing at least one symptom in a subject having an oxalate pathway-associated disease, disorder, or condition. The methods includes administering to the subject a prophylactically effective amount of the agent or a pharmaceutical composition of the invention, thereby preventing at least one symptom in the subject.

In one embodiment, the administration of the dsRNA agent or the pharmaceutical composition to the subject causes a decrease in one or urinary oxalate, tissue oxalate, plasma oxalate, a decrease in LDHA enzymatic activity, a decrease in LDHA protein accumulation, and/or a decrease in HAO1 protein accumulation.

In one embodiment, the oxalate pathway-associated disease, disorder, or condition is an oxalate-associated disease, disorder, or condition, or a lactate dehydrogenase-associated disease, disorder, or condition.

In one embodiment, the oxalate-associated disease, disorder, or condition is a kidney stone formation disease, disorder, or condition, or a calcium oxalate tissue deposition disease, disorder, or condition.

In one embodiment, the kidney stone formation disease, disorder, or condition is a calcium oxalate stone formation disease, disorder, or condition or a non-calcium oxalate stone formation disease, disorder, or condition.

In one embodiment, the calcium oxalate stone formation disease, disorder, or condition is a hyperoxaluria disease, disorder, or condition or a non-hyperoxaluria disease, disorder, or condition.

5 In one embodiment, the hyperoxaluria disease, disorder, or condition is selected from the group consisting of primary hyperoxaluria, enteric hyperoxaluria, dietary hyperoxaluria, and idiopathic hyperoxaluria.

In one embodiment, the non-hyperoxaluria stone formation disease, disorder, or condition is hypercalciuria and/or hypocitraturia.

10 In one embodiment, the non-hyperoxaluria stone formation disease, disorder, or condition is calcium oxalate or non-calcium oxalate kidney stone formation disease.

In one embodiment, the calcium oxalate tissue deposition disease, disorder, or condition is selected from the group consisting of systemic calcium oxalate tissue deposition disease, disorder, or condition or tissue specific calcium oxalate tissue deposition disease, disorder, or condition.

15 In one embodiment, the lactate dehydrogenase-associated disease, disorder, or condition is selected from the group consisting of cancer, fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis of the liver, accumulation of fat in the liver, inflammation of the liver, hepatocellular necrosis, liver fibrosis, and nonalcoholic fatty liver disease (NAFLD).

In one embodiment, the disease, disorder or condition is primary hyperoxaluria 2 (PH2).

20 In one embodiment, the method further comprises altering the diet of the subject (*e.g.*, decreasing protein intake, decreasing sodium intake, decreasing ascorbic acid intake, moderating calcium intake, supplementing phosphate, supplementing magnesium, and pyridoxine treatment; and a combination of any of the foregoing).

In one embodiment, the subject further receives a kidney transplant.

25 In one embodiment, the subject is human.

In one embodiment, the methods further include administering an additional therapeutic to the subject.

In one embodiment, the RNAi agent 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.

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

In one embodiment, the agent does not substantially inhibit expression and/or activity of lactate dehydrogenase B (LDHB).

Brief Description of the Drawings

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

Figure 1B is a schematic of the metabolic pathways associated with LDHA.

Figure 2 is a graph showing the level of *Ldha* mRNA remaining in wild-type C57BL/6J mice at 10 days post-dose of a single 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, or 10 mg/kg dose of AD-84788.

Figure 3 is a graph showing hepatic LDHA activity in adult male Agxt knockout mice 4 weeks after subcutaneous administration of a single 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg dose of AD-84788. Agxt knockout mice administered 0 mg/kg of AD-84788 served as untreated controls.

Figure 4 is a schematic of the study protocol described in Example 3 and referred to in Figures 6-17B.

Figure 5 is a graph showing the amount of urinary oxalate (mg per g of creatinine) excreted by Agxt knockout mice over a twenty-four hour period at weeks 0, 1, 2, 3, 4, 6, 8, 9, and 10 following subcutaneous administration of a single 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg dose of AD-84788. Agxt knockout mice administered 0 mg/kg of AD-84788 served as untreated controls.

Figure 6 is a graph showing the amount of oxalate (mg per g of creatinine) excreted in the urine of Agxt knockout mice, wild-type mice, and Grhpr (glyoxylate reductase/hydroxypyruvate reductase) knockout mice 4 weeks after a single 10 mg/kg dose of AD-84788.

Figure 7 is a graph showing the amount of oxalate (mg per g of creatinine) excreted in the urine of Agxt deficient mice administered the dsRNA agent AD-84788 at Day 0 pre-dose (baseline, *i.e.*, at days -6, -5, -4, and -3); at days 7-10 after a single 10 mg/kg dose of AD-84788; and at days 28-31 following the last administration of four 10 mg/kg doses of AD-84788 on days 0, 11, 18, and 25 (see, Figure 4).

Figure 8A is a graph showing the enzymatic activity of LdhA in wild-type liver homogenates of untreated control mice and mice administered four 10 mg/kg doses of AD-84788 (see, Figure 4) using lactic acid as a substrate. Absorbance increases as NAD is reduced to NADH *via* LDH enzymatic activity. The initial linear range was selected, and absorbances at 1 and 6 minutes were utilized in specific activity calculations as Δ_{abs} across a Δ_{time} of 5 minutes.

Figure 8B is a graph showing the mean specific activity of LdhA in wild-type liver homogenates of untreated control mice and mice administered four 10 mg/kg doses of AD-84788 (see, Figure 4) using lactic acid as a substrate. Specific activity is expressed as $\mu\text{mol NADH formed/min/g protein}$. Calculations were performed for all animals individually, and a t-test was conducted comparing all specific activity data from both treatment groups. Mean specific activity of both treatment groups is presented. ($p < 0.001$).

Figure 9A is a graph showing the enzymatic activity of LdhA in wild-type liver homogenates of untreated control mice and mice administered four 10 mg/kg doses of AD-84788 (see, Figure 4) using glyoxylate as a substrate. Absorbance increases as NAD is reduced to NADH *via* LDH enzymatic activity. The initial linear range was selected, and absorbances at 0 and 4 minutes were utilized in specific activity calculations as Δ_{abs} across a Δ_{time} of 4 minutes.

Figure 9B is a graph showing the mean specific activity of LdhA in wild-type liver homogenates of untreated control mice and mice administered four 10 mg/kg doses of AD-84788 (see, Figure 4) using glyoxylate as a substrate. Specific activity is expressed as $\mu\text{mol NADH formed/min/g protein}$. Calculations were performed for all animals individually, and a t-test was

conducted comparing all specific activity data from both treatment groups. Mean specific activity of both treatment groups is presented. ($p < 0.001$).

Figure 10A is a graph showing the enzymatic activity of LdhA in Agxt deficient liver homogenates of untreated control mice and mice administered four 10 mg/kg doses of AD-84788 (see, Figure 4) using lactic acid as a substrate. Absorbance increases as NAD is reduced to NADH *via* LDH enzymatic activity. The initial linear range was selected, and absorbances at 0 and 4 minutes were utilized in specific activity calculations as Δ_{abs} across a Δ_{time} of 4 minutes. SD is too small to be visualized in the mean treated group.

Figure 10B is a graph showing the mean specific activity of LdhA in Agxt deficient liver homogenates of untreated control mice and mice administered four 10 mg/kg doses of AD-84788 (see, Figure 4) using lactic acid as a substrate. Specific activity is expressed as $\mu\text{mol NADH formed/min/g protein}$. Calculations were performed for all animals individually, and a t-test was conducted comparing all specific activity data from both treatment groups. Mean specific activity of both treatment groups is presented. ($p < 0.001$).

Figure 11A is a graph showing the enzymatic activity of LdhA in Agxt deficient liver homogenates of untreated control mice and mice administered four 10 mg/kg doses of AD-84788 (see, Figure 4) using glyoxylate as a substrate. Absorbance increases as NAD is reduced to NADH *via* LDH enzymatic activity. The initial linear range was selected, and absorbances at 0 and 4 minutes were utilized in specific activity calculations as Δ_{abs} across a Δ_{time} of 4 minutes.

Figure 11B is a graph showing the mean specific activity of LdhA in Agxt deficient liver homogenates of untreated control mice and mice administered four 10 mg/kg doses of AD-84788 (see, Figure 4) using glyoxylate as a substrate. Specific activity is expressed as $\mu\text{mol NADH formed/min/g protein}$. Calculations were performed for all animals individually, and a t-test was conducted comparing all specific activity data from both treatment groups. Mean specific activity of both treatment groups is presented. ($p < 0.001$).

Figure 12A is a graph showing the enzymatic activity of LdhA in wild-type heart homogenates of untreated control mice and mice administered four 10 mg/kg doses of AD-84788 (see, Figure 4) using lactic acid as a substrate. Absorbance for both the control group and the treatment group increases as NAD is reduced to NADH *via* LDH enzymatic activity. The initial linear range was selected, and absorbances at 0 and 4 minutes were utilized in specific activity calculations as Δ_{abs} across a Δ_{time} of 4 minutes.

Figure 12B is a graph showing the mean specific activity of LdhA in wild-type heart homogenates of untreated control mice and mice administered four 10 mg/kg doses of AD-84788 (see, Figure 4) using lactic acid as a substrate. Specific activity is expressed as $\mu\text{mol NADH formed/min/g protein}$. Calculations were performed for all animals individually, and a t-test was conducted comparing all specific activity data from both treatment groups. Mean specific activity of both treatment groups is presented. There is no significant difference.

Figure 12C is a graph showing the enzymatic activity of LdhA in wild-type thigh muscle homogenates of untreated control mice and mice administered four 10 mg/kg doses of AD-84788

(see, Figure 4) using lactic acid as a substrate. Absorbance for both the control group and the treatment group increases as NAD is reduced to NADH *via* LDH enzymatic activity. The initial linear range was selected, and absorbances at 0 and 4 minutes were utilized in specific activity calculations as Δ_{abs} across a Δ_{time} of 4 minutes.

Figure 12D is a graph showing the mean specific activity of LdhA in wild-type thigh muscle homogenates of untreated control mice and mice administered four 10 mg/kg doses of AD-84788 (see, Figure 4) using lactic acid as a substrate. Specific activity is expressed as $\mu\text{mol NADH formed/min/g protein}$. Calculations were performed for all animals individually, and a t-test was conducted comparing all specific activity data from both treatment groups. Mean specific activity of both treatment groups is presented. There is no significant difference.

Figure 13A is a graph showing the mean amount of lactate in wild-type liver homogenates of wild-type mice prior to the administration of four 10 mg/kg doses of AD-84788 (baseline) and the mean amount of lactate in wild-type liver homogenates of wild-type mice four weeks after the administration of four 10 mg/kg doses of AD-84788 (see, Figure 4).

Figure 13B is a graph showing the mean amount of pyruvate in wild-type liver homogenates of wild-type mice prior to the administration of four 10 mg/kg doses of AD-84788 (baseline) and the mean amount of pyruvate in wild-type liver homogenates of wild-type mice four weeks after the administration of four 10 mg/kg doses of AD-84788 (see, Figure 4).

Figure 14A is a graph showing the mean amount of lactate in Agxt deficient liver homogenates of Agxt deficient mice prior to the administration of four 10mg/kg doses of AD-84788 (baseline) and the mean amount of lactate in Agxt deficient liver homogenates of Agxt deficient mice four weeks after the administration of four 10mg/kg doses of AD-84788 (see, Figure 4).

Figure 14B is a graph showing the mean amount of pyruvate in Agxt deficient liver homogenates of Agxt deficient mice prior to the administration of four 10 mg/kg doses of AD-84788 (baseline) and the mean amount of pyruvate in Agxt deficient liver homogenates of Agxt deficient mice four weeks after the administration of four 10 mg/kg doses of AD-84788 (see, Figure 4)

Figure 15A is a graph showing the mean amount of glyoxylate in wild-type liver homogenates of wild-type mice prior to the administration of four 10 mg/kg doses of AD-84788 (baseline) and the mean amount of glyoxylate in wild-type liver homogenates of wild-type mice four weeks after the administration of four 10 mg/kg doses of AD-84788 (see, Figure 4).

Figure 15B is a graph showing the mean amount of glyoxylate in Agxt deficient liver homogenates of Agxt deficient mice prior to the administration of four 10 mg/kg doses of AD-84788 (baseline) and the mean amount of glyoxylate in Agxt deficient liver homogenates of Agxt deficient mice four weeks after the administration of four 10 mg/kg doses of AD-84788 (see, Figure 4).

Figure 16A is a graph showing the mean body weights of wild-type mice prior to the administration of four 10 mg/kg doses of AD-84788 (baseline) and the mean body weights of

wild-type mice four weeks after the administration of four 10 mg/kg doses of AD-84788 (see, Figure 4).

Figure 16B is a graph showing the mean body weights of Agxt deficient mice prior to the administration of four 10 mg/kg doses of AD-84788 (baseline) and the mean body weights of Agxt deficient mice four weeks after the administration of four 10 mg/kg doses of AD-84788 (see, Figure 4).

Figure 17A is a graph showing the mean plasma lactate levels of wild-type mice prior to the administration of four 10 mg/kg doses of AD-84788 (baseline) and the mean plasma lactate levels of wild-type mice four weeks after the administration of four 10 mg/kg doses of AD-84788 (see, Figure 4).

Figure 17B is a graph showing the mean plasma lactate levels of Agxt deficient mice prior to the administration of four 10 mg/kg doses of AD-84788 (baseline) and the mean plasma lactate levels of Agxt deficient mice four weeks after the administration of four 10 mg/kg doses of AD-84788 (see, Figure 4).

Figures 18A-18O depict exemplary dual targeting agents of the invention.

Figure 18A depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand, wherein the 3' end of the first sense strand is covalently attached to the 5' end of the second sense strand with a nucleotide linker comprising 2'OMe modified nucleotides (uuu), wherein the 3' end of the second sense strand comprises a GalNAc ligand, and wherein the two 5'-most nucleotides of the first sense strand each independently comprise a phosphorothioate linkage.

Figure 18B depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 3' end of the first sense strand is covalently attached to the 5' end of the second sense strand with a nucleotide linker comprising 2'Fluoro modified nucleotides (GfAfAf), wherein the 3' end of the second sense strand comprises a GalNAc ligand, and wherein the two 5'-most nucleotides of the first sense strand, the 3'-most nucleotide of the first sense strand, and the 5'-most nucleotide of the second sense strand each independently comprise a phosphorothioate linkage.

Figure 18C depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 3' end of the first sense strand is covalently attached to the 5' end of the second sense strand with a nucleotide linker comprising 2'Fluoro modified nucleotides (GfAfUf), wherein the

3' end of the second sense strand comprises a GalNAc ligand, and wherein the two 5'-most nucleotides of the first sense strand, the 3'-most nucleotide of the first sense strand, and the 5'-most nucleotide of the second sense strand each independently comprise a phosphorothioate linkage.

Figure 18D depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 3' end of the first sense strand is covalently attached to the 5' end of the second sense strand with a nucleotide linker comprising deoxynucleotides (dgdada), wherein the 3' end of the second sense strand comprises a GalNAc ligand, and wherein the two 5'-most nucleotides of the first sense strand, the 3'-most nucleotide of the first sense strand, and the 5'-most nucleotide of the second sense strand each independently comprise a phosphorothioate linkage.

Figure 18E depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 3' end of the first sense strand is covalently attached to the 5' end of the second sense strand with a nucleotide linker comprising deoxynucleotides (dgda), wherein the 3' end of the second sense strand comprises a GalNAc ligand, and wherein the two 5'-most nucleotides of the first sense strand, the 3'-most nucleotide of the first sense strand, and the 5'-most nucleotide of the second sense strand each independently comprise a phosphorothioate linkage.

Figure 18F depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), and the 3' end of the first sense strand is directly attached (no linker) to the 5' end of the second sense strand, wherein the two 5'-most nucleotides of the first sense strand and the two 3'-most nucleotides of the second sense strand each independently comprise a phosphorothioate linkage, and wherein the 3' end of the first sense strand comprises a GalNAc ligand.

Figure 18G depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 5' end of the first antisense strand is covalently attached to the 3' end of the second antisense strand with a nucleotide linker comprising 2'OMe modified nucleotides (acu), wherein the 3' end of the second sense strand comprises a GalNAc ligand, and wherein the two 3'-most nucleotides of the first antisense strand and the two 5'-most nucleotides of the second antisense strand each independently comprise a phosphorothioate linkage.

Figure 18H depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 5' end of the first antisense strand is covalently attached to the 3' end of the second antisense strand with a nucleotide linker comprising 2'Flouro modified nucleotides (AfAfGf), wherein the 3' end of the second sense strand comprises a GalNAc ligand, and wherein the two 3'-most nucleotides of the first antisense strand, the 5' nucleotide of the first antisense strand, the 3' nucleotide of the second antisense strand, and the two 5'-most nucleotides of the second antisense strand each independently comprise a phosphorothioate linkage.

Figure 18I depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 5' end of the first antisense strand is directly attached (no linker) to the 3' end of the second antisense strand, wherein the 3' end of the second sense strand comprises a GalNAc ligand, and wherein the two 3'-most nucleotides of the first antisense strand and the two 5'-most nucleotides of the second antisense strand each independently comprise a phosphorothioate linkage.

Figure 18J depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 3' end of the first sense strand is covalently attached to the 5' end of the second sense strand with a nucleotide linker comprising 2'OMe modified nucleotides (uuu), wherein the 5' end of the first sense strand and the 3' end of the second sense strand each independently comprise a GalNAc ligand, and wherein the 5' nucleotide of the first sense strand comprises a phosphorothioate linkage.

Figure 18K depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 3' end of the first sense strand is covalently attached to the 5' end of the second sense strand with a nucleotide linker comprising 2'Fluoro modified nucleotides (GfAfAf), wherein the 5' end of the first sense strand and the 3' end of the second sense strand each independently comprise a GalNAc ligand, and wherein the 5' nucleotide of the first sense strand, the 3' nucleotide of the first sense strand, and the 5' nucleotide of the second sense strand each independently comprise a phosphorothioate linkage.

Figure 18L depicts an exemplary dual targeting agent of the invention comprising a first

dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 3' end of the first sense strand is directly attached (no linker) to the 5' end of the second sense strand, wherein the 3' end of the first sense strand and the 3' end of the second sense strand each independently comprise a GalNAc ligand, and wherein the two 5'-most nucleotides of the first sense strand each independently comprise a phosphorothioate linkage.

Figure 18M depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 5' end of the first antisense strand is covalently attached to the 3' end of the second antisense strand with a nucleotide linker comprising 2'-O-Me modified nucleotides (acu), wherein the 3' end of the first antisense strand and the 3' end of the second sense strand each independently comprise a GalNAc ligand, and wherein the two most 5' nucleotides of the second antisense strand each independently comprise a phosphorothioate linkage.

Figure 18N depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 5' end of the first antisense strand is covalently attached to the 3' end of the second antisense strand with a nucleotide linker comprising 2'Fluoro modified nucleotides (AfaGf), wherein the 3' end of the first antisense strand and the 3' end of the second sense strand each independently comprise a GalNAc ligand, and wherein the 5' nucleotide of the first antisense strand, the 3' nucleotide of the second antisense strand, and the two 5'-most nucleotides of the second antisense strand each independently comprise a phosphorothioate linkage.

Figure 18O depicts an exemplary dual targeting agent of the invention comprising a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, wherein the first dsRNA agent comprises a first sense strand (S) and a first antisense strand (AS), wherein the second dsRNA agent comprises a second sense strand (S) and a second antisense strand (AS), wherein the 5' end of the first antisense strand is directly attached (no linker) to the 3' end of the second antisense strand, wherein the 3' end of the first antisense strand and the 3' end of the second sense strand each independently comprise a GalNAc ligand, and wherein the two most 5' nucleotides of the second antisense strand each independently comprise a phosphorothioate linkage.

Detailed Description of the Invention

The present invention provides iRNA compositions, which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an LDHA gene. The LDHA

gene may be within a cell, *e.g.*, a cell within a subject, such as a human. The present invention also provides methods of using the iRNA compositions of the invention for inhibiting the expression of an LDHA gene, and for treating a subject who would benefit from inhibiting or reducing the expression of an LDHA gene, *e.g.*, a subject that would benefit from a reduction or inhibition in urinary oxalate production, *e.g.*, a subject suffering or prone to suffering from an oxalate pathway-associated disease disorder, or condition, such as a subject suffering or prone to suffering from an oxalate-associated disease, disorder, or condition, *e.g.*, a kidney stone formation disease, disorder, or condition or a calcium oxalate tissue deposition disease, disorder, or condition; or an LDH-associated disease, disorder, or condition.

The present invention also provides methods of using the iRNA compositions of the invention for inhibiting the expression of an LDHA gene and an HAO1 gene for treating a subject who would benefit from inhibiting or reducing the expression of an LDHA gene and an HAO1 gene, *e.g.*, a subject that would benefit from a reduction or inhibition in urinary oxalate production, *e.g.*, a subject suffering or prone to suffering from an oxalate pathway-associated disease disorder, or condition, such as a subject suffering or prone to suffering from an oxalate-associated disease, disorder, or condition, *e.g.*, a kidney stone formation disease, disorder, or condition or a calcium oxalate tissue deposition disease, disorder, or condition; or an LDH-associated disease, disorder, or condition.

The iRNAs 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 iRNAs 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.

When the RNAi agent is a dual targeting RNAi 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
5 embodiments, such iRNA 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
10 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 iRNA 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.

15 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 iRNA agents described herein enables the targeted degradation of mRNAs of an LDHA gene in mammals or the targeted degradation of an LDHA gene and an
20 HAO1 gene in mammals.

Very low dosages of the iRNAs, in particular, can specifically and efficiently mediate RNA interference (RNAi), resulting in significant inhibition of expression of an LDHA gene or an LDHA gene and an HAO1 gene. Using cell-based and *in vivo* assays, the present inventors have demonstrated that iRNAs targeting LDHA can mediate RNAi, resulting in significant
25 inhibition of expression of an LDHA gene and significant inhibition of oxalate production. Thus, methods and compositions including these iRNAs are useful for treating a subject who would benefit by a reduction or inhibition in LDHA expression or LDHA expression and HAO1 expression, *e.g.*, a subject suffering or prone to suffering from an oxalate pathway-associated disease, disorder, or condition.

30 The following detailed description discloses how to make and use compositions containing iRNAs to inhibit the expression of an LDHA gene, an HAO1 gene, and 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
35 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
5 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 “LDHA” (used interchangeable herein with the term “Ldha”), also known as
10 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
15 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
20 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
25 (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
30 (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.

5 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
10 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 ID NO: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
15 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
20 available at www.ncbi.nlm.nih.gov/projects/SNP.

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 or an HAO1 gene, including mRNA that is a product of RNA processing of a primary transcription product. In one embodiment, the target portion of the sequence will be at least long enough to serve as a
25 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 embodiment, the target portion of the sequence will be at least long enough to serve as a substrate for iRNA-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during the transcription of an HAO1 gene.

30 The target sequence of an LDHA gene may be from about 9-36 nucleotides in length, *e.g.*, about 15-30 nucleotides in length. For example, the target sequence can be from about 15-30 nucleotides, 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-
35 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.

The target sequence of an HAO1 gene may be from about 9-36 nucleotides in length, *e.g.*, about 15-30 nucleotides in length. For example, the target sequence can be from about 15-

30 nucleotides, 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 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.

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

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

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

In one embodiment, an RNAi agent of the invention includes a single stranded RNA that interacts with a target RNA sequence, *e.g.*, an LDHA target mRNA sequence and/or an 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 siRNA by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) *Genes Dev.* 15:485). Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409:363). The

siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, *et al.*, (2001) *Cell* 107:309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleave the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15:188). Thus, in one aspect the invention relates to a single stranded RNA (sssiRNA) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.*, an LDHA gene and/or an 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 RNAi agent that is introduced into a cell or organism to inhibit a target mRNA. Single-stranded RNAi agents (ssRNAi) 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 RNAi agents 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, an “iRNA” for use in the compositions and methods of the invention 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 gene and/or an HAO1 gene. In some embodiments of the invention, a double-stranded RNA (dsRNA) triggers the degradation of a target RNA, *e.g.*, an mRNA, through a post-transcriptional gene-silencing mechanism referred to herein as RNA interference or RNAi.

In 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.

In general, the majority of nucleotides of each strand of a dsRNA molecule are ribonucleotides, but as described in detail herein, each or both strands can also include one or more non-ribonucleotides, *e.g.*, a deoxyribonucleotide and/or a modified nucleotide. In addition, as used in this specification, an “RNAi agent” may include ribonucleotides with chemical modifications; an RNAi agent 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 a 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 agents of the invention include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a siRNA type molecule, are encompassed by “RNAi agent” for the purposes of this specification and claims.

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

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 length of the duplex region of the first agent and the second agent may be the same or different.

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

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 dsRNA agent may comprise a harpin loop, the second dsRNA agent may comprise a hairpin loop, or both the first and the second dsRNA agents may independently comprise a hairpin loop. In addition, 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

dsRNA agent may comprise unpaired nucleotides, the second dsRNA agent may comprise unpaired nucleotides, or both the first and the second dsRNA agents may independently comprise unpaired nucleotides. When both the first and the second dsRNA agents independently comprise unpaired nucleotides, the first dsRNA agent and the second dsRNA agent may

5 comprise the same or a different number of unpaired nucleotides.

Where the two substantially complementary strands of a dsRNA are comprised by separate RNA molecules, those molecules need not, but can be covalently connected. Where the two strands are connected covalently by means other than an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex

10 structure, the connecting structure is referred to as a "linker." The RNA strands may have the same or a different number of nucleotides. The maximum number of base pairs is the number of nucleotides in the shortest strand of the dsRNA minus any overhangs that are present in the duplex. In addition to the duplex structure, an RNAi may comprise one or more nucleotide overhangs.

In one embodiment, an RNAi agent of the invention is a dsRNA, each strand of which comprises 19-23 nucleotides, that interacts with a target RNA sequence, *e.g.*, an LDHA target mRNA sequence, to direct the cleavage of the target RNA. In another embodiment, an RNAi agent of the invention is a dsRNA, each strand of which comprises 19-23 nucleotides, that interacts with a target RNA sequence, *e.g.*, an HAO1 target mRNA sequence, to direct the

20 cleavage of the target RNA. In yet other embodiments an RNAi agent of the invention comprises a first dsRNA agent, each strand of which comprises 19-23 nucleotides, that interacts with a target RNA sequence, *e.g.*, an LDHA target mRNA sequence, to direct the cleavage of the target RNA, and a second dsRNA agent, each strand of which independently comprises 19-23 nucleotides, that interacts with a target RNA sequence, *e.g.*, an HAO1 target mRNA sequence, to

25 direct the cleavage of the target RNA, wherein the first and second dsRNA agents are covalently attached.

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 two strands of the first dsRNA agent may be connected covalently by means other than an uninterrupted

30 chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the two strands of the second dsRNA agent may be connected covalently by means other than an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, or the two strands of the first dsRNA agent and the two strands of the second dsRNA agent may

35 independently be connected covalently by means other than an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure.

As used herein, the term "nucleotide overhang" refers to at least one unpaired nucleotide that protrudes from the duplex structure of an iRNA, *e.g.*, a dsRNA. For example, when a 3'-end

of one strand of a dsRNA extends beyond the 5'-end of the other strand, or vice versa, there is a nucleotide overhang. A dsRNA can comprise an overhang of at least one nucleotide; alternatively the overhang can comprise at least two nucleotides, at least three nucleotides, at least four nucleotides, at least five nucleotides or more. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can be on the sense strand, the antisense strand or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5'-end, 3'-end or both ends of either an antisense or sense strand of a dsRNA.

In 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 a nucleotide overhang, the second agent may comprise a nucleotide overhang, or both the first and the second agent may independently comprise a nucleotide overhang, *e.g.*, the 5' end of the sense strand of the first agent may comprise an overhang, the 3' end of the sense strand of the first agent may comprise an overhang, the 5' end of the antisense strand of the first agent may comprise an overhang, the 3' end of the antisense strand of the first agent may comprise an overhang, the 5' end and the 3' end of the sense strand of the first agent may comprise an overhang, the 5' end and the 3' end of the antisense strand of the first agent may comprise an overhang, the 5' end of the sense strand of the second agent may comprise an overhang, the 3' end of the sense strand of the second agent may comprise an overhang, the 5' end of the antisense strand of the second agent may comprise an overhang, the 3' end of the antisense strand of the second agent may comprise an overhang, the 5' end and the 3' end of the sense strand of the second agent may comprise an overhang, the 5' end and the 3' end of the antisense strand of the second agent may comprise an overhang, or any combination of the foregoing.

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 length of an overhang of the first agent and the second agent may be the same or different.

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

In certain embodiments, the overhang on the sense strand or the antisense strand, or both, can include extended lengths longer than 10 nucleotides, *e.g.*, 10-30 nucleotides, 10-25 nucleotides, 10-20 nucleotides or 10-15 nucleotides in length. In certain embodiments, an extended overhang is on the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 3' end of the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 5' end of the sense strand of the duplex. In certain embodiments, an extended overhang is on the antisense strand of the duplex. In certain

embodiments, an extended overhang is present on the 3' end of the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 5' end of the antisense strand of the duplex. In certain embodiments, one or more of the nucleotides in the extended overhang is replaced with a nucleoside thiophosphate.

5 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), and one and/or both strands of both the first and the second dsRNA agent independently comprise an overhang, *e.g.*, an extended overhang, the length of the overhang may be the same or different, and/or, in some embodiments, one or more of the nucleotides in the overhang in the first dsRNA agent and
10 one or more nucleotides in the overhang of the second dsRNA agent may be independently replaced with a nucleoside thiophosphate.

The terms "blunt" or "blunt ended" as used herein in reference to a dsRNA mean that there are no unpaired nucleotides or nucleotide analogs at a given terminal end of a dsRNA, *i.e.*, no nucleotide overhang. One or both ends of a dsRNA can be blunt. Where both ends of a
15 dsRNA are blunt, the dsRNA is said to be blunt ended. To be clear, a "blunt ended" dsRNA is a dsRNA that is blunt at both ends, *i.e.*, no nucleotide overhang at either end of the molecule. Most often such a molecule will be double-stranded over its entire length.

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), one or both of
20 the dsRNA agents may independently comprise a blunt end.

The term "antisense strand" or "guide strand" refers to the strand of an iRNA, *e.g.*, a dsRNA, which includes a region that is substantially complementary to a target sequence, *e.g.*, an LDHA mRNA or an HAO1 mRNA.

As used herein, the term "region of complementarity" refers to the region on the
25 antisense strand that is substantially complementary to a sequence, for example a target sequence, *e.g.*, an LDHA nucleotide sequence 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'-
30 and/or 3'-terminus of the iRNA.

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), one or both of the dsRNA agents may independently comprise a mismatch.

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

As used herein, the term "cleavage region" refers to a region that is located immediately adjacent to the cleavage site. The cleavage site is the site on the target at which cleavage occurs. In some embodiments, the cleavage region comprises three bases on either end of, and

immediately adjacent to, the cleavage site. In some embodiments, the cleavage region comprises two bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage site specifically occurs at the site bound by nucleotides 10 and 11 of the antisense strand, and the cleavage region comprises nucleotides 11, 12 and 13.

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

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

“Complementary” sequences, as used herein, can also include, or be formed entirely from, non-Watson-Crick base pairs 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.

The terms “complementary,” “fully complementary” and “substantially complementary” herein can be used with respect to the base matching between the sense strand and the antisense

strand of a dsRNA, or between the antisense strand of an iRNA agent and a target sequence, as will be understood from the context of their use.

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

Accordingly, in some embodiments, the antisense strand polynucleotides disclosed herein are fully complementary to the target LDHA sequence. In other embodiments, the antisense strand polynucleotides disclosed herein are substantially complementary to the target LDHA sequence and 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:1, or a fragment of SEQ ID NO:1, 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 one embodiment, an RNAi agent of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target LDHA sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NO:2, or a fragment of any one of SEQ ID NO:2, 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, an iRNA of the invention includes an antisense strand that is substantially complementary to the target LDHA sequence and comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of any one of the sense strands in any one of Tables 2-5, or a fragment of any one of the sense strands in any one of Tables 2-5, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% complementary, or 100% complementary.

Accordingly, in some embodiments, the antisense strand polynucleotides disclosed herein are fully complementary to the target HAO1 sequence. In other embodiments, the antisense strand polynucleotides disclosed herein are substantially complementary to the target HAO1 sequence and 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 one embodiment, an RNAi agent of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target HAO1 sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NO:22, or a fragment of any one of SEQ ID NO:22, 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, an iRNA of the invention includes an antisense strand that is substantially complementary to the target HAO1 sequence and comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of any one of the sense strands in any one of Tables 7-14, or a fragment of any one of the sense strands in any one of Tables 7-14, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% complementary, or 100% complementary.

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

The phrase “inhibiting expression of an LDHA gene,” as used herein, includes inhibition of expression of any LDHA gene (such as, *e.g.*, a mouse LDHA gene, a rat LDHA gene, a monkey LDHA gene, or a human LDHA gene) as well as variants or mutants of an LDHA gene that encode an LDHA protein.

“Inhibiting expression of an LDHA gene” includes any level of inhibition of an LDHA gene, *e.g.*, at least partial suppression of the expression of an LDHA gene, such as an inhibition by at least about 20%. In certain embodiments, inhibition is by at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99%.

The phrase “inhibiting expression of an HAO1 gene,” as used herein, includes inhibition of expression of any HAO1 gene (such as, *e.g.*, a mouse HAO1 gene, a rat HAO1 gene, a monkey HAO1 gene, or a human HAO1 gene) as well as variants or mutants of an HAO1 gene that encode an HAO1 protein.

“Inhibiting expression of an HAO1 gene” includes any level of inhibition of an HAO1 gene, *e.g.*, at least partial suppression of the expression of an HAO1 gene, such as an inhibition by at least about 20%. In certain embodiments, inhibition is by at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at

least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99%.

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

The expression of an LDHA gene and/or an HAO1 gene may be assessed based on the level of any variable associated with LDHA gene expression and/or HAO1 gene expression, *e.g.*, LDHA and/or HAO1 mRNA level or LDHA and/or HAO1 protein level. The expression of an LDHA gene and/or an HAO1 gene may also be assessed indirectly based on the levels of oxalate or glycolate in a urine, a plasma, or a tissue sample, or the enzymatic activity of LDHA in a tissue sample, such as a liver sample, a skeletal muscle sample, and/or a heart sample. Inhibition may be assessed by a decrease in an absolute or relative level of one or more of these variables compared with a control level. The control level may be any type of control level that is utilized in the art, *e.g.*, a pre-dose baseline level, or a level determined from a similar subject, cell, or sample that is untreated or treated with a control (such as, *e.g.*, buffer only control or inactive agent control).

In one embodiment, at least partial suppression of the expression of an LDHA gene, is assessed by a reduction of the amount of LDHA mRNA which can be isolated from, or detected, in a first cell or group of cells in which an LDHA gene is transcribed and which has or have been treated such that the expression of an LDHA gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has or have not been so treated (control cells).

In one embodiment, at least partial suppression of the expression of an HAO1 gene, is assessed by a reduction of the amount of HAO1 mRNA which can be isolated from or detected in a first cell or group of cells in which an HAO1 gene is transcribed and which has or have been treated such that the expression of an HAO1 gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has or have not been so treated (control cells).

In one embodiment, at least partial suppression of the expression of an LDHA gene and an HAO1 gene, is assessed by a reduction of the amount of LDHA mRNA and HAO1 mRNA which can be isolated from or detected in a first cell or group of cells in which an LDHA gene and an HAO1 gene are transcribed and which has or have been treated such that the expression of an LDHA gene and an HAO1 gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has or have not been so treated (control cells).

The degree of inhibition may be expressed in terms of:

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

The phrase “contacting a cell with an RNAi agent,” such as a dsRNA, as used herein, includes contacting a cell by any possible means. Contacting a cell with an RNAi agent includes contacting a cell *in vitro* with the iRNA or contacting a cell *in vivo* with the iRNA. The contacting may be done directly or indirectly. Thus, for example, the RNAi agent may be put
5 into physical contact with the cell by the individual performing the method, or alternatively, the RNAi agent may be put into a situation that will permit or cause it to subsequently come into contact with the cell.

In the methods of the invention 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),
10 contacting a cell may include contacting the cell with the first agent at the same time or at a different time than contacting the cell with the second agent.

Contacting a cell *in vitro* may be done, for example, by incubating the cell with the RNAi agent. Contacting a cell *in vivo* may be done, for example, by injecting the RNAi agent into or near the tissue where the cell is located, or by injecting the RNAi agent into another area, *e.g.*,
15 the bloodstream or the subcutaneous space, such that the agent will subsequently reach the tissue where the cell to be contacted is located. For example, the RNAi agent may contain and/or be coupled to a ligand, *e.g.*, GalNAc3, that directs the RNAi agent to a site of interest, *e.g.*, the liver. Combinations of *in vitro* and *in vivo* methods of contacting are also possible. For example, a cell may also be contacted *in vitro* with an RNAi agent and subsequently transplanted into a subject.

In one embodiment, contacting a cell with an iRNA includes “introducing” or “delivering the iRNA into the cell” by facilitating or effecting uptake or absorption into the cell. Absorption or uptake of an iRNA can occur through unaided diffusive or active cellular processes, or by auxiliary agents or devices. Introducing an iRNA into a cell may be *in vitro* and/or *in vivo*. For example, for *in vivo* introduction, iRNA can be injected into a tissue site or administered
20 systemically. *In vivo* delivery can also be done by a beta-glucan delivery system, such as those described in U.S. Patent Nos. 5,032,401 and 5,607,677, and U.S. Publication No. 2005/0281781, the entire contents of which are hereby incorporated herein by reference. *In vitro* introduction into a cell includes methods known in the art such as electroporation and lipofection. Further approaches are described herein below and/or are known in the art.

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

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 an embodiment, the subject is a human, such as a human being treated or assessed for a disease, disorder or condition that would benefit from reduction in LDHA expression; a human at risk for a disease, disorder or condition that would benefit from reduction in LDHA expression; a human having a disease, disorder or condition that would benefit from reduction in LDHA expression; and/or human being treated for a disease, disorder or condition that would benefit from reduction in LDHA expression as described herein.

It is to be understood that a human being treated or assessed for a disease, disorder or condition that would benefit from reduction in LDHA expression includes a human being treated or assessed for a disease, disorder or condition that would benefit from reduction in LDHA and HAO1 expression; that a human at risk for a disease, disorder or condition that would benefit from reduction in LDHA expression includes a human at risk for a disease, disorder or condition that would benefit from reduction in LDHA and HAO1 expression; that a human having a disease, disorder or condition that would benefit from reduction in LDHA expression includes a human at risk for a disease, disorder or condition that would benefit from reduction in LDHA and HAO1 expression; and that a human being treated for a disease, disorder or condition that would benefit from reduction in LDHA expression includes a human being treated for a disease, disorder or condition that would benefit from reduction in LDHA and HAO1 expression as described herein.

As used herein, the terms “treating” or “treatment” refer to a beneficial or desired result, such as 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 an oxalate pathway-associated disease disorder, or condition, such as, *e.g.*, slowing the course of the disease; reducing the severity of later-developing disease; reduction in edema of the extremities, face, larynx, upper respiratory tract, abdomen, trunk, and/or genitals, prodrome, laryngeal swelling, nonpruritic rash, nausea, vomiting, and/or abdominal pain; decreasing progression of liver disease to cirrhosis or hepatocellular carcinoma; stabilizing current stone burden; decreasing recurrence of stones formed; 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 preferably down 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, disorder or condition thereof, that would benefit from a reduction in expression of an LDHA gene, refers to a reduction in the likelihood that a subject will develop a symptom associated with such disease, disorder, or condition, *e.g.*, stone formation. The likelihood of, *e.g.*, 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, disorder or condition, 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.

There are numerous disorders that would benefit from reduction in expression of an LDHA gene, such as an oxalate pathway-associated disease disorder, or condition.

As used herein, the term “oxalate pathway-associated disease, disorder, or condition” refers to a disease, disorder or condition thereof, in which lactate dehydrogenase knockdown is known or predicted to be therapeutic or otherwise advantageous, *e.g.*, associated with or caused by a disturbance in lactate dehydrogenase production and/or urinary oxalate production.

In one embodiment, an “oxalate pathway-associated disease, disorder, or condition” is a “lactate dehydrogenase-associated disease, disorder, or condition.” As used herein, a “lactate dehydrogenase-associated disease, disorder, or condition” includes any disease, disorder or condition that would benefit from a decrease in lactate dehydrogenase gene expression, replication, or protein activity. Exemplary lactate dehydrogenase-associated disease, disorders, and conditions include, for example, fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis of the liver, accumulation of fat in the liver, inflammation of the liver, hepatocellular necrosis, liver fibrosis, obesity, nonalcoholic fatty liver disease (NAFLD), and cancer, *e.g.*, hepatocellular carcinoma.

In another embodiment, an “oxalate pathway-associated disease, disorder, or condition” is “an oxalate-associated disease, disorder, or condition.” As used herein, “an oxalate-associated disease, disorder, or condition” includes any disease, disorder or condition that would benefit from a decrease in lactate dehydrogenase gene expression, replication, or protein activity. The term “oxalate-associated disease, disorder, or condition” refers to inherited disorders, or induced or acquired disorders. Exemplary “oxalate-associated diseases, disorders, or conditions” include “kidney stone formation diseases, disorders, and conditions” and “calcium oxalate tissue deposition diseases, disorders, and conditions.”

Exemplary kidney stone formation diseases, disorders, and conditions include “calcium oxalate stone formation diseases, disorders, and conditions” and “non-calcium oxalate stone formation diseases, disorders, and conditions.”

Non-limiting examples of “calcium oxalate stone formation diseases, disorders, and conditions” include a hyperoxaluria (*e.g.*, a. primary hyperoxaluria, such as primary hyperoxaluria 1 (PH1), primary hyperoxaluria 2 (PH2), primary hyperoxaluria 3 (PH3) and nonPH1/PH2/PH3; enteric hyperoxaluria; dietary hyperoxaluria; and idiopathic hyperoxaluria) and a non-hyperoxaluria disorder (*e.g.*, a hypercalciuria, such as primary hyperparathyroid, Dent’s disease, absorptive hypercalciuria, and renal hypercalciuria; and hypocitraturia).

Non-limiting examples of “non-calcium oxalate stone formation diseases, disorders, and conditions” include subjects having kidney stones that are comprised of less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, or less than about 10% oxalate, and more than about 50% non-oxalate, *e.g.* calcium phosphate, uric acid, struvite, cystinuria, or other component.

Exemplary “calcium oxalate tissue deposition diseases, disorders, and conditions” include systemic calcium oxalate tissue deposition diseases, disorders, and conditions, such as calcium oxalate tissue deposition due to end-stage renal disease, sarcoidosis, or arthritis; and tissue specific calcium oxalate deposition diseases, disorders, and conditions, *e.g.*, in the kidney (*e.g.*, due to nephrocalcinosis, or medullary sponge kidney), in the thyroid, in the breast, in the bone, in the heart, in the vasculature, or in any soft tissue due to an organ transplant, such as a kidney transplant.

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

“Prophylactically effective amount,” as used herein, is intended to include the amount of an iRNA that, when administered to a subject having an oxalate pathway-associated disease, disorder, or condition, 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 iRNA, how the agent is administered, the degree of risk of disease, and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the patient to be treated.

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

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 prophylactically effective amount of the first dsRNA agent may be the same or different than the prophylactically effective amount of the second dsRNA agent.

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

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (*e.g.*, lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject being treated. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

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

II. iRNAs of the Invention

Described herein are iRNAs which inhibit the expression of a target gene. In one embodiment, the iRNAs inhibit the expression of an LDHA gene. In one embodiment, the iRNA agent includes double stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of an LDHA gene in a cell, such as a liver cell, such as a liver cell within a subject, *e.g.*, a mammal, such as a human having an oxalate pathway-associated disease, disorder, or condition, *e.g.*, a stone formation disease, disorder, or condition. In another embodiment, the iRNAs inhibit the expression of an HAO1 gene. In one embodiment, the iRNA agent includes double stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of an HAO1 gene in a cell, such as a liver cell, such as a liver cell within a subject, *e.g.*, a mammal, such as a human having an oxalate pathway-associated disease, disorder, or condition, *e.g.*, an oxalate-associated disease, disorder, or condition, *e.g.*, a kidney stone formation disease, disorder, or condition or a calcium oxalate tissue deposition disease, disorder, or condition; or an LDH-associated disease, disorder, or condition.

Also provided herein are iRNAs which inhibit the expression of two target genes, referred to as dual targeting RNAi agents. In one embodiment, the dual targeting RNAi agent includes a first double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of an LDHA gene in a cell (such as a liver cell, *e.g.*, a liver cell within a subject) covalently attached to a second double stranded ribonucleic acid (dsRNA) agent for inhibiting the expression of an HAO1 gene in a cell (such as a liver cell, *e.g.*, a liver cell within a subject), such as a cell within a subject, *e.g.*, a mammal, such as a human having an oxalate pathway-associated disease, disorder, or condition, *e.g.*, an oxalate-associated disease, disorder, or condition, *e.g.*, a kidney stone formation disease, disorder, or condition or a calcium oxalate tissue deposition disease, disorder, or condition; or an LDH-associated disease, disorder, or condition.

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. 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.

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 expression or LDHA and HAO1 expression is not generated in the target cell by cleavage of a larger dsRNA.

5 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
10 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.

15 iRNA compounds of the invention may be prepared using a two-step procedure. First, the individual strands of the double-stranded RNA molecule are prepared separately. Then, the component strands are annealed. The individual strands of the siRNA compound can be prepared using solution-phase or solid-phase organic synthesis or both. Organic synthesis offers the advantage that the oligonucleotide strands comprising unnatural or modified nucleotides can be
20 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 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 2-5 and the corresponding nucleotide sequence
25 of the antisense strand of the sense strand is selected from the group of sequences of any one of Tables 2-5. 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
30 (passenger strand) in any one of Tables 2-5 and the second oligonucleotide is described as the corresponding antisense strand (guide strand) of the sense strand in any one of Tables 2-5. 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.

35 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 7-14 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 7-14. 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 7-14 and the second
 5 oligonucleotide is described as the corresponding antisense strand (guide strand) of the sense strand in any one of Tables 7-14. 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.

It will be understood that, although the sequences in Tables 2-5 and 7-14 are described as
 10 modified, unmodified, unconjugated, and/or conjugated sequences, the RNA of the iRNA of the invention *e.g.*, a dsRNA of the invention, may comprise any one of the sequences set forth in any one of Table 2-5 and 7-14 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
 15 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
 20 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
 25 gene or an HAO1 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 2-5 identify a site(s) in an LDHA transcript that is susceptible to RISC-mediated cleavage and those RNAs described in any one of
 30 Tables 7-14 identify a site(s) in an HAO1 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
 35 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.

An iRNA 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, 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 and/or an HAO1 gene. Consideration of the efficacy of iRNAs with mismatches in inhibiting expression of an LDHA gene and/or an

HAO1 gene is important, especially if the particular region of complementarity in an LDHA 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.

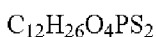
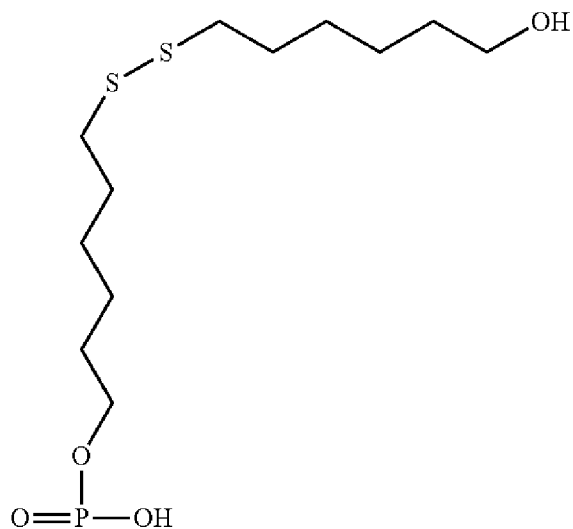
Suitable linkers for use in the dual targeting agent of the invention include those described in U.S. Patent No. 9,187,746, the entire contents of which are incorporated herein by reference.

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); rUUrU (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, preferable 4-15 inclusive, most preferably 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, preferable 4-15 inclusive, most preferably 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, preferable 4-inclusive, most preferably 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



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, preferably comprising 4-5 amino acids, optionally X-Gly-Phe-Gly-Y wherein X and Y represent any amino acid.

5 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.

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

III. Modified iRNAs of the Invention

15 In one embodiment, the RNA of the iRNA of the invention *e.g.*, a dsRNA, is unmodified, and does not comprise, *e.g.*, chemical modifications and/or conjugations known in the art and described herein. In another embodiment, the RNA of an iRNA of the invention, *e.g.*, a dsRNA, is chemically modified to enhance stability or other beneficial characteristics. In certain embodiments of the invention, substantially all of the nucleotides of an iRNA of the invention are modified. In other embodiments of the invention, all of the nucleotides of an iRNA of the invention are modified. iRNAs 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.

25 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), 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 an iRNA of the invention are modified and the iRNA agents 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 dsRNA agent targeting LDHA and a second 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 an iRNA of the invention are modified and the iRNA agents 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 dsRNA agent targeting LDHA and a second 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, the double stranded RNAi agent 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 phosphate (5'-VP).

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 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 iRNA compounds useful in the embodiments described herein include, but are not limited to RNAs containing modified backbones or no natural internucleoside linkages. RNAs having modified backbones include, among others, those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In some embodiments, a modified iRNA will have a phosphorus atom in its internucleoside backbone.

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

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

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

In other embodiments, suitable RNA mimetics are contemplated for use in iRNAs, 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 RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular --CH₂--NH--CH₂--CH₂--N(CH₃)--O--CH₂--[known as a methylene (methylimino) or MMI backbone], --CH₂--O--N(CH₃)--CH₂--, --CH₂--N(CH₃)--N(CH₃)--CH₂-- and --N(CH₃)--CH₂--CH₂--[wherein the native phosphodiester backbone is represented as --O--P--O--CH₂--] of the above-referenced U.S. Patent No. 5,489,677, and the amide backbones of the above-referenced U.S. Patent No.

5,602,240. In some embodiments, the RNAs featured herein have morpholino backbone structures of the above-referenced U.S. Patent No. 5,034,506.

Modified RNAs can also contain one or more substituted sugar moieties. The iRNAs, *e.g.*, dsRNAs, featured herein can include one of the following at the 2'-position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Exemplary suitable modifications include O[(CH₂)_nO]_mCH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an iRNA, or a group for improving the pharmacodynamic properties of an iRNA, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminoethoxy, *i.e.*, a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH₂--O--CH₂--N(CH₂)₂. Further exemplary modifications include: 5'-Me-2'-F nucleotides, 5'-Me-2'-OMe nucleotides, 5'-Me-2'-deoxynucleotides, (both R and S isomers in these three families); 2'-alkoxyalkyl; and 2'-NMA (N-methylacetamide).

Other modifications include 2'-methoxy (2'-OCH₃), 2'-aminopropoxy (2'-OCH₂CH₂CH₂NH₂) and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of an iRNA, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. iRNAs can also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative 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.

An iRNA 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 and other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*, Herdewijn, P. ed. Wiley-VCH, 2008; those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, pages 858-859, Kroschwitz, J. L, ed. John Wiley & Sons, 1990, those disclosed by Englisch *et al.*, (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 O-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.

An iRNA 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).

An iRNA of the invention can also be modified to include one or more bicyclic sugar moieties. 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 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. 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).

An iRNA 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)-O-2' bridge. In one embodiment, a constrained ethyl nucleotide is in the S conformation referred to herein as “S-cEt.”

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

Representative publications that teach the preparation of certain of the above noted CRN include, but are not limited to, 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, an iRNA of the invention comprises one or more monomers that are UNA (unlocked nucleic acid) nucleotides. UNA is unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked "sugar" residue. In one example, UNA also encompasses monomer with bonds between C1'-C4' have been removed (i.e. the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (i.e. the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar has been removed (see *Nuc. Acids Symp. Series*, 52, 133-134 (2008) and Fluiter et al., *Mol. Biosyst.*, 2009, 10, 1039 hereby incorporated by reference).

Representative U.S. publications that teach the preparation of UNA include, but are not limited to, 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 RNA molecules can include N-(acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-O-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"- phosphate, inverted base dT(idT) and others. Disclosure of this modification can be found in PCT Publication No. WO 2011/005861.

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

In certain specific embodiments, an RNAi agent of the present invention is an agent that inhibits the expression of an LDHA gene which is selected from the group of agents listed in any one of Tables 2-5. In other embodiments, an RNAi agent of the present invention is an dual targeting iRNA agent that inhibits the expression of an LDHA gene and an HAO1, wherein the first dsRNA inhibits expression of an LDHA gene and is selected from the group of agents listed in any one of Tables 2-5, and the first dsRNA inhibits expression of an HAO1 gene and is

selected from the group of agents listed in any one of Tables 7-14. Any of these agents may further comprise a ligand.

A. Modified iRNAs 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 or 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 not limited to 2'-sugar modified, such as, 2-F, 2'-O-methyl, thymidine (T), 2'-O-methoxyethyl-5-methyluridine (Teo), 2'-O-methoxyethyladenosine (Aeo), 2'-O-methoxyethyl-5-methylcytidine (m5Ceo), and any combinations 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 ended bluntmer of 19 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 7, 8, 9 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5'end.

In another embodiment, the RNAi agent is a double ended bluntmer 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, 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, 13 from the 5'end.

In yet another embodiment, the RNAi agent is a double ended bluntmer 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, 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, 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, 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, 13 from the 5' end, wherein one end of the RNAi agent is blunt, while the other end comprises a 2 nucleotide overhang. Preferably, the 2

5 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

10 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 3'-fluoro, *e.g.*, in an alternating motif.

15 Optionally, the RNAi agent further comprises a ligand (preferably GalNAc₃).

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

20 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

25 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

30 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.

35 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, 13 from the 5' end; wherein the 3' end of the first strand and the 5' end of the second strand form a

blunt end and the second strand is 1-4 nucleotides longer at its 3' end than the first strand, wherein the duplex region which is at least 25 nucleotides in length, and the second strand is sufficiently complementary to a target mRNA along at least 19 nucleotide of the second strand length to reduce target gene expression when the RNAi agent is introduced into a mammalian cell, and wherein dicer cleavage of the RNAi agent preferentially 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, 11 positions; 10, 11, 12 positions; 11, 12, 13 positions; 12, 13, 14 positions; or 13, 14, 15 positions of the antisense strand, the count starting from the 1st nucleotide from the 5'-end of the antisense strand, or, the count starting from the 1st 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 adjacent to the first motif or is separated by at least one or more nucleotides. When the motifs are immediately adjacent to each other then the chemistry of the motifs are distinct from each other and when the motifs are separated by one or more nucleotide then the chemistries can

be the same or different. Two or more wing modifications may be present. For instance, when two wing modifications are present, each wing modification may occur at one end relative to the first motif which is at or near cleavage site or on either side of the lead motif.

5 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.

10 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.

15 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.

20 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.

25 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; 30 modification or replacement of a naturally occurring base; and replacement or modification of the ribose-phosphate backbone.

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

In 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 deoxy-thymine (dT). In another embodiment, the nucleotide at the 3'-end of the antisense strand is deoxy-thymine (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):



wherein:

i and j are each independently 0 or 1;

p and q are each independently 0-6;

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

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

each n_p and n_q independently represent an overhang nucleotide;

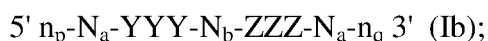
wherein N_b and Y do not have the same modification; and

XXX, YYY and ZZZ each independently represent one motif of three identical modifications on three consecutive nucleotides. Preferably 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 -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. Preferably, 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 17-23 nucleotide in length, the Y'Y'Y' motif can occur at positions 9, 10, 11; 10, 11, 12; 11, 12, 13; 12, 13, 14; or 13, 14, 15 of the antisense strand, with the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'-end. Preferably, 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. Preferably, 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'
(IIIId)

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.

5 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.

10 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.

15 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 0 modified 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.

20 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.

25 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.

30 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.

35 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 via a 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 a ligand. Each of the agents can target the same gene or two different genes; or each of the agents can target same gene at two different target sites.

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

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

Various publications describe multimeric 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.

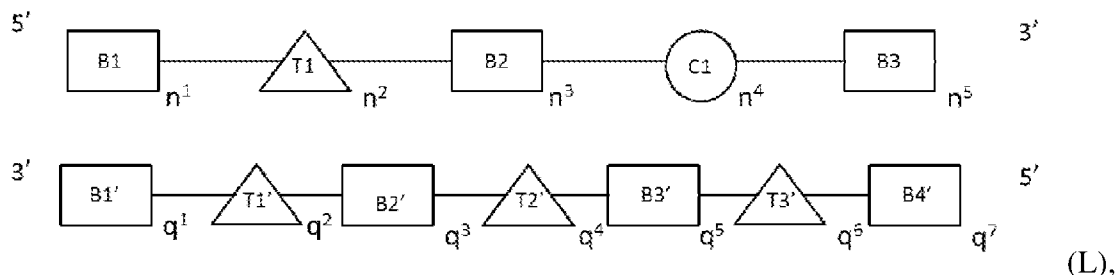
As described in more detail below, the RNAi agent that contains conjugations of one or more carbohydrate moieties to a RNAi agent can optimize one or more properties of the RNAi agent. In many cases, the carbohydrate moiety will be attached to a modified subunit of the RNAi agent. For example, the ribose sugar of one or more ribonucleotide subunits of a dsRNA agent can be replaced with another moiety, e.g., a non-carbohydrate (preferably 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," preferably 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; preferably, the cyclic group is selected from pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane,

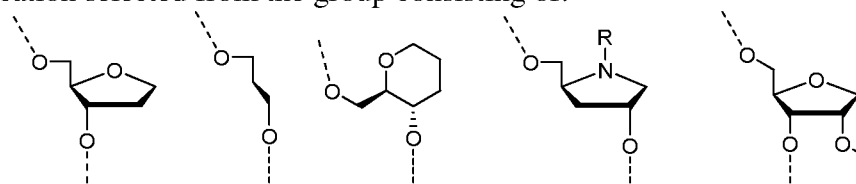
oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxaliny, pyridazinonyl, tetrahydrofuryl and and decalin; preferably, the acyclic group is selected from serinol backbone or diethanolamine backbone.

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):

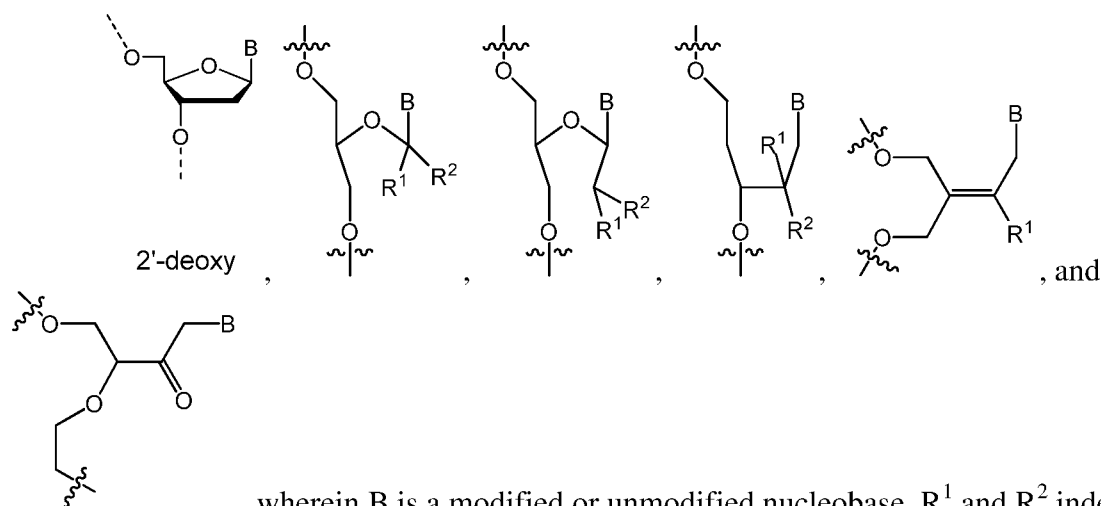


In formula (L), B1, B2, B3, B1', B2', B3', and B4' each are independently a nucleotide containing a modification selected from the group consisting of 2'-O-alkyl, 2'-substituted alkoxy, 2'-substituted alkyl, 2'-halo, ENA, and BNA/LNA. In one embodiment, B1, B2, B3, B1', B2', B3', and B4' each contain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

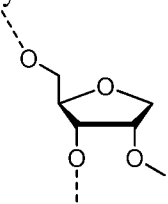


; and iii) sugar modification selected from the group consisting of:



5 one embodiment, the thermally destabilizing modification in C1 is a mismatch selected from the group consisting of G:G, G:A, G:U, G:T, A:A, A:C, C:C, C:U, C:T, U:U, T:T, and U:T; and optionally, at least one nucleobase in the mismatch pair is a 2'-deoxy nucleobase. In one

example, the thermally destabilizing modification in C1 is GNA or



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

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

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

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

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

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

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

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

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

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

5 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

10 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.

15 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).

20 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.

25 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.

30 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.

35 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).

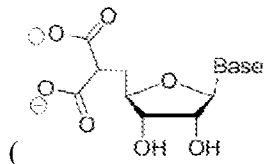
In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4'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

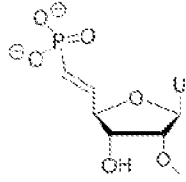
In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and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

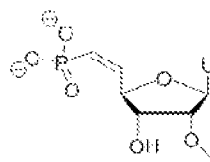
The RNAi agent can comprise a phosphorus-containing group at the 5'-end of the sense strand or antisense strand. The 5'-end phosphorus-containing group can be 5'-end phosphate (5'-P), 5'-end phosphorothioate (5'-PS), 5'-end phosphorodithioate (5'-PS₂), 5'-end vinylphosphonate (5'-VP), 5'-end methylphosphonate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



vinylphosphonate (5'-VP), the 5'-VP can be either 5'-*E*-VP isomer (i.e., *trans*-vinylphosphate,



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



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

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

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

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

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

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

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe

or 2'-F, 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'-PS₂.

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

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

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

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

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

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

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

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

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

and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-PS.

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

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

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

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

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

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

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

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

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

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

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

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

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

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, 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'-PS₂.

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

OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. 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'-PS₂.

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

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

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

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

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

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

is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS₂ and a targeting ligand. In one embodiment, the 5'-PS₂ is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

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

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

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

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and q^7 is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5

of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end). The RNAi agent also comprises a 5'-VP (e.g., a 5'-E-VP, 5'-Z-VP, or combination thereof) and a targeting ligand. In one embodiment, the 5'-VP is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

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

In one embodiment, B1 is 2'-OMe or 2'-F, 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'-PS₂ and a targeting ligand. In one embodiment, the 5'-PS₂ is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

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

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

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

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

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

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

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

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(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

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(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.

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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;

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(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);

25

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

30

(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.

35

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
- 5 (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;
 - 10 (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);
- 15 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;
 - 20 (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
25 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
30 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.

IV. iRNAs Conjugated to Ligands

Another modification of the RNA of an iRNA of the invention involves chemically linking to the RNA one or more ligands, moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the iRNA. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger *et al.*, (1989) *Proc. Natl. Acad. Sci. USA*, 86: 6553-6556), cholic acid (Manoharan *et al.*, (1994) *Biorg. Med. Chem. Lett.*, 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. Lett.*, 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 an iRNA agent into which it is incorporated. In preferred 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. Preferred 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-glycolid) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

Ligands can also include targeting groups, *e.g.*, a cell or tissue targeting agent, *e.g.*, a lectin, glycoprotein, lipid or protein, *e.g.*, an antibody, that binds to a specified cell type such as a kidney cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-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-glucosamine multivalent mannose, or multivalent fucose. The ligand can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an activator of NF- κ B.

The ligand can be a substance, *e.g.*, a drug, which can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.*, by disrupting the cell's microtubules, microfilaments, 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 an iRNA as described herein acts as a pharmacokinetic modulator (PK modulator). PK modulators include lipophiles, bile acids, steroids, phospholipid analogues, peptides, protein binding agents, PEG, vitamins *etc.* Exemplary PK modulators include, but are not limited to, cholesterol, fatty acids, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, phospholipids, sphingolipids, naproxen, ibuprofen, vitamin E, biotin *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 oligonucleotides 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.

A. Lipid Conjugates

In one embodiment, the ligand or conjugate is a lipid or lipid-based molecule. Such a lipid or lipid-based molecule preferably 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 a preferred embodiment, the lipid based ligand binds HSA. Preferably, it binds HSA with a sufficient affinity such that the conjugate will be preferably 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 preferred embodiment, the lipid based ligand binds HSA weakly or not at all, such that the conjugate will be preferably distributed to the kidney. Other moieties that target to kidney cells can also be used in place of or in addition to the lipid based ligand.

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

B. Cell Permeation Agents

In another aspect, the ligand is a cell-permeation agent, preferably a helical cell-permeation agent. Preferably, the agent is amphipathic. An exemplary agent is a peptide such as

tat or antennopodia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. The helical agent is preferably an alpha-helical agent, which preferably has a lipophilic and a lipophobic phase.

5 The ligand can be a peptide or peptidomimetic. A peptidomimetic (also referred to herein as an oligopeptidomimetic) is a molecule capable of folding into a defined three-dimensional structure similar to a natural peptide. The attachment of peptide and peptidomimetics to iRNA agents can affect pharmacokinetic distribution of the iRNA, such as by enhancing cellular recognition and absorption. The peptide or peptidomimetic moiety can be
10 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
15 translocation sequence (MTS). An exemplary hydrophobic MTS-containing peptide is RFGF having the amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO: 2986). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO: 2987) 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
20 across cell membranes. For example, sequences from the HIV Tat protein (GRKKRRQRRRPPQ (SEQ ID NO: 2988) and the Drosophila Antennapedia protein (RQIKIWFQNRRMKWKK (SEQ ID NO: 2989) 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
25 (OBOC) combinatorial library (Lam *et al.*, Nature, 354:82-84, 1991). Examples of a peptide or peptidomimetic tethered to a dsRNA agent via an incorporated monomer unit for cell targeting 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.
30 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.*, glycosylated or methylated, to facilitate targeting to a specific tissue(s). RGD-containing peptides and peptidomimetics may include D-amino acids, as well as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the
35 integrin ligand. Preferred 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

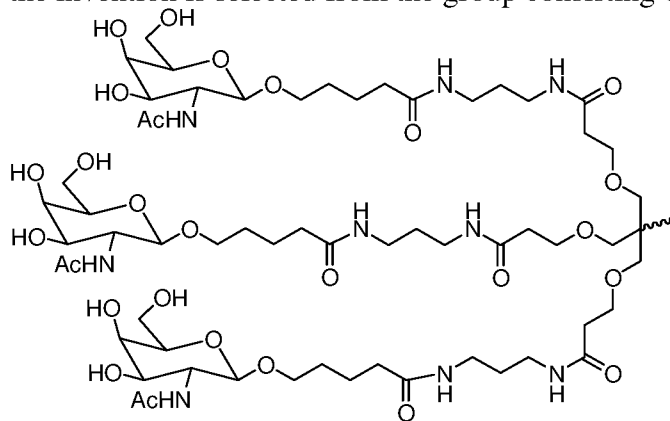
containing only one or two dominating amino acids (*e.g.*, PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni *et al.*, Nucl. Acids Res. 31:2717-2724, 2003).

C. Carbohydrate Conjugates

In some embodiments of the compositions and methods of the invention, an iRNA oligonucleotide further comprises a carbohydrate. The carbohydrate conjugated iRNA 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.

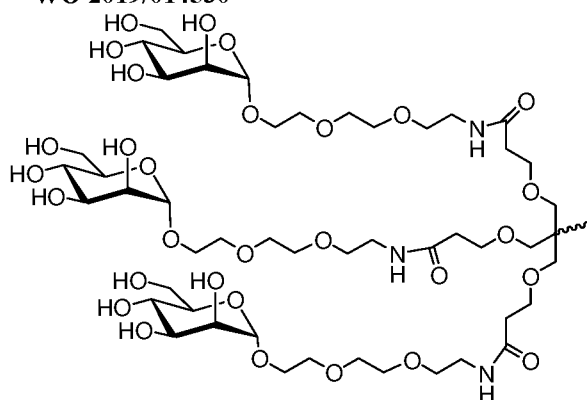
In one embodiment, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



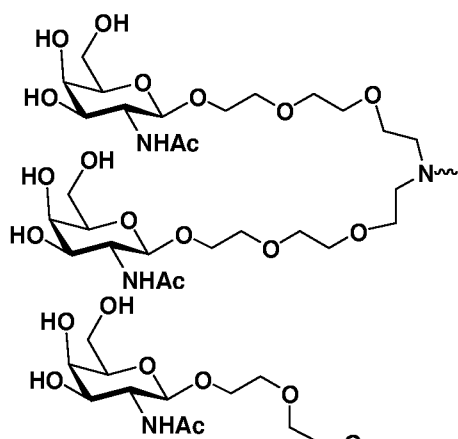
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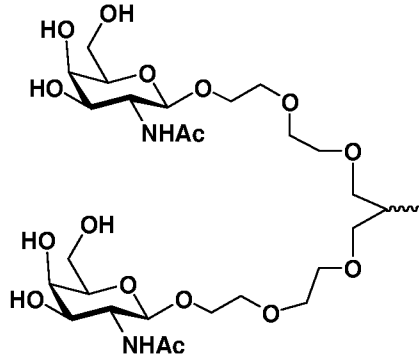
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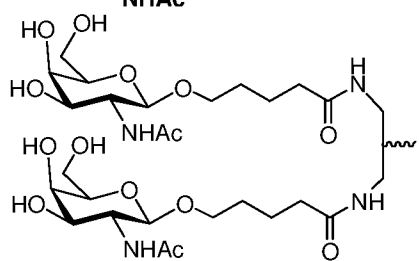
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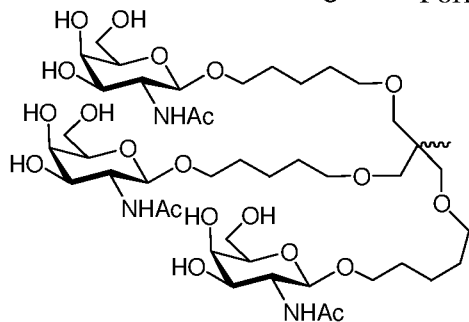
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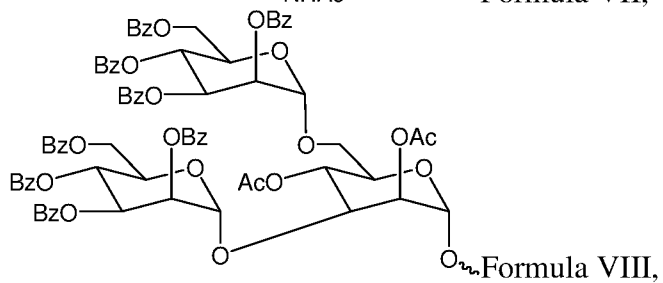
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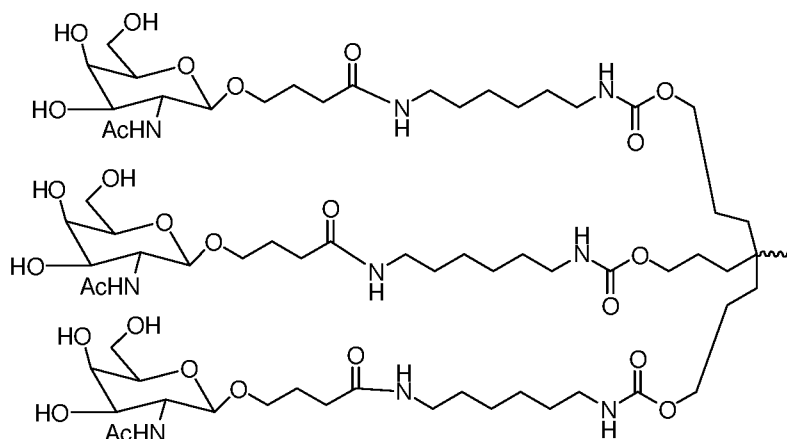
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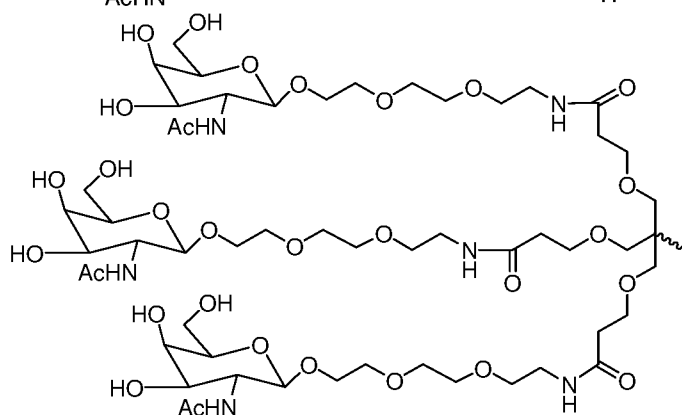
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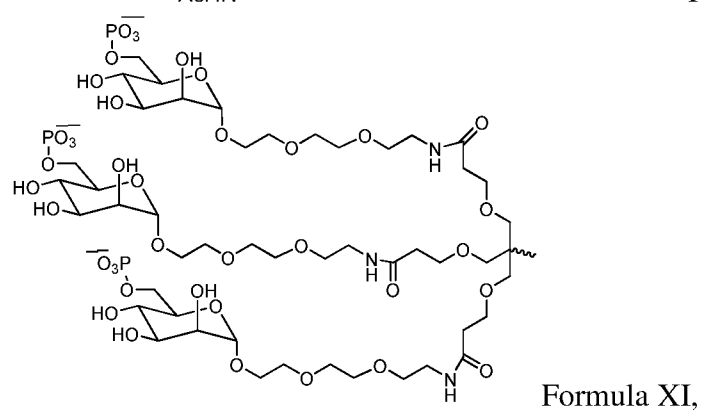
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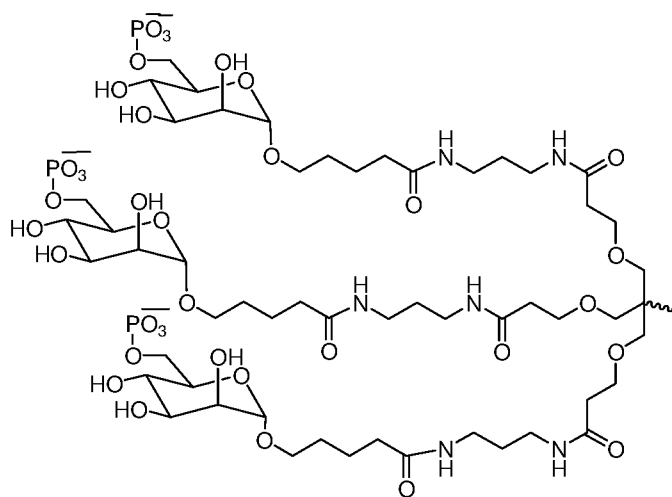
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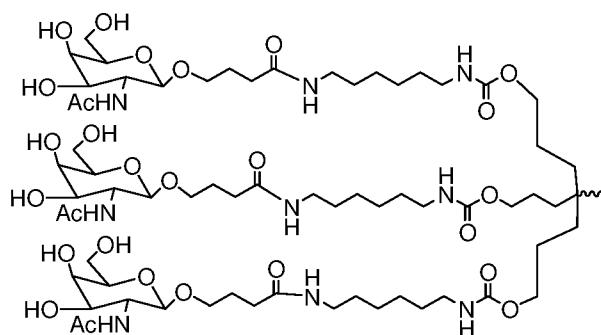
Formula X,



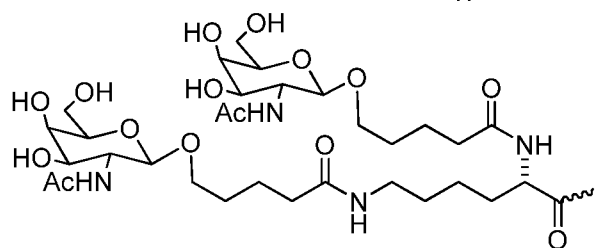
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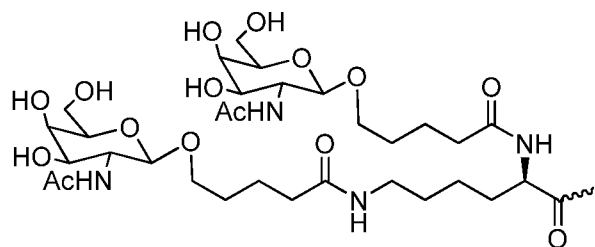
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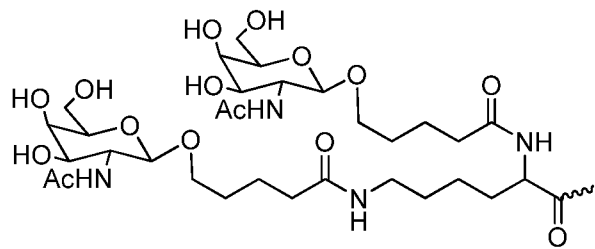
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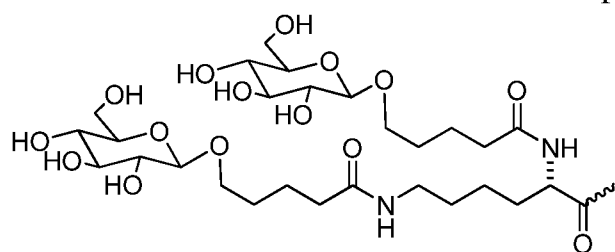
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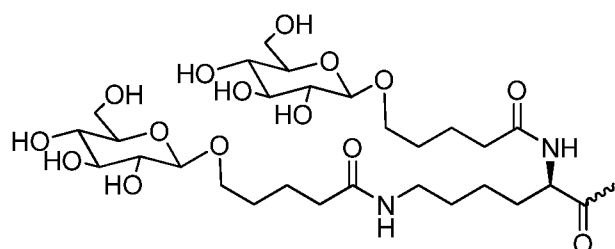
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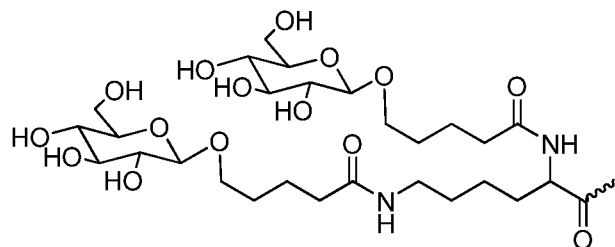
Formula XVI,



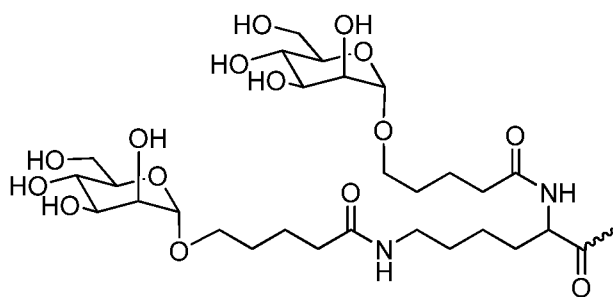
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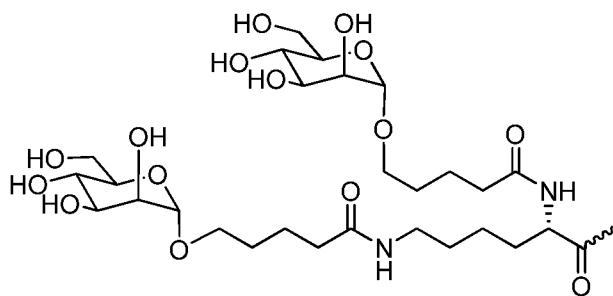
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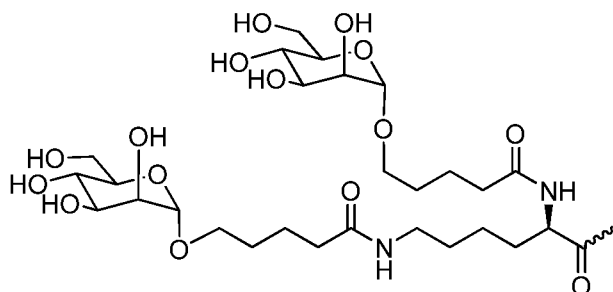
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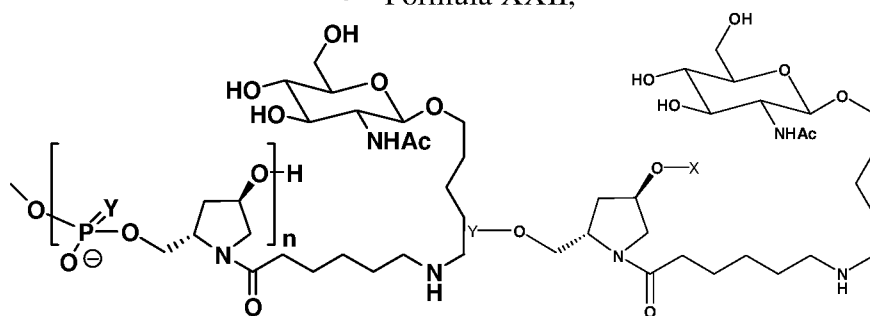
Formula XX,



Formula XXI,



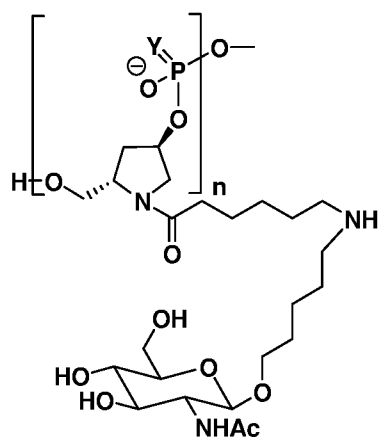
Formula XXII,



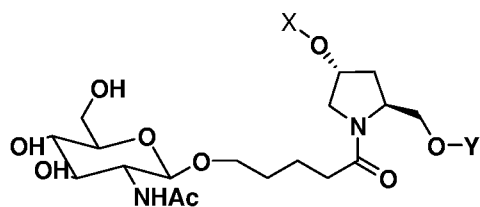
Formula

5 XXIII;

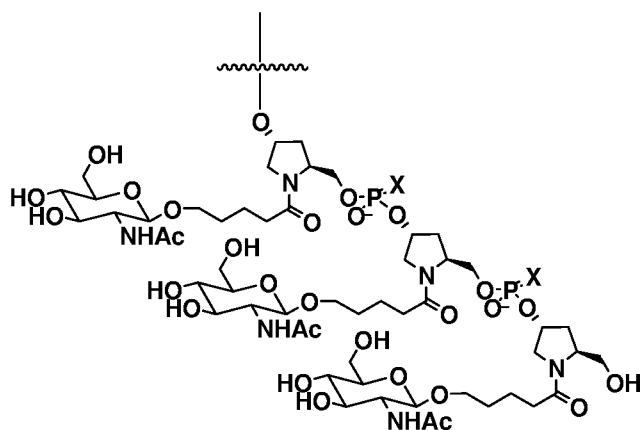
, wherein Y is O or S and n is 3 -6 (Formula XXIV);



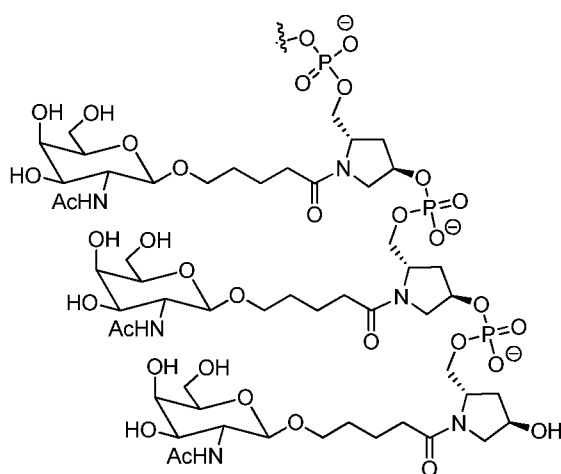
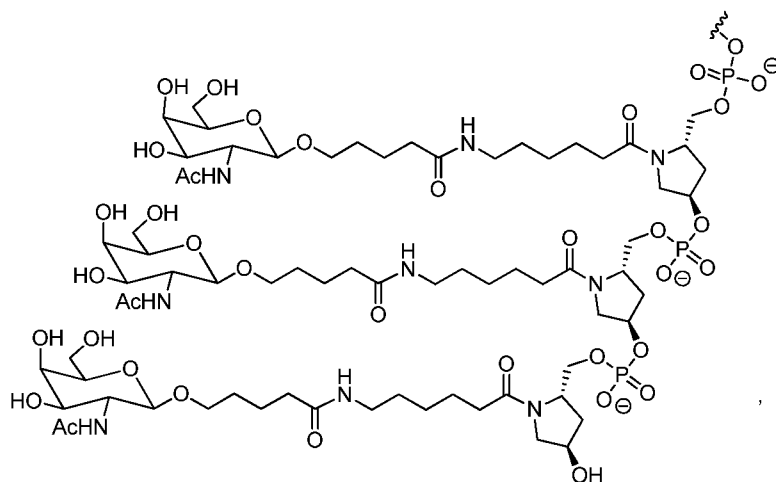
, wherein Y is O or S and n is 3-6 (Formula XXV);



Formula XXVI;

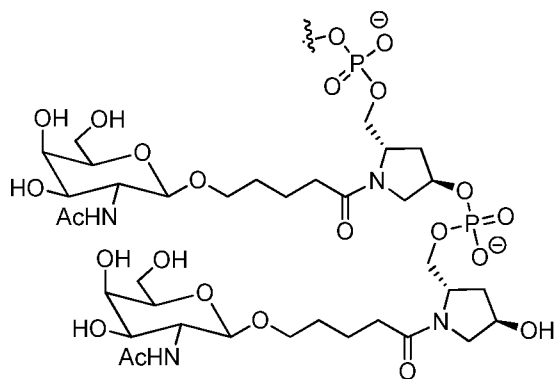
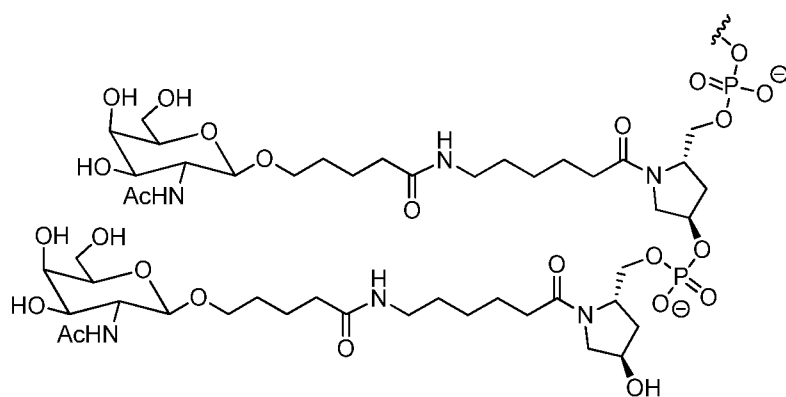


, wherein X is O or S (Formula XXVII);



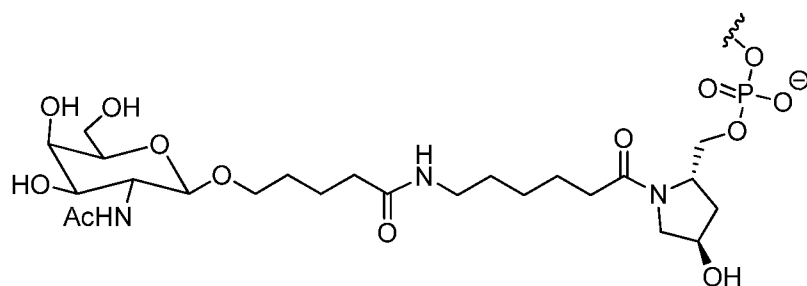
Formula XXVII; Formula

XXIX;

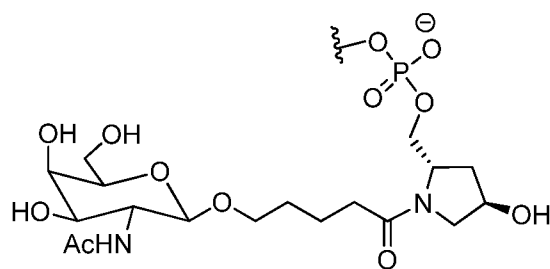


Formula XXX;

Formula XXXI;

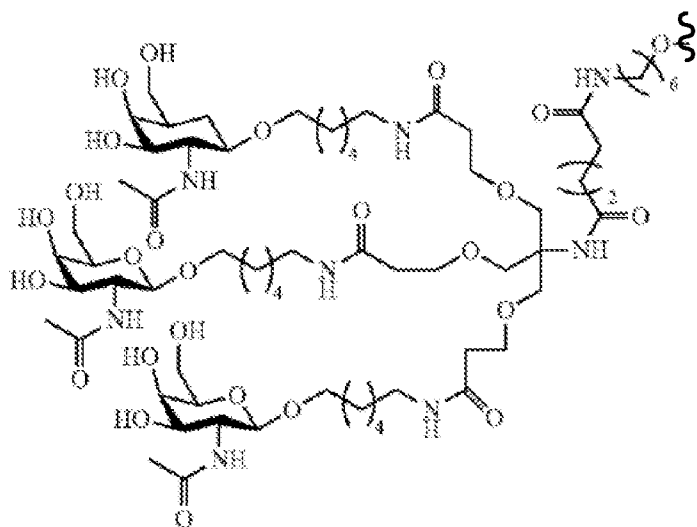


, and



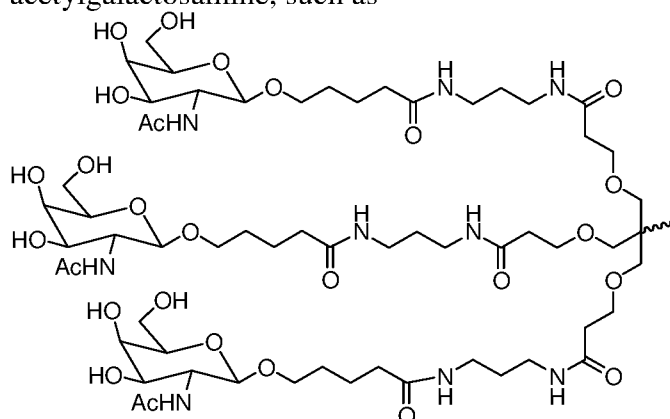
Formula XXXII;

Formula XXXIII.



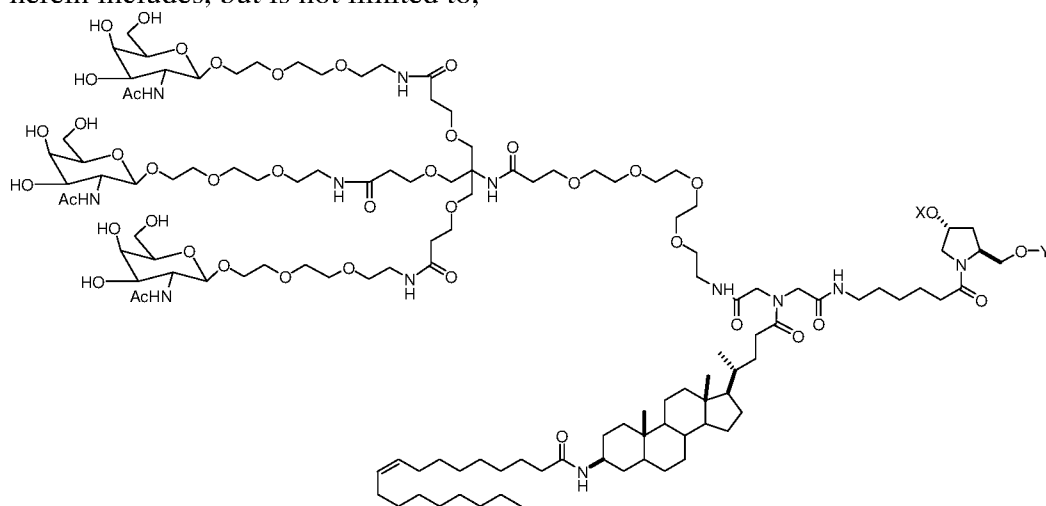
Formula XXXIV.

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



Formula II.

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 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), one or both of the dsRNA agents may independently comprise a GalNAc or GalNAc derivative ligand.

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

In one embodiment, the double stranded RNAi agents of the invention comprise one GalNAc or GalNAc derivative attached to the iRNA agent, *e.g.*, the 5' end of the sense strand of a dsRNA agent, or the 5' end of one or both sense strands of a dual targeting RNAi agent as described herein. In another embodiment, the double stranded RNAi agents of the invention, or one or both dsRNA agents of a dual targeting RNAi agent as described herein, comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently attached to a plurality of nucleotides of the double stranded RNAi agent through a plurality of monovalent linkers.

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

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 and/or a cell permeation peptide.

Additional carbohydrate conjugates (and linkers) suitable for use in the present invention include those described in PCT Publication Nos. WO 2014/179620 and WO 2014/179627, the entire contents of each of which are incorporated herein by reference.

D. Linkers

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

The term "linker" or "linking group" means an organic moiety that connects two parts of a compound, *e.g.*, covalently attaches two parts of a compound. Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR₈, C(O), C(O)NH, SO, SO₂, SO₂NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclalkyl,

heterocyclalkenyl, heterocyclalkynyl, aryl, heteroaryl, heterocycl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclalkyl, alkylheterocyclalkenyl, alkylheterocyclalkynyl, alkenylheterocyclalkyl, alkenylheterocyclalkenyl, alkenylheterocyclalkynyl, alkynylheterocyclalkyl, alkynylheterocyclalkenyl, alkynylheterocyclalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylheteroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO₂, N(R₈), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, 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 a preferred 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 preferred 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
5 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
10 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
15 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 preferred embodiments, useful candidate compounds are cleaved at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times
20 faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

i. Redox cleavable linking groups

In one embodiment, a cleavable linking group is a redox cleavable linking group that is
25 cleaved upon reduction or oxidation. An example of reductively cleavable linking group is a disulphide linking group (-S-S-). To determine if a candidate cleavable linking group is a suitable "reductively cleavable linking group," or for example is suitable for use with a particular iRNA moiety and particular targeting agent one can look to methods described herein. For example, a candidate can be evaluated by incubation with dithiothreitol (DTT), or other reducing
30 agent using reagents known in the art, which mimic the rate of cleavage which would be observed in a cell, *e.g.*, a target cell. The candidates can also be evaluated under conditions which are selected to mimic blood or serum conditions. In one, candidate compounds are cleaved by at most about 10% in the blood. In other embodiments, useful candidate compounds are degraded at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or
35 under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood (or under *in vitro* conditions selected to mimic extracellular conditions). The rate of cleavage of candidate compounds can be determined using standard enzyme kinetics assays under conditions chosen to mimic intracellular media and compared to conditions chosen to mimic extracellular media.

ii. Phosphate-based cleavable linking groups In another embodiment, 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.

5 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-. Preferred embodiments are -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-, -O-P(S)(H)-S-. A preferred embodiment is -O-P(O)(OH)-O-. These candidates can be evaluated using methods analogous to those described above.

iii. Acid cleavable linking groups

15 In another embodiment, a cleavable linker comprises an acid cleavable linking group. An acid cleavable linking group is a linking group that is cleaved under acidic conditions. In preferred 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). A preferred 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.

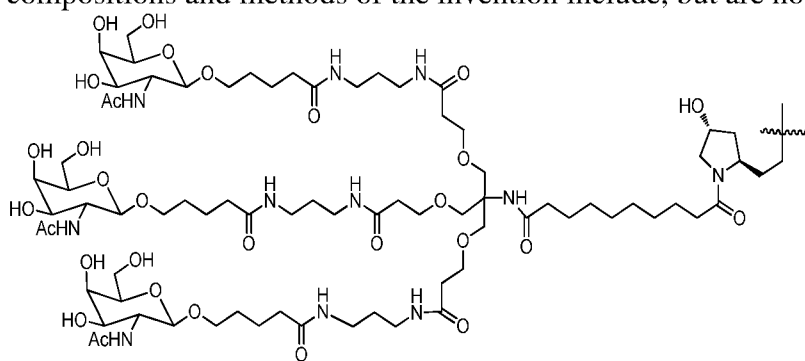
25 *iv. Ester-based linking groups* In another embodiment, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include but are not limited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

v. Peptide-based cleaving groups

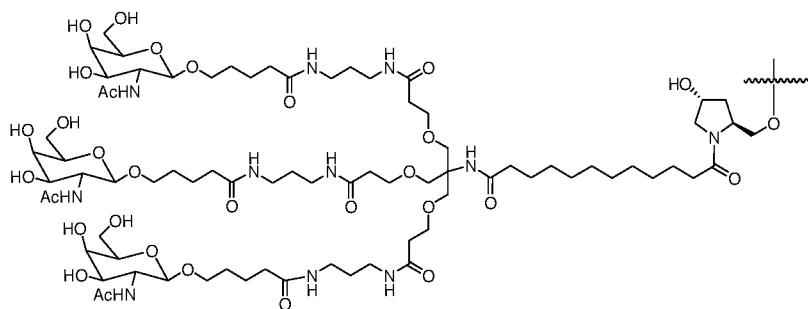
35 In yet another embodiment, a cleavable linker comprises a peptide-based cleavable linking group. A peptide-based cleavable linking group is cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (*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 alkynylene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide based cleavage group is generally limited to the peptide bond (*i.e.*, the amide bond)

formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula – $\text{NHCHRAC(O)NHCHRBC(O)-}$, 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.

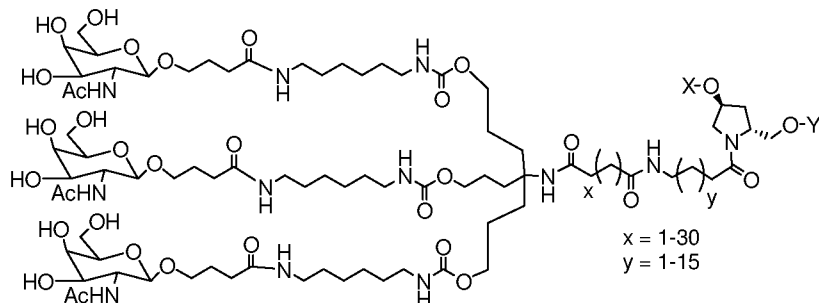
- 5 In one embodiment, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



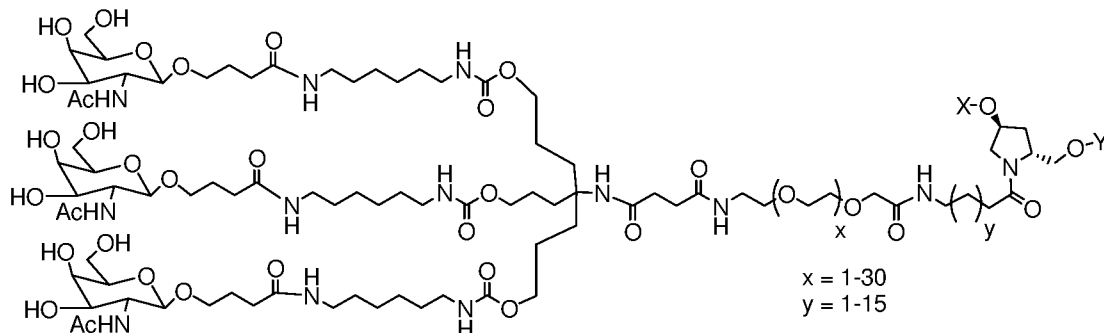
(Formula XXXVII),



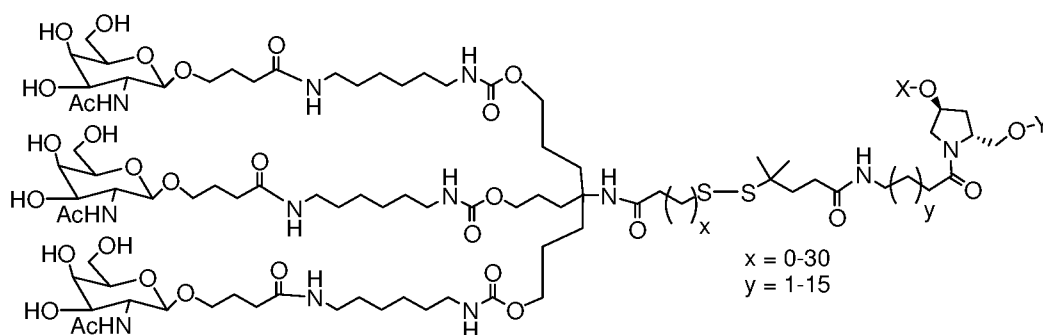
(Formula XXXVIII),



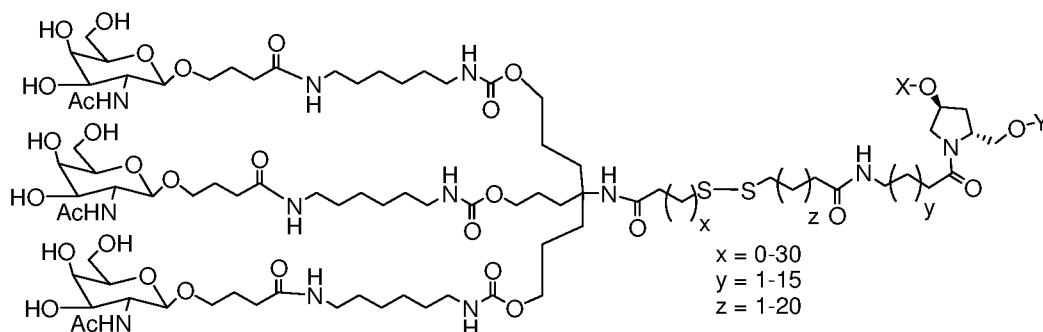
(Formula XXXIX),



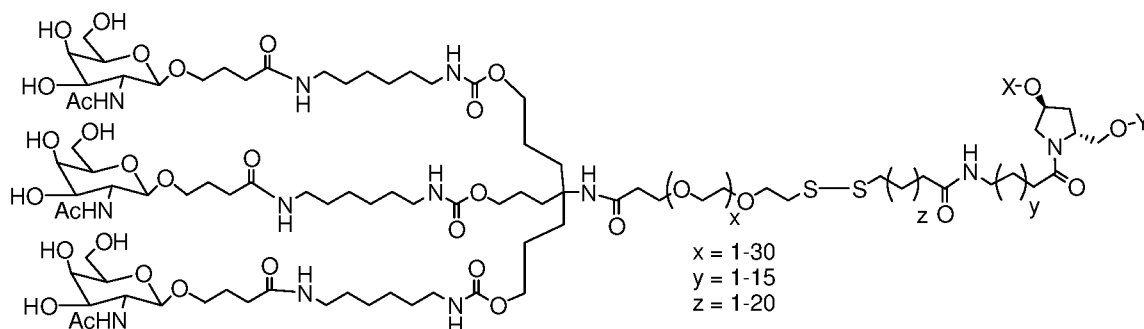
(Formula XL),



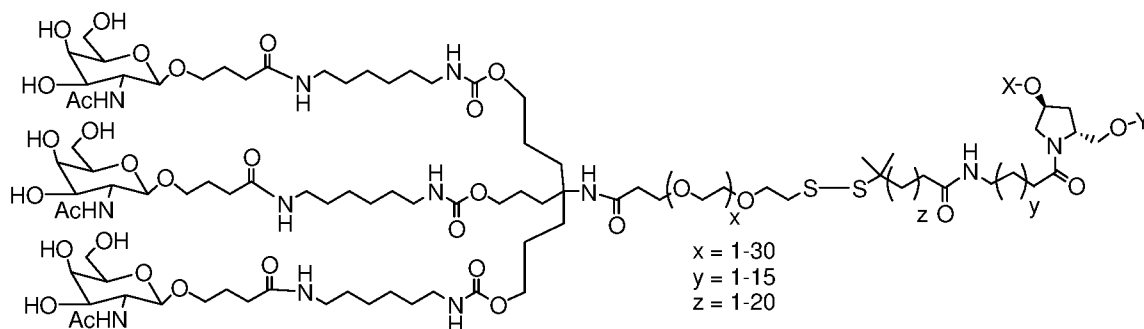
(Formula XLI),



5 (Formula XLII),



(Formula XLIII), and



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

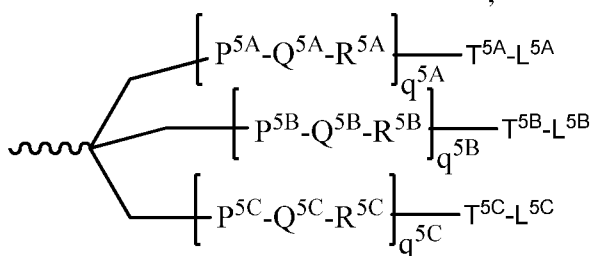
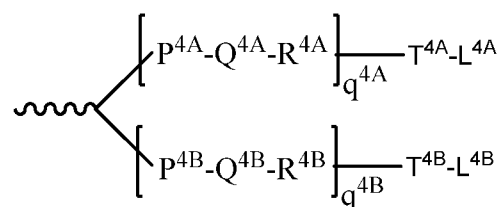
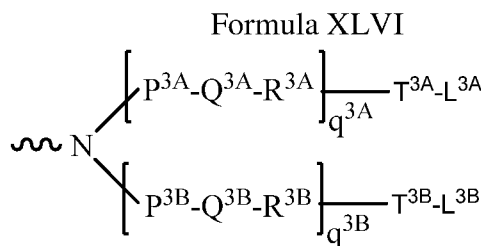
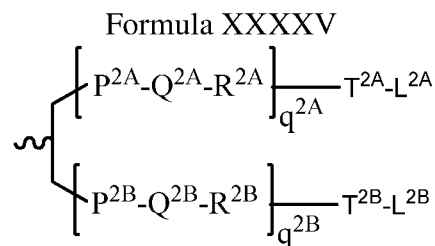
10 In certain embodiments of the compositions and methods of the invention, a ligand is one or more GalNAc (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

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 dsRNA of the invention is conjugated to a bivalent or trivalent branched linker selected from the group of structures shown in any of formula (XLV) – (XLVI):

5



Formula XLVII

Formula XLVIII

wherein:

10 q^{2A}, q^{2B}, q^{3A}, q^{3B}, q^{4A}, q^{4B}, q^{5A}, q^{5B} and q^{5C} represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different;

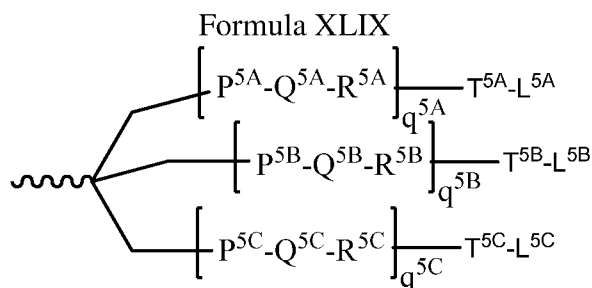
P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{5A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH₂, CH₂NH or CH₂O;

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

R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{5C} are each independently for each occurrence absent, NH, O, S, CH₂, C(O)O, C(O)NH, NHCH(R^a)C(O), -C(O)-CH(R^a)-NH-, CO, CH=N-O,

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



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 RNA 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 an iRNA. The present invention also includes iRNA compounds that are chimeric compounds.

“Chimeric” iRNA compounds or “chimeras,” in the context of this invention, are iRNA compounds, preferably dsRNAs, 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 iRNAs typically contain at least one region wherein the RNA is modified so as to confer upon the iRNA increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. An additional region of the iRNA can serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of iRNA inhibition of gene expression. Consequently, comparable results can often be obtained with shorter iRNAs when chimeric dsRNAs are used, compared to phosphorothioate deoxy dsRNAs hybridizing to the same target region. Cleavage of the RNA

target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

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

IV. Delivery of an iRNA of the Invention

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

In the methods of the invention which include a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1 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 an iRNA of the invention (see *e.g.*, Akhtar S. and Julian RL., (1992) *Trends Cell. Biol.* 2(5):139-144 and WO94/02595, which are incorporated herein by reference in their entireties). For *in vivo* delivery, factors to consider in order to deliver an iRNA molecule include, for example, biological stability of the delivered molecule, prevention of non-specific effects, and accumulation of the delivered molecule in the target tissue. The non-specific effects of an iRNA 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 the iRNA molecule to be administered. Several studies have shown successful knockdown of gene products when an iRNA 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 al.* (2002) *BMC Neurosci.* 3:18; Shishkina, GT., *et al.* (2004) *Neuroscience* 129:521-528; Thakker, ER., *et al.* (2004) *Proc. Natl. Acad. Sci. U.S.A.* 101:17270-17275; Akaneya, Y., *et al.* (2005) *J. Neurophysiol.* 93:594-602) 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 an iRNA systemically for the treatment of a disease, the RNA can be modified or alternatively delivered using a drug delivery system; both methods act to prevent the rapid degradation of the dsRNA by endo- and exo-nucleases *in vivo*. Modification of the RNA or the pharmaceutical carrier can also permit targeting of the iRNA composition to the target tissue and avoid undesirable off-target effects. iRNA molecules can be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For example, an iRNA directed against ApoB conjugated to a lipophilic cholesterol moiety was injected systemically into mice and resulted in knockdown of apoB mRNA in both the liver and jejunum (Soutschek, J. *et al.*, (2004) *Nature* 432:173-178). Conjugation of an iRNA 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 iRNA can be delivered using drug delivery systems such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery systems facilitate binding of an iRNA

molecule (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an iRNA by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an iRNA, or induced to form a vesicle or micelle (see *e.g.*, Kim SH. *et al.*, (2008) *Journal of Controlled Release* 129(2):107-116) that encases an iRNA. The formation of vesicles or micelles further prevents degradation of the iRNA when administered systemically. Methods for making and administering cationic- iRNA complexes are well within the abilities of one skilled in the art (see *e.g.*, Sorensen, DR., *et al.* (2003) *J. Mol. Biol* 327:761-766; Verma, UN. *et al.*, (2003) *Clin. Cancer Res.* 9:1291-1300; Arnold, AS *et al.*, (2007) *J. Hypertens.* 25:197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of iRNAs include DOTAP (Sorensen, DR., *et al* (2003), *supra*; Verma, UN. *et al.*, (2003), *supra*), 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, an iRNA forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of iRNAs and cyclodextrins can be found in U.S. Patent No. 7, 427, 605, which is herein incorporated by reference in its entirety.

A. Vector encoded iRNAs of the Invention

iRNA targeting the LDHA gene and iRNA 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 an iRNA 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 dsRNA 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.

iRNA expression vectors are generally DNA plasmids or viral vectors. Expression vectors compatible with eukaryotic cells, preferably those compatible with vertebrate cells, can be used to produce recombinant constructs for the expression of an iRNA 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 iRNA 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.

V. Pharmaceutical Compositions of the Invention

The present invention also includes pharmaceutical compositions and formulations which include the iRNAs of the invention. Accordingly, in one embodiment, provided herein are pharmaceutical compositions comprising a double stranded ribonucleic acid (dsRNA) agent that inhibits expression of lactic acid dehydrogenase A (LDHA) in a cell, such as a liver cell, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2; and a pharmaceutically acceptable carrier.

In another embodiment, provided herein are pharmaceutical compositions comprising a dsRNA agent that inhibits expression of lactic acid dehydrogenase A (LDHA) in a cell, such as a liver cell, wherein the dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which 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 2-5; and a pharmaceutically acceptable carrier.

In one embodiment, provided herein are pharmaceutical compositions comprising a first double stranded ribonucleic acid (dsRNA) agent that inhibits expression of lactic acid dehydrogenase A (LDHA) in a cell, such as a liver cell, comprising a sense strand and an antisense strand, wherein the sense strand 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 comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2; and a second double stranded ribonucleic acid (dsRNA) agent that inhibits expression of hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) in a cell, such as a liver cell, comprising a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:21, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:22; and a pharmaceutically acceptable carrier.

In another embodiment, provided herein are pharmaceutical compositions a first double stranded ribonucleic acid (dsRNA) agent that inhibits expression of lactic acid dehydrogenase A (LDHA) in a cell, such as a liver cell, comprising a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which 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 2-5; and a second double stranded ribonucleic acid (dsRNA) agent that inhibits expression of hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) in a cell, such as a liver cell, comprising a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which 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 7-14.

In yet another embodiment, the present invention provides pharmaceutical compositions and formulations comprising 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 disease or disorder associated with the expression or activity of an LDHA gene or an LDHA gene and an HAO1 gene, *e.g.*, an oxalate pathway-associated disease, disorder, or condition.

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 or an LDHA gene and an HAO1 gene. In general, a suitable dose of an iRNA of the invention will be in the range of about 0.001 to about

200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of about 1 to 50 mg per kilogram body weight per day. Typically, a suitable dose of an iRNA of the invention will be in the range of about 0.1 mg/kg to about 5.0 mg/kg, preferably about 0.3 mg/kg and about 3.0 mg/kg.

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

A repeat-dose regimen may include administration of a therapeutic amount of iRNA on a regular basis, such as every other day to once a year. In certain embodiments, the iRNA is
10 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
15 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 iRNAs encompassed by the invention can be
20 made using conventional methodologies or on the basis of *in vivo* testing using an appropriate animal model, as described elsewhere herein.

Advances in mouse genetics have generated a number of mouse models for the study of various human diseases, such as an oxalate pathway-associated disease, disorder, or condition that would benefit from reduction in the expression of LDHA and/or LDHA and HAO1. Such
25 models can be used for *in vivo* testing of iRNA, as well as for determining a therapeutically effective dose. Suitable mouse models are known in the art and include, for example, mouse models which may include mutations or deletions in the AGXT or GRHPR genes (see, *e.g.*, Salido EC, *et al.* (2006) *PNAS* 103(48): 18249-18254 and Knight J, *et al.* (2012) *Am. J. Physiol. Renal Physiol.* 302: F688-F693); a PH3 mouse model (see, *e.g.*, Li, *et al.* (2015) *biochem*
30 *Biophys Acta* 1852(12):2700); and the ethylene glycol urolithiasis mouse 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,
35 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 iRNA 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, distearoylphosphatidyl choline) negative (*e.g.*, dimyristoylphosphatidyl glycerol DMPG) and cationic (*e.g.*, dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). iRNAs featured in the invention can be encapsulated within liposomes or can form complexes thereto, in particular to cationic liposomes. Alternatively, iRNAs 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 C₁₋₂₀ 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 minitabets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders can be desirable. In some embodiments, oral formulations are those in which dsRNAs 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, glucolic 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(isohexylcyanoacrylate), 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. Particularly preferred are formulations that target the liver when treating hepatic disorders such as hepatic carcinoma.

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 0.1 μm in diameter (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi *et al.*, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 301). Emulsions are often biphasic systems comprising two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions can be of either the water-in-oil (w/o) or the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase, the resulting composition is called a water-in-oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase, the resulting composition is called an oil-in-water (o/w) emulsion. Emulsions can contain additional components in addition to the dispersed phases, and the active drug which can be present as a solution 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
5 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
10 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
15 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
20 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, attapulgit, hectorite, kaolin, montmorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl
25 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
30 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
35 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

an RNAi agent 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, dicaprinate, tricaprinate, monoolein (1-monooleoyl-rac-glycerol), dilaurin, caprylic acid, arachidonic acid, glycerol 1-monocaprate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, C₁₋₂₀ 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), glucolic acid (sodium glucolate), 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 iRNAs 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, laurth-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 iRNAs 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), XtremeGENE Q2 Transfection Reagent (Roche; Grenzacherstrasse, Switzerland), DOTAP Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), or Eugene (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.

10 *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).

25 *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.

5 Formulations for topical administration of nucleic acids 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
10 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

15 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
20 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,
25 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
30 suspension can also contain stabilizers.

In some embodiments, pharmaceutical compositions featured in the invention include (a) one or more iRNA compounds and (b) one or more agents which function by a non-RNAi mechanism and which are useful in treating an oxalate pathway-associated disease, disorder, or condition. Examples of such agents include, but are not limited to
35 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 LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (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 LD₅₀/ED₅₀. Compounds that exhibit high therapeutic indices are preferred.

The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of compositions featured herein in the invention lies generally within a range of circulating concentrations that include the ED₅₀ 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 IC₅₀ (*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.

In addition to their administration, as discussed above, the iRNAs featured in the invention can be administered in combination with other known agents effective in treatment of pathological processes mediated by LDHA or LDHA and HAO1 expression. In any event, the administering physician can adjust the amount and timing of iRNA administration on the basis of results observed using standard measures of efficacy known in the art or described herein.

VI. Methods of the Invention

The present invention also provides methods of using an iRNA of the invention and/or a composition of the invention to reduce and/or inhibit LDHA or LDHA and HAO1 expression in a cell, such as a cell in a subject. The methods include contacting the cell with a RNAi agent (or pharmaceutical composition comprising an iRNA agent) or pharmaceutical composition of the invention. In some embodiments, the cell is maintained for a time sufficient to obtain degradation of the mRNA transcript of an LDHA gene. In other embodiments, the cell is maintained for a time sufficient to obtain degradation of the mRNA transcript of an LDHA gene and an HAO1 gene in the cell.

It should be noted that, although the compositions of the invention target LDHA, an enzyme involved in numerous cellular processes (see, *e.g.*, Figures 1A and 1B), as demonstrated in the Examples below, contacting a cell with a composition of the invention, or administering a composition of the invention to a subject, does not result in adverse effects in either wild-type or diseased subjects, thereby demonstrating the safety of the compositions of the invention.

Reduction in gene expression can be assessed by any methods known in the art. For example, a reduction in the expression of LDHA, and/or HAO1, and/or glycolate may be determined by determining the mRNA expression level of LDHA, and/or HAO1, and/or glycolate using methods routine to one of ordinary skill in the art, *e.g.*, Northern blotting, qRT-PCR; by determining the protein level of LDHA, and/or HAO1, and/or glycolate using methods routine to one of ordinary skill in the art, such as Western blotting, immunological techniques. A reduction in the expression of LDHA, and/or HAO1, and/or glycolate may also be assessed indirectly by measuring a decrease in biological activity of LDHA, and/or HAO1, and/or glycolate, *e.g.*, a decrease in the enzymatic activity of LDHA and/or a decrease in tissue or plasma oxalate, or urinary oxalate and/or glycolate excretion.

In the methods of the invention the cell may be contacted *in vitro* or *in vivo*, *i.e.*, the cell may be within a subject.

A cell suitable for treatment using the methods of the invention may be any cell that expresses an LDHA gene, a cell that expresses an HAO1 gene, a cell that expresses a glycolate gene, a cell that expresses an LDHA gene and a glycolate gene, a cell that expresses an HAO1 gene and a glycolate gene, a cell that expresses an LDHA gene and an HAO1 gene, or a cell that expresses an LDHA gene, an HAO1 gene, and a glycolate gene. A cell suitable for use in the methods of the invention may be a mammalian cell, *e.g.*, a primate cell (such as a human cell or a non-human primate cell, *e.g.*, a monkey cell or a chimpanzee cell), a non-primate cell (such as a cow cell, a pig cell, a camel cell, a llama cell, a horse cell, a goat cell, a rabbit cell, a sheep cell, a hamster, a guinea pig cell, a cat cell, a dog cell, a rat cell, a mouse cell, a lion cell, a tiger cell, a bear cell, or a buffalo cell), a bird cell (*e.g.*, a duck cell or a goose cell), or a whale cell. In one embodiment, the cell is a human cell, *e.g.*, a human liver cell.

LDHA expression is inhibited in the cell 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, 49, 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, 99, or about 100%. In preferred embodiments, LDHA expression is inhibited by at least 20%.

HAO1 expression may be inhibited in the cell 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, 49, 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, 99, or about 100%. In preferred embodiments, HAO1 expression is inhibited by at least 20%.

In embodiments in which a cell is contacted with a dual targeting RNAi agent of the invention, the level of inhibition of LDHA may be the same or different than the level of HAO1.

5 In one embodiment, the *in vivo* methods of the invention may include administering to a subject a composition containing an iRNA, where the iRNA includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of the LDHA gene of the mammal to be treated. In another embodiment, the *in vivo* methods of the invention may include administering to a subject a composition containing an iRNA, where the iRNA includes a nucleotide sequence
10 that is complementary to at least a part of an RNA transcript of the LDHA gene and a nucleotide sequence that is complementary to at least a part of an RNA transcript of the HAO1 gene of the mammal to be treated.

When the organism to be treated is a mammal such as a human, the composition can be administered by any means known in the art including, but not limited to oral, intraperitoneal, or
15 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.

20 In some embodiments, the administration is *via* a depot injection. A depot injection may release the iRNA 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 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
25 include subcutaneous injections or intramuscular injections. In preferred 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
30 pump may be used for intravenous, subcutaneous, arterial, or epidural infusions. In preferred embodiments, the infusion pump is a subcutaneous infusion pump. In other embodiments, the pump is a surgically implanted pump that delivers the iRNA to the liver.

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

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

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

In one aspect, the present invention also provides methods for inhibiting the expression of an LDHA gene in a mammal. The methods include administering to the mammal a composition comprising a dsRNA that targets an LDHA gene in a cell of the mammal, thereby inhibiting expression of the LDHA gene in the cell.

In another aspect, the present invention also provides methods for inhibiting the expression of an LDHA gene and an HAO1 gene in a mammal. The methods include administering to the mammal a pharmaceutical composition comprising a dsRNA agent that targets an LDHA gene and a dsRNA agent that targets an HAO1 gene in a cell of the mammal, thereby inhibiting expression of the LDHA gene and the HAO1 gene in the mammal. In one aspect, the present invention provides methods for inhibiting the expression of an LDHA gene and an HAO1 gene in a mammal. The methods include administering to the mammal a dual targeting RNAi agent (or pharmaceutical composition comprising a dual targeting agent) that targets an LDHA gene and an HAO1 gene in a cell of the mammal, thereby inhibiting expression of the LDHA gene and the HAO1 gene in the subject.

Reduction in gene expression can be assessed by any methods known in the art and by methods, *e.g.* qRT-PCR, described herein. Reduction in protein production can be assessed by any methods known in the art and by methods, *e.g.* ELISA, enzymatic activity, described herein.

The present invention also provides therapeutic and prophylactic methods which include administering to a subject having, or prone to developing an oxalate-associated disease, disorder, or condition, the iRNA agents, pharmaceutical compositions comprising an iRNA agent, or vectors comprising an iRNA of the invention.

In one aspect, the present invention provides methods of treating a subject having a disorder that would benefit from reduction in LDHA expression, *e.g.*, an oxalate pathway-associated disease, disorder, or condition.

The treatment methods (and uses) of the invention include administering to the subject, *e.g.*, a human, a therapeutically effective amount of a dsRNA agent, a dual targeting iRNA agent or a pharmaceutical composition comprising a dsRNA, a pharmaceutical composition comprising a dual targeting RNAi agent or 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, thereby treating the subject.

In one aspect, the invention provides methods of preventing at least one symptom in a subject having a disorder that would benefit from reduction in LDHA expression, *e.g.*, an oxalate pathway-associated disease, disorder, or condition. The methods include administering to the subject a prophylactically effective amount of dsRNA agent, a dual targeting iRNA agent or a pharmaceutical composition comprising a dsRNA, a pharmaceutical composition comprising a dual targeting RNAi agent or 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, thereby preventing at least one symptom in the subject.

Subjects that would benefit from a reduction and/or inhibition of an LDHA gene expression include subjects that would benefit from reduction in both LDHA and HAO1 gene expression.

Therefore, in one embodiment, a subject that would benefit from reduction in the expression level of LDHA or a reduction in the expression of LDHA and HAO1, has normal urinary oxalate excretion levels, *e.g.*, less than about 40 mg (440 μ mol) in 24 hours (*e.g.*, men have a normal urinary oxalate excretion level of less than about 43 mg/day and women have a normal urinary oxalate excretion level of less than about 32 mg/day). In another embodiment, a subject that would benefit from a reduction in the expression level of LDHA or a reduction in the expression of LDHA and HAO1 has mild hyperoxaluria (a urinary oxalate excretion level of about 40 to about 60 mg/day). In another embodiment, a subject that would benefit from reduction in the expression level of LDHA or a reduction in the expression of LDHA and HAO1 has high hyperoxaluria (a urinary oxalate excretion level of greater than about 60 mg/day).

In one embodiment, a subject that would benefit from reduction in LDHA expression or LDHA and HAO1 expression is a human at risk of developing an oxalate pathway-associated disease, disorder, or condition. In one embodiment, a subject that would benefit from reduction in LDHA expression or LDHA and HAO1 expression is a human having an oxalate pathway-associated disease, disorder, or condition. In yet another embodiment, a subject that would benefit from reduction in LDHA expression or LDHA and HAO1 expression is a human being treated for an oxalate pathway-associated disease, disorder, or condition.

In one embodiment, a subject having an oxalate pathway-associated disease, disorder, or condition has an oxalate-associated disease, disorder, or condition. Non-limiting examples of oxalate-associated disease, disorder, or condition include a kidney stone formation disease, disorder, or condition, or a calcium oxalate tissue deposition disease, disorder, or condition. The kidney stone formation disease, disorder, or condition may be a calcium oxalate stone formation disease, disorder, or condition or a non-calcium oxalate stone formation disease, disorder, or condition. The calcium oxalate stone formation disease, disorder, or condition may be a hyperoxaluria disease, disorder, or condition (*e.g.*, mild hyperoxaluria (a urinary oxalate excretion level of about 40 to about 60 mg/day) or high hyperoxaluria (a urinary oxalate excretion level of greater than about 60 mg/day)); or a non-hyperoxaluria disease, disorder, or condition (*i.e.*, a calcium oxalate stone formation disease without hyperoxaluria, *e.g.*, normal urinary oxalate excretion levels, *e.g.*, less than about 40 mg (440 μ mol) in 24 hours (*e.g.*, men have a normal urinary oxalate excretion level of less than about 43 mg/day and women have a normal urinary oxalate excretion level of less than about 32 mg/day).

In one embodiment, the hyperoxaluria disease, disorder, or condition is selected from the group consisting of primary hyperoxaluria, enteric hyperoxaluria, dietary hyperoxaluria, and idiopathic hyperoxaluria.

In one embodiment, the non-hyperoxaluria stone formation disease, disorder, or condition is hypercalciuria and/or hypocitraturia. In another embodiment, the non-hyperoxaluria stone formation disease, disorder, or condition is calcium oxalate or non-calcium oxalate kidney stone formation disease.

In one embodiment, the calcium oxalate stone formation disease, disorder, or condition is an inherited disorder, such as a Primary Hyperoxaluria (PH), *e.g.*, 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), and PH3 is caused by mutations in HOGA1 (formerly DHAPSL). 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 LDHA expression and/or activity will decrease the level of excess oxalate. In addition, the inhibition of glycolate oxidase (HAO1) will further reduce the level of glyoxylate. 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 haematological 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.

As exemplified in Example 3, the level of endogenous oxalate excreted in the urine of an art recognized animal model of PH1, *e.g.*, an Agxt deficient mouse, was reduced following

administration of an LDHA-specific siRNA (see, *e.g.*, Figure 6). Accordingly, in one aspect, the present invention provides methods for treating a subject having PH1. The methods include administering to the subject a therapeutically effective amount of a dsRNA targeting an LDHA gene and/or an HAO1 gene, a pharmaceutical composition comprising a dsRNA agent that
 5 targets an LDHA gene and/or a dsRNA agent that targets an HAO1 gene.

As also exemplified in Example 3, the level of endogenous oxalate excreted in the urine of an art recognized animal model of PH2, *e.g.*, a Grhpr deficient mouse, was reduced following administration of an LDHA-specific siRNA (see, *e.g.*, Figure 6). Accordingly, in one aspect, the present invention provides methods for treating a subject having PH2. The methods include
 10 administering to the subject a therapeutically effective amount of a dsRNA targeting an LDHA gene and/or an HAO1 gene, a pharmaceutical composition comprising a dsRNA agent that targets an LDHA gene and/or a dsRNA agent that targets an HAO1 gene in a cell of the subject.

In some embodiment, the methods for treating a subject having PH2 further include altering the diet of the subject (*e.g.*, decreasing protein intake, decreasing sodium intake,
 15 decreasing ascorbic acid intake, moderatating calcium intake, supplementing phosphate, supplementing magnesium, or pyridoxine treatment; or a combination of any of the foregoing) and/or transplanting a kidney in the subject

In another embodiment, the calcium oxalate stone formation disease, disorder, or condition is enteric hyperoxaluria. Enteric hyperoxaluria is the formation of calcium oxalate
 20 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 another embodiment, the calcium oxalate stone formation disease, disorder, or condition is dietary hyperoxaluria, *e.g.*, hyperoxaluria as a result of too much oxalate in the diet,
 25 *e.g.*, from too much spinach, rhubarb, almonds, bulgur, millet, corn grits, soy flour, cornmeal, navy beans, *etc.*

In another embodiment, the calcium oxalate stone formation disease, disorder, or condition is idiopathic hyperoxaluria. Subjects having idiopathic hyperoxaluria have above
 30 normal levels of urinary oxalate of unknown cause, but still develop stones. Subjects at risk of developing idiopathic hyperoxaluria include diabetics and obese subjects. For example, epidemiological data has demonstrated that as body mass index (BMI) increases, urinary oxalate excretion increases and subjects having diabetes have increases urinary oxalate levels.

In one embodiment, the non-calcium oxalate stone formation disease, disorder, or condition is hypercalciuria (hypercalcinuria). Hypercalciuria is a condition of elevated calcium
 35 in the urine. Chronic hypercalcinuria may lead to impairment of renal function, nephrocalcinosis, and renal insufficiency. Subjects at risk of developing hypercalciuria include subjects having Dent's disease, absorptive hypercalciuria, and primary hyperparathyroid.

In another embodiment, the non-calcium oxalate stone formation disease, disorder, or condition is hypocitraturia. In one embodiment, the hypocitraturia is severe hypocitraturia, *e.g.*, citrate excretion of less than 100 mg per day. In another embodiment, the hypocitraturia is mild to moderate hypocitraturia, *e.g.*, citrate excretion of 100-320 mg per day.

5 In one embodiment, a non-calcium oxalate stone formation disease, disorder, or condition is a disease, disorder, or condition, such as a ureterolithiasis or a nephrocalcinosis, of calcium stones; struvite (magnesium ammonium phosphate) stones; uric acid stones; or cystine stones. Although the primary component of the stones in such diseases, disorders, and conditions is other than oxalate, oxalate may still be present and form a nidus for further growth
10 of the stones. Accordingly, subjects having a disease, disorder, or condition of calcium stones, struvite (magnesium ammonium phosphate) stones, uric acid stones, or cystine stones would benefit from the methods of the invention.

In one embodiment, an oxalate-associated disease, disorder, or condition is a calcium oxalate tissue deposition disease, disorder, or condition. For example, when glomerular
15 filtration rate (GFR) drops below about 30-40 mL/min per 1.73 m², 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, and bone marrow, myocardium, cardiac conduction system. This leads to cardiomyopathy, heart block and other cardiac conduction defects, vascular disease, retinopathy, synovitis, oxalate
20 osteopathy and anemia that is noted to be resistant to treatment. The deposition of calcium oxalate may be systemic or tissue specific. For example, subjects having arthritis, sarcoidosis, end-stage renal disease are at risk of developing systemic calcium oxalate tissue deposition disease, disorder, or condition. Subjects at risk of developing tissue specific depositions in the kidney, for example, include subjects having medullary sponge kidney, nephrocalcinosis, renal
25 tubular acidosis (RTA), and transplant recipients, *e.g.*, kidney transplant recipients.

In one embodiment, an oxalate pathway-associated disease, disorder, or condition is a lactate dehydrogenase-associated disease, disorder, or condition. Non-limiting examples of lactate dehydrogenase-associated diseases, disorders, or conditions include cancer, *e.g.*, cancer, *e.g.*, hepatocellular carcinoma, fatty liver (steatosis), nonalcoholic steatohepatitis (NASH),
30 cirrhosis of the liver, accumulation of fat in the liver, inflammation of the liver, hepatocellular necrosis, liver fibrosis, and nonalcoholic fatty liver disease (NAFLD).

A diagnosis of nonalcoholic fatty liver disease (NAFLD) requires that (a) there is evidence of hepatic steatosis, either by imaging or by histology and (b) there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic
35 medication or hereditary disorders. In the majority of patients, NAFLD is associated with metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia. NAFLD is histologically further categorized into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NAFL is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes. NASH is defined as the

presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis (Chalasani *et al.*, *Hepatol.* 55:2005-2023, 2012). It is generally agreed that patients with simple steatosis have very slow, if any, histological progression, while patients with NASH can exhibit histological progression to cirrhotic-stage disease. The long term outcomes of patients with NAFLD and NASH have been reported in several studies.

LDHA is required for the initiation, maintenance and progression of tumors (Shi and Pinto, *PLOS ONE* 2014, 9(1), e86365; Le *et al.* *Proc Natl Acad Sci U S A* 107: 2037-2042) and up-regulation of LDHA is a characteristic of many cancer types (Goldman RD *et al.*, *Cancer Res* 24: 389-399.; Koukourakis MI, *et al.*, *Br J Cancer* 89: 877-885.; Koukourakis MI, *et al.*, *LJ Clin Oncol* 24: 4301-4308.; Kolev Y, *et al.*, *Ann Surg Oncol* 15: 2336-2344. ; Zhuang L, *et al.*, *Mod Pathol* 23: 45-53), including, e.g., breast cancer, lymphoma, renal cancer (including renal cell cancer tumors), hereditary leiomyomatosis, pancreatic cancer, liver cancer (including hepatocellular carcinoma), and other forms of cancer.

In another aspect, the present invention provides uses of a therapeutically effective amount of a dsRNA agent, a dual targeting iRNA agent or a pharmaceutical composition comprising a dsRNA, a pharmaceutical compositions comprising a dual targeting RNAi agent or 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 for treating a subject, e.g., a subject that would benefit from a reduction and/or inhibition of LDHA expression or LDHA and HAO1 expression, e.g., an oxalate pathway-associated disease, disorder, or condition.

In a further aspect, the present invention provides uses of a dual targeting iRNA agent or a pharmaceutical composition comprising of a dsRNA agent, a dual targeting iRNA agent or a pharmaceutical composition comprising a dsRNA, a pharmaceutical composition comprising a dual targeting RNAi agent or 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 in the manufacture of a medicament for treating a subject, e.g., a subject that would benefit from a reduction and/or inhibition of LDHA expression or LDHA and HAO1 expression, e.g., an oxalate pathway-associated disease, disorder, or condition.

In the methods (and uses) of the invention which comprise administering to a subject a first dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, the first and second dsRNA agents 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 dsRNA agent 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, preferably about 0.3 mg/kg and about 3.0 mg/kg. In addition, the

The dual targeting RNAi agent 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, preferably about 0.3 mg/kg and about 3.0 mg/kg. In addition, the first dsRNA

agent and the second dsRNA agent may be each independently administered to the subject at a dose of about 0.5 mg/kg to about 50 mg/kg, *e.g.*, in the range of about 0.1 mg/kg to about 5.0 mg/kg, preferably 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 dsRNA agent targeting LDHA and a second dsRNA agent targeting HAO1, the first and second dsRNA agents may be administered to a subject at the same dose or different doses.

The iRNA 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 the iRNA 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 a preferred embodiment, administration of the iRNA can reduce LDHA levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least 20%.

Administration of the iRNA 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 a preferred embodiment, administration of the iRNA can reduce HAO1 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 dsRNA agent targeting LDHA and a second 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 iRNA, 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 iRNA can be administered subcutaneously, *i.e.*, by subcutaneous injection. One or more injections may be used to deliver the desired daily dose of iRNA to a subject. The injections may be repeated over a period of time. The administration may be repeated on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. A repeat-dose regimen may include administration of a therapeutic amount of iRNA on a regular basis, such as every other day or to once a year. In certain embodiments, the iRNA 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 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 about 36 hours. In one embodiment, expression of the target LDHA gene and 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.

Preferably, the iRNAs useful for the methods and compositions featured herein specifically target RNAs (primary or processed) of the target LDHA and 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 dsRNA 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 disorder of lipid metabolism. 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 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. For example, efficacy of treatment of a disorder of lipid metabolism may be assessed, for example, by periodic monitoring of one or more serum lipid levels, *e.g.*, triglyceride levels. 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 an iRNA or pharmaceutical composition thereof, "effective against" a disorder of lipid metabolism indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as an 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 disorder of lipid metabolisms 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 preferably at least 20%, 30%, 40%, 50% or more can be indicative of effective treatment. Efficacy for a given iRNA drug or formulation of that drug can also be judged using an experimental animal model for the given disease as known in the art.

The invention further provides methods for the use of a iRNA agent or a pharmaceutical composition of the invention, *e.g.*, for treating a subject that would benefit from reduction and/or inhibition of LDHA expression or LDHA and HAO1 expression, *e.g.*, a subject having an oxalate pathway-associated disease, disorder, or condition, 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, an iRNA agent 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.

In certain embodiments, an iRNA agent as described herein is administered in combination with an iRNA agent targeting hydroxyproline dehydrogenase (HYPDH; also known as HPOX or PRODH2) (see, *e.g.*, Li, *et al.* (*Biochem Biophys Acta* (2016) 1862:233-239) or an inhibitory analog of HYPDH (see, *e.g.*, Summitt, *et al.* (*Biochem J* (2015) 466:273-281).

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

VII. Kits

The present invention also provides kits for performing any of the methods of the invention. Such kits include one or more RNAi agent(s) and instructions for use, *e.g.*, instructions for inhibiting expression of a LDHA or LDHA and HAO1 in a cell by contacting the cell with an RNAi agent or pharmaceutical composition of the invention in an amount effective to inhibit expression of the LDHA or LDHA and HAO1. The kits may optionally further comprise means for contacting the cell with the RNAi agent (*e.g.*, an injection device), or means for measuring the inhibition of LDHA and/or HAO1 (*e.g.*, means for measuring the inhibition of LDHA and/or HAO1 mRNA and/or LDHA and/or HAO1 protein). Such means for measuring the inhibition of LDHA and/or HAO1 may comprise a means for obtaining a sample from a subject, such as, *e.g.*, a plasma sample. The kits of the invention may optionally further comprise means for administering the RNAi agent(s) to a subject or means for determining the therapeutically effective or prophylactically effective amount.

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 iRNAs 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.

EXAMPLES

Example 1. iRNA Design, Synthesis, Selection, and *In Vitro* Evaluation

Source of reagents

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

Transcripts

A set of iRNAs targeting LDHA that cross-react with mouse and rat *Ldha* (human NCBI refseqID: NM_010699.2) were designed using custom R and Python scripts. The mouse *Ldha*, variant 1 REFSEQ mRNA has a length of 1,661 bases.

An additional set of iRNAs targeting LDHA (human: NCBI refseqID NM_005566.3; NCBI GeneID: 3939) as well as toxicology-species LDHA orthologs (cynomolgus monkey: NM_001283551.1) was designed using custom R and Python scripts. The human NM_005566 REFSEQ mRNA, version 3, has a length of 2226 bases.

A detailed list of the unmodified mouse/rat cross-reactive LDHA sense and antisense strand sequences is shown in Table 2. A detailed list of the modified mouse/rat cross-reactive LDHA sense and antisense strand sequences is shown in Table 3.

A detailed list of the unmodified human/Cynomolgus cross-reactive LDHA sense and antisense strand sequences is shown in Table 4. A detailed list of the modified human/Cynomolgus cross-reactive LDHA sense and antisense strand sequences is shown in Table 5.

As described in PCT Publication, WO 2016/057893 (the entire contents of which is incorporated herein by reference), a set of iRNAs targeting HAO1 were also designed. Design used the following transcripts from the NCBI RefSeq collection: human (*Homo sapiens*) HAO1 mRNA is NM_017545.2; cynomolgus monkey (*Macaca fascicularis*) HAO1 mRNA is XM_005568381.1; Mouse (*Mus musculus*) HAO1 mRNA is NM_010403.2; Rat (*Rattus norvegicus*) HAO1 mRNA is XM_006235096.1.

Tables 7 and 8 provide the modified sense and antisense strand sequences of duplexes targeting HAO1. Tables 9, 10, 11, 14, and 15 provide the unmodified sense and antisense strand sequences of duplexes targeting HAO1. Tables 12, 13, and 16 provide the unmodified and modified sense and antisense strand sequences of duplexes targeting HAO1.

When known, the species of HAO1 that is inhibited by the duplex is noted: Hs indicates that the agent inhibits the expression of human HAO1; Mm indicates that the agent inhibits the expression of mouse HAO1; and Hs/Mm indicates that the agent inhibits expression of both human and mouse HAO.

In vitro screening:

Cell culture and transfections

Primary Mouse Hepatocyte cells (PMH) (MSCP10, Lot# MC613) were transfected by adding 4.9µl of Opti-MEM plus 0.1µl of Lipofectamine RNAiMax per well (Invitrogen,

Carlsbad CA. cat # 13778-150) to 5µl of siRNA duplexes per well into a 384-well plate and incubated at room temperature for 15 minutes. Forty µl of DMEM (Hep3b) of William's E Medium (PMH) containing about 5×10^3 cells was then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Single dose experiments were performed at 10nM and 0.1nM final duplex concentration.

Hep3b cells (ATCC) were transfected by adding 4.9µl of Opti-MEM plus 0.1µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5µl of siRNA duplexes per well into a 384-well plate and incubated at room temperature for 15 minutes. Forty µl of Eagle's Minimal Essential Medium (Life Tech) containing $\sim 5 \times 10^3$ cells were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Single dose experiments were performed at 10nM.

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

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

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

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

Real time PCR

Two µl of cDNA was added to a master mix containing 0.5µl of human GAPDH TaqMan Probe (4326317E), 0.5µl human LDHA, 2µl nuclease-free water and 5µl Lightcycler 480 probe master mix (Roche Cat # 04887301001) per well in a 384 well plates (Roche cat # 04887301001). Real time PCR was performed in a LightCycler480 Real Time PCR system (Roche) using the $\Delta\Delta C_t$ (RQ) assay. Each duplex was tested in at least two independent transfections, unless otherwise noted in the summary tables.

To calculate relative fold change, real time data was analyzed using the $\Delta\Delta C_t$ method and normalized to assays performed with cells transfected with 10nM nonspecific siRNA, or mock transfected cells.

Table 6A shows the results of a single dose screen in primary mouse hepatocytes transfected with the indicated GalNAC conjugated modified iRNAs. Data are expressed as percent of message remaining relative to untreated cells.

Table 6B shows the results of a single dose screen in primary mouse hepatocytes transfected with the indicated GalNAC conjugated modified iRNAs. Data are expressed as percent of message remaining relative to untreated cells.

5 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.

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 (G, A, C, T or U)
a	2'-O-methyladenosine-3'-phosphate

Abbreviation	Nucleotide(s)
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
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl]-4-hydroxyprolinol Hyp-(GalNAc-alkyl) ₃
Y34	2-hydroxymethyl-tetrahydrofuran-4-methoxy-3-phosphate (abasic 2'-OMe furanose)
Y44	inverted abasic DNA (2-hydroxymethyl-tetrahydrofuran-5- phosphate)
(Agn)	Adenosine-glycol nucleic acid (GNA)
(Cgn)	Cytidine-glycol nucleic acid (GNA)
(Ggn)	Guanosine-glycol nucleic acid (GNA)
(Tgn)	Thymidine-glycol nucleic acid (GNA) S-Isomer
P	Phosphate
VP	Vinyl-phosphate
(Aam)	2'-O-(N-methylacetamide)adenosine-3'-phosphate
(Aams)	2'-O-(N-methylacetamide)adenosine-3'-phosphorothioate
(Gam)	2'-O-(N-methylacetamide)guanosine-3'-phosphate
(Gams)	2'-O-(N-methylacetamide)guanosine-3'-phosphorothioate
(Tam)	2'-O-(N-methylacetamide)thymidine-3'-phosphate
(Tams)	2'-O-(N-methylacetamide)thymidine-3'-phosphorothioate
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

Abbreviation	Nucleotide(s)
dUs	2'-deoxyuridine-3'-phosphorothioate
(Aeo)	2'-O-methoxyethyladenosine-3'-phosphate
(Aeos)	2'-O-methoxyethyladenosine-3'-phosphorothioate
(Geo)	2'-O-methoxyethylguanosine-3'-phosphate
(Geos)	2'-O-methoxyethylguanosine-3'-phosphorothioate
(Teo)	2'-O-methoxyethyl-5-methyluridine-3'-phosphate
(Teos)	2'-O-methoxyethyl-5-methyluridine-3'-phosphorothioate
(m5Ceo)	2'-O-methoxyethyl-5-methylcytidine-3'-phosphate
(m5Ceos)	2'-O-methoxyethyl-5-methylcytidine-3'-phosphorothioate
(A3m)	3'-O-methyladenosine-2'-phosphate
(A3mx)	3'-O-methyl-xylofuranosyladenosine-2'-phosphate
(G3m)	3'-O-methylguanosine-2'-phosphate
(G3mx)	3'-O-methyl-xylofuranosylguanosine-2'-phosphate
(C3m)	3'-O-methylcytidine-2'-phosphate
(C3mx)	3'-O-methyl-xylofuranosylcytidine-2'-phosphate
(U3m)	3'-O-methyluridine-2'-phosphate
U3mx)	3'-O-methyl-xylofuranosyluridine-2'-phosphate
(m5Cam)	2'-O-(N-methylacetamide)-5-methylcytidine-3'-phosphate
(m5Cams)	2'-O-(N-methylacetamide)-5-methylcytidine-3'-phosphorothioate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Chds)	2'-O-hexadecyl-cytidine-3'-phosphorothioate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
(Uhds)	2'-O-hexadecyl-uridine-3'-phosphorothioate
(pshe)	Hydroxyethylphosphorothioate

TABLE 2. UNMODIFIED MOUSE/RAT CROSS-REACTIVE LDHA mRNA SEQUENCES

Duplex Name	Sense Oligo Name	Sense Sequence 5' to 3'	SEQ ID NO	Range in NM_010699.2	Antisense Oligo Name	Antisense Sequence 5' to 3'	SEQ ID NO	Range in NM_010699.2
AD-84747	A-169171	AACACCAAAAUUGUCUCAA	2990	357-377	A-169172	UUGGAGACAAUUUUUGGUUUU	3034	355-377
AD-84748	A-169173	AAACCGAGUAAUUGGAAGUGA	2991	603-623	A-169174	UCACUCCAAUUAUCUGGUUUU	3035	601-623
AD-84749	A-169175	AAAUCAUGGCUUCCCAAAA	2992	584-604	A-169176	UUUUGGAAAGCCACUGAUUUUC	3036	582-604
AD-84750	A-169177	UCCCAACAUGUCAGUACAA	2993	501-521	A-169178	UUGUACUUGACAAUGUUGGAAU	3037	499-521
AD-84751	A-169179	UGUGCCAUCAGUAUCUUAUA	2994	241-261	A-169180	UAUUAAGAUACUGAUGGCACAAG	3038	239-261
AD-84752	A-169181	AAAUUGUCUCCAGCAAAAGACU	2995	365-385	A-169182	AGUCUUUGCUGGAGACAAUUUU	3039	363-385
AD-84753	A-169183	ACCUUGAACAGUAAAAAAA	2996	1610-1630	A-169184	UUUUUUUACACUGUUCAGGUUU	3040	1608-1630
AD-84754	A-169185	AAACACCAAAAAAUUGUCUCA	2997	355-375	A-169186	UGAGACAAUUUUUGGUUUUAA	3041	353-375
AD-84755	A-169187	ACCAAAAAUUGUCUCCAGCAA	2998	360-380	A-169188	UUUCUGGAGACAAUUUUUGGUGU	3042	358-380
AD-84756	A-169189	CAAGUUCAUCAUUCCCAACAU	2999	489-509	A-169190	AUGUUGGGAUGAUGAACUUGAA	3043	487-509
AD-84757	A-169191	GCAAUUUUUGUGAGAGUUA	3000	1538-1558	A-169192	UUACAUCUCACAAUAAUUGCAA	3044	1536-1558
AD-84758	A-169193	GUCUCAAAGAUUCAAAGUCA	3001	115-135	A-169194	UGACUUUGAAUCUUUUUGAGCCG	3045	113-135
AD-84759	A-169195	CAUCCCCAACAUUGUCAAGUA	3002	498-518	A-169196	UACUUGACAAUGUUGGGAAUGAU	3046	496-518
AD-84760	A-169197	AAACCUUGAACAGUAAAAAA	3003	1608-1628	A-169198	UUUUUACACUGUUCAGGUUUUA	3047	1606-1628
AD-84761	A-169199	UCAAAGAUUCAAAGUCCAAA	3004	118-138	A-169200	UUUGGACUUUGAAUCUUUUUGAGA	3048	116-138
AD-84762	A-169203	ACAUCUUAAGUUAUCAUUA	3005	482-502	A-169204	UAAUGAUGAACUUGAAGAUUUC	3049	480-502
AD-84763	A-169205	CAGCUGAUUGUGAAUCUUCU	3006	157-177	A-169206	AAGAAAUUCACAAUACAGCUGGU	3050	155-177
AD-84764	A-169207	CUCAAAAGAUUCAAAGUCCAA	3007	117-137	A-169208	UUUGGACUUUGAAUCUUUUUGAGAC	3051	115-137
AD-84765	A-169209	AAACCGAGUAAUUGGAAGUA	3008	602-622	A-169210	UACUCCAAUUAUCUGGUUUUUUG	3052	600-622
AD-84766	A-169213	UGAUGCAUUCUUGUGCAUAA	3009	1469-1489	A-169214	UU AUGCACAAAGAU AUGCAUC AUG	3053	1467-1489
AD-84767	A-169215	CCAUCAGUAUCUUAUUGAAGA	3010	245-265	A-169216	UCUUCAUUAAGAUACUGAUGGCA	3054	243-265
AD-84768	A-169217	AAUCAGUGGCUUUUCCCAAAA	3011	585-605	A-169218	UUUUUGGGAAGCCACUGAUUUU	3055	583-605

AD-84769	A-169219	UUAAAAACACCAAAAAUUUGUCU	3012	353-373	A-169220	AGACAAUUUUUGGUGUUUUAAGG	3056	351-373
AD-84770	A-169221	CUGAUUGUGAAUUCUUCUAAA	3013	160-180	A-169222	UUUAGAAGAUUCACAAUACGCU	3057	158-180
AD-84771	A-169223	AUAAAAACCUUGAACACAGUAAA	3014	1605-1625	A-169224	UUUCACUGUUCAGGUUUUAUUU	3058	1603-1625
AD-84772	A-169225	AGUGUCAUGCCAAAUA AAAACA	3015	1592-1612	A-169226	UGUUUUUUUUGGCAUGACACUUG	3059	1590-1612
AD-84773	A-169227	ACACCAAAAAUUUGUCUCCAGA	3016	358-378	A-169228	UCUGGAGACAAUUUUUGGUGUUU	3060	356-378
AD-84774	A-169229	GCAUUGCAAUAUAUUGUGAGA	3017	1533-1553	A-169230	UCUCACAAUAUAUUGCAAUGCAC	3061	1531-1553
AD-84775	A-169231	GUCAUGCCAAAUA AAAACCUUA	3018	1595-1615	A-169232	UAAGGUUUUAUUUGGCAUGACAC	3062	1593-1615
AD-84776	A-169233	AUAUCUUUGGCAUAAAUGUUA	3019	1475-1495	A-169234	UAAACAUUAUGCACAAGAU AUGC	3063	1473-1495
AD-84777	A-169235	AAACACCAAAAAUUUGUCUCCA	3020	356-376	A-169236	UGGAGACAAUUUUUGGUGUUUA	3064	354-376
AD-84778	A-169237	UAACCUUGGCUCCAGUGUGUAA	3021	1443-1463	A-169238	UUACACACUGGAGCCAGGUUAUA	3065	1441-1463
AD-84779	A-169239	UGCAUAUCUUUGGCAUAAAUA	3022	1472-1492	A-169240	UAUUUAUGCACAAGAU AUGCAUC	3066	1470-1492
AD-84780	A-169241	ACAUUGUCAAGUACAGUCCAA	3023	506-526	A-169242	UUGGACUGUACUUGACAAUGUUG	3067	504-526
AD-84781	A-169243	AACCUUGAACACAGUAAAAAAA	3024	1609-1629	A-169244	UUUUUUUCACUGUUCAAAGUUUU	3068	1607-1629
AD-84782	A-169245	GUGUGCAUUGCAAUAUUAUGU	3025	1529-1549	A-169246	ACAUAAUAUUGCAAUGCACAUA	3069	1527-1549
AD-84783	A-169247	CCAAAAACCGAGUA AUUGGAA	3026	599-619	A-169248	UUCCAAUUAUCUCGGUUUUUGGGA	3070	597-619
AD-84784	A-169249	CAAAAAACCGAGUA AUUGGAAA	3027	600-620	A-169250	UUUCCAAUUAUCUCGGUUUUUGGG	3071	598-620
AD-84785	A-169251	CCAAAGUGGUACUUGUGUAGUA	3028	1285-1305	A-169252	UACUACACAAGUACCAUUGGCA	3072	1283-1305
AD-84786	A-169253	CAGCGAAACGUGAACAUUCUUA	3029	469-489	A-169254	UAGAUGUUCACGUAUUCGUGGA	3073	467-489
AD-84787	A-169255	UGAUUGUGAAUUCUUCUUAAGA	3030	161-181	A-169256	UCUUAAGAAGAUUCACAAUACGC	3074	159-181
AD-84788	A-169257	CUUCAAGUUAUCAUAUCCCAA	3031	486-506	A-169258	UUUGGAAUGAUGAACUUGAAGAU	3075	484-506
AD-84789	A-169259	GGACCAGCUGAUUGUGAAUCU	3032	153-173	A-169260	AGAUUCACAUAUCAGCUGGUCCUU	3076	151-173
AD-84790	A-169261	AUGCCAAAUA AAAACCUUGAAA	3033	1598-1618	A-169262	UUUCAAGGUUUUAUUAUGGCAUGA	3077	1596-1618

AD-84768	asasucagUfgGfCfUfuucccaaaaL96	3099	usUfsuuuGfgGfAfaagcCfaCfugaunusuu	3143	AAAAUCAGUGGCUUUUCCCCAAAA	3187
AD-84769	ususaaaaCfaCfAfaaaauuguculL96	3100	asGfsacaAfuUfUfuuggUfgUfuuaasgsg	3144	CCUUAAAAACACCAAAAAAUUGUCU	3188
AD-84770	csusgaunGfuGfAfAfucuuuuaaL96	3101	usUfsuaaGfaAfGfaunCfAfaucagsesu	3145	AGCUGAUUGUGAAUUCUUCUUAAG	3189
AD-84771	asusaaaaCfcUfUfgfaacagugaaL96	3102	usUfsucaCfuGfuFucaaGfgUfuuaunusuu	3146	AAAUAAAAACCUUGAAACAGUGAAA	3190
AD-84772	asgsugucAfuGfCfCfaaauaaacaL96	3103	usGfsuuuUfaUfUfuggcAfuGfacacususg	3147	CAAGUGUCAUGCCCAAAUAAAAACC	3191
AD-84773	ascsaccaAfaAfAfUfugucuccagaL96	3104	usCfsuggAfgAfcfaauUfUfUfgugusuu	3148	AAACACCAAAAAAUUGUCUCCAGC	3192
AD-84774	gscsaunGcfaAfUfAfaunugugagaL96	3105	usCfsucaCfaUfAfaunUfgCfaaugsasac	3149	GUGCAUUGCAAAUUAUUGUGAGA	3193
AD-84775	gsuscaugCfcAfAfAfuaaaceuuL96	3106	usAfsaggUfuUfUfaunUfgCfaugacsac	3150	GUGUCAUGCCCAAAUAAAAACCUUG	3194
AD-84776	asusaucuUfgUfGfCfaaauaunguaL96	3107	usAfsacaUfuUfAfaugCaCfaAfgaunsgsc	3151	GCAUAUCUUGUGCAUAAAUUGUUG	3195
AD-84777	asasacacCfaAfAfAfaunugucuccaL96	3108	usGfsaggAfcAfAfaunUfgGfuguuusua	3152	UAAAAACACCAAAAAAUUGUCUCCA	3196
AD-84778	usasaccuGfgCfUfCfcaguguguaaL96	3109	usUfsacaCfaCfUfggagCfcAfgguuasua	3153	UAUAACCUUGGCUCCAGUGUGUAC	3197
AD-84779	usgscauaUfcUfUfGfugcauaaualL96	3110	usAfsuuuAfuGfCfacaGfaUfaugcasusc	3154	GAUGCAUAUCUUGUGCAUAAAAUG	3198
AD-84780	ascsaunGUfcAfAfGfuacaguccaaL96	3111	usUfsggaCfuGfUfacuuGfaCfaugusug	3155	CAACAUUGUCAAGUACAGUCCAC	3199
AD-84781	asasccuuGfaAfCfAfgugaaaaaL96	3112	usUfsuuuUfuCfAfcyguUfcAfauguuusuu	3156	AAAACCUUGAAACAGUGAAAAAAA	3200
AD-84782	gsusgugcAfuUfGfCfaaauuuuugulL96	3113	asCfsauaAfuAfUfugcaAfuGfacacsusua	3157	UAGUGUGCAUUGCAAAUUAUUAUGU	3201
AD-84783	cscsaaaaAfcCfGfAfguaauugaaL96	3114	usUfscceAfuUfAfcuugGfuUfuungsgsa	3158	UCCCCAAAAACCGAGUAAUUGGAA	3202
AD-84784	csasaaaaCfcGfAfgfaauuggaalL96	3115	usUfsuccAfaUfUfauucGfgUfuunugsgsg	3159	CCCCAAAAACCGAGUAAUUGGAAAG	3203
AD-84785	cscsaagunGfgUfAfCfuuguguaaL96	3116	usAfsucaCfaCfAfaagCfcAfcuugsgsca	3160	UGCCAAAGUGGUACUUGUGUAGUG	3204
AD-84786	csasgcgaAfaCfGfUfgaacuucuaL96	3117	usAfsagaUfgUfUfcaagUfuUfcgucgsgsa	3161	UCCAGCGAAAACGUGAACAUUCUUC	3205
AD-84787	usgsaunGUfgAfaUfUfcuucuuuagaaL96	3118	usCfsuuuAfgAfafgaunUfAfaucagsac	3162	GCUGAUUGUGAAUUCUUCUUAAGG	3206
AD-84788	csuscaaaGfuUfCfAfuaauuccaaL96	3119	usUfsgggAfaUfgfaugaAfcUfugaagsasu	3163	AUCUUCAAGUUCAUCAUUCUCCAA	3207
AD-84789	gsgsaccaGfcUfGfAfuuguauculL96	3120	asGfsaunCfaCfAfaucGfcUfgguccsusu	3164	AAGGACCGAGUGAUUUGUGAAUCU	3208
AD-84790	asusgccaAfaUfAfAfaacuuugaaL96	3121	usUfsucaAfgGfUfuuaUfUfggcaungsa	3165	UCAUGCCCAAAUAAAAACCUUGAAC	3209

TABLE 4. UNMODIFIED HUMAN/CYNOMOLGUS CROSS-REACTIVE LDHA iRNA SEQUENCES

Duplex Name	Sense Oligo Name	Sense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3	Antisense Oligo Name	Antisense Sequence 5' to 3'	SEQ ID NO	Position in NM_005566.3
AD-159469	A-314810	UUUAUCUGAUCUGUAUAAA	3210	1347-1367	A-314811	UUUAAUCACAGAUCAUAAAA	3396	1345-1367
AD-159607	A-315086	ACUGGUUAGUGUAAAUAUU	3211	1489-1509	A-315087	AACUAAUUCACACUAACCAUUG	3397	1487-1509
AD-159713	A-315298	AACAUGCCUAGUCCAAAUUU	3212	1615-1635	A-315299	AAAGUUGGACUAGGCAUUA	3398	1613-1635
AD-158504	A-312881	CAAGUCCAAUAUGGCAACUCU	3213	263-283	A-312882	AGAGUUGCCAUUUUGGACUUGGA	3399	261-283
AD-159233	A-314338	UCCACCAUGAUUAAAGGUCUU	3214	1092-1112	A-314339	AAGACCCUUAUUAUUGGUGGAAA	3400	1090-1112
AD-159411	A-314694	UCAUUACACUGUCUAGGCUA	3215	1289-1309	A-314695	UUAGCCUAGACAGUGAAUUA	3401	1287-1309
AD-159462	A-314796	UGUCCUUUUUAUCUGAUCUGU	3216	1340-1360	A-314797	ACAGAUCAGAUAAAAGGACAAC	3402	1338-1360
AD-159742	A-315356	CCAGUGUAUAAAUCCAAUAUA	3217	1662-1682	A-315357	UAUAUUGGAUUUAUACACUGGAU	3403	1660-1682
AD-159863	A-315598	UCCAAGUGUAUAACCAACUAA	3218	1791-1811	A-315599	UUAGUUGGUAAUAAACUUGGAUA	3404	1789-1811
AD-158626	A-313124	GUCAUCGAAAGACAAAUUGAAA	3219	429-449	A-313125	UUUCAUUUGUCUUUCGUAUGACAU	3405	427-449
AD-158687	A-313246	GAACACCAAAAGAUUGUCUCUA	3220	490-510	A-313247	UAGAGACAACUUUUGGUGUUCUA	3406	488-510
AD-158688	A-313248	AACACCAAAAGAUUGUCUCUGA	3221	491-511	A-313249	UCAGAGACAAUCUUUUGGUGUUCU	3407	489-511
AD-159458	A-314788	AUGUUGUCCUUUUUAUCUGAU	3222	1336-1356	A-314789	AUCAGAUAAAAGGACAACAUGC	3408	1334-1356
AD-159519	A-314910	UCAACUCCUGAAGUUAGAAA	3223	1401-1421	A-314911	AUUUCUAAACUUCAGGAGUUGAUG	3409	1399-1421
AD-159858	A-315588	AACUAUCCAAGUGUUAUACCA	3224	1786-1806	A-315589	UGGUAAACACUUGGAUAGUUGG	3410	1784-1806
AD-158681	A-313234	UCCUUAGAACACCAAAAGAUUA	3225	484-504	A-313235	UAACUUUUGGUGUUCUUAAGGAAA	3411	482-504
AD-159583	A-315038	GGUAUUAAUUCUUUGUGUAGUCU	3226	1465-1485	A-315039	AGACUACAACAAGAUUAUACCAU	3412	1463-1485
AD-159700	A-315272	GGCUCCUUCACUGAACAUUGCA	3227	1602-1622	A-315273	UGCAUGUUCACUGAAGGAGCCAG	3413	1600-1622
AD-159807	A-315486	UAUCAGUAGUGUACAUUACCA	3228	1728-1748	A-315487	UGGUAAUGUACACUACUGAUUA	3414	1726-1748
AD-158673	A-313218	CAGCCUUUUUCCUUUAGAACA	3229	476-496	A-313219	UGUGUUCUAAAGGAAAAGGCUGCC	3415	474-496

AD-159608	A-315088	CUGGUUAGUGUGAAAUAGUUA	3230	1490-1510	A-315089	UAAUAUUUCACACUAAACCAGUU	3416	1488-1510
AD-159803	A-315478	ACUAUAUCAGUAGUGUACAUU	3231	1724-1744	A-315479	AAUGUACACUACUGAUUAUAGUUC	3417	1722-1744
AD-159805	A-315482	UAUAUCAGUAGUGUACAUUAA	3232	1726-1746	A-315483	UUAUGUACACUACUGAUUAUAGU	3418	1724-1746
AD-159489	A-314850	GUAAUAUUUAAAGAUAGGACUA	3233	1371-1391	A-314851	UAGUCCAUUCUAAAAAUUACUG	3419	1369-1391
AD-159495	A-314862	UUUUAAGAUAGGACUGGGAUAA	3234	1377-1397	A-314863	UUUCCCAGUCCAUUCUUAUAAUA	3420	1375-1397
AD-159609	A-315090	UGGUUAGUGUGAAAUAGUUCU	3235	1491-1511	A-315091	AGAAUAUUUCACACUAACCAGU	3421	1489-1511
AD-159706	A-315284	UUCACUGAACAUGCCUAGUCA	3236	1608-1628	A-315285	UGACUAGGCAUGUUCAGUGAAGG	3422	1606-1628
AD-159855	A-315582	ACCAACUAUCCAAAGUGUUAUA	3237	1783-1803	A-315583	UAUAACACUUGGAUAGUUGGUUG	3423	1781-1803
AD-159864	A-315600	CCAAGUGUUUAUACCAACUAAA	3238	1792-1812	A-315601	UUUAGUUGGUUAUAAACACUUGGAU	3424	1790-1812
AD-158491	A-312855	UUCUUUUUGGUUCCAAAGUCCA	3239	250-270	A-312856	UGGACUUGGAACCAAAAGGAUUC	3425	248-270
AD-158672	A-313216	GCAGCCUUUUCCUUAGAACAA	3240	475-495	A-313217	UUUUCUAAGGAAAGGCUGCCA	3426	473-495
AD-159488	A-314848	AGUAAUAUUUUAAGAUGGACU	3241	1370-1390	A-314849	AGUCCAUUCUAAAAAUUACUGC	3427	1368-1390
AD-159553	A-314978	AAAUCCACAGCUUAUAUCCUA	3242	1435-1455	A-314979	UAGGAUAUAGCUGUGGAUUUAC	3428	1433-1455
AD-159703	A-315278	UCCUUCACUGAACAUAGCCUAA	3243	1605-1625	A-315279	UUAGGCAUGUUCAGUGAAGGAGC	3429	1603-1625
AD-159708	A-315288	CACUGAACAUGCCUAGUCCAA	3244	1610-1630	A-315289	UUGGACUAGGCAUGUUCAGUGAA	3430	1608-1630
AD-159866	A-315604	AAGUGUUUAUACCAACUAAAAAC	3245	1794-1814	A-315605	GUUUUAGUUGGUUAUAAACAUUGG	3431	1792-1814
AD-159232	A-314336	UUCCACCAUGAUUUAAGGGUCU	3246	1091-1111	A-314337	AGACCCUUAUUAUUGGUGGAAAC	3432	1089-1111
AD-159712	A-315296	GAACAUGCCUAGUCCAAACAUU	3247	1614-1634	A-315297	AUGUUGGACUAGGCAUGUUCAG	3433	1612-1634
AD-159808	A-315488	AUCAGUAGUGUACAUUACCAU	3248	1729-1749	A-315489	AUGGUAAUGUACACUACUGAUU	3434	1727-1749
AD-159862	A-315596	AUCCAAGUGUUUAUACCAACUA	3249	1790-1810	A-315597	UAGUUGGUUAUAAACAUUGGAUAG	3435	1788-1810
AD-158503	A-312879	CCAAGUCCAUAUUGGCAACUA	3250	262-282	A-312880	UAGUUGCCAUUAUUGGACUUGGAA	3436	260-282
AD-159311	A-314494	AUCUCAGACCUUGUGAAGGUA	3251	1170-1190	A-314495	UACCUUCACAAGGUCUGAGAUUC	3437	1168-1190
AD-159412	A-314696	CAUUUCACUGUCUAGGCUACA	3252	1290-1310	A-314697	UGUAGCCUAGACAGUGAAAAUGAU	3438	1288-1310
AD-159558	A-314988	CCACAGCUUAUUCUUGAUGCU	3253	1440-1460	A-314989	AGCAUCAGGAUAUAGCUGUGGAU	3439	1438-1460
AD-159705	A-315282	CUUCACUGAACAUAGCCUAGUA	3254	1607-1627	A-315283	UACUAGGCAUGUUCAGUGAAGGA	3440	1605-1627
AD-159113	A-314098	GUGGUUGAGAGUGCUUAUGAA	3255	972-992	A-314099	UUCAUAAGCACUCUCAAACCACCU	3441	970-992

AD-159139	A-314150	CAAACTCAAAGGCUACACAUA	3256	998-1018	A-314151	UAUGUGUAGCCUUUGAGUUUGAU	3442	996-1018
AD-159806	A-315484	AUAUCAGUAGUGUACAUUACA	3257	1727-1747	A-315485	UGUAAUGUACACUACUGAUUAG	3443	1725-1747
AD-159853	A-315578	CAACCAACUAUCCAAAGUGUUA	3258	1781-1801	A-315579	UAACACUUGGAUAGUUGGUUGCA	3444	1779-1801
AD-158627	A-313126	UCAUCGAAGACAAAUUGAAGA	3259	430-450	A-313127	UCUUCAAUUUGUCUUCGAGACA	3445	428-450
AD-159182	A-314236	GCAGAUUUGGCAGAGAGUAUA	3260	1041-1061	A-314237	UAUACUCUCUGCCAAAUCUGCUA	3446	1039-1061
AD-159702	A-315276	CUCCUUCACUGAACAUAGCCUA	3261	1604-1624	A-315277	UAGGCAUGUUCAGUGAAGGAGCC	3447	1602-1624
AD-159715	A-315302	CAUGCCUAGUCCAAACAUUUUU	3262	1617-1637	A-315303	AAAAUGUUGGACUAGGCAUGUU	3448	1615-1637
AD-158575	A-313022	UGCCAUCAGUAUCUUAUUGAA	3263	377-397	A-313023	UUCAUUAAAGAUACUGAUGGCACA	3449	375-397
AD-158576	A-313024	GCCAUCAGUAUCUUAUUGAAA	3264	378-398	A-313025	UUUCAUUAAAGAUACUGAUGGCAC	3450	376-398
AD-158684	A-313240	UUAGAACACCAAAAGAUUGUCU	3265	487-507	A-313241	AGACAAUCUUUUGGUGUUCUAAAG	3451	485-507
AD-159410	A-314692	AUCAUUUCACUGUCUAGGCUA	3266	1288-1308	A-314693	UAGCCUAGACAGUGAAAUUGAUU	3452	1286-1308
AD-159416	A-314704	UCACUGUCUAGGCUACAACAA	3267	1294-1314	A-314705	UUUGUAGGCUAGACAGUGAAA	3453	1292-1314
AD-159738	A-315348	GGAUCCAGUGUAUAAAUCCAA	3268	1658-1678	A-315349	UUGGAUUUAACACUGGAUCCCA	3454	1656-1678
AD-159857	A-315586	CAACUAUCCAAAGUGUUUAUCA	3269	1785-1805	A-315587	UGUAUAAACACUUGGAUAGUUGGU	3455	1783-1805
AD-158497	A-312867	UUGGUUCCAAAGUCCAAUAUGA	3270	256-276	A-312868	UCAUAUUGGACUUGGAACCAAAA	3456	254-276
AD-159124	A-314120	UGCUIAUGAGGUGAUCAAACU	3271	983-1003	A-314121	AGUUUGAUCACCCUCAUAAGCACU	3457	981-1003
AD-159140	A-314152	AAACUCAAAAGGCUACACAUA	3272	999-1019	A-314153	UGAUGUGUAGCCUUUUGAGUUUGA	3458	997-1019
AD-159312	A-314496	UCUCAGACCUUGUGAAGGUGA	3273	1171-1191	A-314497	UCACCUUCACAAGGUCUGAGAUU	3459	1169-1191
AD-159552	A-314976	UAAAUAUCCACAGCUUAUUCU	3274	1434-1454	A-314977	AGGAUAUAGCUGUGGAUUUACA	3460	1432-1454
AD-159704	A-315280	CCUUCACUGAACAUAGCCUAGU	3275	1606-1626	A-315281	ACUAGGCAUGUUUCAGUGAAGGAG	3461	1604-1626
AD-159737	A-315346	GGGAUCCAGUGUAUAAAUCCA	3276	1657-1677	A-315347	UGGAUUUAUACACUGGAUCCAG	3462	1655-1677
AD-159869	A-315610	CAUAAACCUUGAACAGUGAA	3277	1818-1838	A-315611	UUCACUGUUCAAAGGUUUUAUUGGG	3463	1816-1838
AD-158570	A-313012	GGCCUGUGCCAUACAGUAUCUU	3278	371-391	A-313013	AAGAUACUGAUGGACACAGGCCAU	3464	369-391
AD-158618	A-313108	UUGUUGAUGUCAUCCGAAGACA	3279	421-441	A-313109	UGUCUCCGAGACAUCAACAAGA	3465	419-441
AD-159788	A-315448	GGAUCUUAUUUUGUGAACUAU	3280	1708-1728	A-315449	AUAGUUCACAAAAUUAAGAUCCUU	3466	1706-1728
AD-159786	A-315444	AAGGAUCUUAUUUUGUGAACU	3281	1706-1726	A-315445	AGUUCACAAAAUUAAGAUCCUUUG	3467	1704-1726

AD-159760	A-315392	AUCAUGUCUUGUGCAUAAUUA	3282	1680-1700	A-315393	UAAUUAUGCACAAGACAUGAUU	3468	1678-1700
AD-159404	A-314680	UGUCAUAUCAUUUCACUGUCU	3283	1282-1302	A-314681	AGACAGUGAAUUAUGAUUGACAUC	3469	1280-1302
AD-159406	A-314684	UCAUAUCAUUUCACUGUCUAA	3284	1284-1304	A-314685	UUAGACAGUGAAUUAUGAUUGACA	3470	1282-1304
AD-158536	A-312944	AUUUAUAAUCUUCUAAAGGAA	3285	297-317	A-312945	UUCCUUUAGAAGAUUAUAAAUCA	3471	295-317
AD-159545	A-314962	UGGUUUGUAAAUAUCCACAGCU	3286	1427-1447	A-314963	AGCUGUGGAUUUUUACAAACCAUU	3472	1425-1447
AD-159574	A-315020	AUGCUGGAUGGUAAUUAUUCUU	3287	1456-1476	A-315021	AAGAUAUAAUACCAUCCAGCAUCA	3473	1454-1476
AD-159802	A-315476	AACUAUAUCAGUAGUGUACAU	3288	1723-1743	A-315477	AUGUACACUACUGAUUAUAGUUA	3474	1721-1743
AD-159518	A-314908	AUCAACUCCUGAAGUUAGAAA	3289	1400-1420	A-314909	UUUCUAAUUUACAGGAGUUGAUGU	3475	1398-1420
AD-159577	A-315026	CUGGAUGGUAAUUAUUCUUGUA	3290	1459-1479	A-315027	UACAAGAUUAAUACCAUCCAGCA	3476	1457-1479
AD-159409	A-314690	UAUCAUUUCACUGUCUAGGCU	3291	1287-1307	A-314691	AGCCUAGACAGUGAAAAUUGAUUG	3477	1285-1307
AD-159551	A-314974	GUAAAAUCCACAGCUAUAUCA	3292	1433-1453	A-314975	UGAUUAAGCUGUGGGAUUUUACAA	3478	1431-1453
AD-159276	A-314424	UCCUUAUGUUGUCCUUGCAUUU	3293	1135-1155	A-314425	AAUUGCAAGGAACACUAAGGAAG	3479	1133-1155
AD-159407	A-314686	CAUAUCAUUUCACUGUCUAGA	3294	1285-1305	A-314687	UCUAGACAGUGAAAAUUGAUUGAC	3480	1283-1305
AD-159515	A-314902	AACAUCAAUCCUGAAGUUAUA	3295	1397-1417	A-314903	UUAAUUCACAGGAGUUGAUUGUUU	3481	1395-1417
AD-159570	A-315012	CCUGAUGCUGGGAUGGUAAUUA	3296	1452-1472	A-315013	UUAAUACCAUCCAGCAUCCAGGAU	3482	1450-1472
AD-159849	A-315570	AAUGCAACCAACUAUCCAAAGU	3297	1777-1797	A-315571	ACUUGGAUAGUUGGUUGCAUUGU	3483	1775-1797
AD-159252	A-314376	UUUACGGAAUAAAGGAUGAUUA	3298	1111-1131	A-314377	UAUCAUCCUUUAUUAUCCGUAAGA	3484	1109-1131
AD-159275	A-314422	UUCUUAGUGUUCUUGCAUUU	3299	1134-1154	A-314423	AAUGCAAGGAACACUAAGGAAGA	3485	1132-1154
AD-159848	A-315568	CA AUGCAACCAACUAUCCAAA	3300	1776-1796	A-315569	UUUGGAUAGUUGGUUGCAUUGUU	3486	1774-1796
AD-159184	A-314240	AGAUUUGGCAGAGAGUAUAAU	3301	1043-1063	A-314241	AUUUAUCUCUCUGCCAAAUUCUGC	3487	1041-1063
AD-159231	A-314334	UUUCCACCAUGAUUAAGGGUA	3302	1090-1110	A-314335	UACCCUUAAUUAUGGUGGAAACU	3488	1088-1110
AD-159607	A-315086	ACUGGUUAGUGUGAAAAUAGUU	3303	1489-1509	A-315087	AACUAAUUCACACUAACCAUUG	3489	1487-1509
AD-158504	A-312881	CAAGUCCAAUUAUGGCAACUCU	3304	263-283	A-312882	AGAGUUGCCAAUUAUUGGACUUGGA	3490	261-283
AD-159233	A-314338	UCCACCAUGAUUAAGGGUCUU	3305	1092-1112	A-314339	AAGACCCUUAAUUAUGGUGGAAA	3491	1090-1112
AD-159411	A-314694	UCAUUUCACUGUCUAGGCUAA	3306	1289-1309	A-314695	UUAGCCUAGACAGUGAAAAUUGAU	3492	1287-1309
AD-159462	A-314796	UGUCCUUUUUAUUCUGAUCUGU	3307	1340-1360	A-314797	ACAGAUCAGAUAAAAAGGACAAC	3493	1338-1360

AD-159742	A-315356	CCAGUGUAUAAAUCCAUAUA	3308	1662-1682	A-315357	UAUAUUGGAUUUAUACACUGGAU	3494	1660-1682
AD-159863	A-315598	UCCAAAGUGUAUAUACCAACUAA	3309	1791-1811	A-315599	UUAGUUGGUUAUAACACUUGGAUA	3495	1789-1811
AD-159867	A-313246	GAACACCAAGAUUGUCUCUA	3310	490-510	A-313247	UAGAGACAUCUUUUGGUGUUCUA	3496	488-510
AD-158688	A-313248	AACACCAAGAUUGUCUCUGA	3311	491-511	A-313249	UCAGAGACAAUCUUUUGGUGUUCU	3497	489-511
AD-159458	A-314788	AUGUUGUCCUUUUUAUCUGAU	3312	1336-1356	A-314789	AUCAGAUAAAAGGACAACAUGC	3498	1334-1356
AD-159519	A-314910	UCAACUCCUGAAGUUAAGAAU	3313	1401-1421	A-314911	AUUUCUAAACUUCAGGAGUUGAUG	3499	1399-1421
AD-159858	A-315588	AACUAUCCAAGUGUUAUACCA	3314	1786-1806	A-315589	UGGUUAACACUUGGAUAGUUGG	3500	1784-1806
AD-159583	A-315038	GGUAUUAAUCUUGUGUAGUCU	3315	1465-1485	A-315039	AGACUACACAAGAUUAAUACCAU	3501	1463-1485
AD-159700	A-315272	GGUCCUUUCACUGAACAUACA	3316	1602-1622	A-315273	UGCAUGUUCAGUGAAGGAGCCAG	3502	1600-1622
AD-159807	A-315486	UAUCAGUAGUGUACAUAUACCA	3317	1728-1748	A-315487	UGGUAAGUACACUACUGAUUAUA	3503	1726-1748
AD-158673	A-313218	CAGCCUUUUCCUUAGAACAACA	3318	476-496	A-313219	UGUGUUCUAAAGGAAAAGGCUGCC	3504	474-496
AD-159608	A-315088	CUGGUUAGUGUGAAAUAGUUA	3319	1490-1510	A-315089	UAACUAAUUCACACUAAACCAGUU	3505	1488-1510
AD-159803	A-315478	ACUAUAUCAGUAGUGUACAUU	3320	1724-1744	A-315479	AAUGUACACUACUGAUUAUAGUUC	3506	1722-1744
AD-159805	A-315482	UAUAUCAGUAGUGUACAUAUA	3321	1726-1746	A-315483	UUAAUGUACACUACUGAUUAUAGU	3507	1724-1746
AD-159489	A-314850	GUAAUAUUUAAGAUGGACUA	3322	1371-1391	A-314851	UAGUCCAUUCUAAAAUAAUACUG	3508	1369-1391
AD-159495	A-314862	UUUUAAGAUGGACUGGGGAAA	3323	1377-1397	A-314863	UUUCCCAGUCCAUUCUAAAAUA	3509	1375-1397
AD-159706	A-315284	UUCACUGAACAUUGCCUAGUCA	3324	1608-1628	A-315285	UGACUAGGCAUGUUCAGUGAAGG	3510	1606-1628
AD-159855	A-315582	ACCAACUAUCCAAGUGUUAUA	3325	1783-1803	A-315583	UAUAACACUUGGAUAGUUGGUUG	3511	1781-1803
AD-159864	A-315600	CCAAGUGUUAUACCAACUAAA	3326	1792-1812	A-315601	UUUAGUUGGUUAUACACUUGGAU	3512	1790-1812
AD-159488	A-314848	AGUAUAUUUUUAAGAUGGACU	3327	1370-1390	A-314849	AGUCCAUUUAAAAUAAUACUGC	3513	1368-1390
AD-159553	A-314978	AAAUCCACAGCUUAUAUCCUA	3328	1435-1455	A-314979	UAGGAUAUAGCUGUGGAUUUUAC	3514	1433-1455
AD-159703	A-315278	UCCUUCACUGAACAUUGCCUAA	3329	1605-1625	A-315279	UUAGGCAUGUUCAGUGAAGGAGC	3515	1603-1625
AD-159708	A-315288	CACUGAACAUUGCCUAGUCCAA	3330	1610-1630	A-315289	UUGGACUAGGCAUGUUCAGUGAA	3516	1608-1630
AD-159866	A-315604	AAGUGUUAUACCAACUAAAAAC	3331	1794-1814	A-315605	GUUUUAGUUGGUUAUAACACUUGG	3517	1792-1814
AD-159232	A-314336	UUCCACCAUGAUUAAGGGUCU	3332	1091-1111	A-314337	AGACCCUUAUUAUUGGUGGAAAC	3518	1089-1111
AD-159712	A-315296	GAACAUGCCUAGUCCAACAUU	3333	1614-1634	A-315297	AAUGUUGGACUAGGCAUGUUCAG	3519	1612-1634

AD-159808	A-315488	AUCAGUAGUGUACAUUACCAU	3334	1729-1749	A-315489	AUGGUAUUGUACACUACUGAUU	3520	1727-1749
AD-159862	A-315596	AUCCAAGUGUUAUACCAACUA	3335	1790-1810	A-315597	UAGUUGGUUAUAACACUUGGAUAG	3521	1788-1810
AD-159503	A-312879	CCAAGUCCAUAUUGGCAACUA	3336	262-282	A-312880	UAGUUGCCAUUAUUGGACUUGGAA	3522	260-282
AD-159412	A-314696	CAUUCACUGUCUAGGCUACA	3337	1290-1310	A-314697	UGUAGCCUAGACAGUGAAUAGAU	3523	1288-1310
AD-159558	A-314988	CCACAGCUUAUCCUGAUUCU	3338	1440-1460	A-314989	AGCAUCAGGAUUAUAGCUGUGGAU	3524	1438-1460
AD-159705	A-315282	CUUCACUGAACAUAGCCUAGUA	3339	1607-1627	A-315283	UACUAGGCAUGUUCAGUGAAGGA	3525	1605-1627
AD-159113	A-314098	GUGGUUGAGAGUGCUUAUGAA	3340	972-992	A-314099	UUCAUAAGCACUCUCAACCAACCU	3526	970-992
AD-159806	A-315484	AUAUCAGUAGUGUACAUAACA	3341	1727-1747	A-315485	UGUAUUGUACACUACUGAUUAAG	3527	1725-1747
AD-159853	A-315578	CAACCAACUAUCCAAGUGUUA	3342	1781-1801	A-315579	UAACACUUGGAUAGUUGGUUGCA	3528	1779-1801
AD-159182	A-314236	GCAGAUUUUGGACAGAGAGUAUA	3343	1041-1061	A-314237	UAUACUCUCUGGCCAAAUCUGCUA	3529	1039-1061
AD-159702	A-315276	CUCCUUCACUGAACAUAGCCUA	3344	1604-1624	A-315277	UAGGCAUGUUCAGUGAAGGAGCC	3530	1602-1624
AD-159715	A-315302	CAUGCCUAGUCCAACAUAUUUU	3345	1617-1637	A-315303	AAAAUUGUUGGACUAGGCAUGUU	3531	1615-1637
AD-158575	A-313022	UGCCAUCAGUAUCUUAUUGAA	3346	377-397	A-313023	UUCAUUAAGAUACUGAUGGCACA	3532	375-397
AD-158576	A-313024	GCCAUCAGUAUCUUAUUGAAA	3347	378-398	A-313025	UUUCAUUAAGAUACUGAUGGCAC	3533	376-398
AD-158684	A-313240	UUAGAACACCAAAAGAUUGUCU	3348	487-507	A-313241	AGACAAUCUUUGGUGUUCUUAAGG	3534	485-507
AD-159410	A-314692	AUCAUUUCACUGUCUAGGCUA	3349	1288-1308	A-314693	UAGCCUAGACAGUGAAUAGAUUAU	3535	1286-1308
AD-159416	A-314704	UCACUGUCUAGGCUACAACAA	3350	1294-1314	A-314705	UUUUGUAGCCUAGACAGUGAAA	3536	1292-1314
AD-159857	A-315586	CAACUAUCCAAGUGUUUAUACA	3351	1785-1805	A-315587	UGUAUAACACUUGGAUAGUUGGU	3537	1783-1805
AD-158497	A-312867	UUGGUUCCAAGUCCAUAUUGA	3352	256-276	A-312868	UCAUAUUGGACUUGGAACCAAAA	3538	254-276
AD-159124	A-314120	UGCUIAUGAGGUGAUCAAAACU	3353	983-1003	A-314121	AGUUUGAUCACCUCAUAAGCACU	3539	981-1003
AD-159312	A-314496	UCUCAGACCUUGUGAAGGUGA	3354	1171-1191	A-314497	UCACCUUACAAAGGUUGAGAUU	3540	1169-1191
AD-159552	A-314976	UAAAUCCACAGCUUAUUCU	3355	1434-1454	A-314977	AGGAUAUAGCUGUGGAUUUUAACA	3541	1432-1454
AD-159704	A-315280	CCUUCACUGAACAUAGCCUAGU	3356	1606-1626	A-315281	ACUAGGCAUGUUUACAGUGAAGGAG	3542	1604-1626
AD-159737	A-315346	GGGAUCCAGUGUAUAAAUCCA	3357	1657-1677	A-315347	UGGAUUUAUACACUGGAUCCCCAG	3543	1655-1677
AD-159869	A-315610	CAUAUAAACCUUGAACACAGUGAA	3358	1818-1838	A-315611	UUCACUGUUAACAGGUUAUUGGG	3544	1816-1838
AD-158570	A-313012	GGCCUGUGCCAUCAGUAUCUU	3359	371-391	A-313013	AAGAUACUGAUGGCACACAGGCCAU	3545	369-391

AD-158618	A-313108	UUGUUGAUGUCAUCGAAGACA	3360	421-441	A-313109	UGUCUUCGAUGACAUCAACAAGA	3546	419-441
AD-159184	A-314240	AGAUUUUGGCAGAGAGUAUAU	3361	1043-1063	A-314241	AUUUAUCUCUCUGCCAAAUCUGC	3547	1041-1063
AD-159231	A-314334	UUUCCACCAUGAUUAAGGGUA	3362	1090-1110	A-314335	UACCCUUAAUCAUGGUGGAAACU	3548	1088-1110
AD-159423	A-314718	CUAGGCUACAACAGGAUUCUA	3363	1301-1321	A-314719	UAGAAUCCUGUUGUAGCCUAGAC	3549	1299-1321
AD-159446	A-314764	UGGAGGUUGUGCAUGUUGUCA	3364	1324-1344	A-314765	UGACAACAUGCACAAACUCCACC	3550	1322-1344
AD-159701	A-315274	GCUCUUUCACUGAACAUUGCCU	3365	1603-1623	A-315275	AGGCAUGUUCAGUGAAGGAGCCA	3551	1601-1623
AD-158494	A-312861	CUUUUGGUUCCAAAGUCCAAUA	3366	253-273	A-312862	UAUUGGACUUGGAAACCAAAAGGA	3552	251-273
AD-158571	A-313014	GCCUGUGCCAUACAGUAUCUUA	3367	372-392	A-313015	UAAGAUACUGAUGGCACAGGCCA	3553	370-392
AD-159125	A-314122	GCUUAUGAGGUGAUCAAACUA	3368	984-1004	A-314123	UAGUUUGAUCACCUCAUAAGCAC	3554	982-1004
AD-159126	A-314124	CUUAUGAGGUGAUCAAACUCA	3369	985-1005	A-314125	UGAGUUUGAUCACCUCAUAAGCA	3555	983-1005
AD-159287	A-314446	CCUUGCAUUUUUGGGACAGAAU	3370	1146-1166	A-314447	AUUCUGUCCCCAAAUGCAAAGGAA	3556	1144-1166
AD-158499	A-312871	GGUUCCAAAGUCCAAUAUGGCA	3371	258-278	A-312872	UGCCAUUAUUGGACUUGGAACCAA	3557	256-278
AD-159417	A-314706	CACUGUCUAGGCUACAACAGA	3372	1295-1315	A-314707	UCUGUUGAUGCCUAGACAGUGAA	3558	1293-1315
AD-159418	A-314708	ACUGUCUAGGCUACAACAGGA	3373	1296-1316	A-314709	UCCUGUUGAUGCCUAGACAGUGA	3559	1294-1316
AD-158550	A-312972	AAUAAGAUUACAGUUGUUGGA	3374	333-353	A-312973	UCCAACAACUGUAAUUCUUAUUCU	3560	331-353
AD-159116	A-314104	GUUGAGAGUGCUUAUGAGGUA	3375	975-995	A-314105	UACCUCAUAAGCACUCUCAACCA	3561	973-995
AD-159421	A-314714	GUUCAGGCUACAACAGGAUUA	3376	1299-1319	A-314715	UAUUCUUGUUGAUGCCUAGACAG	3562	1297-1319
AD-159422	A-314716	UCUAGGCUACAACAGGAUUCU	3377	1300-1320	A-314717	AGAAUCCUGUUGUAGCCUAGACA	3563	1298-1320
AD-159445	A-314762	GUGGAGGUUGUGCAUGUUGUA	3378	1323-1343	A-314763	UACAACAUGCACAAACCUCCACCU	3564	1321-1343
AD-159130	A-314132	UGAGGUGAUCAAACUCAAGA	3379	989-1009	A-314133	UCUUUGAGUUUGAUCACCUCAUA	3565	987-1009
AD-159134	A-314140	GUGAUCAAACUCAAGGCUA	3380	993-1013	A-314141	UUAGCCUUUGAGUUUGAUCACCU	3566	991-1013
AD-159343	A-314558	UGAGGAAGAGGCCCGUUUGAA	3381	1202-1222	A-314559	UUCAAACGGGGCCUUCUCCUCAGA	3567	1200-1222
AD-159105	A-314082	ACAAGCAGGUGGUUGAGAGUA	3382	964-984	A-314083	UACUCUCAACCAACCUUGUUGA	3568	962-984
AD-159183	A-314238	CAGAUUUUGGCAGAGAGUAUA	3383	1042-1062	A-314239	UUUAUCUCUCUGGCCAAAUCUGCU	3569	1040-1062
AD-159123	A-314118	GUGCUUAUGAGGUGAUCAAAC	3384	982-1002	A-314119	GUUUGAUCACCUCAUAAGCACUC	3570	980-1002
AD-159181	A-314234	AGCAGAUUUUGGCAGAGAGUAU	3385	1040-1060	A-314235	AUACUCUCUGGCCAAAUCUGCUAC	3571	1038-1060

AD-159186	A-314244	AUUUGGCAGAGAGUAUAAUGA	3386	1045-1065	A-314245	UCAUUUAUCUCUCUGCCAAAUCU	3572	1043-1065
AD-159187	A-314246	UUUGGCAGAGAGUAUAAUGAA	3387	1046-1066	A-314247	UUCAUUUAUCUCUCUGCCAAAUC	3573	1044-1066
AD-159288	A-314448	CUUGCAUUUUGGGACAGAAUA	3388	1147-1167	A-314449	UAUUCUGUCCCAAAAUGCAAGGA	3574	1145-1167
AD-159306	A-314484	AUGGAAUCUCAGACCUUGUGA	3389	1165-1185	A-314485	UCACAAGGUCUGAGAUUCCAUUC	3575	1163-1185
AD-159559	A-314990	CACAGCUUAUCCUGAUGCUA	3390	1441-1461	A-314991	UAGCAUCAGGAUAUAGCUGUGGA	3576	1439-1461
AD-159344	A-314560	GAGGAAGAGGCCCGUUUGAAA	3391	1203-1223	A-314561	UUUCAAAACGGGCCUCUCCUCAG	3577	1201-1223
AD-159341	A-314554	UCUGAGGAAGAGGCCCGUUUA	3392	1200-1220	A-314555	UAAACGGGCCUCUCCUCAGGAAG	3578	1198-1220
AD-159729	A-315330	CACAUCUGGGAUCCAGUGUA	3393	1649-1669	A-315331	UACACUGGAUCCACAGGAUGGAC	3579	1647-1669
AD-158674	A-313220	AGCCUUUUCCUUAGAACACCA	3394	477-497	A-313221	UGGUGUUCUAAGGAAAAGGCUGC	3580	475-497
AD-159604	A-315080	UCAACUGGUUAUGUGUGAAAUA	3395	1486-1506	A-315081	UAUUUCACACUAACCAAGUUUGAAG	3581	1484-1506

TABLE 5. MODIFIED HUMAN/CYNOMOLGUS CROSS-REACTIVE LDHA mRNA 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	usuuuacUfgAfUfCfugauuuuL96	3582	usUfsuuUfcAfCfagauCfaGfauaasasa	3768	UUUUUAUCUGAUCUGUGAUUAAA	3954
AD-159607	asesugnuUfaGfUfGfugaaauuL96	3583	asAfsenuUfuUfCfacaUfaAfcaguuug	3769	CAACUGGUUAAGUGUGAAAUAGUU	3955
AD-159713	asascaugCfcUfAfGfuccaauuuL96	3584	asAfsauUfuGfGfacaUfgCfanguuusa	3770	UGAACAUCCUAGUCCAAACAUUU	3956
AD-158504	csasagucCfaAfUfAfugcaacuL96	3585	asGfsagUfgCfCfaauUfgGfauuggsa	3771	UCCAAGUCCAAUUGGCAACUCU	3957
AD-159233	uscsaccAfuGfAfUfuaagggucuuL96	3586	asAfsagCfcUfUfauuAfuGfuggasasa	3772	UUUCCACCAUGAUUAAAGGGUCUU	3958
AD-159411	uscsauuuCfaCfUfGfucuaagcuL96	3587	usUfsagCfuAfgfacaUfgAfaugasa	3773	UAUCAUUUCACUGUCUAGGCUAC	3959
AD-159462	usgsuueuUfuUfAfUfuaagucuuL96	3588	asCfsagaUfcAfGfauuaAfaAfggacasc	3774	GUUGUCCUUUUUAUCUGAUCUGU	3960
AD-159742	csesagugUfaUfAfAfaucacauuuL96	3589	usAfsuuUfgGfAfuuaUfaCfaeuuggsa	3775	AUCCAGUGUAUAAUCCAAUAUC	3961
AD-159863	uscsaagUfgUfUfAfuaaccacuL96	3590	usUfsagUfgGfUfauuaCfaCfanguusa	3776	UAUCCAAGUGUUAUACCAACUAA	3962
AD-158626	gsuscaucGfaAfGfAfcaaaauuL96	3591	usUfsucaAfuUfUfueuUfcGfauagcsa	3777	AUGUCAUCGAAAGACAAAUUGAAG	3963
AD-158687	gsasacacCfaAfAfGfauugucuaL96	3592	usAfsaggAfcAfAfuuuUfgGfugnuusa	3778	UAGAACACCAAAAGAUUGUCUCUG	3964

AD-158688	asascaccAfaAfgfAfiugucucgaL96	3593	usCfsagaGfaCfaAfaucUfuGfgugunscsu	3779	AGAAACACCAAAAGAUUGUCUCUGG	3965
AD-159458	asusguugUfcCfuUfuuuuucugauL96	3594	asUfscagAfuAfaAfaagGfaCfaacausgc	3780	GCAUGUUGUCCUUUUUUAUCUGAU	3966
AD-159519	uscsaacuCfcUfgfAfauguagaauL96	3595	asUfsuucUfaAfcfuaaGfgAfguugasug	3781	CAUCAACUCCUGAAGUUAAGAAAU	3967
AD-159858	asascuauCfcAfaGfguguaauacalL96	3596	usGfsquaUfaAfcfaucUfgAfuaguusgsg	3782	CCAACUAUCCAAGUGUUAUACCA	3968
AD-158681	uscsuuaGfaAfcAfcfaaauuualL96	3597	usAfsaucUfuUfgfgugUfcUfaaggasasa	3783	UUUCCUUAGAACACCAAGAUUG	3969
AD-159583	gsuauuAfaUfcUfuuguguguculL96	3598	asGfsacuAfcAfcfaaGfuAfaauccsasu	3784	AUGGUUUUAUCUUUGUGUAGUCU	3970
AD-159700	gsuscuccUfuCfaCfugacacugcalL96	3599	usGfscuGfuUfcfagUfaGfgagccsag	3785	CUGGCUCCUUCACUGAACAUCC	3971
AD-159807	usasucagUfaGfuGfuacauuacalL96	3600	usGfsquaAfuGfuUfacUfaCfugaauasasa	3786	UAUAUCAGUAGUGUACAUAACCA	3972
AD-158673	csasgccuUfuUfcCfCfuagaacacalL96	3601	usGfsuugUfcUfaAfaagAfaAfggcugscsc	3787	GGCAGCCUUUUCCUUAGAACACC	3973
AD-159608	csusgguuAfgUfgUfgaauuauualL96	3602	usAfsacuAfuUfuUfcacaCfuAfacagssu	3788	AACUGGUUAGUGUGAAAUAUUUC	3974
AD-159803	ascsuauUfcAfgUfagugacauL96	3603	asAfsuagAfcAfcfuacUfuAfaugususc	3789	GAACUAUAUCAGUAGUGUACAUAU	3975
AD-159805	usasuaucAfgUfaGfguacauuualL96	3604	usUfsaauGfuAfcfaaCfuGfaauuasgsu	3790	ACUAUAUCAGUAGUGUACAUAUAC	3976
AD-159489	gsusaauUfuUfuAfaagugaculL96	3605	usAfsuucCfaUfcfuuaaAfaUfauuacsug	3791	CAGUAUAUUUAAGAUGGACUG	3977
AD-159495	usuuuaaGfaUfgGfgacugggaaalL96	3606	usUfsuucCfcAfgGfucaUfcUfuuaasasa	3792	UAUUUAAGAUGGACUGGGAAAA	3978
AD-159609	usgsuuaGfuGfuUfgfaauuuguculL96	3607	asGfsaacUfaUfuUfuacAfcUfaaccasgsu	3793	ACUGGUUAGUGUGAAUAUAGUUCU	3979
AD-159706	ususcacuGfaAfcAfcfagccuagucalL96	3608	usGfsacuAfgGfcfaugUfcAfgugaasgsg	3794	CCUUCACUGAACAUAGCCUAGUCC	3980
AD-159855	ascsaacUfaUfcCfCfaaguguaualL96	3609	usAfsuaaCfaCfuUfggaUfaGfuugugusug	3795	CAACCAACUAUCCAAGUGUUAUA	3981
AD-159864	csasaaguGfuUfuAfufaceacuuaalL96	3610	usUfsuagUfuGfgfuuaAfcAfcuuggsasu	3796	AUCCAAGUGUUAUACCAACUAAA	3982
AD-158491	ususcuuUfuGfgUfufaceagucalL96	3611	usGfsagUfuGfgfaacAfaAfaaggaasusc	3797	GAUCCUUUUUGGUUCCAAGUCCA	3983
AD-158672	gsasagccUfuUfuUfcfuuagacacalL96	3612	usUfsuugCfuAfaAfggaAfaGfgcugscsa	3798	UGGCAGCCUUUUCCUUAGAACAC	3984
AD-159488	asgsuaauAfuUfuUfaagugaculL96	3613	asGfsuccAfuCfuUfaaaAfuAfuuaeusgsc	3799	GCAGUAUAUUUAAGAUGGACU	3985
AD-159553	asasaucCfaCfaGfcuaaucculL96	3614	usAfsagaUfaUfaGfcugUfgGfauuuasasc	3800	GUAAAUAUCCAACAGCUAUUCCUG	3986
AD-159703	uscsuucAfcUfgGfafaceugcualL96	3615	usUfsaggCfaUfgfuuaGfuGfaaggsagsc	3801	GCUCCUUCACUGAACAUGCCUAG	3987
AD-159708	csasucgaAfcAfuGfGfcuagucualL96	3616	usUfsagaCfuAfgGfcuGfuUfcagugsasa	3802	UUCACUGAACAUGCCUAGUCCAA	3988
AD-159866	asasugulUfaUfaCfcfaacuuaaalL96	3617	gsUfsuuuAfgUfuUfggaUfaAfcacuugsg	3803	CCAAGUGUUAUCCAACUAAAAC	3989
AD-159232	ususcacCfaUfgfAfuuaagguguculL96	3618	asGfsaccCfuUfaAfaucUfgGfuggaasasc	3804	GUUCCACCAUGAUUAAGGUUCU	3990
AD-159712	gsasacuGfcCfuAfgucacacauL96	3619	asAfsuugUfgGfAfcuagGfcAfuugcsasg	3805	CUGAACAUGCCUAGUCCAACAUU	3991
AD-159808	asuscaguAfgUfgUfacaaucculL96	3620	asUfsgguAfaUfgfuuaCfuAfcuagausasu	3806	AUAUCAGUAGUGUACAUAUACCAU	3992
AD-159862	asusccaaGfuGfuUfauaaccaculL96	3621	usAfsuugGfgUfaAfuacAfcUfuggausasg	3807	CUAUCCAAGUGUUAUACCAACUA	3993
AD-158503	csasaaguCfcAfaUfauggaagcualL96	3622	usAfsuugGfcCfaAfuauGfgAfcuuggsasa	3808	UCCAAGUCCAUAUAGGCAACUC	3994
AD-159311	asuscuaGfaCfcUfuugugagcualL96	3623	usAfsuucUfcAfcfaagUfcUfgagaususc	3809	GAUUCAGACCCUUGUGAAGGUG	3995
AD-159412	csasuucAfcUfgUfuuaaggeuacalL96	3624	usGfsuagCfcUfaAfgacaGfuGfaauugsasu	3810	AUCAUUACACUGUCUAGGCUACA	3996
AD-159558	csasacagCfuAfuAfuuccugaugculL96	3625	asGfscuCfaGfgfaauAfgCfuguggsasu	3811	AUCCACAGCUAUUCCUGAUGCU	3997
AD-159705	csusucacUfgAfcfaugccuagualL96	3626	usAfsuagGfgCfaAfuugCfaGfugaagsasa	3812	UCCUUCACUGAACAUGCCUAGUC	3998
AD-159113	gsusgguuGfaGfaGfgfuuuuaugaaL96	3627	usUfscuAfaGfcfaucUfcAfacaccscsu	3813	AGGUGGUUGAGAGUGUCUUAUGAG	3999

AD-159139	csasaacuCfaAfaGfgcuacauaL96	3628	usAfsuagGfuAfgfcccUfGfaguuugsasu	3814	AUCAAACUCAAGGCUACACAUC	4000
AD-159806	asusauaGfuAfgUfguacauaL96	3629	usGfsuuaUfgUfAfcacuAfcUfgauuasag	3815	CUAUUCAGUAGUGUACAUUACC	4001
AD-159853	csasaccaAfcUfaUfUfccaguguaL96	3630	usAfsacaCfuUfgGfgauaGfuUfguuugscsa	3816	UGCAACCAACUUAUCCAAGUGUUA	4002
AD-158627	uscsaucaGfaGfAfcfaaauagaL96	3631	usCfsuucAfaUfUfugueUfuCfagauascsa	3817	UGUCAUCGAAGACAAAUAUGAAGG	4003
AD-159182	gscsagauUfuGfGfcfagagauaL96	3632	usAfsuacUfcUfcUfguccAfaAfuucgcsusa	3818	UAGCAGAUUUGGCAGAGAGUAUA	4004
AD-159702	csusccuUfaUfUfGfaacugcuL96	3633	usAfsugcAfuGfUfuucagUfgAfgagagcsc	3819	GGCUCCUUCACUGAACAUUGCCUA	4005
AD-159715	csasugccUfaGfUfCfaacuuuuL96	3634	asAfsaaaUfgUfUfggagUfaGfgcaugsusu	3820	AACAUGCCUAGUCCAAACAUUUUU	4006
AD-158575	usgsccauCfaGfUfAfuuaaagaL96	3635	usUfscuUfaAfgfaucUfgAfgugcascsa	3821	UGUGCCAUCAGUAUCUUAUUGAA	4007
AD-158576	gscscaucAfgUfAfuUfuuuaagaL96	3636	usUfscuUfaAfgfaucUfgAfgugcasc	3822	GUGCCAUCAGUAUCUUAUUGAAG	4008
AD-158684	ususagaaCfaCfAfaagauugcuL96	3637	asGfsacaAfuCfuUfuugUfgUfucuaagsg	3823	CCUUAGAACAACCAAGAUUGUCU	4009
AD-159410	asusauuUfcAfcUfUfucuaagcuL96	3638	usAfsuccUfaGfAfcagUfgAfaugausasu	3824	AUAUCAUUUCACUGUCUAGGCUA	4010
AD-159416	uscsaugUfcUfAfgfGfcuacaacL96	3639	usUfsgguGfuAfgfcccUfaCfagugasasa	3825	UUUCACUGUCUAGGCUACAACAG	4011
AD-159738	gsgsaucAfgUfGfUfauaaaucaL96	3640	usUfsggaUfuUfAfuacaCfuGfaucescsa	3826	UGGGAUCCAGUGUAUAAAUCCAA	4012
AD-159857	csasauaUfcCfaAfaGfguuaaL96	3641	usGfsuuaAfaCfaUfcuagGfaUfauugsgsu	3827	ACCAACUAUCCAAGUGUUAUACC	4013
AD-158497	usugguuUfcAfaGfgfuaaauaL96	3642	usCfsauUfuGfGfacuUfgAfaaccaasasa	3828	UUUUGGUUCCAAGUCCAUAUUGG	4014
AD-159124	usgsuuaUfgAfgGfguaaauaL96	3643	asGfsuuUfaUfCfaccUfaUfaagcascsu	3829	AGUGCUUAUGAGGUGAUCAACU	4015
AD-159140	asasauaAfaAfgGfGfuaaauaL96	3644	usGfsaugUfgUfAfgccUfuGfaguuugsa	3830	UCAACUCAAAAGGCUACACAUC	4016
AD-159312	uscsuagAfcCfUfUfguaagguL96	3645	usCfsaccUfuCfaUfcaagGfuCfugagasusu	3831	AAUCUCAGACCUUGUGAAGGUGA	4017
AD-159552	usasaauCfcAfcAfgcuuaucL96	3646	asGfsagUfuAfgfGfugUfgAfuuuuacsasa	3832	UGUAAAUAUCCACAGCUAUAUCCU	4018
AD-159704	csesuuaCfuGfAfaUfauugcuL96	3647	asCfsuagGfcAfuUfguacUfgUfgaagsgsg	3833	CUCCUUCACUGAACAUUGCCUAGU	4019
AD-159737	gsgsaucCfaGfUfGfuaaaucaL96	3648	usGfsagUfuAfuUfaccUfgGfaucescsag	3834	CUGGGAUCCAGUGUAUAAAUCCA	4020
AD-159869	csasauaaAfcCfUfUfgaagugaaL96	3649	usUfscacUfgUfUfcaagGfuUfuaugsgsg	3835	CCCAAUAAACCUUGAACAGUGAC	4021
AD-158570	gsgsccuUfgCfCfaUfcaugauuL96	3650	asAfsagUfUfGfagugCfaCfaguccesasu	3836	AUGGCCUGUGCCAUCAAGUAUCUU	4022
AD-158618	usugguuAfuGfUfCfaugagaaL96	3651	usGfsuucUfcGfAfuagCfuCfaacaasasa	3837	UCUUGUUAUGUUAUUGUAGAACACA	4023
AD-159788	gsgsaucUfaUfUfUfuguaaauL96	3652	asUfsgauUfcAfcfaaaUfaAfgaucccsusu	3838	AAGGAUCUUUUUUUGUAGAACUAU	4024
AD-159786	asasgguCfuUfAfuUfuuugaaL96	3653	asGfsuucAfcAfaaauAfgAfuuccuussug	3839	CAAAGGAUCUUUUUUUGUAGAACU	4025
AD-159760	asuscaugUfcUfUfGfugcauaaL96	3654	usAfsauUfuGfCfacaGfaCfagauasasu	3840	AUAUCAUGUCUUGUGCAUAUUC	4026
AD-159404	usgsuauAfuCfaUfUfuaucugcuL96	3655	asGfsacaGfuGfAfaagAfuAfuagacauuc	3841	GAUGUCAUAUCAUUUCACUGUCU	4027
AD-159406	uscsauuUfaUfUfUfcaugcuL96	3656	usUfsgaCfaGfUfGfaaaUfgAfuauagcsa	3842	UGUCAUAUCAUUUCACUGUCUAG	4028
AD-158536	asusuuuAfaUfCfUfuaaagaaL96	3657	usUfscuUfuAfgfaagUfuAfuuaaacsasa	3843	UGAUUUAUAUCUUCUAAAAGGAA	4029
AD-159545	usgsuuuGfuAfaUfAfaucacagcuL96	3658	asGfscuUfgGfAfuuuAfcAfaaccasusu	3844	AAUGGUUUGUAAAUAUCCACAGCU	4030
AD-159574	asusguuGfaUfGfGfuuaaauuL96	3659	asAfsagUfaUfUfaccUfcCfagcausasa	3845	UGAUGCUGGAUGGUUAUUAUUCU	4031
AD-159802	asascuauAfuCfaUfGfuauguaL96	3660	asUfsguaCfaCfUfagUfAfuAfuaguuacsasa	3846	UGAACUAUAUCAGUAGUGUAUACU	4032
AD-159518	asuscaucUfcCfUfGfaguuagaL96	3661	usUfscuAfaCfUfucagGfaGfuaugsgsu	3847	ACAUCACUCCUUGAAGUUAAGAA	4033
AD-159577	csusggaUGfgUfAfuUfaaauuL96	3662	usAfscaaGfaUfUfaaauCfcAfucaagcsa	3848	UGCUGGAUGGUUAUUAUUCUUGUG	4034

AD-159409	usasauUfuCfAfCfugucuaagcuL96	3663	asGfscuAfgAfCfagugAfaAfugauasug	3849	CAUAUCAUUUCACUGUCUAGGCU	4035
AD-159551	gsusaaaaUfcCfAfCfagcuauaualL96	3664	usGfsauUfaGfCfugugGfaUfuuaacsasa	3850	UUGUAAAAUCCACACAGCUAUAUCC	4036
AD-159276	uscsuuaGfuGfUfuccuagcuuL96	3665	asAfsaugCfaAfGfagacAfcUfaaggasag	3851	CUUCCUAGUGUUCUUGCAUUU	4037
AD-159407	csasuuaCfuUfUfCfagucuaualL96	3666	usCfsuagAfcAfGfugaaAfuGfaugasac	3852	GUCAUAUCAUUUCACUGUCUAGG	4038
AD-159515	asascauAfaCfUfCfugaaguuuL96	3667	usUfsaacUfuCfAfaggagUfuGfauguuusu	3853	AAAACAUAACUCCUGAAGUUAG	4039
AD-159570	csesugauGfcUfGfGfauguuuL96	3668	usUfsauAfcCfAfuccaGfcAfucaggsau	3854	AUCCUGAUGCUGGAUGGUUUAA	4040
AD-159849	asasugcaAfcCfAfAfcuaucuaualL96	3669	asCfsuugGfaUfAfugugGfuUfcauugsu	3855	ACAUGCAACCAACUAUCCAAAGU	4041
AD-159252	usuuuagGfaUfUfAfaagauualL96	3670	usAfsuaUfcCfUfuuaUfCfCfuaaasga	3856	UCUUACGGAUAUAAGGAUGAUG	4042
AD-159275	ususcuuAfgUfGfUfuccuagcuL96	3671	asAfsugCfaGfGfaacaCfuAfaggaasga	3857	UCUUCCUAGUGUUCUUGCAUU	4043
AD-159848	csasugcAfaCfCfAfacuaucaualL96	3672	usUfsugAfuAfGfugugUfuGfcauugsu	3858	AACAUGCAACCAACUAUCCAAAG	4044
AD-159184	agsauuuGfgCfAfGfagauuaualL96	3673	asUfsuauAfcUfCfucugCfcAfaucugsc	3859	GCAGAUUUGGCAGAGAGUAUAAU	4045
AD-159231	usuuucaCfcAfUfGfauuagguuL96	3674	usAfscccUfuAfAfucuaUfGfUfgaaascsu	3860	AGUUCCACCAUGAUUAAGGGUC	4046
AD-159607	ascsuguuUfaGfUfGfugaauuL96	3675	asAfsuaUfuUfCfCfaacUfaAfccagugusg	3861	CAACUGGUUAGUGUGAAAUAGUU	4047
AD-158504	csasugcCfaAfUfAfuggaacucL96	3676	asGfsaguUfgCfCfaauUfGfcauugsgsa	3862	UCCAAGUCCAUAUUGGCAACUCU	4048
AD-159233	uscsaccAfuGfAfUfuaagguuL96	3677	asAfsagCfcUfUfuaucAfuGfuggasasa	3863	UUUCCACCAUGAUUAAGGGUCUU	4049
AD-159411	uscsauuuCfaCfUfGfucuaagcuuL96	3678	usUfsagCfcUfGfCfaacUfGfAfaugasusa	3864	UAUCAUUUCACUGUCUAGGCUAC	4050
AD-159462	usgsuucUfuUfUfAfucugauuL96	3679	asCfsagaUfcAfGfauaaAfaAfggacacsc	3865	GUUGUCCUUUUUAUCUGAUCUGU	4051
AD-159742	csesagugUfaUfAfaucuaualL96	3680	usAfsuauUfgGfAfuaaUfaCfaguggsasu	3866	AUCCAGUGUAUAUAUCCAAUAUC	4052
AD-159863	uscsaagUfgUfUfAfaucuaualL96	3681	usUfsaguUfgGfUfaaaCfaCfuggasusa	3867	UAUCCAGUGUUUAUACCAACUAA	4053
AD-158687	gsasacCfaAfAfGfaugucuaualL96	3682	usAfsagAfcAfAfucuuUfgGfuguuususa	3868	UAGAACACCAAGAUAUGUCUCUG	4054
AD-158688	asascacAfaAfGfAfugucucuaualL96	3683	usCfsagaGfaCfAfaucUfuGfuguuuscsu	3869	AGAACACCAAGAUAUGUCUCUGG	4055
AD-159458	asusguugUfcCfUfUfuaucuaualL96	3684	asUfscagAfuAfAfaagGfaCfaeacugsc	3870	GCAUGUUGUCCUUUUUAUCUGAU	4056
AD-159519	uscsaacUfcUfGfAfaguuagaaualL96	3685	asUfsuucUfaAfCfuaCfGfAfugugasug	3871	CAUCAACUCCUGAAGUUAGAAAU	4057
AD-159858	asascuacCfcAfAfGfuguuuacuaL96	3686	usGfsguaUfaAfCfauuGfGfAfaugugsg	3872	CCAACUAUCCAAGUGUUUAUACCA	4058
AD-159583	gsgsuauAfaUfCfUfuguguaucuaL96	3687	asGfsacuAfcAfCfagaUfuAfaucacsasu	3873	AUGGUUUUAUCUUUGUGUAGUCU	4059
AD-159700	gsgsuucUfuCfAfCfugaacuaualL96	3688	usGfscuGfuUfCfagugAfaGfagacscasg	3874	CUGGUCCUUCACUGAACAUGCC	4060
AD-159807	usasucugUfaGfUfGfuaacuaualL96	3689	usGfsguaAfuGfUfCfagUfaCfugaasusa	3875	UAUAUCAGUAGUGUACAUAACCA	4061
AD-158673	csasgcuUfuUfCfCfuaagaaacuaL96	3690	usGfsuugUfcUfAfaggaAfaAfggucgscsc	3876	GGCAGCCUUUUCCUUAGAACACC	4062
AD-159608	csusgguuAfgUfGfUfgaauuaguuL96	3691	usAfsacuAfuUfUfCfacaCfuAfaceagssu	3877	AACUGGUUAGUGUGAAAUAAGUUC	4063
AD-159803	ascsuauUfcAfGfUfaguuacuaualL96	3692	asAfsuugAfcAfCfuaCfuAfaugususc	3878	GAACUAUAUCAGUAGUGUACAUAU	4064
AD-159805	usasuaucAfgUfAfGfuguaacuaualL96	3693	usUfsauGfuAfcCfuaCfuGfaauuasgsu	3879	ACUAUAUCAGUAGUGUACAUAUAC	4065
AD-159489	gsusauuaUfuUfUfAfaagugacuaL96	3694	usAfsugCfaUfCfuaaAfaUfauaacsug	3880	CAGUAUAUUUUUAAGAUGGACUG	4066
AD-159495	usuuuuaGfaUfGfGfaguggaauL96	3695	usUfsuucCfcAfGfuaCfuUfuaaasusa	3881	UAUUUAAGAUGGACUGGGAAAA	4067
AD-159706	ususcacuGfaAfCfAfugcuagucuaL96	3696	usGfsacuAfgGfCfauuUfCfAfgugaasgs	3882	CCUUCACUGAACAUUGCCUAGUCC	4068
AD-159855	ascsaacUfaUfCfCfaguuuuaualL96	3697	usAfsuaaCfaCfUfuggaUfaGfugugusug	3883	CAACCAACUAUCCAAAGUGUUAUA	4069

AD-159864	csasaaguGfuUfAfUfaccacuaaalL96	3698	usUfsuagUfuGfGfuuaaAfcAfcuuggsasu	3884	AUCCAAAGUGUUUAUACCAACUAAA	4070
AD-159488	asgsuaauAfuUfUfUfaagugacuL96	3699	asGfsuccAfuCfuUfuuaaAfuAfuuaugsc	3885	GCAGUAAUUAUUUAAGAUUGACU	4071
AD-159553	asasaucCfaCfAfGfauuaucuaL96	3700	usAfsaggUfaUfAfGfcugUfgGfaunuasac	3886	GUAAAUAUCCACAGCUAAUCCUG	4072
AD-159703	uscsuucAfcUfGfAfaccuagcuL96	3701	usUfsaggCfaUfGfuaaCfuGfaaggsac	3887	GCUCUUCACUGAACAUGCCUAG	4073
AD-159708	csasagaaAfcAfUfGfaccuagcuL96	3702	usUfsaggCfuAfcGfcauGfuUfcauggsasa	3888	UUCACUGAAACAUGCCUAGUCCAA	4074
AD-159866	asasguuUfaUfAfCfcauaaaL96	3703	gsUfsuuUfGfUfUfguaUfaAfcacuugsg	3889	CCAAUGUUUAUACCAACUAAAAC	4075
AD-159232	usuccacCfaUfGfAfuaagguL96	3704	asGfsaccCfuUfaAfaucUfgGfuggaasac	3890	GUUCCACCAUGAUUAAGGUCU	4076
AD-159712	gsasacauGfcCfuUfGfuaaauL96	3705	asAfsuUfGfAfcuagGfcAfuucsaag	3891	CUGAAACAUGCCUAGUCCACAUU	4077
AD-159808	asuscauAfgUfGfUfaauuacuaL96	3706	asUfsguUfGfUfGfuacaCfuAfcuagasa	3892	AUAUCAGUAGUGUACAUAUACCAU	4078
AD-159862	asuscauAfgUfGfUfaauuacuaL96	3707	usAfsuUfGfUfAfuacAfcUfuggaasag	3893	CUAUCCAAGUGUUUAUACCAACUA	4079
AD-158503	csasaaguCfcAfAfUfauugcauaL96	3708	usAfsuUfGfcCfAfuaUfGfAfcuuggsasa	3894	UCCAAGUCCAUAUUGGCAACUC	4080
AD-159412	csasuucAfcUfGfUfcaugcuL96	3709	usGfsuagCfcUfAfgacaGfuGfaaugsasu	3895	AUCAUUUCACUGUCUAGGCUACA	4081
AD-159558	csasacagCfuAfuUfAfuuccuagcuL96	3710	asGfscauCfaGfGfauaUfGfuggsasu	3896	AUCCACAGCUAAUUCUUGAUGCU	4082
AD-159705	csuscauUfgAfcUfcaugcuagcuL96	3711	usAfscauGfcCfAfuguuCfaGfugaagsa	3897	UCCUUCACUGAACAUGCCUAGUC	4083
AD-159113	gsusguuGfaGfAfGfugcuuagcuL96	3712	usUfscuAfaGfCfacuUfcAfcacacsu	3898	AGGUGGUUGAGAGUGCUUAUGAG	4084
AD-159806	asusaacaGfuAfgUfugcuuacuaL96	3713	usGfsuaUfGfUfAfcacuAfcUfgaauasag	3899	CUAAUUCAGUAGUGUACAUAUACC	4085
AD-159853	csasaccaAfcUfAfUfcaagguuL96	3714	usAfsacaCfuUfGfguaGfuUfugguagcsa	3900	UGCAACCAACUAUCCAAGUGUUA	4086
AD-159182	gsasagauUfuGfGfCfagagauuaL96	3715	usAfsuacUfcUfCfugccAfaAfcuugcsusa	3901	UAGCAGAUUUGGCAGAGAGUAUA	4087
AD-159702	csuscuuCfaCfuUfGfcauagcuL96	3716	usAfsaggAfuGfUfuacUfgAfgagagcsac	3902	GGCUCUUCACUGAACAUGCCUA	4088
AD-159715	csasugccUfaGfUfCfcauauuL96	3717	asAfsaaaUfgUfUfggacUfaGfcaugsusu	3903	AACAUGCCUAGUCCAACAUAUUUU	4089
AD-158575	usgsccauCfaGfUfAfuuaugaaL96	3718	usUfscuUfaAfcGfaucUfgAfcuagcsasa	3904	UGUGCCAUCAGUAUCUUAUUGAA	4090
AD-158576	gsascauAfgUfAfUfcauuaugaaL96	3719	usUfsucaUfuAfcGfaucUfgAfcuagcsasa	3905	GUGCCAUCAGUAUCUUAUUGAA	4091
AD-158684	ususagaaCfaCfCfAfaagauugcuL96	3720	asGfsacaAfuCfuUfugUfgUfucuaagsg	3906	CCUUAAGAACACCAAGAUUGUCU	4092
AD-159410	asuscauUfcAfcUfugcuagcuL96	3721	usAfsagccUfaGfAfcaguGfaAfaugausasu	3907	AUAUCAUUUCACUGUCUAGGCUA	4093
AD-159416	uscsaagUfcUfAfGfgeuacaaL96	3722	usUfsguuGfuAfcGfcauGfaCfagugasa	3908	UUUCACUGUCUAGGCUACAACAG	4094
AD-159857	csasacuaUfcCfAfAfguguaaL96	3723	usGfsuaUfaCfAfcuagGfaUfaguuggsu	3909	ACCAACUAUCCAAGUGUUAUACC	4095
AD-158497	usugguuUfcAfcAfcuuaaL96	3724	usCfsauUfuGfGfaucUfgAfcacaaasa	3910	UUUUGGUUCCAAGUCCAUAUUGG	4096
AD-159124	usgsuuaUfgAfcGfGfuaaauL96	3725	asGfsuuUfGfUfCfaccUfAfaagcsasu	3911	AGUGCUUAUGAGGUGAUAUACU	4097
AD-159312	uscsuagAfcCfuUfUfguaagguL96	3726	usCfsaccUfuCfAfcuagGfuCfugagasa	3912	AAUCUCAGACCUUGUGAAGGUGA	4098
AD-159552	usasaauCfcAfcAfcuuaucuaL96	3727	asGfsuagAfuAfcGfcuGfgAfuuaucsa	3913	UGUAAAUAUCCAAGUUAUUAUCCU	4099
AD-159704	csesuuaCfuGfAfcuagcuL96	3728	asCfsuagGfcAfuUfguacAfgUfgaaggsag	3914	CUCUUCACUGAACAUGCCUAGU	4100
AD-159737	gsugsuacCfaGfUfGfuaaauL96	3729	usGfsuagUfuAfuUfaccUfgGfauccesag	3915	CUGGGAUCCAGUGUAUAAAUCCA	4101
AD-159869	csasuaaAfcCfuUfUfgaagguL96	3730	usUfscacUfgUfUfcaagGfuUfuaugsgsg	3916	CCCAUAUAACCUUGAUAACAGUGAC	4102
AD-158570	gsugsuagUfgCfCfAfcuuaucuaL96	3731	asAfsuagAfcUfGfauagCfaCfaggsasu	3917	AUGGCCUGUGCCAUCAUUAUUCU	4103
AD-158618	usugsuagAfuGfUfCfauagaaL96	3732	usGfsuucUfcGfAfcuagAfuCfaaaggsa	3918	UCUUGUUGAUGUUAUCCAGAGACA	4104

AD-159184	agsaunufgfcgCfAfGfagaguanuauL96	3733	asUfsuauAfeUfcfucugCfcAfaucugsc	3919	GCAGAUUUGGCAGAGAGUAUAAU	4105
AD-159231	ususucaCfcAfUfGfaunuaagguaL96	3734	usAfseccUfuAfAfucuaGfgUfgaaacsu	3920	AGUUUCCACCAUGAUUAAGGGUC	4106
AD-159423	csusagcUfaCfAfafaggaunuaL96	3735	usAfsaaUfcCfUfgugUfaGfcuagasc	3921	GUCUAGGCUACAACAGGAUUCUA	4107
AD-159446	usgsagcUfuGfUfGfcaugunguaL96	3736	usGfsacaAfcAfUfgeacAfaCfuccasc	3922	GGUGAGGUUGUGCAUGUUUGUC	4108
AD-159701	gsesuccUfcAfCfUfgaauccuL96	3737	asGfsgaUfgUfUfcauGfaAfgagcsa	3923	UGGCUCCUUCACUGAAACAUGCCU	4109
AD-158494	csunuuGfUfCfCfaaguccaauL96	3738	usAfsuugGfaCfUfuggaAfcCfaaagsga	3924	UCCUUUUGGUUCCAAGUCCAAUA	4110
AD-158571	gsesuccUfcCfAfUfcauuaL96	3739	usAfsagaUfaCfUfgaugGfcAfcaggcsa	3925	UGGCCUGUGCCAUCAUGAUUCUA	4111
AD-159125	gsesuuGfGfUfgaacaauL96	3740	usAfsuugUfgAfUfcauGfaAfuagasc	3926	GUGCUUAUGAGGUGAUCAAACUC	4112
AD-159126	csusauGfGfUfgaacaauL96	3741	usGfsaguUfuGfAfucacCfuCfaaagcsa	3927	UGCUUAUGAGGUGAUCAAACUCA	4113
AD-159287	csesunGfGfUfgaacaauL96	3742	asUfsuugGfUfUfggacUfuGfagagcsa	3928	UCCUUUGCAUUUUGGACAGAAU	4114
AD-158499	gsesuuccAfaGfUfcauuaagguaL96	3743	usGfsccaUfaUfUfggacUfuGfagagcsa	3929	UUGGUUCCAAGUCCAUAUUGGCA	4115
AD-159417	csasuccUfuGfGfGfcauuaagguaL96	3744	usCfsuugUfgUfAfgecuAfgAfcagugasa	3930	UUCACUGUCUAGGCUACAACAGG	4116
AD-159418	acsuugUfaGfGfGfcauuaagguaL96	3745	usCfsuugUfuGfUfagccUfaGfagagcsa	3931	UCACUGUCUAGGCUACAACAGGA	4117
AD-158550	asasuagAfuUfAfCfagunuaagguaL96	3746	usCfscaaCfaAfCfuguaAfuCfuuaucsu	3932	AGAAUAAGAUUACAGUUUGGUG	4118
AD-159116	gsusugAfuUfGfGfcauuaagguaL96	3747	usAfsuccCfaUfaAfaagCfuCfuaacsa	3933	UGGUUGAGAGUGCUUAUGAGGUG	4119
AD-159421	gsusucGfCfAfCfcauuaagguaL96	3748	usAfsuucCfuGfUfuguaGfcCfuagacsa	3934	CUGUCUAGGCUACAACAGGAUUC	4120
AD-159422	ususuagCfuUfCfAfaagunuaL96	3749	asGfsauCfUfUfguuaGfcCfuagacsa	3935	UGUCUAGGCUACAACAGGAUUCU	4121
AD-159445	gsusugGfUfUfGfUfgaunuaL96	3750	usAfscaaCfaUfGfcauAfcCfuacacsa	3936	AGGUGGAGGUUGUGCAUGUUUGUC	4122
AD-159130	usgsagGfUfUfCfAfaucuaaL96	3751	usCfsuugGfUfUfguuaGfcAfcuacsa	3937	UAUGAGGUGAUCAAACUCUAAAGG	4123
AD-159134	gsusauCfAfaCfUfcauuaagguaL96	3752	usUfsagCfUfUfUfguuaGfcAfcuacsa	3938	AGGUGAUCAAACUCUAAAGGCUAC	4124
AD-159343	usgsagGfAfaGfGfcauuaagguaL96	3753	usUfscaaAfcGfGfgecuCfuUfcauacsa	3939	UCUGAGGAAGAGGCCCCGUUUGAA	4125
AD-159105	acsasagCfGfUfGfUfgaunuaL96	3754	usAfsuucUfaAfcuacCfuGfcauacsa	3940	UCACAAGCAGGUGGUUGAGAGUG	4126
AD-159183	csasgaUfGfCfAfaagunuaL96	3755	usUfsauaCfuCfUfgecuCfaAfaucacsa	3941	AGCAGAUUUGGCAGAGAGUAUA	4127
AD-159123	gsusgaUfGfCfAfaagunuaL96	3756	gsUfsuugAfuCfAfcuacCfuAfaucacsa	3942	GAGUGCUUAUGAGGUGAUCAAAC	4128
AD-159181	agscagaUfuUfGfGfcauuaagguaL96	3757	asUfsacuCfuCfUfgecuAfaUfcauacsa	3943	GUAGCAGAUUUGGCAGAGAGUAU	4129
AD-159186	asusuugCfAfaGfGfcauuaagguaL96	3758	usCfsauAfuAfcuacCfuUfcauacsa	3944	AGAUUUGGCAGAGAGUAUAUAUGA	4130
AD-159187	ususuugCfAfaGfGfcauuaagguaL96	3759	usUfsacuUfaUfAfcuacCfuUfcauacsa	3945	GAUUUGGCAGAGAGUAUAUAUGAA	4131
AD-159288	csusugCfUfUfUfGfGfcauuaagguaL96	3760	usAfsuucUfgUfCfcauAfaUfcauacsa	3946	UCCUUUGCAUUUUGGACAGAAUG	4132
AD-159306	asusggaaUfcUfCfAfaagunuaL96	3761	usCfsacaAfgGfUfcauAfaUfcauacsa	3947	GAAUGGAUUCUCAGACCCUUGUA	4133
AD-159559	csasagCfUfaUfAfuUfcauuaagguaL96	3762	usAfsuucUfaAfcuacCfuUfcauacsa	3948	UCCACAGCUUAUCCUGAUGCUG	4134
AD-159344	gsasggaaGfAfaGfGfcauuaagguaL96	3763	usUfsuucAfaCfGfgecuUfUfcauacsa	3949	CUGAGGAAGAGGCCCCGUUUGAAG	4135
AD-159341	uscsuagGfAfaGfAfggcccunuaL96	3764	usAfsaacGfGfGfgecuUfUfcauacsa	3950	CUUCUGAGGAAGAGGCCCCGUUUG	4136
AD-159729	csasauCfUfGfGfcauuaagguaL96	3765	usAfsuucUfgGfAfuacCfuUfcauacsa	3951	GUCACAUCCUGGGAUCCAGUGUA	4137
AD-158674	agsccuUfuCfCfUfcauuaagguaL96	3766	usGfsguUfuCfUfcauuaagguaL96	3952	GCAGCCUUUCCUUAGAACACCA	4138
AD-159604	uscsacuGfGfUfUfAfguguaaL96	3767	usAfsuucCfaCfAfcuacCfuAfguguaaL96	3953	CUUCAACUGGUUAUGUGAUAUA	4139

TABLE 6A. Single dose screen in Primary Mouse Hepatocytes

Duplex Name	10nM	STDEV	0.1nM	STDEV
AD-84747	8.1	1.8	38.6	4.1
AD-84748	58.2	11.9	77.0	14.5
AD-84749	12.0	1.6	33.7	8.3
AD-84750	9.9	1.4	38.1	9.7
AD-84751	22.7	8.0	67.2	11.8
AD-84752	23.6	3.5	54.5	21.7
AD-84753	8.2	1.4	26.2	11.4
AD-84754	29.7	7.3	41.7	2.9
AD-84755	24.5	9.3	61.7	9.9
AD-84756	5.2	0.8	32.8	15.6
AD-84757	10.4	0.5	60.5	9.0
AD-84758	18.7	5.8	49.9	20.9
AD-84759	14.9	2.7	68.2	23.8
AD-84760	39.2	4.8	53.3	19.5
AD-84761	5.3	1.3	23.5	8.0
AD-84762	5.4	1.0	24.4	2.5
AD-84763	9.4	1.9	48.3	18.5
AD-84764	9.3	1.5	46.8	19.3
AD-84765	15.8	3.3	81.1	24.6
AD-84766	35.6	5.9	77.6	36.9
AD-84767	46.1	9.5	112.5	21.9
AD-84768	14.4	3.2	73.2	33.0
AD-84769	8.3	3.6	29.9	2.7
AD-84770	8.1	3.1	35.0	4.8
AD-84771	22.3	9.5	90.9	28.2
AD-84772	11.4	5.4	56.4	11.3
AD-84773	35.6	16.7	104.8	20.3
AD-84774	40.5	16.0	98.4	35.0
AD-84775	16.0	6.2	66.6	17.2
AD-84776	26.6	13.9	82.9	26.3
AD-84777	18.1	1.7	54.2	14.7
AD-84778	21.9	7.2	92.5	30.9
AD-84779	31.9	8.6	99.5	39.5
AD-84780	15.4	2.7	53.8	35.9
AD-84781	13.2	2.4	61.8	2.7
AD-84782	14.4	4.1	67.9	33.3
AD-84783	20.8	5.5	89.0	31.1
AD-84784	15.6	3.0	50.3	19.4
AD-84785	12.3	12.3	23.5	23.5
AD-84786	4.7	4.7	35.3	35.3
AD-84787	12.4	12.4	45.5	45.5

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AD-84788	2.3	2.3	7.8	7.8
AD-84789	9.4	9.4	45.7	45.7
AD-84790	2.5	2.5	12.8	12.8

TABLE 6B. Single dose screen in Hep3b

Duplex Name	% of Human Message Remaining	STDEV
AD-159469	16.97	6.86
AD-159607	25.01	8.34
AD-159713	25.91	11.30
AD-158504	21.90	8.34
AD-159233	25.16	10.01
AD-159411	22.65	8.86
AD-159462	31.26	10.89
AD-159742	26.31	4.08
AD-159863	22.44	5.86
AD-158626	11.06	9.33
AD-158687	17.11	9.55
AD-158688	16.22	11.59
AD-159458	16.59	9.47
AD-159519	16.60	2.85
AD-159858	31.03	12.43
AD-158681	12.52	5.04
AD-159583	30.63	8.04
AD-159700	60.23	11.10
AD-159807	12.17	4.73
AD-158673	7.41	0.92
AD-159608	19.93	9.83
AD-159803	29.79	8.75
AD-159805	31.27	12.09
AD-159489	50.07	7.60
AD-159495	22.72	2.15
AD-159609	17.39	9.56
AD-159706	25.44	3.75
AD-159855	16.67	12.67
AD-159864	8.09	1.09
AD-158491	29.16	14.26
AD-158672	29.36	10.12
AD-159488	31.40	6.20
AD-159553	24.36	7.63

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AD-159703	16.04	4.80
AD-159708	100.96	26.91
AD-159866	26.91	5.95
AD-159232	21.82	8.62
AD-159712	30.31	3.10
AD-159808	47.72	11.27
AD-159862	18.26	6.31
AD-158503	32.70	7.50
AD-159311	18.45	3.39
AD-159412	24.28	10.07
AD-159558	34.02	4.51
AD-159705	28.29	4.65
AD-159113	17.03	7.27
AD-159139	33.24	8.38
AD-159806	25.80	17.42
AD-159853	28.52	3.85
AD-158627	35.28	9.47
AD-159182	29.66	7.88
AD-159702	37.01	11.07
AD-159715	22.32	6.78
AD-158575	18.91	11.44
AD-158576	37.74	18.73
AD-158684	15.69	9.50
AD-159410	30.98	3.65
AD-159416	42.29	20.80
AD-159738	20.66	2.83
AD-159857	28.70	8.69
AD-158497	22.79	4.43
AD-159124	16.84	7.19
AD-159140	30.90	7.50
AD-159312	70.66	21.57
AD-159552	29.86	7.83
AD-159704	44.45	7.57
AD-159737	29.05	8.48
AD-159869	28.46	9.39
AD-158570	31.18	7.43
AD-158618	27.03	8.54
AD-159788	19.87	9.21
AD-159786	31.83	27.17
AD-159760	32.68	18.79
AD-159404	47.91	22.88
AD-159406	23.84	10.41

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AD-158536	30.88	20.74
AD-159545	84.72	26.81
AD-159574	29.96	20.03
AD-159802	24.57	9.29
AD-159518	29.06	16.06
AD-159577	34.39	12.83
AD-159409	50.02	25.26
AD-159551	33.79	11.99
AD-159276	40.09	13.96
AD-159407	37.47	9.59
AD-159515	41.82	19.54
AD-159570	12.41	3.87
AD-159849	25.67	14.76
AD-159252	14.25	4.14
AD-159275	22.30	13.03
AD-159848	34.58	13.52
AD-159184	30.50	8.60
AD-159231	103.27	9.11
AD-159607	16.73	1.97
AD-158504	11.46	1.78
AD-159233	15.90	3.55
AD-159411	9.04	1.84
AD-159462	16.08	7.18
AD-159742	10.92	3.23
AD-159863	8.82	2.51
AD-158687	14.93	6.23
AD-158688	15.77	5.03
AD-159458	14.85	9.10
AD-159519	20.25	9.24
AD-159858	22.20	14.11
AD-159583	20.01	1.53
AD-159700	56.12	12.02
AD-159807	16.73	7.03
AD-158673	6.01	2.09
AD-159608	13.52	6.68
AD-159803	30.47	10.26
AD-159805	10.28	1.16
AD-159489	24.20	2.91
AD-159495	22.32	13.94
AD-159706	30.61	17.66
AD-159855	9.32	1.46
AD-159864	10.64	2.41

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AD-159488	19.16	6.42
AD-159553	21.69	13.77
AD-159703	12.05	1.69
AD-159708	68.53	3.86
AD-159866	32.03	21.42
AD-159232	11.99	1.77
AD-159712	37.95	11.97
AD-159808	15.66	5.30
AD-159862	14.03	6.78
AD-158503	38.82	12.61
AD-159412	34.58	22.60
AD-159558	44.20	9.58
AD-159705	29.96	11.90
AD-159113	9.61	0.94
AD-159806	11.45	1.10
AD-159853	18.04	5.87
AD-159182	11.32	2.80
AD-159702	16.90	2.27
AD-159715	18.48	10.27
AD-158575	12.02	1.74
AD-158576	20.78	6.11
AD-158684	11.37	7.57
AD-159410	29.86	7.02
AD-159416	46.73	11.03
AD-159857	24.36	5.16
AD-158497	30.17	3.74
AD-159124	25.97	4.90
AD-159312	70.74	5.44
AD-159552	41.03	6.19
AD-159704	35.64	15.41
AD-159737	20.64	4.47
AD-159869	32.80	5.77
AD-158570	30.61	6.04
AD-158618	23.25	8.74
AD-159184	25.44	9.61
AD-159231	84.40	6.16
AD-159423	14.14	2.24
AD-159446	24.93	8.57
AD-159701	50.20	3.80
AD-158494	11.88	2.84
AD-158571	46.81	7.47
AD-159125	15.81	2.66

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AD-159126	29.28	8.63
AD-159287	25.25	2.91
AD-158499	29.76	5.51
AD-159417	32.69	6.45
AD-159418	24.84	7.31
AD-158550	28.87	4.53
AD-159116	26.12	2.58
AD-159421	22.32	3.28
AD-159422	24.24	7.34
AD-159445	33.50	10.14
AD-159130	24.80	4.33
AD-159134	10.46	1.12
AD-159343	34.97	8.91
AD-159105	92.74	4.56
AD-159183	41.08	12.03
AD-159123	33.69	9.55
AD-159181	32.21	14.92
AD-159186	24.30	1.21
AD-159187	46.71	2.58
AD-159288	21.07	2.58
AD-159306	30.47	5.46
AD-159559	34.55	6.09
AD-159344	14.12	7.20
AD-159341	19.39	9.18
AD-159729	49.48	4.73
AD-158674	15.18	2.82
AD-159604	23.15	13.21

Table 7. 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	usCfscUfaGfgAfcAfcccAfuUfgAfaAfagsu	90	Hs/Mm
AD-62944	GfsasAfaGfuCfaUfcGfGfaCfaAfGfaCfaUfL96	4142	asAfsuGfuCfuUfgUfcgaUfgAfcUfuUfcsasc	91	Hs/Mm
AD-62949	UfscsAfuCfGfAfcAfAfGfaCfaUfuGfgUfgAfL96	4143	usCfsaCfcAfaUfgUfcuuGfuCfGfaUfGfascsu	92	Hs/Mm
AD-62954	UfsusUfcAfaUfgGfGfUfgUfcCfuAfGfaAfL96	4144	usUfscCfuAfgGfaCfaceCfaUfuGfaAfascg	93	Hs/Mm
AD-62959	AfsasUfgGfgUfgUfcCfuAfgGfaAfcCfuUfL96	4145	asAfsGfuUfcCfuAfggaCfaCfcCfaUfugsa	94	Hs/Mm
AD-62964	GfsasCfaGfuGfcAfCfAfaUfuUfuCfcAfL96	4146	usGfsgAfaAfaUfaUfuguGfcAfcUfgUfcsasg	95	Hs/Mm
AD-62969	AfscsUfuUfuCfaAfUfGfGfGfuGfuCfcUfaAfL96	4147	usUfisaGfgAfcAfcCfcuUfgAfaAfaGfscsa	96	Hs/Mm
AD-62934	AfsasGfuCfaUfcGfAfcCfaAfgAfcAfuUfgAfL96	4148	usCfsaAfuGfuCfuUfgucGfaUfgAfcUfusus	97	Hs/Mm
AD-62940	AfsusCfGfAfcAfaGfAfcCfaUfuGfgUfgAfL96	4149	usCfsuCfaCfcAfaUfgucUfuGfuCfGafusgsa	98	Hs/Mm
AD-62945	GfsgsGfaGfaAfaGfGfUfgUfuCfaAfgAfL96	4150	usAfsuCfuUfgAfaCfaceUfuUfcUfcCfscsc	99	Hs/Mm
AD-62950	CfsusUfuUfcAfaUfGfGfUfgUfcCfuAfgAfL96	29	usCfsuAfgGfaCfaCfccaUfuGfaAfaAfgsusc	100	Hs/Mm
AD-62955	UfscsAfaUfgGfgUfGfUfcCfuAfgGfaAfcAfL96	30	usGfsuUfcCfuAfgGfacaCfcCfaUfuGfascsa	101	Hs/Mm
AD-62960	UfsusGfaCfuUfuUfcAfaUfgGfgUfgUfcAfL96	31	usGfisaCfaCfcCfaUfugaAfaAfgUfcAfasasa	102	Hs/Mm
AD-62965	AfsasAfgUfcAfuCfGfAfcAfaGfaCfaUfuAfL96	32	usAfsaUfgUfcUfuGfucgAfuGfaCfuUfscsa	103	Hs/Mm
AD-62970	CfsasGfgGfgGfaGfAfaGfgUfgUfuCfaAfL96	33	usUfsgAfaCfaCfcUfuueUfcCfcCfcUfgsgsa	104	Hs/Mm
AD-62935	CfsasUfuGfgUfgAfGfGfaAfaUfcCfuUfL96	34	asAfsGfaUfuUfuUfccuCfaCfcAfaUfsgusc	105	Hs/Mm
AD-62941	AfscsAfuUfgGfuGfAfGfGfaAfaAfuCfcUfL96	35	asGfsgAfuUfuUfuCfcucAfcCfaAfuGfscsu	106	Hs/Mm
AD-62946	AfsgsGfgGfgAfgAfaAfgGfuGfuUfcAfaAfL96	36	usUfsuGfaAfcAfcCfuuuCfuCfcCfcCfugsg	107	Hs/Mm
AD-62951	AfsusGfgUfgGfuAfaUfuUfgUfgAfuUfL96	37	asAfsaAfuCfaCfaAfaauAfcCfaCfcAfuscsc	108	Hs
AD-62956	GfsasCfuUfgCfaUfcCfuGfgAfaAfuAfL96	38	usAfsuAfuUfuCfcAfggaUfgCfaAfgUfcsesa	109	Hs
AD-62961	GfsgsAfaGfgGfaAfGfGfuAfgAfaGfuUfL96	39	asAfsGfAfcUfuCfuAfcuUfcCfcUfuCfcsasc	110	Hs

AD-62966	UfsgsUfcUfuCfuGfuUfuUfuAfgAfuUfuCfcUfl96	40	asGfsgAfaAfuCfuAfaacAfgAfaGfaCfasgsg	111	Hs
AD-62971	CfsusUfuGfgCfuGfuUfuUfuCfcAfaGfaUfcUfl96	41	asGfsaUfcUfuGfgAfaacAfgCfcAfaAfgsgsa	112	Hs
AD-62936	AfsasUfgUfgUfuUfgGfgGfcAfaCfcUfaUfl96	42	asUfsgAfcGfuUfgCfccaAfaCfaCfaUfususu	113	Hs
AD-62942	UfsgsUfgAfcUfgUfgGfgAfaCfcCfcUfuAfl96	43	usAfsaGfgGfgUfgUfccaCfaGfuCfaCfasasa	114	Hs
AD-62947	GfsasUfgGfgGfuGfcCfcAfaGfcUfaCfuAfuUfl96	44	asAfsuAfgUfaGfcUfggcAfcCfcCfaUfcsesa	115	Hs
AD-62952	GfsasAfaAfuGfuGfuUfuUfuGfgGfcAfaCfgUfl96	45	asCfsgUfuGfcCfcAfaacAfcAfuUfuUfcsasa	116	Hs
AD-62957	GfsgsCfuGfuUfuCfcAfaGfaUfcUfgAfcAfl96	46	usGfsuCfaGfaUfcUfuggAfaAfcAfgCfcsasa	117	Hs
AD-62962	UfscsCfaAfcAfaAfaUfaGfcCfaCfcCfcUfl96	47	asGfsgGfgUfgGfcUfaauUfuGfuUfgGfcsasa	118	Hs
AD-62967	GfsusCfuUfcUfgUfuUfuGfaUfuUfcCfuUfl96	48	asAfgGfaAfaUfcUfaaaCfaGfaAfgAfcasag	119	Hs
AD-62972	UfsgsGfaAfgGfgAfaGfgUfaGfaAfgUfcUfl96	49	asGfsaCfuUfcUfaCfcuuCfcCfuUfcCfascsa	120	Hs
AD-62937	UfscsCfuUfuGfgCfuUfgfuUfuCfcAfaGfaUfl96	50	asUfscUfuGfgAfaAfcagCfcAfaAfgGfasusu	121	Hs
AD-62943	CfsasUfcUfcUfcAfGfCfuGfgGfaUfgAfuAfl96	51	usAfsuCfaUfcCfcAfgcuGfaGfaUfgsgsg	122	Hs
AD-62948	GfsgsGfgUfgCfcAfGfCfuAfcUfaUfuGfaUfl96	52	asUfscAfaUfaGfuAfgcuGfgCfaCfcCfcsasu	123	Hs
AD-62953	AfsusGfuGfuUfuGfgGfcAfaCfgUfcAfuAfl96	53	usAfsuGfaCfgUfuGfcccAfaAfcAfcAfususu	124	Hs
AD-62958	CfsusGfuUfuAfgAfuUfuCfcUfuAfaGfaAfl96	54	usUfscUfuAfaGfgAfaauCfuAfaAfcAfgsasa	125	Hs
AD-62963	AfsgsAfaAfgAfaAfuUfgGfgAfcUfuGfcAfuAfl96	55	usAfsuGfcAfaGfuCfcuUfuCfuUfuCfusasg	126	Hs
AD-62968	GfscsAfuCfcUfgGfAfAfaUfaUfaUfaAfaAfl96	56	usUfsuAfaUfaUfaUfuucCfaGfgAfuGfcsasa	127	Hs
AD-62973	CfscsUfgUfcAfgAfcCfcUfgGfgAfaCfuAfl96	57	usAfgUfuCfcCfaUfgguCfuGfaCfaGfgsgcsu	128	Hs
AD-62938	AfsasAfcAfuGfgUfgUfgGfaUfgGfgAfuAfl96	58	usAfsuCfcCfaUfcCfacaCfcAfuGfuUfusasa	129	Hs
AD-62974	CfsusCfaGfgAfuGfAfAfaAfaUfuUfuGfaAfl96	59	usUfscAfaAfaUfuUfuucAfuCfcUfgAfgsusu	130	Hs
AD-62978	CfsasGfcAfuGfuAfuUfaCfuUfgAfcAfaAfl96	60	usUfsuGfuCfaAfgUfaauAfcAfuGfcUfgsasa	131	Hs
AD-62982	UfsasUfgAfaCfaAfcAfuGfcUfaAfaUfcAfl96	61	usGfsaUfuUfaGfcAfuguUfgUfuCfaUfasasu	132	Hs
AD-62986	AfsusAfuAfuCfcAfAfuGfuUfuUfaGfgAfl96	62	usCfscUfaAfaAfcAfuuuGfgAfuAfuAfususc	133	Hs
AD-62990	CfscsAfgAfuGfgAfaGfcUfgUfaUfcCfaAfl96	63	usUfsgGfaUfaCfaGfcuuCfcAfuCfuGfgsasa	134	Hs
AD-62994	GfsasCfuUfuCfaUfcCfuGfgAfaAfuAfuAfl96	64	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsesa	135	Hs
AD-62998	CfscsCfcGfgCfuAfaUfuUfgUfaUfcAfaUfl96	65	asUfsuGfaUfaCfaAfaauAfgCfcGfgGfgsgsa	136	Hs
AD-63002	UfsusAfaAfcAfuGfgCfuUfgAfaUfgGfgAfl96	66	usCfscCfaUfuCfaAfgccAfuGfuUfaAfascsa	137	Hs
AD-62975	AfsasUfgUfgUfuUfaGfAfaCfaAfcGfuCfaUfl96	67	asUfsgAfcGfuUfgUfcauAfaCfaCfaUfususu	138	Mm
AD-62979	AfscsUfaAfaGfgAfaGfaAfuUfcCfgGfuUfl96	68	asAfcscCfgGfaAfuUfcuuCfcUfuUfaGfufasusu	139	Mm

AD-62983	UfsasUfaUfcCfaAfaUfUfgUfuUfuAfgGfaUfl96	69	asUfscCfuAfaAfaCfaauUfgGfaUfaUfasusu	140	Mm
AD-62987	GfsusGfcGfgAfaAfGfGfcAfcUfgAfuGfuUfl96	70	asAfsaAfuCfaGfuGfcUfuCfcGfcAfcscsc	141	Mm
AD-62991	UfsasAfaAfcAfgUfGfGfuUfcUfuAfaAfuUfl96	71	asAfsuUfuAfaGfaAfcCfaCfuGfuUfuUfasasa	142	Mm
AD-62995	AfsusGfaAfaAfaUfUfuGfaAfaCfcAfgUfl96	72	asCfsuGfgUfuUfcAfaaaUfuUfuUfcAfuscsc	143	Mm
AD-62999	AfsasCfaAfaAfaUfGfCfaAfuCfcCfuUfuUfl96	73	asAfsaAfgGfgAfuUfgcuAfuUfuUfgUfugsg	144	Mm
AD-63003	CfsusGfaAfaCfaGfAfuUfcUfgUfcGfaCfuUfl96	74	asAfsuUfcGfaCfaGfaucUfgUfuUfcAfgscsa	145	Mm
AD-62976	UfsusGfuUfgCfaAfAfGfgGfcAfuUfuUfgAfl96	75	usCfsaAfaAfuGfcCfcuuUfgCfaAfcAfasusu	146	Mm
AD-62980	CfsusCfaUfuGfuUfUfaAfuUfaAfcCfuGfuAfl96	76	usAfsaAfgGfuUfaAfuuaAfcAfaUfgAfgsas	147	Mm
AD-62984	CfsasAfcAfaAfaUfAfuGfcAfaUfcCfcUfuUfl96	77	asAfsaGfgGfaUfuGfuaUfuUfuGfuUfgsgsa	148	Mm
AD-62992	CfsasUfuGfuUfuAfuUfaAfcCfuGfuAfuUfl96	78	asAfsuAfcAfgGfuUfaaAfaAfcAfaUfgsasg	149	Mm
AD-62996	UfsasUfcAfgCfuGfGfGfaAfgAfuCfaAfl96	79	usUfsgAfuAfuCfuUfcccAfgCfuGfaUfasgsa	150	Mm
AD-63000	UfsgsUfcCfuAfgGfAfAfcCfuUfuUfaGfaAfl96	80	usUfscUfaAfaAfgGfuucCfuAfgGfaCfascsc	151	Mm
AD-63004	UfscsCfaAfcAfaAfaUfaGfcAfaUfcCfcUfl96	81	asGfsgGfaUfuGfcUfaaUfuGfuUfgGfasasa	152	Mm
AD-62977	GfsgsUfgUfgCfgGfAfAfaGfgCfaCfuGfaUfl96	82	asUfscAfgUfgCfcUfuucCfgCfaCfaCfscsc	153	Mm
AD-62981	UfsusGfaAfaCfcAfGfUfaCfuUfuCfaUfl96	83	asUfsgAfuAfaAfgUfaaUfgGfuUfuUfcAfasasa	154	Mm
AD-62985	UfsasCfuUfcCfaAfAfGfuCfuAfuAfuAfl96	84	usAfsuAfuAfuAfgAfcuuUfgGfaAfgUfascsu	155	Mm
AD-62989	UfscsCfuAfgGfaAfCfcUfuUfaGfaAfaUfl96	85	asUfsuUfcUfaAfaAfgguUfcCfuAfgGfascsa	156	Mm
AD-62993	CfsusCfcUfgAfgGfAfAfaAfuUfuUfgGfaAfl96	86	usUfscCfaAfaAfaUfuUfuucCfuCfaGfgAfgsasa	157	Mm
AD-62997	GfscsUfcCfgGfaAfUfGfuUfgCfuGfaAfaUfl96	87	asUfsuUfcAfgCfaAfcuuUfcCfgGfaGfcsasu	158	Mm
AD-63001	GfsusGfuUfuGfuGfGfgAfgAfcCfaAfuAfl96	88	usAfsuUfgGfuCfuCfcccAfcAfaAfcAfcscsasg	159	Mm

Table 8. 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	usCfscUfaGfgAfcAfcccAfuUfgAfaAfagsu	90	Hs/Mm
AD-62944.2	GfsasAfaGfuCfaUfcGfGfaCfaAfgAfcAfuUfL96	4142	asAfsuGfuCfuUfgUfegaUfgAfcAfuUfcsasc	91	Hs/Mm
AD-62949.2	UfsesAfuCfGfaCfaAfAfGfaCfaUfuGfgUfgAfL96	4143	usCfsaCfcAfaUfgUfcuuGfuCfcAfuGfasesu	92	Hs/Mm
AD-62954.2	UfsusUfcAfaUfgGfGfUfgUfcCfuAfgGfaAfL96	4144	usUfscCfuAfgGfaCfaccCfaUfuGfaAfasesg	93	Hs/Mm
AD-62959.2	AfsasUfgGfgUfgUfcCfuAfgGfaCfcUfuL96	4145	asAfsGfuUfcCfuAfggaCfaCfcCfaUfugsasg	94	Hs/Mm
AD-62964.2	GfsasCfaGfuGfcAfCfAfaUfaUfuUfuCfcAfL96	4146	usGfsgAfaAfaUfaUfuguGfcAfcUfgUfcsasg	95	Hs/Mm
AD-62969.2	AfsesUfuUfuCfaAfUfGfgGfuGfuCfcUfaAfL96	4147	usUfsaGfgAfcAfcCfcuuUfgAfaAfaGfusesa	96	Hs/Mm
AD-62934.2	AfsasGfuCfaUfcGfAfCfaAfgAfcAfuUfgAfL96	4148	usCfsaAfuGfuCfuUfgucGfaUfgAfcUfususc	97	Hs/Mm
AD-62940.2	AfsusCfGfaCfaAfaGfAfCfaUfuGfgUfgAfgAfL96	4149	usCfsuCfaCfcAfaUfgucUfuGfuCfGfAfgusgsa	98	Hs/Mm
AD-62945.2	GfsgsGfaGfaAfaGfGfUfgUfuCfaAfgAfuAfL96	4150	usAfsuCfuUfgAfaCfaccUfuUfcUfcCfcsesc	99	Hs/Mm
AD-62950.2	CfsusUfuUfcAfaUfgGfgUfgUfcCfuAfgAfL96	29	usCfsuAfgGfaCfaCfccaUfuGfaAfaAfgsusc	100	Hs/Mm
AD-62955.2	UfsesAfaUfgGfgUfgUfcCfuAfgGfaAfcAfL96	30	usGfsuUfcCfuAfgGfacaCfcCfaUfuGfasasa	101	Hs/Mm
AD-62960.2	UfsusGfaCfuUfuUfcAfaUfgGfgUfgUfcAfL96	31	usGfsaCfaCfcCfaUfugaAfaAfgUfcAfasasa	102	Hs/Mm
AD-62965.2	AfsasAfgUfcAfuCfGfAfcAfaGfaCfaUfuAfL96	32	usAfsaUfgUfcUfuGfucgAfuGfaCfuUfusesa	103	Hs/Mm
AD-62970.2	CfsasGfgGfgGfaGfAfAfaGfgUfgUfuCfaAfL96	33	usUfsgAfaCfaCfcUfuucUfcCfcCfcUfgsgsa	104	Hs/Mm
AD-62935.2	CfsasUfuGfgUfgAfgGfaAfaUfcCfuUfL96	34	asAfsGfaUfuUfuUfcuUfcCfaCfcAfaUfgsusc	105	Hs/Mm
AD-62941.2	AfsesAfuUfgGfuGfAfGfgAfaAfaCfuCfcUfL96	35	asGfsgAfuUfuUfuCfucAfcCfaAfuGfusesu	106	Hs/Mm
AD-62946.2	AfsgsGfgGfgAfgAfAfGfgGfuGfuUfcAfaAfL96	36	usUfsuGfaAfcAfcCfuuuCfuCfcCfcCfsgsgg	107	Hs/Mm
AD-62951.2	AfsusGfgUfgGfuAfaUfuUfgUfgAfuUfL96	37	asAfsaAfuCfaCfaAfaauAfcCfaCfcAfusesc	108	Hs
AD-62956.2	GfsasCfuUfgCfaUfcCfuGfgAfaAfuAfL96	38	usAfsuAfuUfuCfcAfggaUfgCfaAfgUfcsesa	109	Hs
AD-62961.2	GfsgsAfaGfgGfaAfgGfuAfgAfaGfuCfuUfL96	39	asAfsGfAfcUfuCfuAfcuUfcCfcUfuCfcsasc	110	Hs
AD-62966.2	UfsgsUfcUfuCfuGfUfuAfgAfuUfuCfcUfL96	40	asGfsgAfaAfuCfuAfaacAfgAfaGfaCfasgsg	111	Hs

AD-62971.2	CfsusUfuGfgCfuGfUfuCfcAfaGfaUfcUfL96	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	asAfsuAfgUfaGfcUfggcAfcCfcCfaUfcsesa	115	Hs
AD-62952.2	GfsasAfaAfuGfuGfUfuUfuGfgGfcAfaCfuUfL96	45	asCfsgUfuGfcCfcAfaacAfcAfuUfuUfcsasa	116	Hs
AD-62957.2	GfsgsCfuGfuUfuCfCfAfaGfaUfcUfgAfcAfl96	46	usGfsuCfaGfaUfcUfuggAfaAfcAfgCfcsasa	117	Hs
AD-62962.2	UfscsCfaAfcAfaAfaUfaGfcCfaCfcCfcUfL96	47	asGfsgGfgUfgGfcUfaauUfuGfuUfgGfasasa	118	Hs
AD-62967.2	GfsgsCfuUfcUfgUfuUfuGfaGfaUfuUfcCfuUfL96	48	asAfsaGfaAfaUfcUfaaaCfaGfaAfgAfcasag	119	Hs
AD-62972.2	UfsgsGfaAfgGfgAfaGfgUfaGfaAfgUfcUfL96	49	asGfsaCfuUfcUfaCfcuUfcCfuUfcCfcsesa	120	Hs
AD-62937.2	UfscsCfuUfuGfgCfUfGfuUfuCfcAfaGfaUfL96	50	asUfscUfuGfgAfaAfcagCfcAfaAfgGfasusu	121	Hs
AD-62943.2	CfsasUfcUfcUfcAfgCfuGfgGfaUfgAfuAfl96	51	usAfsuCfaUfcCfcAfgcuGfaGfaUfgsgsg	122	Hs
AD-62948.2	GfsgsGfgUfgCfcAfgCfuAfcUfaUfuGfaUfL96	52	asUfscAfaUfaGfuAfgcuGfgCfaCfcCfcsasu	123	Hs
AD-62953.2	AfsusGfuGfuUfuGfGfGfcAfaCfuUfcAfuAfl96	53	usAfsuGfaCfuUfuGfcccAfaAfcAfcAfcususu	124	Hs
AD-62958.2	CfsusGfuUfuAfgAfuUfuCfcUfuAfaGfaAfl96	54	usUfscUfuAfaGfgAfaauCfuAfaAfcAfgsasa	125	Hs
AD-62963.2	AfsgsAfaAfgAfaAfuUfgGfgAfcUfuGfcAfuAfl96	55	usAfsuGfcAfaGfuCfcuUfuCfuUfuCfusasg	126	Hs
AD-62968.2	GfscsAfuCfcUfgGfAfaUfaUfaUfuAfaAfl96	56	usUfsuAfaUfaUfaUfuUfuCfaGfgAfuGfcsasa	127	Hs
AD-62973.2	CfscsUfgUfcAfgAfcCfaUfgGfgAfaCfuAfl96	57	usAfsuUfuCfcCfaUfgguCfuGfaCfaGfgsesu	128	Hs
AD-62938.2	AfsasAfcAfuGfgUfgUfgGfaUfgGfgAfuAfl96	58	usAfsuCfcCfaUfcCfacaCfcAfuGfuUfusasa	129	Hs
AD-62974.2	CfsusCfaGfgAfuGfAfaAfaUfuUfuGfaAfl96	59	usUfscAfaAfaUfuUfuUfuCfcUfgAfgsusu	130	Hs
AD-62978.2	CfsasGfcAfuGfuAfuUfuUfaCfuUfgAfcAfaAfl96	60	usUfsuGfuCfaAfgUfaauAfcAfuGfcUfgsasa	131	Hs
AD-62982.2	UfsasUfgAfaCfaAfcAfuGfcUfaAfaUfcAfl96	61	usGfsaUfuUfaGfcAfuUfuUfgUfuCfaUfasasu	132	Hs
AD-62986.2	AfsusAfuCfcAfaAfuGfuUfuUfaGfgAfl96	62	usCfscUfaAfaAfcAfuuuGfgAfuAfuususc	133	Hs
AD-62990.2	CfscsAfgAfuGfgAfaGfcUfgUfaUfcCfaAfl96	63	usUfsgGfaUfaCfaGfcuUfcAfuCfuGfgsasa	134	Hs
AD-62994.2	GfsgsCfuUfuCfaUfcCfuGfgAfaAfuAfuAfl96	64	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsesa	135	Hs
AD-62998.2	CfscsCfcGfgCfuAfaUfuUfuUfgUfaUfcAfaUfL96	65	asUfsuGfaUfaCfaAfaauAfgCfcGfgGfgsgsa	136	Hs
AD-63002.2	UfsusAfaAfcAfuGfGfCfuUfgAfaUfgGfgAfl96	66	usCfscCfaUfuCfaAfgccAfuGfuUfuAfasasa	137	Hs
AD-62975.2	AfsasUfgUfgUfuUfaGfAfaAfcGfuCfaUfL96	67	asUfsgAfcGfuUfgUfcuAfaCfaCfaUfususu	138	Mm
AD-62979.2	AfscsUfaAfaGfgAfaGfaAfuUfcCfgGfuUfL96	68	asAfcCfGfaAfuUfcuUfcUfuUfaGfusasu	139	Mm
AD-62983.2	UfsasUfaUfcCfaAfaUfgUfuUfuAfgGfaUfL96	69	asUfscCfuAfaAfaCfaauUfgGfaUfaUfasusu	140	Mm

AD-62987.2	GfsusGfcGfgAfaAfGfGfcAfcUfgAfuGfuUfl96	70	asAfsaAfuCfaGfuGfcuUfuCfcGfcAfcscasc	141	Mm
AD-62991.2	UfsasAfaAfcAfgUfgGfuUfcUfuAfaAfuUfl96	71	asAfsuUfuAfaGfaAfcCaCfuGfuUfuUfasasa	142	Mm
AD-62995.2	AfsusGfaAfaAfaUfuUfuGfaAfaCfcAfgUfl96	72	asCfsuGfgUfuUfcAfaaaUfuUfuUfcAfusesc	143	Mm
AD-62999.2	AfsasCfaAfaAfaUfuUfuGfaAfaCfcCfuUfuUfl96	73	asAfsaAfgGfgAfuUfgcuAfuUfuUfgUfusgsg	144	Mm
AD-63003.2	CfsusGfaAfaCfaGfaAfuUfcUfgUfcGfaCfuUfl96	74	asAfgUfcGfaCfaGfaucUfgUfuUfcAfgscsa	145	Mm
AD-62976.2	UfsusGfuUfgCfaAfAfGfgGfcAfuUfuUfgAfl96	75	usCfsaAfaAfuGfcCfcuUfgCfaAfcAfasusu	146	Mm
AD-62980.2	CfsusCfaUfuGfuUfuUfaAfuUfaAfcCfuGfuAfl96	76	usAfsaAfgGfuUfaAfuuaAfcAfaUfgAfgsas	147	Mm
AD-62984.2	CfsasAfcAfaAfaUfuUfaAfcAfuUfcCfcUfuUfl96	77	asAfsaGfgGfaUfuGfcuaUfuUfuGfuUfgsgsa	148	Mm
AD-62992.2	CfsasUfuGfuUfuUfuUfaAfcCfuGfuAfuUfl96	78	asAfsuAfcAfgGfuUfaaUfaAfaUfgsasg	149	Mm
AD-62996.2	UfsasUfcAfgCfuGfgGfaAfgAfuAfuCfaAfl96	79	usUfsgAfuAfuCfuUfcccAfgCfuGfaUfasgsa	150	Mm
AD-63000.2	UfsgsUfcCfuAfgGfAfAfCfcUfuUfaGfaAfl96	80	usUfscUfaAfaAfgGfuucCfuAfgGfaCfascsc	151	Mm
AD-63004.2	UfscsCfaAfaAfaAfuUfaGfaAfuUfcCfcUfl96	81	asGfsgGfaUfuGfcUfaaUfuGfuUfgGfasasa	152	Mm
AD-62977.2	GfsgsUfgUfgCfGfAfAfGfgCfaCfuGfaUfl96	82	asUfscAfgUfgCfcUfuucCfGcfaCfaCfscsc	153	Mm
AD-62981.2	UfsusGfaAfaCfcAfgUfuCfuUfuAfuCfaUfl96	83	asUfsgAfuAfaAfgUfacuGfgUfuUfcAfasasa	154	Mm
AD-62985.2	UfsasCfuUfcCfaAfAfGfuCfuAfuAfuAfl96	84	usAfsuAfuAfuAfgAfcuuUfgGfaAfgUfascsu	155	Mm
AD-62989.2	UfscsCfuAfgGfaAfCfcUfuUfuGfaAfaUfl96	85	asUfsuUfcUfaAfaAfgguUfcCfuAfgGfascsa	156	Mm
AD-62993.2	CfsusCfcUfgAfgGfAfAfaAfuUfuUfgGfaAfl96	86	usUfscCfaAfaAfuUfuucCfuCfaGfgAfgsasa	157	Mm
AD-62997.2	GfscsUfcCfGfAfuUfgGfuUfgCfuGfaAfaUfl96	87	asUfsuUfcAfgCfaAfcuUfcCfGfGfaGfcsasu	158	Mm
AD-63001.2	GfscsGfuUfuGfuGfgGfgAfgAfcCfaAfuAfl96	88	usAfsuUfgGfuCfuCfcccAfcAfaAfcAfcscasg	159	Mm
AD-62933.1	GfscsAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	160	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	277	
AD-65630.1	Y44gsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	161	PusUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	278	
AD-65636.1	gsasauguGfaAfAfGfucuuCfGacaaL96	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	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusc	285	
AD-65631.1	asusguGfaAfAfGfucaucgacaaL96	169	usUfsgucGfaugacuuUfcAfcususc	286	

AD-65637.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	170	usUfsgucGfaUfgAfcuuUfcAfcuuucsug	287
AD-65643.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	171	usUfsgucGfaUfgAfcuuUfcAfcuuucsug	288
AD-65648.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	172	usUfsgucGfaUfgAfcuuUfcAfcuuucsug	289
AD-65653.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	173	usUfsgucGfaUfgAfcuuUfcAfcuuucsug	290
AD-65658.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	174	usUfsgucGfaUfgAfcuuUfcAfcuuucsug	291
AD-65663.1	gsasanguGfaAfAfGfucaucgacaal96	175	usUfsgucGfaUfgAfcuuUfcAfcuuucsug	292
AD-65626.1	gsasanguGfaAfAfGfucaucgacaal96	176	usUfsgucGfaUfgAfcuuUfcAfcuuucsug	293
AD-65638.1	gsasanguGfaAfAfGfucaucgacaal96	177	usUfsgucGfaUfgAfcuuUfcAfcuuucsug	294
AD-65644.1	gsasanguGfaAfAfGfucaucgacaal96	178	usUfsgucGfaUfgAfcuuUfcAfcuuucsug	295
AD-65649.1	gsasanguGfaAfAfGfucaucgacaal96	179	usUfsgucGfaUfgAfcuuUfcAfcuuucsug	296
AD-65654.1	gsasangugaaagucuu(Cgn)gacaal96	180	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsug	297
AD-65659.1	gsasaudTgaaagucuu(Cgn)gacaal96	181	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsug	298
AD-65627.1	gsasaudTgaaagucuu(Cgn)gacaal96	182	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsug	299
AD-65633.1	gsasaudTgaaagucuu(Cgn)gacaal96	183	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsug	300
AD-65639.1	gsasaudTgaaagucuu(Cgn)gacaal96	184	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsug	301
AD-65645.1	gsasaudTgaaagucuu(Cgn)gacaal96	185	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsug	302
AD-65650.1	gsasaudTgaaagucuu(Cgn)gacaal96	186	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsug	303
AD-65655.1	gsasaudTgaaagucuu(Cgn)gacaal96	187	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsug	304
AD-65660.1	gsasaudTgaaagucuu(Cgn)gacaal96	188	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsug	305
AD-65665.1	gsasaudTgaaagucuu(Cgn)gacaal96	189	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsug	306
AD-65628.1	gsasaudTgaaagucuu(Cgn)gacaal96	190	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsug	307
AD-65634.1	gsasaudTgaaagucuu(Cgn)gacaal96	191	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsug	308
AD-65646.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	192	usdTsgucgaugdAcuudTcacaucsug	309
AD-65656.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	193	usUsgucgaugdAcuudTcacaucsug	310
AD-65661.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	194	usdTsgucdGaugacuudTcacaucsug	311
AD-65666.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	195	usUsgucdGaugacuudTcacaucsug	312
AD-65629.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	196	usdTsgucgaugacuudTcdAcaucsug	313
AD-65635.1	GfsasAfuGfuGfaAfAfGfuCfaUfcGfaCfaAfl96	197	usdTsgucdGaugacuudTcdAcaucsug	314
AD-65641.1	gsasangugaaagucuu(Cgn)gacaal96	198	usdTsgucgaugdAcuudTcacaucsug	315

AD-62994.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfl96	199	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	316
AD-65595.1	gsascuuuCfaUfCfCfuggaAfaaual96	200	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	317
AD-65600.1	gsascuuuCfaUfCfCfuggaauaual96	201	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	318
AD-65610.1	gsascuuuCfaucCfuggaAfaaual96	202	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	319
AD-65615.1	gsascuuucaucCfuggaAfaaual96	203	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	320
AD-65620.1	gsascuuuCfaucCfuggaauaual96	204	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	321
AD-65584.1	CfsusUfuCfaUfCfCfuGfgAfaAfuAfuAfl96	205	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	322
AD-65590.1	csusuCfaUfCfCfuggaauaual96	206	usAfsuauUfuccaggaUfgAfaagsusc	323
AD-65596.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfl96	207	usAfsuauUfuCfcAfggaUfgAfaagsusc	324
AD-65601.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfl96	208	usAfsuauUfuCfCfaggaUfgAfaagsusc	325
AD-65606.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfl96	209	usAfsuauUfuccaggaUfgAfaagsusc	326
AD-65611.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfl96	210	usAfsuauUfuccaggaUfgaagusc	327
AD-65616.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfuAfl96	211	usAfsuauUfuccaggaUfgaagusc	328
AD-65621.1	gsascuuuCfaUfCfCfuggaauaual96	212	usAfsuauUfuCfcAfggaUfgAfaagsusc	329
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AD-65607.1	gsascuuuCfaucCfuggaauaual96	217	usAfsuauUfuccaggaUfgAfaagsusc	334
AD-65612.1	gsascuuucaucugga(Agn)uauaL96	218	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	335
AD-65622.1	gsascuuucaucCugga(Agn)uauaL96	219	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	336
AD-65586.1	gsascudTucaucdCugga(Agn)uauaL96	220	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	337
AD-65592.1	gsascuudTeaucdCugga(Agn)uauaL96	221	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	338
AD-65598.1	gsascuudCaucdCugga(Agn)uauaL96	222	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	339
AD-65603.1	gsascuuucaucdCuggaadAuaual96	223	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	340
AD-65608.1	gsascuuucaucdCuggaadTuauaL96	224	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	341
AD-65613.1	gsascuuucaucdCuggaY34uauaL96	225	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	342
AD-65618.1	gsascuuucaucdCuggaadAadTuauaL96	226	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	343
AD-65623.1	gsascuuucaucdCuggaadTudAuaL96	227	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfcsca	344

AD-65587.1	gsascuucaudCuggaa(Agn)udAuaL96	228	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfscscsa	345
AD-65593.1	gsascuudTeaucdCuggaadAudAuaL96	229	usAfsuAfuUfuCfcAfggaUfgAfaAfgUfscscsa	346
AD-65599.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfl96	230	usdAsuaunuuccdAggadTgaaagucscsa	347
AD-65604.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfl96	231	usdAsuaunuuccaggadTgaaagucscsa	348
AD-65609.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfl96	232	usAsuaunuuccaggadTgaaagucscsa	349
AD-65614.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfl96	233	usdAsuaudTuccaggadTgaaagucscsa	350
AD-65619.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfl96	234	usAsuaudTuccaggadTgaaagucscsa	351
AD-65624.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfl96	235	usdAsuaunuuccaggadTgdAaagucscsa	352
AD-65588.1	GfsasCfuUfuCfaUfCfCfuGfgAfaAfuAfl96	236	usdAsuaudTuccaggadTgdAaagucscsa	353
AD-65594.1	gsascuucaudCuggaa(Agn)uuaL96	237	usdAsuaunuuccdAggadTgaaagucscsa	354
AD-68309.1	asgsaaagGfuGfUfUfcaagangucaL96	238	usGfsacaUfcUfUfgaacAfcCfuuuucscsc	355
AD-68303.1	csasuccuGfgAfAfAfuauuuuacuaL96	239	asGfsuuaAfuAfUfauuuCfcAfggaugcsasa	356
AD-65626.5	gsasauguGfaAfAfGfucaucgacaaL96	240	usUfsgucGfaUfGfacuuUfcAfcuucscsg	357
AD-68295.1	asgsugcaCfaAfUfAfuuuuuccaual96	241	usAfsuggGfaAfAfauauUfgUfgcacuugsu	358
AD-68273.1	gsasaaguCfaUfCfGfacaagacaaL96	242	asAfsuguCfuUfGfucgaUfgAfcuucscasc	359
AD-68297.1	asasugugAfaAfGfUfcaucgacaaL96	243	usUfsuguCfGfUfUfgacuUfuCfacaauuscu	360
AD-68287.1	csusggaaAfuAfUfAfuuaacuguaL96	244	usAfsacaGfuUfAfaauuAfuUfuccaggsa	361
AD-68300.1	asusuucCfcAfUfCfuguaauuuuL96	245	asAfsauaAfuAfCfagauGfgGfaaausasu	362
AD-68306.1	usgsucguUfcUfUfUfuccaacaual96	246	usUfsuugUfuGfGfaaaaGfaAfcgacascsc	363
AD-68292.1	asusccugGfaAfAfUfauuuuacuaL96	247	usAfsuguAfaUfAfuauUfcCfaggauugsa	364
AD-68298.1	gscsaauuUfgAfGfAfggugaugauL96	248	usAfsucaUfcAfcfcucuCfaAfaaagcscsc	365
AD-68277.1	csasggggGfaGfAfAfagguuguuaL96	249	usUfsgaaCfaCfcfuuuUfcCfcccuggsa	366
AD-68289.1	gsgsaauAfuAfUfUfuaacuguaaaL96	250	usUfsuaaCfaGfUfuaauAfuAfuuuccsasg	367
AD-68272.1	csasuuggUfgAfGfGfaaaauuccuuL96	251	asAfsugaUfuUfUfuccuCfaCfcaaugusc	368
AD-68282.1	gsgsgagaAfaGfGfUfgnucaagauL96	252	usAfsucuUfgAfAfcaccUfuUfuccccscsc	369
AD-68285.1	gsgcauuUfuGfAfGfaggugaugauL96	253	asUfscuAfaCfCfucucAfaAfaugccscsu	370
AD-68290.1	usascaaaGfgGfUfGfucguuuuuuL96	254	asAfsaagAfaCfGfacacCfcUfuuguasusu	371
AD-68296.1	usgggauCfuUfGfGfugugaaucal96	255	usGfsauuCfzAfcfaccAfgAfuucccasusu	372
AD-68288.1	csusgacaGfuGfCfAfcaauuuuuuL96	256	usAfsaaaUfaUfUfugucAfcUfgucaggsasu	373

AD-68299.1	csasgugcAfcAfAfUfauuuuccauL96	257	asUfsgggAfaAfAfuaauGfuGfcacugsusc	374
AD-68275.1	ascsuuuuCfaAfUfGfgguguccuuaL96	258	usUfsaggAfcAfCfccaUfGfAfaaagusc	375
AD-68274.1	ascsaugGfuGfAfGfgaaaauccuL96	259	asGfsgauUfuUfUfccucAfcCfaaugsusu	376
AD-68294.1	ususgcuUfuGfAfCfuuuicaaualL96	260	usCfsauuGfaAfAfagucAfaAfagcaasug	377
AD-68302.1	csasuuiuGfaGfAfGfgugaugauL96	261	usCfsaucAfuCfAfccucUfcAfaaugsusc	378
AD-68279.1	ususgacuUfuUfCfAfauaggugucalL96	262	usGfsacaCfcCfAfuaaGfaAfagcaasasa	379
AD-68304.1	csgsacuuCfuGfUfUfuuaggacagaL96	263	usCfsuguCfcUfAfaaacAfgAfagucgsasc	380
AD-68286.1	csuscugaGfuGfGfGfugccagaaualL96	264	usAfsuucUfgGfCfaccAfcUfcagagusc	381
AD-68291.1	gsgsgugcCfaGfAfAfugagaagualL96	265	usAfsuuUfcAfCfaucUfgGfcaccsasc	382
AD-68283.1	uscsaagGfgUfGfUfcuaggaaualL96	266	usGfsuucCfuAfGfgacaCfcCfaungasasa	383
AD-68280.1	asasagucAfuCfGfAfcaagacaualL96	267	usAfsaugUfcUfUfgucGfAfGfuuuusc	384
AD-68293.1	asusuugAfgAfGfGfugaugauL96	268	usGfscacCfaUfCfaccuCfuCfaaaugsc	385
AD-68276.1	asuscgacAfaGfAfCfauuggugagaL96	269	usCfsucaCfcAfAfugucUfuGfucgausga	386
AD-68308.1	gsgsugccAfgAfAfUfgugaagualL96	270	usGfsacuUfuCfAfcauuCfuGfgaccscsa	387
AD-68278.1	gsascaguGfcAfCfAfauuuuuuccaL96	271	usGfsgaaAfaUfAfuauguGfcAfcugucsasg	388
AD-68307.1	ascsaagAfgAfCfAfucugucagaaL96	272	usUfscugCfaCfAfugugCfuCfuungusc	389
AD-68284.1	ususucaAfuGfGfGfuguccuaggalL96	273	usCfscuaGfgAfcCfaccAfuUfgaaaasgsu	390
AD-68301.1	cscsguuuCfcAfAfGfaucugacaguL96	274	asCfsuguCfaGfAfucuuGfgAfaacggusc	391
AD-68281.1	asgsggggAfgAfAfAfgguguucaaL96	275	usUfsugaAfcAfCfcuuuCfuCfccccgsg	392
AD-68305.1	asgsucauCfgAfCfAfagacaugguL96	276	asCfscacUfgUfCfuuguCfGfAfugacusus	393

Table 9. Unmodified Human/Mouse/Cyno/Rat, Human/Mouse/Cyno, and Human/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	UUGUCGAUGACUUUACACAUUCUG	1072-1094
AD-62939	395	UUUUCAAUGGGUGUCCUAGGA	444	UCCUAGGACACCCAUUGAAAAGU	1302-1324
AD-62944	396	GAAAGUCAUCGACAAAGACAUAU	445	AAUGUCUUGUCGAUGACUUUCAC	1078-1100
AD-62949	397	UCAUCGACAAAGACAUGGUGA	446	UACCAAUGUCUUUGUCGAUGACU	1083-1105
AD-62954	398	UUUCAUUGGGUGUCCUAGGAA	447	UUCUAGGACACCCAUUGAAAAG	1303-1325
AD-62959	399	AUUGGGUGUCCUAGGAACCUU	448	AAGGUCCUAGGACACCCAUUGA	1307-1329
AD-62964	400	GACAGUGCACAAUUAUUUCCA	449	UGGAAAUAUUGUGCACUGUCAG	1134-1156_C21A
AD-62969	401	ACUUUUCAUUGGGUGUCCUAA	450	UUAGGACACCCAUUGAAAAGUCA	1300-1322_G21A
AD-62934	402	AAGUCAUCGACAAAGACAUGA	451	UCAUUGUCUUUGUCGAUGACUUUC	1080-1102_G21A
AD-62940	403	AUCGACAAAGACAUGGUGAGA	452	UCUCACCAUUGUCUUUGUCGAUGA	1085-1107_G21A
AD-62945	404	GGGAGAAAGGUGUUCAGAUUA	453	UAUCUUUGAACACCUUUUCUCCCC	996-1018_G21A
AD-62950	405	CUUUUCAUUGGGUGUCCUAGA	454	UCUAGGACACCCAUUGAAAAGUC	1301-1323_G21A
AD-62955	406	UCAUUGGGUGUCCUAGGAACA	455	UGUUCCUAGGACACCCAUUGAAA	1305-1327_C21A
AD-62960	407	UUGACUUUUCAUUGGGUGUCA	456	UGACACCCAUUGAAAAGUCAAAA	1297-1319_C21A
AD-62965	408	AAAGUCAUCGACAAAGACAUAU	457	UAAUGUCUUUGUCGAUGACUUUCA	1079-1101_G21A
AD-62970	409	CAGGGGAGAAAGGUGUUCAA	458	UUGAACACCUUUUCUCCCCUGGA	992-1014
AD-62935	410	CAUUGGGUGAGGAAAUAUCCUU	459	AAGGAUUUUUCCUCCACCCAAUGUC	1095-1117
AD-62941	411	ACAUUGGGUGAGGAAAUAUCCU	460	AGGAUUUUUCCUCCACCCAAUGUCU	1094-1116
AD-62946	412	AGGGGAGAAAGGUGUUCAA	461	UUUGAACACCUUUUCUCCCCUGG	993-1015_G21A
AD-62974	413	CUCAGGAUGAAAUAUUGAA	462	UUCAAAUAUUUUCAUCCUGAGUU	563-585
AD-62978	414	CAGCAUGUAUUAUUAUUGACAA	463	UUUGUCAAGUAUAUUAUUGCUGAA	1173-1195
AD-62982	415	UAUGAACACAUGCUAAAUAUA	464	UGAUUUAGCAUGUUGUUCAUAUU	53-75
AD-62986	416	AUAUAUCCAAUUGUUUAGGA	465	UCCUAAAACAUAUUUGGAUAUAUU	1679-1701
AD-62990	417	CCAGAUGGAAGCUGUAUCCAA	466	UUUGGAUACAGCUUCCAUUCUGGAA	156-178
AD-62994	418	GACUUUAUCCUGGAAUAUA	467	UAUAUUUCCAGGAUGAAAAGUCCA	1341-1363
AD-62998	419	CCCCGGCUAAUUUGUAUCAAU	468	AUUUGAUACAUAUUAAGCCGGGGA	29-51
AD-63002	420	UUAAACAUGGCUUGAAUGGGA	469	UCCCAUUCAAGGCCAUUGUUUACA	765-787
AD-62975	421	AAUGUGUUUAGACAAACGUCAU	470	AUGACGUUGUCUAAACACAUUUU	1388-1410

AD-62979	422	ACUAAAGGAAGAAUUCGGGUU	471	AACCGGAUUUCUCCUUUAGUAAU	1027-1049
AD-62983	423	UAUAUCCAAAGUUUUUAGGAU	472	AUCCUAAAACAUUUGGAUAUAUU	1680-1702
AD-62987	424	GUGCGGAAGGCACUGAUGUU	473	AACAUACAGUCCUUUCCGCACAC	902-924
AD-62991	425	UAAACACAGUGGUUUCUAAAUAU	474	AAUUUAGAACCACUGUUUUAAA	1521-1543
AD-62995	426	AUGAAAUAUUUGAAACCCAGU	475	ACUGGUUUCAAAUAUUUUCAUCC	569-591
AD-62999	427	AACAAAUAAGCAAUCCCUUUU	476	AAAAGGAUUUGCUAUUUUUUGUUGG	1264-1286
AD-63003	428	CUGAACACAGAUUCUGCGACUU	477	AAGUCGACAGAUUCUGUUUCAGCA	195-217
AD-62976	429	UUGUUGCAAAGGCAUUUUUA	478	UCAAAUGCCCUUUGCAACAUAU	720-742
AD-62980	430	CUCAUUGUUUAUUUACCCUGUA	479	UACAGGUUAUAACAUAUGAGAU	1483-1505
AD-62984	431	CAACAAAUAAGCAAUCCCUUU	480	AAAGGAUUUGCUAUUUUGUUGGA	1263-1285
AD-62992	432	CAUUUUUAUUAAACCUGUAUU	481	AAUACAGGUUAAUAAACAUAUGAG	1485-1507
AD-62996	433	UAUCAGCUGGGAAGAUUAUCA	482	UUGAUAUCUCCCGAGCUGAUAGA	670-692
AD-63000	434	UGUCCUAGGAACCUUUUAGAA	483	UUCUAAAAGGUUCCUAGGACACC	1313-1335
AD-63004	435	UCCAACAUAUAGCAAUCCCU	484	AGGAUUUCUAUUUUUGUUGGAA	1261-1283
AD-62977	436	GGUGGCGGAAGGCACUGAU	485	AUCAGUGCCUUUCCGCACACCCC	899-921
AD-62981	437	UUGAAACCAGUACUUUAUCAU	486	AUGAUAAAGUACUGGUUUUCAA	579-601
AD-62985	438	UACUCCCAAAGUCUAUAUAUA	487	UAUAUAUAGACUUUGGAAUACU	75-97_G21A
AD-62989	439	UCCUAGGAACCUUUUAGAAAU	488	AUUUCUAAAAGGUUCCUAGGACA	1315-1337_G21U
AD-62993	440	CUCCUGAGGAAAUUUUGGAA	489	UUCCAAAUAUUUCCUCAGGAGAA	603-625_G21A
AD-62997	441	GCUCGGGAUGUUGCUGAAAU	490	AUUUCAGCAACAUCUCCGAGCAU	181-203_C21U
AD-63001	442	GUGUUUGUGGGGAGACCAUAU	491	UAUUGGUCUCCCCACAACACAG	953-975_C21A

Table 10. Unmodified Mouse 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_010403.2
AD-62951	492	AUGGUGGUAUUUGUGAUUUU	514	AAAUCACAAAUAUACCAUCC	1642-1664
AD-62956	493	GACUUGCAUCCUGGAAUAUA	515	UAUAUUUCCAGGAUGCAAGUCCA	1338-1360
AD-62961	494	GGAAGGGAAGGUAGAAGUCUU	516	AAGACUUCUACCUUCCCUUCCAC	864-886
AD-62966	495	UGUCUUCUGUUUAGAUUUCCU	517	AGGAAAUCUAAAACAGAAAGACAGG	1506-1528

AD-62971	496	CUUUGGCUUUUCCAAAGAUU	518	AGAUCUUUGGAAACAGCCAAAGGA	1109-1131
AD-62936	497	AAUGUGUUUGGGCAACGUCAU	519	AUGACGUUGGCCAAACACAUUUU	1385-1407
AD-62942	498	UGUGACUGUGGACACCCCUUA	520	UAAAGGGUGUGCCACAGUCACAAA	486-508
AD-62947	499	GAUGGGUGCCAGCUACUAAU	521	AAUAGUAGCUGGACCCCAUCCA	814-836
AD-62952	500	GAAAUGUGUUUGGGCAACGU	522	ACGUUGCCCAACACAUUUUCAA	1382-1404
AD-62957	501	GGCUGUUUCCAAAGAUUGACA	523	UGUCAGAUUUUGGAAACAGCCAA	1113-1135
AD-62962	502	UCCAACAAAUAAGCCACCCCU	524	AGGGUGGCUAUUUUGUUGGAA	1258-1280
AD-62967	503	GUCUUCUGUUUAGAUUUCCU	525	AAGGAAUUCUAAACAGAAAGACAG	1507-1529
AD-62972	504	UGGAAAGGGAAGUAAGUCU	526	AGACUUUCUACCUUCCUUCACA	863-885
AD-62937	505	UCCUUUGGCUGUUUCCAAAGAU	527	AUCUUGGAAACAGCCAAAGGAUU	1107-1129
AD-62943	506	CAUCUCUCAGCUGGGGAUGAU	528	UAUCAUCCAGCUGAGAGAUUGG	662-684
AD-62948	507	GGGUGCCAGCUACUAAUUGAU	529	AUCAAUAGUAGCUGGCACCCCAU	817-839
AD-62953	508	AUGUUUUUGGGCAACGUCUAU	530	UAUGACGUUGCCCCAAACACAUUU	1386-1408_C21A
AD-62958	509	CUGUUUAGAUUUCCUAAAGAA	531	UUCUAAAGGAAAUUCUAAACAGAA	1512-1534_C21A
AD-62963	510	AGAAAGAAUUGGACUUGCAUA	532	UAUGCAAAGUCCAUUUUCUUCUAG	1327-1349_C21A
AD-62968	511	GCAUCCUGGAAAUAUUUAAA	533	UUUAAUAUAUUUCCAGGAUGCAA	1343-1365_C21A
AD-62973	512	CCUGUCAGACCAUGGGAACUA	534	UAGUCCCAUGGUCUGACAGGCU	308-330_G21A
AD-62938	513	AAACAUGGUGGGAUGGGAUA	535	UAUCCCAUCCACACCAUGUUUAA	763-785_C21A

Table 11. Additional Unmodified Human/Cyno/Mouse/Rat, Human/Mouse/Cyno, Human/Cyno, and Mouse/Rat

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	GAAUGUGAAAAGUCAUCGACAA	443	UUUGCGAUGACUUUCACAUUCUG	1072-1094
AD-62939.2	395	UUUUCAAUGGGUGUCCUAGGA	444	UCCUAGGACACCCAUUGAAAAAGU	1302-1324
AD-62944.2	396	GAAAAGUCAUCGACAAGACAUU	445	AAUGUCUUUGCGAUGACUUUCAC	1078-1100
AD-62949.2	397	UCAUCGACAAGACAUUGGUGA	446	UCACCAAUGUCUUUGCGAUGACU	1083-1105
AD-62954.2	398	UUUCAAUUGGGUGUCCUAGGAA	447	UUCCUAGGACACCCCAUUGAAAAG	1303-1325

AD-62959.2	399	AAUGGGUGUCCUAGGAACCUU	448	AAGGUUCCUAGGACACCCAUUGA	1307-1329
AD-62964.2	400	GACAGUGCACAAUUAUUUCCA	449	UGGAAAUAUUGUGCACUGUCAG	1134- 1156_C21A
AD-62969.2	401	ACUUUUCAAUGGGUGUCCUAA	450	UUAGGACACCCAUUGAAAAGUCA	1300- 1322_G21A
AD-62934.2	402	AAGUCAUCGACAAGACAUUGA	451	UCAUGUCUUGUGGAGACUUUC	1080- 1102_G21A
AD-62940.2	403	AUCGACAAGACAUUGGUGAGA	452	UCUCACCAAAUGUCUUGUCGAUGA	1085- 1107_G21A
AD-62945.2	404	GGGAGAAAGGUGUUCAGAUUA	453	UAUCUUUGAACACCUUUUCUCCCCC	996- 1018_G21A
AD-62950.2	405	CUUUUCA AUGGGUGUCCUAGA	454	UCUAGGACACCCAUUGAAAAGUC	1301- 1323_G21A
AD-62955.2	406	UCA AUGGGUGUCCUAGGAACA	455	UGUUCUAGGACACCCAUUGAAA	1305- 1327_C21A
AD-62960.2	407	UUGACUUUUCAAUGGGUGUCA	456	UGACACCCAUUGAAAAGUCAAAA	1297- 1319_C21A
AD-62965.2	408	AAAGUCAUCGACAAGACAUUA	457	UAAUGUCUUGUGGAGACUUUCA	1079- 1101_G21A
AD-62970.2	409	CAGGGGAGAAAGGUGUUCAA	458	UUGAACACCUUUUCUCCCCCUGGA	992-1014
AD-62935.2	410	CAUUGGUGAGGAAAAAUCCUU	459	AAGGAUUUUUCCUCACCAAAUGUC	1095-1117
AD-62941.2	411	ACAUUGGUGAGGAAAAAUCCU	460	AGGAUUUUUCCUCACCAAAUGUCU	1094-1116
AD-62946.2	412	AGGGGGAGAAAGGUGUUCAAA	461	UUUGAACACCUUUUCUCCCCCUGG	993- 1015_G21A
AD-62974.2	413	CUCAGGAUGAAAAAUUUUGAA	462	UUCAAAAUUUUUUCAUCCUGAGUU	563-585
AD-62978.2	414	CAGCAUGUAUUACUUGACAAA	463	UUUGUCAAGUAAUACAUGCUGAA	1173-1195
AD-62982.2	415	UAUGAACACAACUUGCUAAAUCA	464	UGAUUUAGCAUGUUGUUCUAAAU	53-75
AD-62986.2	416	AUAUAUCCAAAUGUUUUUAGGA	465	UCCUAAAACAUAUUUGGAUAUAUUC	1679-1701
AD-62990.2	417	CCAGAUGGAAGCUGUAUCCAA	466	UUUGUAACAGCUUCCAUUCUGGAA	156-178
AD-62994.2	418	GACUUUCAUCCUGGAAAUAUA	467	UAUAUUUCCAGGAUGAAAAGUCCA	1341-1363
AD-62998.2	419	CCCCGGCUAAUUUGUAUCAAU	468	AUUGAUACAAAUAUAGCCGGGGA	29-51
AD-63002.2	420	UUAACAUGGCUUGAAUUGGA	469	UCCCAUUCAAAGCCAUGUUUACA	765-787

AD-62975.2	421	AAUGUGUUUAGACAACGUCAU	470	AUGACGUUGUCUAAACACAUUUU	1388-1410
AD-62979.2	422	ACUAAAGGAAGAAUUCGGGU	471	AACCGGAUUUCUUCUUUAGUAAU	1027-1049
AD-62983.2	423	UAUAUCCAAAUGUUUUAGGAU	472	AUCCUAAAACAUUUGGAUUAUU	1680-1702
AD-62987.2	424	GUGCGGAAAGGCACUGAUGUU	473	AACAUACAGUGCCUUUCCGCACAC	902-924
AD-62991.2	425	UAAAACAGUGGUUCUUAAAUAU	474	AAUUUAGAACCACUGUUUUAAA	1521-1543
AD-62995.2	426	AUGAAAUAUUUGAAAACCCAGU	475	ACUGGUUUCAAAAUUUUUCAUCC	569-591
AD-62999.2	427	AACAAAUAAGCAAUCCUUUUU	476	AAAAGGGAUUGCUAUUUUGUUGG	1264-1286
AD-63003.2	428	CUGAAACAGAUUCUGCGACUU	477	AAGUCGACAGAUUCUGUUUCAGCA	195-217
AD-62976.2	429	UUGUUGCAAAAGGGCAUUUUGA	478	UCAAAAUGCCUUUUGCAACAUAU	720-742
AD-62980.2	430	CUCAUUGUUUAUUAAACUGUA	479	UACAGGUUAUAACAACAUAGAGAU	1483-1505
AD-62984.2	431	CAACAAAUAAGCAAUCCUUUU	480	AAAGGGAUUGCUAUUUUGUUGGA	1263-1285
AD-62992.2	432	CAUUGUUUAUUAAACUGUAUU	481	AAUACAGGUUAUAACAACAUAGAG	1485-1507
AD-62996.2	433	UAUCAGCUGGGGAAGAUUAUCA	482	UUGAUUAUUUUCCCAGCUGAUAGA	670-692
AD-63000.2	434	UGUCCUAGGAACCUUUUAGAA	483	UUCUAAAAGGUUCCUAGGACACC	1313-1335
AD-63004.2	435	UCCAAACAUAUAGCAAUCCCU	484	AGGGAUUGCUAUUUUGUUGGAA	1261-1283
AD-62977.2	436	GGUGUGCGGAAAGGCACUGAU	485	AUCAGUGCCUUUCCGCACACCCC	899-921
AD-62981.2	437	UUGAAACCAGUACUUUAUCAU	486	AUGAUAAAGUACUGGUUUUCAA	579-601
AD-62985.2	438	UACUCCCAAAGUCUAUAUAUA	487	UAUAUAUAGACUUUUGGAAGUACU	75-97_G21A
AD-62989.2	439	UCCUAGGAACCUUUUAGAAA	488	AUUUCUAAAAGGUUCCUAGGACA	1315- 1337_G21U
AD-62993.2	440	CUCCUGAGGAAAUAUUUGGAA	489	UUCCAAAAUAUUUCCUCAGGAGAA	603- 625_G21A
AD-62997.2	441	GCUCCGGAUUGUUGCUGAAA	490	AUUUCAGCAACAUAUCCGGAGCAU	181- 203_C21U
AD-63001.2	442	GUGUUUGUGGGGAGACCAAUA	491	UAUUGGUUCUCCCCCAACAACACAG	953- 975_C21A
AD-62951.2	492	AUGGUGGUAUUUUGUGAUUUU	514	AAAUAUCACAAAUUACCACCAUCC	1642-1664
AD-62956.2	493	GACUUGCAUCCUGGAAAUAUA	515	UAUAUUUCCAGGAUGCAAGUCCA	1338-1360
AD-62961.2	494	GGAAAGGGAAGGUAGAAGUCUU	516	AAGACUUCUACCUUCCCUUCCAC	864-886
AD-62966.2	495	UGUCUUCUGUUUAGAUUUCCU	517	AGGAAAUCUAAAACAGAAAGACAGG	1506-1528

AD-62971.2	496	CUUUGGCGUUUCCAAAGAUUCU	518	AGAUCUUUGGAAACAGCCAAAGGA	1109-1131
AD-62936.2	497	AAUGUGUUUGGGCAACGUCAU	519	AUGACGUUGCCCAACACAUUUU	1385-1407
AD-62942.2	498	UGUGACUGUGGACACCCCUUA	520	UAAAGGGGUGUCCACAGUCACAAA	486-508
AD-62947.2	499	GAUGGGGUGCCAGCUACUAAU	521	AAUAGUAGCUGGCACCCCAUCCA	814-836
AD-62952.2	500	GAAA AUGUGUUUGGGCAACGU	522	ACGUUGCCCAACACAUUUUCAA	1382-1404
AD-62957.2	501	GGCUGUUUCCAAAGAUUCGACA	523	UGUCAGAUUCUUGGAAACAGCCAA	1113-1135
AD-62962.2	502	UCCAAACA AAUAGCCACCCCU	524	AGGGUGGCUAUUUUUGUGGAAA	1258-1280
AD-62967.2	503	GUCUUCUGUUUAGAUUUCCUU	525	AAGGAAUUCUAAACAGAAAGACAG	1507-1529
AD-62972.2	504	UGGAAGGGAAGGUAGAAGUCU	526	AGACUUCUACCUUCCCUUCCACA	863-885
AD-62937.2	505	UCCUUUGGCUGUUUCCAAAGAU	527	AUCUUGGAAACAGCCAAAGGAUU	1107-1129
AD-62943.2	506	CAUCUCUCAGCUGGGGAUGAU	528	UAUCAUCCCGAGCUGAGAGAUUGG	662-684
AD-62948.2	507	GGGUGCCAGCUACUAAUUGAU	529	AUCAAUAGUAGCUGGCACCCCAU	817-839
AD-62953.2	508	AUGUGUUUGGGCAACGUCAUA	530	UAUGACGUUGCCCCAAACACAUUU	1386- 1408_C21A
AD-62958.2	509	CUGUUUAGAUUUCCUUAAAGAA	531	UUCUUAAAGGAAAUUCUAAACAGAA	1512- 1534_C21A
AD-62963.2	510	AGAAAGAAAUUGGACUUUGCAUA	532	UAUGCAAGUCCAUUUUCUUUCUAG	1327- 1349_C21A
AD-62968.2	511	GCAUCCUGGAAAUUAUUAUAAA	533	UUUAAUAUAUUUCCAGGAUGCAA	1343- 1365_C21A
AD-62973.2	512	CCUGUCAGACCAUGGGGAACUA	534	UAGUUCCCAUGGUCUGACAGGCU	308- 330_G21A
AD-62938.2	513	AAACAUGGUGUGGAUGGGGAUA	535	UAUCCCAUCCACACCAUGUUUAA	763- 785_C21A
AD-62933.1	536	GAAUGUGAAAAGUCAUCGACAA	653	UUUGCGAUGACUUUCACAUUCUG	1072-1094
AD-65630.1	537	GAAUGUGAAAAGUCAUCGACAA	654	UUUGCGAUGACUUUCACAUUCUG	1072-1094
AD-65636.1	538	GAAUGUGAAAAGUCAUCGACAA	655	UUUGCGAUGACUUUCACAUUCUG	1072-1094
AD-65642.1	539	GAAUGUGAAAAGUCAUCGACAA	656	UUUGCGAUGACUUUCACAUUCUG	1072-1094
AD-65647.1	540	GAAUGUGAAAAGUCAUCGACAA	657	UUUGCGAUGACUUUCACAUUCUG	1072-1094
AD-65652.1	541	GAAUGUGAAAAGUCAUCGACAA	658	UUUGCGAUGACUUUCACAUUCUG	1072-1094
AD-65657.1	542	GAAUGUGAAAAGUCAUCGACAA	659	UUUGCGAUGACUUUCACAUUCUG	1072-1094

AD-65662.1	543	GAAUGUGAAAAGUCAUCGACAA	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	GAAUGUGAAAAGUCAUCGACAA	663	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65643.1	547	GAAUGUGAAAAGUCAUCGACAA	664	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65648.1	548	GAAUGUGAAAAGUCAUCGACAA	665	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65653.1	549	GAAUGUGAAAAGUCAUCGACAA	666	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65658.1	550	GAAUGUGAAAAGUCAUCGACAA	667	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65663.1	551	GAAUGUGAAAAGUCAUCGACAA	668	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65626.1	552	GAAUGUGAAAAGUCAUCGACAA	669	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65638.1	553	GAAUGUGAAAAGUCAUCGACAA	670	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65644.1	554	GAAUGUGAAAAGUCAUCGACAA	671	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65649.1	555	GAAUGUGAAAAGUCAUCGACAA	672	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65654.1	556	GAAUGUGAAAAGUCAUCGACAA	673	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65659.1	557	GAAUGUGAAAAGUCAUCGACAA	674	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65627.1	558	GAAUGUGAAAAGUCAUCGACAA	675	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65633.1	559	GAAUGUGAAAAGUCAUCGACAA	676	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65639.1	560	GAAUGUGAAAAGUCAUCGACAA	677	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65645.1	561	GAAUGUGAAAAGUCAUCGACAA	678	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65650.1	562	GAAUGUGAAAAGUCAUCGACAA	679	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65655.1	563	GAAUGUGAAAAGUCAUCGACAA	680	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65660.1	564	GAAUGUGAAAAGUCAUCGACAA	681	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65665.1	565	GAAUGUGAAAAGUCAUCGACAA	682	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65628.1	566	GAAUGUGAAAAGUCAUCGACAA	683	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65634.1	567	GAAUGUGAAAAGUCAUCGACAA	684	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65646.1	568	GAAUGUGAAAAGUCAUCGACAA	685	UTGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65656.1	569	GAAUGUGAAAAGUCAUCGACAA	686	UUGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65661.1	570	GAAUGUGAAAAGUCAUCGACAA	687	UTGUCGAUGACUUUCACAUUCUG	1072-1094
AD-65666.1	571	GAAUGUGAAAAGUCAUCGACAA	688	UUGUCGAUGACUUUCACAUUCUG	1072-1094

AD-65629.1	572	GAAUGUGAAAAGUCAUCGACAA	689	UTGUCGAUGACUUTCACAUUCUG	1072-1094
AD-65635.1	573	GAAUGUGAAAAGUCAUCGACAA	690	UTGUCGAUGACUUTCACAUUCUG	1072-1094
AD-65641.1	574	GAAUGUGAAAAGUCAUCGACAA	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
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	GACUUUCAUCCUGGAAUAUA	717	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363

AD-65613.1	601	GACUUUCAUCCUGGAAUAUA	718	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65618.1	602	GACUUUCAUCCUGGAAUAUA	719	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65623.1	603	GACUUUCAUCCUGGAAUAUA	720	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65587.1	604	GACUUUCAUCCUGGAAUAUA	721	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65593.1	605	GACUUTCAUCCUGGAAUAUA	722	UAUAUUUCCAGGAUGAAAGUCCA	1341-1363
AD-65599.1	606	GACUUUCAUCCUGGAAUAUA	723	UAUAUUUCCAGGATGAAAGUCCA	1341-1363
AD-65604.1	607	GACUUUCAUCCUGGAAUAUA	724	UAUAUUUCCAGGATGAAAGUCCA	1341-1363
AD-65609.1	608	GACUUUCAUCCUGGAAUAUA	725	UAUAUUUCCAGGATGAAAGUCCA	1341-1363
AD-65614.1	609	GACUUUCAUCCUGGAAUAUA	726	UAUAUTUCCAGGATGAAAGUCCA	1341-1363
AD-65619.1	610	GACUUUCAUCCUGGAAUAUA	727	UAUAUTUCCAGGATGAAAGUCCA	1341-1363
AD-65624.1	611	GACUUUCAUCCUGGAAUAUA	728	UAUAUUUCCAGGATGAAAGUCCA	1341-1363
AD-65588.1	612	GACUUUCAUCCUGGAAUAUA	729	UAUAUTUCCAGGATGAAAGUCCA	1341-1363
AD-65594.1	613	GACUUUCAUCCUGGAAUAUA	730	UAUAUUUCCAGGATGAAAGUCCA	1341-1363
AD-68309.1	614	AGAAAGGUGUUAAGAUUCA	731	UGACAUCUUUGAACACCUUUCUCC	1001- 1022_C21A
AD-68303.1	615	CAUCCUGGAAUAUAUAUAUA	732	AGUUAUAUAUUUCCAGGAUGAA	1349-1370
AD-65626.5	616	GAAUGUGAAAGUCAUCGACAA	733	UUUGCGAUGACUUUUCACAUUCUG	1072-1094
AD-68295.1	617	AGUGCACAAUAUUUUCUCCAU	734	UAUGGGGAAUAUAUUUGUGCACUGU	1139- 1160_C21A
AD-68273.1	618	GAAAGUCAUCGACAAAGACAUU	735	AAUGUCUUUGUCGAUGACUUUCAC	1080-1100
AD-68297.1	619	AAUGUGAAAGUCAUCGACAAA	736	UUUGUCGAUGACUUUUCACAUUCU	1075- 1096_G21A
AD-68287.1	620	CUGGAAUAUAUAUAUAUAUAUA	737	UAAACAGUUAUAUAUAUUUCCAGGA	1353-1374
AD-68300.1	621	AUUUCCCAUCUGUAUUUAUUU	738	AAAUAUAACAGAUUGGGGAAAAUAU	1149-1170
AD-68306.1	622	UGUCGUUCUUUUUCCAAACAAA	739	UUUUGUUGGAAAGAACGACACC	1252-1273
AD-68292.1	623	AUCCUGGAAUAUAUAUAUAUA	740	UAGUUUAUAUAUUUCCAGGAUGA	1350- 1371_G21A
AD-68298.1	624	GCAUUUUUGAGAGGUGAUGAUA	741	UAUCAUCACCCUCUCAAAAUGCCC	734- 755_G21A
AD-68277.1	625	CAGGGGAGAAAGGUGUUCAA	742	UUUGAACACCUUUCUCCCCCUGGA	994-1014

AD-68289.1	626	GGAAAUUAUUAACUGUUAAA	743	UUUAAACAGUUAAUUAUUUCCAG	1355-1376
AD-68272.1	627	CAUUGGUGAGGAAAUUCCUU	744	AAGGAUUUUUCCUCACCAAUGUC	1097-1117
AD-68282.1	628	GGGAGAAAGGUGUUAAGAU	745	UAUCUUUGAAACACCUUUUCUCCCC	998-1018_G21A
AD-68285.1	629	GGCAUUUUGAGAGGUGAUGAU	746	AUCAUCACCUUCUCAAUUGCCCU	733-754
AD-68290.1	630	UACAAGGGUGUCGUUCUUU	747	AAAAGAACGACACCCUUGUAUU	1243-1264
AD-68296.1	631	UGGAUCUUGGUGUCGAUCA	748	UGAUUCGACACCAAGAUCCCAUU	783-804
AD-68288.1	632	CUGACAGUGCACAAUUAUUUA	749	UAAAAUUAUUGUGCACUGUCAGAU	1134-1155_C21A
AD-68299.1	633	CAGUGCACAAUUAUUUCCCAU	750	AUGGAAAUUAUUGUGCACUGUC	1138-1159
AD-68275.1	634	ACUUUUCAAUUGGGUGUCCUA	751	UUAGGACACCCAUUUGAAAAGUCA	1302-1322_G21A
AD-68274.1	635	ACAUUGGUGAGGAAAUUCCU	752	AGGAUUUUUCCUCACCAAUGUCU	1096-1116
AD-68294.1	636	UUGCUUUUGACUUUUAUGA	753	UCAUUGAAAAGUCAAAAGCAAUG	1293-1314_G21A
AD-68302.1	637	CAUUUUGAGAGGUGAUGA	754	UCAUCAUCACCCUCUCAAAUUGCC	735-756_C21A
AD-68279.1	638	UUGACUUUUAUUGGGUGUCA	755	UGACACCCAUUUGAAAAGUCAAAA	1299-1319_C21A
AD-68304.1	639	CGACUUCUGUUUAGGACAGA	756	UCUGUCCUAAAACAGAAAGUCGAC	212-233
AD-68286.1	640	CUCUGAGUGGGUGCCAGAAUA	757	UAUUCUGGCACCCACUCACAGGCC	1058-1079_G21A
AD-68291.1	641	GGGUGCCAGAAUGUGAAAGUA	758	UACUUUACAUUCUGGCACCCAC	1066-1087_C21A
AD-68283.1	642	UCAAUGGGUGUCCUAGGAACA	759	UGUUCUAGGACACCCCAUUGAAA	1307-1327_C21A
AD-68280.1	643	AAAGUCAUCGACAAGACAUUA	760	UAAUGUCUUUGUGAUGACUUUCA	1081-1101_G21A
AD-68293.1	644	AUUUUGAGAGGUGAUGAUGCA	761	UGCAUCAUCACCCUCUCAAAUUGC	736-757_C21A
AD-68276.1	645	AUCGACAAAGACAUUGGUGAGA	762	UCUCACCAAUGUCUUGUCGAUGA	1087-1107_G21A
AD-68308.1	646	GGUGCCAGAAUGUGAAAGUCA	763	UGACUUUACAUUCUGGCACCCA	1067-1088

AD-68278.1	647	GACAGUGCACAAUUAUUUCCA	764	UGGAAAUAUUGUGCACUGUCAG	1136-1156_C21A
AD-68307.1	648	ACAAAGAGACACUGUGCAGAA	765	UUCUGCACAGUGUCUCUUUGUCA	1191-1212_G21A
AD-68284.1	649	UUUCAAUUGGUGUCCUAGGA	766	UCCUAGGACACCCAUUGAAAAGU	1304-1324
AD-68301.1	650	CCGUUCCAAAGAUCUGACAGU	767	ACUGUCAGAUCUUGGAAACGGCC	1121-1142
AD-68281.1	651	AGGGGGAGAAAGGUGUCAA	768	UUUGAACACCUUUUCUCCCCUGG	995-1015_G21A
AD-68305.1	652	AGUCAUCGACAAAGACAUUGGU	769	ACCAAUGUCUUGUCGAUGACUUU	1083-1104

Table 12. 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	UUCAAUUGGGUGUCCUAGGA	770 & 771
AD-40257.2	uucAAuGGGuGuccuAGGAdTsdT	UUCAAUUGGGUGUCCUAGGA	770 & 771
AD-63102.1	AcAAcuGGAGGAcAucGudTsdT	ACAACUGGAGGACAUUCGU	772 & 773
AD-63102.2	AcAAcuGGAGGAcAucGudTsdT	ACAACUGGAGGACAUUCGU	772 & 773
AD-63102.3	AcAAcuGGAGGAcAucGudTsdT	ACAACUGGAGGACAUUCGU	772 & 773

Table 13. 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	UCCuAGGAcACcAUUGAAdTsdT	UCCUAGGACACCCAUUGAA	774 & 775
AD-40257.2	UCCuAGGAcACcAUUGAAdTsdT	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 14. 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	AfsusCfGfAfcAfaGfAfCfaUfuGfgUfgAfgAfl96	782
AD-62941.2	AfscsAfuUfgGfuGfAfGfgAfaAfaAfuCfcUfL96	783
AD-62944.2	GfsasAfaGfuCfaUfCfGfAfcAfaAfuUfL96	784
AD-62965.2	AfsasAfgUfcAfuCfGfAfcAfaGfaCfaUfuAfl96	785

Table 15. 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	asUfsuUfcUfaAfaAfggUfcCfuAfgGfascsa	786
AD-62994.2	usAfsuAfuUfuCfcAfGgaUfgAfaAfgUfscsa	787
AD-62933.2	usUfsgUfcGfaUfgAfcuuUfcAfcAfuUfcsusg	788
AD-62935.2	asAfsGfAfuUfuUfcuUfcuUfcAfcAfaUfsgusc	789
AD-62940.2	usCfsuCfaCfcAfaUfgucUfuGfuCfGfAfusgsa	790
AD-62941.2	asGfsgAfuUfuUfuCfcuAfcCfaAfuGfuscus	791
AD-62944.2	asAfsuGfuCfuUfgUfcgaUfgAfcUfuUfcsasc	792
AD-62965.2	usAfsaUfgUfcUfuGfucgAfuGfaCfuUfuscscsa	793

Table 16. Additional Human Unmodified and Modified 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
AUGUAGUUACUUCUUAGAGA	794	asusuanGfuUfAfCfuucuuagagaL96	1890	sense	21
UCUCUAGAAGUAACAUAACAUC	795	usCfsucuAfaGfAfaguaAfcAfuaucascsc	1891	antisense	23
UGUAUGUUACUUCUUAGAGAG	796	usgsuauGfuUfAfCfuucuuagagagL96	1892	sense	21
CUCUCUAGAAGUAACAUAACAUC	797	csUfscucUfaAfGfagaUfaCfaucascusc	1893	antisense	23
UAGGAUGUAUGUUACUUCUUA	798	usasggauGfuUfUfGfuuaucuuuaL96	1894	sense	21
UAGAAGUAACAUAACAUCUAAA	799	usAfsagaAfgUfAfacauAfcAfuccuasasa	1895	antisense	23
UUAGGAUGUAUGUUACUUCUU	800	ususaggaUfgUfAfUfguuacuucuuL96	1896	sense	21
AAGAAGUAACAUAACAUCUAAA	801	asAfsagaGfuUfAfcauaCfaUfccuaasasa	1897	antisense	23
AGAAAGGUGUUAAGAUGUCC	802	asgsaaagGfuGfuUfUfcaagauguccL96	1898	sense	21
GGACAUCUUGAACACCUUUUCUC	803	gsGfsacaUfcUfUfgaacAfcCfuucuscsc	1899	antisense	23
GAAAGGUGUUAAGAUGUCCU	804	gsasaaggUfgUfUfCfaagauguccuL96	1900	sense	21
AGGACAUCUUGAACACCUUUUCUC	805	asGfsgacAfuCfuUfugaaCfaCfuuuuscsc	1901	antisense	23
GGGGAGAAAGGUGUUAAGAUA	806	gsgsggagAfaAfGfGfuguaagauL96	1902	sense	21
AUCUUGAACACCUUUUCUCCCCU	807	asUfscuuGfaAfCfaccuUfuCfucccscsu	1903	antisense	23
GGGGAGAAAGGUGUUAAGAUA	808	gsgsgggaGfaAfAfGfuguaagaaL96	1904	sense	21
UCUUGAACACCUUUUCUCCCCUG	809	usCfsuugAfaCfAfccuuUfcUfcccccsug	1905	antisense	23
AGAAACUUUGGCUGAUAUAU	810	asgsaaacUfuUfGfGfcugauaauL96	1906	sense	21
AUAUUUUCAGCCCAAGUUUCUUC	811	asUfsauuAfuCfAfgecaAfaGfuucuscsc	1907	antisense	23
GAAACUUUGGCUGAUAUAUAU	812	gsasaacuUfuGfGfCfugauaauuL96	1908	sense	21
AAUAUUUUCAGCCCAAGUUUCUUC	813	asAfsuauUfaUfCfagccAfaAfguuucsu	1909	antisense	23
AUGAAGAAACUUUGGCUGAUA	814	asusgaagAfaAfCfUfuggcugauaL96	1910	sense	21
UAUCAGCCCAAGUUUCUUAUCA	815	usAfsucaGfcCfAfaaguUfuCfucauscsc	1911	antisense	23
GAUGAAGAAACUUUGGCUGAU	816	gsasuagaGfaAfAfCfuuuggcugauL96	1912	sense	21
AUCAGCCCAAGUUUCUUAUCAU	817	asUfscagCfcAfaFaguUfCfucaucasu	1913	antisense	23
AAGGCACUGAUGUUUCUGAAAG	818	asasggcaCfuGfAfUfguucugaaagL96	1914	sense	21
CUUUCAGAAACAUCAGUGCCUUUC	819	csUfsuucAfgAfAfaucAfgUfgccuuscsc	1915	antisense	23
AGGCACUGAUGUUUCUGAAAGC	820	asgsgcacUfgAfuUfGfuucugaaagL96	1916	sense	21
GCUUUCAGAAACAUCAGUGCCUUU	821	gsCfsuuuCfaGfAfacauCfaGfugccuusu	1917	antisense	23

CGGAAAAGGCACUGAUGUUCUG	822		csgsgaaaGfgCfAfCfugauuuuugL96	1918	sense	21
CAGAAACAUCAGUGCCUUUCCGCA	823		csAfsгааCfaUfCfagugCfCfUfuuccgscsa	1919	antisense	23
GCGGAAAGGCACUGAUGUUCU	824		gscsggaaAfgGfCfAfcugauuuuL96	1920	sense	21
AGAAACAUCAGUGCCUUUCCGCAC	825		asGfsaacAfuCfAfugugCfUfuuccgesasc	1921	antisense	23
AGAAGACUGACAUCAUUGCCA	826		asgsaagaCfuGfAfCfaucauuuL96	1922	sense	21
UGGCAUAUGAUGUCAGUCUUCUCA	827		usGfsgcaAfuGfAfugucAfgUfuuucscsa	1923	antisense	23
GAAGACUGACAUCAUUGCCAA	828		gsasagacUfgAfCfAfucuuuL96	1924	sense	21
UUGGCAUAUGAUGUCAGUCUUCUC	829		usUfsggcAfaUfGfauuGfCfGfuuucsc	1925	antisense	23
GCUGAGAAAGACUGACAUCAUU	830		gscsugagAfaGfAfCfugacauuL96	1926	sense	21
AAUGAUGUCAGUCUUCUCAGCCA	831		asAfsugaUfgUfCfagucUfuCfucagcsca	1927	antisense	23
GGCUGAGAAAGACUGACAUCAU	832		gsgscugaGfaAfgAfCfugacauuL96	1928	sense	21
AUGAUGUCAGUCUUCUCAGCCA	833		asUfsgauGfuCfAfugucUfCfagccsasu	1929	antisense	23
UAAUGCCUGAUUCACACUUCU	834		usasaugcCfuGfAfUfucacauuL96	1930	sense	21
AAAGUUGUGAAUCAGGCAUUAAC	835		asAfsaguUfgUfGfaucAfgGfcauuasc	1931	antisense	23
AAUGCCUGAUUCACAAUUCUUG	836		asasugccUfgAfUfUfcaacuunL96	1932	sense	21
CAAAGUUGUGAAUCAGGCAUUAAC	837		csAfsaagUfuGfUfgauuCfaGfgcauusasc	1933	antisense	23
UUUGGUAUUGCCUGAUUCACAA	838		ususgguaAfuGfCfCfugauuacaaL96	1934	sense	21
UUUGGUAUUCAGGCAUUAACCAACA	839		usUfsgugAfaUfCfaggcAfuUfaccasasc	1935	antisense	23
GUUGGUAUUGCCUGAUUCACA	840		gsusugguAfaUfGfCfugauuacaaL96	1936	sense	21
UGUGAAUCAGGCAUUAACCAACAC	841		usGfsugaAfuCfAfggcaUfuAfccasasc	1937	antisense	23
UAUCAAAUGGCUGAGAAAGACU	842		usasucaaAfuGfGfCfugagaagaaL96	1938	sense	21
AGUCUUCUCAGCCAUUUGAUUAUC	843		asGfsucuUfcUfCfagccAfuUfugauasusc	1939	antisense	23
AUCAAAUGGCUGAGAAAGACUG	844		asuscaaaUfgGfCfUfgagaagacugL96	1940	sense	21
CAGUCUUCUCAGCCAUUUGAUUAU	845		csAfsugcUfuCfUfagcCfaUfuugausasu	1941	antisense	23
AAGAUUAUCAAAUGGCUGAGAA	846		asasgaauUfcAfaAfaUfggugagaaL96	1942	sense	21
UUCUCAGCCAUUUGAUUAUCUUC	847		usUfscucAfgCfCfauuuGfaUfauuucsc	1943	antisense	23
GAAGAUUAUCAAAUGGCUGAGA	848		gsasagauAfuCfAfAfauggugagaaL96	1944	sense	21
UCUCAGCCAUUUGAUUAUCUUC	849		usCfsucaGfcCfAfuuuGfAfuuuucsc	1945	antisense	23
UCUGACAGUGCACAAUUAUUU	850		uscsugacAfgUfGfCfacaauuuuL96	1946	sense	21
AAAUUAUUGUGCACUGUCAGAU	851		asAfsaauAfuUfGfugcaCfuGfucagasc	1947	antisense	23
CUGACAGUGCACAAUUAUUUC	852		csusgacaGfuGfCfAfaauuuuL96	1948	sense	21
GAAAAUAUUGUGCACUGUCAGAU	853		gsAfsaaaUfaUfUfgugCfAfcUfucagscasu	1949	antisense	23

AAGAUCUGACAGUGCACAAUA	854	asasgaucUfgAfCfAfgugcacaual96	1950	sense	21
UAUUGUGCACUGUCAGAUUCUUG	855	usAfsuugUfgCfAfcuGuCfaGfaucuuosg	1951	antisense	23
CAAGAUCUGACAGUGCACAAU	856	csasagauCfuGfAfCfagugcacaual96	1952	sense	21
AUUGUGCACUGUCAGAUUCUUGGA	857	asUfsuguGfcAfCfugucAfgAfucuuogsgsa	1953	antisense	23
ACUGAUGUUCUGAAAGCUCUG	858	ascuagauGfuUfCfUfgaaagcucugL96	1954	sense	21
CAGAGCUUUCAGAACAUACAGUGC	859	csAfsagCfuUfUfcagaAfcAfucagugsc	1955	antisense	23
CUGAUGUUCUGAAAGCUCUGG	860	csusgaugUfuCfuUfgfaagcucugL96	1956	sense	21
CCAGAGCUUUCAGAACAUACAGUG	861	csCfsagaGfcUfUfucagAfaCfaucagsug	1957	antisense	23
AGGCACUGAUGUUCUGAAAGC	862	asgsgcacUfgAfUfGfuucugaaagL96	1958	sense	21
GCUUUCAGAACAUACAGUGCCUUU	863	gsCfsuuuCfaGfAfacauCfaGfugceusuu	1959	antisense	23
AAGGCACUGAUGUUCUGAAAG	864	asasggcaCfuGfAfUfguucugaaagL96	1960	sense	21
CUUUCAGAACAUACAGUGCCUUUC	865	csUfsuucAfgAfAfaucAfgUfgccuusc	1961	antisense	23
AACAACAUGCUAAAUACAGUAC	866	asascacAfuGfCfUfaaaucauacL96	1962	sense	21
GUACUGAUUUCAGAUUGUUGUUA	867	gsUfsacuGfaUfUfuagCfuGfuuguuuessa	1963	antisense	23
ACAACAUGCUAAAUACAGUACU	868	ascsaacaUfgCfUfAfaucaguacuL96	1964	sense	21
AGUACUGAUUUCAGAUUGUUGUUC	869	asGfsuacUfgAfUfuagCfaUfguugusuc	1965	antisense	23
UAUGAACAAACAUAGCUAAAUCA	870	usasugaaCfaAfCfAfgucuaauacL96	1966	sense	21
UGAUUUAGCAUGUUGUUCAUAAU	871	usGfsauuUfaGfCfauguUfgUfucuuasasu	1967	antisense	23
UUAUGAACAAACAUAGCUAAAUUC	872	ususaugaAfcAfAfcfaugcuauacL96	1968	sense	21
GAUUUAGCAUGUUGUUCAUAAUUC	873	gsAfsuuuAfgCfAfuguuGfuUfcauuausc	1969	antisense	23
UCUUUAGUGUCUGAAAUUAUUC	874	uscsuuuaGfuGfUfCfugaauuaucL96	1970	sense	21
GAUAUAUUUCAGACACUAAAGAUG	875	gsAfsuauAfuUfCfagacAfcUfaaagasug	1971	antisense	23
CUUUAGUGUCUGAAUAUAUCC	876	csusuuaGfUfCfUfgaauuaucL96	1972	sense	21
GGUAUAUUUCAGACACUAAAGAU	877	gsGfsauaUfaUfUfcagaCfaCfuaaagsasu	1973	antisense	23
CACAUCUUUAGUGUCUGAAUA	878	csascaucUfuUfAfGfugucugaauL96	1974	sense	21
UAUUCAGACACUAAAGAUGUGAU	879	usAfsuucAfgAfCfacaAfaGfaugugsasu	1975	antisense	23
UCACAUCUUUAGUGUCUGAAU	880	uscsacauCfuUfUfAfgugucugaauL96	1976	sense	21
AUUCAGACACUAAAGAUGUGAUU	881	asUfsucaGfaCfAfcuaaAfgAfugugasuu	1977	antisense	23
UGAUACUUUUUGAAUGUAGA	882	usgsauacUfuCfUfUfugaauaguagaL96	1978	sense	21
UCUACAUUUCAAGAAGUAUCACC	883	usCfsuacAfuUfCfaagAfaGfuaucascsc	1979	antisense	23
GAUACUUUUUGAAUGUAGAU	884	gsasuacuUfcUfUfUfgaauaguagauL96	1980	sense	21
AUCUACAUAUCAAAGAAGUAUCAC	885	asUfscuaCfaUfUfcaaaGfaAfguaucscsc	1981	antisense	23

UUGGUGAUACUUCUUUGAAUG	886	ususggugAfuAfCfUfucuuuugaagL96	1982	sense	21
CAUUCAAAGAAAGUAUACACCAAUU	887	csAfsuucAfaAfGfaaguAfuCfaccasusu	1983	antisense	23
AUUGGUGAUACUUCUUUGAAU	888	asusggugGfaUfAfCfucuuuugaauL96	1984	sense	21
AUUCAAAGAAAGUAUACACCAAUUA	889	asUfsucaAfaGfAfaguaUfcAfccaaususa	1985	antisense	23
AAUAACCCUGUGAAAAGCUC	890	asasuaacCfuGfUfGfaaaugcuccL96	1986	sense	21
GGAGCAUUUUCACAGGUUAUUGC	891	gsGfsagcAfuUfUfucacAfgGfuuausgsc	1987	antisense	23
AUAACCCUGUGAAAAGCUC	892	asusaaccUfgUfGfAfaaagcuccL96	1988	sense	21
GGGAGCAUUUUCACAGGUUAUUG	893	gsGfsagcCfaUfUfuucaCfaGfguuuusug	1989	antisense	23
UAGCAAUAAACCGUGGAAAAG	894	usasgcaaUfaAfCfCfugugaaaagL96	1990	sense	21
CAUUUUCACAGGUUAUUGCUAUC	895	csAfsuuuUfcAfCfagguUfaUfugcuasusc	1991	antisense	23
AUAGCAUUAACCCUGUGAAAAG	896	asusageaAfuAfaAfCfcugugaaaauL96	1992	sense	21
AUUUUCACAGGUUAUUGCUAUC	897	asUfsuuuCfaCfaAfgguAfuUfgcuasusc	1993	antisense	23
AAUCACAUCUUUAGUGUCUGA	898	asasueacAfuCfUfUfugugucugalL96	1994	sense	21
UCAGACACUAAAGAUGUGAUUGG	899	usCfsagaCfaCfUfaagAfuGfugaauusgsg	1995	antisense	23
AUCACAUCUUUAGUGUCUGAA	900	asuscacaUfcUfUfUfugugucugaalL96	1996	sense	21
UUCAGACACUAAAGAUGUGAUUG	901	usUfscagAfcAfCfuuaaGfaUfgugausug	1997	antisense	23
UUCCAAUACACAUCUUUAGUGU	902	ususccaaUfcAfCfAfucuuuagugulL96	1998	sense	21
ACACUAAAGAUGUGAUUGGAAAU	903	asCfsacuAfaAfGfauguGfaUfuggaasasu	1999	antisense	23
UUUCCAUCACAUUUUAGUG	904	ususuccaAfuCfAfCfaucuuuagugL96	2000	sense	21
CACUAAAGAUGUGAUUGGAAAU	905	csAfsucaAfaGfAfugugAfuUfggaaasusc	2001	antisense	23
ACGGGCAUGAUUGAGUUUCC	906	ascsgggcAfuGfAfUfguugaguuccL96	2002	sense	21
GGAAACUCAACAUCAGCCCGUUC	907	gsGfsaacUfcAfAfaucAfuGfcccgsususc	2003	antisense	23
CGGGCAUGAUUGAGUUCCU	908	csGsggcaUfgAfuGfugugaguuccuL96	2004	sense	21
AGGAACUCAACAUCAGCCCGU	909	asGfsgaaCfuCfAfacauCfaUfgcccgsusu	2005	antisense	23
GGGAACGGGCAUGAUUGUUGAG	910	gsgsgaacGfgGfCfAfugauguugagL96	2006	sense	21
CUCAACAUCAGCCCGUUC	911	csUfscaaCfaUfCfaugcCfcGfuucccsag	2007	antisense	23
UGGGAACGGGCAUGAUUGUUGA	912	usgsggaaCfGfGfCfugauguugaL96	2008	sense	21
UCAACAUCAGCCCGUUC	913	usCfsaacAfuCfAfugccCfGfucccasgsg	2009	antisense	23
ACUAAGGUGAAAAGAUAAUGA	914	ascsuaagGfuGfAfAfaagauaaugL96	2010	sense	21
UCAUUAUCUUUUCACCUUAGUGU	915	usCfsauuAfuCfUfuuucAfcCfuuausgsu	2011	antisense	23
CUAAGGUGAAAAGAUAAUGAU	916	csusaaggUfgAfaAfafagaauaagauL96	2012	sense	21
AUCAUUAUCUUUUCACCUUAGUG	917	asUfscuuUfaUfCfuuuuCfaCfuuausgsg	2013	antisense	23

AAACACUAAGGUGAAAGAU	918	asasacacUfaAfGfGfugaaaaaL96	2014	sense	21
UAUCUUUACACCUAAGUUUGC	919	usAfsucuUfuUfCfaccuUfaGfuguusgsc	2015	antisense	23
CAACACUAAGGUGAAAGAU	920	csasaacaCfuAfAfGfugaaaaaL96	2016	sense	21
AUCUUUUCACCUUAGUUUUGCU	921	asUfscuuUfuCfAfccuuAfgUfguuugscsu	2017	antisense	23
AGGUAGCACUGGAGAGAAUUG	922	asgsuguagCfaCfUfGfagagaaugL96	2018	sense	21
CAAUUCUCUCCAGUGCUACCUUC	923	csAfsauuCfuCfUfCfaccagUfgCfuaccusuc	2019	antisense	23
GGUAGCACUGGAGAGAAUUG	924	ggsuagcAfcUfGfGfagagaaugL96	2020	sense	21
CCAAUUUCUCUCCAGUGCUACCUU	925	csCfsauuUfcUfCfucaCfuGfuaaccsusu	2021	antisense	23
GAGAAAGGUAGCACUGGAGAGA	926	gsasgaagGfuAfGfCfacugagagagL96	2022	sense	21
UCUCUCCAGUGCUACCUUCUCAA	927	usCfsucuCfcAfGfugcuAfcCfuucucasa	2023	antisense	23
UGAGAAAGGUAGCACUGGAGAG	928	usgsagaaGfgUfAfGfcaucuggagL96	2024	sense	21
CUCUCCAGUGCUACCUUCUCAAA	929	csUfscucCfaGfUfgeuaCfcUfucucasa	2025	antisense	23
AGUGGACUUGCUGCAUAUGUG	930	asgsuggaCfuUfGfCfugeauaugL96	2026	sense	21
CACAUUAGCAGCAAGUCCACUGU	931	csAfscauAfuGfCfagcaAfgUfccacugsu	2027	antisense	23
GUGGACUUGCUGCAUAUGUGG	932	gsusggacUfuGfCfUfgcauauugL96	2028	sense	21
CCACAUAUGCAGCAAGUCCACUG	933	csCfsacaUfaUfGfcaagAfaGfuccacsug	2029	antisense	23
CGACAGUGGACUUGCUGCAUA	934	csgsacagUfgGfAfCfuugcugcauL96	2030	sense	21
UAUGCAGCAAGUCCACUGUCGUC	935	usAfsugcAfgCfAfagucCfaCfugucgusuc	2031	antisense	23
ACGACAGUGGACUUGCUGCAU	936	ascsagcaGfuGfGfAfcuugcugcauL96	2032	sense	21
AUGCAGCAAGUCCACUGUCGUCU	937	asUfsgcaGfcAfAfugccAfcUfgucguscu	2033	antisense	23
AAGGUGUUCAAGAUUGUCCUG	938	asasggugUfuCfAfAfgauguccucgL96	2034	sense	21
CGAGGACAUUCUUGAACACCUUUC	939	csGfsaggAfcAfUfcuugAfaCfaccuusuc	2035	antisense	23
AGGUGUUCAAGAUUGUCCUGA	940	asgsugulUfcAfAfGfauuguccugL96	2036	sense	21
UCGAGGACAUUCUUGAACACCUUU	941	usCfsgagGfaCfAfucuuGfaAfcaccususu	2037	antisense	23
GAGAAAGGUGUUCAAGAUUGC	942	gsasgaaaGfgUfGfUfucaagaugL96	2038	sense	21
GACAUCUUUGAACACCUUUCUCCC	943	gsAfscauCfuUfGfaacaCfcUfuucscsc	2039	antisense	23
GGAGAAAGGUGUUCAAGAUUG	944	ggsagaaaAfgGfUfGfuaagaugL96	2040	sense	21
ACAUCUUUGAACACCUUUCUCCCC	945	asCfsaucUfuGfAfafacCfuUfucuccsc	2041	antisense	23
AACCGUCUGGAUGAUGUGCGU	946	asascgcuCfuGfGfAfugaugcgulL96	2042	sense	21
ACGCACAUCAUCCAGACGGUUGC	947	asCfsgcaCfaUfCfaucAfgAfcgguusgsc	2043	antisense	23
ACCGUCUGGAUGAUGUGCGUA	948	ascscgucUfgGfAfUfgaugcgualL96	2044	sense	21
UACGCACAUCAUCCAGACGGUUG	949	usAfsccgAfcAfUfcaucCfaGfaccgusug	2045	antisense	23

GGGCAACCGUCUGGAUGAUGU	950	gsgsgcaaCfcGfUfCfuggaugauL96	2046	sense	21
ACAUCAUCCAGACGGUUGCCCGAG	951	asCfsaucAfuCfCfagacGfgUfugcccsasg	2047	antisense	23
UGGGCAACCGUCUGGAUGAUG	952	usgsggcaAfcCfGfUfCfuggaugauL96	2048	sense	21
CAUCAUCCAGACGGUUGCCCGAGG	953	csAfsucaUfcCfAfgacGfgUfugcccsasg	2049	antisense	23
GAAACUUUGGCUGAUAAUAAU	954	gsasaacuUfuGfGfCfugauauauL96	2050	sense	21
AAUAUUAUCAGCCAAAGUUUCUU	955	asAfsuauUfaUfCfagccAfaAfguuucsus	2051	antisense	23
AAACUUUGGCUGAUAAUAAUUG	956	asasaacuUfgGfCfUfgauauauuL96	2052	sense	21
CAUAUAUAUCAGCCAAAGUUUCUU	957	csAfsauaUfuAfUfCfagcCfaAfaguuuusc	2053	antisense	23
UGAAGAAACUUUGGCUGAUAA	958	usgsaagaAfaCfUfUfuggcugauaaL96	2054	sense	21
UUAUCAGCCAAAGUUUCUUAUC	959	usUfsaucAfgCfCfaagUfuUfcuucasc	2055	antisense	23
AUGAAGAAACUUUGGCUGAUAA	960	asusgaagAfaAfcUfUfuggcugauaL96	2056	sense	21
UAUCAGCCAAAGUUUCUUAUCA	961	usAfsucaGfcCfAfaaguUfuCfuucausca	2057	antisense	23
AAAGGUUUAAGAUGUCCUC	962	asasagguGfuUfCfAfaaguccuL96	2058	sense	21
GAGGACAUCUUUGAACACCUUUCU	963	gsAfsaggCfaUfCfuugaAfcAfccuuusc	2059	antisense	23
AAGGUGUUCAAAGAUGUCCUCG	964	asasggugUfuCfAfaAfgauguccucL96	2060	sense	21
CGAGGACAUCUUUGAACACCUUUC	965	csGfsaggAfcAfuUfcuugAfaCfaccuuusc	2061	antisense	23
GGAGAAAGGUGUUAAGAUGU	966	gsgsagaaAfgGfUfGfuucaagaugL96	2062	sense	21
ACAUCUUUGAACACCUUUCUCCCC	967	asCfsaucUfuGfAfacacCfuUfucuccsc	2063	antisense	23
GGGAGAAAGGUGUUAAGAUG	968	gsgsgagaAfaGfGfUfguucagaugL96	2064	sense	21
CAUCUUUGAACACCUUUCUCCCC	969	csAfsueuUfgAfaAfcacUfuUfucuccsc	2065	antisense	23
AAAUCAUAUCUCCAAAGUCU	970	asasaucaGfuAfcUfUfuccaaagucL96	2066	sense	21
AGACUUUGGAAGUACUGAUUUAG	971	asGfsacuUfuGfGfaaguAfcUfgauuuasg	2067	antisense	23
AAUCAGUACUCCAAAGUCUA	972	asasucagUfaCfUfUfccaagucuaL96	2068	sense	21
UAGACUUUGGAAGUACUGAUUUUA	973	usAfsagacUfuUfGfgaagUfaCfugauusua	2069	antisense	23
UGCUAUAUCAGUACUUCCAA	974	usgscuaaAfuCfAfaGfuacuuccaaL96	2070	sense	21
UUUGGAAGUACUGAUUUAGCAUG	975	usUfsuggAfaGfUfagacUfuUfagcasug	2071	antisense	23
AUGCUAAAUACAGUACUCCAA	976	asusgeuaAfaUfCfAfguacuuccaaL96	2072	sense	21
UUUGGAAGUACUGAUUUAGCAUGU	977	usUfsggaAfgUfAfcugaUfuUfagcausgu	2073	antisense	23
ACAUCUUUAAGUGUCUGAAUUAU	978	ascsaacuUfuAfaGfUfgucugauauL96	2074	sense	21
AUAUUCAGACACUAAAGAUGUGA	979	asUfsauuCfaGfaAfcacuAfaAfgaugusga	2075	antisense	23
CAUCUUUAAGUGUCUGAAUUA	980	csasueuuUfaGfUfGfucugauauaL96	2076	sense	21
UAUAUUCAGACACUAAAGAUGUG	981	usAfsuauUfcAfGfacacUfaAfaugaugsug	2077	antisense	23

AAUCACAUUUUAGUGUCUGA	982	asasucacAfuCfUfUfuagugucugL96	2078	sense	21
UCAGACACUAAAGAUUGAUUGG	983	usCfsagaCfaCfUfaaagAfuGfugausgsg	2079	antisense	23
CAAUACAUUUUAGUGUCUG	984	csasaucaCfaUfCfUfuagugucugL96	2080	sense	21
CAGACACUAAAGAUUGAUUGGA	985	csAfsagacAfcUfaAfaagaUfgUfgauugsgsa	2081	antisense	23
GCAUGUAUUACUUGACAAAGA	986	gscsauguAfuUfAfcfuugacaaagL96	2082	sense	21
UCUUUGUCAAGUAAUACAUGCUG	987	usCfsuuuGfuCfAfaguaAfuAfaugcsusg	2083	antisense	23
CAUGUAUUACUUGACAAAGAG	988	csasuguaUfuAfcUfufugacaaagL96	2084	sense	21
CUCUUUGUCAAGUAAUACAUGCU	989	csUfscuuUfgUfCfaaguAfaUfacaugscsu	2085	antisense	23
UUCAGCAUGUAUUACUUGACA	990	ususcagcAfuGfUfAfuacuugacaL96	2086	sense	21
UGUCAAGUAUACAUGCUGAAAA	991	usGfsucaAfgUfAfauacAfuGfcugaasasa	2087	antisense	23
UUUCAGCAUGUAUUACUUGAC	992	ususucagCfaUfGfUfauuacuugacL96	2088	sense	21
GUCAAGUAAUACAUGCUGAAAA	993	gsUfscaaGfuAfaFuacaUfgCfugaasasa	2089	antisense	23
AUGUUACUUCUUAGAGAGAAA	994	asusguuaCfuUfCfUfuagagagaaalL96	2090	sense	21
UUUCUCUCUAAAGAAAGUAACAUC	995	usUfsucuCfuCfUfaagaAfgUfaacausasc	2091	antisense	23
UGUUACUUCUUAGAGAGAAAU	996	usgsuuacUfuCfUfUfagagagaaalL96	2092	sense	21
AUUUCUCUCUAAAGAAAGUAACAUA	997	asUfsuucUfcUfCfuaagAfaGfuacacusa	2093	antisense	23
AUGUAUGUUACUUCUUAGAGA	998	asusguauGfuUfAfcfuucuuagagalL96	2094	sense	21
UCUCUAAAGAAAGUAACAUAUCC	999	usCfsucuAfaGfAfaaguaAfcAfuacauscsc	2095	antisense	23
GAUGUAUGUUACUUCUUAGAG	1000	gsasuguaUfgUfUfAfcuucuuagagL96	2096	sense	21
CUCUAAAGAAAGUAACAUAUCCU	1001	csUfscuaAfgAfaFuuaaCfaUfacaucscsu	2097	antisense	23
ACAACUUUGAGAAAGGUAGCAC	1002	ascsaacuUfuGfAfGfaagguagacL96	2098	sense	21
GUGCUACCUUCUCUAAAGUUUGUGA	1003	gsUfsgcuAfcCfUfucucAfaAfguugsgsa	2099	antisense	23
CAACUUUGAGAAAGGUAGCACU	1004	csasacuUfgAfGfAfagguagcaculL96	2100	sense	21
AGUGCUACCUUCUCUAAAGUUUGUG	1005	asGfsugeUfaCfCfuucuCfaAfauguusg	2101	antisense	23
AUUCACACUUUUGAGAAAGGUA	1006	asusucacAfaCfUfUfugagaaaggualL96	2102	sense	21
UACCUUCUCUAAAGUUUGAGAAUCA	1007	usAfsccuUfcUfCfaagUfuGfugaauasca	2103	antisense	23
GAUUCACACUUUUGAGAAAGGU	1008	gsasuucaCfaAfcUfuugagaaaggulL96	2104	sense	21
ACCUUCUCUAAAGUUUGAGAAUCAG	1009	asCfscuuCfuCfaAfaaguUfgUfgaaucsasg	2105	antisense	23
AACAUGCUAAAUACAGUACUUC	1010	asascaugCfuAfaAfAfucaguacuulL96	2106	sense	21
GAAUACUGAUUUAGCAUGUUGU	1011	gsAfsaguAfcUfGfauuuAfgCfauguusgsu	2107	antisense	23
ACAUGCUAAAUACAGUACUUC	1012	ascsaugcUfaAfaUfucaguacuulL96	2108	sense	21
GGAAGUACUGAUUUAGCAUGUUG	1013	gsGfsaagUfaCfUfgaauUfaGfcaugusg	2109	antisense	23

GAACAAACAUAGCUAAAUCAGUA	1014	gsasacaaCfaUfGfCfuaaaaucaguaL96	2110	sense	21
UACUGAUUUAGCAUGUUGUUCAU	1015	usAfsucgAfuUfUfagcaUfgUfuguucasu	2111	antisense	23
UGAACAAACAUAGCUAAAUCAGU	1016	usgsaacaAfcAfUfGfcaaaucagL96	2112	sense	21
ACUGAUUUAGCAUGUUGUUCAUUA	1017	asCfsugaUfuUfAfGfcgauGfuUfguucasua	2113	antisense	23
AAACCAGUACUUUAUCAUUUU	1018	asasaccaGfuAfCfUfuaucanuulL96	2114	sense	21
AAAUGAUAAAAGUACUGGUUUCA	1019	asAfsaauGfaUfAfaaguAfcUfgguuucsa	2115	antisense	23
AACCAGUACUUUAUCAUUUC	1020	asasccagUfaCfUfUfuaucanuulL96	2116	sense	21
GAAAAUGAUAAAAGUACUGGUUUUC	1021	gsAfsaaaUfgAfUfuaagUfaCfugguuusc	2117	antisense	23
UUUGAAACCCAGUACUUUAUCA	1022	ususugaaAfcCfAfGfuaucuuuaucL96	2118	sense	21
UGAUAAAGUACUGGUUUUCAAAAU	1023	usGfsaauAfaGfUfagugGfuUfuaaasasu	2119	antisense	23
UUUUGAAACCAGUACUUUAUC	1024	ususaugaAfaCfCfAfguacuuuaucL96	2120	sense	21
GAUAAAGUACUGGUUUUCAAAAUU	1025	gsAfsuaaAfgUfAfucggUfuUfcaaaasusu	2121	antisense	23
GAGAAAGUAGGGCUACAAGGCC	1026	gsasgaagAfuGfGfGfcaacaagccL96	2122	sense	21
GGCCUUUGAGCCCCAUCUUCUCUG	1027	gsGfsceuUfgUfAfGcccAfuCfuucucsusg	2123	antisense	23
AGAAAGUAGGGCUACAAGGCCA	1028	asgsaagaUfgGfGfCfuacaaggccL96	2124	sense	21
UGGCCUUGUAGCCCAUCUUCUCU	1029	usGfsgccUfuGfUfagccCfaUfcuucscsu	2125	antisense	23
GGCAGAGAAAGUAGGGCUACAA	1030	gsgscagaGfaAfGfAfugggcuacaaL96	2126	sense	21
UUUAGCCCCAUCUUCUCUGCCUG	1031	usUfsguaGfcCfCfaucuUfcUfcugccsusg	2127	antisense	23
AGCAGAGAGAGUAGGGCUACA	1032	asgsgcagAfgAfAfGfauaggcuacL96	2128	sense	21
UGUAGCCCCAUCUUCUCUGCCUGC	1033	usGfsuagCfcCfAfucuuCfuCfugccusgsc	2129	antisense	23
AACGGGCAUGAUGUUUGAGUUC	1034	asasegggCfaUfGfAfuguuagaguucL96	2130	sense	21
GAACUCAACAUCUAGCCCGUUC	1035	gsAfsacuCfaAfCfaucaUfgCfccguuscsc	2131	antisense	23
ACGGGCAUGAUGUUUGAGUUC	1036	ascsgggcAfuGfAfUfguugaguucL96	2132	sense	21
GGAAUCUCAACAUCUAGCCCGUUC	1037	gsGfsaacUfcAfAfaucAfuGfccccususc	2133	antisense	23
UGGGAACGGGCAUGAUGUUUGA	1038	usgsggaaCfGfGfCfauaguuuagL96	2134	sense	21
UCAACAUCUAGCCCGUUCGCCAGG	1039	usCfsaacAfuCfAfagccCfGfucccasgsg	2135	antisense	23
CUGGGACCGGCAUGAUGUUG	1040	csusgggaAfcGfGfGfcaugauugL96	2136	sense	21
CAACAUCUAGCCCGUUCGCCAGGG	1041	csAfsacaUfcAfUfGcccGfuUfccagsgsg	2137	antisense	23
AUGUGGCUAAAGCAAUAGACC	1042	asusuggCfuAfAfAfgcaauagaccL96	2138	sense	21
GGUCUUAUUGCUUUAAGCCACAUAU	1043	gsGfsucuAfuUfGfuuuAfgCfcacaasasu	2139	antisense	23
UGUGGCUAAAGCAAUAGACCC	1044	usgsuggcUfaAfAfGfcauagaccL96	2140	sense	21
GGGUCUAUUGCUUUAAGCCACAUA	1045	gsGfsgucUfaUfUfgcuUfaGfccaasusa	2141	antisense	23

GCAUAUGUGGCUAAAGCAAUA	1046	gscsauuGfuGfGfCfuaagcaauL96	2142	sense	21
UAUUGCUUUAGCCACAU AUGCAG	1047	usAfsuugCfuUfUfagccAfcAfuauagsasg	2143	antisense	23
UGCAUAUGUGGCUAAAGCAAU	1048	usgscauaUfgUfGfGfcauaagcauL96	2144	sense	21
AUUGCUUUAGCCACAU AUGCAGC	1049	asUfsugeUfuUfAfgccaCfaUfaugcasgsc	2145	antisense	23
AGGAUGCUCCGGAUUGUCU	1050	asgsgaugCfuCfCfGfgaauuguculL96	2146	sense	21
AGCAACAUCUCCGGAGCAUCCUUG	1051	asGfscacCfaUfUfcccgaAfcCfaucousug	2147	antisense	23
GGAUGCUCCGGAAUGUUGCUG	1052	gsgsaugcUfcCfGfGfauugucugL96	2148	sense	21
CAGCAACAUCUCCGGAGCAUCCUU	1053	csAfsgeaAfcAfuUfuccgGfaGfcaucsesu	2149	antisense	23
UCCAAGGAUGCUCCGGAUUGU	1054	uscsaagGfaUfGfCfuccggaugulL96	2150	sense	21
ACAUUCCGGAGCAUCCUUGGAUA	1055	asCfsauuCfcGfGfageaUfcCfuuggasasa	2151	antisense	23
AUCCAAGGAUGCUCCGGAUUG	1056	asusceaaGfgAfuUfGfucccggaugL96	2152	sense	21
CAUUCGGGAGCAUCCUUGGAUAC	1057	csAfsuucCfGfGfAfgcauUfcUfuggausasc	2153	antisense	23
UCACAUCUUUAGUGUCUGAAU	1058	uscsacauCfuUfUfAfgugucugaauL96	2154	sense	21
AUUCAGACACUAAAGAUUGAUU	1059	asUfsucaGfaCfaAfcuaaAfgAfuugugasusu	2155	antisense	23
CACAUCUUUAGUGUCUGAAUA	1060	csascaucUfuUfAfuGfugucugaauL96	2156	sense	21
UAUUCAGACACUAAAGAUUGAU	1061	usAfsuucAfgAfcfacuaAfaGfaugugsasu	2157	antisense	23
CCAUAUCACUUCUUAGUGUCU	1062	csascaucAfcAfuUfCfuuauguguculL96	2158	sense	21
AGACACUAAAGAUUGAUUGGAA	1063	asGfsacaCfuAfaAfaagauGfuGfaugggsasa	2159	antisense	23
UCCAUAUCACUUCUUAGUGUC	1064	uscscauAfcAfcAfuUfucuuuguculL96	2160	sense	21
GACACUAAAGAUUGAUUGGAAA	1065	gsAfscaeUfaAfaAfaugUfgAfuuggasasa	2161	antisense	23
AAUUGUUCUUAGACACACGUCA	1066	asasaugulGfuUfUfAfgacaacgucalL96	2162	sense	21
UGACGUUGUCUAAACACAUUUUC	1067	usGfsacgUfuGfUfucuaAfcAfcuuuusc	2163	antisense	23
AAUGUUCUUAGACACACGUCAU	1068	asasugugUfuUfAfgfacaacgucalL96	2164	sense	21
AUGACGUUGUCUAAACACAUUUU	1069	asUfsgacGfuUfGfucuaAfaCfacaunusu	2165	antisense	23
UUGAAAUAUGUGUUUAGACAAAC	1070	ususgaaaAfuGfUfGfuuaagacaacL96	2166	sense	21
GUUGUCUAAACACAUUUUCAAUG	1071	gsUfsuguCfuAfaAfacacAfuUfuucaausug	2167	antisense	23
AUUGAAAUAUGUUUAGACAA	1072	asusugaaAfaUfGfUfguuuagacaalL96	2168	sense	21
UUUGUCUAAACACAUUUUCAAUGU	1073	usUfsgucUfaAfaAfcacaUfuUfucaausgu	2169	antisense	23
UACUAAAGGAAGAAUUCGGU	1074	usascuaaAfgGfAfaAfgaaucggulL96	2170	sense	21
ACCGGAUUUCUCCUUUAGUAUC	1075	asCfseggAfaUfUfucucCfuUfuaguasusc	2171	antisense	23
ACUAAAGGAAGAAUUCGGGU	1076	ascsuaaaGfgAfaAfgfaauucggulL96	2172	sense	21
AACCGGAUUUCUCCUUUAGUAU	1077	asAfsccgGfaAfuUfucuuCfcUfuuaugasusu	2173	antisense	23

GAGAUACUAAAGGAAGAAUUC	1078	gsasgauCfuAfAfAfggaagaauL96	2174	sense	21
GAAUUCUCCUUAGUAUCUCGA	1079	gsAfsauCfuUfCfcuuAfgUfaucucgsa	2175	antisense	23
CGAGAUACUAAAGGAAGAAUUC	1080	csagsauAfcUfAfAfggaagaauL96	2176	sense	21
AAUUCUCCUUAGUAUCUCGAG	1081	asAfsuucUfuCfCfuuaGfuAfucucgsag	2177	antisense	23
AACUUUGGUGUAUAAUUGC	1082	asascuuGfgCfUfGfauaauuagL96	2178	sense	21
GCAAUUUUUCAGCCAAAGUUUC	1083	gsCfsauAfuUfAfucagCfcAfaaguusuc	2179	antisense	23
ACUUUGGUGUAUAAUUGCA	1084	ascsuuugGfcUfGfAfuauauugcaL96	2180	sense	21
UGCAAUUAUUCAGCCAAAGUUU	1085	usGfscAAUfaUfUfaucaGfcCfaagusus	2181	antisense	23
AAGAAACUUUGGUGUAUAAU	1086	asasgaaCfuUfUfGfgcugauaauL96	2182	sense	21
UAUUAUCAGCCAAAGUUUCUCA	1087	usAfsuuaUfcAfGfccAAfgUfuucuscA	2183	antisense	23
GAAGAAACUUUGGUGUAUAAU	1088	gsasagaaAfcUfUfUfggcuagauaauL96	2184	sense	21
AUUAUCAGCCAAAGUUUCUCAU	1089	asUfsuauCfaGfcfcaaaGfuUfucucasu	2185	antisense	23
AAUUGGUGAGAGACUGACA	1090	asasauggCfuGfAfGfaagacugacalL96	2186	sense	21
UGUCAGUCUUCACAGCCAUUUGA	1091	usGfsucaGfuCfUfucucAfgCfcauuusgsa	2187	antisense	23
AAUUGGUGAGAGACUGACAU	1092	asasuugcUfgAfGfAfagacugacauL96	2188	sense	21
AUGUCAGUCUUCACAGCCAUUUG	1093	asUfsgucAfgUfCfuucCfaGfccauusug	2189	antisense	23
UAUCAAAUGGUGAGAGACU	1094	usasucAAfuGfGfCfugagaagaauL96	2190	sense	21
AGUCUUCUCAGCCAUUUGAUUUC	1095	asGfsucUfcUfCfagccAfuUfugauasuc	2191	antisense	23
AUAUCAAAUGGUGAGAGAC	1096	asusaucAfaUfGfGfcugagaagacL96	2192	sense	21
GUCUUCUCAGCCAUUUGAUUUCU	1097	gsUfscuuCfuCfAfagccUfuUfgauauesu	2193	antisense	23
GUGGUUCUUAUUUGUAAGCU	1098	gsusgguuCfuUfAfAfauguaagcuL96	2194	sense	21
AGCUUACAAUUUAAGAACCCACUG	1099	asGfscuuAfcAfAfuuuaAfgAfaccacsug	2195	antisense	23
UGGUUCUUAUUUGUAAGCUC	1100	usgsguucUfuAfAfAfuguaagcucL96	2196	sense	21
GAGCUUACAAUUUAAGAACCCACU	1101	gsAfsgcuUfaCfAfauuuAfaGfaaccascu	2197	antisense	23
AACAGUGGUUCUUAUUUGUA	1102	asascaguGfgUfUfCfuaauuagL96	2198	sense	21
UACAAUUUAAGAACCCACUGUUU	1103	usAfscaaUfuUfAfagaaCfcAfcuguusuu	2199	antisense	23
AAACAGUGGUUCUUAUUUGU	1104	asasacagUfgGfUfUfcauauuagL96	2200	sense	21
ACAAUUUAAGAACCCACUGUUUUA	1105	asCfsauUfuAfaAfgaacCfaCfuguuusua	2201	antisense	23
AAGUCAUCGACAAAGACAUUGG	1106	asasgucaUfcGfAfCfaagacauugL96	2202	sense	21
CCAUGUCUUGCGAUGACUUUC	1107	csCfsauGfuCfUfugucGfaUfgacuusuc	2203	antisense	23
AGUCAUCGACAAAGACAUUGGU	1108	asgsucauCfGfAfCfAfaagacauugL96	2204	sense	21
ACCAAUGUCUUGCGAUGACUUU	1109	asCfscAAUfgUfCfuuuGfAfuagacusuu	2205	antisense	23

GUGAAAAGUCAUCGACAAAGACA	1110	gsusgaaaGfuCfAfUfcgacaagacaL96	2206	sense	21
UGUCUUUGUCGAUGACUUUCACAU	1111	usGfsucuUfgUfCfgaugAfcUfuucacsasu	2207	antisense	23
UGUGAAAGUCAUCGACAAAGAC	1112	usgsugaaAfgUfCfAfcgacaagacL96	2208	sense	21
GUCUUGUCGAUGACUUUCACAUU	1113	gsUfscuuGfuCfGfauGaCfuUfucacasusu	2209	antisense	23
GAUAAUUAUUGCAGCAUUUUC	1114	gsasuaauAfuUfGfCfagcauuuuccL96	2210	sense	21
GGAAAAGUCUGCAAAUUAUCAG	1115	gsGfsaaaAfuGfCfugcaAfuAfuuaucsaag	2211	antisense	23
AUAUAUUGCAGCAUUUUC	1116	asusaauUfuGfCfAfcgaauuuuccaL96	2212	sense	21
UGGAAAAGUCUGCAAAUUAUCA	1117	usGfsaaaAfuUfGfugcAfaUfauuauccsa	2213	antisense	23
GGCUGAAUUAUUGCAGCAUU	1118	gsgscugaUfaAfuAfuugcagcauL96	2214	sense	21
AAUGCUGCAAAUUAUCAGCCAA	1119	asAfsugcUfgCfAfaauUfaUfcagccsasa	2215	antisense	23
UGGCUGAAUUAUUGCAGCAU	1120	usgsgcugAfuAfuUfauugcagcauL96	2216	sense	21
AUGCUGCAAAUUAUCAGCCAAA	1121	asUfsgcuGfcAfauuUfuCfagccasasa	2217	antisense	23
GCUAAUUGUAUCAUUA	1122	gscsuauUfuGfUfAfucaugaauaL96	2218	sense	21
UAAUCAUUGUAUCAAAUUAAGCCG	1123	usAfsaucAfuUfGfauacAfaAfuuaagcscg	2219	antisense	23
CUAAUUGUAUCAUUAUUAU	1124	csusaauUfgUfAfuUfcaugaauaL96	2220	sense	21
AUAUCAUUGUAUCAAAUUAAGCC	1125	asUfsaaUcfaUfUfgauaCfaAfauuagcsc	2221	antisense	23
CCCGGCUAAUUGUAUCAUUA	1126	cscscggcUfaAfuUfuguaucagL96	2222	sense	21
CAUUGUAUCAAAUUAAGCCGGGG	1127	csAfsuugAfuAfuCfaauUfaGfccggggsgg	2223	antisense	23
CCCCGGCUAAUUGUAUCAU	1128	cscscggcCfuAfuUfuguaucuuL96	2224	sense	21
AUUGUAUCAAAUUAAGCCGGGGA	1129	asUfsugaUfaCfaAfaauUfgCfcggggsgsa	2225	antisense	23
UAAUUGGUAUCUUCUUUGA	1130	usasaauGfuGfAfuUfacuuuuugaL96	2226	sense	21
UCAAAAGAAUAUACCAAAUUAAC	1131	usCfsaaaGfaAfuGfuaucAfcCfaauuascsc	2227	antisense	23
AAUUGGUAUCUUCUUUGAA	1132	asasuuggUfgAfuUfauuucuuugaL96	2228	sense	21
UUCAAAGAAUAUACCAAAUUAAC	1133	usUfscaaAfgAfuAfuuaUcfaCfaauuasc	2229	antisense	23
GCGGUAUUAUUGGUAUACUUCU	1134	gscsgguaAfuUfGfGfugauuuuL96	2230	sense	21
AGAAGUAUACCAAAUUAACCGCCA	1135	asGfsaagUfaUfCfaccAfuUfaccgcsca	2231	antisense	23
GGCGGUAUUAUUGGUAUACUUC	1136	gsgscggUfaUfUfGfugauuuuL96	2232	sense	21
GAAGUAUACCAAAUUAACCGCCAC	1137	gsAfsaguAfuCfAfcuaUfuAfcgcsasac	2233	antisense	23
CAGUGGUUCUUAUUAUUAAG	1138	csasugggUfuCfuUfuaauuuaagL96	2234	sense	21
CUUACAUAUUAAGAACACACUGUU	1139	csUfsuacAfaUfUfuaagAfaCfcacugsusu	2235	antisense	23
AGUGGUUCUUAUUAUUAAGC	1140	asgsuggUfcUfuUfuaauuuaagL96	2236	sense	21
GCUUACAUAUUAAGAACACACUGU	1141	gsCfsuuaCfaUfUfuaaGfaAfcacugsu	2237	antisense	23

AAAACAGUGGUUCUAAAUG	1142	asasaacaGfuGfGfUfucuuuuuuL96	2238	sense	21
CAUUUUAAGAACACACUGUUUAA	1143	csAfsauUfaAfGfaaccAfUfguuusasa	2239	antisense	23
UAAAACAGUGGUUCUAAAUG	1144	usasaacAfGfGfGfuuuuuuL96	2240	sense	21
AAUUUAAGAACACACUGUUUAAA	1145	asAfsuuAfaGfAfaccaCfuGfuuuuasa	2241	antisense	23
ACCUGUAUUCUGUUUACAUGU	1146	ascscuguAfuUfCfUfguuuuacauL96	2242	sense	21
ACAUGUAAACAGAAUACAGGUUA	1147	asCfsaugUfaAfAfcaGfAfaCaggusasa	2243	antisense	23
CCUGUAUUCUGUUUACAUGUC	1148	csCsuguaUfuCfUfGfuuuacauL96	2244	sense	21
GACAUGUAAACAGAAUACAGGUU	1149	gsAfscuGfuAfAfacagAfaUfacaggsusu	2245	antisense	23
AUUAACCGUAUUCUGUUUAC	1150	asusuaacCfuGfUfAfucuguuuacL96	2246	sense	21
GUAAACAGAAUACAGGUUAAUAA	1151	gsUfsaacCfaGfAfauacAfgGfuuausasa	2247	antisense	23
UAUUAACCGUAUUCUGUUUA	1152	usasuuaaCfcUfGfUfauucuguuuL96	2248	sense	21
UAAACAGAAUACAGGUUAAUAAA	1153	usAfsaacAfGfAfuaCaGfGfuaauasasa	2249	antisense	23
AAGAAACUUUGGCUGAAUAA	1154	asasgaaaCfuUfUfGfGfugauauL96	2250	sense	21
UAUUAUCAGCCAAAGUUUCUUA	1155	usAfsuuaUfcAfGfcaAafGfUfuuuucsa	2251	antisense	23
AGAAACUUUGGCUGAAUAAU	1156	asgsaaacUfuUfGfGfGfugauauL96	2252	sense	21
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GAUGAAGAAACUUUGGCUGAU	1158	gsasugaaGfaAfAfCfuunggugauL96	2254	sense	21
AUCAGCCAAAGUUUCUUCUUAU	1159	asUfscagCfcAfAfaguuUfcUfuaucasu	2255	antisense	23
UGAUGAAGAAACUUUGGCUGA	1160	usgsaugaAfGfAfAfAfcuuugcgauL96	2256	sense	21
UCAGCCAAAGUUUCUUCUUAU	1161	usCfsageCfaAfAfaguuUfcUfcaucasu	2257	antisense	23
GAAAGGUGUUAAGAUGUCCU	1162	gsasaaggUfgUfUfCfagauuguccuL96	2258	sense	21
AGGACAUCUUGAACACCUUUCUC	1163	asGfsgacAfuCfUfugaaCfaCfuuuucusc	2259	antisense	23
AAAGGUGUUAAGAUGUCCUC	1164	asasagguGfuUfCfAfagauuguccuL96	2260	sense	21
GAGGACAUCUUGAACACCUUUCU	1165	gsAfsggaCfaUfCfuugaAfcAfccuuucsu	2261	antisense	23
GGGAGAAAGGUGUUAAGAUG	1166	gsGsgagaAfaGfGfUfguuuacauL96	2262	sense	21
CAUCUUGAACACCUUUCUCCCCC	1167	csAfsucuUfgAfAfcaCfuUfucuccscsc	2263	antisense	23
GGGAGAAAGGUGUUAAGAUG	1168	gsGsggagAfaAfGfGfuuuacauL96	2264	sense	21
AUCUUGAACACCUUUCUCCCCCU	1169	asUfscuuGfaAfCfaccuUfuCfuccccscsu	2265	antisense	23
AUCUUGGUGUCGAUUAUGGG	1170	asuscuuGfuGfUfCfGfaucaugggL96	2266	sense	21
CCCAUGAUUCGACACCAAGAUC	1171	csCfscuGfaUfUfGfGfAfaCfaaguscsc	2267	antisense	23
UCUUGGUGUCGAUUAUGGGG	1172	uscsuuggUfgUfCfGfaucauggggL96	2268	sense	21
CCCCAUGAUUCGACACCAAGAUC	1173	csCfscuUfgAfUfucgaCfaCfaaguscsc	2269	antisense	23

UGGGAUCUUGGUGUCGAAUCA	1174	usgsggauCfuUfGfGfugucgaaucL96	2270	sense	21
UGAUUCGACACCAAGAUCCCAUU	1175	usGfsauuCfGfAfCfaccAfGfAfucccausu	2271	antisense	23
AUGGGAUCUUGGUGUCGAAUC	1176	asusgggaUfcUfUfGfGfugucgaaucL96	2272	sense	21
GAUUCGACACCAAGAUCCCAUUC	1177	gsAfsuucGfaCfAfccaaGfaUfccaususc	2273	antisense	23
GCUACAAGGCCAUUUUGUGA	1178	gscsuacaAfGfGfCfCfaauuuugugal96	2274	sense	21
UCACAAAUAUGGCCUUGUAGCCC	1179	usCfsacaAfaUfAfuggcCfuUfguagcsc	2275	antisense	23
CUACAAGGCCAUUUUGUGAC	1180	csusacaaGfGfCfCfAfauuugugacL96	2276	sense	21
GUCACAAAUAUGGCCUUGUAGCC	1181	gsUfscacAfaAfaUfauuggCfcUfuguagcsc	2277	antisense	23
AUGGGCUACAAGGCCAUUUU	1182	asusgggcUfaCfAfAfGgccaauuuL96	2278	sense	21
AAUAUGGCCUUGUAGGCCAUCU	1183	asAfsauaUfGfGfCfcuugUfaGfccaucsu	2279	antisense	23
GAUGGGCUACAAGGCCAUUU	1184	gsasugggCfuAfCfAfagggccaauuL96	2280	sense	21
AAUAUGGCCUUGUAGGCCAUCUU	1185	asAfsauGfGfCfCfuugAfGfccaucsu	2281	antisense	23
ACUGGAGAGAAUUGGAAUGGG	1186	ascusgggaGfaGfAfAfuggaauuggL96	2282	sense	21
CCCAUUCCAUAUUCUCCAGUGC	1187	csCfscuuUfcCfAfaauucUfcUfccaugsc	2283	antisense	23
CUGGAGAGAAUUGGAAUGGGU	1188	csusgggagAfGfAfAfUfuggaauugguL96	2284	sense	21
ACCAUUCUCCAUUCUCUCCAGUG	1189	asCfscacUfuCfCfaauuCfuCfuccagsg	2285	antisense	23
UAGCACUGGAGAGAAUUGGAA	1190	usasgcacUfGfGfAfGfagaauuggaal96	2286	sense	21
UUCCAUAUUCUCCAGUGCACCU	1191	usUfscacAfuUfCfucucCfaGfugcuascsc	2287	antisense	23
GUAGCACUGGAGAGAAUUGGA	1192	gsusagcaCfuGfGfAfGfagaauuggaL96	2288	sense	21
UCCAUAUUCUCCAGUGCACCU	1193	usCfscacUfuCfUfuccAfGfUfGcuacscsu	2289	antisense	23
ACAGUGGACACACCUUACCU	1194	ascasagGfAfaCfAfCfaccuuaccugL96	2290	sense	21
CAGGUAAGGUGUGUCCACUGUCA	1195	csAfsagguAfaGfGfugugUfcCfagugscsa	2291	antisense	23
CAGUGGACACACCUUACCU	1196	csasugggAfCfAfCfAfcuuaccugL96	2292	sense	21
CCAGGUAAGGUGUGUCCACUGUC	1197	csCfsaggUfaAfGfGfugugGfuCfcaugscusc	2293	antisense	23
UGUGACAGUGGACACACCUUA	1198	usgsugacAfGfUfGfGfaccacacuuuL96	2294	sense	21
UAAGGUGUGUCCACUGUCACAAA	1199	usAfsaggUfGfUfGfuccaCfuGfucacasa	2295	antisense	23
UUUGACACAGUGGACACACCUU	1200	ususuggaCfaGfUfGfGfaccacacuuL96	2296	sense	21
AAGGUGUGUCCACUGUCACAAA	1201	asAfsagguGfuGfUfGfaccUfGfUfcaacaasu	2297	antisense	23
GAAGACUGACAUCAUUGCCAA	1202	gsasagacUfGfAfCfAfucuuugccaaL96	2298	sense	21
UUUGCAUUGAUGUCAGUCUCUC	1203	usUfsggcAfaUfGfGfauGfCfaGfucucusc	2299	antisense	23
AAGACUGACAUCAUUGCCAAU	1204	asasgacuGfaCfAfUfcauuugccaaL96	2300	sense	21
AUUGGCAUUGAUGUCAGUCUCUCU	1205	asUfsuggCfaAfUfGfauGfUfcAfGucucusc	2301	antisense	23

CUGAGAAAGACUGACAUCAUUG	1206	csusgagaAfgAfCfUfgacaucauugL96	2302	sense	21
CAAUGAUGUCAGUCUUCUCAGCC	1207	csAfsaugAfuGfUfcaguCfuUfcuagcsc	2303	antisense	23
GCUGAGAAAGACUGACAUCAU	1208	gscsugagAfaGfAfCfugacaucauL96	2304	sense	21
AAUGAUGUCAGUCUUCUCAGCCA	1209	asAfsugaUfgUfcfagucUfuCfucagcscsa	2305	antisense	23
GCUCAGGUUCAAAGUGUUGGU	1210	gscsucagGfuUfCfAfaagugugguL96	2306	sense	21
ACCAACACUUGAACCUAGAGCUU	1211	asCfscaaCfaCfUfuugaAfcCfugagcsusu	2307	antisense	23
CUCAGGUUCAAAGUGUUGGUA	1212	csuscaggUfuCfAfAfagugugguL96	2308	sense	21
UACCAACACUUGAACCUAGAGCU	1213	usAfsccaAfcAfCfuuugAfaCfcugagcscsu	2309	antisense	23
GUAAGCUCAGGUUCAAAGUGU	1214	gsusaagcUfcAfGfGfuucaagugulL96	2310	sense	21
ACACUUUGAACCUAGAGCUUACAA	1215	asCfsaenUfuGfAfafacuGfaGfcuuacsasa	2311	antisense	23
UGUAAAGCUCAGGUUCAAAGUG	1216	usgsuaagCfuCfAfGfguucaaaugL96	2312	sense	21
CACUUUGAACCUAGAGCUUACAAU	1217	csAfsctuUfgAfAfccugAfgCfuuacasa	2313	antisense	23
AUGUAUUACUUGACAAAGAGA	1218	asusguauUfaCfUfUfgacaaagagaL96	2314	sense	21
UCUCUUUGUCAAGUAAUACAUGC	1219	usCfsuauUfuGfUfcaagUfaAfuacausgsc	2315	antisense	23
UGUAUUACUUGACAAAGAGAC	1220	usgsuauuAfcUfUfGfacaagagacL96	2316	sense	21
GUCUCUUUGUCAAGUAAUACAUG	1221	gsUfscucUfuUfGfucuaGfuAfaucasuug	2317	antisense	23
CAGCAUGUAUUACUUGACAA	1222	csasgeauGfuAfUfUfacuugacaaalL96	2318	sense	21
UUUGUCAAGUAAUACAUGCUGAA	1223	usUfsuguCfaAfGfuauuAfcAfugcugsasa	2319	antisense	23
UCAGCAUGUAUUACUUGACAA	1224	uscsagcaUfgUfAfUfuaucAfgUfugcagcsc	2320	sense	21
UUUGUCAAGUAAUACAUGCUGAA	1225	usUfsgucAfaGfUfaauaCfaUfugcugasasa	2321	antisense	23
CUGCAACUGUAUUAUCUACAAG	1226	csusgcaaCfuGfUfAfuaucuaaagL96	2322	sense	21
CUUGUAGUAUUAACAGUUGCAGCC	1227	csUfsuguAfgAfUfaucAfgUfugcagcsc	2323	antisense	23
UGCAACUGUAUUAUCUACAAG	1228	usgscaacUfgUfAfUfaucuaaagL96	2324	sense	21
CCUUGUAGUAUUAACAGUUGCAGC	1229	csCfsuugUfaGfAfuaaCfaGfuugcagcsc	2325	antisense	23
UUGGCUGCAACUGUAUUAUCUA	1230	usugsgcuGfcAfAfCfuguauaucauL96	2326	sense	21
UAGAUUAACAGUUGCAGCCAACG	1231	usAfsgauAfuAfCfaguGfcAfgccaacsag	2327	antisense	23
GUUGGCUGCAACUGUAUUAUCU	1232	gusuggeUfgCfAfAfCfuguauaucauL96	2328	sense	21
AGAUUAACAGUUGCAGCCAACGA	1233	asGfsauaUfaCfAfaguGfcAfgccaacsasa	2329	antisense	23
CAAUUGAUGAAGAAACUUUGG	1234	csasaauGfuGfAfAfgaacuugL96	2330	sense	21
CCAAAGUUUCUUAUCAUUUGCC	1235	csCfsaaaGfuUfUfcuucAfuCfauuugcsc	2331	antisense	23
AAUUGAUGAAGAAACUUUGGC	1236	asasaugaUfgAfAfGfaacuuggeL96	2332	sense	21
GCCAAAGUUUCUUAUCAUUUGC	1237	gsCfscaaAfgUfUfucuuCfaUfcauuugsc	2333	antisense	23

GGGGCAAUAUGAUGAAGAAACU	1238	gsgsggcaAfaUfGfAfugaagaaculL96	2334	sense	21
AGUUUCUUCAUCAUUUGCCCCAG	1239	asGfsuuuCfuUfCfaucAUfUfgcccsasg	2335	antisense	23
UGGGGCAAAUGAUGAAGAAAC	1240	usgsgggcAfaAfUfGfugaagaaculL96	2336	sense	21
GUUUCUUCAUCAUUUGCCCCAGA	1241	gsUfsuucUfuCfAfucAUfUfGfccccasgsa	2337	antisense	23
CAAAGGGUGUCGUUCUUUCC	1242	csasaaggGfuGfUfCfguucuuuclL96	2338	sense	21
GGAAAAGAACGACACCCUUUGUA	1243	gsGfsaaaAfzAfAfagacAfcCfuuuugsusa	2339	antisense	23
AAAGGGUGUCGUUCUUUCCA	1244	asasaggUfgUfCfGfuuuuuuccalL96	2340	sense	21
UGGAAAAGAACGACACCCUUUGU	1245	usGfskaaAfaGfAfacgaCfaCfuuuuusgu	2341	antisense	23
AAUACAAGGGUGUCGUUCU	1246	asasuacaAfaGfGfGfugucguuculL96	2342	sense	21
AAGAACGACACCCUUUGUAUUGA	1247	asAfsgaaCfzAfAfaccUfuUfguaauusgsa	2343	antisense	23
CAAUACAAGGGUGUCGUUCU	1248	csasauacAfaAfGfGfugucguuculL96	2344	sense	21
AGAACGACACCCUUUGUAUUGAA	1249	asGfsaacGfaCfAfccuUfuGfuaauugsasa	2345	antisense	23
AAAGGCACUGAUGUUCUGAAA	1250	asasaggAfcUfGfAfugucugaaalL96	2346	sense	21
UUUCAGAACAUCAUGGCCUUUCC	1251	usUfsucaGfaAfCfaucAUfUfGfuuuuusc	2347	antisense	23
AAGGCACUGAUGUUCUGAAAG	1252	asasggcaCfuGfAfUfguucugaaagL96	2348	sense	21
CUUUCAGAACAUCAUGGCCUUUC	1253	csUfsuucAfgAfAfcaucAfgUfccccusuc	2349	antisense	23
GCGGAAAGGCACUGAUGUUCU	1254	gscsggaaAfgGfCfAfugauguuculL96	2350	sense	21
AGAACAUCAUGGCCUUUCCGCAC	1255	asGfsaacAfuCfAfugucCfuUfuccgesasc	2351	antisense	23
UGCGGAAAGGCACUGAUGUUC	1256	usgscgggAfaGfGfCfacugauguucL96	2352	sense	21
GAACAUCAGGCCUUUCCGCACA	1257	gsAfsacaUfcAfGfugccUfuUfccgcascsa	2353	antisense	23
AAGGAUGCUCCGGAAUGUUUGC	1258	asasggauGfcUfCfCfgggaugugclL96	2354	sense	21
GCAACAUUCCGGAGCAUCCUUGG	1259	gsCfsaacAfuUfCfcggaGfcAfuccuuusgg	2355	antisense	23
AGGAUGCUCCGGAAUGUUUGCU	1260	asgsgaugCfuCfCfGfgaugugculL96	2356	sense	21
AGCAACAUAUCCGGAGCAUCCUUG	1261	asGfscaaCfaUfUfcccggAfgCfaucuuusg	2357	antisense	23
AUCCAAGGAUGCUCCGGAAUG	1262	asusccaaGfgAfUfGfucccggaugL96	2358	sense	21
CAUCCCGGAGCAUCCUUGGAUAC	1263	csAfsuucCfzGfAfgcAUfUfggausasc	2359	antisense	23
UAUCCAAGGAUGCUCCGGAAU	1264	usasucaaAfgGfAfUfgeucccggaalL96	2360	sense	21
AUCCCGGAGCAUCCUUGGAUACA	1265	asUfsuccGfgAfGfcaucCfuUfggauascsa	2361	antisense	23
AAUGGGUGGCGGUAAUUGGUG	1266	asasugggUfgGfCfGfuaauugugL96	2362	sense	21
CACCAAUUACCGCCACCCAUUCC	1267	csAfsecaAfuUfAfcegcCfaCfcauuusc	2363	antisense	23
AUGGGUGGCGGUAAUUGGUGA	1268	asusggguGfgCfGfGfuaauugugaL96	2364	sense	21
UACCAAAUUAACCGCCACCCAUUC	1269	usCfsaccAfaUfUfaccgCfcAfcccausuc	2365	antisense	23

UUGGAAUGGGUGGCGGUAUU	1270	ususggaUfgGfGfUfggcgguaauL96	2366	sense	21
AAUACCGCCACCAUUAUCCAAUU	1271	asAfsuuaCfcGfcfcaccCfaUfuccaasusu	2367	antisense	23
AUUGGAAUGGGUGGCGGUAUU	1272	asusuggaAfuGfGfGfuggcgguaauL96	2368	sense	21
AUUACCGCCACCAUUAUCCAAUUC	1273	asUfsuacCfGcCfcCfaccCfaUfuccaasusc	2369	antisense	23
GGAAAGGCACUGAUGUUCUGA	1274	gsgsaaagGfcAfCfUfGfanguucugaL96	2370	sense	21
UCAGAAACAUCAGUGCCUUUCCGC	1275	usCfsagaAfcAfUfCfaguGfcCfuuccesgsc	2371	antisense	23
GAAAGGCACUGAUGUUCUGAA	1276	ggsaaaggCfaCfUfGfanguucugaalL96	2372	sense	21
UUCAGAACAUACAGUGCCUUUCCG	1277	usUfscagAfaCfAfucagUfgCfcuuccscsg	2373	antisense	23
GUGCGGAAAGGCACUGAUGUU	1278	gsgsgcgAfaAfGfGfcacugaauL96	2374	sense	21
AACAUCAGUGCCUUUCCGCACAC	1279	asAfscuuCfaGfUfGfcuuUfuCfcgcacsasc	2375	antisense	23
UGUGCGGAAAGGCACUGAUGU	1280	usgsugcgGfaAfAfGfGfcacugaauL96	2376	sense	21
ACAUCAGUGCCUUUCCGCACACC	1281	asCfsaucAfgUfGfcuuUfcCfcgcacsasc	2377	antisense	23
AAUUGUAAAGCUCAGGUUCAAA	1282	asasuuguAfaGfCfUfCfagguucaalL96	2378	sense	21
UUUGAACCCUGAGCUUACAAUUUA	1283	usUfsugaAfcCfUfGfagcUfuAfcaauususa	2379	antisense	23
AUUGUAAAGCUCAGGUUCAAG	1284	asusuguaAfgCfUfCfagguucaagL96	2380	sense	21
CUUUGAACCCUGAGCUUACAAUUU	1285	csUfsuugAfaCfCfugagCfuUfacaasusu	2381	antisense	23
CUUAAAUUGUAAAGCUCAGGUU	1286	csusuaaaUfuGfUfAfagcucagguuL96	2382	sense	21
AACCUGAGCUUACAAUUUAAGAA	1287	asAfscuuGfaGfCfuuacAfaUfuaaagsasa	2383	antisense	23
UCUUAAAUUGUAAAGCUCAGGU	1288	uscsuuaaAfuUfGfUfCfagcucagguL96	2384	sense	21
ACCUGAGCUUACAAUUUAAGAAC	1289	asCfscugAfgCfUfuaaAfuUfuaagascasc	2385	antisense	23
GCAAAACACUAAAGGUGAAAAGA	1290	gscsaacAfcUfAfAfggggaaaagL96	2386	sense	21
UCUUUUCACCUUAGUGUUUUGCUA	1291	usCfsuunUfcAfCfcuaaGfuGfuungcsusa	2387	antisense	23
CAAAACACUAAAGGUGAAAAGAU	1292	csasaacaCfuAfAfGfugaaaagL96	2388	sense	21
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GGUAGCAAAACACUAAAGGUGAA	1294	gsgsuagcAfaAfCfAfcuaaggugaalL96	2390	sense	21
UUCACCUUAGUGUUUUGCUACCUC	1295	usUfscacCfuUfAfuguguUfuGfcuaccsusc	2391	antisense	23
AGGUAGCAAAACACUAAAGGUGA	1296	asgsguagCfaAfAfCfaaaggugaL96	2392	sense	21
UCACCUUAGUGUUUUGCUACCUC	1297	usCfsaccUfuAfGfuguuUfgCfuaccsusc	2393	antisense	23
AGGUAGCAAAACACUAAAGGUGA	1298	asgsguagCfaAfAfCfaaaggugaL96	2394	sense	21
UCACCUUAGUGUUUUGCUACCUC	1299	usCfsaccUfuAfGfuguuUfgCfuaccsusc	2395	antisense	23
GGUAGCAAAACACUAAAGGUGAA	1300	gsgsuagcAfaAfCfAfcuaaggugaalL96	2396	sense	21
UUCACCUUAGUGUUUUGCUACCUC	1301	usUfscacCfuUfAfuguguUfuGfcuaccsusc	2397	antisense	23

UUGGAGGUAGCAAAACACUAAAG	1302	ususggagGfuAfGfCfaaacacuaaL96	2398	sense	21
CUUAGUGUUUGCUACCUCCAAUU	1303	csUfsuagUfgUfUfugcuAfcCfuccaasusu	2399	antisense	23
AUUGGAGGUAGCAAAACACUAA	1304	asusuggaGfgUfAfGfcaaacacuaaL96	2400	sense	21
UUAGUGUUUGCUACCUCCAAUUU	1305	usUfsaguGfuUfUfgcuAfcUfccaasusu	2401	antisense	23
UAAAGUGCUGUAUCCUUUAGU	1306	usasaauguGfcUfGfUfauccuuuagL96	2402	sense	21
ACUAAAAGGAUACAGCACUUUAGC	1307	asCfsuaaAfgGfAfuacaGfcAfcuuuagssc	2403	antisense	23
AAAGUGCUGUAUCCUUUAGUA	1308	asasagugCfuGfUfAfucuuuagL96	2404	sense	21
UACUAAAAGGAUACAGCACUUUAG	1309	usAfscuaAfaGfGfauacAfgCfacuuiusag	2405	antisense	23
AGGCUAAAAGUGCUGUAUCCUU	1310	asgsgcuAfaGfUfGfcuguaucuuL96	2406	sense	21
AAGGAUACAGCACUUUAGCCUGC	1311	asAfsggaUfaCfAfgcacUfuUfagceusgsc	2407	antisense	23
CAGGCUAAAAGUGCUGUAUCCU	1312	csasggcuAfaAfgUfGfcuguaucuuL96	2408	sense	21
AGGAUACAGCACUUUAGCCUGCC	1313	asGfsgauAfcAfgfcacuUfuAfgccugscsc	2409	antisense	23
AAGACAUUGGUGAGGAAAAAU	1314	asasgacaUfuGfGfUfgaggaauL96	2410	sense	21
AUUUUUCCUCACCCAAUGUCUUGU	1315	asUfsuuUfcCfUfcaccAfaUfgucuuusgu	2411	antisense	23
AGACAUUGGUGAGGAAAAAUC	1316	asgsacauUfgGfUfGfaggaauL96	2412	sense	21
GAUUUUUCCUCACCCAAUGUCUUG	1317	gsAfssuuUfuCfCfucacCfaAfugucusug	2413	antisense	23
CGACAAGACAUUGGUGAGGAA	1318	csgsacaaGfaCfAfUfuggugaggaalL96	2414	sense	21
UUCCUCACCCAAUGUCUUGUGGAU	1319	usUfscuuCfaCfCfaugUfcUfugucgsasu	2415	antisense	23
UCGACAAGACAUUGGUGAGGA	1320	uscsagacaAfgAfCfAfuuggugaggaL96	2416	sense	21
UCCUCACCCAAUGUCUUGUGGAU	1321	usCfscucAfcCfAfauguCfuUfgucgasug	2417	antisense	23
AAGAUGUCCUCGAGGAUACUAA	1322	asasgaugUfcCfUfCfagauacuaaL96	2418	sense	21
UUAGUAUCUCGAGGACAUUCUUA	1323	usUfsaguAfuCfUfcgagGfaCfauuiusgsa	2419	antisense	23
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UUUAGUAUCUCGAGGACAUUCUUG	1325	usUfsuagUfaUfCfucgaGfgAfcuucisug	2421	antisense	23
GUUCAAGAUUGUCCUCGAGAU	1326	gsusucaaGfaUfGfUfccucgagauaL96	2422	sense	21
UAUCUCGAGGACAUUCUUGAACAC	1327	usAfssucuCfGfAfggacaUfcUfugaacsasc	2423	antisense	23
UGUUCAAGAUUGUCCUCGAGAU	1328	usgsuucaAfgAfUfGfuccucgagauL96	2424	sense	21
AUCUCGAGGACAUUCUUGAACACC	1329	asUfscucGfaGfGfacaUfUfgaacsasc	2425	antisense	23
GAGAAAGGUGUUCUUGAAGUUC	1330	gsasgaaaGfgUfGfUfucagaugucL96	2426	sense	21
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AGAAAGGUGUUCUUGAAGUUC	1332	asgsaaagGfuGfUfUfcaagauguccL96	2428	sense	21
GGACAUUCUUGAACACCUUUCUCC	1333	gsGfsacaUfcUfUfgaacAfcCfuuiucscsc	2429	antisense	23

GGGGGAGAAAGGUGUUUCAAGA	1334	gsgsgggaGfaAfAfGfguguucaagaL96	2430	sense	21
UCUUGAACACCUUUCUCCCCCUG	1335	usCfsuugAfaCfAfccuuUfcUfcccccsug	2431	antisense	23
AGGGGAGAAAGGUGUUCAAG	1336	asgsggggAfgAfAfAfgguguucaagL96	2432	sense	21
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GCUGGGAAGAUACAUAUGGC	1338	gscsugggAfaGfAfUfaucaaauagcL96	2434	sense	21
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CUGGGAAGAUACAUAUGGCU	1340	csusgggaAfgAfUfAfucaaauggcuL96	2436	sense	21
AGCCAUUUGAUUUCUCCCCAGCU	1341	asGfscuUfuUfGfauauCfuUfccccgscsu	2437	antisense	23
AUCAGCUGGGAAGAUACAUA	1342	asuscageUfgGfGfAfagauaucaaaL96	2438	sense	21
UUUGAUUUCUCCCCAGCUGAUAG	1343	usUfsugaUfaUfCfuuccCfaGfcugausasg	2439	antisense	23
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UUGAUAUCUCCCCAGCUGAUAGA	1345	usUfsgauAfuCfUfucccAfgCfugauasgsa	2441	antisense	23
UCUGUCGACUUCUGUUUAGG	1346	uscsugucGfaCfUfUfuguuuuaggL96	2442	sense	21
CCUAAAACAGAAAGUCGACAGAU	1347	csCfsuaaAfaCfAfagaagUfcGfacagasusc	2443	antisense	23
CUGUCGACUUCUGUUUAGGA	1348	csusgucgAfcUfUfCfuguuuuaggalL96	2444	sense	21
UCCUAAAACAGAAAGUCGACAGAU	1349	usCfscuaAfaAfcfagaaGfuCfagacagsasu	2445	antisense	23
CAGAUUCUGACUUCUGUUU	1350	csasgaucUfgUfCfGfaeuucuguuuL96	2446	sense	21
AAACAGAAAGUCGACAGAUUCGUU	1351	asAfsacaGfaAfGfucgaCfaGfaucugsusu	2447	antisense	23
ACAGAUUCUGUCGACUUCUGUU	1352	ascsagauCfuGfUfCfagacuuuguuL96	2448	sense	21
AACAGAAAGUCGACAGAUUCUGUUU	1353	asAfsacagAfaGfUfegacAfgAfucugususu	2449	antisense	23
UACUUCUUUGAAUGUAGAUUU	1354	usascuucUfuUfGfAfauguauguuuL96	2450	sense	21
AAAUUCUACAUAUCAAAGAAAGUAUC	1355	asAfsaucUfaCfAfuucaAfaGfaaguasusc	2451	antisense	23
ACUUCUUUGAAUGUAGAUUUC	1356	ascsuucUfuGfAfaAfauguaguuuL96	2452	sense	21
GAAAUUCACAUUCAAAGAAAGUAU	1357	gsAfsaauCfuAfCfaucAfaAfgaugsasu	2453	antisense	23
GUGAUACUUCUUUGAAUGUAG	1358	gsgugauaCfuUfCfUfuugauguagL96	2454	sense	21
CUACAUAUCAAAGAAAGUAUCACCA	1359	csUfsacaUfuCfAfaagaAfgUfaucacsca	2455	antisense	23
GGUGAUACUUCUUUGAAUGUA	1360	gsgsugauAfcUfUfCfuugauguuaL96	2456	sense	21
UACAUUCAAAGAAAGUAUCACCAA	1361	usAfscauUfcAfAfagaaGfuAfucacsasa	2457	antisense	23
UGGGAAGAUACAUAUAAUGGCUG	1362	usgsggaaGfaUfAfUfcaauaggcugL96	2458	sense	21
CAGCCAUUUGAUUUCUCCCCAGC	1363	csAfsgccAfuUfUfgauaUfcUfucccsagsc	2459	antisense	23
GGGAAGAUACAUAUAAUGGCUGA	1364	gsgsgaagAfuAfUfCfaaugggcugaL96	2460	sense	21
UCAGCCAUUUGAUACAUAUCCCCAG	1365	usCfsagcCfaUfUfugauAfuCfuucccsasg	2461	antisense	23

CAGCUGGGAGAAUUAUCAAUG	1366	csasgengGfgAfaFgfauaucaaaugL96	2462	sense	21
CAUUUGAAUACUCCCCAGCUGAU	1367	csAfsuuuGfaUfaFucuuCfcCfagcugsasu	2463	antisense	23
UCAGCUGGGAGAAUUAUCAAU	1368	uscsageuGfgGfaFafgaaaucaaaL96	2464	sense	21
AUUUGAAUACUCCCCAGCUGAU	1369	asUfsuugAfuAfUfcuucCfcAfgcugasusa	2465	antisense	23
UCCAAAGUCUAUAUAUGACUA	1370	uscscaaGfuCfuFafuaauagacuaL96	2466	sense	21
UAGUCAUAUAUAGACUUUGGAAG	1371	usAfsugcAfuAfUfauagAfcUfuuggasag	2467	antisense	23
CCAAGUCUAUAUAUGACUAU	1372	cscsaaagUfcUfAfUfauuagacuaL96	2468	sense	21
AUAGUCAUAUAUAGACUUUGGAA	1373	asUfsaguCfaUfaFuaaGfaCfuuuggsasa	2469	antisense	23
UACUCCCAAAGUCUAUAUAUG	1374	usascuucCfaAfaGfucuaauaauL96	2470	sense	21
CAUAUAUAGACUUUGGAAGUACU	1375	csAfsuauAfuAfGfacuuUfgGfaaguascsu	2471	antisense	23
GUACUCCCAAAGUCUAUAUAU	1376	gsusacuuCfcAfaAfafgucuaauaL96	2472	sense	21
AUAUAUAGACUUUGGAAGUACUG	1377	asUfsauaUfaGfaFcuuuGfgAfaguacsusg	2473	antisense	23
UUAUGAACACAACUAAUAC	1378	ususaugaAfcAfaCfcaugcuuaaL96	2474	sense	21
GAUUAGCAUGUUGUUAUCAAUAC	1379	gsAfsuuuAfgCfAfuguuGfuUfcauaasusc	2475	antisense	23
UAUGAACACAACUAAUACA	1380	usasugaaCfaAfaCfAfugcuuaaL96	2476	sense	21
UGAUUAGCAUGUUGUUAUCAAU	1381	usGfsauuUfaGfCfauguUfgUfcauasasu	2477	antisense	23
AUGAUUAUGAACACAACUACUA	1382	asusganuAfuGfaAfaCfaacauaL96	2478	sense	21
UAGCAUGUUGUUAUCAAUAAUUG	1383	usAfsgeaUfgUfUfguucAfuAfaucaususg	2479	antisense	23
AAUGAUUAUGAACACAACUACU	1384	asasugauUfaUfGfAfaacacauaL96	2480	sense	21
AGCAUGUUGUUAUCAAUUAUUGA	1385	asGfscuuGfuUfGfuuaUfaAfucauusgsa	2481	antisense	23
AAUCCCCACUUAUUAUCAA	1386	asasuuccCfcAfaCfUfcauaaL96	2482	sense	21
UUUGUAUUUGAAGUGGGAAUUAUAC	1387	usUfsuguAfuUfGfaaguGfgGfgaausasc	2483	antisense	23
AUCCCCACUUAUUAUCAAAG	1388	asusucccCfaCfUfUfcauaaL96	2484	sense	21
CUUUGUAUUUGAAGUGGGAAUUA	1389	csUfsuugUfaUfUfugaagUfgGfggaauususa	2485	antisense	23
CUGUAAUUCUCCACUUAUUA	1390	csusguuaUfuCfCfCfcauuaL96	2486	sense	21
UAUUGAAGUGGGAAUUAUACAGAC	1391	usAfsuugAfaGfUfggggAfaUfuacagsasc	2487	antisense	23
UCUGUAAUUCUCCACUUAUUA	1392	uscsuguaAfuUfCfCfcauuaL96	2488	sense	21
AUUUGAAGUGGGAAUUAUACAGACU	1393	asUfsugaAfgUfggggaAfuUfacagascsu	2489	antisense	23
UGAUGUGCGUAAACAGAUUCAA	1394	usgsauguGfcGfUfAfacagauuaL96	2490	sense	21
UUUGAUCUGUUAACGACAUCAUAC	1395	usUfsgaaUfcUfGfuuaGfcAfaucasusc	2491	antisense	23
GAUGUGCGUAAACAGAUUCAA	1396	gsasugugCfGfUfAfaCfagauuaL96	2492	sense	21
UUUGAUCUGUUAACGACAUCAUAC	1397	usUfsugaAfuCfUfguuuAfcGfcaucasasu	2493	antisense	23

UGGAUGAUGUGCGUAAACAGAU	1398	usgsgaugAfuGfUfGfcguaacagauL96	2494	sense	21
AUCUGUUAACGCACAUCAUCCAGA	1399	asUfscugUfuAfCfcgcaAfuCfauccagsa	2495	antisense	23
CUGGAUGAUGUGCGUAAACAGA	1400	csusggauGfaUfGfUfGfcguaacagaL96	2496	sense	21
UCUGUUACGCACAUCAUCCAGAC	1401	usCfsuguUfaCfGfcacaUfcAfuccagsasc	2497	antisense	23
GAAUGGGUGGCGGUAAUUGGU	1402	gsasauggGfuGfGfCfcgguauugguL96	2498	sense	21
ACCAAUUACCGCCACCCAUUCCA	1403	asCfscaaUfuAfCfcgccAfcCfcauucscsa	2499	antisense	23
AAUGGGUGGCGGUAAUUGGUG	1404	asasugggUfgGfCfGfguaauuggugL96	2500	sense	21
CACCAAUUACCGCCACCCAUUCC	1405	csAfsccaAfuUfaFfccgcCfaCfccauuscsc	2501	antisense	23
AUUGGAAUUGGGUGGCGGUAAU	1406	asusuggaAfuGfGfGfugggcguaauL96	2502	sense	21
AUUACCGCCACCCAUUCCAAUUC	1407	asUfsuacCfGcCfCfacecAfuUfccaauusc	2503	antisense	23
AAUUGGAAUUGGGUGGCGGUAA	1408	asasuuggAfaUfGfGfugggcguaaL96	2504	sense	21
UUACCGCCACCCAUUCCAAUUCU	1409	usUfsaccGfcCfAfcccaUfuCfcauuscscu	2505	antisense	23
UCCGGAAUGUUGCUGAAACAG	1410	uscscggaAfuGfUfUfGfcugaacagL96	2506	sense	21
CUGUUUCAGCAACAUAUCCGGAGC	1411	csUfsguuUfcAfGfcaacAfuUfcccggsgsc	2507	antisense	23
CCGGAAGUUGUCUGAAACAGA	1412	cscsggaaUfgUfUfGfcgaaacagaL96	2508	sense	21
UCUGUUUCAGCAACAUAUCCGGAG	1413	usCfsuguUfuCfAfscgaCfaUfuccggsasg	2509	antisense	23
AUGCUCGGAAUGUUGCUGAA	1414	asusgcucCfGfAfaFuguugcugaaL96	2510	sense	21
UUCAGCAACAUAUCCGGAGCAUCC	1415	usUfscagCfaAfCfauncCfGfagcauscsc	2511	antisense	23
GAUGCUCGGAAUGUUGCUGA	1416	gsasugcuCfcGfGfAfauguugcugaL96	2512	sense	21
UCAGCAACAUAUCCGGAGCAUCCU	1417	usCfsageAfaCfafuuccGfzAfzcauscscu	2513	antisense	23
UGUCCUCGAGAUACUAAAGGA	1418	usgsuccuCfGfAfGfAfaucuaaggalL96	2514	sense	21
UCCUUUAGUAUCUCGAGGACAUC	1419	usCfscuuUfaGfUfaucuCfGfaggacascsc	2515	antisense	23
GUCCUCGAGAUACUAAAGGAA	1420	gsusccucGfaGfAfUfacuaaaggaaL96	2516	sense	21
UUCUUUAGUAUCUCGAGGACAUC	1421	usUfscuuUfuAfGfuaucUfcGfaggacsasu	2517	antisense	23
AAGAUGUCCUCGAGAUACUAA	1422	asasgaugUfcCfUfCfGgagauacuaaL96	2518	sense	21
UUAGUAUCUCGAGGACAUCUUGA	1423	usUfsaguAfuCfUfGfcgagGfaCfcauucgsa	2519	antisense	23
CAAGAUGUCCUCGAGAUACUA	1424	csasagauGfuCfCfUfGfcgagauacuaL96	2520	sense	21
UAGUAUCUCGAGGACAUCUUGAA	1425	usAfsguaUfcUfCfGaggAfcAfucuuugsasa	2521	antisense	23
ACAACAUGCUAAAUACUACU	1426	ascsaacaUfgCfUfAfauacaguacuL96	2522	sense	21
AGUACUGAUUUAGCAUGUUGUUC	1427	asGfsuacUfgAfUfuuagCfaUfguuugsusc	2523	antisense	23
CAACAUGCUAAAUACUACUUCU	1428	csasacauGfcUfAfAfaucaguacuL96	2524	sense	21
AAGUACUGAUUUAGCAUGUUGUUC	1429	asAfsguaCfuGfAfuaaGfcAfuguugsusu	2525	antisense	23

AUGAACAAACAUGCUAAAUACAG	1430	asusgaacAfaCfAfUfgcuauaagL96	2526	sense	21
CUGAUUAGCAUGUUGUUAUAA	1431	csUfsgauUfuAfGfcaugUfuGfuucausasa	2527	antisense	23
UAUGAACAAACAUGCUAAAUCA	1432	usasugaaCfaAfCfAfugcuauaual96	2528	sense	21
UGAUUAGCAUGUUGUUAUAAU	1433	usGfsauuUfaGfCfauugUfgUfucuaasasu	2529	antisense	23
GCCAAAGCUGUGUUGUGGGG	1434	gscscaagGfcUfGfUfguuuggggG96	2530	sense	21
CCCACAAACACAGCCUUGGCGC	1435	csCfsccaCfaAfAfcaCfCfuugcgsc	2531	antisense	23
CCAAGGUGUGUUGUGGGGA	1436	cscsaaggCfuGfUfGfuuguggggaL96	2532	sense	21
UCCCCACAAACACAGCCUUGGCG	1437	usCfscccAfcAfAfafacAfGcfuugggscg	2533	antisense	23
UGGCGCCAAGGCGUGUUUGU	1438	usgsggcCfaAfGfGfcuguuuugL96	2534	sense	21
ACAACACAGCCUUGGCGCCAAG	1439	asCfsaaaCfaCfAfgecuUfgGfcgccasag	2535	antisense	23
UUGGCGCCAAGGCGUGUUUG	1440	ususggcgCfcAfAfGfGfcuguuuugL96	2536	sense	21
CAAACACAGCCUUGGCGCCAAGA	1441	csAfsaacAfcAfGfgecuUfgCfGCCaasgsa	2537	antisense	23
UGAAAGCUCUGGCGUCUUGGCG	1442	usgsaaagCfuCfUfGfgecuugggcL96	2538	sense	21
CGCCAAGAGCCAGAGCUUUUCAGA	1443	csGfsccaAfgAfGfccagAfgCfuucacgsa	2539	antisense	23
GAAAGCUCUGGCGUCUUGGCGC	1444	gsasaaagUfcUfGfGfgecuugggcL96	2540	sense	21
GCGCCAAGAGCCAGAGCUUUCAG	1445	gsCfsgccAfaGfAfGCCaGfGfcuuucasag	2541	antisense	23
GUUCUGAAAGCUCUGGCGUCU	1446	gsusucugAfaAfGfCfucuggecuuL96	2542	sense	21
AAGAGCCAGAGCUUUUCAGAACAU	1447	asAfsagCfcAfGfGfagcuUfuCfagaacsasu	2543	antisense	23
UGUUCUGAAAGCUCUGGCGUCU	1448	usgsuuuGfaAfAfGfGfcucuggecuL96	2544	sense	21
AGAGCCAGAGCUUUUCAGAACAU	1449	asGfsageCfaGfAfgecuUfcAfgaacacusc	2545	antisense	23
CAGCCACUAUUGAUUGUUCUGC	1450	csasgccaCfuAfUfUfgauuugcL96	2546	sense	21
GCAGAACAUCAUAGUGGCGUGG	1451	gsCfsagaAfcAfUfcauUfgUfggugsgsc	2547	antisense	23
AGCCACUAUUGAUUGUUCUGCC	1452	asgsccacUfaUfUfGfauuugcL96	2548	sense	21
GGCAGAACAUCAUAGUGGCGUG	1453	gsGfscagAfaCfAfucuaUfaGfuggeusgsg	2549	antisense	23
GUGCCAGCCACUAUUGAUUGU	1454	gsusgccaGfcCfaCfauuugauuL96	2550	sense	21
AACAUCUAUAGUGGCGUGGACCC	1455	asAfscauCfaAfUfagugGfcUfggcaescsc	2551	antisense	23
GGUGCCAGCCACUAUUGAUUGU	1456	gsgsugccAfgCfCfAfcuaugauuL96	2552	sense	21
ACAUCAUAUAGUGGCGUGGACCC	1457	asCfsaucAfaUfAfugggCfuGfGcacescsc	2553	antisense	23
ACAAGGACCCGAGAGUCACCA	1458	ascsaaggAfcCfGfAfgaagucacal96	2554	sense	21
UGGUGACUUCUGGCGUCCUUGUAG	1459	usGfsgugAfcUfUfcugGfuCfcuugusag	2555	antisense	23
CAAGGACCCGAGAGUCACCA	1460	csasaggaCfcGfAfGfagucacacal96	2556	sense	21
UUGGUGACUUCUGGCGUCCUUGUA	1461	usUfsgguGfaCfUfucucGfGfUfcuugusua	2557	antisense	23

AUCUACAAAGGACCGAGAAGUC	1462	asuscuacAfaGfGfAfcgagagucL96	2558	sense	21
GACUUCUCGGUCCUUGUAGAUU	1463	gsAfsuuCfuCfGfuccUfuGfugaasasu	2559	antisense	23
UAUCUACAAGGACCGAGAAGU	1464	usasucuaCfaAfGfGfaccgagagucL96	2560	sense	21
ACUUCUCGGUCCUUGUAGAUUA	1465	asCfsuucUfcGfGfuccuUfgUfagauasusa	2561	antisense	23
CAGAAUGUGAAAGUCAUCGAC	1466	csasgaauGfuGfAfAfagucaucgacL96	2562	sense	21
GUCGAUGACUUUCACAUUCUGGC	1467	gsUfscgaUfgAfCfuucAfcAfuucgsgsc	2563	antisense	23
AGAAUGUGAAAGUCAUCGACA	1468	asgsaaugUfgAfAfAfagucaucgacal96	2564	sense	21
UGUCGAUGACUUUCACAUUCUGG	1469	usGfsucgAfuGfAfcuuuCfaCfaucucsgsg	2565	antisense	23
GUGCCAGAAUGUGAAAGUCAU	1470	gsusgccaGfaAfUfGfugaagucual96	2566	sense	21
AUGACUUUCACAUUCUGGCACCC	1471	asUfsgacUfuUfCfcauUfcUfggcacscsc	2567	antisense	23
GGUGCCAGAAUGUGAAAGUCA	1472	gsgsugccAfgAfAfUfugaaagucal96	2568	sense	21
UGACUUUCACAUUCUGGCACCCA	1473	usGfsacuUfuCfAfcuuCfuGfaccscsa	2569	antisense	23
AGAUGUCCUCGAGAUACUAA	1474	asgsaauCfcUfCfGfagauacuual96	2570	sense	21
UUUAGUAUCUCGAGGACAUUCUUG	1475	usUfsuagUfaUfCfucgaGfgAfcuucsusg	2571	antisense	23
GAUGUCCUCGAGAUACUAAAG	1476	gsasugucCfuCfGfAfgauacuuaagL96	2572	sense	21
CUUAGUAUCUCGAGGACAUUCU	1477	csUfsuuaGfuAfUfucgAfgGfacaucsuu	2573	antisense	23
UUCAAAGAUUGUCCUCGAGAUAC	1478	ususcaagAfuGfUfCfucgagagucal96	2574	sense	21
GUUUCUCGAGGACAUUCUGAACA	1479	gsUfsaucUfcGfAfggacAfuCfuugaascsa	2575	antisense	23
GUUCAAGAUGUCCUCGAGAU	1480	gsusucuaGfaUfGfUfuccugagauaL96	2576	sense	21
UAUCUCGAGGACAUUCUGAACAC	1481	usAfsucuCfGfAfggacaUfcUfugaacsasc	2577	antisense	23
GUGGACUUGCUGCAUAUGUGG	1482	gsusggacUfuGfCfUfgcauauuggL96	2578	sense	21
CCACAUUAGCAGCAAGUCCACUG	1483	csCfsacaUfaUfGfcaGfAfguccacsusg	2579	antisense	23
UGGACUUGCUGCAUAUGUGGC	1484	usgsgacuUfgCfUfGfcauauuggcL96	2580	sense	21
GCCACAUUAGCAGCAAGUCCACU	1485	gsCfscacAfuAfUfGcagCfaAfguccacsu	2581	antisense	23
GACAGUGGACUUUGCUGCAUAU	1486	gsascaguGfgAfCfUfugcugcauauL96	2582	sense	21
AUAUGCAGCAAGUCCACUGUCGU	1487	asUfsaugCfaGfCfaaguCfcAfcugcsgsu	2583	antisense	23
CGACAGUGGACUUUGCUGCAUA	1488	csgsacagUfgGfAfCfuugcugcaual96	2584	sense	21
UAUGCAGCAAGUCCACUGUCGUC	1489	usAfsugcAfgCfAfgucCfaCfugucgsgsc	2585	antisense	23
AACCAGUACUUUAUCAUUUC	1490	asascagUfaCfUfUfuaucuuuucL96	2586	sense	21
GAAAAUGAUAAAGUACUGGUUUC	1491	gsAfsaaaUfgAfUfaagUfaCfugguusc	2587	antisense	23
ACCAGUACUUUAUCAUUUCU	1492	ascscaguAfcUfUfUfaucuuuucL96	2588	sense	21
AGAAAAUGAUAAAGUACUGGUUU	1493	asGfsaaaAfuGfAfuuaaGfuAfcuggusuu	2589	antisense	23

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

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

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 213

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of lactic acid dehydrogenase A (LDHA) in a cell, wherein said dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which 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 2-5.

2. The dsRNA agent of claim 1, wherein said dsRNA agent comprises at least one modified nucleotide.

3. The dsRNA agent of any one of claims 1 or 2, wherein substantially all of the nucleotides of the sense strand comprise a modification; substantially all of the nucleotides of the antisense strand comprise a modification; or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification.

4. The dsRNA agent of claim 3, wherein all of the nucleotides of the sense strand comprise a modification; all of the nucleotides of the antisense strand comprise a modification; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

5. The dsRNA agent of any one of claims 2-4, wherein at least one of said modified nucleotides is selected from the group consisting of 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'-hydroxyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a glycol modified nucleotide, and a 2-O-(N-methylacetamide) modified nucleotide, and combinations thereof.

6. The dsRNA agent of claim 1, wherein the region of complementarity is at least 17 nucleotides in length.

5 7. The dsRNA agent of claim 1, wherein the region of complementarity is 19 to 30 nucleotides in length.

8. The dsRNA agent of claim 7, wherein the region of complementarity is 19-25 nucleotides in length.

10 9. The dsRNA agent of claim 7, wherein the region of complementarity is 21 to 23 nucleotides in length.

10. The dsRNA agent of any one of claims 1-9, wherein each strand is no more than 30 nucleotides in length.

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11. The dsRNA agent of any one of claims 1-10, wherein each strand is independently 19-30 nucleotides in length.

12. The dsRNA agent of claim 11, wherein each strand is independently 19-25 nucleotides in length.

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13. The dsRNA agent of claim 11, wherein each strand is independently 21-23 nucleotides in length.

25 14. The dsRNA agent of any one of claims 1-13, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

15. The dsRNA agent of any one of claims 1-13, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

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16. The dsRNA agent of any one of claims 1-15, wherein said agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

17. The dsRNA agent of claim 16, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

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18. The dsRNA agent of claim 17, wherein said strand is the antisense strand.

19. The dsRNA agent of claim 17, wherein said strand is the sense strand.

20. The dsRNA agent of claim 16, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand.

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21. The dsRNA agent of claim 20, wherein said strand is the antisense strand.

22. The dsRNA agent of claim 20, wherein said strand is the sense strand.

10 23. The dsRNA agent of claim 16, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand.

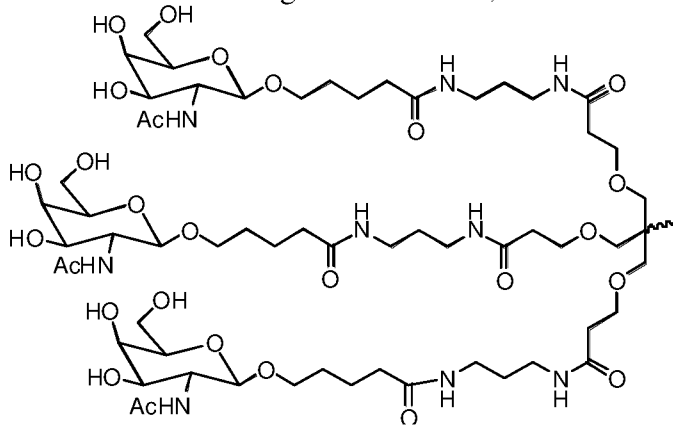
24. The dsRNA agent of any one of claims 1-23, further comprising a ligand.

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25. The dsRNA agent of claim 24, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

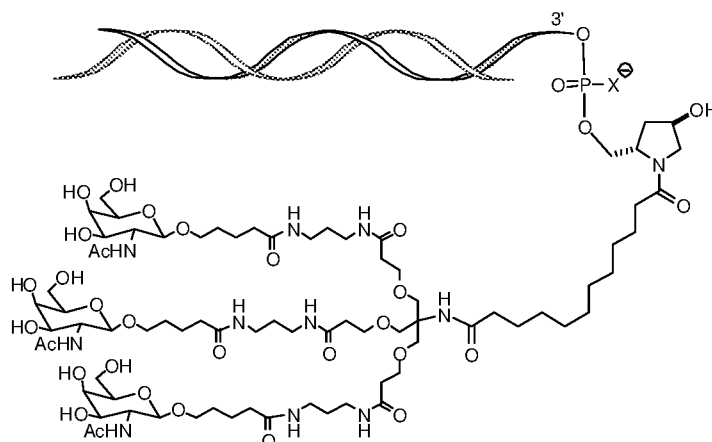
20 26. The dsRNA agent of claim 24 or 25, wherein the ligand is one or more N-acetylgalactosamine (GalNAc) derivatives attached through a monovalent, bivalent, or trivalent branched linker.

27. The dsRNA agent of claim 26, wherein the ligand is



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28. The dsRNA agent of claim 27, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

29. The dsRNA agent of claim 28, wherein the X is O.

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30. The dsRNA agent of claim 1, wherein the region of complementarity consists of one of the antisense sequences listed in any one of Tables 2-5.

31. The dsRNA agent of claim 1, wherein the sense strand and the antisense strand comprise nucleotide sequences selected from the group consisting of the nucleotide sequences of any one of the agents listed in any one of Tables 2-5.

32. A dual targeting RNAi agent, comprising
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.

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33. The dual targeting RNAi agent of claim 32, 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.

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34. The dual targeting RNAi agent of claim 32, wherein the antisense strand of the first dsRNA agent comprises a region of complementarity which 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 2-5.

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35. The dual targeting RNAi agent of claim 32, 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.

36. The dual targeting RNAi agent of claim 32, wherein the antisense strand of the second dsRNA agent comprises a region of complementarity which 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 7-14.

37. The dual targeting RNAi agent of any one of claims 32-36, wherein the first dsRNA agent and the second dsRNA agent each independently comprise at least one modified nucleotide.

38. The dual targeting RNAi agent of any one of claims 32-36, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand of the first dsRNA agent and substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand of the second dsRNA agent are modified nucleotides.

39. The dual targeting RNAi agent of claim 38, wherein at least one of the modified nucleotides of the first dsRNA agent and at least one of the modified nucleotides of the second dsRNA agent are each independently selected from the group consisting of 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 phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

40. The dual targeting RNAi agent of claim 38, wherein at least one of the modified nucleotides of the first dsRNA agent and at least one of the modified nucleotides of the second dsRNA agent are each independently selected from the group consisting of 2'-O-methyl and 2'fluoro modifications.

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41. The dual targeting RNAi agent of claim 34 or 36, wherein the region of complementarity of the first dsRNA agent and /or the region of complementarity of the second dsRNA agent are each independently 19 to 30 nucleotides in length.

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42. The dual targeting RNAi agent of any one of claims 32-36, wherein each strand of the first dsRNA agent and each strand of the second dsRNA agent are each independently 19-30 nucleotides in length.

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43. The dual targeting RNAi agent of any one of claims 32-36, wherein at least one strand of the first dsRNA agent and/or at least one strand of the second dsRNA agent each independently comprise a 3' overhang of at least 1 nucleotide.

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44. The dual targeting RNAi agent of any one of claims 32-36, wherein the first dsRNA agent and/or the second dsRNA agent each independently further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage.

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45. The dual targeting RNAi agent of any one of claims 32-36, wherein the first dsRNA agent and/or the second dsRNA agent each independently further comprise at least one ligand.

46. The dual targeting RNAi agent of claim 45, wherein the at least one ligand is conjugated to the sense strand of the first dsRNA agent and/or the second dsRNA agent.

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47. The dual targeting RNAi agent of claim 45, wherein the at least one ligand is conjugated to the 3'-end, 5'-end, or an internal position of one of the sense strands.

48. The dual targeting RNAi agent of claim 45, wherein the at least one ligand is conjugated to the antisense strand of the first dsRNA agent and/or the second dsRNA agent.

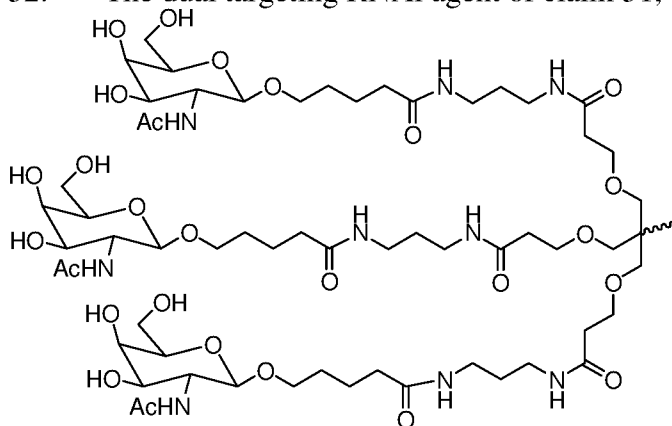
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49. The dual targeting RNAi agent of claim 45, wherein the at least one ligand is conjugated to the 3'-end, 5'-end, or an internal position of one of the antisense strands.

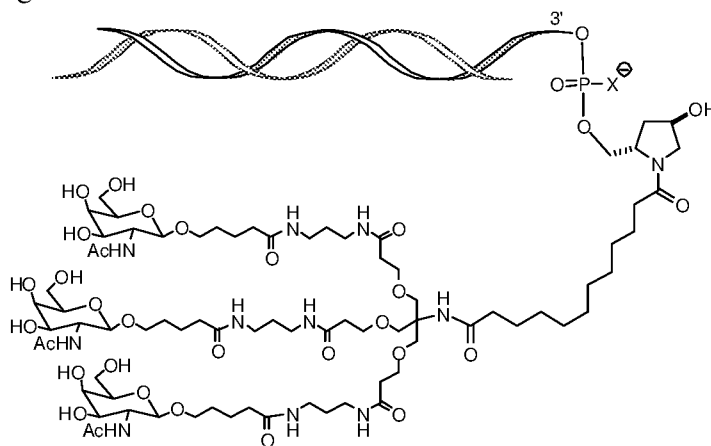
50. The dual targeting RNAi agent of claim 45, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

51. The dual targeting RNAi agent of claim 50, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, a bivalent, or a trivalent branched linker.

52. The dual targeting RNAi agent of claim 51, wherein the ligand is



53. The dual targeting RNAi agent of claim 52, wherein the first dsRNA agent and the second dsRNA agent are each independently conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

54. The dual targeting RNAi agent of claim 53, wherein, the X is O.

55. The dual targeting RNAi agent of any one of claims 32-36, wherein the first dsRNA agent and the second dsRNA agent are covalently attached via a covalent linker.

56. The dual targeting RNAi agent of claim 55, wherein the covalent linker is selected from the group consisting of a single stranded nucleic acid linker, a double stranded

nucleic acid linker, a partially single stranded nucleic acid linker, a partially double stranded nucleic acid linker, a carbohydrate moiety linker, and a peptide linker.

57. The dual targeting RNAi agent of claim 55, wherein the covalent linker is a cleavable linker or a non-cleavable linker.

58. The dual targeting RNAi agent of claim 55, wherein the covalent linker attaches the sense strand of the first dsRNA agent to the sense strand of the second dsRNA agent.

59. The dual targeting RNAi agent of claim 55, wherein the covalent linker attaches the antisense strand of the first dsRNA agent to the antisense strand of the second dsRNA agent.

60. The dual targeting RNAi agent of claim 55, wherein the covalent linker further comprises at least one ligand.

61. The dual targeting RNAi agent of any one of claims 32-36, wherein contacting a cell with the dual targeting RNAi agent inhibits 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.

62. The dual targeting RNAi agent of any one of claims 32-36, wherein contacting a cell with the dual targeting RNAi agent inhibits 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.

63. The dual targeting RNAi agent of claim 61, wherein the level of inhibition of LDHA expression is at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or about 100% higher than the level of inhibition of expression obtained by the contacting of a cell with both dsRNA agents individually.

64. The dual targeting RNAi agent of claim 61, wherein the level of inhibition of HAO1 expression is at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or about 100% higher than the level of inhibition of expression obtained by the contacting of a cell with both dsRNA agents individually.

65. The dual targeting RNAi agent of any one of claims 32-36, wherein contacting a cell with the dual targeting RNAi agent inhibits oxalate and/or glyoxylate protein production to a level lower than the level of protein production obtained by the contacting of a cell with both dsRNA agents individually.

66. The dual targeting RNAi agent of any one of claims 32-36, wherein contacting a cell with the dual targeting RNAi agent inhibits oxalate and/or glyoxylate protein production to a level lower than the level of protein production obtained by the contacting of a cell with both dsRNA agents individually.

67. A cell containing the dsRNA agent of any one of claims 1-31.

68. A cell containing the dual targeting RNAi agent of any one of claims 32-66.

69. A vector encoding at least one strand of the dsRNA agent of any one of claims 1-31.

70. A vector encoding at least one strand of the dual targeting RNAi agent of any one of claims 32-66.

71. A pharmaceutical composition for inhibiting expression of a lactic acid dehydrogenase A (LDHA) gene comprising the agent of any one of claims 1-31.

72. A pharmaceutical composition for inhibiting expression of a lactic acid dehydrogenase A (LDHA) gene and an hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) gene comprising the dual targeting RNAi agent of any one of claims 32-66.

73. A pharmaceutical composition, comprising
a first double stranded ribonucleic acid (dsRNA) agent that inhibits expression of lactic acid dehydrogenase A (LDHA) comprising a sense strand and an antisense strand, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2; 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 said sense strand 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 comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:22.

5 74. A pharmaceutical composition, comprising
a first double stranded ribonucleic acid (dsRNA) agent that inhibits expression of lactic acid dehydrogenase A (LDHA) comprising a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense
10 sequences listed in any one of Tables 2-5; 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, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from
15 any one of the antisense sequences listed in any one of Tables 7-14.

75. The pharmaceutical composition of any one of claims 71-74, wherein the agent is formulated in an unbuffered solution.

20 76. The pharmaceutical composition of claim 75, wherein the unbuffered solution is saline or water.

77. The pharmaceutical composition of any one of claims 71-74, wherein the agent is formulated with a buffered solution.

25 78. The pharmaceutical composition of claim 77, wherein said buffered solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

79. The pharmaceutical composition of claim 77, wherein the buffered solution is
30 phosphate buffered saline (PBS).

80. A method of inhibiting lactic acid dehydrogenase A (LDHA) expression in a cell, the method comprising contacting the cell with the agent of any one of claims 1-66, or a pharmaceutical composition of any one of claims 71-74, thereby inhibiting expression of
35 LDHA in the cell.

81. A method of inhibiting lactic acid dehydrogenase A (LDHA) expression and hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) expression in a cell, the method

comprising contacting the cell with the agent of any one of claims 32-66, or a pharmaceutical composition of any one of claims 72-74, thereby inhibiting expression of LDHA and HAO1 in the cell.

5 82. The method of claim 80 or 81, wherein said cell is within a subject.

 83. The method of claim 82, wherein the subject is a human.

 84. The method of any one of claims 80-83, wherein the LDHA expression is
10 inhibited by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or to below the level of
detection of LDHA expression.

 85. The method of any one of claims 81-83, wherein the HAO1 expression is
15 inhibited by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or to below the level of
detection of HAO1 expression.

 86. The method of claim 83, wherein the human subject suffers from an oxalate
pathway-associated disease, disorder, or condition.

20 87. The method of claim 86, wherein the oxalate pathway-associated disease,
disorder, or condition is an oxalate-associated disease, disorder, or condition, or a lactate
dehydrogenase-associated disease, disorder, or condition.

 88. The method of claim 87, wherein the oxalate-associated disease, disorder, or
25 condition is a kidney stone formation disease, disorder, or condition, or a calcium oxalate
tissue deposition disease, disorder, or condition.

 89. The method of claim 88, wherein the kidney stone formation disease, disorder,
or condition is a calcium oxalate stone formation disease, disorder, or condition or a non-
30 calcium oxalate stone formation disease, disorder, or condition.

 90. The method of claim 89, wherein the calcium oxalate stone formation disease,
disorder, or condition is a hyperoxaluria disease, disorder, or condition or a non-
hyperoxaluria disease, disorder, or condition.

35 91. The method of claim 90, wherein the hyperoxaluria disease, disorder, or
condition is selected from the group consisting of primary hyperoxaluria, enteric
hyperoxaluria, dietary hyperoxaluria, and idiopathic hyperoxaluria.

92. The method of claim 90, wherein the non-hyperoxaluria stone formation disease, disorder, or condition is hypercalciuria and/or hypocitraturia.

5 93. The method of claim 90, wherein the non-hyperoxaluria stone formation disease, disorder, or condition is calcium oxalate or non-calcium oxalate kidney stone formation disease.

10 94. The method of claim 88, wherein the calcium oxalate tissue deposition disease, disorder, or condition is selected from the group consisting of systemic calcium oxalate tissue deposition disease, disorder, or condition or tissue specific calcium oxalate tissue deposition disease, disorder, or condition.

15 95. The method of claim 88, wherein the lactate dehydrogenase-associated disease, disorder, or condition is selected from the group consisting of cancer, fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis of the liver, accumulation of fat in the liver, inflammation of the liver, hepatocellular necrosis, liver fibrosis, and nonalcoholic fatty liver disease (NAFLD).

20 96. The method of any one of claims 80-95, wherein the cell is a liver cell.

97. A method of inhibiting the expression of LDHA in a subject, the method comprising
administering to the subject a therapeutically effective amount of the agent of any one
25 of claims 1-66, or a pharmaceutical composition of any one of claims 71-74, thereby inhibiting the expression of LDHA in said subject.

98. A method of inhibiting lactic acid dehydrogenase A (LDHA) expression and hydroxyacid oxidase 1 (glycolate oxidase) (HAO1) expression in a subject, comprising
30 administering to the subject a therapeutically effective amount of any one of claims 32-66, or a pharmaceutical composition of any one of claims 72-74, thereby inhibiting expression of LDHA and HAO1 in the subject.

99. A method of treating a subject having a disorder that would benefit from a
35 reduction in LDHA expression, comprising
administering to the subject a therapeutically effective amount of the agent of any one of claims 1-66, or a pharmaceutical composition of any one of claims 71-74, thereby treating said subject.

100. A method of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in expression of an LDHA gene, comprising administering to the subject a prophylactically effective amount of the agent of any one of claims 1-66, or a pharmaceutical composition of any one of claims 71-74, thereby preventing at least one symptom in the subject.

101. The method of claim 99 or 100, wherein the disorder is an oxalate pathway-associated disease, disorder, or condition.

102. A method of treating a subject having an oxalate pathway-associated disease, disorder, or condition, comprising administering to the subject a therapeutically effective amount of the agent of any one of claims 1-66, or a pharmaceutical composition of any one of claims 71-74, thereby treating the subject.

103. A method of preventing at least one symptom in a subject having an oxalate pathway-associated disease, disorder, or condition, comprising administering to the subject a prophylactically effective amount of the agent of any one of claims 1-66, or a pharmaceutical composition of any one of claims 71-74, thereby preventing at least one symptom in the subject.

104. The method of any one of claims 98-103, wherein the administration of the dsRNA agent or the pharmaceutical composition to the subject causes a decrease in urinary oxalate, tissue oxalate, plasma oxalate, a decrease in LDHA enzymatic activity, a decrease in LDHA protein accumulation, and/or a decrease in HAO1 protein accumulation.

105. The method of any one of claims 101-104, wherein the oxalate pathway-associated disease, disorder, or condition is an oxalate-associated disease, disorder, or condition, or a lactate dehydrogenase-associated disease, disorder, or condition.

106. The method of claim 105, wherein the oxalate-associated disease, disorder, or condition is a kidney stone formation disease, disorder, or condition, or a calcium oxalate tissue deposition disease, disorder, or condition.

107. The method of claim 106, wherein the kidney stone formation disease, disorder, or condition is a calcium oxalate stone formation disease, disorder, or condition or a non-calcium oxalate stone formation disease, disorder, or condition.

108. The method of claim 107, wherein the calcium oxalate stone formation disease, disorder, or condition is a hyperoxaluria disease, disorder, or condition or a non-hyperoxaluria disease, disorder, or condition.

5

109. The method of claim 108, wherein the hyperoxaluria disease, disorder, or condition is selected from the group consisting of primary hyperoxaluria, enteric hyperoxaluria, dietary hyperoxaluria, and idiopathic hyperoxaluria.

10

110. The method of claim 109, wherein the non-hyperoxaluria stone formation disease, disorder, or condition is hypercalciuria and/or hypocitraturia.

111. The method of claim 110, wherein the non-hyperoxaluria stone formation disease, disorder, or condition is calcium oxalate or non-calcium oxalate kidney stone formation disease.

15

112. The method of claim 101, wherein the calcium oxalate tissue deposition disease, disorder, or condition is selected from the group consisting of systemic calcium oxalate tissue deposition disease, disorder, or condition or tissue specific calcium oxalate tissue deposition disease, disorder, or condition.

20

113. The method of any one of claims 101-104, wherein the lactate dehydrogenase-associated disease, disorder, or condition is selected from the group consisting of cancer, fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis of the liver, accumulation of fat in the liver, inflammation of the liver, hepatocellular necrosis, liver fibrosis, and nonalcoholic fatty liver disease (NAFLD).

25

114. The method of any one of claims 97-99 wherein the disease, disorder or condition is primary hyperoxaluria 2 (PH2).

30

115. The method of claim 114, further comprising altering the diet of the subject.

116. The method of claim 114 or 115, wherein the subject receives a kidney transplant.

35

117. The method of any one of claims 98-116, wherein the subject is human.

118. The method of any one of claims 98-117, further comprising administering an additional therapeutic to the subject.

5 119. The method of any one of claims 98-118, wherein the agent 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.

10 120. The method of any one of claims 98-119, wherein the agent is administered to the subject subcutaneously.

121. The method of any one of claims 98-120, wherein the agent does not substantially inhibit expression and/or activity of lactate dehydrogenase B (LDHB).

15

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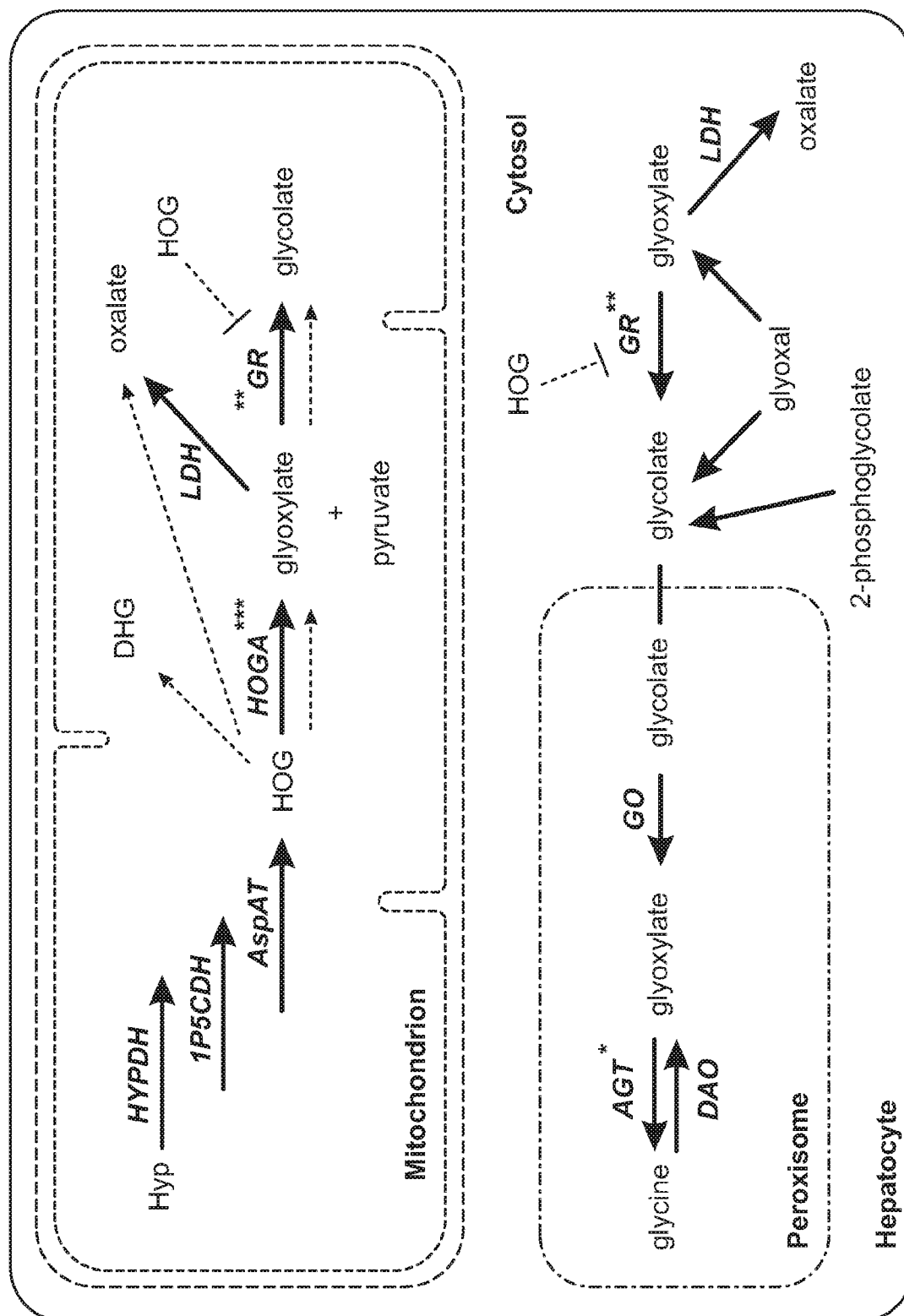


FIG. 1A



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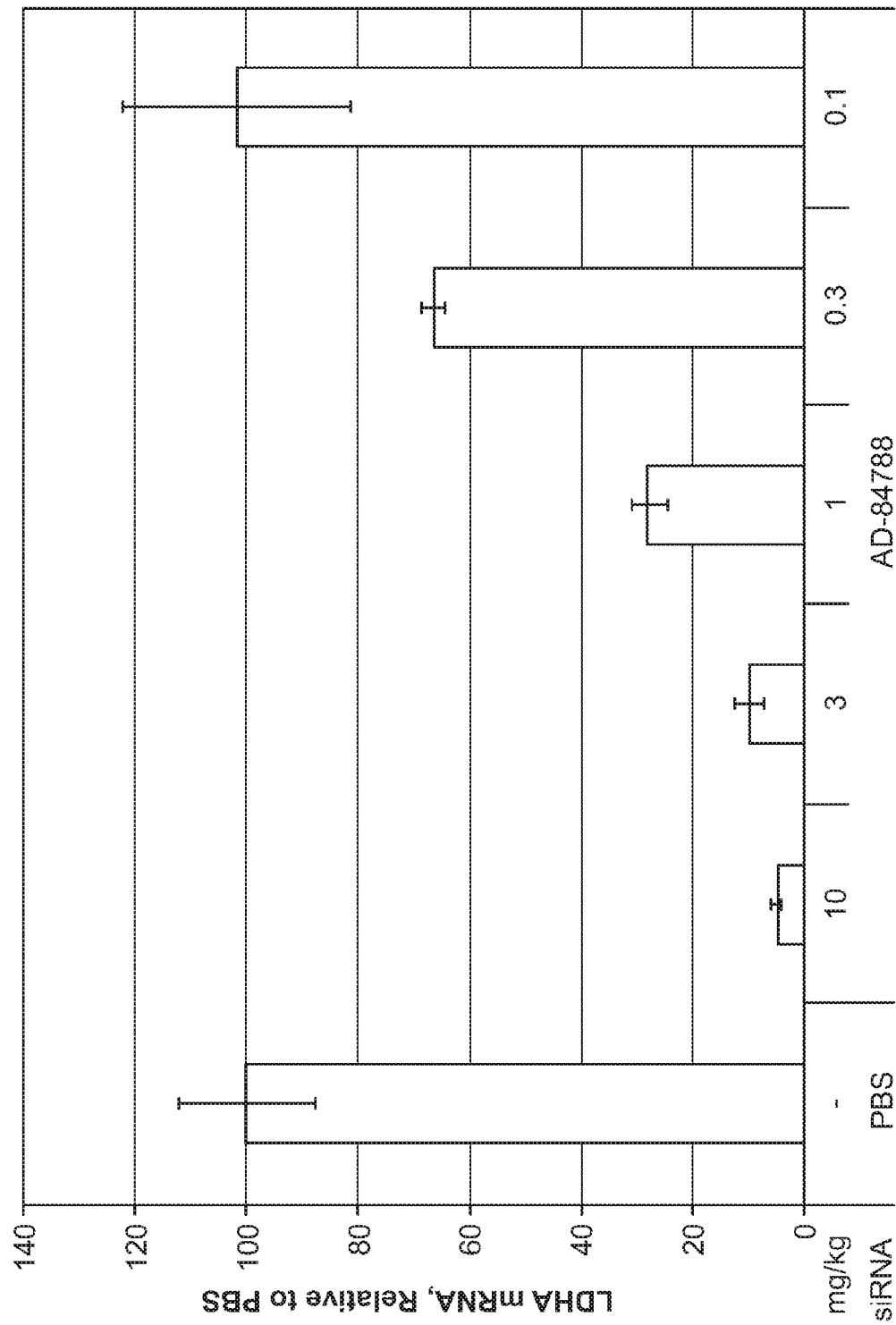


FIG. 2

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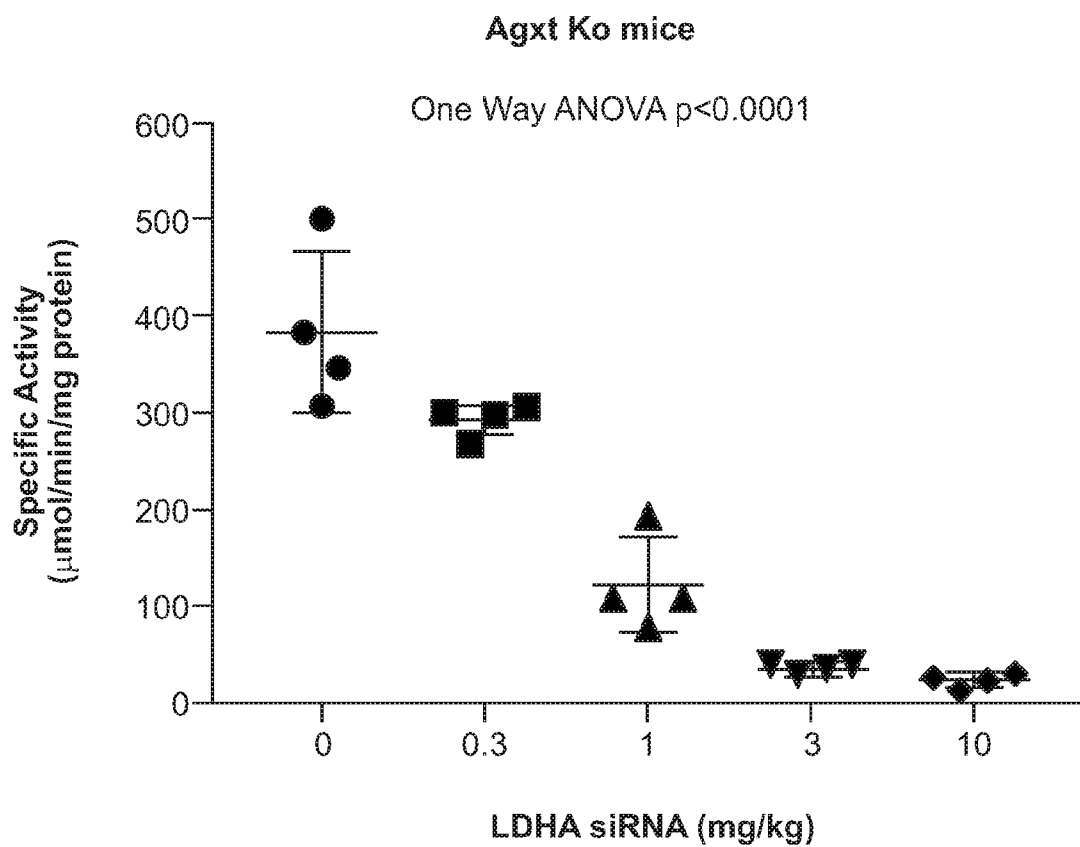


FIG. 3

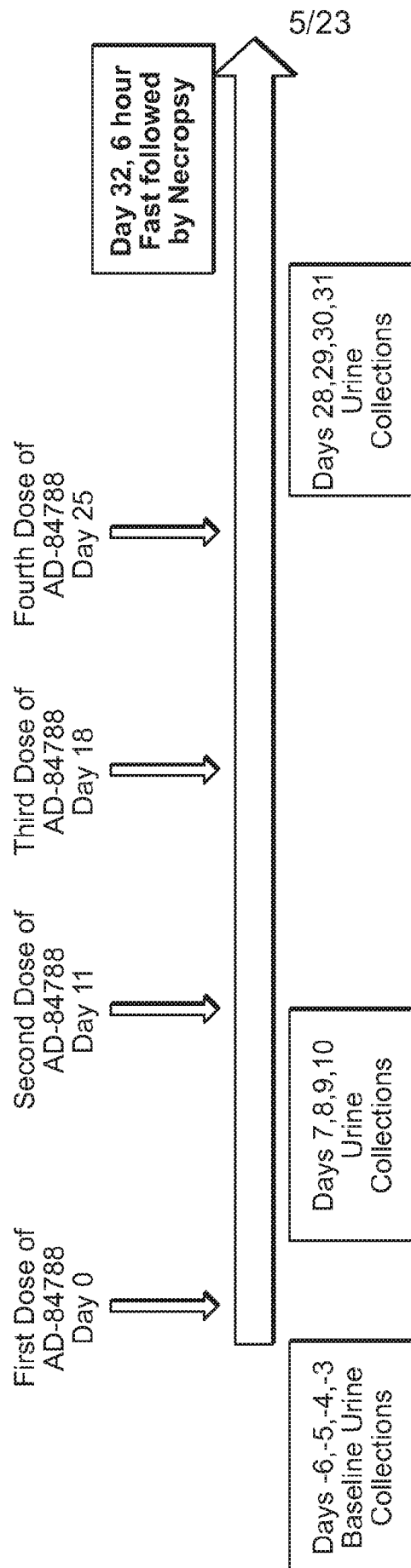


FIG. 4

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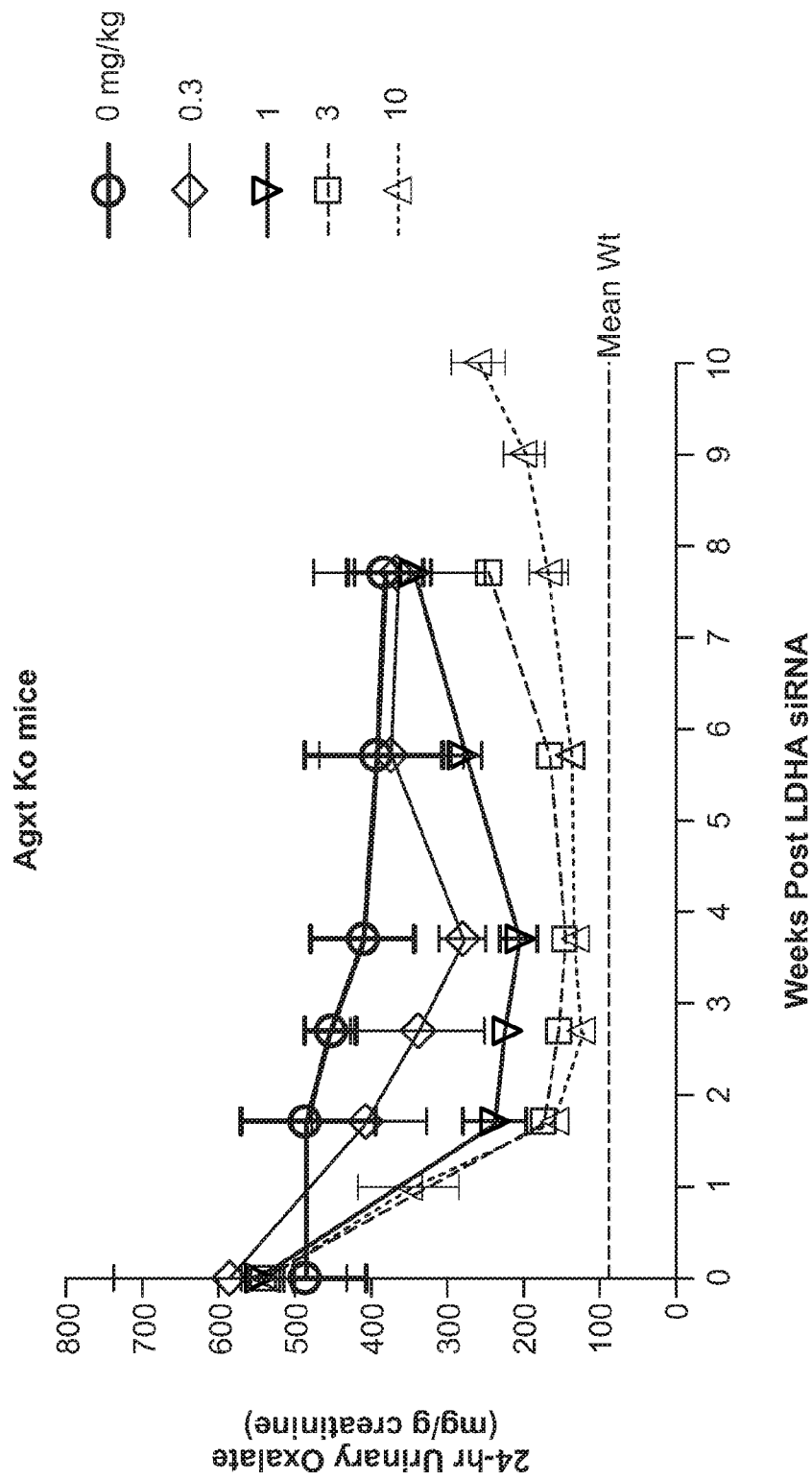


FIG. 5

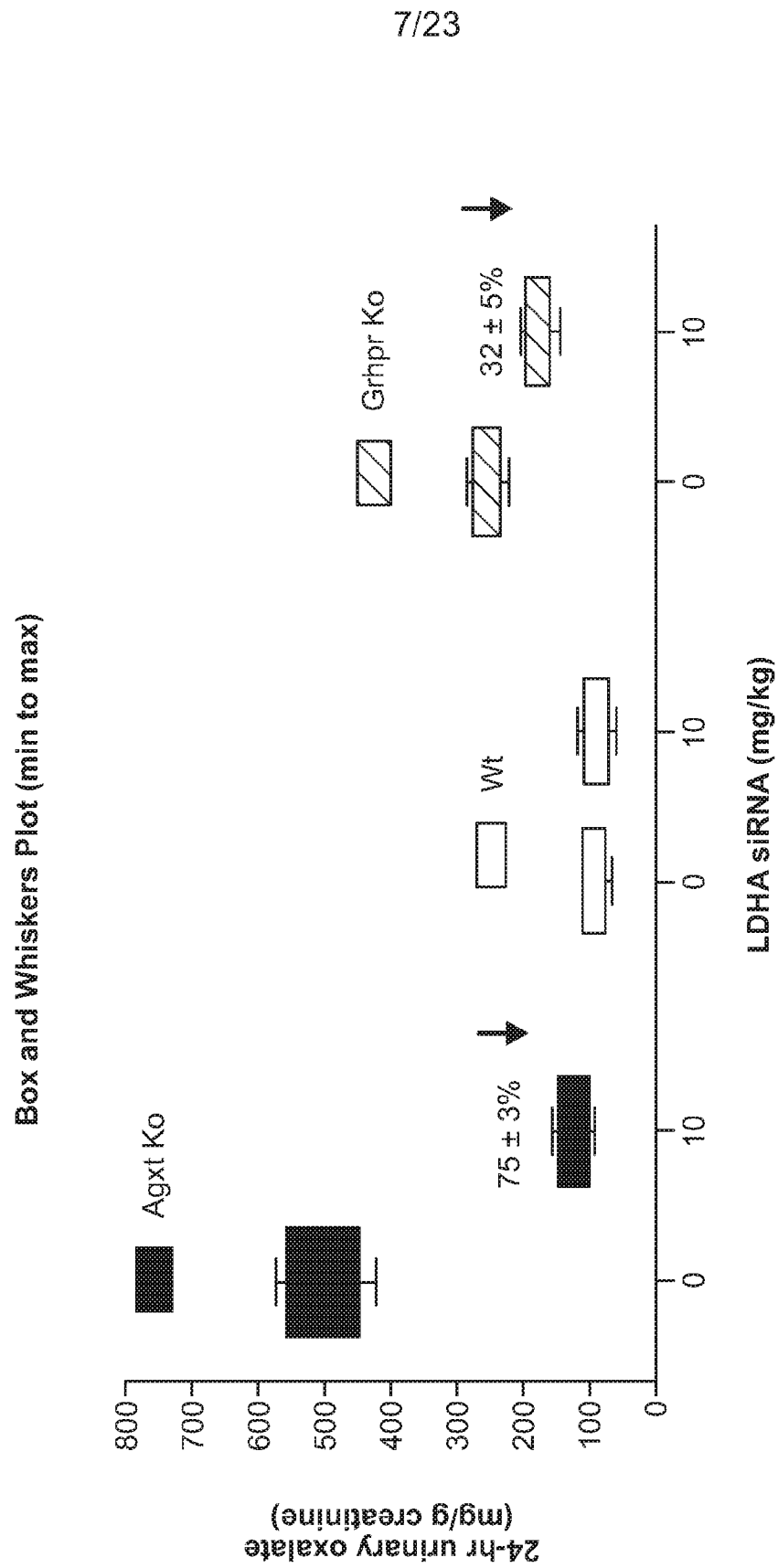


FIG. 6

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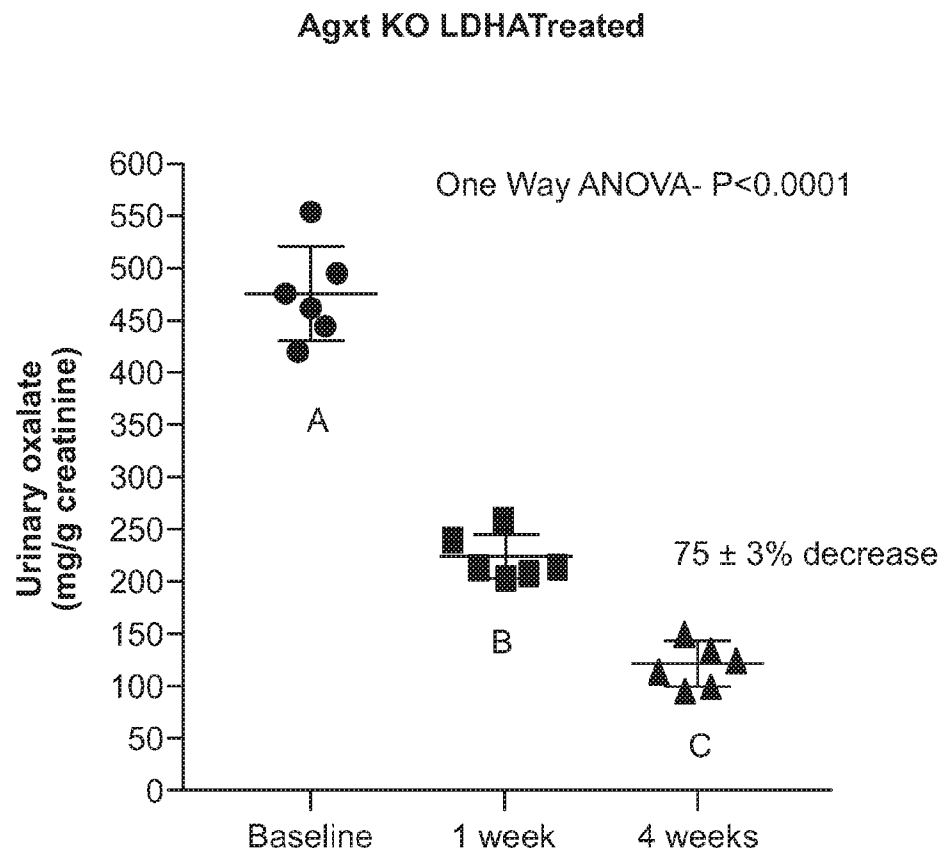


FIG. 7

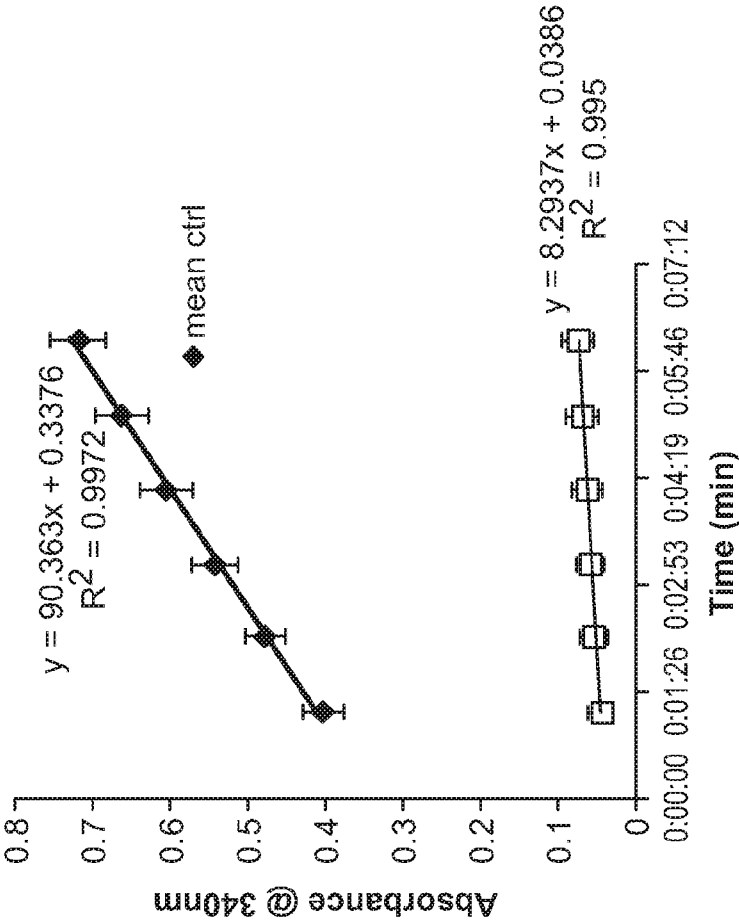


FIG. 8A

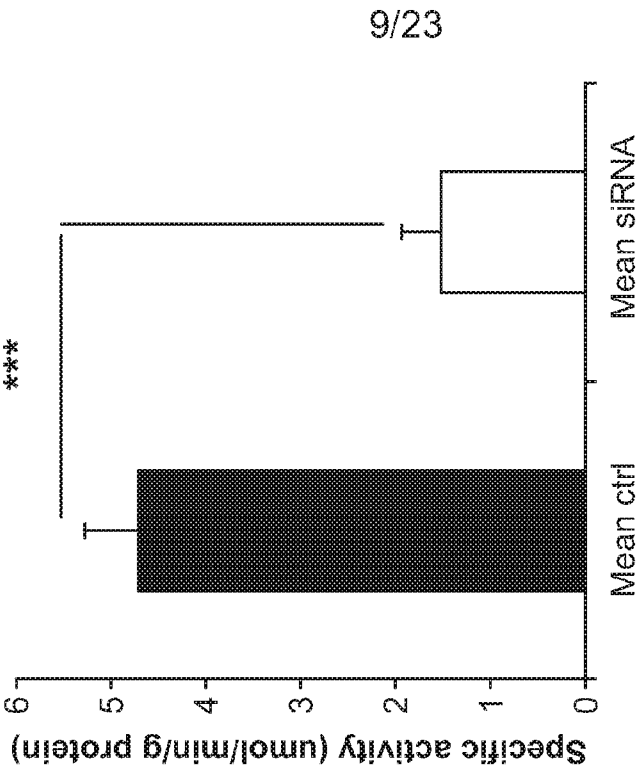


FIG. 8B

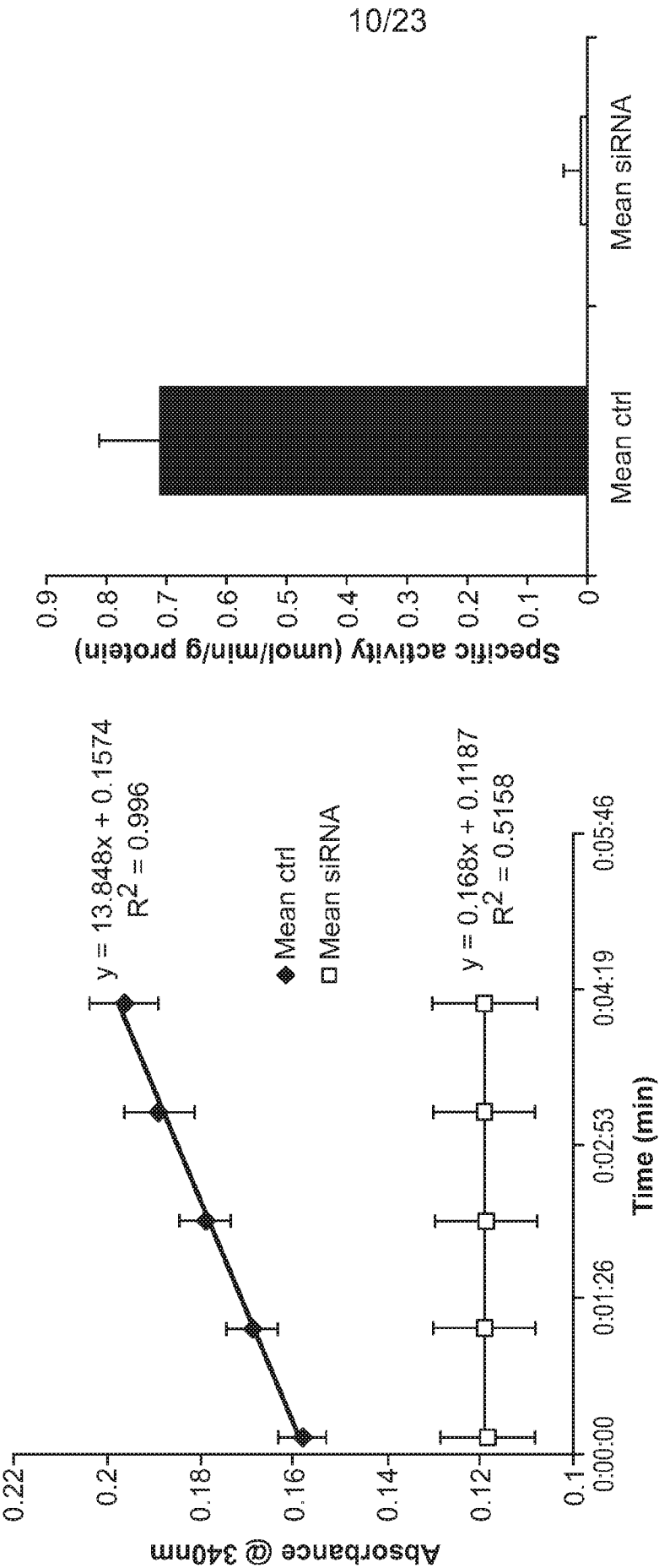


FIG. 9B

FIG. 9A

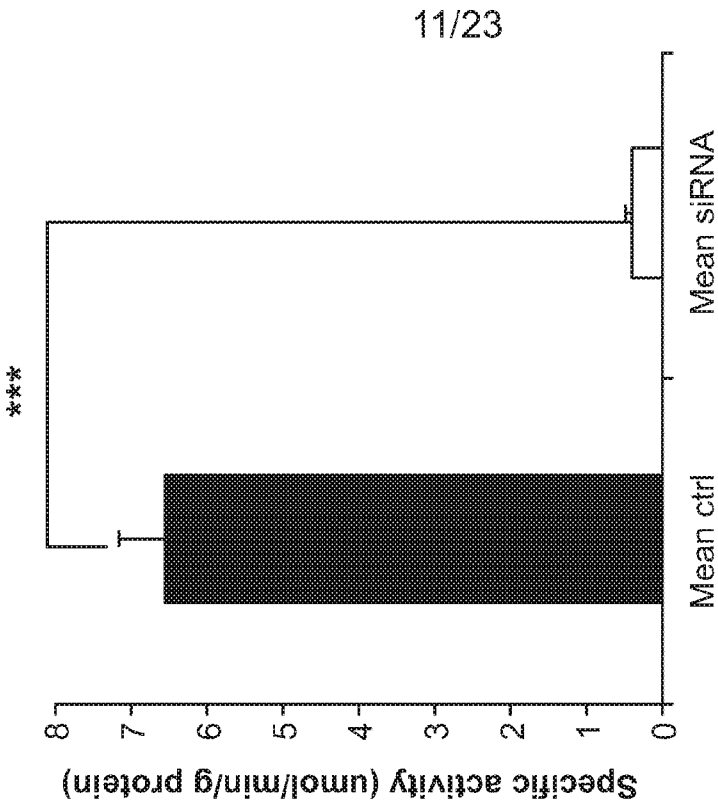


FIG. 10B

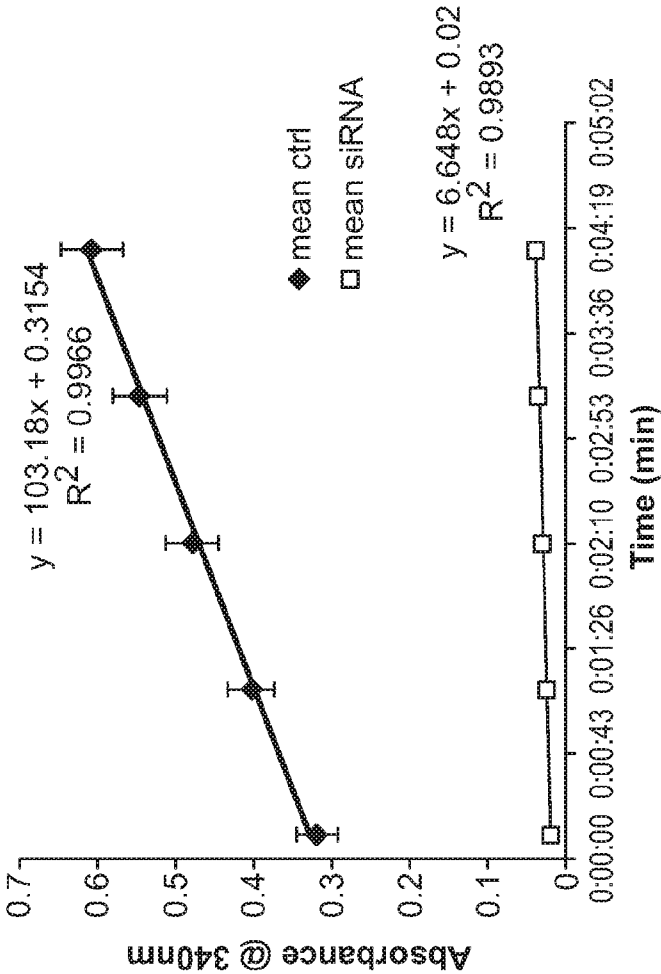


FIG. 10A

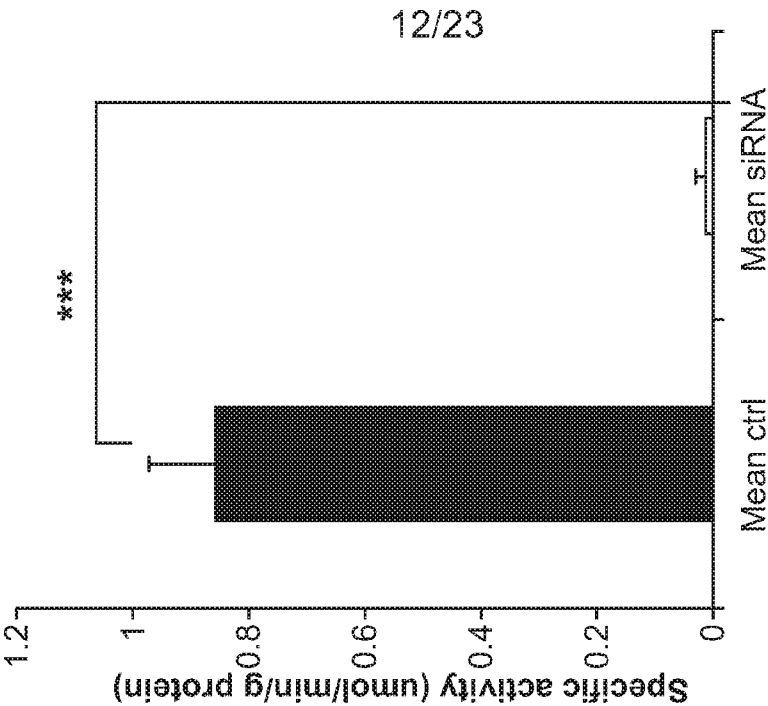


FIG. 11B

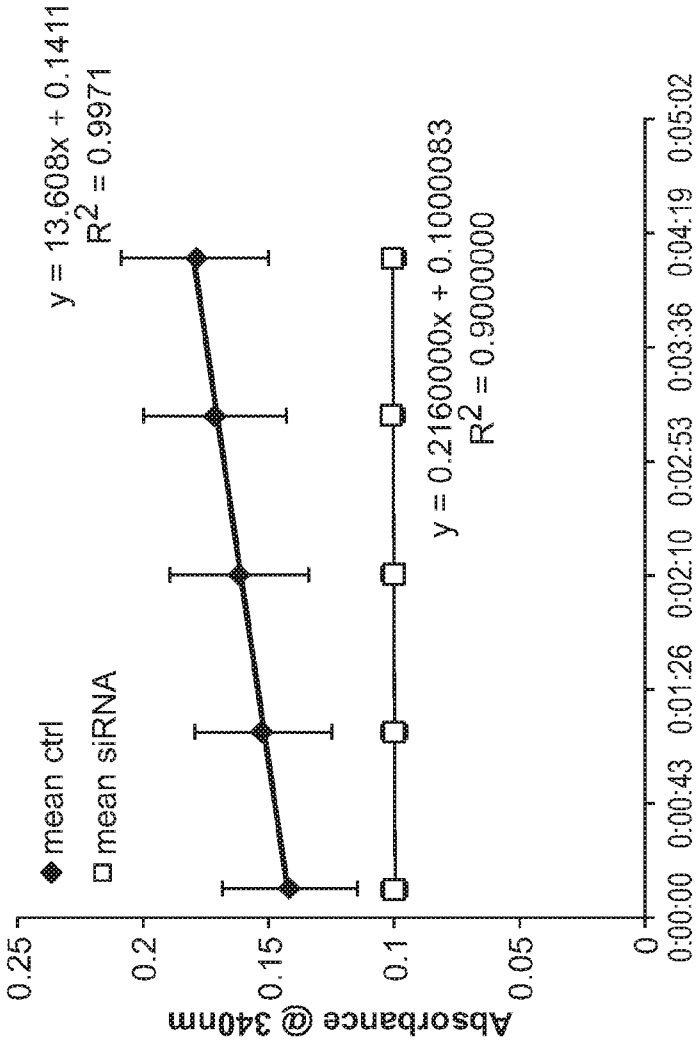


FIG. 11A

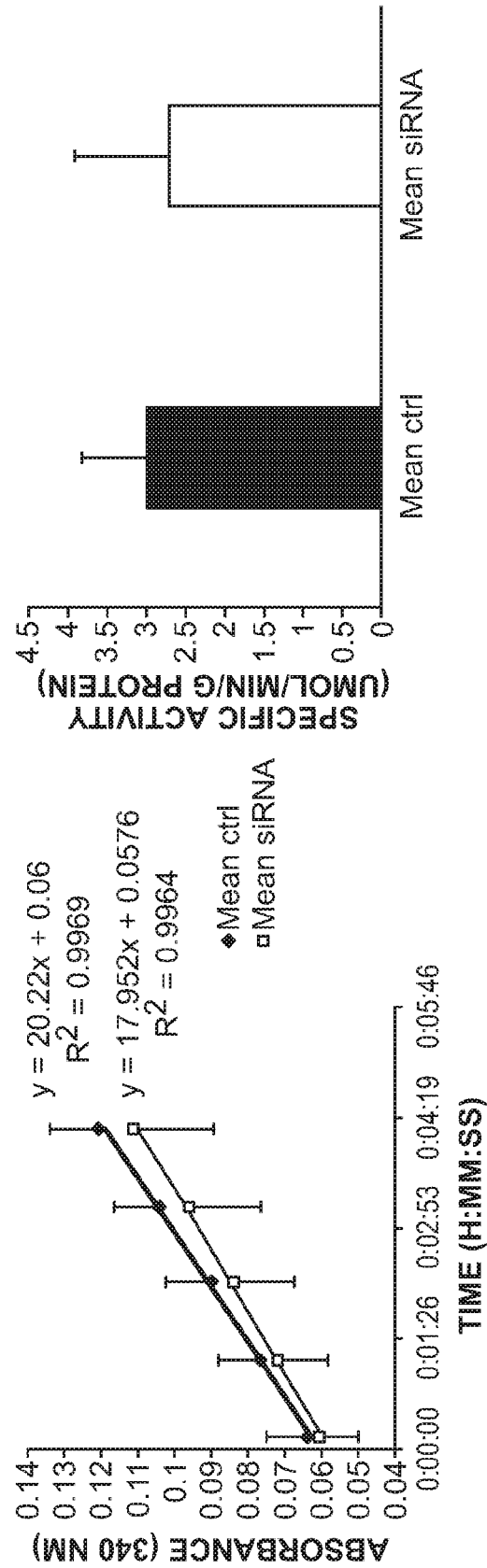


FIG. 12B

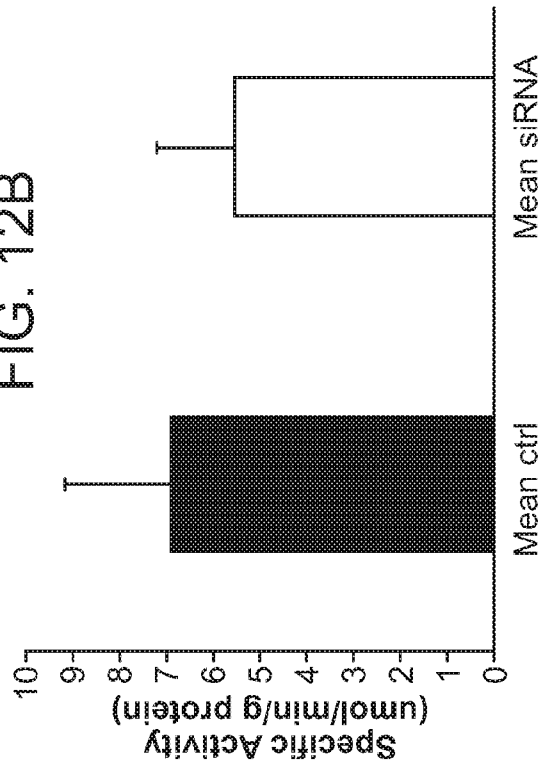
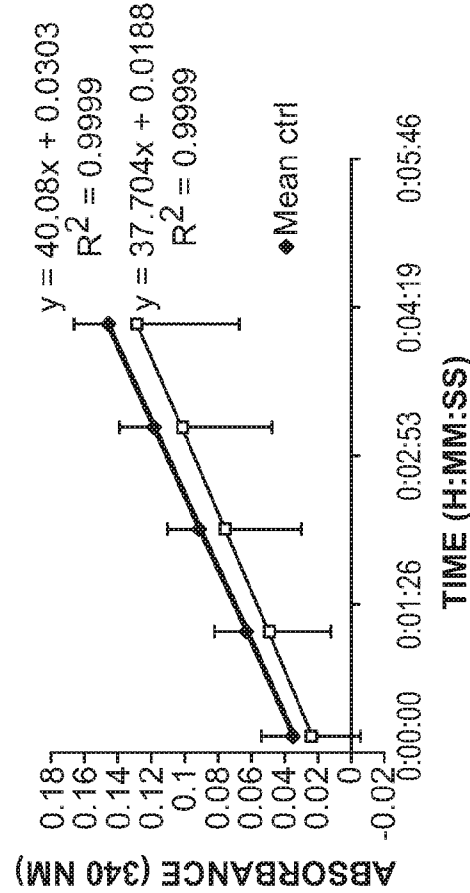


FIG. 12D



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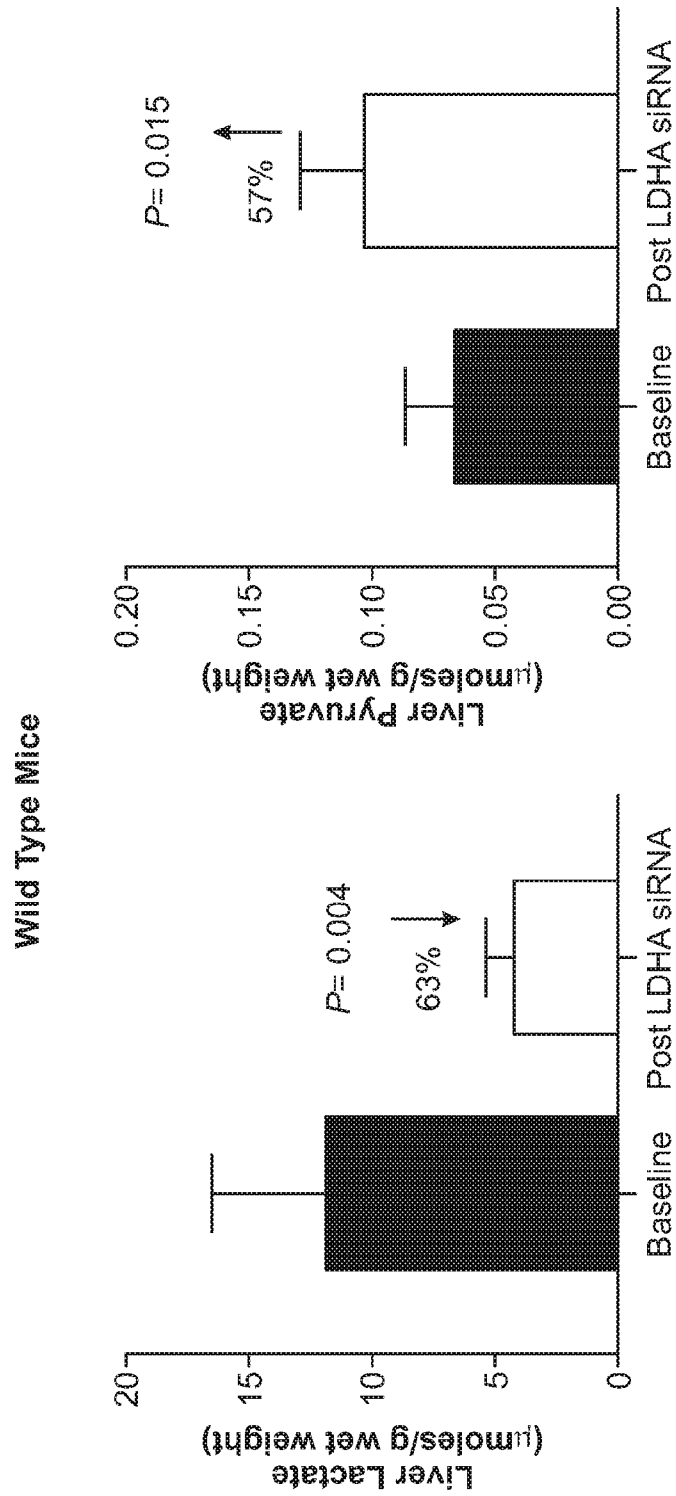


FIG. 13A

FIG. 13B

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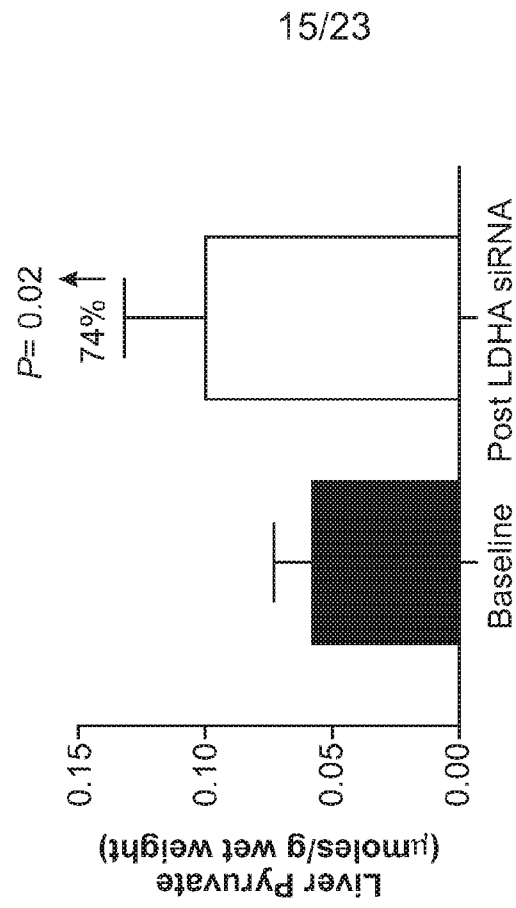


FIG. 14B

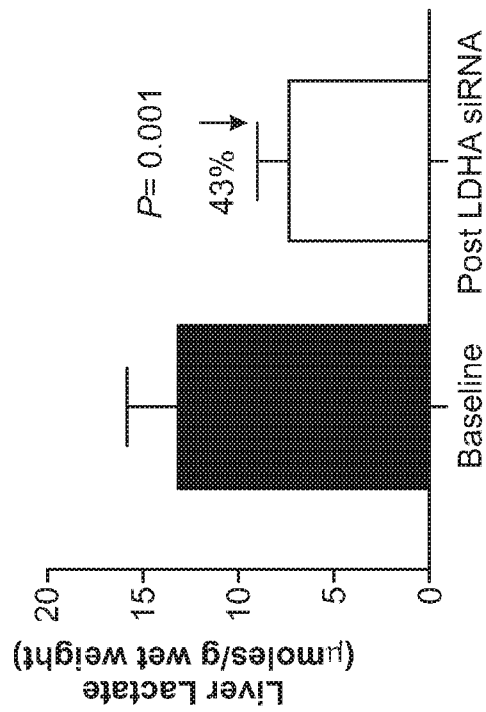


FIG. 14A

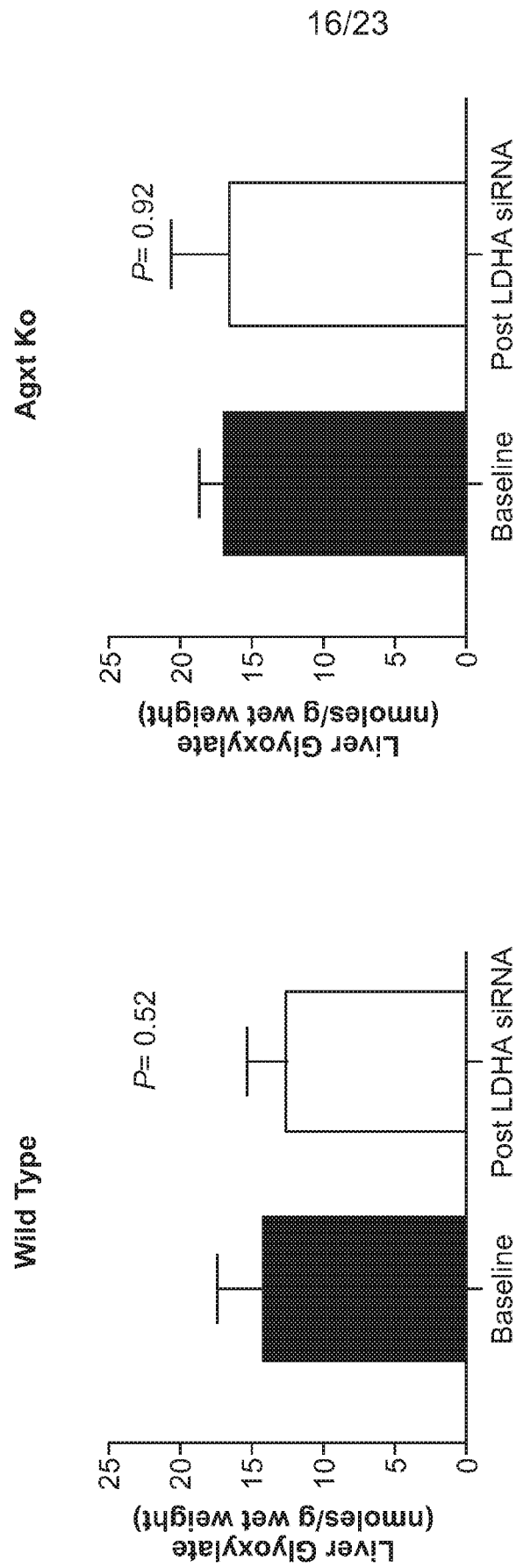


FIG. 15A

FIG. 15B

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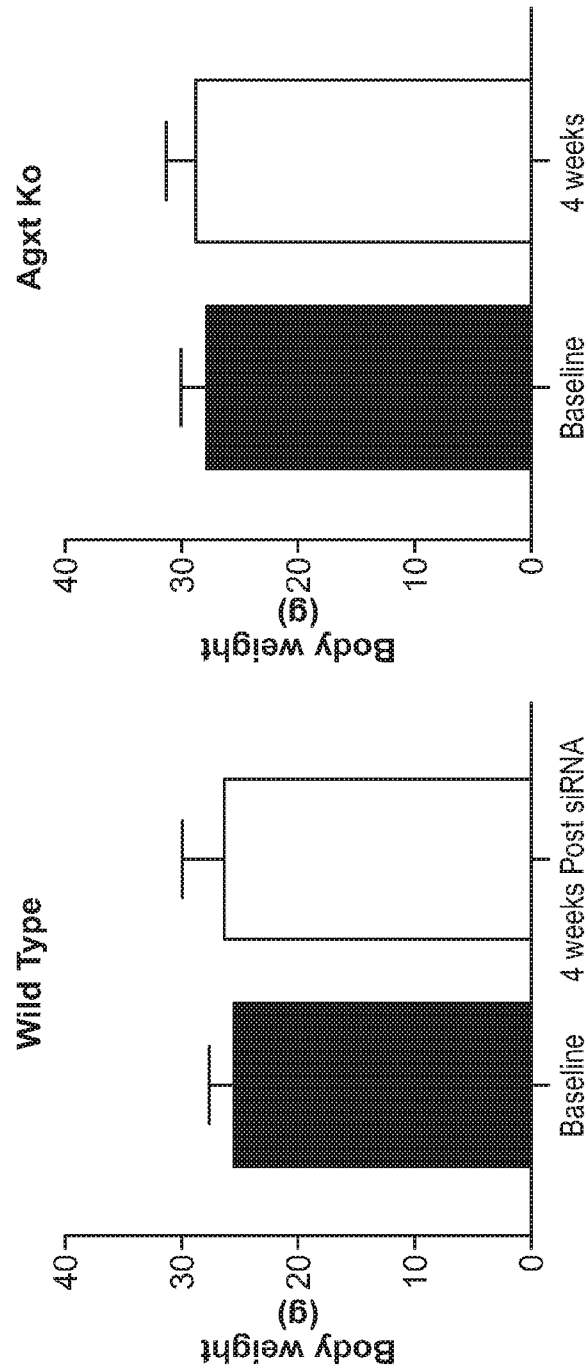


FIG. 16B

FIG. 16A

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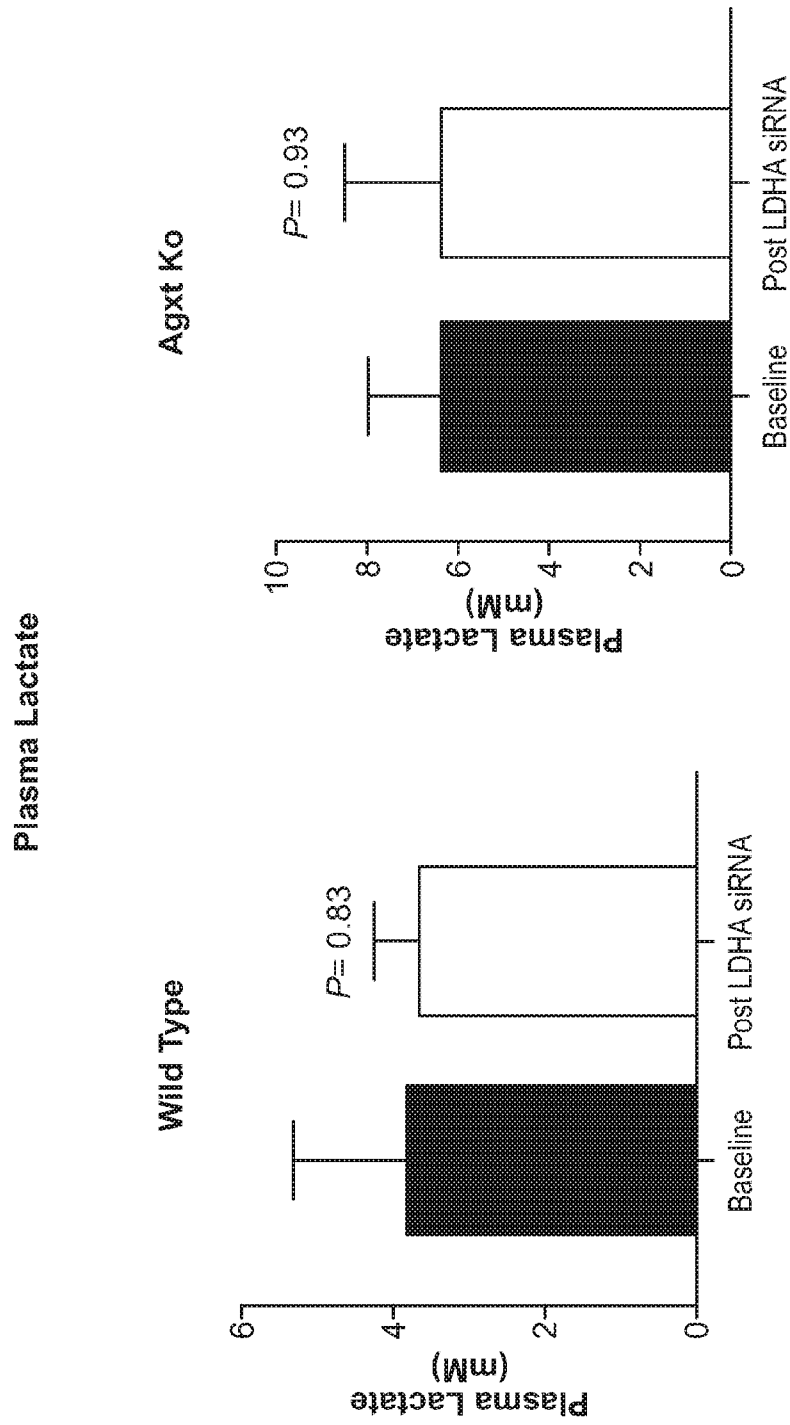
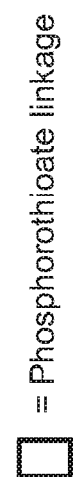
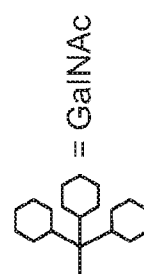
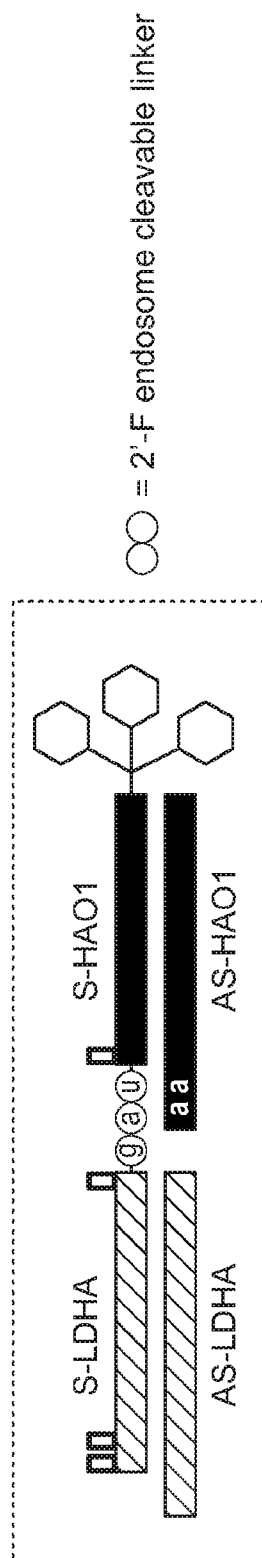
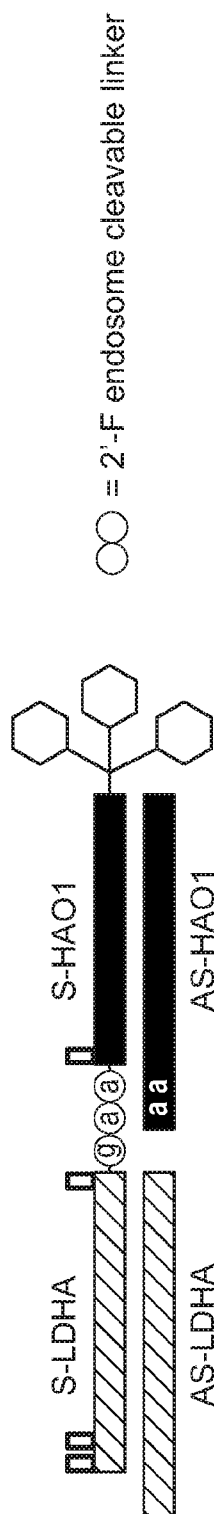
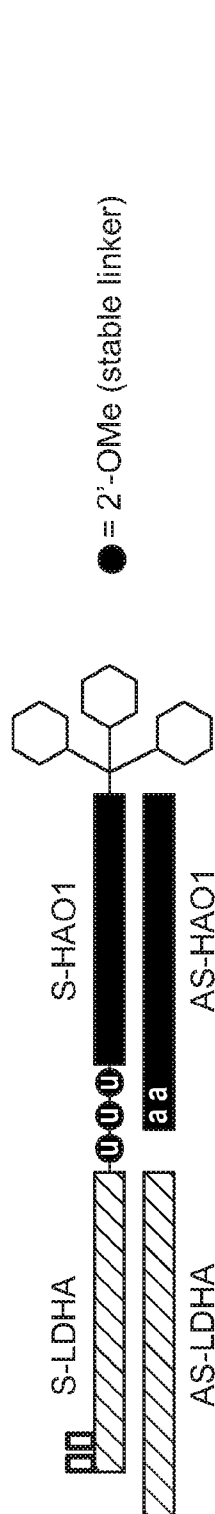


FIG. 17B

FIG. 17A

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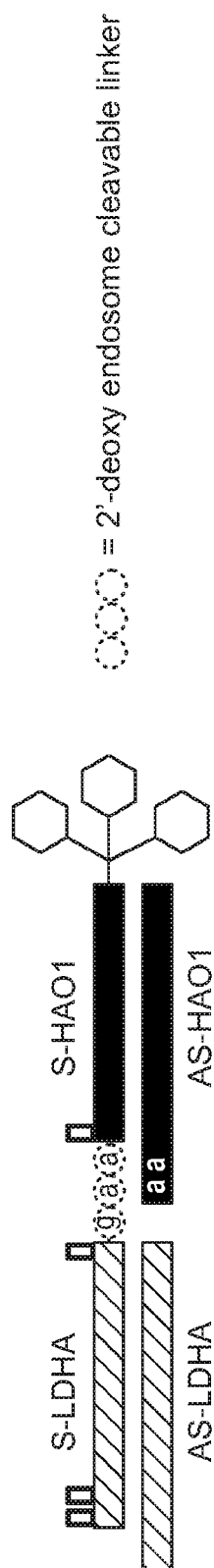


FIG. 18D

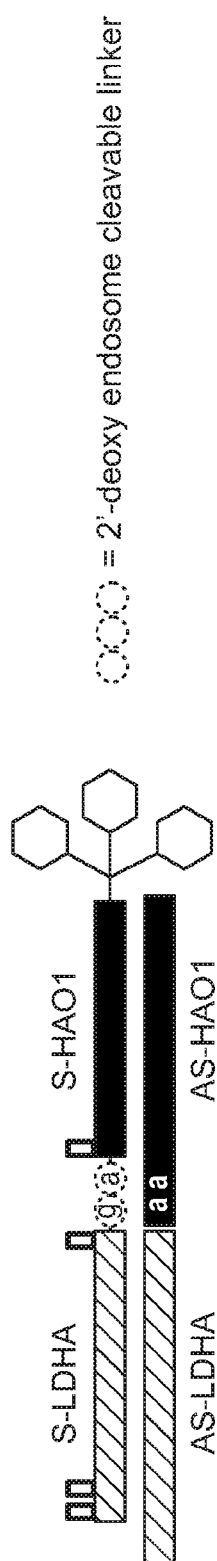


FIG. 18E

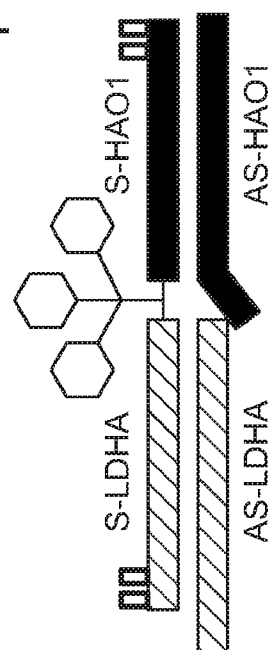
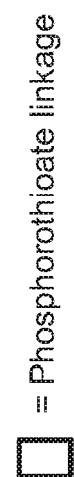
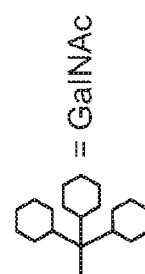


FIG. 18F



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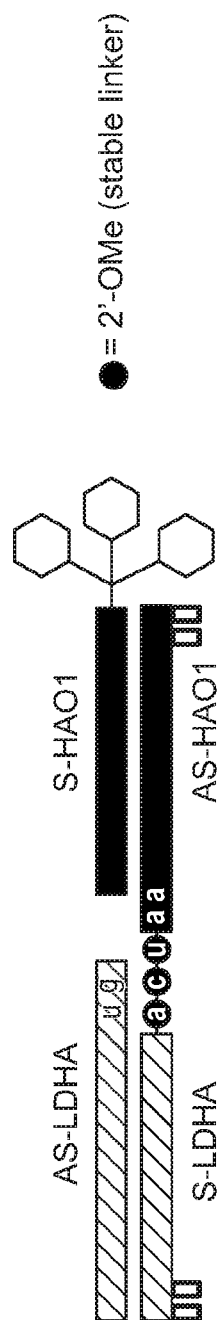


FIG. 18G

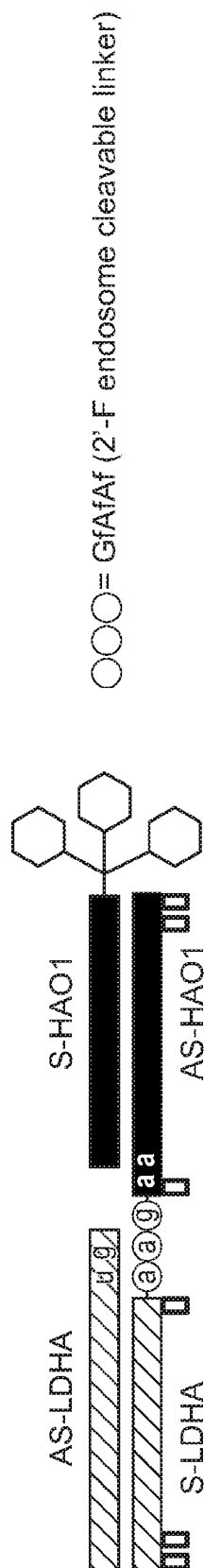


FIG. 18H

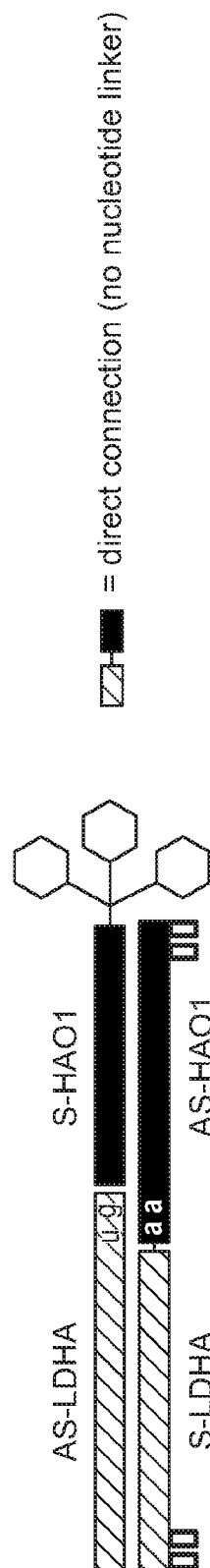
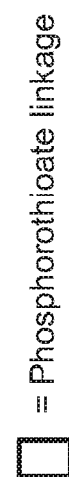
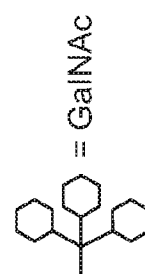


FIG. 18I



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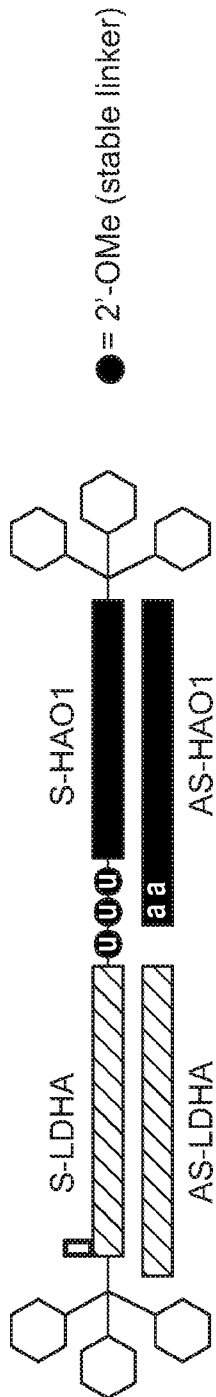


FIG. 18J

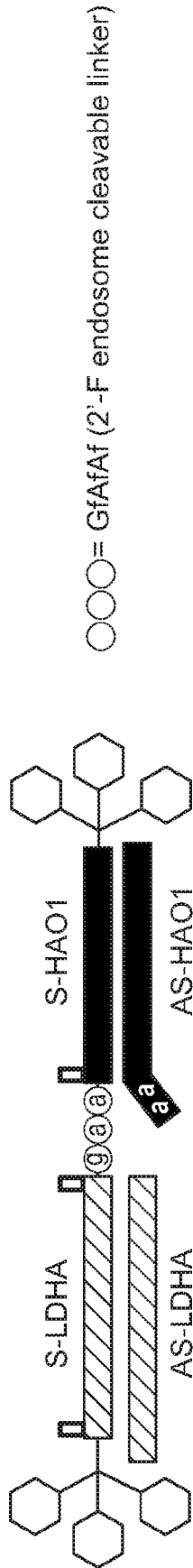
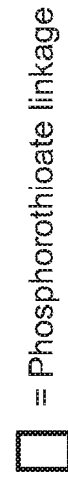
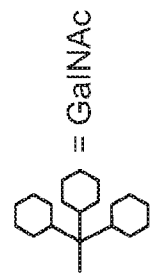


FIG. 18K



FIG. 18L



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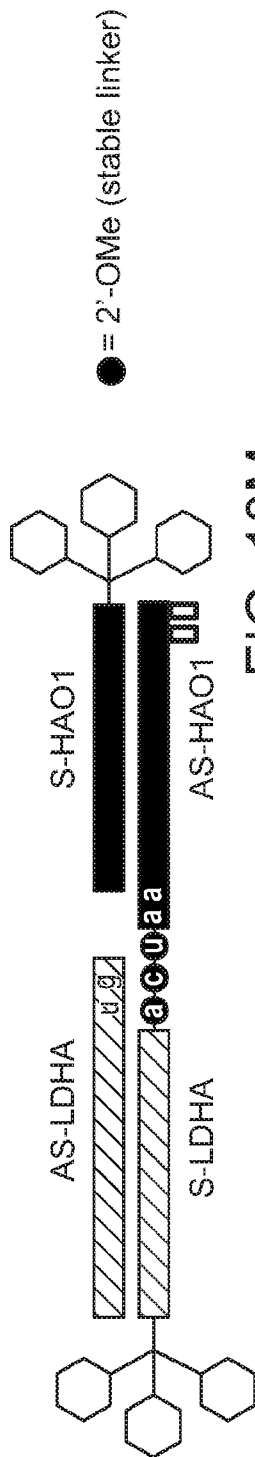


FIG. 18M

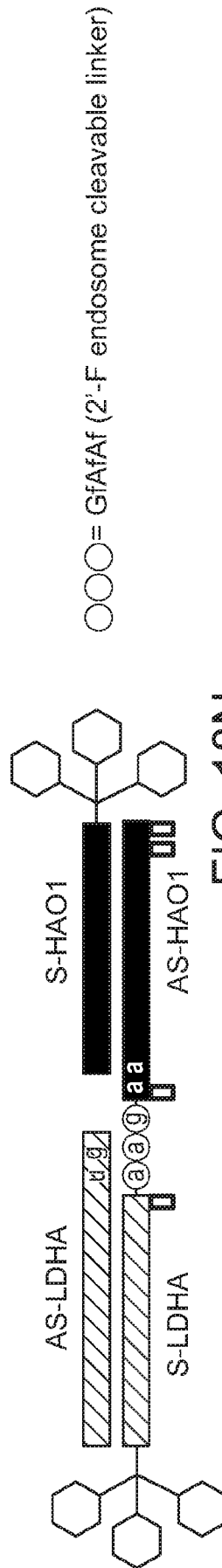


FIG. 18N

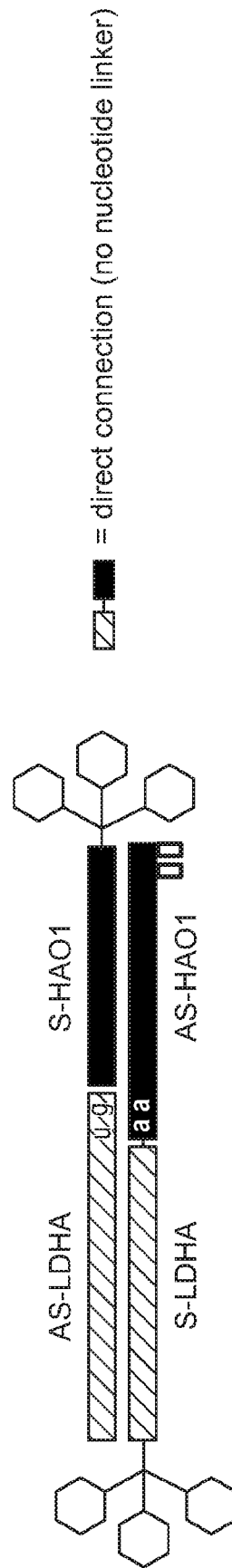
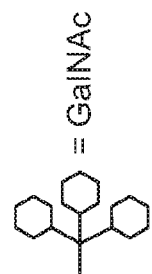


FIG. 18O



□ = Phosphorothioate linkage