COMPLEMENT FACTOR B (CFB) IRNA COMPOSITIONS AND METHODS OF USE THEREOF

Related Application

This application claims the benefit of priority to U.S. Provisional Application No. 63/273,215, filed on October 29, 2021. The entire contents of the foregoing application are incorporated herein by reference.

Background of the Invention

Complement was first discovered in the 1890s when it was found to aid or "complement" the killing of bacteria by heat-stable antibodies present in normal serum (Walport, M.J. (2001) *N Engl J Med.* 344:1058). The complement system consists of more than 30 proteins that are either present as soluble proteins in the blood or are present as membrane-associated proteins. Activation of complement leads to a sequential cascade of enzymatic reactions, known as complement activation pathways resulting in the formation of the potent anaphylatoxins C3a and C5a that elicit a plethora of physiological responses that range from chemoattraction to apoptosis. Initially, complement was thought to play a major role in innate immunity where a robust and rapid response is mounted against invading pathogens. However, recently it is becoming increasingly evident that complement also plays an important role in adaptive immunity involving T and B cells that help in elimination of pathogens (Dunkelberger JR and Song WC. (2010) *Cell Res.* 20:34; Molina H, *et al.* (1996) *Proc Natl Acad Sci U S A.* 93:3357), in maintaining immunologic memory preventing pathogenic re-invasion, and is involved in numerous human pathological states (Qu, H, *et al.* (2009) *Mol Immunol.* 47:185; Wagner, E. and Frank MM. (2010) *Nat Rev Drug Discov.* 9:43).

Complement activation is known to occur through three different pathways: alternate, classical and lectin (Figure 1) involving proteins that mostly exist as inactive zymogens that are then sequentially cleaved and activated.

The classical pathway is often activated by antibody-antigen complexes or by the C-reactive protein (CRP), both of which interact with complement component C1q. In addition, the classical pathway can be activated by phosphatidyl serine present in apoptotic bodies in the absence of immune complexes.

The lectin pathway is initiated by the mannose-binding lectins (MBL) that bind to complex carbohydrate residues on the surface of pathogens. The activation of the classical pathway or the lectin pathway leads to activation of the (C4b2b) C3 convertase.

The alternate pathway is activated by the binding of C3b, which is spontaneously generated by the hydrolysis of C3, on targeted surfaces. This surface-bound C3b is then recognized by factor B, forming the complex C3bB. The C3bB complex, in turn, is cleaved by factor D to yield the active form of the C3 convertase of the AP (C3bBb). Both types of C3 convertases will cleave C3, forming C3b. C3b then either binds to more factor B, enhancing the complement activation

through the AP (the so-called alternative or amplification loop), or leads to the formation of the active C5 convertase (C3bBbC3b or C4bC2bC3b), which cleaves C5 and triggers the late events that result in the formation of the membrane attack complex (MAC) (C5b-9).

Inappropriate activation of the complement system is responsible for propagating or initiating pathology in many different diseases, including, for example, C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration, atypical hemolytic uremic syndrome, thrombotic microangiopathy, myasthenia gravis, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria, and rheumatoid arthritis.

To date, only one therapeutic that targets the alternate pathway, *e.g.,* the C5-C5a axis, is available for the treatment of complement component-associated diseases, the anti-C5 antibody, eculizumab (Soliris®). Although eculizumab has been shown to be effective for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and Myasthenia Gravis, and is currently being evaluated in clinical trials for additional complement component-associated diseases, eculizumab therapy requires weekly high dose infusions followed by biweekly maintenance infusions at a high cost. Furthermore, approximately 50% of eculizumab-treated PNH subjects have low level of hemolysis and require residual transfusions (Hill A, *et al.* (2010) *Haematologica* 95(4):567-73).

Accordingly, there is a need in the art for compositions and methods for treating diseases, disorders, and conditions associated with complement activation by, for example, activation of complement factor B activity.

Summary of the Invention

The present invention provides iRNA compositions which affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding complement factor B (CFB). The complement factor B (CFB) may be within a cell, *e.g.,* a cell within a subject, such as a human subject.

Accordingly, in one aspect, the invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement factor B (CFB) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the corresponding portion of the nucleotide sequence of SEQ ID NO:8.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) for inhibiting expression of complement factor B (CFB) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand

comprises a region of complementarity to an mRNA encoding complement factor B (CFB) , and wherein the region of complementarity comprises at least 15, *e.g.,* 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-3.

In one embodiment, the dsRNA agent comprises a sense strand comprising any of the sense nucleotide sequences in any one of Tables 2-3.

In one embodiment, the dsRNA agent comprises an antisense strand comprising any of the antisense nucleotide sequences in any one of Tables 2-3.

In one embodiment, the dsRNA agent comprises a sense strand comprising any of the sense nucleotide sequences in any one of Tables 2-3 and an antisense strand comprising any of the antisense nucleotide sequences in any one of Tables 2-3.

In one embodiment, the dsRNA agent comprises a sense strand comprising a nucleotide sequence which differs by no more than 4 nucleotides from any of the sense nucleotide sequences in any one of Tables 2-3 and an antisense strand comprising a nucleotide sequence which differs by no more than 4 nucleotides from any of the antisense nucleotide sequences in any one of Tables 2-3.

In one embodiment, the dsRNA agent comprises a sense strand comprising a nucleotide sequence which differs by no more than 3 nucleotides from any of the sense nucleotide sequences in any one of Tables 2-3 and an antisense strand comprising a nucleotide sequence which differs by no more than 3 nucleotides from any of the antisense nucleotide sequences in any one of Tables 2-3.

In one embodiment, the dsRNA agent comprises a sense strand comprising a nucleotide sequence which differs by no more than 2 nucleotides from any of the sense nucleotide sequences in any one of Tables 2-3 and an antisense strand comprising a nucleotide sequence which differs by no more than 2 nucleotides from any of the antisense nucleotide sequences in any one of Tables 2-3.

In one embodiment, the dsRNA agent comprises a sense strand comprising a nucleotide sequence which differs by no more than 1 nucleotide from any of the sense nucleotide sequences in any one of Tables 2-3 and an antisense strand comprising a nucleotide sequence which differs by no more than 1 nucleotide from any of the antisense nucleotide sequences in any one of Tables 2-3.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) for inhibiting expression of complement factor B (CFB) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, e.g., 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than 0, 1, 2, 3 or 4 nucleotides from any one of the nucleotide sequence of nucleotides 504-526, 640-662, 641-663, 995-1017, 997-1019, 1034-1056, 1141-1163, 1145-1167, 1389-1411, 1473-1495, 1826-1848, 1828-1850, 1842-1864, 2242-2264, 2391-2413, 2393-2415, 2438-2460, or 2453-2475 of SEQ ID NO: 1, and the antisense strand comprises at least 15, e.g., 15, 16, 17, 18, 19, 20, 21, 22 or 23, contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:8.

In one embodiment, the antisense strand comprises at least 15 , e.g., 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, 3, or 4 nucleotides from any one

of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1726057; AD-1725763; AD-1725777; AD-1725057; AD-1725096; AD-1728786; AD-1725059; AD-1728276; AD-1728278; AD-1726936; AD-1725472; AD-1724715; AD-1727292; AD-1730477; AD-1727288; AD-1730167; AD-1725408; and AD-1725761.

In one embodiment, the sense strand and the antisense strand comprise at least 15, e.g., 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides differing by no more than 0, 1, 2, 3, or 4 nucleotides from any one of the sense strand and the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1726057; AD-1725763; AD-1725777; AD-1725057; AD-1725096; AD-1728786; AD-1725059; AD-1728276; AD-1728278; AD-1726936; AD-1725472; AD-1724715; AD-1727292; AD-1730477; AD-1727288; AD-1730167; AD-1725408; and AD-1725761.

In one embodiment, the sense strand and the antisense strand comprise the sense strand and the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1726057; AD-1725763; AD-1725777; AD-1725057; AD-1725096; AD-1728786; AD-1725059; AD-1728276; AD-1728278; AD-1726936; AD-1725472; AD-1724715; AD-1727292; AD-1730477; AD-1727288; AD-1730167; AD-1725408; and AD-1725761.

In one embodiment, the sense strand and the antisense strand consist of the sense strand and the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1726057; AD-1725763; AD-1725777; AD-1725057; AD-1725096; AD-1728786; AD-1725059; AD-1728276; AD-1728278; AD-1726936; AD-1725472; AD-1724715; AD-1727292; AD-1730477; AD-1727288; AD-1730167; AD-1725408; and AD-1725761.

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

In one embodiment, substantially all of the nucleotides of the sense strand; 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 one embodiment, 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 the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythimidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 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 nucleotide comprising a 2'-phospahte group, *e.g.,* cytidine-2`-phosphate (C2p); guanosine-2`-phosphate (G2p); uridine-2`-phosphate (U2p); adenosine-2`-phosphate (A2p); a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

In one embodiment, the modifications on the nucleotides are selected from the group consisting of LNA, HNA, CeNA, 2′-methoxyethyl, 2′-O-alkyl, 2′-O-allyl, 2′-C- allyl, 2′-fluoro, 2′-deoxy, 2'-hydroxyl, and glycol; and combinations thereof.

In one embodiment, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), *e.g.,* Ggn, Cgn, Tgn, or Agn, a nucleotide comprising a 2'-phospahte group, and, a vinyl-phosphonate nucleotide; and combinations thereof.

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

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

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

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

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

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

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

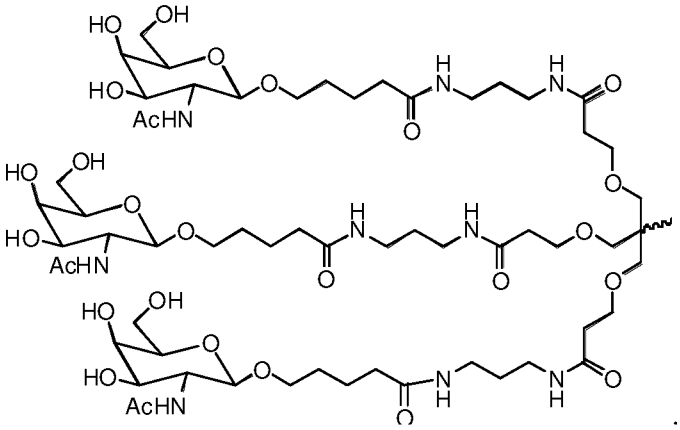
In one embodiment, the dsRNA agent further comprises a ligand.

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

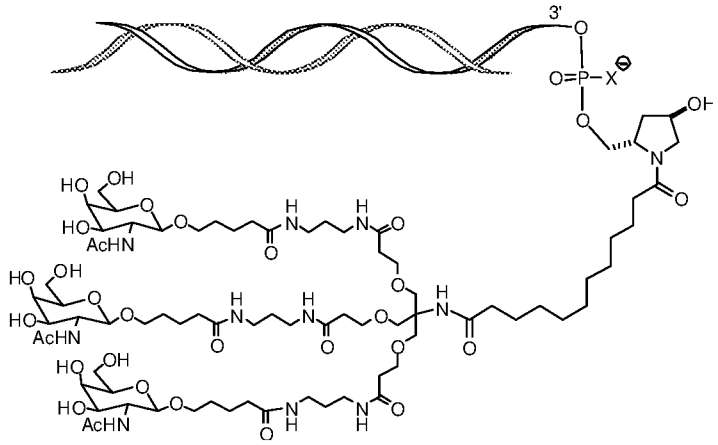
In one embodiment, the ligand is an N-acetylgalactosamine (GalNAc) derivative.

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

In one embodiment, the ligand is



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



and, wherein X is O or S.

In one embodiment, the X is O.

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

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

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

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

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

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

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

In one aspect, the present invention provides a method of inhibiting expression of a complement factor B (CFB) gene in a cell. The method includes contacting the cell with any of the dsRNAs of the invention or any of the pharmaceutical compositions of the invention, thereby inhibiting expression of the CFB gene in the cell.

In one embodiment, the cell is within a subject, *e.g.,* a human subject, *e.g.,* a subject having a complement factor B-associated disorder. Such disorders are typically associated with inflammation or immune system activation, *e.g.*, membrane attack complex-mediated lysis, anaphylaxis, or hemolysis. Non-limiting examples of complement factor B-associated disorders include paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), asthma, rheumatoid arthritis (RA); antiphospholipid antibody syndrome; lupus nephritis; ischemia-reperfusion injury; typical or infectious hemolytic uremic syndrome (tHUS); dense deposit disease (DDD); neuromyelitis optica (NMO); multifocal motor neuropathy (MMN); multiple sclerosis (MS); macular degeneration (e.g., age-related macular degeneration (AMD)); hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP); spontaneous fetal loss; Pauci-immune vasculitis; epidermolysis bullosa; recurrent fetal loss; pre-eclampsia, traumatic brain injury, myasthenia gravis, cold agglutinin disease, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, C3 neuropathy, anti-neutrophil cytoplasmic antibody-associated vasculitis (e.g., granulomatosis with polyangiitis (previously known as Wegener granulomatosis), Churg-Strauss syndrome, and microscopic polyangiitis), humoral and vascular transplant rejection, graft dysfunction, myocardial infarction (*e.g.*, tissue damage and ischemia in myocardial infarction), an allogenic transplant, sepsis (*e.g.*, poor outcome in sepsis), Coronary artery disease, dermatomyositis, Graves' disease, atherosclerosis, Alzheimer's disease, systemic inflammatory response sepsis, septic shock, spinal cord injury, glomerulonephritis, Hashimoto's thyroiditis, type I diabetes, psoriasis, pemphigus, autoimmune hemolytic anemia (AIHA), ITP, Goodpasture syndrome, Degos disease, antiphospholipid syndrome (APS), catastrophic APS (CAPS), a cardiovascular disorder, myocarditis, a cerebrovascular disorder, a peripheral (e.g., musculoskeletal) vascular disorder, a renovascular disorder, a mesenteric/enteric vascular disorder, vasculitis, Henoch-Schönlein purpura nephritis, systemic lupus erythematosus-associated vasculitis, vasculitis associated with rheumatoid arthritis, immune complex vasculitis, Takayasu's disease, dilated cardiomyopathy, diabetic angiopathy, Kawasaki's disease (arteritis), venous gas embolus (VGE), and restenosis following stent placement, rotational atherectomy, and percutaneous transluminal coronary angioplasty (PTCA) (see, *e.g.*, Holers (2008) *Immunological Reviews* 223:300-316; Holers and Thurman (2004) *Molecular Immunology* 41:147-152; U.S. Patent Publication No. 20070172483).

In one embodiment, the complement factor B-associate disease is selected from the group consisting of C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration, atypical hemolytic uremic syndrome, thrombotic microangiopathy,

myasthenia gravis, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria, and rheumatoid arthritis

In another embodiment, the complement factor B-associate disease is selected from the group consisting of C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease.

In one embodiment, contacting the cell with the dsRNA agent inhibits the expression of CFB by at least 50%, 60%, 70%, 80%, 90%, or 95%.

In one embodiment, inhibiting expression of CFB decreases CFB protein level in serum of the subject by at least 50%, 60%, 70%, 80%, 90%, or 95%.

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

In another aspect, the present invention provides a method of preventing development of a disorder that would benefit from reduction in complement factor B (CFB) expression in a subject having at least one sign or symptom of a disorder who does not yet meet the diagnostic criteria for that disorder. The method includes administering to the subject a prophylactically effective amount of any of the dsRNAs of the invention or any of the pharmaceutical compositions of the invention, thereby preventing the subject progressing to meet the diagnostic criteria of the disorder that would benefit from reduction in CFB expression.

In one embodiment, the disorder is a complement factor B- (CFB)-associated disorder.

In one embodiment, the subject is human.

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

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

In one embodiment, the level of CFB in the subject sample(s) is a CFB protein level in a blood or serum sample(s).

In one embodiment, the administration of the agent to the subject causes a decrease in hemolysis or a decrease in CFB protein accumulation.

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

In some aspects, the additional therapeutic agent is an iRNA agent targeting a C5 gene, such as those described in U.S. Patent No.: 9,249,415, the entire contents of which are hereby incorporated herein by reference.

In other aspects, the additional therapeutic agent is an iRNA agent targeting a complement factor B (CFB) gene, such as those described in U.S. Patent No.: 10,465,194, the entire contents of which are hereby incorporated herein by reference.

In other aspects, the additional therapeutic agent is an inhibitor of C5, such as an anti-complement component C5 antibody, or antigen-binding fragment thereof (*e.g.*, eculizumab, ravulizumab-cwvz, or pozelimab (REGN3918)) or a C5 peptide inhibitor (*e.g.*, zilucoplan). Eculizumab is a humanized monoclonal IgG2/4, kappa light chain antibody that specifically binds complement component C5 with high affinity and inhibits cleavage of C5 to C5a and C5b, thereby inhibiting the generation of the terminal complement complex C5b-9. Eculizumab is described in U.S. Patent No. 6,355,245, the entire contents of which are incorporated herein by reference. Ravulizumab-cwvz is a humanized IgG2/4 monoclonal antibody that specifically binds complement component C5 with high affinity and inhibits cleavage of C5 to C5a and C5b, thereby inhibiting the generation of the terminal complement complex C5b-9. Ravulizumab-cwvz is described in WO2015134894, the entire contents of which are incorporated herein by reference. Pozelimab (also known as H4H12166P, described in US20170355757, the entire contents of which are incorporated herein by reference) is a fully-human IgG4 monoclonal antibody designed to block complement factor C5. Zilucoplan is a synthetic, macrocyclic peptide that binds complement component 5 (C5) with sub-nanomolar affinity and allosterically inhibits its cleavage into C5a and C5b upon activation of the classical, alternative, or lectin pathways (see, *e.g.*, WO2017105939, the entire contects of which are incorporated herein by reference).

In yet other aspects, the additional therapeutic is a C3 peptide inhibitor, or analog thereof. In one embodiment, the C3 peptide inhibitor is compstatin. Compstatin is a cyclic tridecapeptide with potent and selective C3 inhibitory activity. Compstatin, and its analogs, are described in U.S. Patent Nos. 7,888,323, 7,989,589, and 8,442,776, in U.S. Patent Publication No. 2012/0178694 and 2013/0053302, and in PCT Publication Nos. WO 2012/174055, WO 2012/2178083, WO 2013/036778, the entire contents of each of which are incorporated herein by reference.

In certain embodiments, treatments known in the art for the various CFB-associated diseases are used in combination with the RNAi agents of the invention.

The present invention also provides kits comprising any of the dsRNAs of the invention or any of the pharmaceutical compositions of the invention, and optionally, instructions for use.

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

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

strand of 23 nt in length may be provided as a salt having up to 42 cations (*e.g,* 42 sodium cations). In the preceding example, where the RNAi agent also includes a 5'-terminal phosphate or a 5'-terminal vinylphosphonate group, the RNAi agent may be provided as a salt having up to 44 cations (*e.g*, 44 sodium cations).

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

Brief Description of the Drawings

Figure 1 depicts the three complement pathways: alternative, classical and lectin.

Figure 2 is a graph depicting the level of human CFB protein in mice (n=3 per group) subcutaneously administered a single 1 mg/kg dose of the indicated dsRNA duplexes on day 7. Human CFB protein levels were shown relative to control levels determined with PBS treatment.

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 a complement factor B (CFB) gene. The gene may be within a cell, *e.g.*, a cell within a subject, such as a human. The use of these iRNAs enables the targeted degradation of mRNAs of the corresponding gene (complement factor B gene) in mammals.

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

Accordingly, the present invention provides methods for treating and preventing a complement factor B-associated disorder, disease, or condition, *e.g.*, a disorder, disease, or condition with inflammation or immune system activation, *e.g.*, membrane attack complex-mediated lysis, anaphylaxis, or hemolysis, *e.g.,* C3 glomerulopathy, systemic lupus erythematosus (SLE), e.g., Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease, using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a complement factor B gene.

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

antisense strand) having a region which is about 21-23 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of a complement factor B gene.

In certain embodiments, one or both of the strands of the double stranded RNAi agents of the invention is up to 66 nucleotides in length, *e.g.*, 36-66, 26-36, 25-36, 31-60, 22-43, 27-53 nucleotides in length, with a region of at least 19 contiguous nucleotides that is substantially complementary to at least a part of an mRNA transcript of a complement factor B 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.

The use of iRNAs of the invention enables the targeted degradation of mRNAs of the corresponding gene (complement factor B gene) in mammals. Using *in vitro* and *in vivo* assays, the present inventors have demonstrated that iRNAs targeting a complement factor B gene can potently mediate RNAi, resulting in significant inhibition of expression of a complement factor B gene. Thus, methods and compositions including these iRNAs are useful for treating a subject having a complement factor B -associated disorder, *e.g.*, C3 glomerulopathy, systemic lupus erythematosus (SLE), e.g., Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease.

Accordingly, the present invention provides methods and combination therapies for treating a subject having a disorder that would benefit from inhibiting or reducing the expression of a complement factor B gene, *e.g.*, a complement factor B-associated disease, such as C3 glomerulopathy, systemic lupus erythematosus (SLE), e.g., Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease, using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a CFB gene.

The present invention also provides methods for preventing at least one symptom in a subject having a disorder that would benefit from inhibiting or reducing the expression of a complement factor B gene, *e.g.*, C3 glomerulopathy, systemic lupus erythematosus (SLE), e.g., Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease.

In certain embodiments, the administration of the dsRNA to the subject causes a decrease in CFB mRNA level, CFB protein level, CH_{50} activity (a measure of total hemolytic complement), AH_{50} (a measure the hemolytic activity of the alternate pathway of complement), lactate dehydrogenase (LDH) (a measure of intravascular hemolysis), hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, and soluble C5b-9 complex.

The following detailed description discloses how to make and use compositions containing iRNAs to inhibit the expression of a complement factor B gene as well as compositions, uses, and methods for treating subjects that would benefit from inhibition or reduction of the expression of a complement factor B gene, *e.g.*, subjects susceptible to or diagnosed with a complement factor B-associated disorder.

I. Definitions

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

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

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

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

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

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

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

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

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

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

As used herein, the term "Complement Factor B," used interchangeably with the term "CFB," refers to the well-known gene and polypeptide, also known in the art as AHUS, BF, CFAB, BFD,

FB, GBG, FBI12, B-Factor, Properdin, H2-Bf, Glycine-Rich Beta Glycoprotein, C3 Proaccelerator, Properdin Factor 2B, C3 Proactivator, PBF2, Glycine-Rich Beta-Glycoprotein, C3/C5 Convertase, EC 3.4.21, and EC 3.4.21.473.

The term "CFB" includes human CFB, the amino acid and nucleotide sequence of which may be found in, for example, GenBank Accession No. GI:1732746151; mouse CFB, the amino acid and nucleotide sequence of which may be found in, for example, GenBank Accession Nos. GI:218156288 and GI:218156290; rat CFB, the amino acid and nucleotide sequence of which may be found in, for example, GenBank Accession No. GI:218156284; and chimpanzee CFB, the amino acid and nucleotide sequence of which may be found in, for example, GenBank Accession No. GI:57114201. The term "CFB" also includes *Macaca fascicularis* CFB, the amino acid and nucleotide sequence of which may be found in, for example, GenBank Accession No. GI:544428919 and in the entry for the gene, ENSMMUP00000000985 (locus=scaffold3881:47830:53620), in the *Macaca* genome project web site (macaque.genomics.org.cn/page/species/index.jsp). Additional examples of CFB mRNA sequences are readily available using, *e.g.*, GenBank, UniProt, OMIM, and the *Macaca* genome project web site. Exemplary CFB nucleotide sequences may also be found in SEQ ID NOs:1-7. SEQ ID NOs:8-14 are the antisense sequences of SEQ ID NOs: 1-7, respectively.

The term "CFB," as used herein, also refers to naturally occurring DNA sequence variations of the CFB gene. Non-limiting examples of sequence variations within the CFB gene include 1598A>G in exon 12, which results in a lysine being changed to an arginine at amino acid residue 533; 858C>G in exon 6, which results in a phenylalanine being changed to a leucine at amino acid residue 286; and 967A>G in exon 7, which results in a lysine being changed to an alanine at amino acid residue 323 (Tawadrous H. *et al.* (2010) *Pediatr Nephrol.* 25:947; Goicoechea de Jorge E *et al.* (2007) *Proc Natl Acad Sci. USA* 104:240). The term"CFB," as used herein, also refers to single nucleotide polymorphisms in the CFB gene. Numerous sequence variations within the CFB gene have been identified and may be found at, for example, NCBI dbSNP and UniProt (see, *e.g.*, ncbi.nlm.nih.gov/snp).

Further information on CFB can be found, for example, at www.ncbi.nlm.nih.gov/gene/629.

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

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

As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a complement factor B gene, including mRNA that is a product of RNA processing of a primary transcription product. The target portion of the sequence will be at least long enough to serve as a substrate for iRNA-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a CFB gene. In one embodiment, the target sequence is within the protein coding region of CFB.

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

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 a complement factor B 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.,* a complement factor B target mRNA sequence, to direct the cleavage of the target RNA. Without wishing to be bound by theory it is believed that long double stranded RNA introduced into cells is broken down into siRNA by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) *Genes Dev.* 15:485). Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409:363). The siRNAs are then incorporated into an RNA-induced

silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, *et al.*, (2001) *Cell* 107:309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleave the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15:188). Thus, in one aspect the invention relates to a single stranded RNA (siRNA) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.,* a complement factor B (CFB) gene. Accordingly, the term "siRNA" is also used herein to refer to an iRNA as described above.

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

In certain embodiments, an "iRNA" for use in the compositions, uses, and methods of the invention is a double stranded RNA and is referred to herein as a "double stranded RNA agent," "double stranded RNA (dsRNA) molecule," "dsRNA agent," or "dsRNA". The term "dsRNA", refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary nucleic acid strands, referred to as having "sense" and "antisense" orientations with respect to a target RNA, *i.e.,* a complement factor B (CFB) 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.

As used herein, the term "modified nucleotide" refers to a nucleotide having, independently, a modified sugar moiety, a modified internucleotide linkage, or modified nucleobase, or any combination thereof. Thus, the term modified nucleotide encompasses substitutions, additions or removal of, *e.g.,* a functional group or atom, to internucleoside linkages, sugar moieties, or nucleobases. The modifications suitable for use in the agents of the invention include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a siRNA type molecule, are encompassed by "iRNA" or "RNAi agent" for the purposes of this specification and claims.

In certain embodiments of the instant disclosure, inclusion of a deoxy-nucleotide – which is acknowledged as a naturally occurring form of nucleotide – if present within a RNAi agent can be considered to constitute a modified nucleotide.

The duplex region may be of any length that permits specific degradation of a desired target RNA through a RISC pathway, and may range from about 19 to 36 base pairs in length, *e.g.*, about 19-30 base pairs in length, for example, about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,

24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 base pairs in length, such as about 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In certain embodiments, the duplex region is 19-21 base pairs in length, *e.g.*, 21 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

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

In certain embodiment, the two strands of double-stranded oligomeric compound can be linked together. The two strands can be linked to each other at both ends, or at one end only. By linking at one end is meant that 5'-end of first strand is linked to the 3'-end of the second strand or 3'-end of first strand is linked to 5'-end of the second strand. When the two strands are linked to each other at both ends, 5'-end of first strand is linked to 3'-end of second strand and 3'-end of first strand is linked to 5'-end of second strand. The two strands can be linked together by an oligonucleotide linker including, but not limited to, (N)n; wherein N is independently a modified or unmodified nucleotide and n is 3-23. In some embodiemtns, n is 3-10, e.g., 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, the oligonucleotide linker is selected from the group consisting of GNRA, (G)4, (U)4, and (dT)4, wherein N is a modified or unmodified nucleotide and R is a modified or unmodified purine nucleotide. Some of the nucleotides in the linker can be involved in base-pair interactions with other nucleotides in the linker. The two strands can also be linked together by a non-nucleosidic linker, e.g. a linker described herein. It will be appreciated by one of skill in the art that any oligonucleotide chemical modifications or variations describe herein can be used in the oligonucleotide linker.

Hairpin and dumbbell type oligomeric compounds will have a duplex region equal to or at least 14, 15, 15, 16, 17, 18, 19, 29, 21, 22, 23, 24, or 25 nucleotide pairs. The duplex region can be equal to or less than 200, 100, or 50, in length. In some embodiments, ranges for the duplex region are 15-30, 17 to 23, 19 to 23, and 19 to 21 nucleotides pairs in length.

The hairpin oligomeric compounds can have a single strand overhang or terminal unpaired region, in some embodiments at the 3', and in some embodiments on the antisense side of the hairpin. In some embodiments, the overhangs are 1-4, more generally 2-3 nucleotides in length. The hairpin oligomeric compounds that can induce RNA interference are also referred to as "shRNA" herein.

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

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

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

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

In one embodiment of the dsRNA, at least one strand comprises a 3' overhang of at least 1 nucleotide. In another embodiment, at least one strand comprises a 3' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In other embodiments, at least one strand of the RNAi agent comprises a 5' overhang of at least 1 nucleotide. In certain embodiments, at least one strand comprises a 5' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In still other embodiments, both the 3' and the 5' end of one strand of the RNAi agent comprise an overhang of at least 1 nucleotide.

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

In certain embodiments, the antisense strand of a dsRNA has a 1-10 nucleotides, *e.g.,* a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end or the 5'-end. In certain embodiments, the overhang on the sense strand or the antisense strand, or both, can include extended lengths longer than 10 nucleotides, *e.g.*, 1-30 nucleotides, 2-30 nucleotides, 10-30 nucleotides, 10-25 nucleotides, 10-20 nucleotides, or 10-15 nucleotides in length. In certain embodiments, an extended overhang is on the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 3' end of the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 5' end of the sense strand of the duplex. In certain embodiments, an extended overhang is on the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 3'end of the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 5'end of the antisense strand of the duplex. In certain embodiments, one or more of the nucleotides in the extended overhang is replaced with a nucleoside thiophosphate. In certain embodiments, the overhang includes a self-complementary portion such that the overhang is capable of forming a hairpin structure that is stable under physiological conditions.

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

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

As used herein, the term "region of complementarity" refers to the region on the antisense strand that is substantially complementary to a sequence, for example a target sequence, *e.g.,* a complement factor B nucleotide sequence, as defined herein. Where the region of complementarity is not fully complementary to the target sequence, the mismatches can be in the internal or terminal regions of the molecule. Generally, the most tolerated mismatches are in the terminal regions, *e.g.*, within 5, 4, or 3 nucleotides of the 5'- or 3'-end of the iRNA. In some embodiments, a double stranded RNA agent of the invention includes a nucleotide mismatch in the antisense strand. In some embodiments, the antisense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the target mRNA, *e.g.*, the antisense strand includes 4, 3, 2, 1, or 0 mismatches with the target mRNA. In some embodiments, the antisense strand double stranded RNA agent of the invention includes no more than 4 mismatches with the sense strand, *e.g.*, the antisense

strand includes 4, 3, 2, 1, or 0 mismatches with the sense strand. In some embodiments, a double stranded RNA agent of the invention includes a nucleotide mismatch in the sense strand. In some embodiments, the sense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the antisense strand, *e.g.*, the sense strand includes 4, 3, 2, 1, or 0 mismatches with the antisense strand. In some embodiments, the nucleotide mismatch is, for example, within 5, 4, 3 nucleotides from the 3'-end of the iRNA. In another embodiment, the nucleotide mismatch is, for example, in the 3'-terminal nucleotide of the iRNA agent. In some embodiments, the mismatch(s) is not in the seed region.

Thus, an RNAi agent as described herein can contain one or more mismatches to the target sequence. In one embodiment, a RNAi agent as described herein contains no more than 3 mismatches (*i.e.,* 3, 2, 1, or 0 mismatches). In one embodiment, an RNAi agent as described herein contains no more than 2 mismatches. In one embodiment, an RNAi agent as described herein contains no more than 1 mismatch. In one embodiment, an RNAi agent as described herein contains 0 mismatches. In certain embodiments, if the antisense strand of the RNAi agent contains mismatches to the target sequence, the mismatch can optionally be restricted to be within the last 5 nucleotides from either the 5'- or 3'-end of the region of complementarity. For example, in such embodiments, for a 23 nucleotide RNAi agent, the strand which is complementary to a region of a CFB gene, generally does not contain any mismatch within the central 13 nucleotides. The methods described herein or methods known in the art can be used to determine whether an RNAi agent containing a mismatch to a target sequence is effective in inhibiting the expression of a CFB gene. Consideration of the efficacy of RNAi agents with mismatches in inhibiting expression of a CFB gene is important, especially if the particular region of complementarity in a CFB gene is known to have polymorphic sequence variation within the population.

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

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

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

As used herein, and unless otherwise indicated, the term "complementary," when used to describe a first nucleotide sequence in relation to a second nucleotide sequence, refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize and form a

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

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

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

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

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

Accordingly, in some embodiments, the antisense polynucleotides disclosed herein are fully complementary to the target CFB sequence.

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

In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target CFB sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to a fragment of SEQ ID NO: 1 selected from the group of nucleotides 504-526, 640-662, 641-663, 995-1017, 997-1019, 1034-1056, 1141-1163, 1145-1167, 1389-1411, 1473-1495, 1826-1848, 1828-1850, 1842-1864, 2242-2264, 2391-2413, 2393-2415, 2438-2460, or 2453-2475 of SEQ ID NO: 1, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target CFB sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the sense strand nucleotide sequences in any one of any one of Tables 2-3, or a fragment of any one of the sense strand nucleotide sequences in any one of Tables 2-3, such as about 85%, about 90%, about 95%, or fully complementary.

In one embodiment, an RNAi agent of the disclosure includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is the same as a target CFB sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs: 8-14, or a fragment of any one of SEQ ID NOs:8-14, such as about 85%, about 90%, about 95%, or fully complementary.

In some embodiments, an iRNA of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target complement factor B sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the antisense strand nucleotide sequences in any one of any one of Tables 2-3, or a fragment of any one of the antisense strand nucleotide sequences in any one of Tables 2-3, such as about 85%, about 90%, about 95%, or fully complementary.

In some embodiments, the sense and antisense strands are selected from the group consisting of AD-1726057; AD-1725763; AD-1725777; AD-1725057; AD-1725096; AD-1728786; AD-

1725059; AD-1728276; AD-1728278; AD-1726936; AD-1725472; AD-1724715; AD-1727292; AD-1730477; AD-1727288; AD-1730167; AD-1725408; and AD-1725761.

In one embodiment, the sense and antisense strands are selected from duplex AD-1726057.

In one embodiment, the sense and antisense strands are selected from duplex AD-1725763.

In one embodiment, the sense and antisense strands are selected from duplex AD-1725777.

In one embodiment, the sense and antisense strands are selected from duplex AD-1725057.

In one embodiment, the sense and antisense strands are selected from duplex AD-1725096.

In one embodiment, the sense and antisense strands are selected from duplex AD-1728786.

In one embodiment, the sense and antisense strands are selected from duplex AD-1725059.

In one embodiment, the sense and antisense strands are selected from duplex AD-1728276.

In one embodiment, the sense and antisense strands are selected from duplex AD-1728278.

In one embodiment, the sense and antisense strands are selected from duplex AD-1726936.

In one embodiment, the sense and antisense strands are selected from duplex AD-1725472.

In one embodiment, the sense and antisense strands are selected from duplex AD-1724715.

In one embodiment, the sense and antisense strands are selected from duplex AD-1727292.

In one embodiment, the sense and antisense strands are selected from duplex AD-1730477.

In one embodiment, the sense and antisense strands are selected from duplex AD-1727288.

In one embodiment, the sense and antisense strands are selected from duplex AD-1730167.

In one embodiment, the sense and antisense strands are selected from duplex AD-1725408.

In one embodiment, the sense and antisense strands are selected from duplex AD-1725761.

In some embodiments, the double-stranded region of a double-stranded iRNA agent is equal to or at least, 17, 18, 19, 20, 21, 22, 23, 23, 24, 25, 26, 27, 28, 29, 30 or more nucleotide pairs in length.

In some embodiments, the antisense strand of a double-stranded iRNA agent is equal to or at least 17, 18, 19, 20, 21, 22, 23, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

In some embodiments, the sense strand of a double-stranded iRNA agent is equal to or at least 17, 18, 19, 20, 21, 22, 23, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

In one embodiment, the sense and antisense strands of the double-stranded iRNA agent are each 18 to 30 nucleotides in length.

In one embodiment, the sense and antisense strands of the double-stranded iRNA agent are each 19 to 25 nucleotides in length.

In one embodiment, the sense and antisense strands of the double-stranded iRNA agent are each 21 to 23 nucleotides in length.

In one embodiment, the sense strand of the iRNA agent is 21- nucleotides in length, and the antisense strand is 23-nucleotides in length, wherein the strands form a double-stranded region of 21 consecutive base pairs having a 2-nucleotide long single stranded overhangs at the 3'-end.

In some embodiments, the majority of nucleotides of each strand are ribonucleotides, but as described in detail herein, each or both strands can also include one or more non-ribonucleotides, e.g.,

a deoxyribonucleotide or a modified nucleotide. In addition, an "iRNA" may include ribonucleotides with chemical modifications. Such modifications may include all types of modifications disclosed herein or known in the art. Any such modifications, as used in an iRNA molecule, are encompassed by "iRNA" for the purposes of this specification and claims.

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

In one embodiment, at least partial suppression of the expression of a CFB gene, is assessed by a reduction of the amount of CFB mRNA which can be isolated from or detected in a first cell or group of cells in which a CFB gene is transcribed and which has or have been treated such that the expression of a CFB 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 iRNA," such as a dsRNA, as used herein, includes contacting a cell by any possible means. Contacting a cell with an iRNA includes contacting a cell *in vitro* with the iRNA or contacting a cell *in vivo* with the iRNA. The contacting may be done directly or indirectly. Thus, for example, the iRNA may be put into physical contact with the cell by the individual performing the method, or alternatively, the iRNA may be put into a situation that will permit or cause it to subsequently come into contact with the cell.

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

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

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 rabbit, a sheep, a hamster, a guinea pig, a dog, a rat, or a mouse), or a bird that expresses the target gene, either endogenously or heterologously. In an embodiment, the subject is a human, such as a human being treated or assessed for a disease or disorder that would benefit from reduction in CFB expression; a human at risk for a disease or disorder that would benefit from reduction in CFB expression; a human having a disease or disorder that would benefit from reduction in CFB expression; or human being treated for a disease or disorder that would benefit from reduction in CFB expression as described herein. In some embodiments, the subject is a female human. In other embodiments, the subject is a male human. In one embodiment, the subject is an adult subject. In another embodiment, the subject is a pediatric subject.

As used herein, the terms "treating" or "treatment" refer to a beneficial or desired result, such as reducing at least one sign or symptom of a CFB -associated disorder in a subject. Treatment also includes a reduction of one or more sign or symptoms associated with unwanted CFB expression; diminishing the extent of unwanted CFB activation or stabilization; amelioration or palliation of unwanted CFB activation or stabilization. "Treatment" can also mean prolonging survival as compared to expected survival in the absence of treatment.

The term "lower" in the context of the level of CFB in a subject or a disease marker or symptom refers to a statistically significant decrease in such level. The decrease can be, for example, at least 10%, 15%, 20%, 25%, 30%, %, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more. In certain embodiments, a decrease is at least 20%. In certain embodiments, the decrease is at least 50% in a disease marker, *e.g.*, protein or gene expression level. "Lower" in the context of the level of CFB in a subject is a decrease to a level accepted as within the range of normal for an individual without such disorder. In certain embodiments, the expression of the target is normalized, *i.e.*, decreased towards or to a level accepted as within the range of normal for an individual without such disorder, *e.g.*, normalization of body weight, blood pressure, or a serum lipid level. As used here, "lower" in a subject can refer to lowering of gene expression or protein production in a cell in a subject does not require lowering of expression in all cells or tissues of a subject. For example, as used herein, lowering in a subject can include lowering of gene expression or protein production in the liver of a subject.

The term "lower" can also be used in association with normalizing a symptom of a disease or condition, *i.e.* decreasing the difference between a level in a subject suffering from a CFB -associated disease towards or to a level in a normal subject not suffering from a CFB-associated disease. For example, if a subject with a normal weight of 70 kg weighs 90 kg prior to treatment (20 kg overweight) and 80 kg after treatment (10 kg overweight), the subject's weight is lowered towards a normal weight by 50% (10/20 x 100%). Similarly, if the HDL level of a woman is increased from 50

mg/dL (poor) to 57 mg/dL, with a normal level being 60 mg/dL, the difference between the prior level of the subject and the normal level is decreased by 70% (difference of 10 mg/dL between subject level and normal is decreased by 7 mg/dL, 7/10 x 100%). As used herein, if a disease is associated with an elevated value for a symptom, "normal" is considered to be the upper limit of normal. If a disease is associated with a decreased value for a symptom, "normal" is considered to be the lower limit of normal.

As used herein, "prevention" or "preventing," when used in reference to a disease, disorder or condition thereof, that would benefit from a reduction in expression of a CFB gene or production of CFB protein, refers to preventing a subject who has at least one sign or symptom of a disease from developing further signs and symtoms thereby meeting the diagnostic criteria for that disease. In certain embodiments, prevention includes delayed progression to meeting the diagnostic criteria of the disease by days, weeks, months or years as compared to what would be predicted by natural history studies or the typical progression of the disease.

As used herein, the term " complement factor B disease" or "CFB-associated disease," is a disease or disorder that is caused by, or associated with, complement activation. The term "CFB-associated disease" includes a disease, disorder or condition that would benefit from a decrease in CFB gene expression, replication, or protein activity. Non-limiting examples of CFB-associated diseases include, for example, paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), asthma, rheumatoid arthritis (RA); antiphospholipid antibody syndrome; lupus nephritis; ischemia-reperfusion injury; typical or infectious hemolytic uremic syndrome (tHUS); dense deposit disease (DDD); neuromyelitis optica (NMO); multifocal motor neuropathy (MMN); multiple sclerosis (MS); macular degeneration (e.g., age-related macular degeneration (AMD)); hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP); spontaneous fetal loss; Pauci-immune vasculitis; epidermolysis bullosa; recurrent fetal loss; pre-eclampsia, traumatic brain injury, myasthenia gravis, cold agglutinin disease, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, C3 neuropathy, anti-neutrophil cytoplasmic antibody-associated vasculitis (*e.g.*, granulomatosis with polyangiitis (previously known as Wegener granulomatosis), Churg-Strauss syndrome, and microscopic polyangiitis), humoral and vascular transplant rejection, graft dysfunction, myocardial infarction (*e.g.*, tissue damage and ischemia in myocardial infarction), an allogenic transplant, sepsis (*e.g.*, poor outcome in sepsis), Coronary artery disease, dermatomyositis, Graves' disease, atherosclerosis, Alzheimer's disease, systemic inflammatory response sepsis, septic shock, spinal cord injury, glomerulonephritis, Hashimoto's thyroiditis, type I diabetes, psoriasis, pemphigus, autoimmune hemolytic anemia (AIHA), ITP, Goodpasture syndrome, Degos disease, antiphospholipid syndrome (APS), catastrophic APS (CAPS), a cardiovascular disorder, myocarditis, a cerebrovascular disorder, a peripheral (*e.g.*, musculoskeletal) vascular disorder, a renovascular disorder, a mesenteric/enteric vascular disorder, vasculitis, Henoch-Schönlein purpura nephritis, systemic lupus erythematosus-associated vasculitis, vasculitis associated with rheumatoid arthritis,

immune complex vasculitis, Takayasu's disease, dilated cardiomyopathy, diabetic angiopathy, Kawasaki's disease (arteritis), venous gas embolus (VGE), and restenosis following stent placement, rotational atherectomy, and percutaneous transluminal coronary angioplasty (PTCA) (see, *e.g.*, Holers (2008) *Immunological Reviews* 223:300-316; Holers and Thurman (2004) *Molecular Immunology* 41:147-152; U.S. Patent Publication No. 20070172483).

In one embodiment, the complement factor B-associate disease is selected from the group consisting of C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration, atypical hemolytic uremic syndrome, thrombotic microangiopathy, myasthenia gravis, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria, and rheumatoid arthritis

In another embodiment, the complement factor B-associate disease is selected from the group consisting of C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease.

Further details regarding signs and symptoms of the various disesases or conditions are provided herein and are well known in the art.

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

"Prophylactically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having at least one sign or symptom of a CFB-associated disorder, is sufficient to prevent or delay the subject's progression to meeting the full diagnostic criteria of the disease. Prevention of the disease includes slowing the course of progression to full blown disease. The "prophylactically effective amount" may vary depending on the RNAi agent, how the agent is administered, the degree of risk of disease, and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the patient to be treated.

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

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, or dosage forms which are, within the scope of sound medical judgment,

suitable for use in contact with the tissues of human subjects and animal subjects without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material (including salts), composition, or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (*e.g.*, lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject being treated. Such carriers are known in the art. Pharmaceutically acceptable carriers include carriers for administration by injection.

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

II. iRNAs of the Invention

The present invention provides iRNAs which inhibit the expression of a complement factor B gene. In certain embodiments, the iRNA includes double stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of a CFB gene in a cell, such as a cell within a subject, *e.g.,* a mammal, such as a human susceptible to developing a complement factor B-associated disorder. The dsRNAi agent includes an antisense strand having a region of complementarity which is complementary to at least a part of an mRNA formed in the expression of a CFB gene. The region of complementarity is about 19-30 nucleotides in length (*e.g.,* about 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, or 19 nucleotides in length). Upon contact with a cell expressing the CFB gene, the iRNA inhibits the expression of the CFB gene (*e.g.,* a human, a primate, a non-primate, or a rat CFB gene) by at least about 50% as assayed by, for example, a PCR or branched DNA (bDNA)-based method, or by a protein-based method, such as by immunofluorescence analysis, using, for example, western blotting or flow cytometric techniques. In certain embodiments, inhibition of expression is determined by the qPCR method provided in the examples herein with the siRNA at, *e.g.,* a 10 nM concentration, in an appropriate organism cell line provided therein. In certain embodiments, inhibition of expression *in vivo* is determined by knockdown of the human gene in a rodent expressing

the human gene, *e.g.*, a mouse or an AAV-infected mouse expressing the human target gene, *e.g.*, when administered as single dose, *e.g.*, at 3 mg/kg at the nadir of RNA expression.

A dsRNA includes two RNA strands that are complementary and hybridize to form a duplex structure under conditions in which the dsRNA will be used. One strand of a dsRNA (the antisense strand) includes a region of complementarity that is substantially complementary, and generally fully complementary, to a target sequence. The target sequence can be derived from the sequence of an mRNA formed during the expression of a CFB gene. The other strand (the sense strand) includes a region that is complementary to the antisense strand, such that the two strands hybridize and form a duplex structure when combined under suitable conditions. As described elsewhere herein and as known in the art, the complementary sequences of a dsRNA can also be contained as self-complementary regions of a single nucleic acid molecule, as opposed to being on separate oligonucleotides.

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

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

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

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

sequence of an mRNA target of sufficient length to allow it to be a substrate for RNAi-directed cleavage (*i.e.*, cleavage through a RISC pathway).

One of skill in the art will also recognize that the duplex region is a primary functional portion of a dsRNA, *e.g.*, a duplex region of about 19 to about 30 base pairs, *e.g.*, about 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs. Thus, in one embodiment, to the extent that it becomes processed to a functional duplex, of *e.g.*, 15-30 base pairs, that targets a desired RNA for cleavage, an RNA molecule or complex of RNA molecules having a duplex region greater than 30 base pairs is a dsRNA. Thus, an ordinarily skilled artisan will recognize that in one embodiment, a miRNA is a dsRNA. In another embodiment, a dsRNA is not a naturally occurring miRNA. In another embodiment, an iRNA agent useful to target complement factor B gene expression is not generated in the target cell by cleavage of a larger dsRNA.

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

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

Regardless of the method of synthesis, the siRNA preparation can be prepared in a solution (e.g., an aqueous or organic solution) that is appropriate for formulation. For example, the siRNA preparation can be precipitated and redissolved in pure double-distilled water, and lyophilized. The dried siRNA can then be resuspended in a solution appropriate for the intended formulation process.

In an aspect, a dsRNA of the invention includes at least two nucleotide sequences, a sense sequence and an anti-sense sequence. The sense strand is selected from the group of sequences provided in any one of Tables 2-3, and the corresponding antisense strand of the sense strand is selected from the group of sequences of any one of Tables 2-3. In this aspect, one of the two sequences is complementary to the other of the two sequences, with one of the sequences being substantially complementary to a sequence of an mRNA generated in the expression of a complement

factor B gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand in any one of Tables 2-3, and the second oligonucleotide is described as the corresponding antisense strand of the sense strand in any one of Tables 2-3.

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

It will be understood that, although the sequences in Table 2 are not described as modified or conjugated sequences, the RNA of the iRNA of the invention *e.g.*, a dsRNA of the invention, may comprise any one of the sequences set forth in any one of Tables 2-3 that is un-modified, un-conjugated, or modified or conjugated differently than described therein. In other words, the invention encompasses dsRNA of Tables 2-3 which are un-modified, un-conjugated, modified, or conjugated, as described herein.

The skilled person is well aware that dsRNAs having a duplex structure of about 20 to 23 base pairs, *e.g.,* 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir *et al.*, *EMBO* 2001, 20:6877-6888). However, others have found that shorter or longer RNA duplex structures can also be effective (Chu and Rana (2007) *RNA* 14:1714-1719; Kim *et al.* (2005) *Nat Biotech* 23:222-226). In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided in any one of Tables 2-3, dsRNAs described herein can include at least one strand of a length of minimally 21 nucleotides. It can be reasonably expected that shorter duplexes having any one of the sequences in any one of Tables 2-3 minus only a few nucleotides on one or both ends can be similarly effective as compared to the dsRNAs described above. Hence, dsRNAs having a sequence of at least 19, 20, or more contiguous nucleotides derived from any one of the sequences of any one of Tables 2-3, and differing in their ability to inhibit the expression of a complement factor B gene by not more than about 5, 10, 15, 20, 25, or 30 % inhibition from a dsRNA comprising the full sequence, are contemplated to be within the scope of the present invention.

In addition, the RNAs provided in Tables 2-3 identify a site(s) in a complement factor B transcript that is susceptible to RISC-mediated cleavage. As such, the present invention further features iRNAs that target within one of these sites. As used herein, an iRNA is said to target within a particular site of an RNA transcript if the iRNA promotes cleavage of the transcript anywhere within that particular site. Such an iRNA will generally include at least about 19 contiguous nucleotides from any one of the sequences provided in any one of Tables 2-3 coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in a complement factor B gene.

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

mismatches. In certain embodiments, if the antisense strand of the RNAi agent contains mismatches to the target sequence, the mismatch can optionally be restricted to be within the last 5 nucleotides from either the 5'- or 3'-end of the region of complementarity. For example, in such embodiments, for a 23 nucleotide RNAi agent, the strand which is complementary to a region of a CFB gene generally does not contain any mismatch within the central 13 nucleotides. The methods described herein or methods known in the art can be used to determine whether an RNAi agent containing a mismatch to a target sequence is effective in inhibiting the expression of a CFB gene. Consideration of the efficacy of RNAi agents with mismatches in inhibiting expression of a CFB gene is important, especially if the particular region of complementarity in a CFB gene is known to have polymorphic sequence variation within the population.

III. Modified iRNAs of the Invention

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

The nucleic acids featured in the invention can be synthesized or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S.L. *et al.* (Edrs.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference. Modifications include, for example, end modifications, *e.g.*, 5'-end modifications (phosphorylation, conjugation, inverted linkages) or 3'-end modifications (conjugation, DNA nucleotides, inverted linkages, *etc.*); base modifications, *e.g.*, replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases; sugar modifications (*e.g.*, at the 2'-position or 4'-position) or replacement of the sugar; or backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of iRNA compounds useful in the embodiments described herein include, but are not limited to RNAs containing modified backbones or no natural internucleoside linkages. RNAs having modified backbones include, among others, those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In some embodiments, a modified iRNA will have a phosphorus atom in its internucleoside backbone.

Modified RNA backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl

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

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

Modified RNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S, and CH_2 component parts.

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

5,677,437; and 5,677,439, the entire contents of each of which are hereby incorporated herein by reference.

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

Some embodiments featured in the invention include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular --CH_2--NH--CH_2-, --CH_2--$N(CH_3)$--O--CH_2--[known as a methylene (methylimino) or MMI backbone], --CH_2--O--$N(CH_3)$--CH_2--, --CH_2--$N(CH_3)$--$N(CH_3)$--CH_2-- and --$N(CH_3)$--CH_2--CH_2-- of the above-referenced U.S. Patent No. 5,489,677, and the amide backbones of the above-referenced U.S. Patent No. 5,602,240. In some embodiments, the RNAs featured herein have morpholino backbone structures of the above-referenced U.S. Patent No. 5,034,506. The native phosphodiester backbone can be represented as O-P(O)(OH)-OCH_2-.

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 C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nOCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an iRNA, or a group for improving the pharmacodynamic properties of an iRNA, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminooxyethoxy, *i.e.*, a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in

examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH_2--O--CH_2--$N(CH_2)_2$. Further exemplary modifications include : 5'-Me-2'-F nucleotides, 5'-Me-2'-OMe nucleotides, 5'-Me-2'-deoxynucleotides, (both R and S isomers in these three families); 2'-alkoxyalkyl; and 2'-NMA (N-methylacetamide).

Other modifications include 2'-methoxy (2'-OCH_3), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$) and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of an iRNA, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. iRNAs can also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative US patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Patent Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application,. The entire contents of each of the foregoing are hereby incorporated herein by reference.

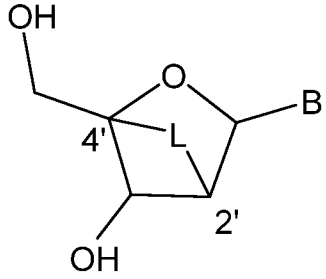
An iRNA can also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as deoxythimidine (dT), 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl anal other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P. ed. Wiley-VCH, 2008; those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. L, ed. John Wiley & Sons, 1990, these disclosed by Englisch *et al.*, Angewandte Chemie, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y S., Chapter 15, dsRNA Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds featured in the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., dsRNA Research and Applications, CRC Press,

Boca Raton, 1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

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

In some embodiments, an iRNA agent of the disclosure can also be modified to include one or more bicyclic sugar moieties. A "bicyclic sugar" is a furanosyl ring modified by the bridging of two atoms. A "bicyclic sugar" is a furanosyl ring modified by a ring formed by the bridging of two carbons, whether adjacent or non-adjacentatoms. A "bicyclic nucleoside" ("BNA") is a nucleoside having a sugar moiety comprising a bridge a ring formed by bridging connecting two carbons, whether adjacent or non-adjacent, 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, optionally, via the 2'-acyclic oxygen atoms. 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'-CH_2-O-2' bridge. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193). Examples of bicyclic nucleosides for use in the polynucleotides of the invention include without limitation nucleosides comprising a bridge between the 4′ and the 2′ ribosyl ring atoms. In certain embodiments, the antisense polynucleotide agents of the invention include one or more bicyclic nucleosides comprising a 4′ to 2′ bridge.

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



wherein B is a nucleobase or modified nucleobase and L is the linking group that joins the 2'-carbon to the 4'-carbon of the ribose ring.

Examples of such 4′ to 2′ bridged bicyclic nucleosides, include but are not limited to 4′-(CH_2)—O-2′ (LNA); 4′-(CH_2)—S-2′; 4′-(CH_2)$_2$—O-2′ (ENA); 4′-CH(CH_3)—O-2′ (also referred to as "constrained ethyl" or "cEt") and 4′-CH(CH_2OCH_3)—O-2′ (and analogs thereof; see, *e.g.*, U.S. Patent No. 7,399,845); 4′-C(CH_3)(CH_3)—O-2′ (and analogs thereof; see *e.g.*, U.S. Patent No. 8,278,283); 4′-CH_2—N(OCH_3)-2′ (and analogs thereof; see *e.g.*, U.S. Patent No. 8,278,425); 4′-CH_2—O—N(CH_3)-2′ (see, *e.g.*, U.S. Patent Publication No. 2004/0171570); 4′-CH_2—N(R)—O-2′, wherein R is H, C1-C12 alkyl, or a nitrogen protecting group (see, *e.g.*, U.S. Patent No. 7,427,672); 4′-CH_2—C(H)(CH_3)-2′ (see, *e.g.*, Chattopadhyaya *et al., J. Org. Chem.*, 2009, 74, 118-134); and 4′-CH_2—C(=CH_2)-2′ (and analogs thereof; see, *e.g.*, U.S. Patent No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein by reference.

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

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

An iRNA agent of the disclosure 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(CH_3)-O-2' bridge (i.e., L in the preceding structure). In one embodiment, a constrained ethyl nucleotide is in the S conformation referred to herein as "S-cEt."

An iRNA of the invention may also include one or more "conformationally restricted nucleotides" ("CRN"). CRN are nucleotide analogs with a linker connecting the C2'and C4' carbons of ribose or the CFB 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, US2013/0190383; and WO2013/036868, 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, US8,314,227; and US2013/0096289; US2013/0011922; and US2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.

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

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

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

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

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

Other modifications of the nucleotides of an iRNA of the invention include a 5' phosphate or 5' phosphate mimic, *e.g.,* a 5'-terminal phosphate or phosphate mimic on the antisense strand of an iRNA. Suitable phosphate mimics are disclosed in, for example US2012/0157511, the entire contents of which are incorporated herein by reference.

A. Modified iRNAs Comprising Motifs of the Invention

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

of the sense or antisense strand. The dsRNAi agent may be optionally conjugated with a GalNAc derivative ligand, for instance on the sense strand.

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

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

The sense strand and antisense strand typically form a duplex double stranded RNA ("dsRNA"), also referred to herein as "dsRNAi agent." The duplex region of a dsRNAi agent may be, for example, the duplex region can be 27-30 nucleotide pairs in length, 19-25 nucleotide pairs in length, 19-23 nucleotide pairs in length, 19- 21 nucleotide pairs in length, 21-25 nucleotide pairs in length, or 21-23 nucleotide pairs in length. In another example, the duplex region is selected from 19, 20, 21, 22, 23, 24, 25, 26, and 27 nucleotides in length.

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

In certain embodiments, the nucleotides in the overhang region of the dsRNAi agent can each independently be a modified or unmodified nucleotide including, but no 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 dsRNAi agent may be phosphorylated. In some embodiments, the overhang region(s) contains two nucleotides having a phosphorothioate between the two nucleotides, where the two nucleotides can be the same or different. In some embodiments, the overhang is present at the 3'-end of the sense strand, antisense strand, or both strands. In some embodiments, this 3'-overhang is present in the antisense strand. In some embodiments, this 3'-overhang is present in the sense strand.

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'- end of the sense strand or, alternatively, at the 3'-end of the antisense strand. The RNAi may also have a blunt end, located at the 5'-end of the antisense strand (i.e., the 3'-end of the sense strand) or *vice versa*. Generally, the antisense strand of the dsRNAi agent has a nucleotide overhang at the 3'-end, and the 5'-end is blunt. While not wishing to be bound by theory, the asymmetric blunt end at the 5'-end of the antisense strand and 3'-end overhang of the antisense strand favor the guide strand loading into RISC process.

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

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

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

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

When the two nucleotide overhang is at the 3'-end of the antisense strand, there may be two phosphorothioate internucleotide linkages between the terminal three nucleotides, wherein two of the

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

In certain embodiments, the dsRNAi agent comprises a sense and an antisense strand, wherein the sense strand is 25-30 nucleotide residues in length, wherein starting from the 5' terminal nucleotide (position 1) positions 1 to 23 of the first strand comprise at least 8 ribonucleotides; the antisense strand is 36-66 nucleotide residues in length and, starting from the 3' terminal nucleotide, comprises at least 8 ribonucleotides in the positions paired with positions 1- 23 of sense strand to form a duplex; wherein at least the 3 ' terminal nucleotide of antisense strand is unpaired with sense strand, and up to 6 consecutive 3' terminal nucleotides are unpaired with sense strand, thereby forming a 3' single stranded overhang of 1-6 nucleotides; wherein the 5' terminus of antisense strand comprises from 10-30 consecutive nucleotides which are unpaired with sense strand, thereby forming a 10-30 nucleotide single stranded 5' overhang; wherein at least the sense strand 5' terminal and 3' terminal nucleotides are base paired with nucleotides of antisense strand when sense and antisense strands are aligned for maximum complementarity, thereby forming a substantially duplexed region between sense and antisense strands; and antisense strand is sufficiently complementary to a target RNA along at least 19 ribonucleotides of antisense strand length to reduce target gene expression when the double stranded nucleic acid is introduced into a mammalian cell; and wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at or near the cleavage site.

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

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

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

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

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

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

Like the sense strand, the antisense strand of the dsRNAi agent may contain more than one motifs of three identical modifications on three consecutive nucleotides, with at least one of the motifs occurring at or near the cleavage site of the strand. This antisense strand may also contain one or

more wing modifications in an alignment similar to the wing modifications that may be present on the sense strand.

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

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

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

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

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

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

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

In some embodiments, each residue of the sense strand and antisense strand is independently modified with LNA, CRN, cET, UNA, HNA, CeNA, 2'-methoxyethyl, 2'- O-methyl, 2'-O-allyl, 2'-C- allyl, 2'-deoxy, 2'-hydroxyl, or 2'-fluoro. The strands can contain more than one modification. In one embodiment, each residue of the sense strand and antisense strand is independently modified with 2'- O-methyl or 2'-fluoro.

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

In certain embodiments, the N_a or N_b comprise modifications of an alternating pattern. The term "alternating motif" as used herein refers to a motif having one or more modifications, each modification occurring on alternating nucleotides of one strand. The alternating nucleotide may refer to one per every other nucleotide or one per every three nucleotides, or a similar pattern. For example, if A, B and C each represent one type of modification to the nucleotide, the alternating motif can be "ABABABABABAB…," "AABBAABBAABB…," "AABAABAABAAB…," "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 some embodiments, the dsRNAi agent of the invention comprises the modification pattern for the alternating motif on the sense strand relative to the modification pattern for the alternating motif on the antisense strand is shifted. The shift may be such that the modified group of nucleotides of the sense strand corresponds to a differently modified group of nucleotides of the antisense strand and *vice versa*. For example, the sense strand when paired with the antisense strand in the dsRNA duplex, the alternating motif in the sense strand may start with "ABABAB" from 5'to 3' of the strand and the alternating motif in the antisense strand may start with "BABABA" from 5' to 3' of the strand within the duplex region. As another example, the alternating motif in the sense strand may start with "AABBAABB" from 5' to 3' of the strand and the alternating motif in the antisense strand may start

with "BBAABBAA" from 5' to 3' of the strand within the duplex region, so that there is a complete or partial shift of the modification patterns between the sense strand and the antisense strand.

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

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

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

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

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

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

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

In some embodiments, when the motif of three identical modifications on three consecutive nucleotides is introduced to any of the strands, the modification of the nucleotide next to the motif is a different modification than the modification of the motif. For example, the portion of the sequence containing the motif is "…N_aYYYN_b…," where "Y" represents the modification of the motif of three identical modifications on three consecutive nucleotide, and "N_a" and "N_b" represent a modification to the nucleotide next to the motif "YYY" that is different than the modification of Y, and where N_a and

N_b can be the same or different modifications. Alternatively, N_a or N_b may be present or absent when there is a wing modification present.

The iRNA may further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage. The phosphorothioate or methylphosphonate internucleotide linkage modification may occur on any nucleotide of the sense strand, antisense strand, or both strands in any position of the strand. For instance, the internucleotide linkage modification may occur on every nucleotide on the sense strand or antisense strand; each internucleotide linkage modification may occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand may contain both internucleotide linkage modifications in an alternating pattern. The alternating pattern of the internucleotide linkage modification on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the internucleotide linkage modification on the sense strand may have a shift relative to the alternating pattern of the internucleotide linkage modification on the antisense strand. In one embodiment, a double-stranded RNAi agent comprises 6-8 phosphorothioate internucleotide linkages. In some embodiments, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-end and two phosphorothioate internucleotide linkages at the 3'-end, and the sense strand comprises at least two phosphorothioate internucleotide linkages at either the 5'-end or the 3'-end.

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

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

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

In certain embodiments, the dsRNAi agent comprises at least one of the first 1, 2, 3, 4, or 5 base pairs within the duplex regions from the 5'-end of the antisense strand independently selected from the group of: A:U, G:U, I:C, and mismatched pairs, *e.g.*, non-canonical or other than canonical pairings or pairings which include a universal base, to promote the dissociation of the antisense strand at the 5'-end of the duplex.

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

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

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

$$5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3' \qquad (I)$$

wherein:

i and j are each independently 0 or 1;

p and q are each independently 0-6;

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

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

each n_p and n_q independently represent an overhang nucleotide;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5' $n_{q'}$-N_a'-(Z'Z'Z')$_k$-N_b'-Y'Y'Y'-N_b'-(X'X'X')$_l$-N'_a-n_p' 3' (II)

wherein:

k and l are each independently 0 or 1;

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

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

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

each n_p' and n_q' independently represent an overhang nucleotide;

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

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

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

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

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

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

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

5' $n_{q'}$-N_a'-Z'Z'Z'-N_b'-Y'Y'Y'-N_a'-$n_{p'}$ 3' (IIb);

5' $n_{q'}$-N_a'-Y'Y'Y'-N_b'-X'X'X'-$n_{p'}$ 3' (IIc); or

5' $n_{q'}$-N_a'- Z'Z'Z'-N_b'-Y'Y'Y'-N_b'- X'X'X'-N_a'-$n_{p'}$ 3' (IId).

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

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

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

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

5' $n_{p'}$-$N_{a'}$-Y'Y'Y'- $N_{a'}$-$n_{q'}$ 3' (Ia).

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

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

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

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

sense: 5' n_p -N_a-(X X X)$_i$ -N_b- Y Y Y -N_b -(Z Z Z)$_j$-N_a-n_q 3'

antisense: 3' n_p'-N_a'-(X'X'X')$_k$-N_b'-Y′Y′Y′-N_b'-(Z′Z′Z′)$_l$-N_a'-n_q' 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 N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

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

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

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

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

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

5' n_p - N_a -Y Y Y -N_a-n_q 3'

3' n_p'-N_a'-Y′Y′Y′ -N_a'n_q' 5'

(IIIa)

5' n_p -N_a -Y Y Y -N_b -Z Z Z -N_a-n_q 3'

3' n_p'-N_a'-Y′Y′Y′-N_b'-Z′Z′Z′-N_a'n_q' 5'

(IIIb)

5' n_p-N_a- X X X -N_b -Y Y Y - N_a-n_q 3'

3' n_p'-N_a'-X′X′X′-N_b'-Y′Y′Y′-N_a'-n_q' 5'

(IIIc)

5' n_p -N_a -X X X -N_b-Y Y Y -N_b- Z Z Z -N_a-n_q 3'

3' n_p'-N_a'-X′X′X′-N_b'-Y′Y′Y′-N_b'-Z′Z′Z′-N_a-n_q' 5'

(IIId)

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

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

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

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

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

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

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

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

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

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

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

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

In some embodiments, the dsRNAi agent is a multimer containing three, four, five, six, or more duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further

comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

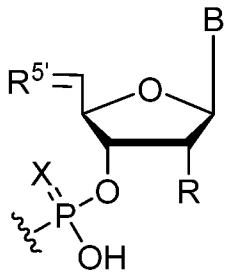
In one embodiment, two dsRNAi agents represented by at least one of formulas (III), (IIIa), (IIIb), (IIIc), and (IIId) are linked to each other at the 5' end, and one or both of the 3' ends, and are optionally conjugated to a ligand. Each of the agents can target the same gene or two different genes; 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 of 0 nucleotides with a 2'-fluoro modification. In a specific embodiment, the RNAi agent may contain 2 nucleotides with a 2'-fluoro modification, *e.g.*, 0 nucleotides with a 2-fluoro modification in the sense strand and 2 nucleotides with a 2'-fluoro modification in the antisense strand.

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

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



wherein X is O or S;

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

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

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

In one embodiment, $R^{5'}$ is =C(H)-P(O)$(OH)_2$ and the double bond between the C5' carbon and R5' is in the E orientation. In another embodiment, R is methoxy and $R^{5'}$ is =C(H)-P(O)$(OH)_2$ and the double bond between the C5' carbon and R5' is in the E orientation. In another embodiment, X is S, R is methoxy, and $R^{5'}$ is =C(H)-P(O)$(OH)_2$ and the double bond between the C5' carbon and R5' is in the E orientation.

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

Vinyl phosphonate modifications are also contemplated for the compositions and methods of the instant disclosure. An exemplary vinyl phosphonate structure includes the preceding structure, where R5' is =C(H)-OP(O)(OH)2 and the double bond between the C5' carbon and R5' is in the E or Z orientation (e.g., E orientation).

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

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

amino group, or generally, provide a bond, that is suitable for incorporation or tethering of another chemical entity, *e.g.*, a ligand to the constituent ring.

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

i. Thermally Destabilizing Modifications

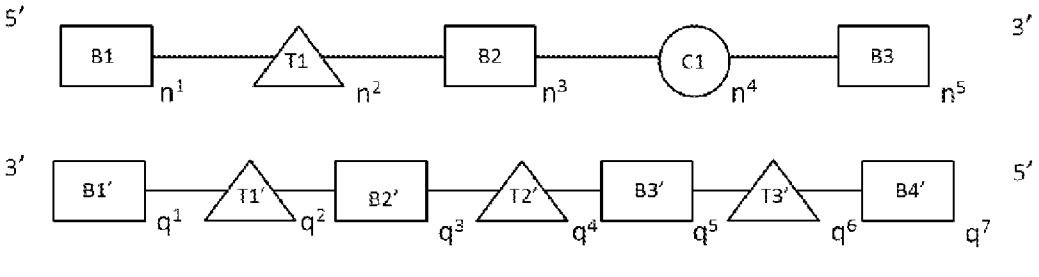
In certain embodiments, a dsRNA molecule can be optimized for RNA interference by incorporating thermally destabilizing modifications in the seed region of the antisense strand. As used herein "seed region" means at positions 2-9 of the 5'-end of the referenced strand or at positions 2-8 of the 5'-end of the referenced strand. For example, thermally destabilizing modifications can be incorporated in the seed region of the antisense strand to reduce or inhibit off-target gene silencing.

The term "thermally destabilizing modification(s)" includes modification(s) that would result with a dsRNA with a lower overall melting temperature (Tm) than the Tm of the dsRNA without having such modification(s). For example, the thermally destabilizing modification(s) can decrease the Tm of the dsRNA by 1 – 4 °C, such as one, two, three or four degrees Celcius. And, the term "thermally destabilizing nucleotide" refers to a nucleotide containing one or more thermally destabilizing modifications.

It has been discovered that dsRNAs with an antisense strand comprising at least one thermally destabilizing modification of the duplex within the first 9 nucleotide positions, counting from the 5' end, of the antisense strand have reduced off-target gene silencing activity. Accordingly, in some embodiments, the antisense strand comprises at least one (*e.g.*, one, two, three, four, five or more) thermally destabilizing modification of the duplex within the first 9 nucleotide positions of the 5' region of the antisense strand. In some embodiments, one or more thermally destabilizing modification(s) of the duplex is/are located in positions 2-9, such as, positions 4-8, from the 5'-end of the antisense strand. In some further embodiments, the thermally destabilizing modification(s) of the duplex is/are located at position 6, 7 or 8 from the 5'-end of the antisense strand. In still some further embodiments, the thermally destabilizing modification of the duplex is located at position 7 from the 5'-end of the antisense strand. In some embodiments, the thermally destabilizing modification of the duplex is located at position 2, 3, 4, 5 or 9 from the 5'-end of the antisense strand.

The thermally destabilizing modifications can include, but are not limited to, abasic modification; mismatch with the opposing nucleotide in the opposing strand; and sugar modification such as 2'-deoxy modification, acyclic nucleotide, e.g., unlocked nucleic acids (UNA) or glycol nucleic acid (GNA); and 2'-5'-linked ribonucleotides ("3'-RNA").

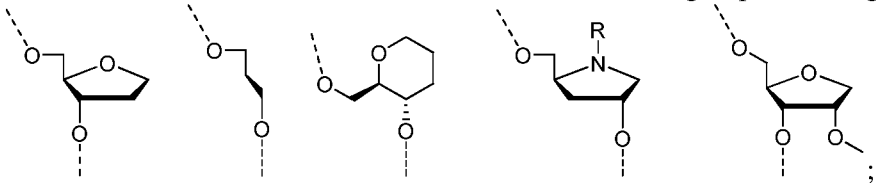
An iRNA agent comprises a sense strand and an antisense strand, each strand having 14 to 40 nucleotides. The RNAi agent may be represented by formula (L):



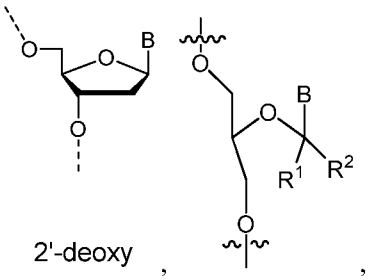
(L),

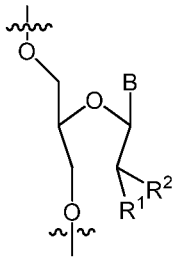
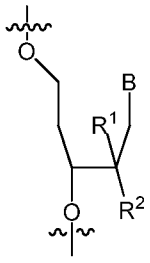
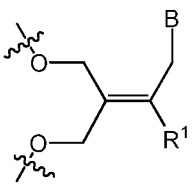
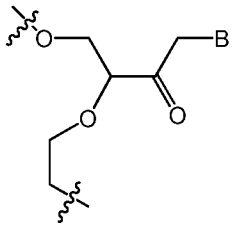
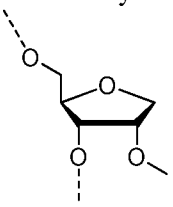
In formula (L), B1, B2, B3, B1', B2', B3', and B4' each are independently a nucleotide containing a modification selected from the group consisting of 2'-O-alkyl, 2'-substituted alkoxy, 2'-substituted alkyl, 2'-halo, ENA, and BNA/LNA. In one embodiment, B1, B2, B3, B1', B2', B3', and B4' each contain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

C1 is a thermally destabilizing nucleotide placed at a site opposite to the seed region of the antisense strand (*i.e.*, at positions 2-8 of the 5'-end of the antisense strand or at positions 2-9 of the 5'-end of the referenced 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:






, and

, wherein B is a modified or unmodified nucleobase, R^1 and R^2 independently are H, halogen, OR_3, or alkyl; and R_3 is H, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar. In one embodiment, the thermally destabilizing modification in C1 is a mismatch selected from the group consisting of G:G, G:A, G:U, G:T, A:A, A:C, C:C, C:U, C:T, U:U, T:T, and U:T; and optionally, at least one nucleobase in the mismatch pair is a 2'-deoxy nucleobase. In one example, the thermally destabilizing modification in C1 is GNA or .

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

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

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

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

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

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

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

In one embodiment, n^4 can be 0. In one example, n^4 is 0, and q^2 and q^6 are 1. In another example, n^4 is 0, and q^2 and q^6 are 1, with two phosphorothioate internucleotide linkage modifications

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

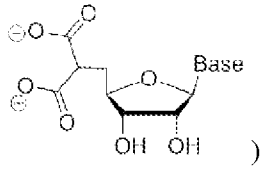
In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and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

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

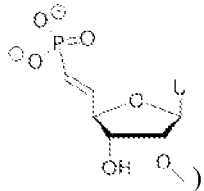
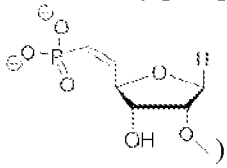
phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the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

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

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

The 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'-PS_2), 5'-end vinylphosphonate (5'-VP), 5'-end methylphosphonate (MePhos), or 5'-deoxy-5'-*C*-malonyl (

). When the 5'-end phosphorus-containing group is 5'-end vinylphosphonate (5'-VP), the 5'-VP can be either

5'-*E*-VP isomer (*i.e.*, *trans*-vinylphosphonate, ), 5'-*Z*-VP isomer (*i.e.*, *cis*-vinylphosphonate, ), or mixtures thereof.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' is 2'-F, and q^7 is 1. The dsRNAi RNA agent also comprises a 5'- PS_2.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

(iii) 2'-OMe modifications at positions 1 to 6, 8, 10, and 12 to 21, 2'-F modifications at positions 7, and 9, and a deoxy-nucleotide (*e.g.* dT) at position 11 (counting from the 5' end); and

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) 2'-OMe modifications at positions 1, 3, 7, 9, 11, 13, 15, 17, and 19 to 23, and 2'-F modifications at positions 2, 4 to 6, 8, 10, 12, 14, 16, and 18 (counting from the 5' end); and

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

(iii) 2'-OMe modifications at positions 1 to 6, 8, 10, 12, 14, and 16 to 21, and 2'-F modifications at positions 7, 9, 11, 13, and 15; and

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) 2'-OMe modifications at positions 1, 5, 7, 9, 11, 13, 15, 17, 19, and 21 to 23, and 2'-F modifications at positions 2 to 4, 6, 8, 10, 12, 14, 16, 18, and 20 (counting from the 5' end); and

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

(iii) 2'-OMe modifications at positions 1 to 9, and 12 to 21, and 2'-F modifications at positions 10, and 11; and

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 25 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

and

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

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

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

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

and

(b) an antisense strand having:
(i) a length of 21 nucleotides;

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

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

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

In certain embodiments, the iRNA for use in the methods of the invention is an agent selected from agents listed in any one of Tables 2-3. These agents may further comprise a ligand.

III. iRNAs Conjugated to Ligands

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

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

Ligands can include a naturally occurring substance, such as a protein (*e.g.*, human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (*e.g.*, a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin, N-acetylglucosamine, N-acetylgalactosamine, or hyaluronic acid); or a lipid. The ligand can also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.*, a synthetic polyamino acid. Examples of polyamino acids include polyamino acid is a

polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

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

Other examples of ligands include dyes, intercalating agents (*e.g.* acridines), cross-linkers (*e.g.* psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial endonucleases (*e.g.* EDTA), lipophilic molecules, *e.g.*, cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid,O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine)and peptide conjugates (*e.g.*, antennapedia peptide, Tat peptide), alkylating agents, phosphate, amino, mercapto, PEG (*e.g.*, PEG-40K), MPEG, $[MPEG]_2$, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (*e.g.* biotin), transport/absorption facilitators (*e.g.*, aspirin, vitamin E, folic acid), synthetic ribonucleases (*e.g.*, imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu3+ complexes of tetraazamacrocycles), dinitrophenyl, HRP, or AP.

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

The ligand can be a substance, *e.g.*, a drug, which can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.*, by disrupting the cell's microtubules, microfilaments, or intermediate filaments. The drug can be, for example, taxol,

vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin.

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

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

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

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

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

A. Lipid Conjugates

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

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

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

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

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

B. Cell Permeation Agents

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

The ligand can be a peptide or peptidomimetic. A peptidomimetic (also referred to herein as an oligopeptidomimetic) is a molecule capable of folding into a defined three-dimensional structure similar to a natural peptide. The attachment of peptide and peptidomimetics to iRNA agents can affect pharmacokinetic distribution of the iRNA, such as by enhancing cellular recognition and absorption. The peptide or peptidomimetic moiety can be about 5-50 amino acids long, *e.g.*, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

A peptide or peptidomimetic can be, for example, a cell permeation peptide, cationic peptide, amphipathic peptide, or hydrophobic peptide (*e.g.*, consisting primarily of Tyr, Trp, or Phe). The peptide moiety can be a dendrimer peptide, constrained peptide or crosslinked peptide. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). An exemplary hydrophobic MTS-containing peptide is RFGF having the amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO:15). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO:16) containing a hydrophobic MTS can also be a targeting moiety. The peptide moiety can be a "delivery" peptide, which can carry large polar molecules including peptides, oligonucleotides, and protein across cell membranes. For example, sequences from the HIV Tat protein (GRKKRRQRRRPPQ (SEQ ID NO:17) and the Drosophila Antennapedia protein (RQIKIWFQNRRMKWKK (SEQ ID NO:18) have been found to be capable of functioning as delivery peptides. A peptide or peptidomimetic can be encoded by a random sequence of DNA, such as a peptide identified from a phage-display library, or one-bead-one-compound (OBOC) combinatorial library (Lam *et al.*, Nature, 354:82-84, 1991). Examples of a peptide or peptidomimetic tethered to a dsRNA agent *via* an incorporated monomer unit for cell targeting purposes is an arginine-glycine-aspartic acid (RGD)-peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.

An RGD peptide for use in the compositions and methods of the invention may be linear or cyclic, and may be modified, *e.g.,* glycosylated or methylated, to facilitate targeting to a specific tissue(s). RGD-containing peptides and peptidiomimemtics may include D-amino acids, as well as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the integrin ligand, such as, 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, an α-helical linear peptide (*e.g.*, LL-37 or Ceropin P1), a disulfide bond-containing peptide (*e.g.*, α -defensin, β-defensin or bactenecin), or a peptide containing only one or two dominating amino acids (*e.g.*, PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni *et al.*, Nucl. Acids Res. 31:2717-2724, 2003).

C. Carbohydrate Conjugates

In some embodiments of the compositions and methods of the invention, an iRNA further comprises a carbohydrate. The carbohydrate conjugated iRNA is advantageous for the *in vivo* delivery of nucleic acids, as well as compositions suitable for *in vivo* therapeutic use, as described herein. As used herein, "carbohydrate" refers to a compound which is either a carbohydrate *per se*

made up of one or more monosaccharide units having at least 6 carbon atoms (which can be linear, branched or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom; or a compound having as a part thereof a carbohydrate moiety made up of one or more monosaccharide units each having at least six carbon atoms (which can be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Representative carbohydrates include the sugars (mono-, di-, tri-, and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9 monosaccharide units), and polysaccharides such as starches, glycogen, cellulose and polysaccharide gums. Specific monosaccharides include C5 and above (*e.g.,* C5, C6, C7, or C8) sugars; di- and trisaccharides include sugars having two or three monosaccharide units (*e.g.,* C5, C6, C7, or C8).

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

In certain embodiments, the monosaccharide is an N-acetylgalactosamine (GalNAc). GalNAc conjugates, which comprise one or more N-acetylgalactosamine (GalNAc) derivatives, are described, for example, in US 8,106,022, the entire content of which is hereby incorporated herein by reference. In some embodiments, the GalNAc conjugate serves as a ligand that targets the iRNA to particular cells. In some embodiments, the GalNAc conjugate targets the iRNA to liver cells, *e.g.*, by serving as a ligand for the asialoglycoprotein receptor of liver cells (*e.g.*, hepatocytes).

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

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

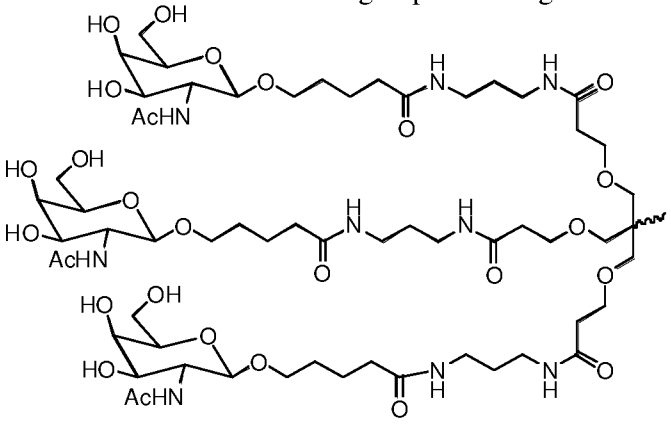
In certain embodiments, the double stranded RNAi agents of the invention comprise one GalNAc or GalNAc derivative attached to the iRNA agent. In certain embodiments, the double stranded RNAi agents of the invention comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently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

In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end

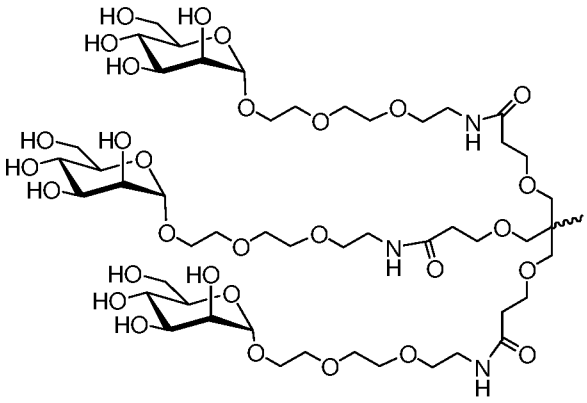
of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker. The hairpin loop may also be formed by an extended overhang in one strand of the duplex.

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

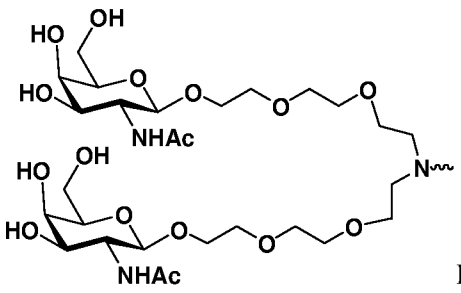
In one embodiment, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



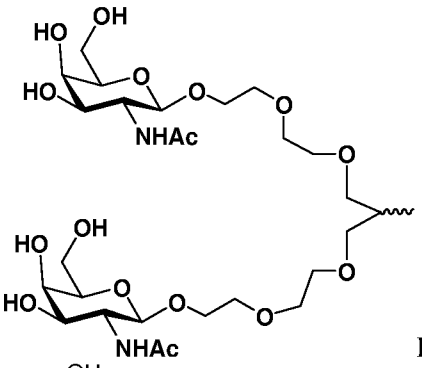
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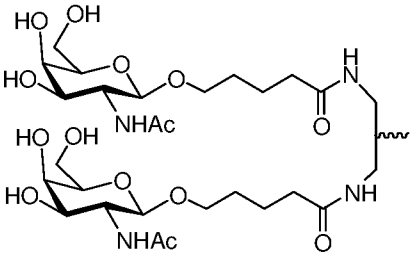
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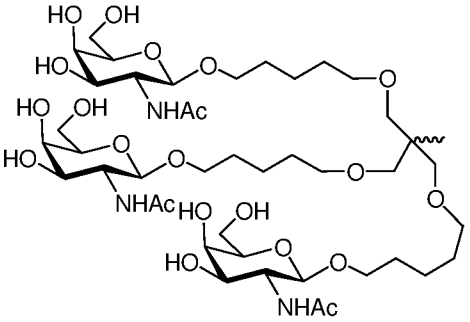
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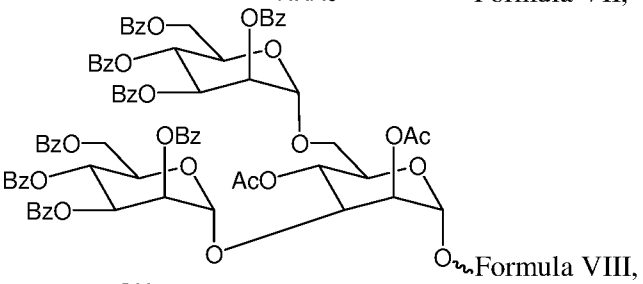
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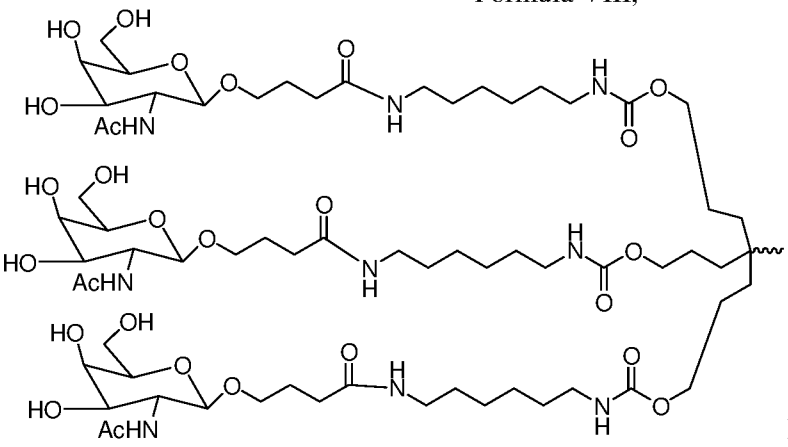
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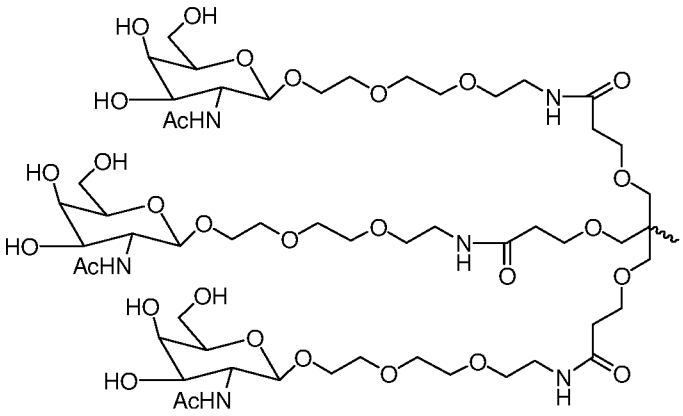
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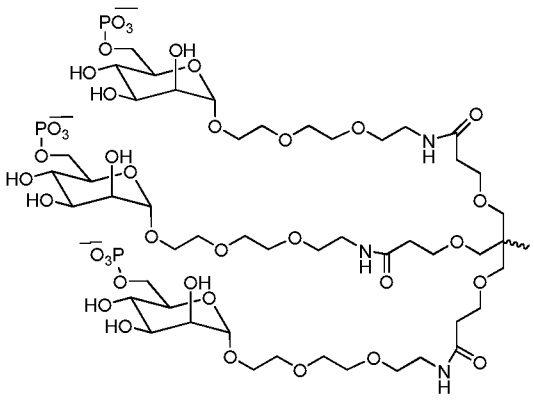
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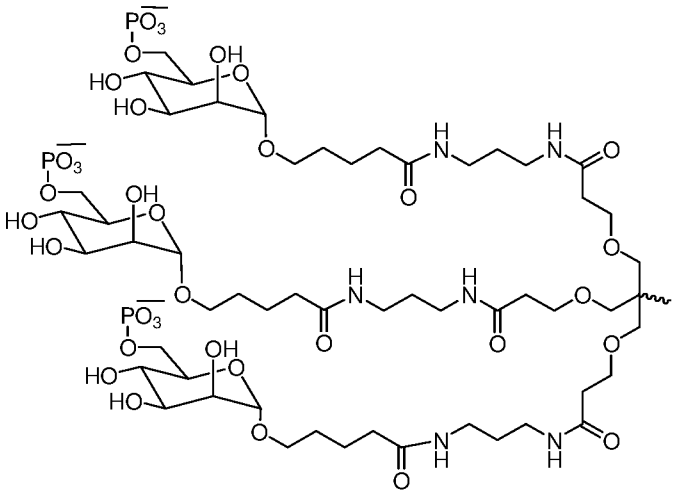
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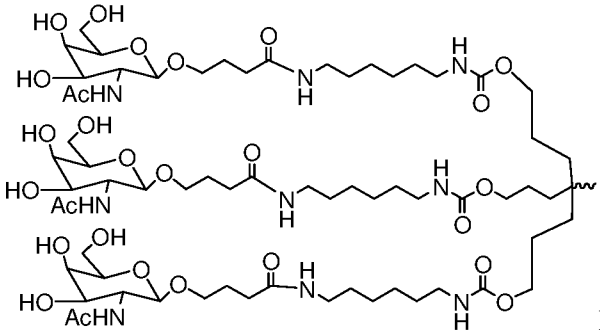
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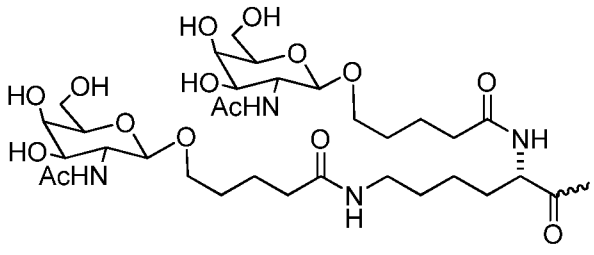
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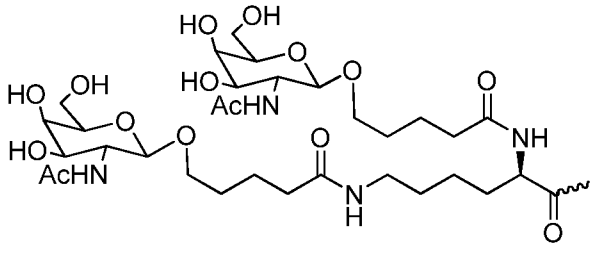
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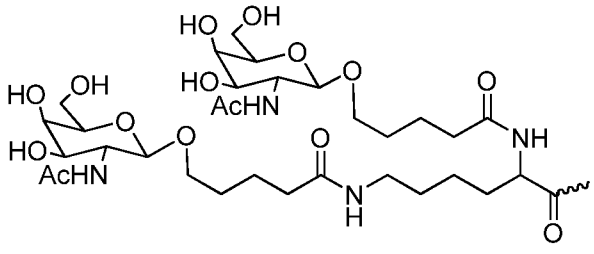
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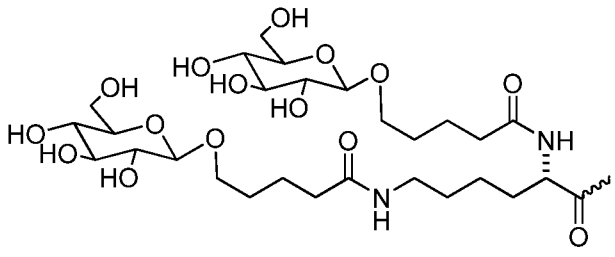
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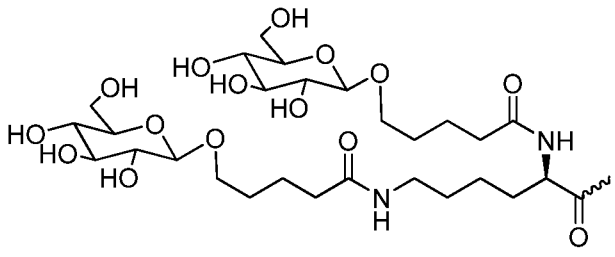
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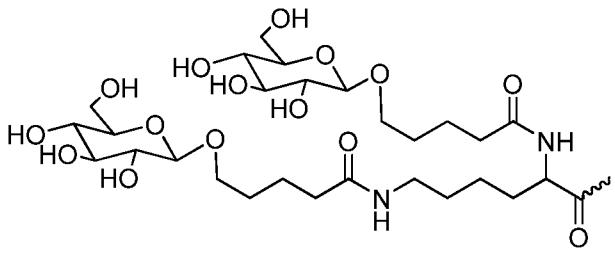
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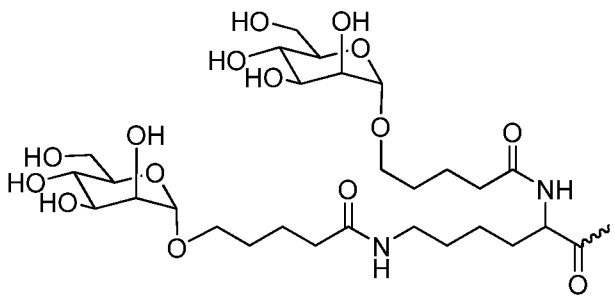
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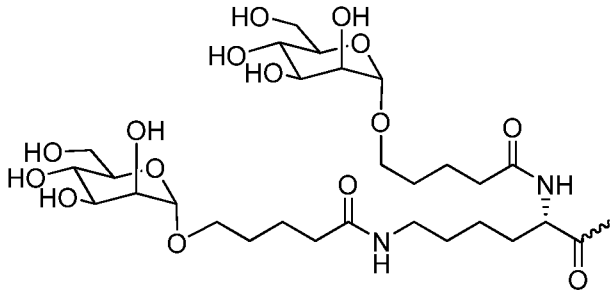
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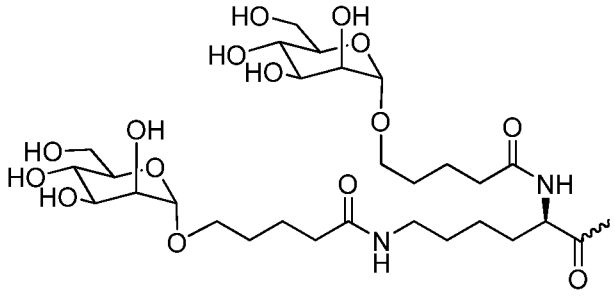
Formula XIX,



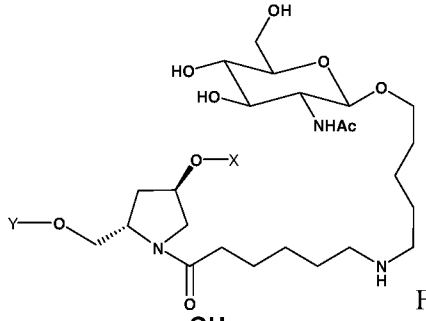
Formula XX,



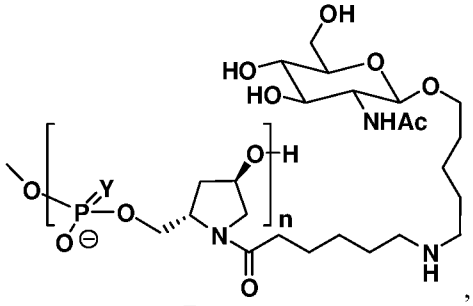
Formula XXI,



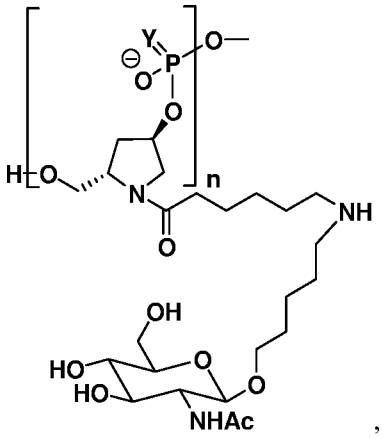
Formula XXII,



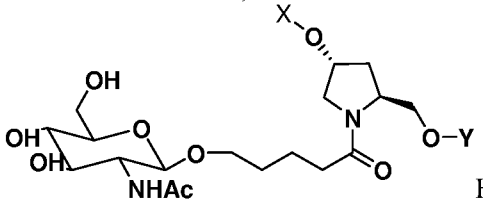
Formula XXIII;



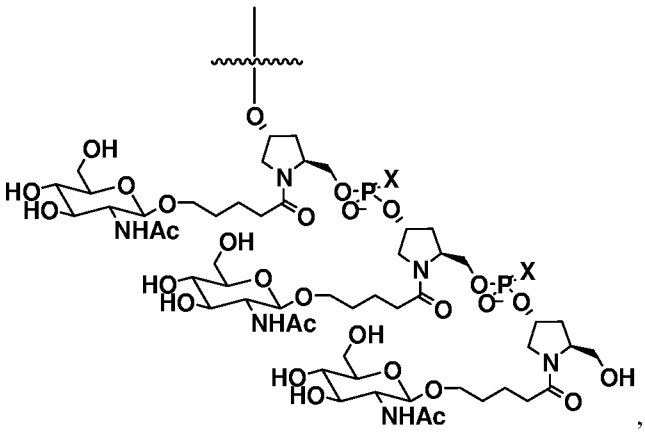
, wherein Y is O or S and n is 3 -6 (Formula XXIV);



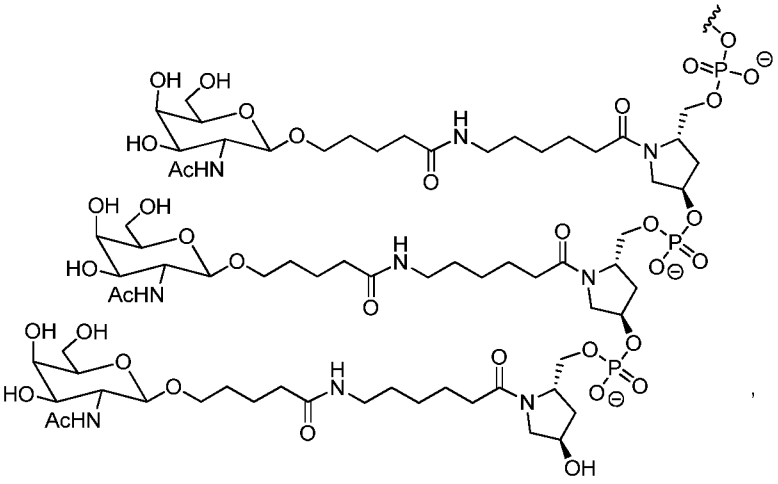
, wherein Y is O or S and n is 3-6 (Formula XXV);



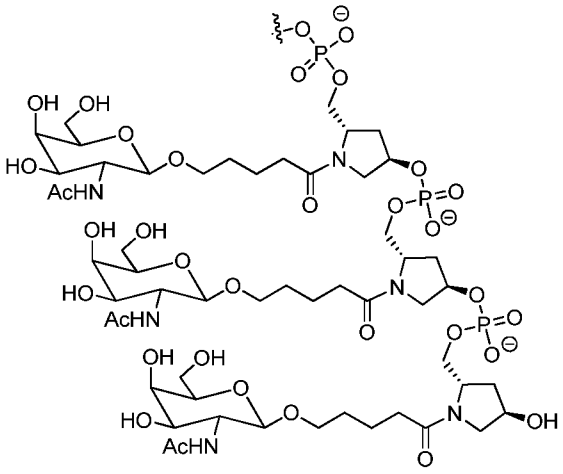
Formula XXVI;



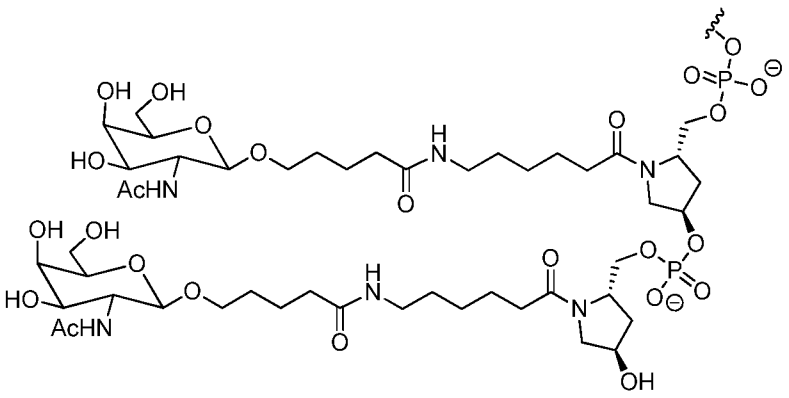
, wherein X is O or S (Formula XXVII);



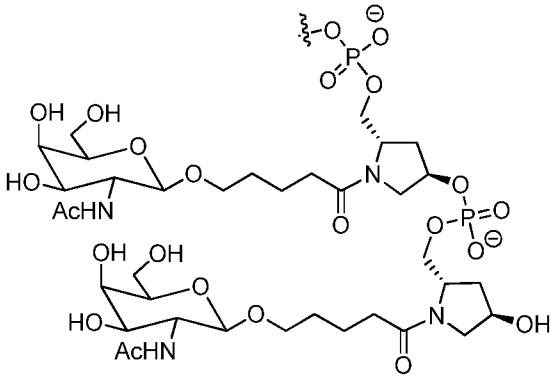
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Formula XXVII; Formula XXIX;



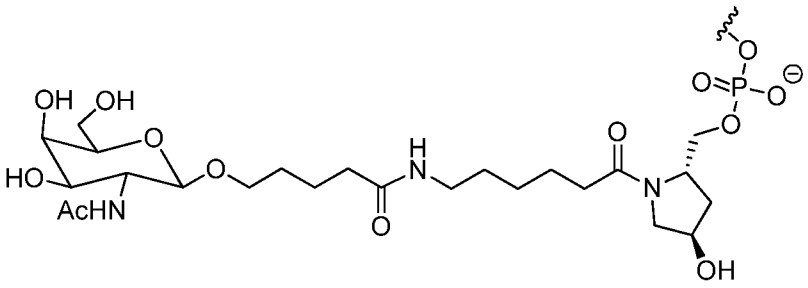
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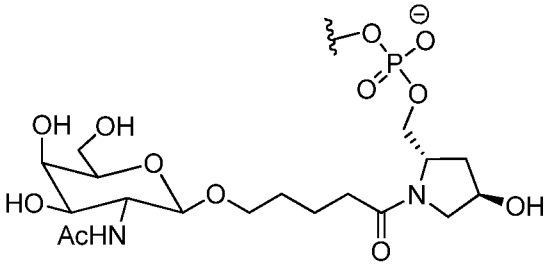
,

Formula XXX;

Formula XXXI;



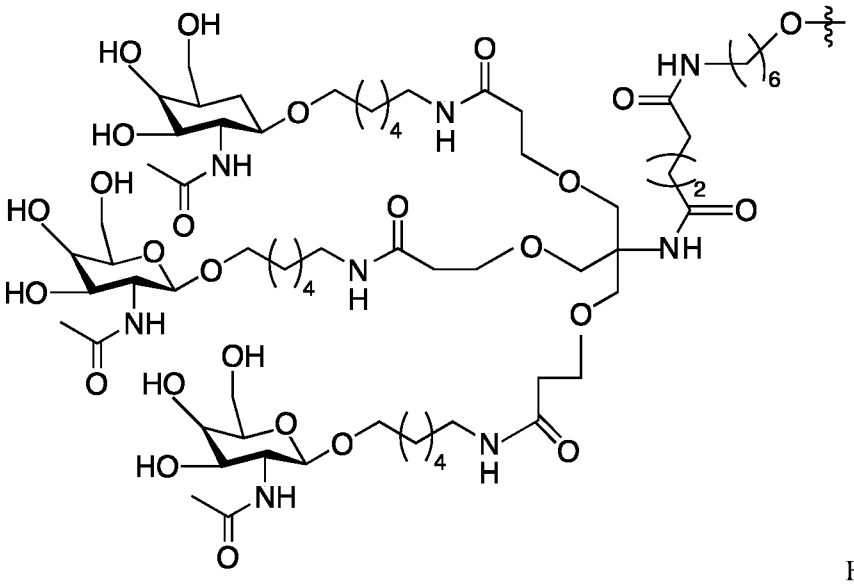
, and



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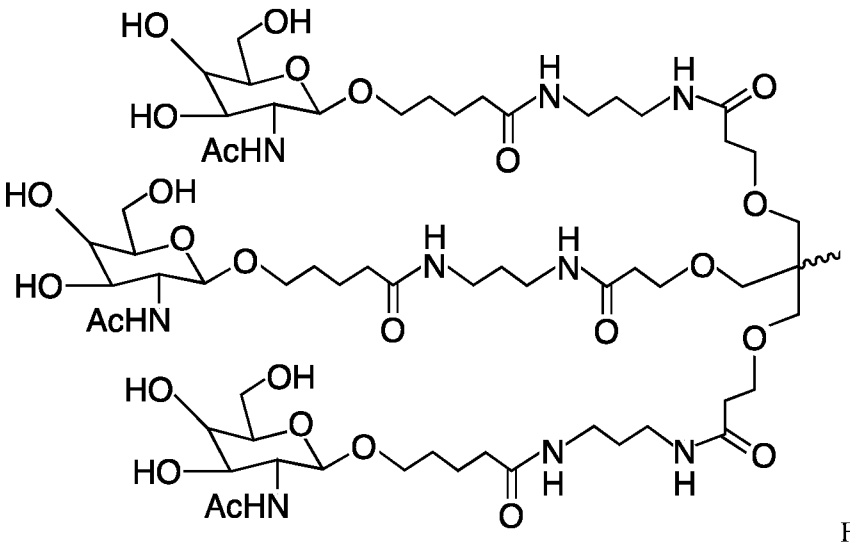
Formula XXXII;

Formula XXXIII.



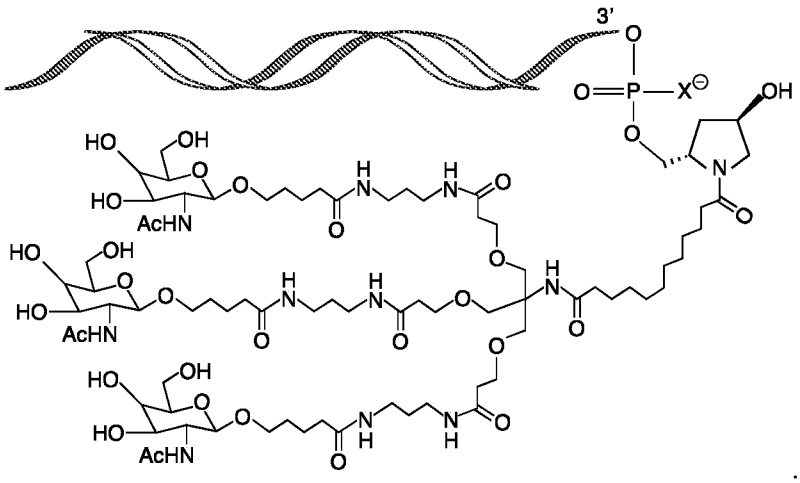
Formula XXXIV.

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

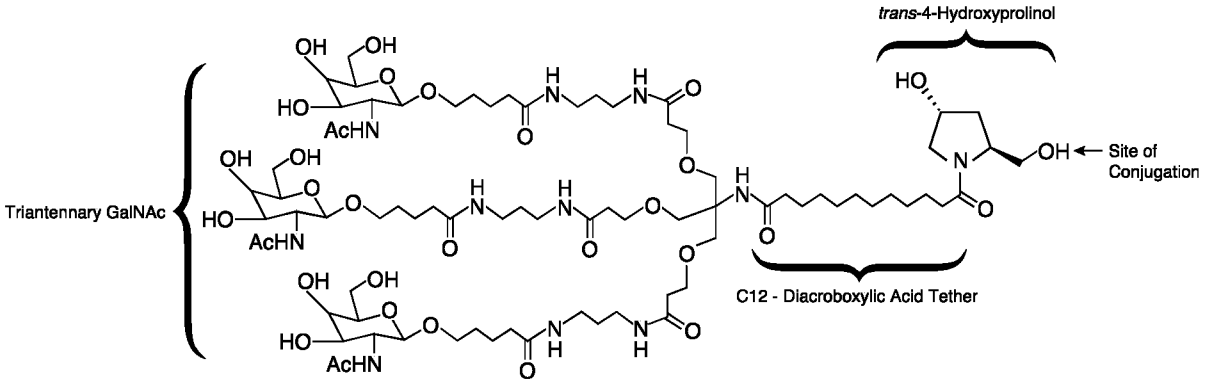


Formula II.

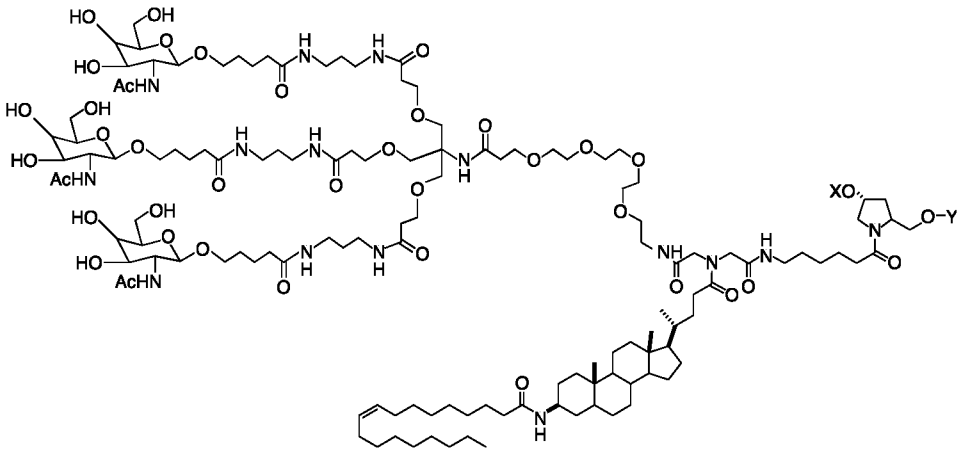
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate *via* a linker as shown in the following schematic, wherein X is O or S



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

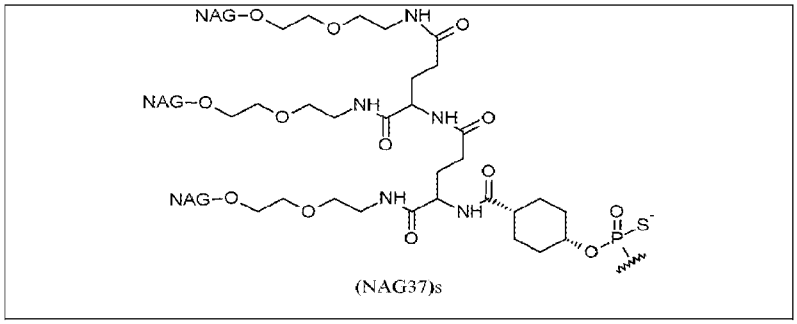


Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,



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

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



In certain embodiments 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 or more GalNAc or GalNAc derivative attached to the iRNA agent. The GalNAc may be attached to any nucleotide *via* a linker on the sense strand or antsisense strand. The GalNac may be attached to the 5'-end of the sense strand, the 3' end of the sense strand, the 5'-end of the antisense strand, or the 3' – end of the antisense strand. In one embodiment, the GalNAc is attached to the 3' end of the sense strand, *e.g., via* a trivalent linker.

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

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

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

Additional carbohydrate conjugates and linkers suitable for use in the present invention include those described in PCT Publication Nos. WO 2014/179620 and WO 2014/179627, the entire 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, SO_2, SO_2NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclylalkyl, alkylheterocyclylalkenyl, alkylhererocyclylalkynyl, alkenylheterocyclylalkyl, alkenylheterocyclylalkenyl, alkenylheterocyclylalkynyl, alkynylheterocyclylalkyl, alkynylheterocyclylalkenyl, alkynylheterocyclylalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylhereroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO_2, N(R8), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclic; where R8 is hydrogen, acyl, aliphatic, or substituted aliphatic. In one embodiment, the linker is about 1-24 atoms, 2-24, 3-24, 4-24, 5-24, 6-24, 6-18, 7-18, 8-18, 7-17, 8-17, 6-16, 7-17, or 8-16 atoms.

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

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

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

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

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

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

i. Redox cleavable linking groups

In certain embodiments, a cleavable linking group is a redox cleavable linking group that is cleaved upon reduction or oxidation. An example of reductively cleavable linking group is a disulphide linking group (-S-S-). To determine if a candidate cleavable linking group is a suitable "reductively cleavable linking group," or for example is suitable for use with a particular iRNA moiety and particular targeting agent one can look to methods described herein. For example, a candidate can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent using reagents know in the art, which mimic the rate of cleavage which would be observed in a cell, *e.g.*, a target cell. The candidates can also be evaluated under conditions which are selected to mimic blood or serum conditions. In one, candidate compounds are cleaved by at most about 10% in the blood. In

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

ii. Phosphate-based cleavable linking groups

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

iii. Acid cleavable linking groups

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

iv. Ester-based linking groups

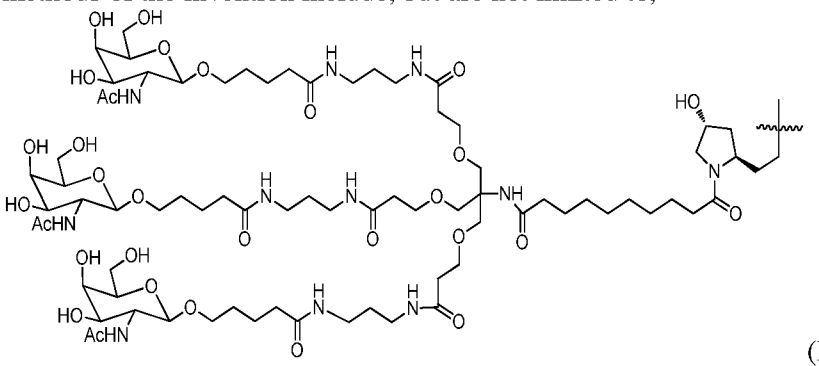
In other embodiments, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include, but are not limited to, esters of alkylene,

alkenylene and alkynylene groups. Ester cleavable linking groups have the general formula -C(O)O-, or -OC(O)-. These candidates can be evaluated using methods analogous to those described above.

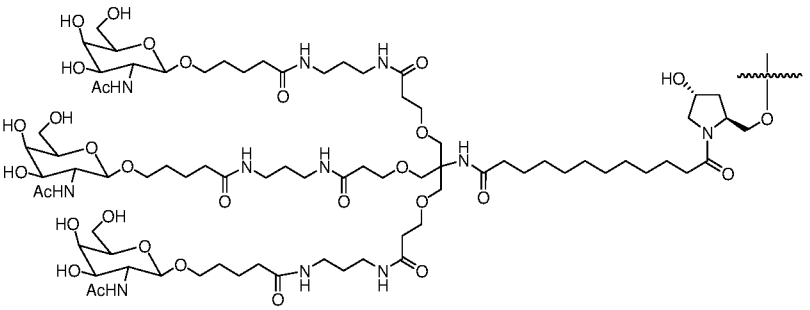
v. Peptide-based cleaving groups

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

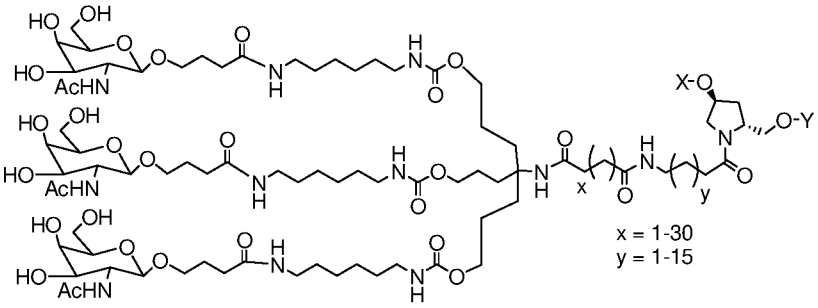
In some embodiments, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



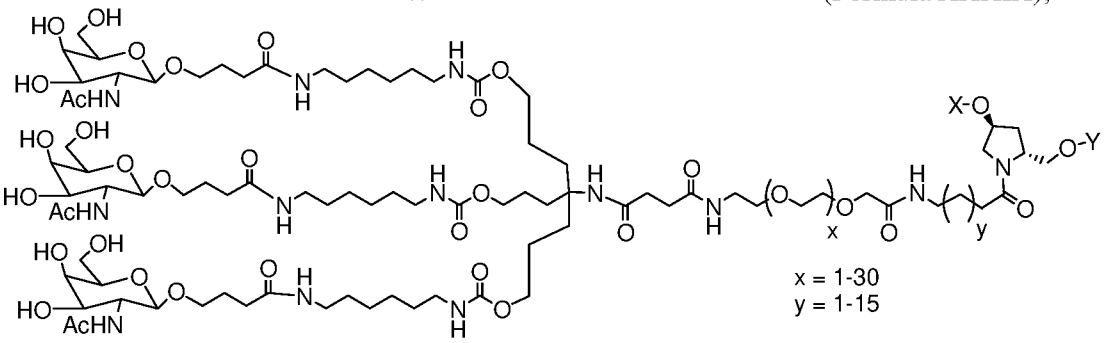
(Formula XXXVII),



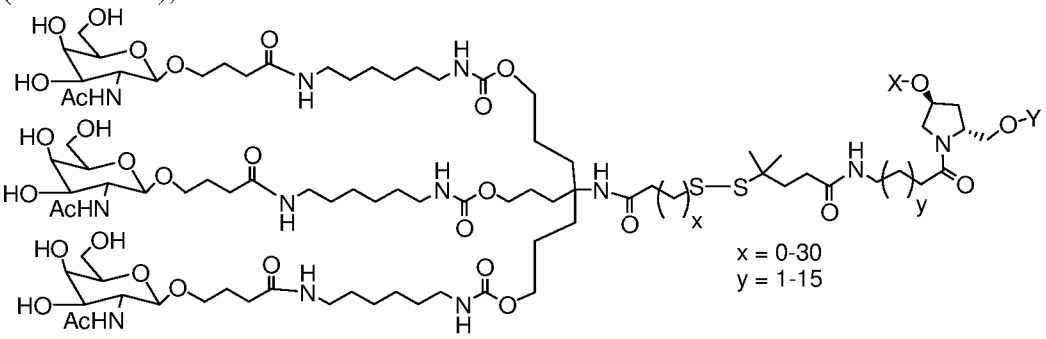
(Formula XXXVIII),



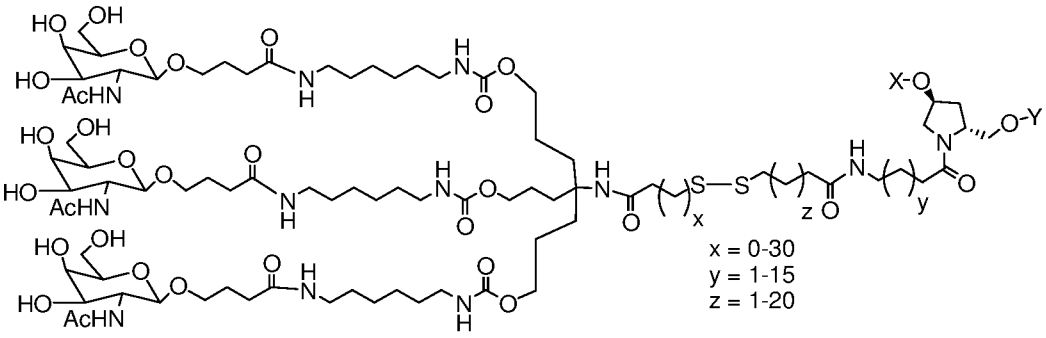
(Formula XXXIX),



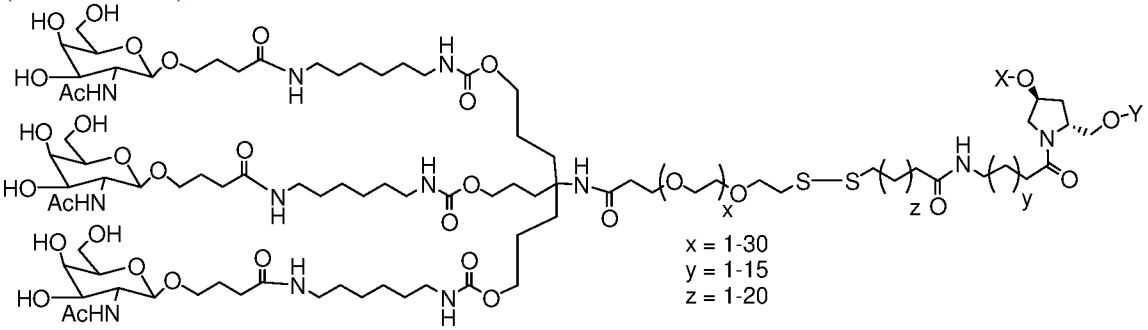
(Formula XL),



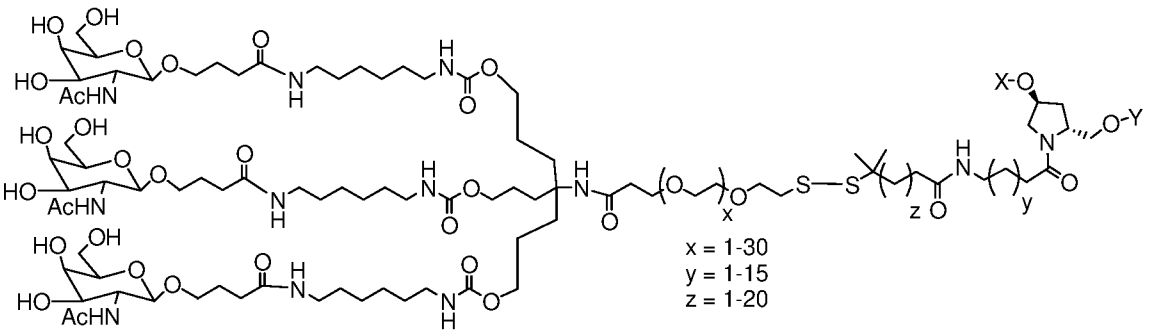
(Formula XLI),



(Formula XLII),



(Formula XLIII), and

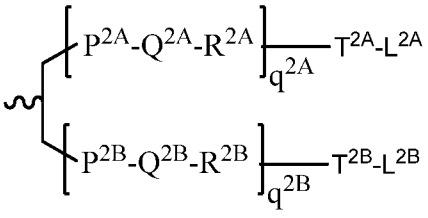


(Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

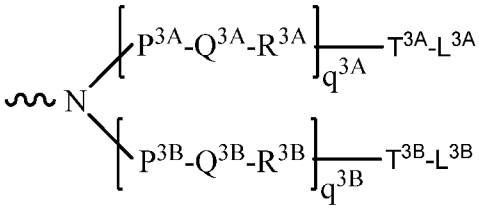
In certain embodiments of the compositions and methods of the invention, a ligand is one or more "GalNAc" (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

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

Formula XLV

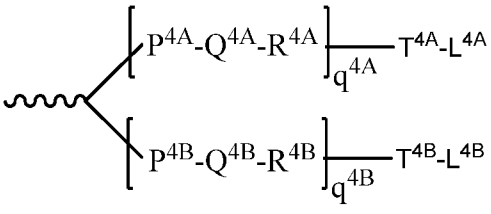


Formula XLVI

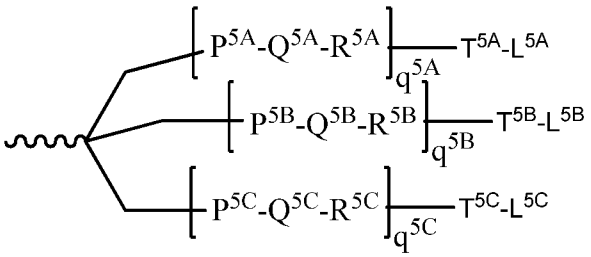


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, or



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Formula XLVII

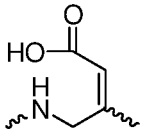
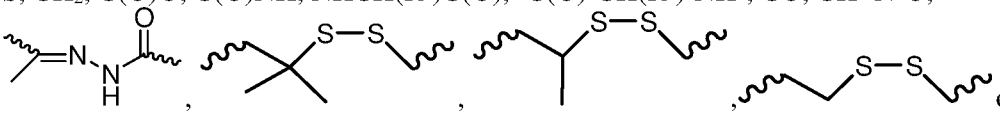
Formula XLVIII

wherein:

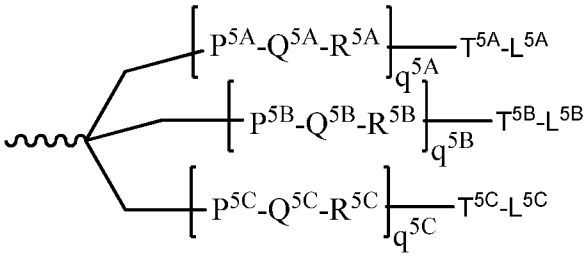
q2A, q2B, q3A, q3B, q4A, q4B, q5A, q5B and q5C represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different;

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

Q^{2A}, Q^{2B}, Q^{3A}, Q^{3B}, Q^{4A}, Q^{4B}, Q^{5A}, Q^{5B}, Q^{5C} are independently for each occurrence absent, alkylene, substituted alkylene wherein one or more methylenes can be interrupted or terminated by one or more of O, S, S(O), SO_2, $N(R^N)$, C(R')=C(R''), C≡C or C(O);

R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{5C} are each independently for each occurrence absent, NH, O, S, CH_2, C(O)O, C(O)NH, NHCH(R^a)C(O), -C(O)-CH(R^a)-NH-, CO, CH=N-O, , , or heterocyclyl; L^{2A}, L^{2B}, L^{3A}, L^{3B}, L^{4A}, L^{4B}, L^{5A}, L^{5B} and L^{5C} represent the ligand; *i.e.* each independently for each occurrence a monosaccharide (such as GalNAc), disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, or polysaccharide; 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):

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. Patent Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928;5,688,941; 6,294,664; 6,320,017; 6,576,752; 6,783,931; 6,900,297; 7,037,646; and 8,106,022, the entire contents of each of which are hereby incorporated herein by reference.

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

"Chimeric" iRNA compounds or "chimeras," in the context of this invention, are iRNA compounds, such as, dsRNAi agents, that contain two or more chemically distinct regions, each made up of at least one monomer unit, *i.e.*, a nucleotide in the case of a dsRNA compound. These iRNAs

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

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

IV. Delivery of an iRNA of the Invention

The delivery of an iRNA of the invention to a cell *e.g.,* a cell within a subject, such as a human subject (*e.g.,* a subject in need thereof, such as a subject susceptible to or diagnosed with a complement factor B-associated disorder) can be achieved in a number of different ways. For

example, delivery may be performed by contacting a cell with an iRNA of the invention either *in vitro* or *in vivo*. *In vivo* delivery may also be performed directly by administering a composition comprising an iRNA, *e.g.,* a dsRNA, to a subject. Alternatively, *in vivo* delivery may be performed indirectly by administering one or more vectors that encode and direct the expression of the iRNA. These alternatives are discussed further below.

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

In an alternative embodiment, the iRNA can be delivered using drug delivery systems such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery systems facilitate binding of an iRNA molecule (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an iRNA by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an iRNA, or induced to form a vesicle or micelle (see *e.g.*, Kim SH, *et al* (2008) *Journal of Controlled Release* 129(2):107-116) that encases an iRNA. The formation of vesicles or micelles further prevents degradation of the iRNA when administered systemically. Methods for making and administering cationic- iRNA complexes are well within the abilities of one skilled in the art (see *e.g.*, Sorensen, DR, *et al* (2003) *J. Mol. Biol* 327:761-766; Verma, UN, *et al* (2003) Clin. *Cancer Res.* 9:1291-1300; Arnold, AS *et al* (2007) *J. Hypertens.* 25:197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of iRNAs include DOTAP (Sorensen, DR., *et al* (2003), supra; Verma, UN, *et al* (2003), *supra*), "solid nucleic acid lipid particles" (Zimmermann, TS, *et al* (2006) *Nature* 441:111-114), cardiolipin (Chien, PY, *et al* (2005) *Cancer Gene Ther.* 12:321-328; Pal, A, *et al* (2005) *Int J. Oncol.* 26:1087-1091), polyethyleneimine (Bonnet ME, *et al* (2008) *Pharm. Res.* Aug 16 Epub ahead of print; Aigner, A. (2006) *J. Biomed. Biotechnol.* 71659), Arg-Gly-Asp (RGD) peptides (Liu, S. (2006) *Mol. Pharm.*

3:472-487), and polyamidoamines (Tomalia, DA, *et al* (2007) *Biochem. Soc. Trans.* 35:61-67; Yoo, H., *et al* (1999) *Pharm. Res.* 16:1799-1804). In some embodiments, an iRNA forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of iRNAs and cyclodextrins can be found in U.S. Patent No. 7,427,605, which is herein incorporated by reference in its entirety.

A. Vector encoded iRNAs of the Invention

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

Viral vector systems which can be utilized with the methods and compositions described herein include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but not limited to lentiviral vectors, moloney murine leukemia virus, *etc.*; (c) adeno- associated virus vectors; (d) herpes simplex virus vectors; (e) SV 40 vectors; (f) polyoma virus vectors; (g) papilloma virus vectors; (h) picornavirus vectors; (i) pox virus vectors such as an orthopox, *e.g.*, vaccinia virus vectors or avipox, *e.g.* canary pox or fowl pox; and (j) a helper-dependent or gutless adenovirus. Replication-defective viruses can also be advantageous. Different vectors will or will not become incorporated into the cells' genome. The constructs can include viral sequences for transfection, if desired. Alternatively, the construct can be incorporated into vectors capable of episomal replication, *e.g.* EPV and EBV vectors. Constructs for the recombinant expression of an iRNA will generally require regulatory elements, *e.g.*, promoters, enhancers, *etc.*, to ensure the expression of the iRNA in target cells. Other aspects to consider for vectors and constructs are known in the art.

V. Pharmaceutical Compositions of the Invention

The present invention also includes pharmaceutical compositions and formulations which include the iRNAs of the invention. In one embodiment, provided herein are pharmaceutical compositions containing an iRNA, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the iRNA are useful for preventing or treating a complement factor B-associated disorder. Such pharmaceutical compositions are formulated based on the mode of delivery. One example is compositions that are formulated for systemic administration *via* parenteral delivery, *e.g.*, by subcutaneous (SC), intramuscular (IM), or intravenous (IV) delivery.

The pharmaceutical compositions of the invention may be administered in dosages sufficient to inhibit expression of a complement factor B gene.

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

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

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

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

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

The iRNA can be delivered in a manner to target a particular tissue (*e.g.*, hepatocytes).

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

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

A. Additional Formulations

i. Emulsions

The compositions of the present invention can be prepared and formulated as emulsions. Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1 μm in diameter (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi *et al.*, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 301). Emulsions are often biphasic systems comprising two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions can be of either the water-in-oil (w/o) or the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase, the resulting composition is called a water-in-oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase, the resulting composition is called an oil-in-water (o/w) emulsion. Emulsions can contain additional components in addition to the dispersed phases, and the active drug which can be present as a solution either in the aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants can also be present in emulsions as needed. Pharmaceutical emulsions can also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o) and water-in-oil-in-water (w/o/w) emulsions. Such complex formulations often provide certain advantages that simple binary emulsions do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion. Likewise a system of oil droplets enclosed in globules of water stabilized in an oily continuous phase provides an o/w/o emulsion.

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

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

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

The application of emulsion formulations *via* dermatological, oral, and parenteral routes, and methods for their manufacture have been reviewed in the literature (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

ii. Microemulsions

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).

iii. Microparticles

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

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

v. 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. Such agent are well known in the art.

vi. Other Components

The compositions of the present invention can additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions can contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or can contain

additional materials useful in physically formulating various dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present invention. The formulations can be sterilized and, if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings, 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, or dextran. The suspension can also contain stabilizers.

In some embodiments, pharmaceutical compositions featured in the invention include (a) one or more iRNA and (b) one or more agents which function by a non-iRNA mechanism and which are useful in treating a complement factor B-associated disorder.

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

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

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

VI. Methods For Inhibiting Complement Factor B Expression

The present invention also provides methods of inhibiting expression of a CFB gene in a cell. The methods include contacting a cell with an RNAi agent, *e.g.*, double stranded RNA agent, in an amount effective to inhibit expression of CFB in the cell, thereby inhibiting expression of CFB in the cell.

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

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

The phrase "inhibiting expression of a complement factor B gene" is intended to refer to inhibition of expression of any complement factor B gene (such as, *e.g.*, a mouse complement factor B gene, a rat complement factor B gene, a monkey complement factor B gene, or a human complement factor B gene) as well as variants or mutants of a complement factor B gene. Thus, the complement factor B gene may be a wild-type complement factor B gene, a mutant complement factor B gene, or a transgenic complement factor B gene in the context of a genetically manipulated cell, group of cells, or organism.

"Inhibiting expression of a complement factor B gene" includes any level of inhibition of a complement factor B gene, *e.g.*, at least partial suppression of the expression of a complement factor B gene, such as a clinically relevant level of supression. The expression of the complement factor B gene may be assessed based on the level, or the change in the level, of any variable associated with complement factor B gene expression, *e.g.*, complement factor B mRNA level or complement factor B protein level, or, for example, CH_{50} activity as a measure of total hemolytic complement, AH_{50} to measure the hemolytic activity of the alternate pathway of complement, or lactate dehydrogenase (LDH) levels as a measure of intravascular hemolysis, or hemoglobin levels. Levels of C3, C9, C5, C5a, C5b, and soluble C5b-9 complex may also be measured to assess CFB expression. 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. This level may be assessed in an individual cell or in a group of cells, including, for example, a sample derived from a subject. It is understood that complement factor B is expressed predominantly in the liver, and is present in circulation.

Inhibition may be assessed by a decrease in an absolute or relative level of one or more variables that are associated with complement factor B expression compared with a control level. The control level may be any type of control level that is utilized in the art, *e.g.*, a pre-dose baseline level,

or a level determined from a similar subject, cell, or sample that is untreated or treated with a control (such as, *e.g.*, buffer only control or inactive agent control).

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

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

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

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

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

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

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

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

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

Isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or northern analyses, polymerase chain reaction (PCR) analyses and probe arrays. One method for the determination of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to complement factor B mRNA. In one embodiment, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative embodiment, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix® gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in determining the level of complement factor B mRNA.

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

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

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

The level of CFB protein expression may be determined using any method known in the art for the measurement of protein levels. Such methods include, for example, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, fluid or gel precipitin reactions, absorption spectroscopy, a colorimetric assays, spectrophotometric assays, flow cytometry, immunodiffusion (single or double), immunoelectrophoresis, western blotting, radioimmunoassay (RIA), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays, electrochemiluminescence assays, and the like.

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

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

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

VII. Prophylactic and Treatment Methods of the Invention

The present invention also provides methods of using an iRNA of the invention or a composition containing an iRNA of the invention to inhibit expression of complement factor B, thereby preventing or treating a complement factor B-associated disorder, *e.g.,* paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), asthma, rheumatoid arthritis (RA); antiphospholipid antibody syndrome; lupus nephritis; ischemia-reperfusion injury; typical or infectious hemolytic uremic syndrome (tHUS); dense deposit disease (DDD); neuromyelitis optica (NMO); multifocal motor neuropathy (MMN); multiple sclerosis (MS); macular degeneration (e.g., age-related macular degeneration (AMD)); hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP); spontaneous fetal loss; Pauci-immune vasculitis; epidermolysis bullosa; recurrent fetal loss; pre-eclampsia, traumatic brain injury, myasthenia gravis, cold agglutinin disease, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, C3 neuropathy, anti-neutrophil cytoplasmic antibody-associated vasculitis (e.g., granulomatosis with polyangiitis (previously known as Wegener granulomatosis), Churg-Strauss syndrome, and microscopic polyangiitis), humoral and vascular transplant rejection, graft dysfunction, myocardial infarction (*e.g.*, tissue damage and ischemia in myocardial infarction), an allogenic transplant, sepsis (*e.g.*, poor outcome in sepsis), Coronary artery disease, dermatomyositis, Graves' disease, atherosclerosis, Alzheimer's disease, systemic inflammatory response sepsis, septic shock, spinal cord injury, glomerulonephritis, Hashimoto's thyroiditis, type I diabetes, psoriasis, pemphigus, autoimmune hemolytic anemia (AIHA), ITP, Goodpasture syndrome, Degos disease, antiphospholipid syndrome (APS), catastrophic APS (CAPS), a cardiovascular disorder, myocarditis, a cerebrovascular disorder, a peripheral (e.g., musculoskeletal) vascular disorder, a renovascular disorder, a mesenteric/enteric vascular disorder, vasculitis, Henoch-Schönlein purpura nephritis, systemic lupus erythematosus-associated vasculitis, vasculitis associated with rheumatoid arthritis, immune complex vasculitis, Takayasu's disease, dilated cardiomyopathy, diabetic angiopathy, Kawasaki's disease (arteritis), venous gas embolus (VGE), and restenosis following stent placement, rotational atherectomy, and percutaneous transluminal coronary angioplasty (PTCA) (see, *e.g.*, Holers (2008) *Immunological Reviews* 223:300-316; Holers and Thurman (2004) *Molecular Immunology* 41:147-152; U.S. Patent Publication No. 20070172483).

In one embodiment, the complement factor B-associate disease is selected from the group consisting of C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration, atypical hemolytic uremic syndrome, thrombotic microangiopathy,

myasthenia gravis, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria, and rheumatoid arthritis

In another embodiment, the complement factor B-associate disease is selected from the group consisting of C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease.

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

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

The *in vivo* methods of the invention may include administering to a subject a composition containing an iRNA, where the iRNA includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of the complement factor B gene of the mammal to which the RNAi agent is to be administered. The composition can be administered by any means known in the art including, but not limited to oral, intraperitoneal, or parenteral routes, including intracranial (*e.g.*, intraventricular, intraparenchymal, and intrathecal), intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), nasal, rectal, and topical (including buccal and sublingual) administration. In certain embodiments, the compositions are administered by intravenous infusion or injection. In certain embodiments, the compositions are administered by subcutaneous injection. In certain embodiments, the compositions are administered by intramuscular injection.

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 CFB, or a therapeutic or prophylactic effect. A depot injection may also provide more consistent serum concentrations. Depot injections may include subcutaneous injections or intramuscular injections. In certain embodiments, the depot injection is a subcutaneous injection.

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

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

The present invention further provides methods of treatment in a subject in need thereof, *e.g.*, a subject diagnosed with a complement factor B-associated disorder, such as, C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease.

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

In one embodiment, a complement factor B-associated disease is selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), asthma, rheumatoid arthritis (RA); antiphospholipid antibody syndrome; lupus nephritis; ischemia-reperfusion injury; typical or infectious hemolytic uremic syndrome (tHUS); dense deposit disease (DDD); neuromyelitis optica (NMO); multifocal motor neuropathy (MMN); multiple sclerosis (MS); macular degeneration (e.g., age-related macular degeneration (AMD)); hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP); spontaneous fetal loss; Pauci-immune vasculitis; epidermolysis bullosa; recurrent fetal loss; pre-eclampsia, traumatic brain injury, myasthenia gravis, cold agglutinin disease, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, C3 neuropathy, anti-neutrophil cytoplasmic antibody-associated vasculitis (e.g., granulomatosis with polyangiitis (previously known as Wegener granulomatosis), Churg-Strauss syndrome, and microscopic polyangiitis), humoral and vascular transplant rejection, graft dysfunction, myocardial infarction (*e.g.*, tissue damage and ischemia in myocardial infarction), an allogenic transplant, sepsis (*e.g.*, poor outcome in sepsis), Coronary artery disease, dermatomyositis, Graves' disease, atherosclerosis,

Alzheimer's disease, systemic inflammatory response sepsis, septic shock, spinal cord injury, glomerulonephritis, Hashimoto's thyroiditis, type I diabetes, psoriasis, pemphigus, autoimmune hemolytic anemia (AIHA), ITP, Goodpasture syndrome, Degos disease, antiphospholipid syndrome (APS), catastrophic APS (CAPS), a cardiovascular disorder, myocarditis, a cerebrovascular disorder, a peripheral (e.g., musculoskeletal) vascular disorder, a renovascular disorder, a mesenteric/enteric vascular disorder, vasculitis, Henoch-Schönlein purpura nephritis, systemic lupus erythematosus-associated vasculitis, vasculitis associated with rheumatoid arthritis, immune complex vasculitis, Takayasu's disease, dilated cardiomyopathy, diabetic angiopathy, Kawasaki's disease (arteritis), venous gas embolus (VGE), and restenosis following stent placement, rotational atherectomy, and percutaneous transluminal coronary angioplasty (PTCA) (see, *e.g.*, Holers (2008) *Immunological Reviews* 223:300-316; Holers and Thurman (2004) *Molecular Immunology* 41:147-152; US20070172483).

In one embodiment, the complement factor B-associate disease is selected from the group consisting of C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration, atypical hemolytic uremic syndrome, thrombotic microangiopathy, myasthenia gravis, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria, and rheumatoid arthritis

In another embodiment, the complement factor B-associate disease is selected from the group consisting of C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease.

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

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

Subjects that would benefit from an inhibition of complement factor B gene expression are subjects susceptible to or diagnosed with a CFB-associated disorder, *e.g.,* C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease.

In an embodiment, the method includes administering a composition featured herein such that expression of the target complement component B gene is decreased, such as for about 1, 2, 3, 4, 5, 6, 1-6, 1-3, or 3-6 months per dose. In certain embodiments, the composition is administered once every 3-6 months.

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

Administration of the iRNA according to the methods of the invention may result prevention or treatment of a complement factor B-associated disorder, *e.g.*, C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease.

Subjects can be administered a therapeutic amount of iRNA, such as about 0.01 mg/kg to about 200 mg/kg. Subjects can be administered a therapeutic amount of iRNA, such as about 5 mg to about 1000 mg as a fixed dose, regardless of body weight.

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

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

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

Accordingly, in some aspects of the invention, the methods which include either a single iRNA agent of the invention, further include administering to the subject one or more additional therapeutic agents. The iRNA agent and an additional therapeutic agent or treatment may be administered at the same time or in the same combination, *e.g.*, parenterally, or the additional therapeutic agent can be administered as part of a separate composition or at separate times or by another method known in the art or described herein.

In one embodiment, an iRNA agent of the invention is administered in combination with an anti-complement component C5 antibody, or antigen-binding fragment thereof (*e.g.,* eculizumab or ravulizumab-cwvz), an iRNA agent targeting complement component C5, an iRNA agent targeting complement component C3, or a C3 peptide inhibitor (*e.g.,* compstatin). In one embodiment, the iRNA agent of the invention is administered to the patient, and then the additional therapeutic agent is administered to the patient (or vice versa). In another embodiment, the iRNA agent of the invention and the additional therapeutic agent are administered at the same time.

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

VIII. Kits

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

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

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

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

EXAMPLES

Example 1. iRNA Synthesis

Source of reagents

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

siRNA Design

siRNAs targeting the human complement factor B (CFB) gene, (human: NCBI refseqID NM_001710.6; NCBI GeneID: 629) was designed using custom R and Python scripts. The human NM_001710 REFSEQ mRNA, version 6, has a length of 2476 bases. Detailed lists of the unmodified CFB sense and antisense strand nucleotide sequences are shown in Table 2. Detailed lists of the modified CFB sense and antisense strand nucleotide sequences are shown in Table 3.

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

siRNA Synthesis

siRNAs were synthesized and annealed using routine methods known in the art.

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

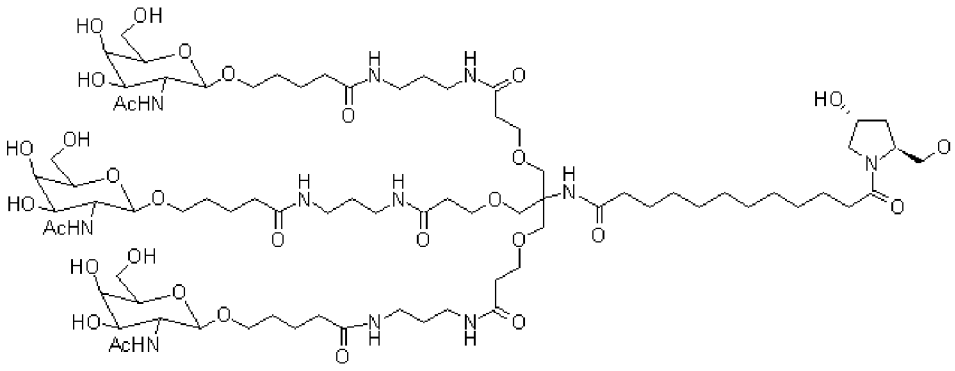
Upon completion of the solid phase synthesis, solid-supported oligoribonucleotides were treated with 300 μL of Methylamine (40% aqueous) at room temperature in 96 well plates for approximately 2 hours to afford cleavage from the solid support and subsequent removal of all additional base-labile protecting groups. For sequences containing any natural ribonucleotide linkages (2'-OH) protected with a tert-butyl dimethyl silyl (TBDMS) group, a second deprotection step was

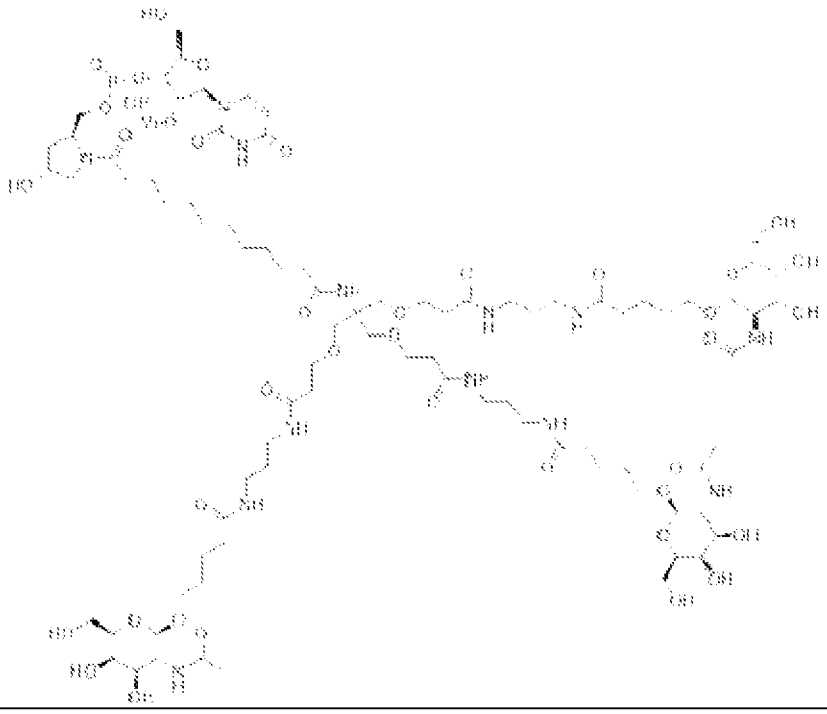
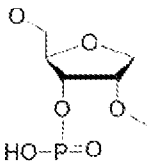
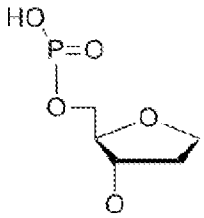
performed using TEA.3HF (triethylamine trihydrofluoride). To each oligonucleotide solution in aqueous methylamine was added 200 µL of dimethyl sulfoxide (DMSO) and 300 µL TEA.3HF and the solution was incubated for approximately 30 mins at 60 °C. After incubation, the plate was allowed to come to room temperature and crude oligonucleotides were precipitated by the addition of 1 mL of 9:1 acetontrile:ethanol or 1:1 ethanol:isopropanol. The plates were then centrifuged at 4 °C for 45 mins and the supernatant carefully decanted with the aid of a multichannel pipette. The oligonucleotide pellet was resuspended in 20 mM NaOAc and subsequently desalted using a HiTrap size exclusion column (5 mL, GE Healthcare) on an Agilent LC system equipped with an autosampler, UV detector, conductivity meter, and fraction collector. Desalted samples were collected in 96 well plates and then analyzed by LC-MS and UV spectrometry to confirm identity and quantify the amount of material, respectively.

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

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

Abbre*via*tion	**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

Abbre*via*tion	Nucleotide(s)
Gs	guanosine-3'-phosphorothioate
T	5'-methyluridine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate
Ts	5-methyluridine-3'-phosphorothioate
U	Uridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine -3'-phosphorothioate
Us	uridine -3'-phosphorothioate
N	any nucleotide, modified or unmodified
a	2'-O-methyladenosine-3'-phosphate
as	2'-O-methyladenosine-3'- phosphorothioate
c	2'-O-methylcytidine-3'-phosphate
cs	2'-O-methylcytidine-3'- phosphorothioate
g	2'-O-methylguanosine-3'-phosphate
gs	2'-O-methylguanosine-3'- phosphorothioate
t	2'-O-methyl-5-methyluridine-3'-phosphate
ts	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u	2'-O-methyluridine-3'-phosphate
us	2'-O-methyluridine-3'-phosphorothioate
s	phosphorothioate linkage
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol (Hyp-(GalNAc-alkyl)3) (2S,4R)-1-[29-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-14,14-bis[[3-[[3-[[5-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-1-oxopentyl]amino]propyl]amino]-3-oxopropoxy]methyl]-1,12,19,25-tetraoxo-16-oxa-13,20,24-triazanonacos-1-yl]-4-hydroxy-2-hydroxymethylpyrrolidine 

Abbre*via*tion	Nucleotide(s)
uL96	2'-O-methyluridine-3'-phosphate ((2S,4R)-1-[29-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-14,14-bis[[3-[[3-[[5-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-1-oxopentyl]amino]propyl]amino]-3-oxopropoxy]methyl]-1,12,19,25-tetraoxo-16-oxa-13,20,24-triazanonacos-1-yl]-4-hydroxy-2-pyrrolidinyl)methyl ester 
Y34	2-hydroxymethyl-tetrahydrofurane-4-methoxy-3-phosphate (abasic 2'-OMe furanose) 
Y44	inverted abasic DNA (2-hydroxymethyl-tetrahydrofurane-5-phosphate) 

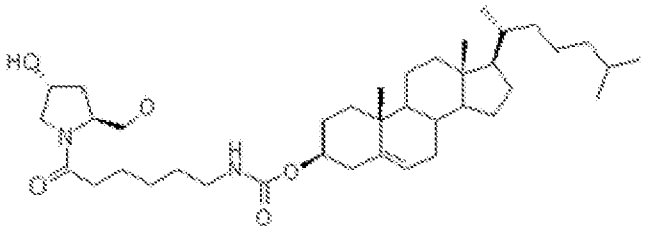
Abbre*via*tion	Nucleotide(s)
L10	N-(cholesterylcarboxamidocaproyl)-4-hydroxyprolinol (Hyp-C6-Chol) 
(Agn)	Adenosine-glycol nucleic acid (GNA) S-Isomer
(Cgn)	Cytidine-glycol nucleic acid (GNA) S-Isomer
(Ggn)	Guanosine-glycol nucleic acid (GNA) S-Isomer
(Tgn)	Thymidine-glycol nucleic acid (GNA) S-Isomer
P	Phosphate
VP	Vinyl-phosphonate
dA	2`-deoxyadenosine-3`-phosphate
dAs	2`-deoxyadenosine-3`-phosphorothioate
dC	2`-deoxycytidine-3`-phosphate
dCs	2`-deoxycytidine-3`-phosphorothioate
dG	2`-deoxyguanosine-3`-phosphate
dGs	2`-deoxyguanosine-3`-phosphorothioate
dT	2`-deoxythymidine-3`-phosphate
dTs	2`-deoxythymidine-3`-phosphorothioate
dU	2`-deoxyuridine
dUs	2`-deoxyuridine-3`-phosphorothioate
(C2p)	cytidine-2`-phosphate
(G2p)	guanosine-2`-phosphate
(U2p)	uridine-2`-phosphate
(A2p)	adenosine-2`-phosphate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(Ahds)	2'-O-hexadecyl-adenosine-3'-phosphorothioate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Chds)	2'-O-hexadecyl-cytidine-3'-phosphorothioate
(Ghd)	2'-O-hexadecyl-guanosine-3'-phosphate
(Ghds)	2'-O-hexadecyl-guanosine-3'-phosphorothioate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
(Uhds)	2'-O-hexadecyl-uridine-3'-phosphorothioate

Table 2. Unmodified Sense and Antisense Strand Sequences of Complement Factor B dsRNA Agents

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1724362	AAGGGAAUGUGACCAGGUCUU	4-24		AAGACCUGGUCACAUUCCCUUCC	2-24	
AD-1724363	AGGGAAUGUGACCAGGUCUAU	5-25		ATAGACCUGGUCACAUUCCCUUC	3-25	
AD-1724364	GGGAAUGUGACCAGGUCUAGU	6-26		ACUAGACCUGGUCACAUUCCCUU	4-26	
AD-1724365	GGAAUGUGACCAGGUCUAGGU	7-27		ACCUAGACCUGGUCACAUUCCCU	5-27	
AD-1724369	UGUGACCAGGUCUAGGUCUGU	11-31		ACAGACCUAGACCUGGUCACAUU	9-31	
AD-1724370	GUGACCAGGUCUAGGUCUGGU	12-32		ACCAGACCUAGACCUGGUCACAU	10-32	
AD-1724376	AGGUCUAGGUCUGGAGUUUCU	18-38		AGAAACTCCAGACCUAGACCUGG	16-38	
AD-1724384	GUCUGGAGUUUCAGCUUGGAU	26-46		ATCCAAGCUGAAACUCCAGACCU	24-46	
AD-1724385	UCUGGAGUUUCAGCUUGGACU	27-47		AGUCCAAGCUGAAACUCCAGACC	25-47	
AD-1724386	CUGGAGUUUCAGCUUGGACAU	28-48		ATGUCCAAGCUGAAACUCCAGAC	26-48	
AD-1724530	UCCUUCCGACUUCUCCAAGAU	269-289		ATCUTGGAGAAGUCGGAAGGAGC	267-289	
AD-1724572	UGUCCUUCUGGCUUCUACCCU	311-331		AGGGTAGAAGCCAGAAGGACACA	309-331	
AD-1724574	UCCUUCUGGCUUCUACCCGUU	313-333		AACGGGTAGAAGCCAGAAGGACA	311-333	
AD-1724575	CCUUCUGGCUUCUACCCGUAU	314-334		ATACGGGUAGAAGCCAGAAGGAC	312-334	
AD-1724576	CUUCUGGCUUCUACCCGUACU	315-335		AGUACGGGUAGAAGCCAGAAGGA	313-335	
AD-1724579	CUGGCUUCUACCCGUACCCUU	318-338		AAGGGUACGGGTAGAAGCCAGAA	316-338	
AD-1724586	CUACCCGUACCCUGUGCAGAU	325-345		ATCUGCACAGGGUACGGGUAGAA	323-345	
AD-1724600	UGCAGACACGUACCUGCAGAU	339-359		ATCUGCAGGUACGUGUCUGCACA	337-359	
AD-1724651	AAGGCAGAGUGCAGAGCAAUU	410-430		AAUUGCTCUGCACUCUGCCUUCC	408-430	
AD-1724653	GGCAGAGUGCAGAGCAAUCCU	412-432		AGGATUGCUCUGCACUCUGCCUU	410-432	
AD-1724685	CGGUCUCCCUACUACAAUGUU	476-496		AACATUGUAGUAGGGAGACCGGG	474-496	
AD-1724691	CCCUACUACAAUGUGAGUGAU	482-502		ATCACUCACACAUTGUAGUAGGGAG	480-502	
AD-1724692	CCUACUACAAUGUGAGUGAUU	483-503		AAUCACTCACATUGUAGUAGGGA	481-503	
AD-1724693	CUACUACAAUGUGAGUGAUGU	484-504		ACAUCACUCACACAUUGUAGUAGGG	482-504	
AD-1724695	ACUACAAUGUGAGUGAUGAGU	486-506		ACUCAUCACUCACACAUUGUAGUAG	484-506	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1724698	ACAAUGUGAGUGAUGAGAUCU	489-509		AGAUCUCAUCACUCACAUUGUAG	487-509	
AD-1724699	CAAUGUGAGUGAUGAGAUCUU	490-510		AAGATCTCAUCACUCACAUUGUA	488-510	
AD-1724700	AAUGUGAGUGAUGAGAUCUCU	491-511		AGAGAUCUCAUCACUCACAUUGU	489-511	
AD-1724701	AUGUGAGUGAUGAGAUCUCUU	492-512		AAGAGATCUCATCACUCACAUUG	490-512	
AD-1724702	UGUGAGUGAUGAGAUCUCUUU	493-513		AAAGAGAUCUCAUCACUCACAUU	491-513	
AD-1724703	GUGAGUGAUGAGAUCUCUUUU	494-514		AAAAGAGAUCUCAUCACUCACAU	492-514	
AD-1724704	UGAGUGAUGAGAUCUCUUUCU	495-515		AGAAAGAGAUCTCAUCACUCACA	493-515	
AD-1724705	GAGUGAUGAGAUCUCUUUCCU	496-516		AGGAAAGAGAUCUCAUCACUCAC	494-516	
AD-1724706	AGUGAUGAGAUCUCUUUCCAU	497-517		ATGGAAAGAGATCUCAUCACUCA	495-517	
AD-1724707	GUGAUGAGAUCUCUUUCCACU	498-518		AGUGGAAAGAGAUCUCAUCACUC	496-518	
AD-1724708	UGAUGAGAUCUCUUUCCACUU	499-519		AAGUGGAAAGAGAUCUCAUCACU	497-519	
AD-1724714	GAUCUCUUUCCACUGCUAUGU	505-525		ACAUAGCAGUGGAAAGAGAUCUC	503-525	
AD-1724715	AUCUCUUUCCACUGCUAUGAU	506-526		ATCATAGCAGUGGAAAGAGAUCU	504-526	
AD-1724716	UCUCUUUCCACUGCUAUGACU	507-527		AGUCAUAGCAGTGGAAAGAGAUC	505-527	
AD-1724717	CUCUUUCCACUGCUAUGACGU	508-528		ACGUCATAGCAGUGGAAAGAGAU	506-528	
AD-1724718	UCUUUCCACUGCUAUGACGGU	509-529		ACCGTCAUAGCAGUGGAAAGAGA	507-529	
AD-1724725	ACUGCUAUGACGGUUACACUU	516-536		AAGUGUAACCGTCAUAGCAGUGG	514-536	
AD-1724726	CUGCUAUGACGGUUACACUCU	517-537		AGAGTGTAACCGUCAUAGCAGUG	515-537	
AD-1724730	UAUGACGGUUACACUCUCCGU	521-541		ACGGAGAGUGUAACCGUCAUAGC	519-541	
AD-1724731	AUGACGGUUACACUCUCCGGU	522-542		ACCGGAGAGUGTAACCGUCAUAG	520-542	
AD-1724741	AUCGCACCUGCCAAGUGAAUU	552-572		AAUUCACUUGGCAGGUGCGAUUG	550-572	
AD-1724742	UCGCACCUGCCAAGUGAAUGU	553-573		ACAUTCACUUGGCAGGUGCGAUU	551-573	
AD-1724743	CGCACCUGCCAAGUGAAUGGU	554-574		ACCATUCACUUGGCAGGUGCGAU	552-574	
AD-1724776	CAGACAGCGAUCUGUGACAAU	587-607		ATUGTCACAGATCGCUGUCUGCC	585-607	
AD-1724777	AGACAGCGAUCUGUGACAACU	588-608		AGUUGUCACAGAUCGCUGUCUGC	586-608	
AD-1724778	GACAGCGAUCUGUGACAACGU	589-609		ACGUTGTCACAGAUCGCUGUCUG	587-609	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
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AD-1724780	CAGCGAUCUGUGACAACGGAU	591-611		ATCCGUTGUCACAGAUCGCUGUC	589-611	
AD-1724781	AGCGAUCUGUGACAACGGAGU	592-612		ACUCCGTUGUCACAGAUCGCUGU	590-612	
AD-1724792	UGGCACAAGGAAGGUGGGCAU	643-663		ATGCCCACCUUCCUUGUGCCAAU	641-663	
AD-1724819	CCGCCUUGAAGACAGCGUCAU	670-690		ATGACGCUGUCTUCAAGGCGGUA	668-690	
AD-1724823	CUUGAAGACAGCGUCACCUAU	674-694		ATAGGUGACGCTGUCUUCAAGGC	672-694	
AD-1724824	UUGAAGACAGCGUCACCUACU	675-695		AGUAGGTGACGCUGUCUUCAAGG	673-695	
AD-1724825	UGAAGACAGCGUCACCUACCU	676-696		AGGUAGGUGACGCUGUCUUCAAG	674-696	
AD-1724860	GUGUCAGGAAGGUGGCUCUUU	739-759		AAAGAGCCACCTUCCUGACACGU	737-759	
AD-1724894	CCUUCCUGCCAAGACUCCUUU	773-793		AAAGGAGUCUUGGCAGGAAGGCU	771-793	
AD-1724897	UCCUGCCAAGACUCCUUCAUU	776-796		AAUGAAGGAGUCUUGGCAGGAAG	774-796	
AD-1724899	CUGCCAAGACUCCUUCAUGUU	778-798		AACATGAAGGAGUCUUGGCAGGA	776-798	
AD-1724900	UGCCAAGACUCCUUCAUGUAU	779-799		ATACAUGAAGGAGUCUUGGCAGG	777-799	
AD-1724903	CAAGACUCCUUCAUGUACGAU	782-802		ATCGTACAUGAAGGAGUCUUGGC	780-802	
AD-1724904	AAGACUCCUUCAUGUACGACU	783-803		AGUCGUACAUGAAGGAGUCUUGG	781-803	
AD-1724905	AGACUCCUUCAUGUACGACAU	784-804		ATGUCGTACAUGAAGGAGUCUUG	782-804	
AD-1724906	GACUCCUUCAUGUACGACACU	785-805		AGUGTCGUACATGAAGGAGUCUU	783-805	
AD-1724910	CAAGAGGUGGCCGAAGCUUUU	809-829		AAAAGCTUCGGCCACCUCUUGAG	807-829	
AD-1724919	GCCGAAGCUUUCCUGUCUUCU	818-838		AGAAGACAGGAAAGCUUCGGCCA	816-838	
AD-1724945	AGAGACCAUAGAAGGAGUCGU	844-864		ACGACUCCUUCTAUGGUCUCUGU	842-864	
AD-1724946	GAGACCAUAGAAGGAGUCGAU	845-865		ATCGACTCCUUCUAUGGUCUCUG	843-865	
AD-1724947	AGACCAUAGAAGGAGUCGAUU	846-866		AAUCGACUCCUTCUAUGGUCUCU	844-866	
AD-1724948	GACCAUAGAAGGAGUCGAUGU	847-867		ACAUCGACUCCTUCUAUGGUCUC	845-867	
AD-1724949	ACCAUAGAAGGAGUCGAUGCU	848-868		AGCATCGACUCCUUCUAUGGUCU	846-868	
AD-1725000	CCUUCAGGCUCCCAUGAACAUU	920-940		AAUGTUCAUGGAGCCUGAAGGGU	918-940	
AD-1725003	UCAGGCUCCCAUGAACAUCUAU	923-943		ATAGAUGUUCATGGAGCCUGAAG	921-943	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1725004	CAGGCUCCAUGAACAUCUACU	924-944		AGUAGATGUUCAUGGAGCCUGAA	922-944	
AD-1725013	UGAACAUCUACCUGGUGCUAU	933-953		ATAGCACCAGGTAGAUGUUCAUG	931-953	
AD-1725015	AACAUCUACCUGGUGCUAGAU	935-955		ATCUAGCACCAGGUAGAUGUUCA	933-955	
AD-1725017	CAUCUACCUGGUGCUAGAUGU	937-957		ACAUCUAGCACCAGGUAGAUGUU	935-957	
AD-1725018	AUCUACCUGGUGCUAGAUGGU	938-958		ACCATCTAGCACCAGGUAGAUGU	936-958	
AD-1725019	UCUACCUGGUGCUAGAUGGAU	939-959		ATCCAUCUAGCACCAGGUAGAUG	937-959	
AD-1725020	CUACCUGGUGCUAGAUGGAUU	940-960		AAUCCATCUAGCACCAGGUAGAU	938-960	
AD-1725021	UACCUGGUGCUAGAUGGAUCU	941-961		AGAUCCAUCUAGCACCAGGUAGA	939-961	
AD-1725022	ACCUGGUGCUAGAUGGAUCAU	942-962		ATGATCCAUCUAGCACCAGGUAG	940-962	
AD-1725023	CCUGGUGCUAGAUGGAUCAGU	943-963		ACUGAUCCAUCTAGCACCAGGUA	941-963	
AD-1725025	UGGUGCUAGAUGGAUCAGACU	945-965		AGUCTGAUCCATCUAGCACCAGG	943-965	
AD-1725027	GUGCUAGAUGGAUCAGACAGU	947-967		ACUGTCTGAUCCAUCUAGCACCA	945-967	
AD-1725028	UGCUAGAUGGAUCAGACAGCU	948-968		AGCUGUCUGAUCCAUCUAGCACC	946-968	
AD-1725033	GAUGGAUCAGACAGCAUUGGU	953-973		ACCAAUGCUGUCUGAUCCAUCUA	951-973	
AD-1725039	CAACUUCACAGGAGCCAAAAU	979-999		ATUUTGGCUCCTGUGAAGUUGCU	977-999	
AD-1725040	AACUUCACAGGAGCCAAAAAU	980-1000		ATUUTUGGCUCCUGUGAAGUUGC	978-1000	
AD-1725041	ACUUCACAGGAGCCAAAAAGU	981-1001		ACUUTUTGGCUCCUGUGAAGUUG	979-1001	
AD-1725042	CUUCACAGGAGCCAAAAAGUU	982-1002		AACUTUTUGGCTCCUGUGAAGUU	980-1002	
AD-1725043	UUCACAGGAGCCAAAAAGUGU	983-1003		ACACTUTUUGGCUCCUGUGAAGU	981-1003	
AD-1725044	UCACAGGAGCCAAAAAGUGUU	984-1004		AACACUTUUUGGCUCCUGUGAAG	982-1004	
AD-1725045	CACAGGAGCCAAAAAGUGUCU	985-1005		AGACACTUUUUGGCUCCUGUGAA	983-1005	
AD-1725046	ACAGGAGCCAAAAAGUGUCUU	986-1006		AAGACACUUUUTGGCUCCUGUGA	984-1006	
AD-1725047	CAGGAGCCAAAAAGUGUCUAU	987-1007		ATAGACACUUUTUGGCUCCUGUG	985-1007	
AD-1725048	AGGAGCCAAAAAGUGUCUAGU	988-1008		ACUAGACACUUTUUGGCUCCUGU	986-1008	
AD-1725049	GGAGCCAAAAAGUGUCUAGUU	989-1009		AACUAGACACUTUUUGGCUCCUG	987-1009	
AD-1725050	GAGCCAAAAAGUGUCUAGUCU	990-1010		AGACTAGACACTUUUUGGCUCCU	988-1010	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1725051	AGCCAAAAAGUGUCUAGUCAU	991-1011		ATGACUAGACACUUUUUGGCUCC	989-1011	
AD-1725052	GCCAAAAAGUGUCUAGUCAAU	992-1012		ATUGACTAGACACUUUUUGGCUC	990-1012	
AD-1725053	CCAAAAAGUGUCUAGUCAACU	993-1013		AGUUGACUAGACACUUUUUGGCU	991-1013	
AD-1725054	CAAAAAGUGUCUAGUCAACUU	994-1014		AAGUTGACUAGACACUUUUUGGC	992-1014	
AD-1725055	AAAAAGUGUCUAGUCAACUUU	995-1015		AAAGTUGACUAGACACUUUUUGG	993-1015	
AD-1725056	AAAAGUGUCUAGUCAACUUAU	996-1016		ATAAGUTGACUAGACACUUUUUG	994-1016	
AD-1725057	AAAGUGUCUAGUCAACUUAAU	997-1017		ATUAAGTUGACTAGACACUUUUU	995-1017	
AD-1725058	AAGUGUCUAGUCAACUUAAUU	998-1018		AAUUAAGUUGACUAGACACUUUU	996-1018	
AD-1725059	AGUGUCUAGUCAACUUAAUUU	999-1019		AAAUTAAGUUGACUAGACACUUU	997-1019	
AD-1725060	GUGUCUAGUCAACUUAAUUGU	1000-1020		ACAATUAAGUUGACUAGACACUU	998-1020	
AD-1725061	UGUCUAGUCAACUUAAUUGAU	1001-1021		ATCAAUTAAGUTGACUAGACACU	999-1021	
AD-1725062	GUCUAGUCAACUUAAUUGAGU	1002-1022		ACUCAATUAAGTUGACUAGACAC	1000-1022	
AD-1725066	AGUCAACUUAAUUGAGAAGGU	1006-1026		ACCUTCTCAAUTAAGUUGACUAG	1004-1026	
AD-1725074	UAAUUGAGAAGGUGGCAAGUU	1014-1034		AACUTGCCACCTUCUCAAUUAAG	1012-1034	
AD-1725075	AAUUGAGAAGGUGGCAAGUUU	1015-1035		AAACTUGCCACCUUCUCAAUUAA	1013-1035	
AD-1725079	GAGAAGGUGGCAAGUUAUGGU	1019-1039		ACCATAACUUGCCACCUUCUCAA	1017-1039	
AD-1725080	AGAAGGUGGCAAGUUAUGGUU	1020-1040		AACCAUAACUUGCCACCUUCUCA	1018-1040	
AD-1725082	AAGGUGGCAAGUUAUGGUGUU	1022-1042		AACACCAUAACTUGCCACCUUCU	1020-1042	
AD-1725083	AGGUGGCAAGUUAUGGUGUGU	1023-1043		ACACACCAUAACUUGCCACCUUC	1021-1043	
AD-1725088	GCAAGUUAUGGUGUGAAGCCU	1028-1048		AGGCTUCACACCAUAACUUGCCA	1026-1048	
AD-1725092	GUUAUGGUGUGAAGCCAAGAU	1032-1052		ATCUTGGCUUCACACCAUAACUU	1030-1052	
AD-1725095	AUGGUGUGAAGCCAAGAUAUU	1035-1055		AAUATCTUGGCTUCACACCAUAA	1033-1055	
AD-1725096	UGGUGUGAAGCCAAGAUAUGU	1036-1056		ACAUAUCUUGGCUUCACACCAUA	1034-1056	
AD-1725122	AAAAUUUGGGUCAAAGUGUCU	1082-1102		AGACACTUUGACCCAAAUUUUGG	1080-1102	
AD-1725123	AAAUUUGGGUCAAAGUGUCUU	1083-1103		AAGACACUUUGACCCAAAUUUUG	1081-1103	
AD-1725125	AUUUGGGUCAAAGUGUCUGAU	1085-1105		ATCAGACACUUTGACCCAAAUUU	1083-1105	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1725156	GUAAUGCAGACUGGGUCACGU	1116-1136		ACGUGACCCAGTCUGCAUUACUG	1114-1136	
AD-1725157	UAAUGCAGACUGGGUCACGAU	1117-1137		ATCGTGACCCAGUCUGCAUUACU	1115-1137	
AD-1725158	AAUGCAGACUGGGUCACGAAU	1118-1138		ATUCGUGACCCAGUCUGCAUUAC	1116-1138	
AD-1725159	AUGCAGACUGGGUCACGAAGU	1119-1139		ACUUCGTGACCCAGUCUGCAUUA	1117-1139	
AD-1725184	AAUGAAAUCAAUUAUGAAGAU	1145-1165		ATCUTCAUAAUTGAUUUCAUUGA	1143-1165	
AD-1725186	UGAAAUCAAUUAUGAAGACCU	1147-1167		AGGUCUTCAUAAUUGAUUUCAUU	1145-1167	
AD-1725189	AAUCAAUUAUGAAGACCACAU	1150-1170		ATGUGGTCUUCAUAAUUGAUUUC	1148-1170	
AD-1725190	AUCAAUUAUGAAGACCACAAU	1151-1171		ATUGTGGUCUUCAUAAUUGAUUU	1149-1171	
AD-1725191	UCAAUUAUGAAGACCACAAGU	1152-1172		ACUUGUGGUCUTCAUAAUUGAUU	1150-1172	
AD-1725192	CAAUUAUGAAGACCACAAGUU	1153-1173		AACUTGTGGUCTUCAUAAUUGAU	1151-1173	
AD-1725193	AAUUAUGAAGACCACAAGUUU	1154-1174		AAACTUGUGGUCUUCAUAAUUGA	1152-1174	
AD-1725194	AUUAUGAAGACCACAAGUUGU	1155-1175		ACAACUTGUGGTCUUCAUAAUUG	1153-1175	
AD-1725195	UUAUGAAGACCACAAGUUGAU	1156-1176		ATCAACTUGUGGUCUUCAUAAUU	1154-1176	
AD-1725196	UAUGAAGACCACAAGUUGAAU	1157-1177		ATUCAACUUGUGGUCUUCAUAAU	1155-1177	
AD-1725197	AUGAAGACCACAAGUUGAAGU	1158-1178		ACUUCAACUUGTGGUCUUCAUAA	1156-1178	
AD-1725198	UGAAGACCACAAGUUGAAGUU	1159-1179		AACUTCAACUUGUGGUCUUCAUA	1157-1179	
AD-1725199	GAAGACCACAAGUUGAAGUCU	1160-1180		AGACTUCAACUTGUGGUCUUCAU	1158-1180	
AD-1725200	AAGACCACAAGUUGAAGUCAU	1161-1181		ATGACUTCAACTUGUGGUCUUCA	1159-1181	
AD-1725201	AGACCACAAGUUGAAGUCAGU	1162-1182		ACUGACTUCAACUUGUGGUCUUC	1160-1182	
AD-1725203	ACCACAAGUUGAAGUCAGGGU	1164-1184		ACCCTGACUUCAACUUGUGGUCU	1162-1184	
AD-1725204	CCACAAGUUGAAGUCAGGGAU	1165-1185		ATCCCUGACUUCAACUUGUGGUC	1163-1185	
AD-1725205	CACAAGUUGAAGUCAGGGACU	1166-1186		AGUCCCTGACUTCAACUUGUGGU	1164-1186	
AD-1725206	ACAAGUUGAAGUCAGGGACUU	1167-1187		AAGUCCCUGACTUCAACUUGUGG	1165-1187	
AD-1725208	AAGUUGAAGUCAGGGACUAAU	1169-1189		ATUAGUCCCUGACUUCAACUUGU	1167-1189	
AD-1725211	UUGAAGUCAGGGACUAACACU	1172-1192		AGUGTUAGUCCCUGACUUCAACU	1170-1192	
AD-1725212	UGAAGUCAGGGACUAACACCU	1173-1193		AGGUGUTAGUCCCUGACUUCAAC	1171-1193	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1725215	AGUCAGGGACUAACACCAAGU	1176-1196		ACUUGGTGUUAGUCCCUGACUUC	1174-1196	
AD-1725216	GUCAGGGACUAACACCAAGAU	1177-1197		ATCUTGGUGUUAGUCCCUGACUU	1175-1197	
AD-1725243	CCAGGCAGUGUACAGCAUGAU	1204-1224		ATCATGCUGUACACUGCCUGGAG	1202-1224	
AD-1725244	CAGGCAGUGUACAGCAUGAUU	1205-1225		AAUCAUGCUGUACACUGCCUGGA	1203-1225	
AD-1725245	AGGCAGUGUACAGCAUGAUGU	1206-1226		ACAUCATGCUGTACACUGCCUGG	1204-1226	
AD-1725247	GCAGUGUACAGCAUGAUGAGU	1208-1228		ACUCAUCAUGCTGUACACUGCCU	1206-1228	
AD-1725327	CUGAUGGAUUGCACACAACAUGU	1290-1310		ACAUGUTGUGCAAUCCAUCAGUC	1288-1310	
AD-1725328	UGAUGGAUUGCACAACAUGGU	1291-1311		ACCATGTUGUGCAAUCCAUCAGU	1289-1311	
AD-1725329	GAUGGAUUGCACAACAUGGGU	1292-1312		ACCCAUGUUGUGCAAUCCAUCAG	1290-1312	
AD-1725330	AUGGAUUGCACAACAUGGGCU	1293-1313		AGCCCATGUUGTGCAAUCCAUCA	1291-1313	
AD-1725331	UGGAUUGCACAACAUGGGCGU	1294-1314		ACGCCCAUGUUGUGCAAUCCAUC	1292-1314	
AD-1725332	GGAUUGCACAACAUGGGCGGU	1295-1315		ACCGCCCAUGUTGUGCAAUCCAU	1293-1315	
AD-1725333	GACCCAAUUACUGUCAUUGAU	1316-1336		ATCAAUGACAGTAAUUGGGUCCC	1314-1336	
AD-1725334	ACCCAAUUACUGUCAUUGAUU	1317-1337		AAUCAATGACAGUAAUUGGGUCC	1315-1337	
AD-1725336	CCAAUUACUGUCAUUGAUGAU	1319-1339		ATCATCAAUGACAGUAAUUGGGU	1317-1339	
AD-1725344	UGUCAUUGAUGAGAUCCGGGU	1327-1347		ACCCGGAUCUCAUCAAUGACAGU	1325-1347	
AD-1725345	GUCAUUGAUGAGAUCCGGGAU	1328-1348		ATCCCGGAUCUCAUCAAUGACAG	1326-1348	
AD-1725347	CAUUGAUGAGAUCCGGGACUU	1330-1350		AAGUCCCGGAUCUCAUCAAUGAC	1328-1350	
AD-1725348	AUUGAUGAGAUCCGGGACUUU	1331-1351		AAAGTCCCGGATCUCAUCAAUGA	1329-1351	
AD-1725376	UUGGCAAGGAUCGCAAAAACU	1359-1379		AGUUTUTGCGATCCUUGCCAAUG	1357-1379	
AD-1725377	UGGCAAGGAUCGCAAAAACCU	1360-1380		AGGUTUTUGCGAUCCUUGCCAAU	1358-1380	
AD-1725378	GGCAAGGAUCGCAAAAACCCU	1361-1381		AGGGTUTUUGCGAUCCUUGCCAA	1359-1381	
AD-1725397	CAAGGGAGGAUUAUCUGGAUU	1380-1400		AAUCCAGAUAATCCUCCCUUGGG	1378-1400	
AD-1725402	GAGGAUUAUCUGGAUGUCUAU	1385-1405		ATAGACAUCCAGAUAAUCCUCCC	1383-1405	
AD-1725403	AGGAUUAUCUGGAUGUCUAUU	1386-1406		AAUAGACAUCCAGAUAAUCCUCC	1384-1406	
AD-1725404	GGAUUAUCUGGAUGUCUAUGU	1387-1407		ACAUAGACAUCCAGAUAAUCCUC	1385-1407	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1725405	GAUUAUCUGGAUGUCUAUGUU	1388-1408		AACATAGACAUCCAGAUAAUCCU	1386-1408	
AD-1725406	AUUAUCUGGAUGUCUAUGUGU	1389-1409		ACACAUAGACATCCAGAUAAUCC	1387-1409	
AD-1725407	UUAUCUGGAUGUCUAUGUGUU	1390-1410		AACACATAGACAUCCAGAUAAUC	1388-1410	
AD-1725408	UAUCUGGAUGUCUAUGUGUUU	1391-1411		AAACACAUAGACAUCCCAGAUAAU	1389-1411	
AD-1725409	AUCUGGAUGUCUAUGUGUUUU	1392-1412		AAAACACAUAGACAUCCCAGAUAA	1390-1412	
AD-1725410	UCUGGAUGUCUAUGUGUUUGU	1393-1413		ACAAACACAUAGACAUCCCAGAUA	1391-1413	
AD-1725411	CUGGAUGUCUAUGUGUUUGGU	1394-1414		ACCAAACACAUAGACAUCCCAGAU	1392-1414	
AD-1725427	AACCAAGUGAACAUCAAUGCU	1430-1450		AGCATUGAUGUTCACUUGGUUCA	1428-1450	
AD-1725428	ACCAAGUGAACAUCAAUGCUU	1431-1451		AAGCAUTGAUGTUCACUUGGUUC	1429-1451	
AD-1725429	CCAAGUGAACAUCAAUGCUUU	1432-1452		AAAGCATUGAUGUUCACUUGGUU	1430-1452	
AD-1725430	CAAGUGAACAUCAAUGCUUUU	1433-1453		AAAAGCAUUGATGUUCACUUGGU	1431-1453	
AD-1725439	AUCAAUGCUUUGGCUUCCAAU	1442-1462		ATUGGAAGCCAAAGCAUUGAUGU	1440-1462	
AD-1725440	UCAAUGCUUUGGCUUCCAAGU	1443-1463		ACUUGGAAGCCAAAGCAUUGAUG	1441-1463	
AD-1725441	CAAUGCUUUGGCUUCCAAGAU	1444-1464		ATCUTGGAAGCCAAAGCAUUGAU	1442-1464	
AD-1725449	UGGCUUCCAAGAAAGACAAUU	1452-1472		AAUUGUCUUUCTUGGAAGCCAAA	1450-1472	
AD-1725453	UUCCAAGAAAGACAAUGAGCU	1456-1476		AGCUCATUGUCTUUCUUGGAAGC	1454-1476	
AD-1725454	UCCAAGAAAGACAAUGAGCAU	1457-1477		ATGCTCAUUGUCUUUCUUGGAAG	1455-1477	
AD-1725456	CAAGAAAGACAAUGAGCAACU	1459-1479		AGUUGCTCAUUGUCUUUCUUGGA	1457-1479	
AD-1725457	AAGAAAGACAAUGAGCAACAU	1460-1480		ATGUTGCUCAUTGUCUUUCUUGG	1458-1480	
AD-1725460	AAAGACAAUGAGCAACAUGUU	1463-1483		AACATGTUGCUCAUUGUCUUUCU	1461-1483	
AD-1725462	AGACAAUGAGCAACAUGUGUU	1465-1485		AACACATGUUGCUCAUUGUCUUU	1463-1485	
AD-1725463	GACAAUGAGCAACAUGUGUUU	1466-1486		AAACACAUGUUGCUCAUUGUCUU	1464-1486	
AD-1725464	ACAAUGAGCAACAUGUGUUCU	1467-1487		AGAACACAUGUTGCUCAUUGUCU	1465-1487	
AD-1725465	CAAUGAGCAACAUGUGUUCAU	1468-1488		ATGAACACAUGTUGCUCAUUGUC	1466-1488	
AD-1725467	AUGAGCAACAUGUGUUCAAAU	1470-1490		ATUUGAACACATGUUGCUCAUUG	1468-1490	
AD-1725469	GAGCAACAUGUGUUCAAAGUU	1472-1492		AACUTUGAACACAUGUUGCUCAU	1470-1492	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1725470	AGCAACAUGUGUUCAAAGUCU	1473-1493		AGACUUUGAACACAUGUUGCUCA	1471-1493	
AD-1725472	CAACAUGUGUUCAAAGUCAAU	1475-1495		ATUGACUUUGAACACAUGUUGCU	1473-1495	
AD-1725473	AACAUGUGUUCAAAGUCAAGU	1476-1496		ACUUGACUUUGAACACAUGUUGC	1474-1496	
AD-1725474	ACAUGUGUUCAAAGUCAAGGU	1477-1497		ACCUUGACUUUGAACACAUGUUG	1475-1497	
AD-1725476	AUGUGUUCAAAGUCAAGGAUU	1479-1499		AAUCCUUGACUUUGAACACAUGU	1477-1499	
AD-1725477	UGUGUUCAAAGUCAAGGAUAU	1480-1500		ATAUCCUUGACUUUGAACACAUG	1478-1500	
AD-1725478	GUGUUCAAAGUCAAGGAUAUU	1481-1501		AAUATCCUUGACUUUGAACACAU	1479-1501	
AD-1725481	UUCAAAGUCAAGGAUAUGGAU	1484-1504		ATCCAUAUCCUUGACUUUGAACA	1482-1504	
AD-1725482	UCAAAGUCAAGGAUAUGGAAU	1485-1505		ATUCCATAUCCUUGACUUUGAAC	1483-1505	
AD-1725483	CAAAGUCAAGGAUAUGGAAAU	1486-1506		ATUUCCAUAUCCUUGACUUUGAA	1484-1506	
AD-1725534	UGAAAGCCAGUCUCUGAGUCU	1537-1557		AGACUCAGAGACUGGCUUUCAUC	1535-1557	
AD-1725535	GAAAGCCAGUCUCUGAGUCUU	1538-1558		AAGACUCAGAGACUGGCUUUCAU	1536-1558	
AD-1725548	UGAGUCUCUGUGGCAUGGUUU	1551-1571		AAACCATGCCACAGAGACUCAGA	1549-1571	
AD-1725552	UCUCUGUGGCAUGGUUUGGGU	1555-1575		ACCCAAACCAUGCCACAGAGACU	1553-1575	
AD-1725556	UGUGGCAUGGUUUGGGAACAU	1559-1579		ATGUTCCCAAACCAUGCCACAGA	1557-1579	
AD-1725558	UGGCAUGGUUUGGGAACACAU	1561-1581		ATGUGUTCCCAAACCAUGCCACA	1559-1581	
AD-1725580	AAGGGUACCGAUUACCACAAU	1583-1603		ATUGTGGUAAUCGGUACCCUUCC	1581-1603	
AD-1725582	GGGUACCGAUUACCACAAGCU	1585-1605		AGCUTGTGGUAAUCGGUACCCUU	1583-1605	
AD-1725585	UACCGAUUACCACAAGCAACU	1588-1608		AGUUGCTUGUGGUAAUCGGUACC	1586-1608	
AD-1725587	CCGAUUACCACAAGCAACCAU	1590-1610		ATGGTUGCUUGTGGUAAUCGGUA	1588-1610	
AD-1725588	CGAUUACCACAAGCAACCAUU	1591-1611		AAUGGUTGCUUGUGGUAAUCGGU	1589-1611	
AD-1725590	AUUACCACAAGCAACCAUGGU	1593-1613		ACCATGGUUGCTUGUGGUAAUCG	1591-1613	
AD-1725591	UUACCACAAGCAACCAUGGCU	1594-1614		AGCCAUGGUUGCUUGUGGUAAUC	1592-1614	
AD-1725592	UACCACAAGCAACCAUGGCAU	1595-1615		ATGCCATGGUUGCUUGUGGUAAU	1593-1615	
AD-1725593	ACCACAAGCAACCAUGGCAGU	1596-1616		ACUGCCAUGGUTGCUUGUGGUAA	1594-1616	
AD-1725598	AAGCAACCAUGGCAGGCCAAU	1601-1621		ATUGGCCUGCCAUGGUUGCUUGU	1599-1621	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1725603	ACCAUGGCAGGCCAAGAUCUU	1606-1626		AAGATCTUGGCCUGCCAUGGUUG	1604-1626	
AD-1725604	CCAUGGCAGGCCAAGAUCUCU	1607-1627		AGAGAUCUUGGCCUGCCAUGGUU	1605-1627	
AD-1725605	CAUGGCAGGCCAAGAUCUCAU	1608-1628		ATGAGATCUUGGCCUGCCAUGGU	1606-1628	
AD-1725643	GCUGUGGUGUCUGAGUACUUU	1667-1687		AAAGTACUCAGACACCACAGCCC	1665-1687	
AD-1725644	CUGUGGUGUCUGAGUACUUUU	1668-1688		AAAAGUACUCAGACACCACAGCC	1666-1688	
AD-1725645	UGUGGUGUCUGAGUACUUUGU	1669-1689		ACAAAGTACUCAGACACCACAGC	1667-1689	
AD-1725646	GUGGUGUCUGAGUACUUUGUU	1670-1690		AACAAAGUACUCAGACACCACAG	1668-1690	
AD-1725647	UGGUGUCUGAGUACUUUGUGU	1671-1691		ACACAAAGUACTCAGACACCACA	1669-1691	
AD-1725667	CUGACAGCAGCACAUUGUUUU	1691-1711		AAAACAAUGUGCUGCUGUCAGCA	1689-1711	
AD-1725716	AAGCGGGACCUGGAGAUAGAU	1760-1780		ATCUAUCUCCAGGUCCCGCUUCU	1758-1780	
AD-1725717	AGCGGGACCUGGAGAUAGAAU	1761-1781		ATUCTATCUCCAGGUCCCGCUUC	1759-1781	
AD-1725756	GAAGCAGGAAUUCCUGAAUUU	1823-1843		AAAUTCAGGAATUCCUGCUUCUU	1821-1843	
AD-1725757	AAGCAGGAAUUCCUGAAUUUU	1824-1844		AAAATUCAGGAAUUCCUGCUUCU	1822-1844	
AD-1725759	GCAGGAAUUCCUGAAUUUUAU	1826-1846		ATAAAATUCAGGAAUUCCUGCUU	1824-1846	
AD-1725760	CAGGAAUUCCUGAAUUUUAUU	1827-1847		AAUAAAAUUCAGGAAUUCCUGCU	1825-1847	
AD-1725761	AGGAAUUCCUGAAUUUUAUGU	1828-1848		ACAUAAAAUUCAGGAAUUCCUGC	1826-1848	
AD-1725762	GGAAUUCCUGAAUUUUAUGAU	1829-1849		ATCATAAAAUUCAGGAAUUCCUG	1827-1849	
AD-1725763	GAAUUCCUGAAUUUUAUGACU	1830-1850		AGUCAUAAAAUTCAGGAAUUCCU	1828-1850	
AD-1725764	AAUUCCUGAAUUUUAUGACUU	1831-1851		AAGUCATAAAATUCAGGAAUUCC	1829-1851	
AD-1725765	AUUCCUGAAUUUUAUGACUAU	1832-1852		ATAGTCAUAAAAUUCAGGAAUUC	1830-1852	
AD-1725766	UUCCUGAAUUUUAUGACUAUU	1833-1853		AAUAGUCAUAAAAUUCAGGAAUU	1831-1853	
AD-1725767	UCCUGAAUUUUAUGACUAUGU	1834-1854		ACAUAGTCAUAAAAUUCAGGAAU	1832-1854	
AD-1725768	CCUGAAUUUUAUGACUAUGAU	1835-1855		ATCATAGUCAUAAAAUUCAGGAA	1833-1855	
AD-1725769	CUGAAUUUUAUGACUAUGACU	1836-1856		AGUCAUAGUCATAAAAUUCAGGA	1834-1856	
AD-1725771	GAAUUUUAUGACUAUGACGUU	1838-1858		AACGTCAUAGUCAUAAAAUUCAG	1836-1858	
AD-1725772	AAUUUUAUGACUAUGACGUUU	1839-1859		AAACGUCAUAGTCAUAAAAUUCA	1837-1859	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1725773	AUUUUAUGACUAUGACGUUGU	1840-1860		ACAACGTCAUAGUCAUAAAAUUC	1838-1860	
AD-1725775	UUUAUGACUAUGACGUUGCCU	1842-1862		AGGCAACGUCATAGUCAUAAAAU	1840-1862	
AD-1725776	UUAUGACUAUGACGUUGCCCU	1843-1863		AGGGCAACGUCAUAGUCAUAAAA	1841-1863	
AD-1725777	UAUGACUAUGACGUUGCCCUU	1844-1864		AAGGGCAACGUCAUAGUCAUAAA	1842-1864	
AD-1725778	AUGACUAUGACGUUGCCCUGU	1845-1865		ACAGGGCAACGTCAUAGUCAUAA	1843-1865	
AD-1725779	UGACUAUGACGUUGCCCUGAU	1846-1866		ATCAGGGCAACGUCAUAGUCAUA	1844-1866	
AD-1725780	GACUAUGACGUUGCCCUGAUU	1847-1867		AAUCAGGGCAACGUCAUAGUCAU	1845-1867	
AD-1725784	AUGACGUUGCCCUGAUCAAGU	1851-1871		ACUUGATCAGGGCAACGUCAUAG	1849-1871	
AD-1725785	UGACGUUGCCCUGAUCAAGCU	1852-1872		AGCUTGAUCAGGGCAACGUCAUA	1850-1872	
AD-1725786	GACGUUGCCCUGAUCAAGCUU	1853-1873		AAGCTUGAUCAGGGCAACGUCAU	1851-1873	
AD-1725787	ACGUUGCCCUGAUCAAGCUCU	1854-1874		AGAGCUTGAUCAGGGCAACGUCA	1852-1874	
AD-1725789	GUUGCCCUGAUCAAGCUCAAU	1856-1876		ATUGAGCUUGATCAGGGCAACGU	1854-1876	
AD-1725790	UUGCCCUGAUCAAGCUCAAGU	1857-1877		ACUUGAGCUUGAUCAGGGCAACG	1855-1877	
AD-1725828	CAGACUAUCAGGCCCAUUUGU	1895-1915		ACAAAUGGGCCTGAUAGUCUGGC	1893-1915	
AD-1725829	AGACUAUCAGGCCCAUUUGUU	1896-1916		AACAAATGGGCCUGAUAGUCUGG	1894-1916	
AD-1725830	GACUAUCAGGCCCAUUUGUCU	1897-1917		AGACAAAUGGGCCUGAUAGUCUG	1895-1917	
AD-1725831	ACUAUCAGGCCCAUUUGUCUU	1898-1918		AAGACAAAUGGGCCUGAUAGUCU	1896-1918	
AD-1725832	CUAUCAGGCCCAUUUGUCUCU	1899-1919		AGAGACAAAUGGGCCUGAUAGUC	1897-1919	
AD-1725840	CGAGGGAACAACUCGAGCUUU	1927-1947		AAAGCUCGAGUTGUUCCCUCGGU	1925-1947	
AD-1725841	GAGGGAACAACUCGAGCUUUU	1928-1948		AAAAGCTCGAGTUGUUCCCUCGG	1926-1948	
AD-1725842	AGGGAACAACUCGAGCUUUGU	1929-1949		ACAAAGCUCGAGUUGUUCCCUCG	1927-1949	
AD-1725845	GAACAACUCGAGCUUUGAGGU	1932-1952		ACCUCAAAGCUCGAGUUGUUCCC	1930-1952	
AD-1725846	AACAACUCGAGCUUUGAGGCU	1933-1953		AGCCTCAAAGCTCGAGUUGUUCC	1931-1953	
AD-1725848	CAACUCGAGCUUUGAGGCUUU	1935-1955		AAAGCCTCAAAGCUCGAGUUGUU	1933-1955	
AD-1725849	AACUCGAGCUUUGAGGCUUCU	1936-1956		AGAAGCCUCAAAGCUCGAGUUGU	1934-1956	
AD-1725850	ACUCGAGCUUUGAGGCUUCCU	1937-1957		AGGAAGCCUCAAAGCUCGAGUUG	1935-1957	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1725854	GAGCUUUGAGGCUUCCUCCAU	1941-1961		ATGGAGGAAGCCUCAAAGCUCGA	1939-1961	
AD-1725855	AGCUUUGAGGCUUCCUCCAAU	1942-1962		ATUGGAGGAAGCCUCAAAGCUCG	1940-1962	
AD-1725856	GCUUUGAGGCUUCCUCCAACU	1943-1963		AGUUGGAGGAAGCCUCAAAGCUC	1941-1963	
AD-1725857	CUUUGAGGCUUCCUCCAACUU	1944-1964		AAGUTGGAGGAAGCCUCAAAGCU	1942-1964	
AD-1725858	UUUGAGGCUUCCUCCAACUAU	1945-1965		ATAGTUGGAGGAAGCCUCAAAGC	1943-1965	
AD-1725861	GAGGCUUCCUCCAACUACCAU	1948-1968		ATGGTAGUUGGAGGAAGCCUCAA	1946-1968	
AD-1725862	AGGCUUCCUCCAACUACCACU	1949-1969		AGUGGUAGUUGGAGGAAGCCUCA	1947-1969	
AD-1725864	GCUUCCUCCAACUACCACUUU	1951-1971		AAAGTGGUAGUTGGAGGAAGCCU	1949-1971	
AD-1725866	UUCCUCCAACUACCACUUGCU	1953-1973		AGCAAGTGGUAGUUGGAGGAAGC	1951-1973	
AD-1725867	UCCUCCAACUACCACUUGCCU	1954-1974		AGGCAAGUGGUAGUUGGAGGAAG	1952-1974	
AD-1725872	CAACUACCACUUGCCAGCAAU	1959-1979		ATUGCUGGCAAGUGGUAGUUGGA	1957-1979	
AD-1725874	ACUACCACUUGCCAGCAACAU	1961-1981		ATGUTGCUGGCAAGUGGUAGUUG	1959-1981	
AD-1725907	CUCCCUGCACAGGAUAUCAAU	1994-2014		ATUGAUAUCCUGUGCAGGGAGCA	1992-2014	
AD-1725908	UCCCUGCACAGGAUAUCAAAU	1995-2015		ATUUGATAUCCTGUGCAGGGAGC	1993-2015	
AD-1725909	CCCUGCACAGGAUAUCAAAGU	1996-2016		ACUUTGAUAUCCUGUGCAGGGAG	1994-2016	
AD-1725911	CUGCACAGGAUAUCAAAGCUU	1998-2018		AAGCTUTGAUATCCUGUGCAGGG	1996-2018	
AD-1725916	CAGGAUAUCAAAGCUCUGUUU	2003-2023		AAACAGAGCUUTGAUAUCCUGUG	2001-2023	
AD-1725919	GAUAUCAAAGCUCUGUUUGUU	2006-2026		AACAAACAGAGCUUUGAUAUCCU	2004-2026	
AD-1725925	AAAGCUCUGUUUGUGUCUGAU	2012-2032		ATCAGACACAAACAGAGCUUUGA	2010-2032	
AD-1725957	GCUGACUCGGAAGGAGGUCUU	2044-2064		AAGACCTCCUUCCGAGUCAGCUU	2042-2064	
AD-1725958	CUGACUCGGAAGGAGGUCUAU	2045-2065		ATAGACCUCCUTCCGAGUCAGCU	2043-2065	
AD-1725961	ACUCGGAAGGAGGUCUACAUU	2048-2068		AAUGTAGACCUCCUUCCGAGUCA	2046-2068	
AD-1725963	UCGGAAGGAGGUCUACAUCAU	2050-2070		ATGATGTAGACCUCCUUCCGAGU	2048-2070	
AD-1725964	CGGAAGGAGGUCUACAUCAAU	2051-2071		ATUGAUGUAGACCUCCUUCCGAG	2049-2071	
AD-1725967	AAGGAGGUCUACAUCAAGAAU	2054-2074		ATUCTUGAUGUAGACCUCCUUCC	2052-2074	
AD-1725968	AGGAGGUCUACAUCAAGAAUU	2055-2075		AAUUCUTGAUGTAGACCUCCUUC	2053-2075	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1725974	AAGAAAGGCAGCUGUGAGAGU	2081-2101		ACUCTCACAGCTGCCUUUCUUAU	2079-2101	
AD-1725977	AAAGGCAGCUGUGAGAGAGAU	2084-2104		ATCUCUCUCACAGCUGCCUUUCU	2082-2104	
AD-1725983	AGCUGUGAGAGAGAUGCUCAU	2090-2110		ATGAGCAUCUCTCUCACAGCUGC	2088-2110	
AD-1725985	CUGUGAGAGAGAUGCUCAAUU	2092-2112		AAUUGAGCAUCTCUCUCACAGCU	2090-2112	
AD-1725986	UGUGAGAGAGAUGCUCAAUAU	2093-2113		ATAUTGAGCAUCUCUCUCACAGC	2091-2113	
AD-1725987	GUGAGAGAGAUGCUCAAUAUU	2094-2114		AAUATUGAGCATCUCUCUCACAG	2092-2114	
AD-1725988	UGAGAGAGAUGCUCAAUAUGU	2095-2115		ACAUAUTGAGCAUCUCUCUCACA	2093-2115	
AD-1725989	GAGAGAGAUGCUCAAUAUGCU	2096-2116		AGCATATUGAGCAUCUCUCUCAC	2094-2116	
AD-1725991	CAGGCUAUGACAAAGUCAAGU	2118-2138		ACUUGACUUUGTCAUAGCCUGGG	2116-2138	
AD-1725992	AGGCUAUGACAAAGUCAAGGU	2119-2139		ACCUTGACUUUGUCAUAGCCUGG	2117-2139	
AD-1725993	GGCUAUGACAAAGUCAAGGAU	2120-2140		ATCCTUGACUUTGUCAUAGCCUG	2118-2140	
AD-1725999	GACAAAGUCAAGGACAUCUCU	2126-2146		AGAGAUGUCCUTGACUUUGUCAU	2124-2146	
AD-1726014	UCGGUUCCUUUGUACUGGAGU	2161-2181		ACUCCAGUACAAAGGAACCGAGG	2159-2181	
AD-1726015	CGGUUCCUUUGUACUGGAGGU	2162-2182		ACCUCCAGUACAAAGGAACCGAG	2160-2182	
AD-1726016	GGUUCCUUUGUACUGGAGGAU	2163-2183		ATCCTCCAGUACAAAGGAACCGA	2161-2183	
AD-1726018	UUCCUUUGUACUGGAGGAGUU	2165-2185		AACUCCTCCAGTACAAAGGAACC	2163-2185	
AD-1726020	CCUUUGUACUGGAGGAGUGAU	2167-2187		ATCACUCCUCCAGUACAAAGGAA	2165-2187	
AD-1726023	UUGUACUGGAGGAGUGAGUCU	2170-2190		AGACTCACUCCTCCAGUACAAAG	2168-2190	
AD-1726024	UGUACUGGAGGAGUGAGUCCU	2171-2191		AGGACUCACUCCUCCAGUACAAA	2169-2191	
AD-1726025	GUACUGGAGGAGUGAGUCCCU	2172-2192		AGGGACTCACUCCUCCAGUACAA	2170-2192	
AD-1726027	ACUGGAGGAGUGAGUCCCUAU	2174-2194		ATAGGGACUCACUCCUCCAGUAC	2172-2194	
AD-1726029	UGGAGGAGUGAGUCCCUAUGU	2176-2196		ACAUAGGGACUCACUCCUCCAGU	2174-2196	
AD-1726031	GAGGAGUGAGUCCCUAUGCUU	2178-2198		AAGCAUAGGGACUCACUCCUCCA	2176-2198	
AD-1726033	GGAGUGAGUCCCUAUGCUGAU	2180-2200		ATCAGCAUAGGGACUCACUCCUC	2178-2200	
AD-1726034	GAGUGAGUCCCUAUGCUGACU	2181-2201		AGUCAGCAUAGGGACUCACUCCU	2179-2201	
AD-1726036	CAAUACUUGCAGAGGUGAUUU	2203-2223		AAAUCACCUCUGCAAGUAUUGGG	2201-2223	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1726037	AAUACUUGCAGAGGUGAUUCU	2204-2224		AGAATCACCUCTGCAAGUAUUGG	2202-2224	
AD-1726039	UACUUGCAGAGGUGAUUCUGU	2206-2226		ACAGAATCACCTCUGCAAGUAUU	2204-2226	
AD-1726041	CUUGCAGAGGUGAUUCUGGCU	2208-2228		AGCCAGAAUCACCUCUGCAAGUA	2206-2228	
AD-1726042	UUGCAGAGGUGAUUCUGGCGU	2209-2229		ACGCCAGAAUCACCUCUGCAAGU	2207-2229	
AD-1726048	UGAUAGUUCACACAAGAGAAGUU	2235-2255		AACUTCTCUUGTGAACUAUCAAG	2233-2255	
AD-1726049	GAUAGUUCACACAAGAGAAGUCU	2236-2256		AGACTUCUCUUGUGAACUAUCAA	2234-2256	
AD-1726050	AUAGUUCACACAAGAGAAGUCGU	2237-2257		ACGACUTCUCUTGUGAACUAUCA	2235-2257	
AD-1726051	UAGUUCACACAAGAGAAGUCGUU	2238-2258		AACGACTUCUCTUGUGAACUAUC	2236-2258	
AD-1726052	AGUUCACACAAGAGAAGUCGUUU	2239-2259		AAACGACUUCUCTUGUGAACUAU	2237-2259	
AD-1726053	GUUCACACAAGAGAAGUCGUUUU	2240-2260		AAAACGACUUCTCTUGUGAACUA	2238-2260	
AD-1726054	UUCACACAAGAGAAGUCGUUUCU	2241-2261		AGAAACGACUUCTCTUGUGAACU	2239-2261	
AD-1726055	UCACACAAGAGAAGUCGUUUCAU	2242-2262		ATGAAACGACUTCTCTUGUGAAC	2240-2262	
AD-1726056	CACAAGAGAAGUCGUUUCAUU	2243-2263		AAUGAAACGACTUCTCTUGUGAA	2241-2263	
AD-1726057	ACAAGAGAAGUCGUUUCAUUU	2244-2264		AAAUGAAACGACUUCTCTUGUGA	2242-2264	
AD-1726058	CAAGAGAAGUCGUUUCAUUCU	2245-2265		AGAATGAAACGACUUCTCTUGUG	2243-2265	
AD-1726059	AAGAGAAGUCGUUUCAUUCAU	2246-2266		ATGAAUGAAACGACUUCTCTUGU	2244-2266	
AD-1726060	AGAGAAGUCGUUUCAUUCAAU	2247-2267		ATUGAATGAAACGACUUCTCTUG	2245-2267	
AD-1726061	GAGAAGUCGUUUCAUUCAAGU	2248-2268		ACUUGAAUGAAACGACUUCTCTU	2246-2268	
AD-1726062	AGAAGUCGUUUCAUUCAAGUU	2249-2269		AACUTGAAUGAAACGACUUCTCT	2247-2269	
AD-1726063	GAAGUCGUUUCAUUCAAGUUU	2250-2270		AAACTUGAAUGAAACGACUUCTC	2248-2270	
AD-1726064	AAGUCGUUUCAUUCAAGUUGU	2251-2271		ACAACUTGAAUGAAACGACUUCT	2249-2271	
AD-1726065	AGUCGUUUCAUUCAAGUUGGU	2252-2272		ACCAACTUGAATGAAACGACUUC	2250-2272	
AD-1726079	GAGUAGUGGAUGUCUGCAAAU	2286-2306		ATUUGCAGACATCCACUACUCCC	2284-2306	
AD-1726080	AGUAGUGGAUGUCUGCAAAAU	2287-2307		ATUUTGCAGACAUCCACUACUCC	2285-2307	
AD-1726081	GUAGUGGAUGUCUGCAAAAAU	2288-2308		ATUUTUGCAGACAUCCACUACUC	2286-2308	
AD-1726082	UAGUGGAUGUCUGCAAAAACU	2289-2309		AGUUTUTGCAGACAUCCACUACU	2287-2309	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1726083	AGUGGAUGUCUGCAAAAACCU	2290-2310		AGGUTUTUGCAGACAUCCACUAC	2288-2310	
AD-1726084	GUGGAUGUCUGCAAAAACCAU	2291-2311		ATGGTUTUUGCAGACAUCCACUA	2289-2311	
AD-1726085	UGGAUGUCUGCAAAAACCAGU	2292-2312		ACUGGUTUUUGCAGACAUCCACU	2290-2312	
AD-1726086	GGAUGUCUGCAAAAACCAGAU	2293-2313		ATCUGGTUUUUGCAGACAUCCAC	2291-2313	
AD-1726087	GAUGUCUGCAAAAACCAGAAU	2294-2314		ATUCTGGUUUUTGCAGACAUCCA	2292-2314	
AD-1726090	GUCUGCAAAAACCAGAAGCGU	2297-2317		ACGCTUCUGGUTUUUGCAGACAU	2295-2317	
AD-1726091	UCUGCAAAAACCAGAAGCGGU	2298-2318		ACCGCUTCUGGTUUUUGCAGACA	2296-2318	
AD-1726092	CUGCAAAAACCAGAAGCGGCU	2299-2319		AGCCGCTUCUGGUUUUUGCAGAC	2297-2319	
AD-1726095	CAAAAACCAGAAGCGGCAAAU	2302-2322		ATUUGCCGCUUCUGGUUUUUGCA	2300-2322	
AD-1726096	AAAAACCAGAAGCGGCAAAAU	2303-2323		ATUUTGCCGCUTCUGGUUUUUGC	2301-2323	
AD-1726097	AAAACCAGAAGCGGCAAAAGU	2304-2324		ACUUTUGCCGCTUCUGGUUUUUG	2302-2324	
AD-1726098	AAACCAGAAGCGGCAAAAGCU	2305-2325		AGCUTUTGCCGCUUCUGGUUUUU	2303-2325	
AD-1726099	AACCAGAAGCGGCAAAAGCAU	2306-2326		ATGCTUTUGCCGCUUCUGGUUUU	2304-2326	
AD-1726103	AGAAGCGGCAAAAGCAGGUAU	2310-2330		ATACCUGCUUUTGCCGCUUCUGG	2308-2330	
AD-1726113	AAAGCAGGUACCUGCUCACGU	2320-2340		ACGUGAGCAGGTACCUGCUUUUG	2318-2340	
AD-1726159	CAAGUGCUGCCCUGGCUGAAU	2366-2386		ATUCAGCCAGGGCAGCACUUGAA	2364-2386	
AD-1726171	UGGCUGAAGGAGAAACUCCAU	2378-2398		ATGGAGTUUCUCCUUCAGCCAGG	2376-2398	
AD-1726184	AACUCCAAGAUGAGGAUUUGU	2391-2411		ACAAAUCCUCATCUUGGAGUUUC	2389-2411	
AD-1726187	UCCAAGAUGAGGAUUUGGGUU	2394-2414		AACCCAAAUCCTCAUCUUGGAGU	2392-2414	
AD-1726189	CAAGAUGAGGAUUUGGGUUUU	2396-2416		AAAACCCAAAUCCUCAUCUUGGA	2394-2416	
AD-1726191	AGAUGAGGAUUUGGGUUUUCU	2398-2418		AGAAAACCCAAAUCCUCAUCUUG	2396-2418	
AD-1726201	GUGGGAUUGAAUUAAAAACAGU	2446-2466		ACUGTUTUAAUTCAAUCCCACGC	2444-2466	
AD-1726202	UGGGAUUGAAUUAAAAACAGCU	2447-2467		AGCUGUTUUAATUCAAUCCCACG	2445-2467	
AD-1726203	GGGAUUGAAUUAAAAACAGCUU	2448-2468		AAGCTGTUUUAAUUCAAUCCCAC	2446-2468	
AD-1726206	AUUGAAUUAAAAACAGCUGCGU	2451-2471		ACGCAGCUGUUTUAAUUCAAUCC	2449-2471	
AD-1726207	UUGAAUUAAAAACAGCUGCGAU	2452-2472		ATCGCAGCUGUTUUAAUUCAAUC	2450-2472	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1726208	UGAAUUAAAAACAGCUGCGACU	2453-2473		AGUCGCAGCUGUTUUUAAUUCAAU	2451-2473	
AD-1726209	GAAUUAAAAACAGCUGCGACAU	2454-2474		ATGUCGCAGCUGUUUUUAAUUCAA	2452-2474	
AD-1726815	CUGGCUUCUACCCGUACCCUU	469-489		AAGGGUACGGGUAGAAGCCAGAA	467-489	
AD-1726927	CCCUACUACAAUGUGAGUGAU	633-653		AUCACUCACAUUGUAGUAGGGAG	631-653	
AD-1726928	CCUACUACAAUGUGAGUGAUU	634-654		AAUCACUCACAUUGUAGUAGGGA	632-654	
AD-1726931	ACUACAAUGUGAGUGAUGAGU	637-657		ACUCAUCACUCACAUUGUAGUAG	635-657	
AD-1726934	ACAAUGUGAGUGAUGAGAUCU	640-660		AGAUCUCAUCACUCACAUUGUAG	638-660	
AD-1726935	CAAUGUGAGUGAUGAGAUCUU	641-661		AAGAUCUCAUCACUCACAUUGUA	639-661	
AD-1726936	AAUGUGAGUGAUGAGAUCUCU	642-662		AGAGAUCUCAUCACUCACAUUGU	640-662	
AD-1726937	AUGUGAGUGAUGAGAUCUCUU	643-663		AAGAGAUCUCAUCACUCACAUUG	641-663	
AD-1726938	UGUGAGUGAUGAGAUCUCUUU	644-664		AAAGAGAUCUCAUCACUCACAUU	642-664	
AD-1726939	GUGAGUGAUGAGAUCUCUUUU	645-665		AAAAGAGAUCUCAUCACUCACAU	643-665	
AD-1726940	UGAGUGAUGAGAUCUCUUUCU	646-666		AGAAAGAGAUCUCAUCACUCACA	644-666	
AD-1726941	GAGUGAUGAGAUCUCUUUCCU	647-667		AGGAAAGAGAUCUCAUCACUCAC	645-667	
AD-1726942	AGUGAUGAGAUCUCUUUCCAU	648-668		AUGGAAAGAGAUCUCAUCACUCA	646-668	
AD-1726944	UGAUGAGAUCUCUUUCCACUU	650-670		AAGUGGAAAGAGAUCUCAUCACU	648-670	
AD-1726952	UCUCUUUCCACUGCUAUGACU	658-678		AGUCAUAGCAGUGGAAAGAGAUC	656-678	
AD-1726961	ACUGCUAUGACGGUUACACUU	667-687		AAGUGUAACCGUCAUAGCAGUGG	665-687	
AD-1727012	CAGACAGCGAUCUGUGACAAU	738-758		AUUGUCACAGAUCGCUGUCUGCC	736-758	
AD-1727059	CUUGAAGACAGCGUCACCUAU	825-845		AUAGGUGACGCUGUCUUCAAGGC	823-845	
AD-1727140	AAGACUCCUUCAUGUACGACU	934-954		AGUCGUACAUGAAGGAGUCUUGG	932-954	
AD-1727142	GACUCCUUCAUGUACGACACU	936-956		AGUGUCGUACAUGAAGGAGUCUU	934-956	
AD-1727181	AGAGACCAUAGAAGGAGUCGU	995-1015		ACGACUCCUUCUAUGGUCUCUGU	993-1015	
AD-1727183	AGACCAUAGAAGGAGUCGAUU	997-1017		AAUCGACUCCUUCUAUGGUCUCU	995-1017	
AD-1727184	GACCAUAGAAGGAGUCGAUGU	998-1018		ACAUCGACUCCUUCUAUGGUCUC	996-1018	
AD-1727249	UGAACAUCUACCUGGUGCUAU	1084-1104		AUAGCACCAGGUAGAUGUUCAUG	1082-1104	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1727261	UGGUGCUAGAUGGAUCAGACU	1096-1116		AGUCUGAUCCAUCUAGCACCAGG	1094-1116	
AD-1727263	GUGCUAGAUGGAUCAGACAGU	1098-1118		ACUGUCUGAUCCAUCUAGCACCA	1096-1118	
AD-1727275	CAACUUCACAGGAGCCAAAAU	1130-1150		AUUUUGGCUCCUGUGAAGUUGCU	1128-1150	
AD-1727276	AACUUCACAGGAGCCAAAAAU	1131-1151		AUUUUUGGCUCCUGUGAAGUUGC	1129-1151	
AD-1727278	CUUCACAGGAGCCAAAAAGUU	1133-1153		AACUUUUUGGCUCCUGUGAAGUU	1131-1153	
AD-1727285	GGAGCCAAAAAGUGUCUAGUU	1140-1160		AACUAGACACUUUUUGGCUCCUG	1138-1160	
AD-1727286	GAGCCAAAAAGUGUCUAGUCU	1141-1161		AGACUAGACACUUUUUGGCUCCU	1139-1161	
AD-1727288	GCCAAAAAGUGUCUAGUCAAU	1143-1163		AUUGACUAGACACUUUUUGGCUC	1141-1163	
AD-1727289	CCAAAAAGUGUCUAGUCAACU	1144-1164		AGUUGACUAGACACUUUUUGGCU	1142-1164	
AD-1727290	CAAAAAGUGUCUAGUCAACUU	1145-1165		AAGUUGACUAGACACUUUUUGGC	1143-1165	
AD-1727291	AAAAAGUGUCUAGUCAACUUU	1146-1166		AAAGUUGACUAGACACUUUUUGG	1144-1166	
AD-1727292	AAAAGUGUCUAGUCAACUUAU	1147-1167		AUAAGUUGACUAGACACUUUUUG	1145-1167	
AD-1727293	AAAGUGUCUAGUCAACUUAAU	1148-1168		AUUAAGUUGACUAGACACUUUUU	1146-1168	
AD-1727298	GUCUAGUCAACUUAAUUGAGU	1153-1173		ACUCAAUUAAGUUGACUAGACAC	1151-1173	
AD-1727310	UAAUUGAGAAGGUGGCAAGUU	1165-1185		AACUUGCCACCUUCUCAAUUAAG	1163-1185	
AD-1727318	AAGGUGGCAAGUUAUGGUGUU	1173-1193		AACACCAUAACUUGCCACCUUCU	1171-1193	
AD-1727324	GCAAGUUAUGGUGUGAAGCCU	1179-1199		AGGCUUCACACCAUAACUUGCCA	1177-1199	
AD-1727331	AUGGUGUGAAGCCAAGAUAUU	1186-1206		AAUAUCUUGGCUUCACACCAUAA	1184-1206	
AD-1727358	AAAAUUUGGGUCAAAGUGUCU	1233-1253		AGACACUUUGACCCAAAUUUUGG	1231-1253	
AD-1727359	AAAUUUGGGUCAAAGUGUCUU	1234-1254		AAGACACUUUGACCCAAAUUUUG	1232-1254	
AD-1727361	AUUUGGGUCAAAGUGUCUGAU	1236-1256		AUCAGACACUUUGACCCAAAUUU	1234-1256	
AD-1727392	GUAAUGCAGACUGGGUCACGU	1267-1287		ACGUGACCCAGUCUGCAUUACUG	1265-1287	
AD-1727420	AAUGAAAUCAAUUAUGAAGAU	1296-1316		AUCUUCAUAAUUGAUUUCAUUGA	1294-1316	
AD-1727427	UCAAUUAUGAAGACCACAAGU	1303-1323		ACUUGUGGUCUUCAUAAUUGAUU	1301-1323	
AD-1727428	CAAUUAUGAAGACCACAAGUU	1304-1324		AACUUGUGGUCUUCAUAAUUGAU	1302-1324	
AD-1727430	AUUAUGAAGACCACAAGUUGU	1306-1326		ACAACUUGUGGUCUUCAUAAUUG	1304-1326	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1727431	UUAUGAAGACCACAAGUUGAU	1307-1327		AUCAACUUGUGGUCUUCAUAAUU	1305-1327	
AD-1727432	UAUGAAGACCACAAGUUGAAU	1308-1328		AUUCAACUUGUGGUCUUCAUAAU	1306-1328	
AD-1727433	AUGAAGACCACAAGUUGAAGU	1309-1329		ACUUCAACUUGUGGUCUUCAUAA	1307-1329	
AD-1727434	UGAAGACCACAAGUUGAAGUU	1310-1330		AACUUCAACUUGUGGUCUUCAUA	1308-1330	
AD-1727435	GAAGACCACAAGUUGAAGUCU	1311-1331		AGACUUCAACUUGUGGUCUUCAU	1309-1331	
AD-1727436	AAGACCACAAGUUGAAGUCAU	1312-1332		AUGACUUCAACUUGUGGUCUUCA	1310-1332	
AD-1727441	CACAAGUUGAAGUCAGGGACU	1317-1337		AGUCCCUGACUUCAACUUGUGGU	1315-1337	
AD-1727442	ACAAGUUGAAGUCAGGGACUU	1318-1338		AAGUCCCUGACUUCAACUUGUGG	1316-1338	
AD-1727481	AGGCAGUGUACAGCAUGAUGU	1357-1377		ACAUCAUGCUGUACACUGCCUGG	1355-1377	
AD-1727483	GCAGUGUACAGCAUGAUGAGU	1359-1379		ACUCAUCAUGCUGUACACUGCCU	1357-1379	
AD-1727565	GAUGGAUUGCACAACAUGGGU	1443-1463		ACCCAUGUUGUGCAAUCCAUCAG	1441-1463	
AD-1727566	AUGGAUUGCACAACAUGGGCU	1444-1464		AGCCCAUGUUGUGCAAUCCAUCA	1442-1464	
AD-1727568	GGAUUGCACAACAUGGGCGGU	1446-1466		ACCGCCCAUGUUGUGCAAUCCAU	1444-1466	
AD-1727569	GACCCAAUUACUGUCAUUGAU	1467-1487		AUCAAUGACAGUAAUUGGGUCCC	1465-1487	
AD-1727570	ACCCAAUUACUGUCAUUGAUU	1468-1488		AAUCAAUGACAGUAAUUGGGUCC	1466-1488	
AD-1727572	CCAAUUACUGUCAUUGAUGAU	1470-1490		AUCAUCAAUGACAGUAAUUGGGU	1468-1490	
AD-1727584	AUUGAUGAGAUCCGGGACUUU	1482-1502		AAAGUCCCGGAUCUCAUCAAUGA	1480-1502	
AD-1727612	UUGGCAAGGAUCGCAAAAACU	1510-1530		AGUUUUUGCGAUCCUUGCCAAUG	1508-1530	
AD-1727633	CAAGGGAGGAUUAUCUGGAUU	1531-1551		AAUCCAGAUAAAUCCUCCCUUGGG	1529-1551	
AD-1727638	GAGGAUUAUCUGGAUGUCUAU	1536-1556		AUAGACAUCCAGAUAAAUCCUCCC	1534-1556	
AD-1727639	AGGAUUAUCUGGAUGUCUAUU	1537-1557		AAUAGACAUCCAGAUAAAUCCUCC	1535-1557	
AD-1727640	GGAUUAUCUGGAUGUCUAUGU	1538-1558		ACAUAGACAUCCAGAUAAAUCCUC	1536-1558	
AD-1727641	GAUUAUCUGGAUGUCUAUGUU	1539-1559		AACAUAGACAUCCAGAUAAAUCCU	1537-1559	
AD-1727642	AUUAUCUGGAUGUCUAUGUGU	1540-1560		ACACAUAGACAUCCAGAUAAAUCC	1538-1560	
AD-1727643	UUAUCUGGAUGUCUAUGUGUU	1541-1561		AACACAUAGACAUCCAGAUAAAUC	1539-1561	
AD-1727644	UAUCUGGAUGUCUAUGUGUUU	1542-1562		AAACACAUAGACAUCCAGAUAAAU	1540-1562	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1727645	AUCUGGAUGUCUAUGUGUUUU	1543-1563		AAAACACAUAGACAUCCAGAUAA	1541-1563	
AD-1727646	UCUGGAUGUCUAUGUGUUUGU	1544-1564		ACAAACACAUAGACAUCCAGAUA	1542-1564	
AD-1727663	AACCAAGUGAACAUCAAUGCU	1581-1601		AGCAUUGAUGUUCACUUGGUUCA	1579-1601	
AD-1727664	ACCAAGUGAACAUCAAUGCUU	1582-1602		AAGCAUUGAUGUUCACUUGGUUC	1580-1602	
AD-1727665	CCAAGUGAACAUCAAUGCUUU	1583-1603		AAAGCAUUGAUGUUCACUUGGUU	1581-1603	
AD-1727666	CAAGUGAACAUCAAUGCUUUU	1584-1604		AAAAGCAUUGAUGUUCACUUGGU	1582-1604	
AD-1727675	AUCAAUGCUUUGGCUUCCAAU	1593-1613		AUUGGAAGCCAAAGCAUUGAUGU	1591-1613	
AD-1727677	CAAUGCUUUGGCUUCCAAGAU	1595-1615		AUCUUGGAAGCCAAAGCAUUGAU	1593-1615	
AD-1727685	UGGCUUCCAAGAAAGACAAUU	1603-1623		AAUUGUCUUUCUUGGAAGCCAAA	1601-1623	
AD-1727689	UUCCAAGAAAGACAAUGAGCU	1607-1627		AGCUCAUUGUCUUUCUUGGAAGC	1605-1627	
AD-1727690	UCCAAGAAAGACAAUGAGCAU	1608-1628		AUGCUCAUUGUCUUUCUUGGAAG	1606-1628	
AD-1727693	AAGAAAGACAAUGAGCAACAU	1611-1631		AUGUUGCUCAUUGUCUUUCUUGG	1609-1631	
AD-1727696	AAAGACAAUGAGCAACAUGUU	1614-1634		AACAUGUUGCUCAUUGUCUUUCU	1612-1634	
AD-1727698	AGACAAUGAGCAACAUGUGUU	1616-1636		AACACAUGUUGCUCAUUGUCUUU	1614-1636	
AD-1727699	GACAAUGAGCAACAUGUGUUU	1617-1637		AAACACAUGUUGCUCAUUGUCUU	1615-1637	
AD-1727700	ACAAUGAGCAACAUGUGUUCU	1618-1638		AGAACACAUGUUGCUCAUUGUCU	1616-1638	
AD-1727701	CAAUGAGCAACAUGUGUUCAU	1619-1639		AUGAACACAUGUUGCUCAUUGUC	1617-1639	
AD-1727703	AUGAGCAACAUGUGUUCAAAU	1621-1641		AUUUGAACACAUGUUGCUCAUUG	1619-1641	
AD-1727705	GAGCAACAUGUGUUCAAAGUU	1623-1643		AACUUUGAACACAUGUUGCUCAU	1621-1643	
AD-1727708	CAACAUGUGUUCAAAGUCAAU	1626-1646		AUUGACUUUGAACACAUGUUGCU	1624-1646	
AD-1727709	AACAUGUGUUCAAAGUCAAGU	1627-1647		ACUUGACUUUGAACACAUGUUGC	1625-1647	
AD-1727710	ACAUGUGUUCAAAGUCAAGGU	1628-1648		ACCUUGACUUUGAACACAUGUUG	1626-1648	
AD-1727712	AUGUGUUCAAAGUCAAGGAUU	1630-1650		AAUCCUUGACUUUGAACACAUGU	1628-1650	
AD-1727713	UGUGUUCAAAGUCAAGGAUAU	1631-1651		AUAUCCUUGACUUUGAACACAUG	1629-1651	
AD-1727714	GUGUUCAAAGUCAAGGAUAUU	1632-1652		AAUAUCCUUGACUUUGAACACAU	1630-1652	
AD-1727717	UUCAAAGUCAAGGAUAUGGAU	1635-1655		AUCCAUAUCCUUGACUUUGAACA	1633-1655	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1727718	UCAAAGUCAAGGAUAUGGAAU	1636-1656		AUUCCAUAUCCUUGACUUUGAAC	1634-1656	
AD-1727821	UACCGAUUACCACAAGCAACU	1739-1759		AGUUGCUUGUGGUAAUCGGUACC	1737-1759	
AD-1727823	CCGAUUACCACAAGCAACCAU	1741-1761		AUGGUUGCUUGUGGUAAUCGGUA	1739-1761	
AD-1727826	AUUACCACAAGCAACCAUGGU	1744-1764		ACCAUGGUUGCUUGUGGUAAUCG	1742-1764	
AD-1727829	ACCACAAGCAACCAUGGCAGU	1747-1767		ACUGCCAUGGUUGCUUGUGGUAA	1745-1767	
AD-1727883	UGGUGUCUGAGUACUUUGUGU	1822-1842		ACACAAAGUACUCAGACACCACA	1820-1842	
AD-1727977	GAAGCAGGAAUUCCUGAAUUU	1974-1994		AAAUUCAGGAAUUCCUGCUUCUU	1972-1994	
AD-1727978	AAGCAGGAAUUCCUGAAUUUU	1975-1995		AAAAUUCAGGAAUUCCUGCUUCU	1973-1995	
AD-1727980	GCAGGAAUUCCUGAAUUUUAU	1977-1997		AUAAAAUUCAGGAAUUCCUGCUU	1975-1997	
AD-1727981	CAGGAAUUCCUGAAUUUUAUU	1978-1998		AAUAAAAUUCAGGAAUUCCUGCU	1976-1998	
AD-1727984	GAAUUCCUGAAUUUUAUGACU	1981-2001		AGUCAUAAAAUUCAGGAAUUCCU	1979-2001	
AD-1727985	AAUUCCUGAAUUUUAUGACUU	1982-2002		AAGUCAUAAAAUUCAGGAAUUCC	1980-2002	
AD-1727986	AUUCCUGAAUUUUAUGACUAU	1983-2003		AUAGUCAUAAAAUUCAGGAAUUC	1981-2003	
AD-1727987	UUCCUGAAUUUUAUGACUAUU	1984-2004		AAUAGUCAUAAAAUUCAGGAAUU	1982-2004	
AD-1727989	CCUGAAUUUUAUGACUAUGAU	1986-2006		AUCAUAGUCAUAAAAUUCAGGAA	1984-2006	
AD-1727990	CUGAAUUUUAUGACUAUGACU	1987-2007		AGUCAUAGUCAUAAAAUUCAGGA	1985-2007	
AD-1727992	GAAUUUUAUGACUAUGACGUU	1989-2009		AACGUCAUAGUCAUAAAAUUCAG	1987-2009	
AD-1727993	AAUUUUAUGACUAUGACGUUU	1990-2010		AAACGUCAUAGUCAUAAAAUUCA	1988-2010	
AD-1727994	AUUUUAUGACUAUGACGUUGU	1991-2011		ACAACGUCAUAGUCAUAAAAUUC	1989-2011	
AD-1727996	UUUAUGACUAUGACGUUGCCU	1993-2013		AGGCAACGUCAUAGUCAUAAAAU	1991-2013	
AD-1727999	AUGACUAUGACGUUGCCCUGU	1996-2016		ACAGGGCAACGUCAUAGUCAUAA	1994-2016	
AD-1728049	CAGACUAUCAGGCCCAUUUGU	2046-2066		ACAAAUGGGCCUGAUAGUCUGGC	2044-2066	
AD-1728050	AGACUAUCAGGCCCAUUUGUU	2047-2067		AACAAAUGGGCCUGAUAGUCUGG	2045-2067	
AD-1728061	CGAGGGAACAACUCGAGCUUU	2078-2098		AAAGCUCGAGUUGUUCCCUCGGU	2076-2098	
AD-1728062	GAGGGAACAACUCGAGCUUUU	2079-2099		AAAAGCUCGAGUUGUUCCCUCGG	2077-2099	
AD-1728067	AACAACUCGAGCUUUGAGGCU	2084-2104		AGCCUCAAAGCUCGAGUUGUUCC	2082-2104	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1728085	GCUUCCUCCCAACUACCACUUU	2102-2122		AAAGUGGUAGUUGGGAGGAAGCCU	2100-2122	
AD-1728132	CUGCACAGGAUAUCAAAGCUU	2149-2169		AAGCUUUGAUAUCCUGUGCAGGG	2147-2169	
AD-1728137	CAGGAUAUCAAAGCUCUGUUU	2154-2174		AAACAGAGCUUUGAUAUCCUGUG	2152-2174	
AD-1728140	GAUAUCAAAGCUCUGUUUGUU	2157-2177		AACAAACAGAGCUUUGAUAUCCU	2155-2177	
AD-1728146	AAAGCUCUGUUUGUGUCUGAU	2163-2183		AUCAGACACAAACAGAGCUUUGA	2161-2183	
AD-1728195	AAGAAAGGCAGCUGUGAGAGU	2232-2252		ACUCUCACAGCUGCCUUUCUUAU	2230-2252	
AD-1728204	AGCUGUGAGAGAGAUGCUCAU	2241-2261		AUGAGCAUCUCUCUCACAGCUGC	2239-2261	
AD-1728206	CUGUGAGAGAGAUGCUCAAUU	2243-2263		AAUUGAGCAUCUCUCUCACAGCU	2241-2263	
AD-1728207	UGUGAGAGAGAUGCUCAAUAU	2244-2264		AUAUUGAGCAUCUCUCUCACAGC	2242-2264	
AD-1728208	GUGAGAGAGAUGCUCAAUAUU	2245-2265		AAUAUUGAGCAUCUCUCUCACAG	2243-2265	
AD-1728209	UGAGAGAGAUGCUCAAUAUGU	2246-2266		ACAUAUUGAGCAUCUCUCUCACA	2244-2266	
AD-1728210	GAGAGAGAUGCUCAAUAUGCU	2247-2267		AGCAUAUUGAGCAUCUCUCUCAC	2245-2267	
AD-1728212	CAGGCUAUGACAAAGUCAAGU	2269-2289		ACUUGACUUUGUCAUAGCCUGGG	2267-2289	
AD-1728214	GGCUAUGACAAAGUCAAGGAU	2271-2291		AUCCUUGACUUUGUCAUAGCCUG	2269-2291	
AD-1728220	GACAAAGUCAAGGACAUCUCU	2277-2297		AGAGAUGUCCUUGACUUUGUCAU	2275-2297	
AD-1728244	UUGUACUGGAGGAGUGAGUCU	2321-2341		AGACUCACUCCUCCAGUACAAAG	2319-2341	
AD-1728258	AAUACUUGCAGAGGUGAUUCU	2355-2375		AGAAUCACCUCUGCAAGUAUUGG	2353-2375	
AD-1728260	UACUUGCAGAGGUGAUUCUGU	2357-2377		ACAGAAUCACCUCUGCAAGUAUU	2355-2377	
AD-1728269	UGAUAGUUCACAAGAGAAGUU	2386-2406		AACUUCUCUUGUGAACUAUCAAG	2384-2406	
AD-1728270	GAUAGUUCACAAGAGAAGUCU	2387-2407		AGACUUCUCUUGUGAACUAUCAA	2385-2407	
AD-1728271	AUAGUUCACAAGAGAAGUCGU	2388-2408		ACGACUUCUCUUGUGAACUAUCA	2386-2408	
AD-1728272	UAGUUCACAAGAGAAGUCGUU	2389-2409		AACGACUUCUCUUGUGAACUAUC	2387-2409	
AD-1728273	AGUUCACAAGAGAAGUCGUUU	2390-2410		AAACGACUUCUCUUGUGAACUAU	2388-2410	
AD-1728274	GUUCACAAGAGAAGUCGUUUU	2391-2411		AAAACGACUUCUCUUGUGAACUA	2389-2411	
AD-1728275	UUCACAAGAGAAGUCGUUUCU	2392-2412		AGAAACGACUUCUCUUGUGAACU	2390-2412	
AD-1728276	UCACAAGAGAAGUCGUUUCAU	2393-2413		AUGAAACGACUUCUCUUGUGAAC	2391-2413	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1728277	CACAAGAGAAGUCGUUUCAUU	2394-2414		AAUGAAACGACUUCUCUUGUGAA	2392-2414	
AD-1728278	ACAAGAGAAGUCGUUUCAUUU	2395-2415		AAAUGAAACGACUUCUCUUGUGA	2393-2415	
AD-1728279	CAAGAGAAGUCGUUUCAUUCU	2396-2416		AGAAUGAAACGACUUCUCUUGUG	2394-2416	
AD-1728280	AAGAGAAGUCGUUUCAUUCAU	2397-2417		AUGAAUGAAACGACUUCUCUUGU	2395-2417	
AD-1728282	GAGAAGUCGUUUCAUUCAAGU	2399-2419		ACUUGAAUGAAACGACUUCUCUU	2397-2419	
AD-1728283	AGAAGUCGUUUCAUUCAAGUU	2400-2420		AACUUGAAUGAAACGACUUCUCU	2398-2420	
AD-1728284	GAAGUCGUUUCAUUCAAGUUU	2401-2421		AAACUUGAAUGAAACGACUUCUC	2399-2421	
AD-1728285	AAGUCGUUUCAUUCAAGUUGU	2402-2422		ACAACUUGAAUGAAACGACUUCU	2400-2422	
AD-1728286	AGUCGUUUCAUUCAAGUUGGU	2403-2423		ACCAACUUGAAUGAAACGACUUC	2401-2423	
AD-1728300	GAGUAGUGGAUGUCUGCAAAU	2437-2457		AUUUGCAGACAUCCACUACUCCC	2435-2457	
AD-1728301	AGUAGUGGAUGUCUGCAAAAU	2438-2458		AUUUUGCAGACAUCCACUACUCC	2436-2458	
AD-1728302	GUAGUGGAUGUCUGCAAAAAU	2439-2459		AUUUUUGCAGACAUCCACUACUC	2437-2459	
AD-1728303	UAGUGGAUGUCUGCAAAAACU	2440-2460		AGUUUUUGCAGACAUCCACUACU	2438-2460	
AD-1728307	GGAUGUCUGCAAAAACCAGAU	2444-2464		AUCUGGUUUUUGCAGACAUCCAC	2442-2464	
AD-1728308	GAUGUCUGCAAAAACCAGAAU	2445-2465		AUUCUGGUUUUUGCAGACAUCCA	2443-2465	
AD-1728311	GUCUGCAAAAACCAGAAGCGU	2448-2468		ACGCUUCUGGUUUUUGCAGACAU	2446-2468	
AD-1728312	UCUGCAAAAACCAGAAGCGGU	2449-2469		ACCGCUUCUGGUUUUUGCAGACA	2447-2469	
AD-1728317	AAAAACCAGAAGCGGCAAAAU	2454-2474		AUUUUGCCGCUUCUGGUUUUUGC	2452-2474	
AD-1728318	AAAACCAGAAGCGGCAAAAGU	2455-2475		ACUUUUGCCGCUUCUGGUUUUUG	2453-2475	
AD-1728320	AACCAGAAGCGGCAAAAGCAU	2457-2477		AUGCUUUUGCCGCUUCUGGUUUU	2455-2477	
AD-1728324	AGAAGCGGCAAAAGCAGGUAU	2461-2481		AUACCUGCUUUUGCCGCUUCUGG	2459-2481	
AD-1728405	AACUCCAAGAUGAGGAUUUGU	2542-2562		ACAAAUCCUCAUCUUGGAGUUUC	2540-2562	
AD-1728408	UCCAAGAUGAGGAUUUGGGUU	2545-2565		AACCCAAAUCCUCAUCUUGGAGU	2543-2565	
AD-1728410	CAAGAUGAGGAUUUGGGUUUU	2547-2567		AAACCCAAAUCCUCAUCUUGGA	2545-2567	
AD-1728412	AGAUGAGGAUUUGGGUUUUCU	2549-2569		AGAAAACCCAAAUCCUCAUCUUG	2547-2569	
AD-1728422	GUGGGAUUGAAUUAAAAACAGU	2597-2617		ACUGUUUUAAUUCAAUCCCACGC	2595-2617	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1728423	UGGGAUUGAAUUAAAACAGCU	2598-2618		AGCUGUUUUAAUUCAAUCCCACG	2596-2618	
AD-1728424	GGGAUUGAAUUAAAACAGCUU	2599-2619		AAGCUGUUUUAAUUCAAUCCCAC	2597-2619	
AD-1728427	AUUGAAUUAAAACAGCUGCGU	2602-2622		ACGCAGCUGUUUUAAUUCAAUCC	2600-2622	
AD-1728447	AAGGGAAUGUGACCAGGUCUU	155-175		AAGACCUGGUCACAUUCCCUUCC	153-175	
AD-1728461	AGGUCUAGGUCUGGAGUUUCU	169-189		AGAAACTCCAGACCUAGACCUGG	167-189	
AD-1728470	UCUGGAGUUUCAGCUUGGACU	178-198		AGUCCAAGCUGAAACUCCAGACC	176-198	
AD-1728471	CUGGAGUUUCAGCUUGGACAU	179-199		AUGUCCAAGCUGAAACUCCAGAC	177-199	
AD-1728659	UCCUUCUGGCUUCUACCCGUU	464-484		AACGGGTAGAAGCCAGAAGGACA	462-484	
AD-1728664	CUGGCUUCUACCCGUACCCUU	469-489		AAGGGUACGGGUAGAAGCCAGAA	467-489	
AD-1728671	CUACCCGUACCCUGUGCAGAU	476-496		AUCUGCACAGGGUACGGGUAGAA	474-496	
AD-1728685	UGCAGACACGUACCUGCAGAU	490-510		AUCUGCAGGUACGUGUCUGCACA	488-510	
AD-1728736	AAGGCAGAGUGCAGAGCAAUU	561-581		AAUUGCTCUGCACUCUGCCUUCC	559-581	
AD-1728777	CCUACUACAAUGUGAGUGAUU	634-654		AAUCACTCACAUUGUAGUAGGGA	632-654	
AD-1728784	CAAUGUGAGUGAUGAGAUCUU	641-661		AAGATCTCAUCACUCACAUUGUA	639-661	
AD-1728786	AUGUGAGUGAUGAGAUCUCUU	643-663		AAGAGATCUCAUCACUCACAUUG	641-663	
AD-1728787	UGUGAGUGAUGAGAUCUCUUU	644-664		AAAGAGAUCUCAUCACUCACAUU	642-664	
AD-1728789	UGAGUGAUGAGAUCUCUUUCU	646-666		AGAAAGAGAUCUCAUCACUCACA	644-666	
AD-1728793	UGAUGAGAUCUCUUUCCACUU	650-670		AAGUGGAAAGAGAUCUCAUCACU	648-670	
AD-1728801	UCUCUUUCCACUGCUAUGACU	658-678		AGUCAUAGCAGUGGAAAGAGAUC	656-678	
AD-1728802	CUCUUUCCACUGCUAUGACGU	659-679		ACGUCATAGCAGUGGAAAGAGAU	657-679	
AD-1728810	ACUGCUAUGACGGUUACACUU	667-687		AAGUGUAACCGUCAUAGCAGUGG	665-687	
AD-1728811	CUGCUAUGACGGUUACACUCU	668-688		AGAGTGTAACCGUCAUAGCAGUG	666-688	
AD-1728827	UCGCACCUGCCAAGUGAAUGU	704-724		ACAUTCACUUGGCAGGUGCGAUU	702-724	
AD-1728861	CAGACAGCGAUCUGUGACAAU	738-758		AUUGTCACAGAUCGCUGUCUGCC	736-758	
AD-1728863	GACAGCGAUCUGUGACAACGU	740-760		ACGUTGTCACAGAUCGCUGUCUG	738-760	
AD-1728877	UGGCACAAGGAAGGUGGGGCAU	794-814		AUGCCCACCUUCCUUGUGCCAAU	792-814	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1728909	UUGAAGACAGCGUCACCUACU	826-846		AGUAGGUGACGCUGUCUUCAAGG	824-846	
AD-1728990	AGACUCCUUCAUGUACGACAU	935-955		AUGUCGUACAUGAAGGAGUCUUG	933-955	
AD-1728995	CAAGAGGUGGCCGAAGCUUUU	960-980		AAAAGCUUCGGCCACCUCUUGAG	958-980	
AD-1729031	GAGACCAUAGAAGGAGUCGAU	996-1016		AUCGACUCCUUCUAUGGUCUCUG	994-1016	
AD-1729089	CAGGCUCCAUGAACAUCUACU	1075-1095		AGUAGAUGUUCAUGGAGCCUGAA	1073-1095	
AD-1729103	AUCUACCUGGUGCUAGAUGGU	1089-1109		ACCAUCUAGCACCAGGUAGAUGU	1087-1109	
AD-1729105	CUACCUGGUGCUAGAUGGAUU	1091-1111		AAUCCAUCUAGCACCAGGUAGAU	1089-1111	
AD-1729106	UACCUGGUGCUAGAUGGAUCU	1092-1112		AGAUCCAUCUAGCACCAGGUAGA	1090-1112	
AD-1729110	UGGUGCUAGAUGGAUCAGACU	1096-1116		AGUCUGAUCCAUCUAGCACCAGG	1094-1116	
AD-1729112	GUGCUAGAUGGAUCAGACAGU	1098-1118		ACUGUCUGAUCCAUCUAGCACCA	1096-1118	
AD-1729130	CACAGGAGCCAAAAAGUGUCU	1136-1156		AGACACUUUUUGGCUCCUGUGAA	1134-1156	
AD-1729132	CAGGAGCCAAAAAGUGUCUAU	1138-1158		AUAGACACUUUUUGGCUCCUGUG	1136-1158	
AD-1729134	GGAGCCAAAAAGUGUCUAGUU	1140-1160		AACUAGACACUUUUUGGCUCCUG	1138-1160	
AD-1729136	AGCCAAAAAGUGUCUAGUCAU	1142-1162		AUGACUAGACACUUUUUGGCUCC	1140-1162	
AD-1729137	GCCAAAAAGUGUCUAGUCAAU	1143-1163		AUUGACUAGACACUUUUUGGCUC	1141-1163	
AD-1729139	CAAAAAGUGUCUAGUCAACUU	1145-1165		AAGUUGACUAGACACUUUUUGGC	1143-1165	
AD-1729141	AAAAGUGUCUAGUCAACUUAU	1147-1167		AUAAGUUGACUAGACACUUUUUG	1145-1167	
AD-1729142	AAAGUGUCUAGUCAACUUAAU	1148-1168		AUUAAGUUGACUAGACACUUUUU	1146-1168	
AD-1729151	AGUCAACUUAAUUGAGAAGGU	1157-1177		ACCUUCUCAAUUAAGUUGACUAG	1155-1177	
AD-1729180	AUGGUGUGAAGCCAAGAUAUU	1186-1206		AAUAUCUUGGCUUCACACCAUAA	1184-1206	
AD-1729207	AAAAUUUGGGUCAAAGUGUCU	1233-1253		AGACACUUUGACCCAAAUUUUGG	1231-1253	
AD-1729242	UAAUGCAGACUGGGUCACGAU	1268-1288		AUCGUGACCCAGUCUGCAUUACU	1266-1288	
AD-1729269	AAUGAAAUCAAUUAUGAAGAU	1296-1316		AUCUUCAUAAUUGAUUUCAUUGA	1294-1316	
AD-1729271	UGAAAUCAAUUAUGAAGACCU	1298-1318		AGGUCUUCAUAAUUGAUUUCAUU	1296-1318	
AD-1729274	AAUCAAUUAUGAAGACCACAU	1301-1321		AUGUGGUCUUCAUAAUUGAUUUC	1299-1321	
AD-1729277	CAAUUAUGAAGACCACAAGUU	1304-1324		AACUUGUGGUCUUCAUAAUUGAU	1302-1324	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1729280	UUAUGAAGACCACAAGUUGAU	1307-1327		AUCAACTUGUGGUCUUCAUAAUU	1305-1327	
AD-1729285	AAGACCACAAGUUGAAGUCAU	1312-1332		AUGACUTCAACUUGUGGUCUUCA	1310-1332	
AD-1729288	ACCACAAGUUGAAGUCAGGGU	1315-1335		ACCCTGACUUCAACUUGUGGUCU	1313-1335	
AD-1729290	CACAAGUUGAAGUCAGGGACU	1317-1337		AGUCCCTGACUUCAACUUGUGGU	1315-1337	
AD-1729296	UUGAAGUCAGGGACUAACACU	1323-1343		AGUGTUAGUCCCUGACUUCAACU	1321-1343	
AD-1729297	UGAAGUCAGGGACUAACACCU	1324-1344		AGGUGUTAGUCCCUGACUUCAAC	1322-1344	
AD-1729300	AGUCAGGGACUAACACCAAGU	1327-1347		ACUUGGTGTUUAGUCCCUGACUUC	1325-1347	
AD-1729413	UGAUGGAUUGCACAACAUGGU	1442-1462		ACCATGTUGUGCAAUCCAUCAGU	1440-1462	
AD-1729461	UUGGCAAGGAUCGCAAAAACU	1510-1530		AGUUTUTGCGAUCCUUGCCAAUG	1508-1530	
AD-1729462	UGGCAAGGAUCGCAAAAACCU	1511-1531		AGGUTUTUGCGAUCCUUGCCAAU	1509-1531	
AD-1729463	GGCAAGGAUCGCAAAAACCCU	1512-1532		AGGGTUTUUGCGAUCCUUGCCAA	1510-1532	
AD-1729487	GAGGAUUAUCUGGAUGUCUAU	1536-1556		AUAGACAUCCAGAUAAUCCUCCC	1534-1556	
AD-1729514	CCAAGUGAACAUCAAUGCUUU	1583-1603		AAAGCATUGAUGUUCACUUGGUU	1581-1603	
AD-1729515	CAAGUGAACAUCAAUGCUUUU	1584-1604		AAAAGCAUUGAUGUUCACUUGGU	1582-1604	
AD-1729524	AUCAAUGCUUUGGCUUCCAAU	1593-1613		AUUGGAAGCCAAAGCAUUGAUGU	1591-1613	
AD-1729525	UCAAUGCUUUGGCUUCCAAGU	1594-1614		ACUUGGAAGCCAAAGCAUUGAUG	1592-1614	
AD-1729538	UUCCAAGAAAGACAAUGAGCU	1607-1627		AGCUCATUGUCUUUCUUGGAAGC	1605-1627	
AD-1729539	UCCAAGAAAGACAAUGAGCAU	1608-1628		AUGCTCAUUGUCUUUCUUGGAAG	1606-1628	
AD-1729541	CAAGAAAGACAAUGAGCAACU	1610-1630		AGUUGCTCAUUGUCUUUCUUGGA	1608-1630	
AD-1729545	AAAGACAAUGAGCAACAUGUU	1614-1634		AACATGTUGCUCAUUGUCUUUCU	1612-1634	
AD-1729548	GACAAUGAGCAACAUGUGUUU	1617-1637		AAACACAUGUUGCUCAUUGUCUU	1615-1637	
AD-1729550	CAAUGAGCAACAUGUGUUCAU	1619-1639		AUGAACACAUGUUGCUCAUUGUC	1617-1639	
AD-1729552	AUGAGCAACAUGUGUUCAAAU	1621-1641		AUUUGAACACAUGUUGCUCAUUG	1619-1641	
AD-1729555	AGCAACAUGUGUUCAAAGUCU	1624-1644		AGACTUTGAACACAUGUUGCUCA	1622-1644	
AD-1729557	CAACAUGUGUUCAAAGUCAAU	1626-1646		AUUGACTUUGAACACAUGUUGCU	1624-1646	
AD-1729559	ACAUGUGUUCAAAGUCAAGGU	1628-1648		ACCUTGACUUUGAACACAUGUUG	1626-1648	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1729561	AUGUGUUCAAAGUCAAGGAUU	1630-1650		AAUCCUUGACUUUGAACACAUGU	1628-1650	
AD-1729562	UGUGUUCAAAGUCAAGGAUAU	1631-1651		AUAUCCUUGACUUUGAACACAUG	1629-1651	
AD-1729567	UCAAAGUCAAGGAUAUGGAAU	1636-1656		AUUCCAUAUCCUUGACUUUGAAC	1634-1656	
AD-1729568	CAAAGUCAAGGAUAUGGAAAU	1637-1657		AUUUCCAUAUCCUUGACUUUGAA	1635-1657	
AD-1729619	UGAAAGCCAGUCUCUGAGUCU	1688-1708		AGACUCAGAGACUGGCUUUCAUC	1686-1708	
AD-1729643	UGGCAUGGUUUGGGAACACAU	1712-1732		AUGUGUUCCCAAACCAUGCCACA	1710-1732	
AD-1729667	GGGUACCGAUUACCACACAAGCU	1736-1756		AGCUUGUGGUAAUCGGUACCCUU	1734-1756	
AD-1729670	UACCGAUUACCACACAAGCAACU	1739-1759		AGUUGCUUGUGGUAAUCGGUACC	1737-1759	
AD-1729673	CGAUUACCACACAAGCAACCAUU	1742-1762		AAUGGUUGCUUGUGGUAAUCGGU	1740-1762	
AD-1729677	UACCACACAAGCAACCAUGGCAU	1746-1766		AUGCCAUGGUUGCUUGUGGUAAU	1744-1766	
AD-1729688	ACCAUGGCAGGCCAAGAUCUU	1757-1777		AAGATCUUGGCCUGCCAUGGUUG	1755-1777	
AD-1729690	CAUGGCAGGCCAAGAUCUCAU	1759-1779		AUGAGATCUUGGCCUGCCAUGGU	1757-1779	
AD-1729729	CUGUGGUGUCUGAGUACUUUU	1819-1839		AAAAGUACUCAGACACCACAGCC	1817-1839	
AD-1729802	AGCGGGACCUGGAGAUAGAAU	1912-1932		AUUCTATCUCCAGGUCCCGCUUC	1910-1932	
AD-1729841	GAAGCAGGAAUUCCUGAAUUU	1974-1994		AAAUTCAGGAAUUCCUGCUUCUU	1972-1994	
AD-1729849	AAUUCCUGAAUUUUAUGACUU	1982-2002		AAGUCATAAAAUUCAGGAAUUCC	1980-2002	
AD-1729850	AUUCCUGAAUUUUAUGACUAU	1983-2003		AUAGTCAUAAAAUUCAGGAAUUC	1981-2003	
AD-1729852	UCCUGAAUUUUAUGACUAUGU	1985-2005		ACAUAGTCAUAAAAUUCAGGAAU	1983-2005	
AD-1729854	CUGAAUUUUAUGACUAUGACU	1987-2007		AGUCAUAGUCAUAAAAUUCAGGA	1985-2007	
AD-1729856	GAAUUUUAUGACUAUGACGUU	1989-2009		AACGTCAUAGUCAUAAAAUUCAG	1987-2009	
AD-1729861	UUAUGACUAUGACGUUGCCCU	1994-2014		AGGGCAACGUCAUAGUCAUAAAA	1992-2014	
AD-1729862	UAUGACUAUGACGUUGCCCUU	1995-2015		AAGGGCAACGUCAUAGUCAUAAA	1993-2015	
AD-1729869	AUGACGUUGCCCUGAUCAAGU	2002-2022		ACUUGATCAGGGCAACGUCAUAG	2000-2022	
AD-1729870	UGACGUUGCCCUGAUCAAGCU	2003-2023		AGCUTGAUCAGGGCAACGUCAUA	2001-2023	
AD-1729872	ACGUUGCCCUGAUCAAGCUCU	2005-2025		AGAGCUTGAUCAGGGCAACGUCA	2003-2025	
AD-1729926	GAGGGAACAACUCGAGCUUUU	2079-2099		AAAAGCTCGAGUUGUUCCCUCGG	2077-2099	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1729933	CAACUCGAGCUUUGAGGCUUU	2086-2106		AAAGCCTCAAAGCUCGAGUUGUU	2084-2106	
AD-1729941	GCUUUGAGGCUUCCUCCAACU	2094-2114		AGUUGGAGGAAGCCUCAAAGCUC	2092-2114	
AD-1729947	AGGCUUCCUCCAACUACCACU	2100-2120		AGUGGUAGUUGGAGGAAGCCUCA	2098-2120	
AD-1729951	UUCCUCCAACUACCACUUGCU	2104-2124		AGCAAGTGGUAGUUGGAGGAAGC	2102-2124	
AD-1729992	CUCCCUGCACAGGAUAUCAAU	2145-2165		AUUGAUAUCCUGUGCAGGGAGCA	2143-2165	
AD-1729993	UCCCUGCACAGGAUAUCAAAU	2146-2166		AUUUGATAUCCUGUGCAGGGAGC	2144-2166	
AD-1729994	CCCUGCACAGGAUAUCAAAGU	2147-2167		ACUUTGAUAUCCUGUGCAGGGAG	2145-2167	
AD-1729996	CUGCACAGGAUAUCAAAGCUU	2149-2169		AAGCTUTGAUAUCCUGUGCAGGG	2147-2169	
AD-1730001	CAGGAUAUCAAAGCUCUGUUU	2154-2174		AAACAGAGCUUUGAUAUCCUGUG	2152-2174	
AD-1730042	GCUGACUCGGAAGGAGGUCUU	2195-2215		AAGACCTCCUUCCGAGUCAGCUU	2193-2215	
AD-1730048	UCGGAAGGAGGUCUACAUCAU	2201-2221		AUGATGTAGACCUCCUUCCGAGU	2199-2221	
AD-1730053	AGGAGGUCUACAUCAAGAAUU	2206-2226		AAUUCUTGAUGUAGACCUCCUUC	2204-2226	
AD-1730059	AAGAAAGGCAGCUGUGAGAGU	2232-2252		ACUCTCACAGCUGCCUUUCUUAU	2230-2252	
AD-1730068	AGCUGUGAGAGAGAUGCUCAU	2241-2261		AUGAGCAUCUCUCUCACAGCUGC	2239-2261	
AD-1730071	UGUGAGAGAGAUGCUCAAUAU	2244-2264		AUAUTGAGCAUCUCUCUCACAGC	2242-2264	
AD-1730077	AGGCUAUGACAAAGUCAAGGU	2270-2290		ACCUTGACUUUGUCAUAGCCUGG	2268-2290	
AD-1730103	UUCCUUUGUACUGGAGGAGUU	2316-2336		AACUCCTCCAGUACAAAGGAACC	2314-2336	
AD-1730108	UUGUACUGGAGGAGUGAGUCU	2321-2341		AGACTCACUCCUCCAGUACAAAG	2319-2341	
AD-1730110	GUACUGGAGGAGUGAGUCCCU	2323-2343		AGGGACTCACUCCUCCAGUACAA	2321-2343	
AD-1730112	ACUGGAGGAGUGAGUCCCUAU	2325-2345		AUAGGGACUCACUCCUCCAGUAC	2323-2345	
AD-1730118	GGAGUGAGUCCCUAUGCUGAU	2331-2351		AUCAGCAUAGGGACUCACUCCUC	2329-2351	
AD-1730122	AAUACUUGCAGAGGUGAUUCU	2355-2375		AGAATCACCUCUGCAAGUAUUGG	2353-2375	
AD-1730133	UGAUAGUUCACAAGAGAAGUU	2386-2406		AACUTCTCUUGUGAACUAUCAAG	2384-2406	
AD-1730143	CAAGAGAAGUCGUUUCAUUCU	2396-2416		AGAATGAAACGACUUCUCUUGUG	2394-2416	
AD-1730164	GAGUAGUGGAUGUCUGCAAAU	2437-2457		AUUUGCAGACAUCCACUACUCCC	2435-2457	
AD-1730167	UAGUGGAUGUCUGCAAAAACU	2440-2460		AGUUTUTGCAGACAUCCACUACU	2438-2460	

Duplex Name	Sense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	Range in NM_001710.6	SEQ ID NO:
AD-1730168	AGUGGAUGUCUGCAAAAACCU	2441-2461		AGGUTUTUGCAGACAUCCACUAC	2439-2461	
AD-1730169	GUGGAUGUCUGCAAAAACCAU	2442-2462		AUGGTUTUUGCAGACAUCCACUA	2440-2462	
AD-1730171	GGAUGUCUGCAAAAACCAGAU	2444-2464		AUCUGGTUUUUGCAGACAUCCAC	2442-2464	
AD-1730183	AAACCAGAAGCGGCAAAAGCU	2456-2476		AGCUTUTGCCGCUUCUGGUUUUU	2454-2476	
AD-1730184	AACCAGAAGCGGCAAAAGCAU	2457-2477		AUGCTUTUGCCGCUUCUGGUUUU	2455-2477	
AD-1730256	UGGCUGAAGGAGAAACUCCAU	2529-2549		AUGGAGTUUCUCCUUCAGCCAGG	2527-2549	
AD-1730287	UGGGAUUGAAUUAAAACAGCU	2598-2618		AGCUGUTUUAAUUCAAUCCCACG	2596-2618	
AD-1730288	GGGAUUGAAUUAAAACAGCUU	2599-2619		AAGCTGTUUUAAUUCAAUCCCAC	2597-2619	
AD-1730293	UGAAUUAAAACAGCUGCGACU	2604-2624		AGUCGCAGCUGUUUUAAUUCAAU	2602-2624	
AD-1730476	AAUUAAAACAGCUGCGACAAU	2455-2475		AUUGUCGCAGCUGUUUUAAUUCA	2453-2475	
AD-1730477	AAUUAAAACAGCUGCGACAAU	2455-2475		ATUGTCGCAGCTGUUUUAAUUCA	2453-2475	
AD-1730478	AUUAAAACAGCUGCGACAACU	2456-2476		AGUUGUCGCAGCUGUUUUAAUUC	2454-2476	

Table 3. Modified Sense and Antisense Strand Sequences of Complement Factor B dsRNA Agents

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1724362	asasgggaauGfUfGfaccaggucuuL96		asdAsgadCcdTggucdAcAfuucccuuscsc		GGAAGGGAAUGUGACCAGGUCUA	
AD-1724363	asgsggaaugUfGfAfccaggucuauL96		asdTsagdAcdCuggudCaCfauucccususc		GAAGGGAAUGUGACCAGGUCUAG	
AD-1724364	gsgsgaauguGfAfCfcaggucuaguL96		asdCsuadGadCcuggdTcAfcauucccsusu		AAGGGAAUGUGACCAGGUCUAGG	
AD-1724365	gsgsaaugugAfCfCfaggucuagguL96		asdCscudAgdAccugdGuCfacauucccscsu		AGGGAAUGUGACCAGGUCUAGGU	
AD-1724369	usgsugaccaGfGfUfcuaggucuguL96		asdCsagdAcdCuagadCcUfggucacasusu		AAUGUGACCAGGUCUAGGUCUGG	
AD-1724370	gsusgaccagGfUfCfuaggucugguL96		asdCscadGadCcuagdAcCfuggucacsasu		AUGUGACCAGGUCUAGGUCUGGA	
AD-1724376	asgsgucuagGfUfCfuggaguuucuL96		asdGsaadAcdTccagdAcCfuagaccusgsg		CCAGGUCUAGGUCUGGAGUUUCA	
AD-1724384	gsuscuggagUfUfUfcagcuuggauL96		asdTsccdAadGcugadAaCfuccagacscsu		AGGUCUGGAGUUUCAGCUUGGAC	
AD-1724385	uscsuggaguUfUfCfagcuuggacuL96		asdGsucdCadAgcugdAaAfcuccagascsc		GGUCUGGAGUUUCAGCUUGGACA	
AD-1724386	csusggaguuUfCfAfgcuuggacauL96		asdTsgudCcdAagcudGaAfacuccagsasc		GUCUGGAGUUUCAGCUUGGACAC	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1724530	uscscuuccgAfCfUfucuccaagauL96		asdTscudTgdGagaadGuCfggaaggasgsc		GCUCCUUCCGACUUCUCCAAGAG	
AD-1724572	usgsuccuucUfGfGfcuucuacccuL96		asdGsggdTadGaagcdCaGfaaggacascsa		UGUGUCCUUCUGGCUUCUACCCG	
AD-1724574	uscscuucugGfCfUfucuacccguuL96		asdAscgdGgdTagaadGcCfagaaggascsa		UGUCCUUCUGGCUUCUACCCGUA	
AD-1724575	cscsuucuggCfUfUfcuacccguauL96		asdTsacdGgdGuagadAgCfcagaaggsasc		GUCCUUCUGGCUUCUACCCGUAC	
AD-1724576	csusucuggcUfUfCfuacccguacuL96		asdGsuadCgdGguagdAaGfccagaagsgsa		UCCUUCUGGCUUCUACCCGUACC	
AD-1724579	csusggcuucUfAfCfccguacccuuL96		asdAsggdGudAcgggdTaGfaagccagsasa		UUCUGGCUUCUACCCGUACCCUG	
AD-1724586	csusacccguAfCfCfcugugcagauL96		asdTscudGcdAcaggdGuAfcggguagsasa		UUCUACCCGUACCCUGUGCAGAC	
AD-1724600	usgscagacaCfGfUfaccugcagauL96		asdTscudGcdAgguadCgUfgucugcascsa		UGUGCAGACACGUACCUGCAGAU	
AD-1724651	asasggcagaGfUfGfcagagcaauuL96		asdAsuudGcdTcugcdAcUfcugccuuscsc		GGAAGGCAGAGUGCAGAGCAAUC	
AD-1724653	gsgscagaguGfCfAfgagcaauccuL96		asdGsgadTudGcucudGcAfcucugccsusu		AAGGCAGAGUGCAGAGCAAUCCA	
AD-1724685	csgsgucuccCfUfAfcuacaauguuL96		asdAscadTudGuagudAgGfgagaccgsgsg		CCCGGUCUCCCUACUACAAUGUG	
AD-1724691	cscscuacuaCfAfAfugugagugauL96		asdTscadCudCacaudTgUfaguagggsasg		CUCCCUACUACAAUGUGAGUGAU	
AD-1724692	cscsuacuacAfAfUfgugagugauuL96		asdAsucdAcdTcacadTuGfuaguaggsgsa		UCCCUACUACAAUGUGAGUGAUG	
AD-1724693	csusacuacaAfUfGfugagugauguL96		asdCsaudCadCucacdAuUfguaguagsgsg		CCCUACUACAAUGUGAGUGAUGA	
AD-1724695	ascsuacaauGfUfGfagugaugaguL96		asdCsucdAudCacucdAcAfuuguagusasg		CUACUACAAUGUGAGUGAUGAGA	
AD-1724698	ascsaaugugAfGfUfgaugagaucuL96		asdGsaudCudCaucadCuCfacauugusasg		CUACAAUGUGAGUGAUGAGAUCU	
AD-1724699	csasaugugaGfUfGfaugagaucuuL96		asdAsgadTcdTcaucdAcUfcacauugsusa		UACAAUGUGAGUGAUGAGAUCUC	
AD-1724700	asasugugagUfGfAfugagaucucuL96		asdGsagdAudCucaudCaCfucacauusgsu		ACAAUGUGAGUGAUGAGAUCUCU	
AD-1724701	asusgugaguGfAfUfgagaucucuuL96		asdAsgadGadTcucadTcAfcucacaususg		CAAUGUGAGUGAUGAGAUCUCUU	
AD-1724702	usgsugagugAfUfGfagaucucuuuL96		asdAsagdAgdAucucdAuCfacucacasusu		AAUGUGAGUGAUGAGAUCUCUUU	
AD-1724703	gsusgagugaUfGfAfgaucucuuuuL96		asdAsaadGadGaucudCaUfcacucacsasu		AUGUGAGUGAUGAGAUCUCUUUC	
AD-1724704	usgsagugauGfAfGfaucucuuucuL96		asdGsaadAgdAgaucdTcAfucacucascsa		UGUGAGUGAUGAGAUCUCUUUCC	
AD-1724705	gsasgugaugAfGfAfucucuuuccuL96		asdGsgadAadGagaudCuCfaucacucsasc		GUGAGUGAUGAGAUCUCUUUCCA	
AD-1724706	asgsugaugaGfAfUfcucuuuccauL96		asdTsggdAadAgagadTcUfcaucacuscsa		UGAGUGAUGAGAUCUCUUUCCAC	
AD-1724707	gsusgaugagAfUfCfucuuuccacuL96		asdGsugdGadAagagdAuCfucaucacsusc		GAGUGAUGAGAUCUCUUUCCACU	
AD-1724708	usgsaugagaUfCfUfcuuuccacuuL96		asdAsgudGgdAaagadGaUfcucaucascsu		AGUGAUGAGAUCUCUUUCCACUG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1724714	gsasucucuuUfCfCfacugcuauguL96		asdCsaudAgdCagugdGaAfagagaucsusc		GAGAUCUCUUUCCACUGCUAUGA	
AD-1724715	asuscucuuuCfCfAfcugcuaugauL96		asdTscadTadGcagudGgAfaagagauscsu		AGAUCUCUUUCCACUGCUAUGAC	
AD-1724716	uscsucuuucCfAfCfugcuaugacuL96		asdGsucdAudAgcagdTgGfaaagagasusc		GAUCUCUUUCCACUGCUAUGACG	
AD-1724717	csuscuuuccAfCfUfgcuaugacguL96		asdCsgudCadTagcadGuGfgaaagagsasu		AUCUCUUUCCACUGCUAUGACGG	
AD-1724718	uscsuuuccaCfUfGfcuaugacgguL96		asdCscgdTcdAuagcdAgUfggaaagasgsa		UCUCUUUCCACUGCUAUGACGGU	
AD-1724725	ascsugcuauGfAfCfgguuacacuuL96		asdAsgudGudAaccgdTcAfuagcagusgsg		CCACUGCUAUGACGGUUACACUC	
AD-1724726	csusgcuaugAfCfGfguuacacucuL96		asdGsagdTgdTaaccdGuCfauagcagsusg		CACUGCUAUGACGGUUACACUCU	
AD-1724730	usasugacggUfUfAfcacucuccguL96		asdCsggdAgdAgugudAaCfcgucauasgsc		GCUAUGACGGUUACACUCUCCGG	
AD-1724731	asusgacgguUfAfCfacucuccgguL96		asdCscgdGadGagugdTaAfccgucausasg		CUAUGACGGUUACACUCUCCGGG	
AD-1724741	asuscgcaccUfGfCfcaagugaauuL96		asdAsuudCadCuuggdCaGfgugcgaususg		CAAUCGCACCUGCCAAGUGAAUG	
AD-1724742	uscsgcaccuGfCfCfaagugaauguL96		asdCsaudTcdAcuugdGcAfggugcgasusu		AAUCGCACCUGCCAAGUGAAUGG	
AD-1724743	csgscaccugCfCfAfagugaaugguL96		asdCscadTudCacuudGgCfaggugcgsasu		AUCGCACCUGCCAAGUGAAUGGC	
AD-1724776	csasgacagcGfAfUfcugugacaauL96		asdTsugdTcdAcagadTcGfcugucugscsc		GGCAGACAGCGAUCUGUGACAAC	
AD-1724777	asgsacagcgAfUfCfugugacaacuL96		asdGsuudGudCacagdAuCfgcugucusgsc		GCAGACAGCGAUCUGUGACAACG	
AD-1724778	gsascagcgaUfCfUfgugacaacguL96		asdCsgudTgdTcacadGaUfcgcugucsusg		CAGACAGCGAUCUGUGACAACGG	
AD-1724779	ascsagcgauCfUfGfugacaacgguL96		asdCscgdTudGucacdAgAfucgcuguscsu		AGACAGCGAUCUGUGACAACGGA	
AD-1724780	csasgcgaucUfGfUfgacaacggauL96		asdTsccdGudTgucadCaGfaucgcugsusc		GACAGCGAUCUGUGACAACGGAG	
AD-1724781	asgscgaucuGfUfGfacaacggaguL96		asdCsucdCgdTugucdAcAfgaucgcusgsu		ACAGCGAUCUGUGACAACGGAGC	
AD-1724792	usgsgcacaaGfGfAfaggugggcauL96		asdTsgcdCcdAccuudCcUfugugccasasu		AUUGGCACAAGGAAGGUGGGCAG	
AD-1724819	cscsgccuugAfAfGfacagcgucauL96		asdTsgadCgdCugucdTuCfaaggcggsusa		UACCGCCUUGAAGACAGCGUCAC	
AD-1724823	csusugaagaCfAfGfcgucaccuauL96		asdTsagdGudGacgcdTgUfcuucaagsgsc		GCCUUGAAGACAGCGUCACCUAC	
AD-1724824	ususgaagacAfGfCfgucaccuacuL96		asdGsuadGgdTgacgdCuGfucuucaasgsg		CCUUGAAGACAGCGUCACCUACC	
AD-1724825	usgsaagacaGfCfGfucaccuaccuL96		asdGsgudAgdGugacdGcUfgucuucasasg		CUUGAAGACAGCGUCACCUACCA	
AD-1724860	gsusgucaggAfAfGfguggcucuuuL96		asdAsagdAgdCcaccdTuCfcugacacsgsu		ACGUGUCAGGAAGGUGGCUCUUG	
AD-1724894	cscsuuccugCfCfAfagacuccuuuL96		asdAsagdGadGucuudGgCfaggaaggscsu		AGCCUUCCUGCCAAGACUCCUUC	
AD-1724897	uscscugccaAfGfAfcuccuucauuL96		asdAsugdAadGgagudCuUfggcaggasasg		CUUCCUGCCAAGACUCCUUCAUG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1724899	csusgccaagAfCfUfccuucauguuL96		asdAscadTgdAaggadGuCfuuggcagsgsa		UCCUGCCAAGACUCCUUCAUGUA	
AD-1724900	usgsccaagaCfUfCfcuucauguauL96		asdTsacdAudGaaggdAgUfcuuggcasgsg		CCUGCCAAGACUCCUUCAUGUAC	
AD-1724903	csasagacucCfUfUfcauguacgauL96		asdTscgdTadCaugadAgGfagucuugsgsc		GCCAAGACUCCUUCAUGUACGAC	
AD-1724904	asasgacuccUfUfCfauguacgacuL96		asdGsucdGudAcaugdAaGfgagucuusgsg		CCAAGACUCCUUCAUGUACGACA	
AD-1724905	asgsacuccuUfCfAfuguacgacauL96		asdTsgudCgdTacaudGaAfggagucususg		CAAGACUCCUUCAUGUACGACAC	
AD-1724906	gsascuccuuCfAfUfguacgacacuL96		asdGsugdTcdGuacadTgAfaggagucsusu		AAGACUCCUUCAUGUACGACACC	
AD-1724910	csasagagguGfGfCfcgaagcuuuuL96		asdAsaadGcdTucggdCcAfccucuugsasg		CUCAAGAGGUGGCCGAAGCUUUC	
AD-1724919	gscscgaagcUfUfUfccugucuucuL96		asdGsaadGadCaggadAaGfcuucggcscsa		UGGCCGAAGCUUUCCUGUCUUCC	
AD-1724945	asgsagaccaUfAfGfaaggagucguL96		asdCsgadCudCcuucdTaUfggucucusgsu		ACAGAGACCAUAGAAGGAGUCGA	
AD-1724946	gsasgaccauAfGfAfaggagucgauL96		asdTscgdAcdTccuudCuAfuggucucsusg		CAGAGACCAUAGAAGGAGUCGAU	
AD-1724947	asgsaccauaGfAfAfggagucgauuL96		asdAsucdGadCuccudTcUfauggucuscsu		AGAGACCAUAGAAGGAGUCGAUG	
AD-1724948	gsasccauagAfAfGfgagucgauguL96		asdCsaudCgdAcuccdTuCfuauggucsusc		GAGACCAUAGAAGGAGUCGAUGC	
AD-1724949	ascscauagaAfGfGfagucgaugcuL96		asdGscadTcdGacucdCuUfcuauggucscsu		AGACCAUAGAAGGAGUCGAUGCU	
AD-1725000	cscsuucaggCfUfCfcaugaacauuL96		asdAsugdTudCauggdAgCfcugaaggsgsu		ACCCUUCAGGCUCCAUGAACAUC	
AD-1725003	uscsaggcucCfAfUfgaacaucuauL96		asdTsagdAudGuucadTgGfagccugasasg		CUUCAGGCUCCAUGAACAUCUAC	
AD-1725004	csasggcuccAfUfGfaacaucuacuL96		asdGsuadGadTguucdAuGfgagccugsasa		UUCAGGCUCCAUGAACAUCUACC	
AD-1725013	usgsaacaucUfAfCfcuggugcuauL96		asdTsagdCadCcaggdTaGfauguucasusg		CAUGAACAUCUACCUGGUGCUAG	
AD-1725015	asascaucuaCfCfUfggugcuagauL96		asdTscudAgdCaccadGgUfagauguuscsa		UGAACAUCUACCUGGUGCUAGAU	
AD-1725017	csasucuaccUfGfGfugcuagauguL96		asdCsaudCudAgcacdCaGfguagaugsusu		AACAUCUACCUGGUGCUAGAUGG	
AD-1725018	asuscuaccuGfGfUfgcuagaugguL96		asdCscadTcdTagcadCcAfgguagausgsu		ACAUCUACCUGGUGCUAGAUGGA	
AD-1725019	uscsuaccugGfUfGfcuagauggauL96		asdTsccdAudCuagcdAcCfagguagasusg		CAUCUACCUGGUGCUAGAUGGAU	
AD-1725020	csusaccuggUfGfCfuagauggauuL96		asdAsucdCadTcuagdCaCfcagguagsasu		AUCUACCUGGUGCUAGAUGGAUC	
AD-1725021	usasccugguGfCfUfagauggaucuL96		asdGsaudCcdAucuadGcAfccagguasgsa		UCUACCUGGUGCUAGAUGGAUCA	
AD-1725022	ascscuggugCfUfAfgauggaucauL96		asdTsgadTcdCaucudAgCfaccaggusasg		CUACCUGGUGCUAGAUGGAUCAG	
AD-1725023	cscsuggugcUfAfGfauggaucaguL96		asdCsugdAudCcaucdTaGfcaccaggsusa		UACCUGGUGCUAGAUGGAUCAGA	
AD-1725025	usgsgugcuaGfAfUfggaucagacuL96		asdGsucdTgdAuccadTcUfagccaccasgsg		CCUGGUGCUAGAUGGAUCAGACA	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1725027	gsusgcuagaUfGfGfaucagacaguL96		asdCsugdTcdTgaucdCaUfcuagcacscsa		UGGUGCUAGAUGGAUCAGACAGC	
AD-1725028	usgscuagauGfGfAfucagacagcuL96		asdGscudGudCugaudCcAfucuagcascsc		GGUGCUAGAUGGAUCAGACAGCA	
AD-1725033	gsasuggaucAfGfAfcagcauugguL96		asdCscadAudGcugudCuGfauccaucsusa		UAGAUGGAUCAGACAGCAUUGGG	
AD-1725039	csasacuucaCfAfGfgagccaaaauL96		asdTsuudTgdGcuccdTgUfgaaguugscsu		AGCAACUUCACAGGAGCCAAAAA	
AD-1725040	asascuucacAfGfGfagccaaaaauL96		asdTsuudTudGgcucdCuGfugaaguusgsc		GCAACUUCACAGGAGCCAAAAAG	
AD-1725041	ascsuucacaGfGfAfgccaaaaaguL96		asdCsuudTudTggcudCcUfgugaagususg		CAACUUCACAGGAGCCAAAAAGU	
AD-1725042	csusucacagGfAfGfccaaaaaguuL96		asdAscudTudTuggcdTcCfugugaagsusu		AACUUCACAGGAGCCAAAAAGUG	
AD-1725043	ususcacaggAfGfCfcaaaaaguguL96		asdCsacdTudTuuggdCuCfcugugaasgsu		ACUUCACAGGAGCCAAAAAGUGU	
AD-1725044	uscsacaggaGfCfCfaaaaaguguuL96		asdAscadCudTuuugdGcUfccugugasasg		CUUCACAGGAGCCAAAAAGUGUC	
AD-1725045	csascaggagCfCfAfaaaaagugucuL96		asdGsacdAcdTuuuudGgCfuccugugsasa		UUCACAGGAGCCAAAAAGUGUCU	
AD-1725046	ascsaggagcCfAfAfaaagugucuuL96		asdAsgadCadCuuuudTgGfcuccugusgsa		UCACAGGAGCCAAAAAGUGUCUA	
AD-1725047	csasggagccAfAfAfaagugucuauL96		asdTsagdAcdAcuuudTuGfgcuccugsusg		CACAGGAGCCAAAAAGUGUCUAG	
AD-1725048	asgsgagccaAfAfAfagugucuaguL96		asdCsuadGadCacuudTuUfggcuccusgsu		ACAGGAGCCAAAAAGUGUCUAGU	
AD-1725049	gsgsagccaaAfAfAfgugucuaguuL96		asdAscudAgdAcacudTuUfuggcuccsusg		CAGGAGCCAAAAAGUGUCUAGUC	
AD-1725050	gsasgccaaaAfAfGfugucuagucuL96		asdGsacdTadGacacdTuUfuuggcucscsu		AGGAGCCAAAAAGUGUCUAGUCA	
AD-1725051	asgsccaaaaAfGfUfgucuagucauL96		asdTsgadCudAgacadCuUfuuuggcuscsc		GGAGCCAAAAAGUGUCUAGUCAA	
AD-1725052	gscscaaaaaGfUfGfucuagucaauL96		asdTsugdAcdTagacdAcUfuuuuggcsusc		GAGCCAAAAAGUGUCUAGUCAAC	
AD-1725053	cscsaaaaagUfGfUfcuagucaacuL96		asdGsuudGadCuagadCaCfuuuuuggscsu		AGCCAAAAAGUGUCUAGUCAACU	
AD-1725054	csasaaaaguGfUfCfuagucaacuuL96		asdAsgudTgdAcuagdAcAfcuuuuugsgsc		GCCAAAAAGUGUCUAGUCAACUU	
AD-1725055	asasaaagugUfCfUfagucaacuuuL96		asdAsagdTudGacuadGaCfacuuuuusgsg		CCAAAAAGUGUCUAGUCAACUUA	
AD-1725056	asasaaguguCfUfAfgucaacuuauL96		asdTsaadGudTgacudAgAfcacuuuususg		CAAAAAGUGUCUAGUCAACUUAA	
AD-1725057	asasagugucUfAfGfucaacuuaauL96		asdTsuadAgdTugacdTaGfacacuuususu		AAAAAGUGUCUAGUCAACUUAAU	
AD-1725058	asasgugucuAfGfUfcaacuuaauuL96		asdAsuudAadGuugadCuAfgacacuususu		AAAAGUGUCUAGUCAACUUAAUU	
AD-1725059	asgsugucuaGfUfCfaacuuaauuuL96		asdAsaudTadAguugdAcUfagacacususu		AAAGUGUCUAGUCAACUUAAUUG	
AD-1725060	gsusgucuagUfCfAfacuuaauuguL96		asdCsaadTudAaguudGaCfuagacacsusu		AAGUGUCUAGUCAACUUAAUUGA	
AD-1725061	usgsucuaguCfAfAfcuuaauugauL96		asdTscadAudTaagudTgAfcuagacascsu		AGUGUCUAGUCAACUUAAUUGAG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1725062	gsuscuagucAfAfCfuuaauugaguL96		asdCsucdAadTuaagdTuGfacuagacsasc		GUGUCUAGUCAACUUAAUUGAGA	
AD-1725066	asgsucaacuUfAfAfuugagaaggguL96		asdCscudTcdTcaaudTaAfguugacusasg		CUAGUCAACUUAAUUGAGAAGGU	
AD-1725074	usasauuugagAfAfGfguggcaaguuL96		asdAscudTgdCcaccdTuCfucaauuasasg		CUUAAUUGAGAAGGUGGCAAGUU	
AD-1725075	asasuugagaAfGfGfuggcaaguuuL96		asdAsacdTudGccacdCuUfucaauusasa		UUAAUUGAGAAGGUGGCAAGUUA	
AD-1725079	gsasgaagguGfGfCfaaguuauggaL96		asdCscadTadAcuugdCcAfccuucucsasa		UUGAGAAGGUGGCAAGUUAUGGU	
AD-1725080	asgsaaggugGfCfAfaguuauggguuL96		asdAsccdAudAacuudGcCfaccuucuscsa		UGAGAAGGUGGCAAGUUAUGGUG	
AD-1725082	asasgguggcAfAfGfuuauggugguuL96		asdAscadCcdAuaacdTuGfccaccuuscsu		AGAAGGUGGCAAGUUAUGGUGUG	
AD-1725083	asgsguggcaAfGfUfuauggugugguL96		asdCsacdAcdCauaadCuUfgccaccuusuc		GAAGGUGGCAAGUUAUGGUGUGA	
AD-1725088	gscsaaguuaUfGfGfugugaagccuL96		asdGsgcdTudCacacdCaUfaacuugcscsa		UGGCAAGUUAUGGUGUGAAGCCA	
AD-1725092	gsusuaugguGfUfGfaagccaagauL96		asdTscudTgdGcuucdAcAfccauaacsusu		AAGUUAUGGUGUGAAGCCAAGAU	
AD-1725095	asusggugugAfAfGfccaagauaauuL96		asdAsuadTcdTuggcdTuCfacaccausasa		UUAUGGUGUGAAGCCAAGAUAUG	
AD-1725096	usgsgugugaAfGfCfcaagauaaguL96		asdCsaudAudCuuggdCuUfcacaccasusa		UAUGGUGUGAAGCCAAGAUAUGG	
AD-1725122	asasaauuugGfGfUfcaaagugucuL96		asdGsacdAcdTuugadCcCfaaauuuusgsg		CCAAAAUUUGGGUCAAAGUGUCU	
AD-1725123	asasauuuggGfUfCfaaagugucuuL96		asdAsgadCadCuuugdAcCfcaaauuususg		CAAAAUUUGGGUCAAAGUGUCUG	
AD-1725125	asusuuggguCfAfAfagugucugauL96		asdTscadGadCacuudTgAfcccaaaususu		AAAUUUGGGUCAAAGUGUCUGAA	
AD-1725156	gsusaaugcaGfAfCfuggucacguL96		asdCsgudGadCccagdTcUfgcauuacsusg		CAGUAAUGCAGACUGGGUCACGA	
AD-1725157	usasaugcagAfCfUfgggucacgauL96		asdTscgdTgdAcccadGuCfugcauuascsu		AGUAAUGCAGACUGGGUCACGAA	
AD-1725158	asasugcagaCfUfGfggucacgaauL96		asdTsucdGudGacccdAgUfcugcauusasc		GUAAUGCAGACUGGGUCACGAAG	
AD-1725159	asusgcagacUfGfGfgucacgaaguL96		asdCsuudCgdTgacccdCaGfucugcaususa		UAAUGCAGACUGGGUCACGAAGC	
AD-1725184	asasugaaauCfAfAfuuaugaagauL96		asdTscudTcdAuaaudTgAfuuucauusgsa		UCAAUGAAAUCAAUUAUGAAGAC	
AD-1725186	usgsaaaucaAfUfUfuagaagacccuL96		asdGsgudCudTcauadAuUfgauuucasusu		AAUGAAAUCAAUUAUGAAGACCA	
AD-1725189	asasucaauuAfUfGfaagaccacauL96		asdTsgudGgdTcuucdAuAfauugauususc		GAAAUCAAUUAUGAAGACCACAA	
AD-1725190	asuscaauuaUfGfAfagaccacaauL96		asdTsugdTgdGucuudCaUfaauugaususu		AAAUCAAUUAUGAAGACCACAAG	
AD-1725191	uscsaauuauGfAfAfgaccacaaguL96		asdCsuudGudGgucudTcAfuaauugasusu		AAUCAAUUAUGAAGACCACAAGU	
AD-1725192	csasauuaugAfAfGfaccacaaguuL96		asdAscudTgdTggucdTuCfauaauugsasu		AUCAAUUAUGAAGACCACAAGUU	
AD-1725193	asasuuaugaAfGfAfccacaaguuuL96		asdAsacdTudGuggudCuUfcauaauusgsa		UCAAUUAUGAAGACCACAAGUUG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1725194	asusuaugaaGfAfCfcacaaguuguL96		asdCsaadCudTguggdTcUfucauaaususg		CAAUUAUGAAGACCACAAGUUGA	
AD-1725195	ususaugaagAfCfCfacaaguugauL96		asdTscadAcdTugugdGuCfuucauaasusu		AAUUAUGAAGACCACAAGUUGAA	
AD-1725196	usasugaagaCfCfAfcaaguugaauL96		asdTsucdAadCuugudGgUfcuucauasasu		AUUAUGAAGACCACAAGUUGAAG	
AD-1725197	asusgaagacCfAfCfaaguugaaguL96		asdCsuudCadAcuugdTgGfucuucausasa		UUAUGAAGACCACAAGUUGAAGU	
AD-1725198	usgsaagaccAfCfAfaguugaaguuL96		asdAscudTcdAacuudGuGfgucuucasusa		UAUGAAGACCACAAGUUGAAGUC	
AD-1725199	gsasagaccaCfAfAfguugaagucuL96		asdGsacdTudCaacudTgUfggcuuucsasu		AUGAAGACCACAAGUUGAAGUCA	
AD-1725200	asasgaccacAfAfGfuugaagucauL96		asdTsgadCudTcaacdTuGfuggcuuuscsa		UGAAGACCACAAGUUGAAGUCAG	
AD-1725201	asgsaccacaAfGfUfugaagucaguL96		asdCsugdAcdTucaadCuUfguggcususc		GAAGACCACAAGUUGAAGUCAGG	
AD-1725203	ascscacaagUfUfGfaagucaggguL96		asdCsccdTgdAcuucdAaCfuuguggcscsu		AGACCACAAGUUGAAGUCAGGGA	
AD-1725204	cscsacaaguUfGfAfagucagggauL96		asdTsccdCudGacuudCaAfcuuguggsusc		GACCACAAGUUGAAGUCAGGGAC	
AD-1725205	csascaaguuGfAfAfgucagggacuL96		asdGsucdCcdTgacudTcAfacuugugsgsu		ACCACAAGUUGAAGUCAGGGACU	
AD-1725206	ascsaaguugAfAfGfucagggacuuL96		asdAsgudCcdCugacdTuCfaacuugusgsg		CCACAAGUUGAAGUCAGGGACUA	
AD-1725208	asasguugaaGfUfCfagggacuaauL96		asdTsuadGudCccugdAcUfucaacuusgsu		ACAAGUUGAAGUCAGGGACUAAC	
AD-1725211	ususgaagucAfGfGfgacuaacacuL96		asdGsugdTudAguccdCuGfacuucaascsu		AGUUGAAGUCAGGGACUAACACC	
AD-1725212	usgsaagucaGfGfGfacuaacaccuL96		asdGsgudGudTagucdCcUfgacuucasasc		GUUGAAGUCAGGGACUAACACCA	
AD-1725215	asgsucagggAfCfUfaacaccaaguL96		asdCsuudGgdTguuadGuCfccugacususc		GAAGUCAGGGACUAACACCAAGA	
AD-1725216	gsuscagggaCfUfAfacaccaagauL96		asdTscudTgdGuguudAgUfcccugacsusu		AAGUCAGGGACUAACACCAAGAA	
AD-1725243	cscsaggcagUfGfUfacagcaugauL96		asdTscadTgdCuguadCaCfugccuggsasg		CUCCAGGCAGUGUACAGCAUGAU	
AD-1725244	csasggcaguGfUfAfcagcaugauuL96		asdAsucdAudGcugudAcAfcugccugsgsa		UCCAGGCAGUGUACAGCAUGAUG	
AD-1725245	asgsgcagugUfAfCfagcaugauguL96		asdCsaudCadTgcugdTaCfacugccusgsg		CCAGGCAGUGUACAGCAUGAUGA	
AD-1725247	gscsaguguaCfAfGfcaugaugaguL96		asdCsucdAudCaugcdTgUfacacugcscsu		AGGCAGUGUACAGCAUGAUGAGC	
AD-1725327	csusgauggaUfUfGfcacaacauguL96		asdCsaudGudTgugcdAaUfccaucagsusc		GACUGAUGGAUUGCACAACAUGG	
AD-1725328	usgsauggauUfGfCfacaacaugguL96		asdCscadTgdTugugdCaAfuccaucasgsu		ACUGAUGGAUUGCACAACAUGGG	
AD-1725329	gsasuggauuGfCfAfcaacauggguL96		asdCsccdAudGuugudGcAfauccaucsasg		CUGAUGGAUUGCACAACAUGGGC	
AD-1725330	asusggauugCfAfCfaacaugggcuL96		asdGsccdCadTguugdTgCfaauccauscsa		UGAUGGAUUGCACAACAUGGGCG	
AD-1725331	usgsgauugcAfCfAfacaugggcguL96		asdCsgcdCcdAuguudGuGfcaauccasusc		GAUGGAUUGCACAACAUGGGCGG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1725332	gsgsauugcaCfAfAfcaugggcgguL96		asdCscgdCcdCaugudTgUfgcaauccsasu		AUGGAUUGCACAACAUGGGCGGG	
AD-1725333	gsascccaauUfAfCfugucauugauL96		asdTscadAudGacagdTaAfuugggucscsc		GGGACCCAAUUACUGUCAUUGAU	
AD-1725334	ascsccaauuAfCfUfgucauugauuL96		asdAsucdAadTgacadGuAfauugggcscsc		GGACCCAAUUACUGUCAUUGAUG	
AD-1725336	cscsaauuacUfGfUfcauugaugauL96		asdTscadTcdAaugadCaGfuaauuggsgsu		ACCCAAUUACUGUCAUUGAUGAG	
AD-1725344	usgsucauugAfUfGfagauccggguL96		asdCsccdGgdAucucdAuCfaaugacasgsu		ACUGUCAUUGAUGAGAUCCGGGA	
AD-1725345	gsuscauugaUfGfAfgauccgggauL96		asdTsccdCgdGaucudCaUfcaaugacsasg		CUGUCAUUGAUGAGAUCCGGGAC	
AD-1725347	csasuugaugAfGfAfuccgggacuuL96		asdAsgudCcdCggaudCuCfaucaaugsasc		GUCAUUGAUGAGAUCCGGGACUU	
AD-1725348	asusugaugaGfAfUfccgggacuuuL96		asdAsagdTcdCcggadTcUfcaucaausgsa		UCAUUGAUGAGAUCCGGGACUUG	
AD-1725376	ususggcaagGfAfUfcgcaaaaacuL96		asdGsuudTudTgcgadTcCfuugccaasusg		CAUUGGCAAGGAUCGCAAAAACC	
AD-1725377	usgsgcaaggAfUfCfgcaaaaaccuL96		asdGsgudTudTugcgdAuCfcuugccasasu		AUUGGCAAGGAUCGCAAAAACCC	
AD-1725378	gsgscaaggaUfCfGfcaaaaacccuL96		asdGsggdTudTuugcdGaUfccuugccsasa		UUGGCAAGGAUCGCAAAAACCCA	
AD-1725397	csasagggagGfAfUfuaucuggauuL96		asdAsucdCadGauaadTcCfucccuugsgsg		CCCAAGGGAGGAUUAUCUGGAUG	
AD-1725402	gsasggauuaUfCfUfggaugucuauL96		asdTsagdAcdAuccadGaUfaauccucscsc		GGGAGGAUUAUCUGGAUGUCUAU	
AD-1725403	asgsgauuauCfUfGfgaugucuauuL96		asdAsuadGadCauccdAgAfuaauccuscsc		GGAGGAUUAUCUGGAUGUCUAUG	
AD-1725404	gsgsauuaucUfGfGfaugucuauguL96		asdCsaudAgdAcaucdCaGfauaauccsusc		GAGGAUUAUCUGGAUGUCUAUGU	
AD-1725405	gsasuuaucuGfGfAfugucuauguuL96		asdAscadTadGacaudCcAfgauaaucscsu		AGGAUUAUCUGGAUGUCUAUGUG	
AD-1725406	asusuaucugGfAfUfgucuauguguL96		asdCsacdAudAgacadTcCfagauaauscsc		GGAUUAUCUGGAUGUCUAUGUGU	
AD-1725407	ususaucuggAfUfGfucuauguguuL96		asdAscadCadTagacdAuCfcagauaasusc		GAUUAUCUGGAUGUCUAUGUGUU	
AD-1725408	usasucuggaUfGfUfcuauguguuuL96		asdAsacdAcdAuagadCaUfccagauasasu		AUUAUCUGGAUGUCUAUGUGUUU	
AD-1725409	asuscuggauGfUfCfuauguguuuuL96		asdAsaadCadCauagdAcAfuccagausasa		UUAUCUGGAUGUCUAUGUGUUUG	
AD-1725410	uscsuggaugUfCfUfauguguuuguL96		asdCsaadAcdAcauadGaCfauccagasusa		UAUCUGGAUGUCUAUGUGUUUGG	
AD-1725411	csusggauguCfUfAfuguguuugguL96		asdCscadAadCacaudAgAfcauccagsasu		AUCUGGAUGUCUAUGUGUUUGGG	
AD-1725427	asasccaaguGfAfAfcaucaaugcuL96		asdGscadTudGaugudTcAfcuugguuscsa		UGAACCAAGUGAACAUCAAUGCU	
AD-1725428	ascscaagugAfAfCfaucaaugcuuL96		asdAsgcdAudTgaugdTuCfacuuggususc		GAACCAAGUGAACAUCAAUGCUU	
AD-1725429	cscsaagugaAfCfAfucaaugcuuuL96		asdAsagdCadTugaudGuUfcacuuggsusu		AACCAAGUGAACAUCAAUGCUUU	
AD-1725430	csasagugaaCfAfUfcaaugcuuuuL96		asdAsaadGcdAuugadTgUfucacuugsgsu		ACCAAGUGAACAUCAAUGCUUUG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1725439	asuscaaugcUfUfUfggcuuccaauL96		asdTsugdGadAgccadAaGfcauugausgsu		ACAUCAAUGCUUUGGCUUCCAAG	
AD-1725440	uscsaaugcuUfUfGfgcuuccaaguL96		asdCsuudGgdAagccdAaAfgcauugasusg		CAUCAAUGCUUUGGCUUCCAAGA	
AD-1725441	csasaugcuuUfGfGfcuuccaagauL96		asdTscudTgdGaagcdCaAfagcauugsasu		AUCAAUGCUUUGGCUUCCAAGAA	
AD-1725449	usgsgcuuccAfAfGfaaagacaauuL96		asdAsuudGudCuuucdTuGfgaagccasasa		UUUGGCUUCCAAGAAAGACAAUG	
AD-1725453	ususccaagaAfAfGfacaaugagcuL96		asdGscudCadTugucdTuUfcuuggaasgsc		GCUUCCAAGAAAGACAAUGAGCA	
AD-1725454	uscscaagaaAfGfAfcaaugagcauL96		asdTsgcdTcdAuugudCuUfucuuggasasg		CUUCCAAGAAAGACAAUGAGCAA	
AD-1725456	csasagaaagAfCfAfaugagcaacuL96		asdGsuudGcdTcauudGuCfuuucuugsgsa		UCCAAGAAAGACAAUGAGCAACA	
AD-1725457	asasgaaagaCfAfAfugagcaacauL96		asdTsgudTgdCucaudTgUfcuuucuusgsg		CCAAGAAAGACAAUGAGCAACAU	
AD-1725460	asasagacaaUfGfAfgcaacauguuL96		asdAscadTgdTugcudCaUfugucuuuscsu		AGAAAGACAAUGAGCAACAUGUG	
AD-1725462	asgsacaaugAfGfCfaacauguguuL96		asdAscadCadTguugdCuCfauugucususu		AAAGACAAUGAGCAACAUGUGUU	
AD-1725463	gsascaaugaGfCfAfacauguguuuL96		asdAsacdAcdAuguudGcUfcauugucsusu		AAGACAAUGAGCAACAUGUGUUC	
AD-1725464	ascsaaugagCfAfAfcauguguucuL96		asdGsaadCadCaugudTgCfucauugucscsu		AGACAAUGAGCAACAUGUGUUCA	
AD-1725465	csasaugagcAfAfCfauguguucauL96		asdTsgadAcdAcaugdTuGfcucauugsusc		GACAAUGAGCAACAUGUGUUCAA	
AD-1725467	asusgagcaaCfAfUfguguucaaauL96		asdTsuudGadAcacadTgUfugcucaususg		CAAUGAGCAACAUGUGUUCAAAG	
AD-1725469	gsasgcaacaUfGfUfguucaaaguuL96		asdAscudTudGaacadCaUfguugcucsasu		AUGAGCAACAUGUGUUCAAAGUC	
AD-1725470	asgscaacauGfUfGfuucaaagucuL96		asdGsacdTudTgaacdAcAfuguugcuscsa		UGAGCAACAUGUGUUCAAAGUCA	
AD-1725472	csasacauguGfUfUfcaaagucaauL96		asdTsugdAcdTuugadAcAfcauguugscsu		AGCAACAUGUGUUCAAAGUCAAG	
AD-1725473	asascaugugUfUfCfaaagucaaguL96		asdCsuudGadCuuugdAaCfacauguusgsc		GCAACAUGUGUUCAAAGUCAAGG	
AD-1725474	ascsauguguUfCfAfaagucaagguL96		asdCscudTgdAcuuudGaAfcacaugususg		CAACAUGUGUUCAAAGUCAAGGA	
AD-1725476	asusguguucAfAfAfgucaaggauuL96		asdAsucdCudTgacudTuGfaacacausgsu		ACAUGUGUUCAAAGUCAAGGAUA	
AD-1725477	usgsuguucaAfAfGfucaaggauauL96		asdTsaudCcdTugacdTuUfgaacacasusg		CAUGUGUUCAAAGUCAAGGAUAU	
AD-1725478	gsusguucaaAfGfUfcaaggauauuL96		asdAsuadTcdCuugadCuUfugaacacsasu		AUGUGUUCAAAGUCAAGGAUAUG	
AD-1725481	ususcaaaguCfAfAfggauauggauL96		asdTsccdAudAuccudTgAfcuuugaasesa		UGUUCAAAGUCAAGGAUAUGGAA	
AD-1725482	uscsaaagucAfAfGfgauauggaauL96		asdTsucdCadTauccdTuGfacuuugasasc		GUUCAAAGUCAAGGAUAUGGAAA	
AD-1725483	csasaagucaAfGfGfauauggaaauL96		asdTsuudCcdAuaucdCuUfgacuuugsasa		UUCAAAGUCAAGGAUAUGGAAAA	
AD-1725534	usgsaaagccAfGfUfcucugagucuL96		asdGsacdTcdAgagadCuGfgcuuucasusc		GAUGAAAGCCAGUCUCUGAGUCU	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1725535	gsasaagccaGfUfCfucugagucuuL96		asdAsgadCudCagagdAcUfggcuuucsasu		AUGAAAGCCAGUCUCUGAGUCUC	
AD-1725548	usgsagucucUfGfUfggcaugguuuL96		asdAsacdCadTgccadCaGfagacucasgsa		UCUGAGUCUCUGUGGCAUGGUUU	
AD-1725552	uscsucugugGfCfAfugguuuggguL96		asdCscdAadAccaudGcCfacagagascsu		AGUCUCUGUGGCAUGGUUUGGGA	
AD-1725556	usgsuggcauGfGfUfuugggaacauL96		asdTsgudTcdCcaaadCcAfugccacasgsa		UCUGUGGCAUGGUUUGGGAACAC	
AD-1725558	usgsgcauggUfUfUfgggaacacauL96		asdTsgudGudTcccadAaCfcaugccascsa		UGUGGCAUGGUUUGGGAACACAG	
AD-1725580	asasggguacCfGfAfuuaccacaauL96		asdTsugdTgdGuaaudCgGfuacccuuscsc		GGAAGGGUACCGAUUACCACAAG	
AD-1725582	gsgsguaccgAfUfUfaccacaagcuL96		asdGscudTgdTgguadAuCfgguacccsusu		AAGGGUACCGAUUACCACAAGCA	
AD-1725585	usascegauuAfCfCfacaagcaacuL96		asdGsuudGcdTugugdGuAfaucgguascsc		GGUACCGAUUACCACAAGCAACC	
AD-1725587	cscsgauuacCfAfCfaagcaaccauL96		asdTsggdTudGcuugdTgGfuaaucggsusa		UACCGAUUACCACAAGCAACCAU	
AD-1725588	csgsauuaccAfCfAfagcaaccauuL96		asdAsugdGudTgcuudGuGfguaaucgsgsu		ACCGAUUACCACAAGCAACCAUG	
AD-1725590	asusuaccacAfAfGfcaaccaugguL96		asdCscadTgdGuugcdTuGfugguaauscsg		CGAUUACCACAAGCAACCAUGGC	
AD-1725591	ususaccacaAfGfCfaaccauggcuL96		asdGsccdAudGguugdCuUfgugguaasusc		GAUUACCACAAGCAACCAUGGCA	
AD-1725592	usasccacaaGfCfAfaccauggcauL96		asdTsgcdCadTgguudGcUfugugguasasu		AUUACCACAAGCAACCAUGGCAG	
AD-1725593	ascscacaagCfAfAfccauggcaguL96		asdCsugdCcdAuggudTgCfuuguggusasa		UUACCACAAGCAACCAUGGCAGG	
AD-1725598	asasgcaaccAfUfGfgcaggccaauL96		asdTsugdGcdCugccdAuGfguugcuusgsu		ACAAGCAACCAUGGCAGGCCAAG	
AD-1725603	ascscauggcAfGfGfccaagaucuuL96		asdAsgadTcdTuggcdCuGfccauggususg		CAACCAUGGCAGGCCAAGAUCUC	
AD-1725604	cscsauggcaGfGfCfcaagaucucuL96		asdGsagdAudCuuggdCcUfgccauggsusu		AACCAUGGCAGGCCAAGAUCUCA	
AD-1725605	csasuggcagGfCfCfaagaucucauL96		asdTsgadGadTcuugdGcCfugccaugsgsu		ACCAUGGCAGGCCAAGAUCUCAG	
AD-1725643	gscsugugguGfUfCfugaguacuuuL96		asdAsagdTadCucagdAcAfccacagcscsc		GGGCUGUGGUGUCUGAGUACUUU	
AD-1725644	csusguggugUfCfUfgaguacuuuuL96		asdAsaadGudAcucadGaCfaccacagscsc		GGCUGUGGUGUCUGAGUACUUUG	
AD-1725645	usgsugguguCfUfGfaguacuuuguL96		asdCsaadAgdTacucdAgAfcaccacasgsc		GCUGUGGUGUCUGAGUACUUUGU	
AD-1725646	gsusggugucUfGfAfguacuuuguuL96		asdAscadAadGuacudCaGfacaccacsasg		CUGUGGUGUCUGAGUACUUUGUG	
AD-1725647	usgsgugucuGfAfGfuacuuuguguL96		asdCsacdAadAguacdTcAfgacaccascsa		UGUGGUGUCUGAGUACUUUGUGC	
AD-1725667	csusgacagcAfGfCfacauuguuuuL96		asdAsaadCadAugugdCuGfcugucagscsa		UGCUGACAGCAGCACAUUGUUUC	
AD-1725716	asasgcgggaCfCfUfggagauagauL96		asdTscudAudCuccadGgUfcccgcuuscsu		AGAAGCGGGACCUGGAGAUAGAA	
AD-1725717	asgscgggacCfUfGfgagauagaauL96		asdTsucdTadTcuccdAgGfucccgcususc		GAAGCGGGACCUGGAGAUAGAAG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1725756	gsasagcaggAfAfUfuccugaauuuL96		asdAsaudTcdAggaadTuCfcugcuucsusu		AAGAAGCAGGAAUUCCUGAAUUU	
AD-1725757	asasgcaggaAfUfUfccugaauuuuL96		asdAsaadTudCaggadAuUfccugcuuscsu		AGAAGCAGGAAUUCCUGAAUUUU	
AD-1725759	gscsaggaauUfCfCfugaauuuuauL96		asdTsaadAadTucagdGaAfuuccugcsusu		AAGCAGGAAUUCCUGAAUUUUAU	
AD-1725760	csasggaauuCfCfUfgaauuuuauuL96		asdAsuadAadAuucadGgAfauuccugscsu		AGCAGGAAUUCCUGAAUUUUAUG	
AD-1725761	asgsgaauucCfUfGfaauuuuauguL96		asdCsaudAadAauucdAgGfaauuccusgsc		GCAGGAAUUCCUGAAUUUUAUGA	
AD-1725762	gsgsaauuccUfGfAfauuuuaugauL96		asdTscadTadAaauudCaGfgaauuccsusg		CAGGAAUUCCUGAAUUUUAUGAC	
AD-1725763	gsasauuccuGfAfAfuuuuaugacuL96		asdGsucdAudAaaaudTcAfggaauucscsu		AGGAAUUCCUGAAUUUUAUGACU	
AD-1725764	asasuuccugAfAfUfuuuaugacuuL96		asdAsgudCadTaaaadTuCfaggaauuscsc		GGAAUUCCUGAAUUUUAUGACUA	
AD-1725765	asusuccugaAfUfUfuuaugacuauL96		asdTsagdTcdAuaaadAuUfcaggaaususc		GAAUUCCUGAAUUUUAUGACUAU	
AD-1725766	ususccugaaUfUfUfuaugacuauuL96		asdAsuadGudCauaadAaUfucaggaasusu		AAUUCCUGAAUUUUAUGACUAUG	
AD-1725767	uscscugaauUfUfUfaugacuauguL96		asdCsaudAgdTcauadAaAfuucaggasasu		AUUCCUGAAUUUUAUGACUAUGA	
AD-1725768	cscsugaauuUfUfAfugacuaugauL96		asdTscadTadGucaudAaAfauucaggsasa		UUCCUGAAUUUUAUGACUAUGAC	
AD-1725769	csusgaauuuUfAfUfgacuaugacuL96		asdGsucdAudAgucadTaAfaauucagsgsa		UCCUGAAUUUUAUGACUAUGACG	
AD-1725771	gsasauuuuaUfGfAfcuaugacguuL96		asdAscgdTcdAuagudCaUfaaaauucsasg		CUGAAUUUUAUGACUAUGACGUU	
AD-1725772	asasuuuuauGfAfCfuaugacguuuL96		asdAsacdGudCauagdTcAfuaaaauuscsa		UGAAUUUUAUGACUAUGACGUUG	
AD-1725773	asusuuuaugAfCfUfaugacguuguL96		asdCsaadCgdTcauadGuCfauaaaaususc		GAAUUUUAUGACUAUGACGUUGC	
AD-1725775	ususuaugacUfAfUfgacguugccuL96		asdGsgcdAadCgucadTaGfucauaaasasu		AUUUUAUGACUAUGACGUUGCCC	
AD-1725776	ususaugacuAfUfGfacguugcccuL96		asdGsggdCadAcgucdAuAfgucauaasasa		UUUUAUGACUAUGACGUUGCCCU	
AD-1725777	usasugacuaUfGfAfcguugcccuuL96		asdAsggdGcdAacgudCaUfagucauasasa		UUUAUGACUAUGACGUUGCCCUG	
AD-1725778	asusgacuauGfAfCfguugcccuguL96		asdCsagdGgdCaacgdTcAfuagucausasa		UUAUGACUAUGACGUUGCCCUGA	
AD-1725779	usgsacuaugAfCfGfuugcccugauL96		asdTscadGgdGcaacdGuCfauagucasusa		UAUGACUAUGACGUUGCCCUGAU	
AD-1725780	gsascuaugaCfGfUfugcccugauuL96		asdAsucdAgdGgcaadCgUfcauagucsasu		AUGACUAUGACGUUGCCCUGAUC	
AD-1725784	asusgacguuGfCfCfcugaucaaguL96		asdCsuudGadTcaggdGcAfacgucausasg		CUAUGACGUUGCCCUGAUCAAGC	
AD-1725785	usgsacguugCfCfCfugaucaagcuL96		asdGscudTgdAucagdGgCfaacgucasusa		UAUGACGUUGCCCUGAUCAAGCU	
AD-1725786	gsascguugcCfCfUfgaucaagcuuL96		asdAsgcdTudGaucadGgGfcaacgucsasu		AUGACGUUGCCCUGAUCAAGCUC	
AD-1725787	ascsguugccCfUfGfaucaagcucuL96		asdGsagdCudTgaucdAgGfgcaacguscsa		UGACGUUGCCCUGAUCAAGCUCA	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1725789	gsusugcccuGfAfUfcaagcucaauL96		asdTsugdAgdCuugadTcAfgggcaacsgsu		ACGUUGCCCUGAUCAAGCUCAAG	
AD-1725790	ususgcccugAfUfCfaagcucaaguL96		asdCsuudGadGcuugdAuCfagggcaascsg		CGUUGCCCUGAUCAAGCUCAAGA	
AD-1725828	csasgacuauCfAfGfgcccauuuguL96		asdCsaadAudGggccdTgAfuagucugsgsc		GCCAGACUAUCAGGGCCCAUUUGU	
AD-1725829	asgsacuaucAfGfGfcccauuuguuL96		asdAscadAadTgggcdCuGfauagucusgsg		CCAGACUAUCAGGGCCCAUUUGUC	
AD-1725830	gsascuaucaGfGfCfccauuugucuL96		asdGsacdAadAugggdCcUfgauagucsusg		CAGACUAUCAGGGCCCAUUUGUCU	
AD-1725831	ascsuaucagGfCfCfccauuuguccuuL96		asdAsgadCadAauggdGcCfugauagucscsu		AGACUAUCAGGGCCCAUUUGUCUC	
AD-1725832	csusaucaggCfCfCfcauuuguccucuL96		asdGsagdAcdAaaugdGgCfcugauagsusc		GACUAUCAGGGCCCAUUUGUCUCC	
AD-1725840	csgsagggaaCfAfAfcucgagcuuuuL96		asdAsagdCudCgagudTgUfucccucgsgsu		ACCGAGGGAACAACUCGAGCUUU	
AD-1725841	gsasgggaacAfAfCfucgagcuuuuL96		asdAsaadGcdTcgagdTuGfuucccucsgsg		CCGAGGGAACAACUCGAGCUUUG	
AD-1725842	asgsggaacaAfCfUfcgagcuuuguL96		asdCsaadAgdCucgadGuUfguucccuscsg		CGAGGGAACAACUCGAGCUUUGA	
AD-1725845	gsasacaacuCfGfAfgcuuugagguL96		asdCscudCadAagcudCgAfguuguucscsc		GGGAACAACUCGAGCUUUGAGGC	
AD-1725846	asascaacucGfAfGfcuuugaggcuL96		asdGsccdTcdAaagcdTcGfaguuguuscsc		GGAACAACUCGAGCUUUGAGGCU	
AD-1725848	csasacucgaGfCfUfuugaggcuuuL96		asdAsagdCcdTcaaadGcUfcgaguugsusu		AACAACUCGAGCUUUGAGGCUUC	
AD-1725849	asascucgagCfUfUfugaggcuucuL96		asdGsaadGcdCucaadAgCfucgaguusgsu		ACAACUCGAGCUUUGAGGCUUCC	
AD-1725850	ascsucgagcUfUfUfgaggcuuccuL96		asdGsgadAgdCcucadAaGfcucgagususg		CAACUCGAGCUUUGAGGCUUCCU	
AD-1725854	gsasgcuuugAfGfGfcuucuccauuL96		asdTsggdAgdGaagcdCuCfaaagcucsgsa		UCGAGCUUUGAGGCUUCCUCCAA	
AD-1725855	asgscuuugaGfGfCfuucuccaauuL96		asdTsugdGadGgaagdCcUfcaaagcuscsg		CGAGCUUUGAGGCUUCCUCCAAC	
AD-1725856	gscsuuugagGfCfUfuccuccaacuL96		asdGsuudGgdAggaadGcCfucaaagcsusc		GAGCUUUGAGGCUUCCUCCAACU	
AD-1725857	csusuugaggCfUfUfccuccaacuuL96		asdAsgudTgdGaggadAgCfcucaaagscsu		AGCUUUGAGGCUUCCUCCAACUA	
AD-1725858	ususugaggcUfUfCfcuccaacuauL96		asdTsagdTudGgaggdAaGfccucaaasgsc		GCUUUGAGGCUUCCUCCAACUAC	
AD-1725861	gsasggcuucCfUfCfcaacuaccauL96		asdTsggdTadGuuggdAgGfaagccucsasa		UUGAGGCUUCCUCCAACUACCAC	
AD-1725862	asgsgcuuccUfCfCfaacuaccacuL96		asdGsugdGudAguugdGaGfgaagccuscsa		UGAGGCUUCCUCCAACUACCACU	
AD-1725864	gscsuuccucCfAfAfcuaccacuuuL96		asdAsagdTgdGuagudTgGfaggaagcscsu		AGGCUUCCUCCAACUACCACUUG	
AD-1725866	ususccuccaAfCfUfaccacuugcuL96		asdGscadAgdTgguadGuUfggaggaasgsc		GCUUCCUCCAACUACCACUUGCC	
AD-1725867	uscscuccaaCfUfAfccacuugccuL96		asdGsgcdAadGuggudAgUfuggaggasasg		CUUCCUCCAACUACCACUUGCCA	
AD-1725872	csasacuaccAfCfUfugccagcaauL96		asdTsugdCudGgcaadGuGfguaguugsgsa		UCCAACUACCACUUGCCAGCAAC	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1725874	ascsuaccacUfUfGfccagcaacauL96		asdTsgudTgdCuggcdAaGfugguagususg		CAACUACCACUUGCCAGCAACAA	
AD-1725907	csuscccugcAfCfAfggauaucaauL96		asdTsugdAudAuccudGuGfcagggagscsa		UGCUCCCUGCACAGGAUAUCAAA	
AD-1725908	uscsccugcaCfAfGfgauaucaaauL96		asdTsuudGadTauccdTgUfgcagggasgsc		GCUCCCUGCACAGGAUAUCAAAG	
AD-1725909	cscscugcacAfGfGfauaucaaaguL96		asdCsuudTgdAuaucdCuGfugcagggsasg		CUCCCUGCACAGGAUAUCAAAGC	
AD-1725911	csusgcacagGfAfUfaucaaagcuuL96		asdAsgcdTudTgauadTcCfugugcagsgsg		CCCUGCACAGGAUAUCAAAGCUC	
AD-1725916	csasggauauCfAfAfagcucuguuuL96		asdAsacdAgdAgcuudTgAfuauccugsusg		CACAGGAUAUCAAAGCUCUGUUU	
AD-1725919	gsasuaucaaAfGfCfucuguuuguuL96		asdAscadAadCagagdCuUfugauaucscsu		AGGAUAUCAAAGCUCUGUUUGUG	
AD-1725925	asasagcucuGfUfUfugugucugauL96		asdTscadGadCacaadAcAfgagcuuusgsa		UCAAAGCUCUGUUUGUGUCUGAG	
AD-1725957	gscsugacucGfGfAfaggaggucuuL96		asdAsgadCcdTccuudCcGfagucagcsusu		AAGCUGACUCGGAAGGAGGUCUA	
AD-1725958	csusgacucgGfAfAfggaggucuauL96		asdTsagdAcdCuccudTcCfgagucagscsu		AGCUGACUCGGAAGGAGGUCUAC	
AD-1725961	ascsucggaaGfGfAfggucuacauuL96		asdAsugdTadGaccudCcUfuccgaguscsa		UGACUCGGAAGGAGGUCUACAUC	
AD-1725963	uscsggaaggAfGfGfucuacaucauL96		asdTsgadTgdTagacdCuCfcuuccgasgsu		ACUCGGAAGGAGGUCUACAUCAA	
AD-1725964	csgsgaaggaGfGfUfcuacaucaauL96		asdTsugdAudGuagadCcUfccuuccgsasg		CUCGGAAGGAGGUCUACAUCAAG	
AD-1725967	asasggagguCfUfAfcaucaagaauL96		asdTsucdTudGaugudAgAfccuccuuscsc		GGAAGGAGGUCUACAUCAAGAAU	
AD-1725968	asgsgaggucUfAfCfaucaagaauuL96		asdAsuudCudTgaugdTaGfaccuccususc		GAAGGAGGUCUACAUCAAGAAUG	
AD-1725974	asasgaaaggCfAfGfcugugagaguL96		asdCsucdTcdAcagcdTgCfcuuucuusasu		AUAAGAAAGGCAGCUGUGAGAGA	
AD-1725977	asasaggcagCfUfGfugagagagauL96		asdTscudCudCucacdAgCfugccuuuscsu		AGAAAGGCAGCUGUGAGAGAGAU	
AD-1725983	asgscugugaGfAfGfagaugcucauL96		asdTsgadGcdAucucdTcUfcacagcusgsc		GCAGCUGUGAGAGAGAUGCUCAA	
AD-1725985	csusgugagaGfAfGfaugcucaauuL96		asdAsuudGadGcaucdTcUfcucacagscsu		AGCUGUGAGAGAGAUGCUCAAUA	
AD-1725986	usgsugagagAfGfAfugcucaauauL96		asdTsaudTgdAgcaudCuCfucucacasgsc		GCUGUGAGAGAGAUGCUCAAUAU	
AD-1725987	gsusgagagaGfAfUfgcucaauauuL96		asdAsuadTudGagcadTcUfcucucacsasg		CUGUGAGAGAGAUGCUCAAUAUG	
AD-1725988	usgsagagagAfUfGfcucaauauguL96		asdCsaudAudTgagcdAuCfucucucascsa		UGUGAGAGAGAUGCUCAAUAUGC	
AD-1725989	gsasgagagaUfGfCfucaauaugcuL96		asdGscadTadTugagdCaUfcucucucsasc		GUGAGAGAGAUGCUCAAUAUGCC	
AD-1725991	csasggcuauGfAfCfaaagucaaguL96		asdCsuudGadCuuugdTcAfuagccugsgsg		CCCAGGCUAUGACAAAGUCAAGG	
AD-1725992	asgsgcuaugAfCfAfaagucaagguL96		asdCscudTgdAcuuudGuCfauagccusgsg		CCAGGCUAUGACAAAGUCAAGGA	
AD-1725993	gsgscuaugaCfAfAfagucaaggauL96		asdTsccdTudGacuudTgUfcauagccsusg		CAGGCUAUGACAAAGUCAAGGAC	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1725999	gsascaaaguCfAfAfggacaucucuL96		asdGsagdAudGuccudTgAfcuuugucsasu		AUGACAAAGUCAAGGACAUCUCA	
AD-1726014	uscsgguuccUfUfUfguacuggaguL96		asdCsucdCadGuacadAaGfgaaccgasgsg		CCUCGGUUCCUUUGUACUGGAGG	
AD-1726015	csgsguuccuUfUfGfuacuggagguL96		asdCscudCcdAguacdAaAfggaaccgsasg		CUCGGUUCCUUUGUACUGGAGGA	
AD-1726016	gsgsuuccuuUfGfUfacuggaggauL96		asdTsccdTcdCaguadCaAfaggaaccsgsa		UCGGUUCCUUUGUACUGGAGGAG	
AD-1726018	ususccuuugUfAfCfuggaggaguuL96		asdAscudCcdTccagdTaCfaaaggaascsc		GGUUCCUUUGUACUGGAGGAGUG	
AD-1726020	cscsuuuguaCfUfGfgaggagugauL96		asdTscadCudCcuccdAgUfacaaaggsasa		UUCCUUUGUACUGGAGGAGUGAG	
AD-1726023	ususguacugGfAfGfgagugagucuL96		asdGsacdTcdAcuccdTcCfaguacaasasg		CUUUGUACUGGAGGAGUGAGUCC	
AD-1726024	usgsuacuggAfGfGfagugaguccuL96		asdGsgadCudCacucdCuCfcaguacasasa		UUUGUACUGGAGGAGUGAGUCCC	
AD-1726025	gsusacuggaGfGfAfgugagucccuL96		asdGsggdAcdTcacudCcUfccaguacsasa		UUGUACUGGAGGAGUGAGUCCCU	
AD-1726027	ascsuggaggAfGfUfgagucccuauL96		asdTsagdGgdAcucadCuCfcuccagusasc		GUACUGGAGGAGUGAGUCCCUAU	
AD-1726029	usgsgaggagUfGfAfgucccuauguL96		asdCsaudAgdGgacudCaCfuccuccasgsu		ACUGGAGGAGUGAGUCCCUAUGC	
AD-1726031	gsasggagugAfGfUfcccuaugcuuL96		asdAsgcdAudAgggadCuCfacuccucscsa		UGGAGGAGUGAGUCCCUAUGCUG	
AD-1726033	gsgsagugagUfCfCfcuaugcugauL96		asdTscadGcdAuaggdGaCfucacuccsusc		GAGGAGUGAGUCCCUAUGCUGAC	
AD-1726034	gsasgugaguCfCfCfuaugcugacuL96		asdGsucdAgdCauagdGgAfcucacucscsu		AGGAGUGAGUCCCUAUGCUGACC	
AD-1726036	csasauacuuGfCfAfgaggugauuuL96		asdAsaudCadCcucudGcAfaguauugsgsg		CCCAAUACUUGCAGAGGUGAUUC	
AD-1726037	asasuacuugCfAfGfaggugauucuL96		asdGsaadTcdAccucdTgCfaaguauusgsg		CCAAUACUUGCAGAGGUGAUUCU	
AD-1726039	usascuugcaGfAfGfgugauucuguL96		asdCsagdAadTcaccdTcUfgcaaguasusu		AAUACUUGCAGAGGUGAUUCUGG	
AD-1726041	csusugcagaGfGfUfgauucuggcuL96		asdGsccdAgdAaucadCcUfcugcaagsusa		UACUUGCAGAGGUGAUUCUGGCG	
AD-1726042	ususgcagagGfUfGfauucuggcguL96		asdCsgcdCadGaaucdAcCfucugcaasgsu		ACUUGCAGAGGUGAUUCUGGCGG	
AD-1726048	usgsauaguuCfAfCfaagagaaguuL96		asdAscudTcdTcuugdTgAfacuaucasasg		CUUGAUAGUUCACAAGAGAAGUC	
AD-1726049	gsasuaguucAfCfAfagagaagucuL96		asdGsacdTudCucuudGuGfaacuaucsasa		UUGAUAGUUCACAAGAGAAGUCG	
AD-1726050	asusaguucaCfAfAfgagaagucguL96		asdCsgadCudTcucudTgUfgaacuauscsa		UGAUAGUUCACAAGAGAAGUCGU	
AD-1726051	usasguucacAfAfGfagaagucguuL96		asdAscgdAcdTucucdTuGfugaacuasusc		GAUAGUUCACAAGAGAAGUCGUU	
AD-1726052	asgsuucacaAfGfAfgaagucguuuL96		asdAsacdGadCuucudCuUfgugaacusasu		AUAGUUCACAAGAGAAGUCGUUU	
AD-1726053	gsusucacaaGfAfGfaagucguuuuL96		asdAsaadCgdAcuucdTcUfugugaacsusa		UAGUUCACAAGAGAAGUCGUUUC	
AD-1726054	ususcacaagAfGfAfagucguuucuL96		asdGsaadAcdGacuudCuCfuugugaascsu		AGUUCACAAGAGAAGUCGUUUCA	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1726055	uscsacaagaGfAfAfgucguuucauL96		asdTsgadAadCgacudTcUfcuugugasasc		GUUCACAAGAGAAGUCGUUUCAU	
AD-1726056	csascaagagAfAfGfucguuucaauL96		asdAsugdAadAcgacdTuCfucuugugsasa		UUCACAAGAGAAGUCGUUUCAUU	
AD-1726057	ascsaagagaAfGfUfcguuucaauuL96		asdAsaudGadAacgadCuUfcucuugusgsa		UCACAAGAGAAGUCGUUUCAUUC	
AD-1726058	csasagagaaGfUfCfguuucauucuL96		asdGsaadTgdAaacgdAcUfucucuugsusg		CACAAGAGAAGUCGUUUCAUUCA	
AD-1726059	asasgagaagUfCfGfuuucauucauL96		asdTsgadAudGaaacdGaCfuucucuusgsu		ACAAGAGAAGUCGUUUCAUUCAA	
AD-1726060	asgsagaaguCfGfUfuucauucaauL96		asdTsugdAadTgaaadCgAfcuucucususg		CAAGAGAAGUCGUUUCAUUCAAG	
AD-1726061	gsasgaagucGfUfUfucauucaaguL96		asdCsuudGadAugaadAcGfacuucucsusu		AAGAGAAGUCGUUUCAUUCAAGU	
AD-1726062	asgsaagucgUfUfUfcauucaaguuL96		asdAscudTgdAaugadAaCfgacuucuscsu		AGAGAAGUCGUUUCAUUCAAGUU	
AD-1726063	gsasagucguUfUfCfauucaaguuuL96		asdAsacdTudGaaugdAaAfcgacuucsusc		GAGAAGUCGUUUCAUUCAAGUUG	
AD-1726064	asasgucguuUfCfAfuucaaguuguL96		asdCsaadCudTgaaudGaAfacgacuuscsu		AGAAGUCGUUUCAUUCAAGUUGG	
AD-1726065	asgsucguuuCfAfUfucaaguugguL96		asdCscadAcdTugaadTgAfaacgacususc		GAAGUCGUUUCAUUCAAGUUGGU	
AD-1726079	gsasguaugugGfAfUfgucugcaaauL96		asdTsuudGcdAgacadTcCfacuacucscsc		GGGAGUAGUGGAUGUCUGCAAAA	
AD-1726080	asgsuaguggAfUfGfucugcaaaauL96		asdTsuudTgdCagacdAuCfcacuacuscsc		GGAGUAGUGGAUGUCUGCAAAAA	
AD-1726081	gsusaguggaUfGfUfcugcaaaauuL96		asdTsuudTudGcagadCaUfccacuacussc		GAGUAGUGGAUGUCUGCAAAAAC	
AD-1726082	usasguggauGfUfCfugcaaaaacuL96		asdGsuudTudTgcagdAcAfuccacuascsu		AGUAGUGGAUGUCUGCAAAAACC	
AD-1726083	asgsuggauGfUfCfUfgcaaaaaccuL96		asdGsgudTudTugcadGaCfauccacusasc		GUAGUGGAUGUCUGCAAAAACCA	
AD-1726084	gsusggauguCfUfGfcaaaaaccauL96		asdTsggdTudTuugcdAgAfcauccacsusa		UAGUGGAUGUCUGCAAAAACCAG	
AD-1726085	usgsgaugucUfGfCfaaaaaccagUL96		asdCsugdGudTuuugdCaGfacauccascsu		AGUGGAUGUCUGCAAAAACCAGA	
AD-1726086	gsgsaugucuGfCfAfaaaaccagaUL96		asdTscudGgdTuuuudGcAfgacauccsasc		GUGGAUGUCUGCAAAAACCAGAA	
AD-1726087	gsasugucugCfAfAfaaaccagaaUL96		asdTsucdTgdGuuuudTgCfagacauccscsa		UGGAUGUCUGCAAAAACCAGAAG	
AD-1726090	gsuscugcaaAfAfAfccagaagcgguL96		asdCsgcdTudCuggdTuUfugcagacsasu		AUGUCUGCAAAAACCAGAAGCGG	
AD-1726091	uscsugcaaaAfAfCfcagaagcggUL96		asdCscgdCudTcuggdTuUfuugcagascsa		UGUCUGCAAAAACCAGAAGCGGC	
AD-1726092	csusgcaaaaAfCfCfagaagcggcuL96		asdGsccdGcdTucugdGuUfuuugcagsasc		GUCUGCAAAAACCAGAAGCGGCA	
AD-1726095	csasaaaaccAfGfAfagcggcaaauL96		asdTsuudGcdCgcuudCuGfguuuuugscsa		UGCAAAAACCAGAAGCGGCAAAA	
AD-1726096	asasaaaccaGfAfAfgcggcaaaauL96		asdTsuudTgdCcgcudTcUfgguuuuusgsc		GCAAAAACCAGAAGCGGCAAAAG	
AD-1726097	asasaaccagAfAfGfcggcaaaaguL96		asdCsuudTudGccgcdTuCfuggguuuususg		CAAAAACCAGAAGCGGCAAAAGC	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1726098	asasaccagaAfGfCfggcaaaagcuL96		asdGscudTudTgccgdCuUfcugguuususu		AAAAACCAGAAGCGGCAAAAGCA	
AD-1726099	asasccagaaGfCfGfgcaaaagcauL96		asdTsgcdTudTugccdGcUfucuggususu		AAAACCAGAAGCGGCAAAAGCAG	
AD-1726103	asgsaagcggCfAfAfaagcagguauL96		asdTsacdCudGcuuudTgCfcgcuucusgsg		CCAGAAGCGGCAAAAGCAGGUAC	
AD-1726113	asasagcaggUfAfCfcugcucacguL96		asdCsgudGadGcaggdTaCfcugcuuususg		CAAAAGCAGGUACCUGCUCACGC	
AD-1726159	csasaggucuGfCfCfcuggcugaauL96		asdTsucdAgdCcaggdGcAfgcacuugsasa		UUCAAGUGCUGCCCUGGCUGAAG	
AD-1726171	usgsgcugaaGfGfAfgaaacuccauL96		asdTsggdAgdTuucudCcUfucagccasgsg		CCUGGCUGAAGGAGAAACUCCAA	
AD-1726184	asascuccaaGfAfUfgaggauuuguL96		asdCsaadAudCcucadTcUfuggaguususc		GAAACUCCAAGAUGAGGAUUUGG	
AD-1726187	uscscaagauGfAfGfgauuuggguuL96		asdAsccdCadAauccdTcAfucuuggasgsu		ACUCCAAGAUGAGGAUUUGGGUU	
AD-1726189	csasagaugaGfGfAfuuuggguuuuL96		asdAsaadCcdCaaaudCcUfcaucuugsgsa		UCCAAGAUGAGGAUUUGGGUUUU	
AD-1726191	asgsaugaggAfUfUfuggguuuucuL96		asdGsaadAadCccaadAuCfcucaucususg		CAAGAUGAGGAUUUGGGUUUUCU	
AD-1726201	gsusgggauuGfAfAfuuaaaacagaL96		asdCsugdTudTuaaudTcAfaucccacsgsc		GCGUGGGAUUGAAUUAAAACAGC	
AD-1726202	usgsggauugAfAfUfuaaaacagcuL96		asdGscudGudTuuaadTuCfaaucccasc sg		CGUGGGAUUGAAUUAAAACAGCU	
AD-1726203	gsgsgauugaAfUfUfaaaacagcuuL96		asdAsgcdTgdTuuuadAuUfcaaucccsasc		GUGGGAUUGAAUUAAAACAGCUG	
AD-1726206	asusugaauuAfAfAfacagcugcguL96		asdCsgcdAgdCuguudTuAfauucaauscsc		GGAUUGAAUUAAAACAGCUGCGA	
AD-1726207	ususgaauuaAfAfAfcagcugcgauL96		asdTscgdCadGcugudTuUfaauucaasusc		GAUUGAAUUAAAACAGCUGCGAC	
AD-1726208	usgsaauuaaAfAfCfagcugcgacuL96		asdGsucdGcdAgcugdTuUfuaauucasasu		AUUGAAUUAAAACAGCUGCGACA	
AD-1726209	gsasauuaaaAfCfAfgcugcgacauL96		asdTsgudCgdCagcudGuUfuuaauucsasa		UUGAAUUAAAACAGCUGCGACAA	
AD-1726815	csusggcuUfcUfAfCfccguacccuuL96		asAfsggguUfacggguaGfaAfgccagsasa		UUCUGGCUUCUACCCGUACCCUG	
AD-1726927	cscscuacUfaCfAfAfugugagugaugauL96		asUfscacUfcacauugUfaGfuagggsasg		CUCCCUACUACAAUGUGAGUGAU	
AD-1726928	cscsuacuAfcAfAfUfgugagugauuL96		asAfsucaCfucacauuGfuAfguagggsgsa		UCCCUACUACAAUGUGAGUGAUG	
AD-1726931	ascsuacaAfuGfUfGfagugaugaguL96		asCfsucaUfcacucacAfuUfguagusasg		CUACUACAAUGUGAGUGAUGAGA	
AD-1726934	ascsaaugUfgAfGfUfgaugagaucuL96		asGfsaucUfcaucacuCfaCfauugusasg		CUACAAUGUGAGUGAUGAGAUCU	
AD-1726935	csasauguGfaGfUfGfaugagaucuuL96		asAfsgauCfucaucacUfcAfcauugsusa		UACAAUGUGAGUGAUGAGAUCUC	
AD-1726936	asasugugAfgUfGfAfugagaucucuL96		asGfsagaUfcucaucaCfuCfacauusgsu		ACAAUGUGAGUGAUGAGAUCUCU	
AD-1726937	asusgugaGfuGfAfUfgagaucucuuL96		asAfsgagAfucucaucAfcUfcacaususg		CAAUGUGAGUGAUGAGAUCUCUU	
AD-1726938	usgsugagUfgAfUfGfagaucucuuuL96		asAfsagaGfaucucauCfaCfucacasusu		AAUGUGAGUGAUGAGAUCUCUUU	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1726939	gsusgaguGfaUfGfAfgaucucuuuuL96		asAfsaagAfgaucucaUfcAfcucacsasu		AUGUGAGUGAUGAGAUCUCUUUC	
AD-1726940	usgsagugAfuGfAfGfaucucuucuL96		asGfsaaaGfagaucucAfuCfacucascsa		UGUGAGUGAUGAGAUCUCUUUCC	
AD-1726941	gsasgugaUfgAfGfAfucucuuuccuL96		asGfsgaaAfgagaucuCfaUfcacucsasc		GUGAGUGAUGAGAUCUCUUUCCA	
AD-1726942	asgsgauGfaGfAfUfcucuuuccauL96		asUfsggaAfagagaucUfcAfucacuscsa		UGAGUGAUGAGAUCUCUUUCCAC	
AD-1726944	usgsaugaGfaUfCfUfcuuuccacuuL96		asAfsgugGfaaagagaUfcUfcaucascsu		AGUGAUGAGAUCUCUUUCCACUG	
AD-1726952	uscsucuuUfcCfAfCfugcuaugacuL96		asGfsucaUfagcagugGfaAfagagasusc		GAUCUCUUUCCACUGCUAUGACG	
AD-1726961	ascsugcuAfuGfAfCfgguuacacuuL96		asAfsguGfuaccgucAfuAfgcagusgsg		CCACUGCUAUGACGGUUACACUC	
AD-1727012	csasgacaGfcGfAfUfcugugacaauL96		asUfsuguCfacagaucGfcUfgucugscsc		GGCAGACAGCGAUCUGUGACAAC	
AD-1727059	csusugaaGfaCfAfGfcgucaccuauL96		asUfsaggUfgacgcugUfcUfucaagsgsc		GCCUUGAAGACAGCGUCACCUAC	
AD-1727140	asasgacuCfcUfUfCfauguacgacuL96		asGfsucgUfacaugaaGfgAfgucuusgsg		CCAAGACUCCUUCAUGUACGACA	
AD-1727142	gsascuccUfuCfAfUfguacgacacuL96		asGfsuguCfguacaugAfaGfgagucsusu		AAGACUCCUUCAUGUACGACACC	
AD-1727181	asgsagacCfaUfAfGfaaggagucguL96		asCfsgacUfccuucuaUfgGfucucusgsu		ACAGAGACCAUAGAAGGAGUCGA	
AD-1727183	asgsaccaUfaGfAfAfggagucgauuL96		asAfsucgAfcuccuucUfaUfggucuscsu		AGAGACCAUAGAAGGAGUCGAUG	
AD-1727184	gsasccauAfgAfAfGfgagucgauguL96		asCfsaucGfacuccuuCfuAfuggucsusc		GAGACCAUAGAAGGAGUCGAUGC	
AD-1727249	usgsaacaUfcUfAfCfcuggugcuauL96		asUfsagcAfccagguaGfaUfguucasusg		CAUGAACAUCUACCUGGUGCUAG	
AD-1727261	usgsgugcUfaGfAfUfggaucagacuL96		asGfsucuGfauccaucUfaGfcaccasgsg		CCUGGUGCUAGAUGGAUCAGACA	
AD-1727263	gsusgcuaGfaUfGfGfaucagacaguL96		asCfsuguCfugauccaUfcUfagcacscsa		UGUGCUAGAUGGAUCAGACAGC	
AD-1727275	csasacuuCfaCfAfGfgagccaaaauL96		asUfsuuuGfgccuccugUfgAfaguugscsu		AGCAACUUCACAGGAGCCAAAAA	
AD-1727276	asascuucAfcAfGfGfGfagccaaaaauL96		asUfsuuuUfggcuccuGfuGfaaguusgsc		GCAACUUCACAGGAGCCAAAAAG	
AD-1727278	csusucacAfgGfAfGfGfccaaaaaguuL96		asAfscuuUfuuggcucCfuGfugaagsusu		AACUUCACAGGAGCCAAAAAGUG	
AD-1727285	ggsgagccAfaAfAfAfAfgugucuaguuL96		asAfscuaGfacacuuuUfuGfgcuccsusg		CAGGAGCCAAAAAGUGUCUAGUC	
AD-1727286	gsasgccaAfaAfAfGfGfugucuagucuL96		asGfsacuAfgacacuuUfuUfggcucscsu		AGGAGCCAAAAAGUGUCUAGUCA	
AD-1727288	gscscaaaAfaGfUfGfGfucuagucaauL96		asUfsugaCfuagacacUfuUfuuggcsusc		GAGCCAAAAAGUGUCUAGUCAAC	
AD-1727289	cscsaaaaAfgUfGfUfUfcuagucaacuL96		asGfsuugAfcuagacaCfuUfuuuggscsu		AGCCAAAAAGUGUCUAGUCAACU	
AD-1727290	csasaaaaGfuGfUfCfUfuagucaacuuL96		asAfsguuGfacuagacAfcUfuuuugsgsc		GCCAAAAAGUGUCUAGUCAACUU	
AD-1727291	asasaaagUfgUfCfUfUfagucaacuuuL96		asAfsaguUfgacuagaCfaCfuuuuusgsg		CCAAAAAGUGUCUAGUCAACUUA	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1727292	asasaaguGfuCfUfAfgucaacuuauL96		asUfsaagUfugacuagAfcAfcuuuususg		CAAAAAGUGUCUAGUCAACUUAA	
AD-1727293	asasagugUfcUfAfGfucaacuuaauL96		asUfsuaaGfuugacuaGfaCfacuuususu		AAAAAGUGUCUAGUCAACUUAAU	
AD-1727298	gsuscuagUfcAfAfCfuuaauugaguL96		asCfsucaAfuuaaguuGfaCfuagacsasc		GUGUCUAGUCAACUUAAUUGAGA	
AD-1727310	usasauugAfgAfAfGfguggcaaguuL96		asAfscuuGfccaccuuCfuCfaauuasasg		CUUAAUUGAGAAGGUGGCAAGUU	
AD-1727318	asasggugGfcAfAfGfuuaugguguuL96		asAfscacCfauaacuuGfcCfaccuuscsu		AGAAGGUGGCAAGUUAUGGUGUG	
AD-1727324	gscsaaguUfaUfGfGfugugaagccuL96		asGfsgcuUfcacaccaUfaAfcuugcscsa		UGGCAAGUUAUGGUGUGAAGCCA	
AD-1727331	asusggugUfgAfAfGfccaagauauuL96		asAfsuauCfuuggcuuCfaCfaccausasa		UUAUGGUGUGAAGCCAAGAUAUG	
AD-1727358	asasaauuUfgGfGfUfcaaagugucuL96		asGfsacaCfuuugaccCfaAfauuuusgsg		CCAAAAUUUGGGUCAAAGUGUCU	
AD-1727359	asasauuuGfgGfUfCfaaagugucuuL96		asAfsgacAfcuuugacCfcAfaauuususg		CAAAAUUUGGGUCAAAGUGUCUG	
AD-1727361	asusuuggGfuCfAfAfagugucugauL96		asUfscagAfcacuuugAfcCfcaaaususu		AAAUUUGGGUCAAAGUGUCUGAA	
AD-1727392	gsusaaugCfaGfAfCfugggucacguL96		asCfsgugAfcccagucUfgCfauuacsusg		CAGUAAUGCAGACUGGGUCACGA	
AD-1727420	asasugaaAfuCfAfAfuuaugaagauL96		asUfscuuCfauaauugAfuUfucauusgsa		UCAAUGAAAUCAAUUAUGAAGAC	
AD-1727427	uscsaauuAfuGfAfAfgaccacaaguL96		asCfsuugUfggucuucAfuAfauugasusu		AAUCAAUUAUGAAGACCACAAGU	
AD-1727428	csasauuaUfgAfAfGfaccacaaguuL96		asAfscuuGfuggucuuCfaUfaauugsasu		AUCAAUUAUGAAGACCACAAGUU	
AD-1727430	asusuaugAfaGfAfCfcacaaguuguL96		asCfsaacUfuguggucUfuCfauaaususg		CAAUUAUGAAGACCACAAGUUGA	
AD-1727431	ususaugaAfgAfCfCfacaaguugauL96		asUfscaaCfuugugguCfuUfcauaasusu		AAUUAUGAAGACCACAAGUUGAA	
AD-1727432	usasugaaGfaCfCfAfcaaguugaauL96		asUfsucaAfcuuguggUfcUfucauasasu		AUUAUGAAGACCACAAGUUGAAG	
AD-1727433	asusgaagAfcCfAfCfaaguugaaguL96		asCfsuucAfacuugugGfuCfuucausasa		UUAUGAAGACCACAAGUUGAAGU	
AD-1727434	usgsaagaCfcAfCfAfaguugaaguuL96		asAfscuuCfaacuuguGfgUfcuucasusa		UAUGAAGACCACAAGUUGAAGUC	
AD-1727435	gsasagacCfaCfAfAfguugaagucuL96		asGfsacuUfcaacuugUfgGfucuucsasu		AUGAAGACCACAAGUUGAAGUCA	
AD-1727436	asasgaccAfcAfAfGfuugaagucauL96		asUfsgacUfucaacuuGfuGfgucuuscsa		UGAAGACCACAAGUUGAAGUCAG	
AD-1727441	csascaagUfuGfAfAfgucagggacuL96		asGfsuccCfugacuucAfaCfuugugsgsu		ACCACAAGUUGAAGUCAGGGACU	
AD-1727442	ascsaaguUfgAfAfGfucagggacuuL96		asAfsgucCfcugacuuCfaAfcuugusgsg		CCACAAGUUGAAGUCAGGGACUA	
AD-1727481	asgsgcagUfgUfAfCfagcaugauguL96		asCfsaucAfugcuguaCfaCfugccusgsg		CCAGGCAGUGUACAGCAUGAUGA	
AD-1727483	gscsagugUfaCfAfGfcaugaugaguL96		asCfsucaUfcaugcugUfaCfacugcscsu		AGGCAGUGUACAGCAUGAUGAGC	
AD-1727565	gsasuggaUfuGfCfAfcaacaugggguL96		asCfsccaUfguugugcAfaUfccaucsasg		CUGAUGGAUUGCACAACAUGGGC	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1727566	asusggauUfgCfAfCfaacaugggcuL96		asGfscccAfuguugugCfaAfuccauscsa		UGAUGGAUUGCACAACAUGGGCG	
AD-1727568	gsgsauugCfaCfAfAfcaugggcggguL96		asCfscgcCfcauguugUfgCfaauccsasu		AUGGAUUGCACAACAUGGGCGGG	
AD-1727569	gsascccaAfuUfAfCfugucauugauL96		asUfscaaUfgacaguaAfuUfgggucscsc		GGGACCCAAUUACUGUCAUUGAU	
AD-1727570	ascsccaaUfuAfCfUfgucauugauuL96		asAfsucaAfugacaguAfaUfuggguscsc		GGACCCAAUUACUGUCAUUGAUG	
AD-1727572	cscsaauuAfcUfGfUfcauugaugauL96		asUfscauCfaaugacaGfuAfauuggsgsu		ACCCAAUUACUGUCAUUGAUGAG	
AD-1727584	asusugauGfaGfAfUfccgggacuuuL96		asAfsaguCfccggaucUfcAfucaausgsa		UCAUUGAUGAGAUCCGGGACUUG	
AD-1727612	ususggcaAfgGfAfUfcgcaaaaacuL96		asGfsuuuUfugcgaucCfuUfgccaasusg		CAUUGGCAAGGAUCGCAAAAACC	
AD-1727633	csasagggAfgGfAfUfuaucuggaauL96		asAfsuccAfgauaaucCfuCfccuugsgsg		CCCAAGGGAGGAUUAUCUGGAUG	
AD-1727638	gsasggauUfaUfCfUfggaugucuauL96		asUfsagaCfauccagaUfaAfucucscsc		GGGAGGAUUAUCUGGAUGUCUAU	
AD-1727639	asgsgauuAfuCfUfGfgaugucuauuL96		asAfsuagAfcauccagAfuAfauccuscsc		GGAGGAUUAUCUGGAUGUCUAUG	
AD-1727640	gsgsauuaUfcUfGfGfaugucuauguL96		asCfsauaGfacauccaGfaUfuaauccsusc		GAGGAUUAUCUGGAUGUCUAUGU	
AD-1727641	gsasuuauCfuGfGfAfugucuauguuL96		asAfscauAfgacauccAfgAfuaaucscsu		AGGAUUAUCUGGAUGUCUAUGUG	
AD-1727642	asusuaucUfgGfAfUfgucuaugugL96		asCfsacaUfagacauccCfaGfauaauscsc		GGAUUAUCUGGAUGUCUAUGUGU	
AD-1727643	ususaucuGfgAfUfGfucuauguguuL96		asAfscacAfuagacauCfcAfgauaasusc		GAUUAUCUGGAUGUCUAUGUGUU	
AD-1727644	usasucugGfaUfGfUfcuauguguuuL96		asAfsacaCfauagacaUfcCfagauasasu		AUUAUCUGGAUGUCUAUGUGUUU	
AD-1727645	asuscuggAfuGfUfCfuauguguuuuL96		asAfsaacAfcauagacAfuCfcagausasa		UUAUCUGGAUGUCUAUGUGUUUG	
AD-1727646	uscsuggaUfgUfCfUfauguguuuguL96		asCfsaaaCfacauagaCfaUfccagasusa		UAUCUGGAUGUCUAUGUGUUUGG	
AD-1727663	asasccaaGfuGfAfAfcaucaaugcuL96		asGfscauUfgauguucAfcUfugguuscsa		UGAACCAAGUGAACAUCAAUGCU	
AD-1727664	ascscaagUfgAfAfCfaucaaugcuuL96		asAfsgcaUfugauguuCfaCfuuggususc		GAACCAAGUGAACAUCAAUGCUU	
AD-1727665	cscsaaguGfaAfCfAfucaaugcuuuL96		asAfsagcAfuugauguUfcAfcuuggsusu		AACCAAGUGAACAUCAAUGCUUU	
AD-1727666	csasagugAfaCfAfUfcaaugcuuuuL96		asAfsaagCfauugaugUfuCfacuugsgsu		ACCAAGUGAACAUCAAUGCUUUG	
AD-1727675	asuscaauGfcUfUfUfUfggcuuccaauL96		asUfsuggAfagccaaaGfcAfuugausgsu		ACAUCAAUGCUUUGGCUUCCAAG	
AD-1727677	csasaugcUfuUfGfGfcuuccaagauL96		asUfscuuGfgaagccaAfaGfcauugsasu		AUCAAUGCUUUGGCUUCCAAGAA	
AD-1727685	usgsgcuuCfcAfAfGfaaagacaauuL96		asAfsuugUfcuuucuuGfgAfagccasasa		UUUGGCUUCCAAGAAAGACAAUG	
AD-1727689	ususccaaGfaAfAfGfacaaugagcuL96		asGfscucAfuugucuuUfcUfuggaasgsc		GCUUCCAAGAAAGACAAUGAGCA	
AD-1727690	uscscaagAfaAfGfAfcaaugagcauL96		asUfsgcuCfauugucuUfuCfuuggasasg		CUUCCAAGAAAGACAAUGAGCAA	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1727693	asasgaaaGfaCfAfAfugagcaacauL96		asUfsguuGfcucauugUfcUfuucuusgsg		CCAAGAAAGACAAUGAGCAACAU	
AD-1727696	asasagacAfaUfGfAfgcaacauguuL96		asAfscauGfuugcucaUfuGfucuuuscsu		AGAAAGACAAUGAGCAACAUGUG	
AD-1727698	asgsacaaUfgAfGfCfaacauguguuL96		asAfscacAfuguugcuCfaUfugucususu		AAAGACAAUGAGCAACAUGUGUU	
AD-1727699	gsascaauGfaGfCfAfacauguguuuL96		asAfsacaCfauguugcUfcAfuugucsusu		AAGACAAUGAGCAACAUGUGUUC	
AD-1727700	ascsaaugAfgCfAfAfcauguguucuL96		asGfsaacAfcauguugCfuCfauuguscsu		AGACAAUGAGCAACAUGUGUUCA	
AD-1727701	csasaugaGfcAfAfCfauguguucauL96		asUfsgaaCfacauguuGfcUfcauugsusc		GACAAUGAGCAACAUGUGUUCAA	
AD-1727703	asusgagcAfaCfAfUfguguucaaauL96		asUfsuugAfacacaugUfuGfcucaususg		CAAUGAGCAACAUGUGUUCAAAG	
AD-1727705	gsasgcaaCfaUfGfUfguucaaaguuL96		asAfscuuUfgaacacaUfgUfugcucsasu		AUGAGCAACAUGUGUUCAAAGUC	
AD-1727708	csasacauGfuGfUfUfcaaagucaauL96		asUfsugaCfuuugaacAfcAfuguugscsu		AGCAACAUGUGUUCAAAGUCAAG	
AD-1727709	asascaugUfgUfUfCfaaagucaaguL96		asCfsuugAfcuuugaaCfaCfauguusgsc		GCAACAUGUGUUCAAAGUCAAGG	
AD-1727710	ascsauguGfuUfCfAfaagucaagguL96		asCfscuuGfacuuugaAfcAfcaugususg		CAACAUGUGUUCAAAGUCAAGGA	
AD-1727712	asusguguUfcAfAfAfgucaaggauuL96		asAfsuccUfugacuuuGfaAfcacausgsu		ACAUGUGUUCAAAGUCAAGGAUA	
AD-1727713	usgsuguuCfaAfAfGfucaaggauauL96		asUfsaucCfuugacuuUfgAfacacasusg		CAUGUGUUCAAAGUCAAGGAUAU	
AD-1727714	gsusguucAfaAfGfUfcaaggauauuL96		asAfsuauCfcuugacuUfuGfaacacsasu		AUGUGUUCAAAGUCAAGGAUAUG	
AD-1727717	ususcaaaGfuCfAfAfggauauggauL96		asUfsccaUfauccuugAfcUfuugaascsa		UGUUCAAAGUCAAGGAUAUGGAA	
AD-1727718	uscsaaagUfcAfAfGfgauauggaauL96		asUfsuccAfuauccuuGfaCfuuugasasc		GUUCAAAGUCAAGGAUAUGGAAA	
AD-1727821	usascgaUfuAfCfCfacaagcaacuL96		asGfsuugCfuugugguAfaUfcgguascsc		GGUACCGAUUACCACAAGCAACC	
AD-1727823	cscsgauuAfcCfAfCfaagcaaccauL96		asUfsgguUfgcuugugGfuAfaucggsusa		UACCGAUUACCACAAGCAACCAU	
AD-1727826	asusuaccAfcAfAfGfcaaccaugguL96		asCfscauGfguugcuuGfuGfguaauscsg		CGAUUACCACAAGCAACCAUGGC	
AD-1727829	ascscacaAfgCfAfAfccauggcaguL96		asCfsugcCfaugguugCfuUfguggusasa		UUACCACAAGCAACCAUGGCAGG	
AD-1727883	usgsguguCfuGfAfGfuacuuuguguL96		asCfsacaAfaguacucAfgAfcaccascsa		UGUGGUGUCUGAGUACUUUGUGC	
AD-1727977	gsasagcaGfgAfAfUfuccugaauuuL96		asAfsauuCfaggaauuCfcUfgcuucsusu		AAGAAGCAGGAAUUCCUGAAUUU	
AD-1727978	asasgcagGfgAfAfUfUfccugaauuuuL96		asAfsaauUfcaggaauUfcCfugcuuscsu		AGAAGCAGGAAUUCCUGAAUUUU	
AD-1727980	gscsaggaAfuUfCfCfugaauuuuauL96		asUfsaaaAfuucaggaAfuUfccugcsusu		AAGCAGGAAUUCCUGAAUUUUAU	
AD-1727981	csasggaaUfuCfCfUfgaauuuuauuL96		asAfsuaaAfauucaggAfaUfuccugscsu		AGCAGGAAUUCCUGAAUUUUAUG	
AD-1727984	gsasauucCfuGfAfAfuuuuaugacuL96		asGfsucaUfaaaauucAfgGfaauucscsu		AGGAAUUCCUGAAUUUUAUGACU	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1727985	asasuuccUfgAfAfUfuuuaugacuuL96		asAfsgucAfuaaaauuCfaGfgaauuscsc		GGAAUUCCUGAAUUUUAUGACUA	
AD-1727986	asususccuGfaAfUfUfuuaugacuauL96		asUfsaguCfauaaaauUfcAfggaaususc		GAAUUCCUGAAUUUUAUGACUAU	
AD-1727987	ususccugAfaUfUfUfuaugacuauuL96		asAfsuagUfcauaaaaUfuCfaggaasusu		AAUUCCUGAAUUUUAUGACUAUG	
AD-1727989	cscsugaaUfuUfUfAfugacuaugauL96		asUfscauAfgucauaaAfaUfucaggsasa		UUCCUGAAUUUUAUGACUAUGAC	
AD-1727990	csusgaauUfuUfAfUfgacuaugacuL96		asGfsucaUfagucauaAfaAfuucagsgsa		UCCUGAAUUUUAUGACUAUGACG	
AD-1727992	gsasauuuUfaUfGfAfcuaugacguuL96		asAfscguCfauagucaUfaAfaauucsasg		CUGAAUUUUAUGACUAUGACGUU	
AD-1727993	asasuuuuAfuGfAfCfuaugacguuuL96		asAfsacgUfcauagucAfuAfaaauuscsa		UGAAUUUUAUGACUAUGACGUUG	
AD-1727994	asusuuuaUfgAfCfUfaugacguuguL96		asCfsaacGfucauaguCfaUfaaaaususc		GAAUUUUAUGACUAUGACGUUGC	
AD-1727996	ususuaugAfcUfAfUfgacguugccuL96		asGfsgcaAfcgucauaGfuCfauaaasasu		AUUUUAUGACUAUGACGUUGCCC	
AD-1727999	asusgacuAfuGfAfCfguugcccuguL96		asCfsaggGfcaacgucAfuAfgucausasa		UUAUGACUAUGACGUUGCCCUGA	
AD-1728049	csasgacuAfuCfAfGfgcccauuuguL96		asCfsaaaUfgggccugAfuAfgucugsgsc		GCCAGACUAUCAGGCCCAUUUGU	
AD-1728050	asgsacuaUfcAfGfGfcccauuuguuL96		asAfscaaAfugggccuGfaUfagucusgsg		CCAGACUAUCAGGCCCAUUUGUC	
AD-1728061	csgsagggAfaCfAfAfcucgagcuuuL96		asAfsagcUfcgaguugUfuCfccucgsgsu		ACCGAGGGAACAACUCGAGCUUU	
AD-1728062	gsasgggaAfcAfAfCfucgagcuuuuL96		asAfsaagCfucgaguuGfuUfcccucsgsg		CCGAGGGAACAACUCGAGCUUUG	
AD-1728067	asascaacUfcGfAfGfcuuugaggcuL96		asGfsccuCfaaagcucGfaGfuuguuscsc		GGAACAACUCGAGCUUUGAGGCU	
AD-1728085	gscsuuccUfcCfAfAfcuaccacuuuL96		asAfsaguGfguaguugGfaGfgaagcscsu		AGGCUUCCUCCAACUACCACUUG	
AD-1728132	csusgcacAfgGfAfUfaucaaagcuuL96		asAfsgcuUfugauaucCfuGfugcagsgsg		CCCUGCACAGGAUAUCAAAGCUC	
AD-1728137	csasggauAfuCfAfAfagcucuguuuL96		asAfsacaGfagcuuugAfuAfuccugsusg		CACAGGAUAUCAAAGCUCUGUUU	
AD-1728140	gsasuaucAfaAfGfCfucuguuuguuL96		asAfscaaAfcagagcuUfuGfauaucscsu		AGGAUAUCAAAGCUCUGUUUGUG	
AD-1728146	asasagcuCfuGfUfUfugugucugauL96		asUfscagAfcacaaacAfgAfgcuuusgsa		UCAAAGCUCUGUUUGUGUCUGAG	
AD-1728195	asasgaaaGfgCfAfGfcugugagaguL96		asCfsucuCfacagcugCfcUfuucuusasu		AUAAGAAAGGCAGCUGUGAGAGA	
AD-1728204	asgscuguGfaGfAfGfagaugcucauL96		asUfsgagCfaucucucUfcAfcagcusgsc		GCAGCUGUGAGAGAGAUGCUCAA	
AD-1728206	csusgugaGfaGfAfGfaugcucaauuL96		asAfsuugAfgcaucucUfcUfcacagscsu		AGCUGUGAGAGAGAUGCUCAAUA	
AD-1728207	usgsugagAfgAfGfAfugcucaauauL96		asUfsauuGfagcaucuCfuCfucacasgsc		GCUGUGAGAGAGAUGCUCAAUAU	
AD-1728208	gsusgagaGfaGfAfUfgcucaauauuL96		asAfsuauUfgagcaucUfcUfcucacsasg		CUGUGAGAGAGAUGCUCAAUAUG	
AD-1728209	usgsagagAfgAfUfGfcucaauauguL96		asCfsauaUfugagcauCfuCfucucascsa		UGUGAGAGAGAUGCUCAAUAUGC	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1728210	gsasgagaGfaUfGfCfucaauaugcuL96		asGfscauAfuugagcaUfcUfcucucsasc		GUGAGAGAGAUGCUCAAUAUGCC	
AD-1728212	csasggcuAfuGfAfCfaaagucaaguL96		asCfsuugAfcuuugucAfuAfgccugsgsg		CCCAGGCUAUGACAAAGUCAAGG	
AD-1728214	gsgscuauGfaCfAfAfagucaaggauL96		asUfsccuUfgacuuugUfcAfuagccsusg		CAGGCUAUGACAAAGUCAAGGAC	
AD-1728220	gsascaaaGfuCfAfAfggacaucucuL96		asGfsagaUfgucccuugAfcUfuugucsasu		AUGACAAAGUCAAGGACAUCUCA	
AD-1728244	ususguacUfgGfAfGfgagugagucuL96		asGfsacuCfacuccucCfaGfuacaasasg		CUUUGUACUGGAGGAGUGAGUCC	
AD-1728258	asasuacuUfgCfAfGfaggugauucuL96		asGfsaauCfaccucugCfaAfguauusgsg		CCAAUACUUGCAGAGGUGAUUCU	
AD-1728260	usascuugCfaGfAfGfgugauucugL96		asCfsagaAfucaccucUfgCfaaguasusu		AAUACUUGCAGAGGUGAUUCUGG	
AD-1728269	usgsauagUfuCfAfCfaagagaaguL96		asAfscuuCfucuugugAfaCfuaucasasg		CUUGAUAGUUCACAAGAGAAGUC	
AD-1728270	gsasuaguUfcAfCfAfagagaagucuL96		asGfsacuUfcucuuguGfaAfcuaucsasa		UUGAUAGUUCACAAGAGAAGUCG	
AD-1728271	asusaguuCfaCfAfAfgagaagucgL96		asCfsgacUfucucuugUfgAfacuauscsa		UGAUAGUUCACAAGAGAAGUCGU	
AD-1728272	usasguucAfcAfAfGfagaagucguL96		asAfscgaCfuucucuuGfuGfaacuasusc		GAUAGUUCACAAGAGAAGUCGUU	
AD-1728273	asgsuucaCfaAfGfAfgaagucguuuL96		asAfsacgAfcuucucuUfgUfgaacusasu		AUAGUUCACAAGAGAAGUCGUUU	
AD-1728274	gsusucacAfaGfAfGfaagucguuuuL96		asAfsaacGfacuucucUfuGfugaacsusa		UAGUUCACAAGAGAAGUCGUUUC	
AD-1728275	ususcacaAfgAfGfAfagucguuucuL96		asGfsaaaCfgacuucuCfuUfgugaascsu		AGUUCACAAGAGAAGUCGUUUCA	
AD-1728276	uscsacaaGfaGfAfAfgucguuucauL96		asUfsgaaAfcgacuucUfcUfugugasasc		GUUCACAAGAGAAGUCGUUUCAU	
AD-1728277	csascaagAfgAfAfGfucguuucauuL96		asAfsugaAfacgacuuCfuCfuugugsasa		UUCACAAGAGAAGUCGUUUCAUU	
AD-1728278	ascsaagaGfaAfGfUfcguuucauuuL96		asAfsaugAfaacgacuUfcUfcuugusgsa		UCACAAGAGAAGUCGUUUCAUUC	
AD-1728279	csasagagAfaGfUfCfguuucauucuL96		asGfsaauGfaaacgacUfuCfucuugsusg		CACAAGAGAAGUCGUUUCAUUCA	
AD-1728280	asasgagaAfgUfCfCfGfuuucauucauL96		asUfsgaaUfgaaacgaCfuUfcucuusgsu		ACAAGAGAAGUCGUUUCAUUCAA	
AD-1728282	gsasgaagUfcGfUfUfUfucauucaaguL96		asCfsuugAfaugaaacGfaCfuucucsusu		AAGAGAAGUCGUUUCAUUCAAGU	
AD-1728283	asgsaaguCfgUfUfUfUfcauucaaguuL96		asAfscuuGfaaugaaaCfgAfcuucuscsu		AGAGAAGUCGUUUCAUUCAAGUU	
AD-1728284	gsasagucGfuUfUfCfUfauucaaguuuL96		asAfsacuUfgaaugaaAfcGfacuucsusc		GAGAAGUCGUUUCAUUCAAGUUG	
AD-1728285	asasgucgUfuUfCfAfuucaaguugL96		asCfsaacUfugaaugaAfaCfgacuucsu		AGAAGUCGUUUCAUUCAAGUUGG	
AD-1728286	asgsucguUfuCfAfUfucaaguuggL96		asCfscaaCfuugaaugAfaAfcgacususc		GAAGUCGUUUCAUUCAAGUUGGU	
AD-1728300	gsasguagUfgGfAfUfgucugcaaauL96		asUfsuugCfagacaucCfaCfuacucscsc		GGAGUAGUGGAUGUCUGCAAAA	
AD-1728301	asgsuaguGfgAfUfGfucugcaaaauL96		asUfsuuuGfcagacauCfcAfcuacuscsc		GGAGUAGUGGAUGUCUGCAAAAA	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1728302	gsusagugGfaUfGfUfcugcaaaaauL96		asUfsuuuUfgcagacaUfcCfacuacsusc		GAGUAGUGGAUGUCUGCAAAAAC	
AD-1728303	usasguggAfuGfUfCfugcaaaaacuL96		asGfsuuuUfugcagacAfuCfcacuascsu		AGUAGUGGAUGUCUGCAAAAACC	
AD-1728307	gsgsauguCfuGfCfAfaaaaccagauL96		asUfscugGfuuuuugcAfgAfcauccsasc		GUGGAUGUCUGCAAAAACCAGAA	
AD-1728308	gsasugucUfgCfAfAfaaaccagaauL96		asUfsucuGfguuuuugCfaGfacaucscsa		UGGAUGUCUGCAAAAACCAGAAG	
AD-1728311	gsuscugcAfaAfAfAfccagaagcguL96		asCfsgcuUfcugguuuUfuGfcagacsasu		AUGUCUGCAAAAACCAGAAGCGG	
AD-1728312	uscsugcaAfaAfAfCfcagaagcgguL96		asCfscgcUfucugguuUfuUfgcagascsa		UGUCUGCAAAAACCAGAAGCGGC	
AD-1728317	asasaaacCfaGfAfAfgcggcaaaauL96		asUfsuuuGfccgcuucUfgGfuuuuusgsc		GCAAAAACCAGAAGCGGCAAAAG	
AD-1728318	asasaaccAfgAfAfGfcggcaaaaguL96		asCfsuuuUfgccgcuuCfuGfguuuususg		CAAAAACCAGAAGCGGCAAAAGC	
AD-1728320	asasccagAfaGfCfGfgcaaaagcauL96		asUfsgcuUfuugccgcUfuCfugguususu		AAAACCAGAAGCGGCAAAAGCAG	
AD-1728324	asgsaagcGfgCfAfAfaagcagguauL96		asUfsaccUfgcuuuugCfcGfcuucusgsg		CCAGAAGCGGCAAAAGCAGGUAC	
AD-1728405	asascuccAfaGfAfUfgaggauuuguL96		asCfsaaaUfccucaucUfuGfgaguususc		GAAACUCCAAGAUGAGGAUUUGG	
AD-1728408	uscscaagAfuGfAfGfgauuuggguuL96		asAfscccAfaauccucAfuCfuuggasgsu		ACUCCAAGAUGAGGAUUUGGGUU	
AD-1728410	csasagauGfaGfGfAfuuuggguuuuL96		asAfsaacCfcaaauccUfcAfucuugsgsa		UCCAAGAUGAGGAUUUGGGUUUU	
AD-1728412	asgsaugaGfgAfUfUfuggguuuucuL96		asGfsaaaAfcccaaauCfcUfcaucususg		CAAGAUGAGGAUUUGGGUUUUCU	
AD-1728422	gsusgggaUfuGfAfAfuuaaaacaguL96		asCfsuguUfuuaauucAfaUfcccacsgsc		GCGUGGGAUUGAAUUAAAACAGC	
AD-1728423	usgsggauUfgAfAfUfuaaaacagcuL96		asGfscugUfuuuaauuCfaAfucccascsg		CGUGGGAUUGAAUUAAAACAGCU	
AD-1728424	gsgsgauuGfaAfUfUfaaaacagcuuL96		asAfsgcuGfuuuuaauUfcAfaucccsasc		GUGGGAUUGAAUUAAAACAGCUG	
AD-1728427	asusugaaUfuAfAfAfacagcugcguL96		asCfsgcaGfcuguuuuAfaUfucaauscsc		GGAUUGAAUUAAAACAGCUGCGA	
AD-1728447	asasgggaAfuGfUfGfaccaggucuuL96		asAfsgadCc(Tgn)ggucacAfuUfcccuuscsc		GGAAGGGAAUGUGACCAGGUCUA	
AD-1728461	asgsgucuAfgGfUfCfuggaguuucuL96		asGfsaadAc(Tgn)ccagacCfuAfgaccusgsg		CCAGGUCUAGGUCUGGAGUUUCA	
AD-1728470	uscsuggaGfuUfUfCfagcuuggacuL96		asGfsucdCa(Agn)gcugaaAfcUfccagascsc		GGUCUGGAGUUUCAGCUUGGACA	
AD-1728471	csusggagUfuUfCfAfgcuuggacauL96		asUfsgudCc(Agn)agcugaAfaCfuccagsasc		GUCUGGAGUUUCAGCUUGGACAC	
AD-1728659	uscscuucUfgGfCfUfucuacccguuL96		asAfscgdGg(Tgn)agaagcCfaGfaaggascsa		UGUCCUUCUGGCUUCUACCCGUA	
AD-1728664	csusggcuUfcUfAfCfccguacccuuL96		asAfsggdGu(Agn)cggguaGfaAfgccagsasa		UUCUGGCUUCUACCCGUACCCUG	
AD-1728671	csusacccGfuAfCfCfcugugcagauL96		asUfscudGc(Agn)caggguAfcGfgguagsasa		UUCUACCCGUACCCUGUGCAGAC	
AD-1728685	usgscagaCfaCfGfUfaccugcagauL96		asUfscudGc(Agn)gguacgUfgUfcugcascsa		UGUGCAGACACGUACCUGCAGAU	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1728736	asasggcaGfaGfUfGfcagagcaauuL96		asAfsuudGc(Tgn)cugcacUfcUfgccuuscsc		GGAAGGCAGAGUGCAGAGCAAUC	
AD-1728777	cscsuacuAfcAfAfUfgugagugauuL96		asAfsucdAc(Tgn)cacauuGfuAfguaggsgsa		UCCCUACUACAAUGUGAGUGAUG	
AD-1728784	csasauguGfaGfUfGfaugagaucuuL96		asAfsgadTc(Tgn)caucacUfcAfcauugsusa		UACAAUGUGAGUGAUGAGAUCUC	
AD-1728786	asusgugaGfuGfAfUfgagaucucuuL96		asAfsgadGa(Tgn)cucaucAfcUfcacaususg		CAAUGUGAGUGAUGAGAUCUCUU	
AD-1728787	usgsugagUfgAfUfGfagaucucuuuL96		asAfsagdAg(Agn)ucucauCfaCfucacasusu		AAUGUGAGUGAUGAGAUCUCUUU	
AD-1728789	usgsagugAfuGfAfGfaucucuuucuL96		asGfsaadAg(Agn)gaucucAfuCfacucascsa		UGUGAGUGAUGAGAUCUCUUUCC	
AD-1728793	usgsaugaGfaUfCfUfcuuuccacuuL96		asAfsgudGg(Agn)aagagaUfcUfcaucascsu		AGUGAUGAGAUCUCUUUCCACUG	
AD-1728801	uscsucuuUfcCfAfCfugcuaugacuL96		asGfsucdAu(Agn)gcagugGfaAfagagasusc		GAUCUCUUUCCACUGCUAUGACG	
AD-1728802	csuscuuuCfcAfCfUfgcuaugacguL96		asCfsgudCa(Tgn)agcaguGfgAfaagagsasu		AUCUCUUUCCACUGCUAUGACGG	
AD-1728810	ascsugcuAfuGfAfCfgguuacacuuL96		asAfsgudGu(Agn)accgucAfuAfgcagusgsg		CCACUGCUAUGACGGUUACACUC	
AD-1728811	csusgcuaUfgAfCfGfguuacacucuL96		asGfsagdTg(Tgn)aaccguCfaUfagcagsusg		CACUGCUAUGACGGUUACACUCU	
AD-1728827	uscsgcacCfuGfCfCfaagugaauguL96		asCfsaudTc(Agn)cuuggcAfgGfugcgasusu		AAUCGCACCUGCCAAGUGAAUGG	
AD-1728861	csasgacaGfcGfAfUfcugugacaauL96		asUfsugdTc(Agn)cagaucGfcUfgucugscsc		GGCAGACAGCGAUCUGUGACAAC	
AD-1728863	gsascagcGfaUfCfUfgugacaacguL96		asCfsgudTg(Tgn)cacagaUfcGfcugucsusg		CAGACAGCGAUCUGUGACAACGG	
AD-1728877	usgsgcacAfaGfGfAfaggugggcauL96		asUfsgcdCc(Agn)ccuuccUfuGfugccasasu		AUUGGCACAAGGAAGGUGGGCAG	
AD-1728909	ususgaagAfcAfGfCfgucaccuacuL96		asGfsuadGg(Tgn)gacgcuGfuCfuucaasgsg		CCUUGAAGACAGCGUCACCUACC	
AD-1728990	asgsacucCfuUfCfAfuguacgacauL96		asUfsgudCg(Tgn)acaugaAfgGfagucususg		CAAGACUCCUUCAUGUACGACAC	
AD-1728995	csasagagGfuGfGfCfcgaagcuuuuL96		asAfsaadGc(Tgn)ucggccAfcCfucuugsasg		CUCAAGAGGUGGCCGAAGCUUUC	
AD-1729031	gsasgaccAfuAfGfAfaggagucgauL96		asUfscgdAc(Tgn)ccuucuAfuGfgucucsusg		CAGAGACCAUAGAAGGAGUCGAU	
AD-1729089	csasggcuCfcAfUfGfaacaucuacuL96		asGfsuadGa(Tgn)guucauGfgAfgccugsasa		UUCAGGCUCCAUGAACAUCUACC	
AD-1729103	asuscuacCfuGfGfUfgcuagaugguL96		asCfscadTc(Tgn)agcaccAfgGfuagausgsu		ACAUCUACCUGGUGCUAGAUGGA	
AD-1729105	csusaccuGfgUfGfCfuagauggauuL96		asAfsucdCa(Tgn)cuagcaCfcAfgguagsasu		AUCUACCUGGUGCUAGAUGGAUC	
AD-1729106	usasccugGfuGfCfUfagauggaucuL96		asGfsaudCc(Agn)ucuagcAfcCfagguasgsa		UCUACCUGGUGCUAGAUGGAUCA	
AD-1729110	usgsgugcUfaGfAfUfggaucagacuL96		asGfsucdTg(Agn)uccaucUfaGfcaccasgsg		CCUGGUGCUAGAUGGAUCAGACA	
AD-1729112	gsusgcuaGfaUfGfGfaucagacaguL96		asCfsugdTc(Tgn)gauccaUfcUfagcacscsa		UGGUGCUAGAUGGAUCAGACAGC	
AD-1729130	csascaggAfgCfCfAfaaaagugucuL96		asGfsacdAc(Tgn)uuuuggCfuCfcugugsasa		UUCACAGGAGCCAAAAAGUGUCU	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1729132	csasggagCfcAfAfAfaagugucuauL96		asUfsagdAc(Agn)cuuuuuGfgCfuccugsusg		CACAGGAGCCAAAAAGUGUCUAG	
AD-1729134	gsgsagccAfaAfAfAfgugucuaguuL96		asAfscudAg(Agn)cacuuuUfuGfgcuccsusg		CAGGAGCCAAAAAGUGUCUAGUC	
AD-1729136	asgsccaaAfaAfGfUfgucuagucauL96		asUfsgadCu(Agn)gacacuUfuUfuggcuscsc		GGAGCCAAAAAGUGUCUAGUCAA	
AD-1729137	gscscaaaAfaGfUfGfucuagucaauL96		asUfsugdAc(Tgn)agacacUfuUfuuggcsusc		GAGCCAAAAAGUGUCUAGUCAAC	
AD-1729139	csasaaaaGfuGfUfCfuagucaacuuL96		asAfsgudTg(Agn)cuagacAfcUfuuuugsgsc		GCCAAAAAGUGUCUAGUCAACUU	
AD-1729141	asasaaguGfuCfUfAfgucaacuuauL96		asUfsaadGu(Tgn)gacuagAfcAfcuuuususg		CAAAAAGUGUCUAGUCAACUUAA	
AD-1729142	asasagugUfcUfAfGfucaacuuaauL96		asUfsuadAg(Tgn)ugacuaGfaCfacuuususu		AAAAAGUGUCUAGUCAACUUAAU	
AD-1729151	asgsucaaCfuUfAfAfuugagaagguL96		asCfscudTc(Tgn)caauuaAfgUfugacusasg		CUAGUCAACUUAAUUGAGAAGGU	
AD-1729180	asusggugUfgAfAfGfccaagauauuL96		asAfsuadTc(Tgn)uggcuuCfaCfaccausasa		UUAUGGUGUGAAGCCAAGAUAUG	
AD-1729207	asasaauuUfgGfGfUfcaaagugucuL96		asGfsacdAc(Tgn)uugaccCfaAfauuuusgsg		CCAAAAUUUGGGUCAAAGUGUCU	
AD-1729242	usasaugcAfgAfCfUfgggucacgauL96		asUfscgdTg(Agn)cccaguCfuGfcauuascsu		AGUAAUGCAGACUGGGUCACGAA	
AD-1729269	asasugaaAfuCfAfAfuuaugaagauL96		asUfscudTc(Agn)uaauugAfuUfucauusgsa		UCAAUGAAAUCAAUUAUGAAGAC	
AD-1729271	usgsaaauCfaAfUfUfaugaagaccuL96		asGfsgudCu(Tgn)cauaauUfgAfuuucasusu		AAUGAAAUCAAUUAUGAAGACCA	
AD-1729274	asasucaaUfuAfUfGfaagaccacauL96		asUfsgudGg(Tgn)cuucauAfaUfugauususc		GAAAUCAAUUAUGAAGACCACAA	
AD-1729277	csasauuaUfgAfAfGfaccacaaguuL96		asAfscudTg(Tgn)ggucuuCfaUfaauugsasu		AUCAAUUAUGAAGACCACAAGUU	
AD-1729280	ususaugaAfgAfCfCfacaaguugauL96		asUfscadAc(Tgn)ugugguCfuUfcauaasusu		AAUUAUGAAGACCACAAGUUGAA	
AD-1729285	asasgaccAfcAfAfGfuugaagucauL96		asUfsgadCu(Tgn)caacuuGfuGfgucuuscsa		UGAAGACCACAAGUUGAAGUCAG	
AD-1729288	ascscacaAfgUfUfGfaagucaggguL96		asCfsccdTg(Agn)cuucaaCfuUfgugguscsu		AGACCACAAGUUGAAGUCAGGGA	
AD-1729290	csascaagUfuGfAfAfgucagggacuL96		asGfsucdCc(Tgn)gacuucAfaCfuugugsgsu		ACCACAAGUUGAAGUCAGGGACU	
AD-1729296	ususgaagUfcAfGfGfgacuaacacuL96		asGfsugdTu(Agn)gucccuGfaCfuucaascsu		AGUUGAAGUCAGGGACUAACACC	
AD-1729297	usgsaaguCfaGfGfGfacuaacaccuL96		asGfsgudGu(Tgn)agucccUfgAfcuucasasc		GUUGAAGUCAGGGACUAACACCA	
AD-1729300	asgsucagGfgAfCfUfaacaccaaguL96		asCfsuudGg(Tgn)guuaguCfcCfugacususc		GAAGUCAGGGACUAACACCAAGA	
AD-1729413	usgsauggAfuUfGfCfacaacaugguL96		asCfscadTg(Tgn)ugugcaAfuCfcaucasgsu		ACUGAUGGAUUGCACAACAUGGG	
AD-1729461	ususggcaAfgGfAfUfcgcaaaaacuL96		asGfsuudTu(Tgn)gcgaucCfuUfgccaasusg		CAUUGGCAAGGAUCGCAAAAACC	
AD-1729462	usgsgcaaGfgAfUfCfgcaaaaaccuL96		asGfsgudTu(Tgn)ugcgauCfcUfugccasasu		AUUGGCAAGGAUCGCAAAAACCC	
AD-1729463	gsgscaagGfaUfCfGfcaaaaacccuL96		asGfsggdTu(Tgn)uugcgaUfcCfuugccsasa		UUGGCAAGGAUCGCAAAAACCCA	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1729487	gsasggauUfaUfCfUfggaugucuauL96		asUfsagdAc(Agn)uccagaUfaAfuccucscsc		GGGAGGAUUAUCUGGAUGUCUAU	
AD-1729514	cscsaaguGfaAfCfAfucaaugcuuuL96		asAfsagdCa(Tgn)ugauguUfcAfcuuggsusu		AACCAAGUGAACAUCAAUGCUUU	
AD-1729515	csasagugAfaCfAfUfcaaugcuuuuL96		asAfsaadGc(Agn)uugaugUfuCfacuugsgsu		ACCAAGUGAACAUCAAUGCUUUG	
AD-1729524	asuscaauGfcUfUfUfggcuuccaauL96		asUfsugdGa(Agn)gccaaaGfcAfuugausgsu		ACAUCAAUGCUUUGGCUUCCAAG	
AD-1729525	uscsaaugCfuUfUfGfgcuuccaaguL96		asCfsuudGg(Agn)agccaaAfgCfauugasusg		CAUCAAUGCUUUGGCUUCCAAGA	
AD-1729538	ususccaaGfaAfAfGfacaaugagcuL96		asGfscudCa(Tgn)ugucuuUfcUfuggaasgsc		GCUUCCAAGAAAGACAAUGAGCA	
AD-1729539	uscscaagAfaAfGfAfcaaugagcauL96		asUfsgcdTc(Agn)uugucuUfuCfuuggasasg		CUUCCAAGAAAGACAAUGAGCAA	
AD-1729541	csasagaaAfgAfCfAfaugagcaacuL96		asGfsuudGc(Tgn)cauuguCfuUfucuugsgsa		UCCAAGAAAGACAAUGAGCAACA	
AD-1729545	asasagacAfaUfGfAfgcaacauguuL96		asAfscadTg(Tgn)ugcucaUfuGfucuuuscsu		AGAAAGACAAUGAGCAACAUGUG	
AD-1729548	gsascaauGfaGfCfAfacauguguuuL96		asAfsacdAc(Agn)uguugcUfcAfuugucsusu		AAGACAAUGAGCAACAUGUGUUC	
AD-1729550	csasaugaGfcAfAfCfauguguucauL96		asUfsgadAc(Agn)cauguuGfcUfcauugsusc		GACAAUGAGCAACAUGUGUUCAA	
AD-1729552	asusgagcAfaCfAfUfguguucaaauL96		asUfsuudGa(Agn)cacaugUfuGfcucaususg		CAAUGAGCAACAUGUGUUCAAAG	
AD-1729555	asgscaacAfuGfUfGfuucaaagucuL96		asGfsacdTu(Tgn)gaacacAfuGfuugcuscsa		UGAGCAACAUGUGUUCAAAGUCA	
AD-1729557	csasacauGfuGfUfUfcaaagucaauL96		asUfsugdAc(Tgn)uugaacAfcAfuguugscsu		AGCAACAUGUGUUCAAAGUCAAG	
AD-1729559	ascsauguGfuUfCfAfaagucaagguL96		asCfscudTg(Agn)cuuugaAfcAfcaugususg		CAACAUGUGUUCAAAGUCAAGGA	
AD-1729561	asusguguUfcAfAfAfgucaaggauuL96		asAfsucdCu(Tgn)gacuuuGfaAfcacausgsu		ACAUGUGUUCAAAGUCAAGGAUA	
AD-1729562	usgsuguuCfaAfAfGfucaaggauauL96		asUfsaudCc(Tgn)ugacuuUfgAfacacasusg		CAUGUGUUCAAAGUCAAGGAUAU	
AD-1729567	uscsaaagUfcAfAfGfgauauggaauL96		asUfsucdCa(Tgn)auccuuGfaCfuuugasasc		GUUCAAAGUCAAGGAUAUGGAAA	
AD-1729568	csasaaguCfaAfGfGfauauggaaauL96		asUfsuudCc(Agn)uauccuUfgAfcuuugsasa		UUCAAAGUCAAGGAUAUGGAAAA	
AD-1729619	usgsaaagCfcAfGfUfcucugagucuL96		asGfsacdTc(Agn)gagacuGfgCfuuucasusc		GAUGAAAGCCAGUCUCUGAGUCU	
AD-1729643	usgsgcauGfgUfUfUfgggaacacauL96		asUfsgudGu(Tgn)cccaaaCfcAfugccascsa		UGUGGCAUGGUUUGGGAACACAG	
AD-1729667	gsgsguacCfgAfUfUfaccacaagcuL96		asGfscudTg(Tgn)gguaauCfgGfuacccsusu		AAGGGUACCGAUUACCACAAGCA	
AD-1729670	usascegaUfuAfCfCfacaagcaacuL96		asGfsuudGc(Tgn)ugugguAfaUfcgguascsc		GGUACCGAUUACCACAAGCAACC	
AD-1729673	csgsauuaCfcAfCfAfagcaaccauuL96		asAfsugdGu(Tgn)gcuuguGfgUfaaucgsgsu		ACCGAUUACCACAAGCAACCAUG	
AD-1729677	usasccacAfaGfCfAfaccauggcauL96		asUfsgcdCa(Tgn)gguugcUfuGfugguasasu		AUUACCACAAGCAACCAUGGCAG	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1729688	ascscaugGfcAfGfGfccaagaucuuL96		asAfsgadTc(Tgn)uggccuGfcCfauggususg		CAACCAUGGCAGGCCAAGAUCUC	
AD-1729690	csasuggcAfgGfCfCfaagaucucauL96		asUfsgadGa(Tgn)cuuggcCfuGfccaugsgsu		ACCAUGGCAGGCCAAGAUCUCAG	
AD-1729729	csusguggUfgUfCfUfgaguacuuuuL96		asAfsaadGu(Agn)cucagaCfaCfcacagscsc		GGCUGUGGUGUCUGAGUACUUUG	
AD-1729802	asgscgggAfcCfUfGfgagauagaauL96		asUfsucdTa(Tgn)cuccagGfuCfccgcususc		GAAGCGGGACCUGGAGAUAGAAG	
AD-1729841	gsasagcaGfgAfAfUfuccugaauuuL96		asAfsaudTc(Agn)ggaauuCfcUfgcuucsusu		AAGAAGCAGGAAUUCCUGAAUUU	
AD-1729849	asasuuccUfgAfAfUfuuuaugacuuL96		asAfsgudCa(Tgn)aaaauuCfaGfgaauuscsc		GGAAUUCCUGAAUUUUAUGACUA	
AD-1729850	asusuccuGfaAfUfUfuuaugacuauL96		asUfsagdTc(Agn)uaaaauUfcAfggaaususc		GAAUUCCUGAAUUUUAUGACUAU	
AD-1729852	uscscugaAfuUfUfUfaugacuauguL96		asCfsaudAg(Tgn)cauaaaAfuUfcaggasasu		AUUCCUGAAUUUUAUGACUAUGA	
AD-1729854	csusgaauUfuUfAfUfgacuaugacuL96		asGfsucdAu(Agn)gucauaAfaAfuucagsgsa		UCCUGAAUUUUAUGACUAUGACG	
AD-1729856	gsasauuuUfaUfGfAfcuaugacguuL96		asAfscgdTc(Agn)uagucaUfaAfaauucsasg		CUGAAUUUUAUGACUAUGACGUU	
AD-1729861	ususaugaCfuAfUfGfacguugcccuL96		asGfsggdCa(Agn)cgucauAfgUfcauaasasa		UUUUAUGACUAUGACGUUGCCCU	
AD-1729862	usasugacUfaUfGfAfcguugcccuuL96		asAfsggdGc(Agn)acgucaUfaGfucauasasa		UUUAUGACUAUGACGUUGCCCUG	
AD-1729869	asusgacgUfuGfCfCfcugaucaaguL96		asCfsuudGa(Tgn)cagggcAfaCfgucausasg		CUAUGACGUUGCCCUGAUCAAGC	
AD-1729870	usgsacguUfgCfCfCfugaucaagcuL96		asGfscudTg(Agn)ucagggCfaAfcgucasusa		UAUGACGUUGCCCUGAUCAAGCU	
AD-1729872	ascsguugCfcCfUfGfaucaagcucuL96		asGfsagdCu(Tgn)gaucagGfgCfaacguscsa		UGACGUUGCCCUGAUCAAGCUCA	
AD-1729926	gsasgggaAfcAfAfCfucgagcuuuuL96		asAfsaadGc(Tgn)cgaguuGfuUfcccucsgsg		CCGAGGGAACAACUCGAGCUUUG	
AD-1729933	csasacucGfaGfCfUfuugaggcuuuL96		asAfsagdCc(Tgn)caaagcUfcGfaguugsusu		AACAACUCGAGCUUUGAGGCUUC	
AD-1729941	gscsuuugAfgGfCfUfuccuccaacuL96		asGfsuudGg(Agn)ggaagcCfuCfaaagcsusc		GAGCUUUGAGGCUUCCUCCAACU	
AD-1729947	asgsgcuuCfcUfCfCfaacuaccacuL96		asGfsugdGu(Agn)guuggaGfgAfagccuscsa		UGAGGCUUCCUCCAACUACCACU	
AD-1729951	ususccucCfaAfCfUfaccacuugcuL96		asGfscadAg(Tgn)gguaguUfgGfaggaasgsc		GCUUCCUCCAACUACCACUUGCC	
AD-1729992	csuscccuGfcAfCfAfggauaucaauL96		asUfsugdAu(Agn)uccuguGfcAfgggagscsa		UGCUCCCUGCACAGGAUAUCAAA	
AD-1729993	uscsccugCfaCfAfGfgauaucaaauL96		asUfsuudGa(Tgn)auccugUfgCfagggasgsc		GCUCCCUGCACAGGAUAUCAAAG	
AD-1729994	cscscugcAfcAfGfGfauaucaaaguL96		asCfsuudTg(Agn)uauccuGfuGfcagggsasg		CUCCCUGCACAGGAUAUCAAAGC	
AD-1729996	csusgcacAfgGfAfUfaucaaagcuuL96		asAfsgcdTu(Tgn)gauaucCfuGfugcagsgsg		CCCUGCACAGGAUAUCAAAGCUC	
AD-1730001	csasggauAfuCfAfAfagcucuguuuL96		asAfsacdAg(Agn)gcuuugAfuAfuccugsusg		CACAGGAUAUCAAAGCUCUGUUU	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1730042	gscsugacUfcGfGfAfaggaggucuuL96		asAfsgadCc(Tgn)ccuuccGfaGfucagcsusu		AAGCUGACUCGGAAGGAGGUCUA	
AD-1730048	uscsggaaGfgAfGfGfucuacaucauL96		asUfsgadTg(Tgn)agaccuCfcUfuccgasgsu		ACUCGGAAGGAGGUCUACAUCAA	
AD-1730053	asgsgaggUfcUfAfCfaucaagaauuL96		asAfsuudCu(Tgn)gauguaGfaCfcuccususc		GAAGGAGGUCUACAUCAAGAAUG	
AD-1730059	asasgaaaGfgCfAfGfcugugagaguL96		asCfsucdTc(Agn)cagcugCfcUfuucuusasu		AUAAGAAAGGCAGCUGUGAGAGA	
AD-1730068	asgscuguGfaGfAfGfagaugcucauL96		asUfsgadGc(Agn)ucucucUfcAfcagcusgsc		GCAGCUGUGAGAGAGAUGCUCAA	
AD-1730071	usgsugagAfgAfGfAfugcucaauauL96		asUfsaudTg(Agn)gcaucuCfuCfucacasgsc		GCUGUGAGAGAGAUGCUCAAUAU	
AD-1730077	asgsgcuaUfgAfCfAfaagucaagguL96		asCfscudTg(Agn)cuuuguCfaUfagccusgsg		CCAGGCUAUGACAAAGUCAAGGA	
AD-1730103	ususccuuUfgUfAfCfuggaggaguuL96		asAfscudCc(Tgn)ccaguaCfaAfaggaascsc		GGUUCCUUUGUACUGGAGGAGUG	
AD-1730108	ususguacUfgGfAfGfgagugagucuL96		asGfsacdTc(Agn)cuccucCfaGfuacaasasg		CUUUGUACUGGAGGAGUGAGUCC	
AD-1730110	gsusacugGfaGfGfAfgugagucccuL96		asGfsggdAc(Tgn)cacuccUfcCfaguacsasa		UUGUACUGGAGGAGUGAGUCCCU	
AD-1730112	ascsuggaGfgAfGfUfgagucccuauL96		asUfsagdGg(Agn)cucacuCfcUfccagusasc		GUACUGGAGGAGUGAGUCCCUAU	
AD-1730118	gsgsagugAfgUfCfCfcuaugcugauL96		asUfscadGc(Agn)uagggaCfuCfacuccsusc		GAGGAGUGAGUCCCUAUGCUGAC	
AD-1730122	asasuacuUfgCfAfGfaggugauucuL96		asGfsaadTc(Agn)ccucugCfaAfguauusgsg		CCAAUACUUGCAGAGGUGAUUCU	
AD-1730133	usgsauagUfuCfAfCfaagagaaguuL96		asAfscudTc(Tgn)cuugugAfaCfuaucasasg		CUUGAUAGUUCACAAGAGAAGUC	
AD-1730143	csasagagAfaGfUfCfguuucauucuL96		asGfsaadTg(Agn)aacgacUfuCfucuugsusg		CACAAGAGAAGUCGUUUCAUUCA	
AD-1730164	gsasguagUfgGfAfUfgucugcaaauL96		asUfsuudGc(Agn)gacaucCfaCfuacucscsc		GGGAGUAGUGGAUGUCUGCAAAA	
AD-1730167	usasguggAfuGfUfCfugcaaaaacuL96		asGfsuudTu(Tgn)gcagacAfuCfcacuascsu		AGUAGUGGAUGUCUGCAAAAACC	
AD-1730168	asgsuggaUfgUfCfUfgcaaaaaccuL96		asGfsgudTu(Tgn)ugcagaCfaUfccacusasc		GUAGUGGAUGUCUGCAAAAACCA	
AD-1730169	gsusggauGfuCfUfGfcaaaaaccauL96		asUfsggdTu(Tgn)uugcagAfcAfuccacsusa		UAGUGGAUGUCUGCAAAAACCAG	
AD-1730171	gsgsauguCfuGfCfAfaaaaccagauL96		asUfscudGg(Tgn)uuuugcAfgAfcauccsasc		GUGGAUGUCUGCAAAAACCAGAA	
AD-1730183	asasaccaGfaAfGfCfggcaaaagcuL96		asGfscudTu(Tgn)gccgcuUfcUfgguuususu		AAAAACCAGAAGCGGCAAAAGCA	
AD-1730184	asasccagAfaGfCfGfgcaaaagcauL96		asUfsgcdTu(Tgn)ugccgcUfuCfugguususu		AAAACCAGAAGCGGCAAAAGCAG	
AD-1730256	usgsgcugAfaGfGfAfgaaacuccauL96		asUfsggdAg(Tgn)uucuccUfuCfagccasgsg		CCUGGCUGAAGGAGAAACUCCAA	
AD-1730287	usgsggauUfgAfAfUfuaaaacagcuL96		asGfscudGu(Tgn)uuaauuCfaAfucccascsg		CGUGGGAUUGAAUUAAAACAGCU	
AD-1730288	gsgsgauuGfaAfUfUfaaaacagcuuL96		asAfsgcdTg(Tgn)uuuaauUfcAfaucccsasc		GUGGGAUUGAAUUAAAACAGCUG	
AD-1730293	usgsaauuAfaAfAfCfagcugcgacuL96		asGfsucdGc(Agn)gcuguuUfuAfauucasasu		AUUGAAUUAAAACAGCUGCGACA	

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-1730476	asasuuaaAfaCfAfGfcugcgacaauL96		asUfsuguCfgcagcugUfuUfuaauuscsa		UGAAUUAAAAACAGCUGCGACAAC	
AD-1730477	asasuuaaaaCfAfGfcugcgacaauL96		asdTsugdTcdGcagcdTgUfuuuaauuscsa		UGAAUUAAAAACAGCUGCGACAAC	
AD-1730478	asusuaaaacAfGfCfugcgacaacuL96		asdGsuudGudCgcagdCuGfuuuuaaususc		GAAUUAAAACAGCUGCGACAACA	

Example 2. *In vitro* screening methods

Cell culture and transfections:

Transfection assays were carried out in primary human hepatocytes (PHH, BioIVT). Transfection was performed by adding of 5µl 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. 40µl of in Invitrogro CP media (BioIVT, Cat # Z99029) containing ~10 x10^3 cells were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Experiments were performed at 10nM, 1nM, and 0.1nM.

Total RNA isolation using DYNABEADS mRNA Isolation Kit:

RNA was isolated using an Highres Biosolution integration system using Dynabeads™ mRNA DIRECT™ Purification Kit (Invitrogen™, Catalog No. 61012). Briefly, 70 µL of Lysis/Binding Buffer and 10 µL of lysis buffer containing 3 µL of magnetic beads were added to the plate with cells. Plates were incubated on an electromagnetic shaker for 10 minutes at room temperature and then magnetic beads were captured and the supernatant was removed. Bead-bound RNA was then washed 2 times with 90 µL Wash Buffer A and once with 90 µL Wash Buffer B. Beads were then washed with 90 µL Elution Buffer, re-captured, and supernatant was removed. Complementary DNA (cDNA) was synthesized using High-Capacity cDNA Reverse Transcription Kit with RNase Inhibitor (Applied Biosystems™, Catalog No. 4374967) according to the manufacturer's recommendations. A master mix containing 1 µL 10X Buffer, 0.4 µL 25X deoxyribonucleotide triphosphate, 1 µL 10X Random primers, 0.5 µL Reverse Transcriptase, 0.5 µL RNase inhibitor, and 6.6 µL of H_2O per reaction was added to RNA isolated above. The plates were sealed, mixed, and incubated on an electromagnetic shaker for 10 minutes at room temperature, followed by 2 hours incubation at 37°C.

CFB mRNA levels were quantified by performing RT-qPCR analysis. 2µl of cDNA were added to a master mix containing 0.5µl of human or cyno GAPDH TaqMan Probe, 0.5µl human or cyno CFB probe (Hs00156060_m1) and 5µl Lightcycler 480 probe master mix (Roche Cat # 04887301001) per well in a 384 well plates. Real time PCR was done in a LightCycler480 Real Time PCR system (Roche). To calculate relative fold change, real-time data were analyzed using the Delta-Delta Threshold Cycle (Relative Quantification) ($\Delta\Delta C_q$[RQ]) method [Schmittgen and Livak 2008] and were normalized to control assays performed using cells transfected with PBS. For all samples, CFB mRNA levels were first normalized to *GAPDH* as a reference gene. Data are expressed as percent of CFB mRNA remaining relative to average PBS control and error is expressed as standard deviation (SD), derived from the 4 transfection replicates.

The results of single dose transfection screens in PHH cells of the dsRNA agents in Tables 2 and 3 are shown in **Table 4**.

Table 4. In Vitro Single dose Screens in Primary Human Hepatocytes

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1728447.1	14	4	13	4	21	3
AD-1724362.1	17	10	13	3	20	4
AD-1724363.1	19	6	26	7	25	1
AD-1724364.1	16	5	19	1	15	4
AD-1724365.1	38	13	47	8	36	4
AD-1724369.1	23	7	27	7	30	9
AD-1724370.1	25	7	48	5	48	8
AD-1724376.1	20	4	19	3	23	6
AD-1728461.1	22	5	28	3	37	5
AD-1724384.1	69	7	52	9	78	14
AD-1728470.1	42	11	43	10	71	12
AD-1724385.1	47	7	66	6	63	9
AD-1728471.1	30	1	40	7	37	10
AD-1724386.1	37	3	49	6	69	15
AD-1724530.1	14	1	30	6	30	5
AD-1724572.1	31	5	62	8	75	18
AD-1728659.1	26	5	36	6	45	9
AD-1724574.1	13	3	16	0	16	4
AD-1724575.1	17	1	32	5	31	6
AD-1724576.1	11	1	15	1	18	3
AD-1724579.1	21	2	21	2	34	7
AD-1728664.1	76	2	85	10	95	9
AD-1726815.1	55	5	67	6	79	9
AD-1728671.1	55	5	60	9	84	8
AD-1724586.1	27	2	41	8	52	4
AD-1728685.1	60	8	66	8	76	11
AD-1724600.1	21	4	32	5	34	5
AD-1728736.1	12	2	17	4	13	2
AD-1724651.1	8	1	11	1	10	2
AD-1724653.1	13	2	17	3	21	6
AD-1724685.1	15	2	33	2	27	3
AD-1726927.1	12	2	22	3	29	5
AD-1724691.1	13	1	17	2	21	2
AD-1728777.1	25	8	50	7	44	6
AD-1726928.1	20	3	32	2	39	4
AD-1724692.1	9	1	16	2	14	3
AD-1724693.1	8	1	11	1	14	2
AD-1726931.1	56	5	61	5	75	3
AD-1724695.1	12	2	24	4	21	1

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1726934.1	25	3	28	10	49	6
AD-1724698.1	18	2	21	1	25	2
AD-1728784.1	7	1	12	2	10	1
AD-1726935.1	9	2	10	2	13	2
AD-1724699.1	6	1	9	1	6	1
AD-1726936.1	6	2	10	2	12	3
AD-1724700.1	8	1	13	2	10	2
AD-1728786.1	9	1	14	4	12	2
AD-1726937.1	7	1	10	1	9	2
AD-1724701.1	9	2	12	1	8	1
AD-1728787.1	54	8	62	7	69	11
AD-1726938.1	12	3	17	3	18	5
AD-1724702.1	6	1	12	3	9	2
AD-1726939.1	4	1	8	1	9	1
AD-1724703.1	7	1	12	3	12	2
AD-1728789.1	12	2	19	3	22	5
AD-1726940.1	10	1	14	4	15	2
AD-1724704.1	8	1	11	2	10	1
AD-1726941.1	14	1	23	8	27	6
AD-1724705.1	13	2	19	6	20	4
AD-1724706.1	3	1	10	2	9	1
AD-1726942.1	7	1	11	3	10	2
AD-1724707.1	10	1	25	2	20	3
AD-1728793.1	14	2	21	8	22	5
AD-1724708.1	10	1	11	1	12	1
AD-1724714.1	12	2	19	5	25	5
AD-1724715.1	10	2	16	5	14	3
AD-1728801.1	6	1	15	8	38	2
AD-1726952.1	12	4	10	3	34	9
AD-1724716.1	15	2	18	3	26	5
AD-1728802.1	52	9	79	13	86	16
AD-1724717.1	31	7	45	9	74	23
AD-1724718.1	8	1	14	3	16	2
AD-1726961.1	6	0	20	3	20	3
AD-1724725.1	5	3	15	2	17	2
AD-1728810.1	59	15	46	11	46	17
AD-1728811.1	35	12	46	4	58	11
AD-1724726.1	20	8	36	7	40	15
AD-1724730.1	16	4	23	7	27	5
AD-1724731.1	31	9	53	10	77	16

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1724741.1	42	8	52	9	64	23
AD-1724742.1	14	4	22	7	22	5
AD-1728827.1	31	10	43	3	51	8
AD-1724743.1	23	10	23	5	60	18
AD-1728861.1	28	10	20	9	28	12
AD-1727012.1	15	5	18	4	22	8
AD-1724776.1	11	4	15	4	18	5
AD-1724777.1	12	6	18	6	25	9
AD-1728863.1	15	5	21	6	33	13
AD-1724778.1	13	3	20	4	24	5
AD-1724779.1	11	4	26	5	37	5
AD-1724780.1	47	6	65	10	88	13
AD-1724781.1	19	4	32	6	42	3
AD-1728877.1	23	4	32	8	37	7
AD-1724792.1	29	9	38	3	47	7
AD-1724819.1	10	1	15	4	21	4
AD-1724823.1	12	1	13	3	23	9
AD-1727059.1	12	2	18	2	15	2
AD-1728909.1	23	5	31	11	46	5
AD-1724824.1	21	4	35	2	30	4
AD-1724825.1	22	4	27	15	44	7
AD-1724860.1	51	11	55	13	73	6
AD-1724894.1	17	3	31	6	41	9
AD-1724897.1	16	1	27	5	26	4
AD-1724899.1	13	4	21	6	19	2
AD-1724900.1	11	2	22	2	26	3
AD-1724903.1	44	5	46	9	69	14
AD-1727140.1	34	21	47	12	75	10
AD-1724904.1	40	4	54	12	54	11
AD-1728990.1	13	2	22	3	16	2
AD-1724905.1	15	1	22	3	25	4
AD-1727142.1	51	11	77	12	81	8
AD-1724906.1	42	6	54	5	53	2
AD-1728995.1	25	4	37	1	26	7
AD-1724910.1	14	1	20	3	12	1
AD-1724919.1	25	5	46	9	38	4
AD-1727181.1	52	11	71	19	76	4
AD-1724945.1	17	4	23	6	26	6
AD-1724946.1	31	6	32	6	61	4
AD-1727183.1	17	4	14	7	20	2

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1724947.1	15	6	18	2	17	4
AD-1727184.1	84	9	87	3	94	11
AD-1724948.1	37	8	43	5	52	5
AD-1724949.1	35	1	52	11	61	8
AD-1725000.1	27	3	47	9	36	5
AD-1725003.1	59	16	65	9	65	5
AD-1729089.1	112	19	122	19	90	20
AD-1725004.1	97	16	106	8	87	13
AD-1725013.1	27	1	43	5	39	5
AD-1725017.1	48	4	75	11	82	9
AD-1729103.1	52	3	74	4	78	9
AD-1725018.1	39	4	43	3	56	7
AD-1725019.1	71	7	102	8	90	7
AD-1729105.1	66	9	84	17	71	13
AD-1725020.1	18	3	31	5	24	2
AD-1729106.1	32	4	48	8	48	6
AD-1725021.1	19	1	30	6	24	3
AD-1725022.1	35	6	43	7	43	10
AD-1725023.1	23	1	39	5	40	2
AD-1729110.1	23	6	36	4	32	4
AD-1725025.1	16	5	29	5	26	6
AD-1729112.1	35	6	49	11	46	8
AD-1727263.1	36	4	52	5	68	13
AD-1725027.1	35	7	47	3	41	11
AD-1725028.1	21	4	44	7	42	3
AD-1725033.1	73	11	89	15	88	10
AD-1727275.1	52	6	52	8	41	2
AD-1725039.1	26	4	28	3	20	2
AD-1727276.1	107	18	99	11	101	10
AD-1725040.1	29	3	41	2	41	13
AD-1725041.1	13	3	24	5	17	3
AD-1727278.1	76	16	83	16	86	10
AD-1725042.1	17	3	24	6	21	3
AD-1725043.1	12	5	21	3	18	3
AD-1725044.1	7	3	14	5	11	1
AD-1729130.1	62	13	81	13	69	7
AD-1725045.1	16	3	25	3	17	4
AD-1725046.1	19	2	21	5	23	6
AD-1729132.1	62	9	50	6	39	6
AD-1725047.1	19	1	25	5	17	3

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1725048.1	15	1	19	2	17	4
AD-1729134.1	34	3	55	11	56	8
AD-1727285.1	23	5	35	3	44	11
AD-1725049.1	14	2	21	5	19	5
AD-1727286.1	32	4	49	9	50	6
AD-1725050.1	17	4	31	9	27	7
AD-1729136.1	16	3	22	3	20	9
AD-1725051.1	10	0	23	3	17	1
AD-1729137.1	7	0	11	2	9	1
AD-1727288.1	5	2	13	2	8	2
AD-1725052.1	9	3	12	1	9	4
AD-1727289.1	9	2	17	2	18	9
AD-1725053.1	11	2	20	4	17	3
AD-1729139.1	7	1	12	2	9	1
AD-1727290.1	8	1	15	4	12	5
AD-1725054.1	5	2	5	0	6	1
AD-1727291.1	9	1	8	2	14	3
AD-1725055.1	6	2	6	2	6	0
AD-1729141.1	9	3	10	4	12	1
AD-1727292.1	7	3	6	2	15	1
AD-1725056.1	15	4	13	2	17	4
AD-1725057.1	8	1	7	2	5	2
AD-1729142.1	16	1	19	5	23	5
AD-1727293.1	9	1	7	1	5	1
AD-1725058.1	12	3	11	4	25	4
AD-1725059.1	8	3	5	1	12	1
AD-1725060.1	22	2	13	5	9	1
AD-1725061.1	18	4	13	3	9	1
AD-1727298.1	29	3	21	3	11	1
AD-1725062.1	27	3	19	2	8	1
AD-1725066.1	28	5	15	2	14	5
AD-1729151.1	40	4	27	3	22	4
AD-1727310.1	85	6	57	13	71	6
AD-1725074.1	25	1	16	2	11	1
AD-1725075.1	22	1	13	3	11	1
AD-1725079.1	38	8	22	4	21	3
AD-1725080.1	65	4	46	5	59	2
AD-1727318.1	38	3	25	3	15	1
AD-1725082.1	26	6	15	4	8	1
AD-1725083.1	30	7	19	5	11	2

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1725088.1	69	5	41	10	40	4
AD-1725092.1	47	7	31	8	19	2
AD-1725095.1	7	2	6	2	5	1
AD-1729180.1	52	5	54	7	57	9
AD-1727331.1	28	3	21	6	30	3
AD-1725096.1	18	1	11	3	6	1
AD-1729207.1	76	9	59	8	90	11
AD-1727358.1	42	4	38	7	50	6
AD-1725122.1	31	3	21	4	21	2
AD-1727359.1	62	11	38	4	29	5
AD-1725123.1	33	3	22	2	41	8
AD-1725125.1	21	5	11	3	6	1
AD-1727361.1	26	3	15	5	9	2
AD-1727392.1	24	2	13	2	9	1
AD-1725156.1	19	1	11	5	16	3
AD-1729242.1	22	2	15	6	11	1
AD-1725158.1	50	6	32	6	40	8
AD-1725159.1	63	10	45	8	42	6
AD-1729269.1	52	1	51	5	51	3
AD-1727420.1	24	4	18	1	13	3
AD-1725184.1	22	4	16	2	9	1
AD-1729271.1	47	5	31	5	23	3
AD-1725186.1	39	5	21	1	16	2
AD-1729274.1	43	5	37	2	40	5
AD-1725189.1	29	5	17	2	14	1
AD-1725190.1	22	5	14	5	12	1
AD-1727427.1	74	8	56	5	66	8
AD-1725191.1	27	3	25	4	21	1
AD-1729277.1	51	12	33	5	35	2
AD-1727428.1	97	4	65	9	70	4
AD-1725192.1	20	2	15	2	9	1
AD-1725193.1	18	1	9	1	12	4
AD-1727430.1	26	6	16	4	17	2
AD-1725194.1	13	2	9	1	8	1
AD-1729280.1	27	5	23	2	20	5
AD-1727431.1	30	8	21	4	20	2
AD-1725195.1	25	6	16	3	13	3
AD-1727432.1	19	4	14	4	9	1
AD-1725196.1	18	5	15	1	11	1
AD-1727433.1	68	19	43	7	65	4

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1725197.1	33	12	27	5	52	3
AD-1727434.1	50	10	49	3	36	2
AD-1725198.1	24	5	21	2	23	3
AD-1727435.1	46	13	36	4	35	4
AD-1725199.1	30	7	27	3	26	6
AD-1729285.1	37	8	38	7	32	3
AD-1727436.1	36	8	25	3	36	9
AD-1725200.1	17	5	16	2	14	1
AD-1729288.1	98	12	91	17	92	15
AD-1725203.1	64	16	69	8	52	4
AD-1725204.1	77	18	77	17	73	7
AD-1729290.1	26	4	25	2	15	2
AD-1727441.1	49	10	52	7	55	7
AD-1725205.1	31	7	35	1	27	4
AD-1725206.1	23	4	31	4	39	4
AD-1727442.1	45	11	44	6	48	5
AD-1725208.1	13	4	16	2	15	2
AD-1729296.1	28	8	33	6	16	5
AD-1725211.1	28	9	32	3	39	3
AD-1725212.1	16	9	21	3	20	4
AD-1729300.1	58	16	48	6	77	15
AD-1725215.1	15	3	20	6	33	5
AD-1725216.1	20	6	28	12	33	5
AD-1725243.1	32	4	37	10	49	8
AD-1725244.1	12	3	16	4	10	3
AD-1727481.1	22	2	36	4	23	0
AD-1725245.1	16	1	22	3	15	4
AD-1727483.1	30	2	41	7	48	9
AD-1725247.1	13	2	25	3	24	3
AD-1725327.1	22	4	35	7	27	5
AD-1729413.1	68	19	82	10	87	6
AD-1725328.1	39	3	57	9	75	10
AD-1727565.1	71	6	90	5	94	5
AD-1725329.1	54	8	91	15	103	16
AD-1727566.1	70	10	90	9	105	13
AD-1725330.1	62	10	76	6	92	10
AD-1725331.1	31	4	67	4	73	17
AD-1727568.1	85	10	105	11	88	8
AD-1725332.1	54	5	59	8	63	7
AD-1727569.1	21	3	37	7	41	7

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1725333.1	24	4	38	4	44	6
AD-1727570.1	22	4	34	5	38	5
AD-1725334.1	20	4	32	4	26	8
AD-1725336.1	17	5	34	10	30	6
AD-1725344.1	39	6	54	10	64	17
AD-1725345.1	38	2	62	5	68	5
AD-1725347.1	35	3	50	11	49	4
AD-1727584.1	32	5	44	2	36	7
AD-1725348.1	15	3	24	1	22	4
AD-1727612.1	35	8	20	1	40	5
AD-1725376.1	16	6	45	13	41	7
AD-1729461.1	66	13	78	16	79	3
AD-1729462.1	34	19	93	6	99	8
AD-1725377.1	62	15	87	16	89	9
AD-1729463.1	28	6	58	2	46	5
AD-1725378.1	25	4	44	4	43	5
AD-1727633.1	47	7	64	14	58	11
AD-1725397.1	16	3	24	6	20	5
AD-1729487.1	13	0	21	1	10	3
AD-1727638.1	11	1	23	2	15	3
AD-1725402.1	14	2	25	3	15	3
AD-1727639.1	14	2	23	6	14	3
AD-1725403.1	12	3	21	4	13	2
AD-1727640.1	37	5	60	6	68	11
AD-1725404.1	16	2	35	3	27	7
AD-1727641.1	13	2	26	5	20	1
AD-1725405.1	9	1	15	2	11	2
AD-1727642.1	47	8	82	13	78	8
AD-1725406.1	17	1	26	4	23	4
AD-1727643.1	21	1	36	9	31	5
AD-1725407.1	13	1	26	3	20	5
AD-1727644.1	14	1	24	2	23	4
AD-1725408.1	8	1	15	1	10	1
AD-1727645.1	14	2	21	2	15	2
AD-1725409.1	12	3	16	3	12	2
AD-1727646.1	47	6	74	10	83	11
AD-1725410.1	22	1	37	4	32	4
AD-1725411.1	24	3	44	6	44	7
AD-1730469.1	72	3	96	11	102	4
AD-1730470.1	36	4	55	11	76	4

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1730471.1	16	3	27	5	30	6
AD-1727663.1	45	4	60	15	54	5
AD-1725427.1	18	2	34	2	27	2
AD-1727664.1	32	5	53	3	45	6
AD-1725428.1	21	3	35	5	29	3
AD-1729514.1	13	2	21	3	15	3
AD-1727665.1	12	3	19	4	20	3
AD-1725429.1	11	2	22	5	14	2
AD-1729515.1	37	5	36	5	34	3
AD-1727666.1	15	2	23	4	14	3
AD-1725430.1	11	1	13	5	13	3
AD-1729524.1	30	3	56	5	49	4
AD-1727675.1	24	5	35	9	26	5
AD-1725439.1	29	6	44	10	45	10
AD-1725440.1	25	1	32	4	29	3
AD-1729525.1	29	8	47	8	59	11
AD-1727677.1	30	6	47	6	41	2
AD-1725441.1	21	2	28	1	26	2
AD-1725449.1	32	7	41	7	29	8
AD-1729538.1	29	3	55	4	51	8
AD-1727689.1	41	5	67	8	61	9
AD-1725453.1	29	9	47	5	54	8
AD-1727690.1	9	4	14	5	16	4
AD-1725454.1	15	3	18	4	24	2
AD-1729541.1	9	4	26	2	17	4
AD-1725456.1	13	3	18	1	15	2
AD-1727693.1	11	1	18	3	11	2
AD-1725457.1	9	2	20	2	11	3
AD-1729545.1	15	3	22	4	18	2
AD-1727696.1	12	3	9	3	15	3
AD-1725460.1	5	2	8	2	11	2
AD-1727698.1	19	1	20	2	23	10
AD-1725462.1	5	1	9	3	8	3
AD-1729548.1	7	2	9	2	7	3
AD-1727699.1	7	2	7	2	10	2
AD-1725463.1	4	1	7	3	7	1
AD-1725464.1	3	1	8	1	10	1
AD-1729550.1	26	1	24	11	38	4
AD-1727701.1	13	2	28	2	33	5
AD-1725465.1	9	1	19	4	19	3

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1729552.1	25	3	33	3	26	4
AD-1727703.1	6	1	11	2	10	1
AD-1725467.1	7	1	12	2	14	3
AD-1725469.1	7	2	11	1	16	2
AD-1727705.1	16	2	29	2	29	8
AD-1729555.1	7	1	10	1	13	1
AD-1725470.1	11	1	17	2	19	5
AD-1729557.1	42	6	60	3	48	4
AD-1727708.1	12	3	16	2	19	3
AD-1725472.1	9	0	13	2	11	2
AD-1725473.1	11	2	18	3	18	1
AD-1729559.1	18	4	28	6	45	4
AD-1727710.1	39	6	68	11	70	7
AD-1725474.1	19	4	40	2	38	3
AD-1729561.1	11	1	17	1	22	3
AD-1727712.1	10	1	16	1	19	1
AD-1725476.1	6	1	9	1	13	1
AD-1729562.1	4	3	4	1	6	2
AD-1727713.1	8	1	10	1	12	1
AD-1725477.1	7	0	10	0	13	1
AD-1727714.1	9	2	15	1	20	3
AD-1725478.1	9	1	12	1	12	1
AD-1727717.1	23	2	38	4	53	6
AD-1725481.1	17	2	29	6	37	1
AD-1727718.1	19	2	33	3	40	3
AD-1725482.1	16	3	31	4	31	9
AD-1729567.1	65	13	60	8	70	6
AD-1729568.1	20	4	23	3	25	4
AD-1725483.1	13	1	12	2	16	1
AD-1725534.1	13	2	23	8	38	8
AD-1725535.1	6	1	6	1	9	0
AD-1725548.1	5	2	12	3	19	3
AD-1725552.1	29	6	67	7	75	9
AD-1725556.1	13	6	22	6	29	5
AD-1729643.1	9	6	24	6	26	5
AD-1725558.1	20	3	32	8	40	6
AD-1725580.1	25	5	32	5	35	4
AD-1729667.1	43	7	59	4	68	10
AD-1725582.1	46	8	47	7	55	9
AD-1729670.1	12	3	25	4	34	3

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1727821.1	19	2	38	9	46	6
AD-1725585.1	15	1	27	4	41	6
AD-1727823.1	72	8	71	11	77	10
AD-1725587.1	21	2	43	1	48	11
AD-1729673.1	22	2	32	8	33	7
AD-1725588.1	19	4	20	4	31	5
AD-1725590.1	17	4	36	4	55	8
AD-1727826.1	99	18	83	7	84	15
AD-1725591.1	42	5	77	4	78	14
AD-1729677.1	17	2	24	1	29	6
AD-1725592.1	20	2	34	2	47	4
AD-1727829.1	88	22	89	14	93	7
AD-1725593.1	14	2	17	3	33	7
AD-1725598.1	94	24	66	11	79	18
AD-1729688.1	24	3	54	12	61	13
AD-1725603.1	11	3	20	3	23	2
AD-1725604.1	15	4	17	3	29	4
AD-1729690.1	88	9	83	12	86	17
AD-1725605.1	64	11	49	8	67	12
AD-1725643.1	7	0	10	2	15	1
AD-1725644.1	2	0	11	3	13	3
AD-1729729.1	28	6	31	7	41	11
AD-1725645.1	18	7	42	7	41	5
AD-1725646.1	13	5	37	7	46	9
AD-1727883.1	16	6	28	6	44	9
AD-1725647.1	14	3	17	5	29	8
AD-1725667.1	23	4	30	6	40	6
AD-1725716.1	67	14	49	12	62	15
AD-1725717.1	22	2	46	9	63	14
AD-1729802.1	102	26	77	11	79	13
AD-1729841.1	3	1	7	2	11	2
AD-1727977.1	2	0	6	1	12	5
AD-1725756.1	3	0	6	2	10	2
AD-1727978.1	11	2	11	2	15	4
AD-1725757.1	6	1	7	2	10	2
AD-1727980.1	7	2	8	2	11	4
AD-1725759.1	7	2	6	1	13	2
AD-1727981.1	6	0	7	1	10	1
AD-1725760.1	7	1	8	2	11	1
AD-1725761.1	6	2	7	2	9	2

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1725762.1	9	3	17	2	19	3
AD-1727984.1	7	1	9	1	10	2
AD-1725763.1	3	1	5	1	8	2
AD-1727985.1	7	1	10	2	17	4
AD-1725764.1	4	1	5	2	11	1
AD-1729849.1	42	10	31	5	41	11
AD-1729850.1	12	4	14	3	21	2
AD-1727986.1	5	1	9	2	13	1
AD-1725765.1	8	1	14	2	22	2
AD-1727987.1	6	1	8	1	12	2
AD-1725766.1	5	1	9	2	12	2
AD-1725767.1	6	1	10	2	14	1
AD-1729852.1	33	7	43	7	58	16
AD-1727989.1	10	2	13	3	16	2
AD-1725768.1	9	2	15	3	18	2
AD-1729854.1	21	1	31	5	32	3
AD-1727990.1	10	1	17	2	19	3
AD-1725769.1	8	1	14	1	20	2
AD-1727992.1	9	1	15	4	21	2
AD-1725771.1	8	2	12	3	7	4
AD-1729856.1	14	4	24	3	29	2
AD-1727993.1	13	1	24	3	18	6
AD-1725772.1	7	1	9	1	10	2
AD-1727994.1	23	2	40	6	43	7
AD-1725773.1	7	2	11	3	15	1
AD-1727996.1	19	8	30	2	53	7
AD-1725775.1	45	10	55	8	71	8
AD-1729861.1	60	5	69	2	79	6
AD-1725776.1	23	6	29	9	57	9
AD-1729862.1	37	10	42	6	42	2
AD-1725777.1	8	2	12	3	15	2
AD-1727999.1	50	7	64	14	78	9
AD-1725778.1	17	5	25	3	35	3
AD-1725779.1	16	1	21	1	29	4
AD-1725780.1	7	1	11	1	11	2
AD-1729869.1	28	1	43	5	57	11
AD-1725784.1	10	2	15	1	17	1
AD-1729870.1	30	2	50	13	59	4
AD-1725785.1	13	1	21	3	34	2
AD-1725786.1	16	4	22	3	30	2

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1729872.1	44	3	51	12	54	5
AD-1725787.1	16	3	24	3	28	5
AD-1725789.1	11	1	16	2	20	3
AD-1725790.1	20	1	29	4	37	6
AD-1728049.1	102	14	94	11	100	14
AD-1725828.1	26	5	34	6	46	9
AD-1725829.1	44	7	50	8	64	3
AD-1725830.1	11	2	21	5	26	5
AD-1725831.1	18	5	21	3	24	2
AD-1725832.1	15	1	26	4	37	4
AD-1728061.1	38	5	40	5	50	10
AD-1725840.1	43	3	32	4	29	2
AD-1729926.1	44	6	50	4	45	5
AD-1728062.1	38	4	37	4	46	6
AD-1725841.1	13	2	15	2	20	3
AD-1725842.1	12	2	17	2	22	6
AD-1725845.1	56	12	74	7	81	18
AD-1728067.1	85	10	98	21	108	12
AD-1725846.1	42	6	68	7	75	11
AD-1729933.1	16	1	22	5	21	1
AD-1725848.1	12	2	14	1	15	3
AD-1725849.1	14	4	17	5	28	5
AD-1725850.1	31	4	39	9	58	6
AD-1725854.1	12	1	15	7	23	7
AD-1725855.1	8	1	10	5	19	2
AD-1729941.1	30	3	47	7	59	5
AD-1725856.1	20	4	32	1	39	6
AD-1725857.1	10	0	15	2	18	4
AD-1725858.1	25	4	36	8	46	7
AD-1725861.1	39	6	41	7	66	12
AD-1729947.1	51	7	46	14	53	2
AD-1725862.1	40	4	51	6	66	7
AD-1728085.1	25	5	50	10	48	8
AD-1725864.1	11	2	20	3	25	4
AD-1729951.1	27	7	45	7	59	11
AD-1725866.1	16	4	29	7	40	9
AD-1725867.1	24	6	34	6	54	5
AD-1725872.1	15	2	17	3	26	6
AD-1725874.1	20	8	25	3	39	8
AD-1729992.1	60	8	34	8	41	13

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1725907.1	45	10	29	10	54	10
AD-1729993.1	51	9	25	4	47	13
AD-1725908.1	15	0	13	4	19	2
AD-1729994.1	47	12	60	10	79	18
AD-1725909.1	17	3	29	10	42	7
AD-1728132.1	31	7	35	7	65	4
AD-1725911.1	36	5	36	7	58	10
AD-1730001.1	6	1	10	4	21	4
AD-1728137.1	6	1	10	2	19	3
AD-1725916.1	5	1	10	2	12	1
AD-1728140.1	7	1	16	6	28	4
AD-1725919.1	7	3	16	5	22	5
AD-1728146.1	10	1	16	2	26	8
AD-1725925.1	6	1	10	2	24	7
AD-1730042.1	18	2	37	4	65	14
AD-1725957.1	24	3	32	3	50	9
AD-1725958.1	18	1	28	6	42	8
AD-1725961.1	8	1	16	4	21	3
AD-1730048.1	10	1	17	2	27	5
AD-1725963.1	15	3	19	4	26	4
AD-1725964.1	18	4	15	3	22	6
AD-1725967.1	15	3	26	8	33	4
AD-1730053.1	62	7	51	11	73	17
AD-1725968.1	46	7	39	7	56	7
AD-1730059.1	31	6	51	6	85	23
AD-1728195.1	23	4	38	4	67	13
AD-1725974.1	11	3	16	1	46	13
AD-1725977.1	20	4	24	2	25	15
AD-1730068.1	11	1	13	2	11	5
AD-1728204.1	15	1	18	3	38	5
AD-1725983.1	11	2	15	3	24	4
AD-1728206.1	11	1	16	3	40	10
AD-1725985.1	7	2	12	2	21	2
AD-1728207.1	12	3	23	2	25	7
AD-1725986.1	18	4	22	3	25	4
AD-1728208.1	13	1	22	1	35	2
AD-1725987.1	13	3	17	2	24	2
AD-1728209.1	46	6	70	6	101	10
AD-1725988.1	20	7	28	5	43	7
AD-1725989.1	23	4	38	1	66	7

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1728210.1	26	4	42	1	65	8
AD-1728212.1	16	2	23	3	57	7
AD-1725991.1	10	1	18	4	31	6
AD-1730077.1	46	2	62	6	102	8
AD-1725992.1	33	2	54	8	92	10
AD-1728214.1	17	2	30	5	74	16
AD-1725993.1	13	2	25	7	50	5
AD-1728220.1	10	2	10	4	34	2
AD-1725999.1	11	2	16	3	32	3
AD-1726014.1	41	5	68	13	100	31
AD-1726015.1	30	5	53	11	98	16
AD-1726016.1	49	9	76	14	114	5
AD-1730103.1	38	8	56	7	92	12
AD-1726018.1	29	10	42	4	80	10
AD-1726020.1	34	5	45	3	74	24
AD-1730108.1	63	5	79	13	109	14
AD-1728244.1	58	9	85	9	109	12
AD-1726023.1	40	6	44	7	105	14
AD-1726024.1	31	9	51	9	88	18
AD-1730110.1	44	6	53	4	108	17
AD-1726025.1	21	3	34	9	65	10
AD-1730112.1	62	12	76	9	92	10
AD-1726027.1	23	5	36	4	66	14
AD-1726029.1	17	5	41	7	76	7
AD-1726031.1	20	3	31	5	53	10
AD-1730118.1	48	8	74	13	96	13
AD-1726033.1	34	4	64	5	99	11
AD-1726034.1	18	5	33	5	53	11
AD-1726036.1	7	1	15	4	22	2
AD-1728258.1	3	0	15	4	43	3
AD-1726037.1	9	2	15	4	32	7
AD-1730122.1	12	3	18	3	37	6
AD-1728260.1	21	2	34	4	70	7
AD-1726039.1	15	1	22	3	55	12
AD-1726041.1	19	2	35	5	75	13
AD-1726042.1	36	8	52	11	96	13
AD-1730472.1	14	5	24	7	66	11
AD-1730133.1	8	2	21	2	32	4
AD-1728269.1	12	2	25	2	55	10
AD-1726048.1	7	2	13	1	24	1

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1728270.1	14	5	35	8	90	20
AD-1726049.1	18	6	42	7	81	6
AD-1728271.1	11	4	20	2	38	10
AD-1726050.1	8	2	13	3	19	4
AD-1726051.1	4	1	6	2	10	3
AD-1728272.1	20	4	30	3	64	16
AD-1728273.1	4	2	9	4	20	3
AD-1726052.1	4	1	9	2	19	5
AD-1728274.1	7	2	13	1	28	7
AD-1726053.1	5	1	9	3	17	4
AD-1728275.1	8	4	15	4	35	9
AD-1726054.1	6	3	12	3	22	6
AD-1728276.1	4	1	8	4	15	5
AD-1726055.1	6	2	11	2	15	1
AD-1728277.1	7	1	9	2	17	3
AD-1726056.1	6	1	7	1	13	2
AD-1728278.1	5	1	10	3	12	3
AD-1726057.1	6	1	7	1	14	2
AD-1726058.1	7	1	12	3	11	5
AD-1730143.1	8	2	14	1	19	3
AD-1728279.1	7	1	13	2	21	2
AD-1726059.1	8	1	16	2	18	3
AD-1726060.1	9	1	16	4	18	2
AD-1728282.1	17	2	29	9	62	11
AD-1726061.1	9	2	17	2	33	7
AD-1728283.1	15	2	30	5	39	3
AD-1726062.1	7	0	14	3	15	2
AD-1728284.1	12	1	20	2	28	5
AD-1726063.1	11	0	15	3	29	6
AD-1728285.1	8	1	16	3	31	3
AD-1726064.1	11	1	17	5	27	5
AD-1728286.1	14	4	25	4	64	10
AD-1726065.1	9	1	14	1	27	6
AD-1730474.1	18	3	28	11	56	6
AD-1730473.1	15	2	28	5	56	8
AD-1730475.1	9	1	13	2	20	3
AD-1730164.1	29	4	42	4	47	7
AD-1728300.1	18	2	27	2	38	1
AD-1726079.1	14	2	23	7	35	4
AD-1728301.1	12	2	16	2	24	3

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1726080.1	9	2	14	2	20	4
AD-1728302.1	6	2	7	3	9	2
AD-1726081.1	7	3	9	3	16	3
AD-1730167.1	8	2	9	5	16	6
AD-1728303.1	9	1	16	1	17	3
AD-1726082.1	10	0	17	2	20	6
AD-1730168.1	27	6	51	7	73	7
AD-1726083.1	21	3	37	8	63	13
AD-1726084.1	11	1	18	1	24	5
AD-1730169.1	20	2	23	3	32	5
AD-1726085.1	9	3	21	2	33	5
AD-1730171.1	21	3	39	3	49	7
AD-1728307.1	17	1	32	5	50	6
AD-1726086.1	15	5	29	4	53	11
AD-1728308.1	16	3	25	3	44	6
AD-1726087.1	11	2	15	2	21	2
AD-1728311.1	50	13	73	14	109	15
AD-1726090.1	21	2	42	9	70	10
AD-1728312.1	55	4	60	12	104	19
AD-1726091.1	18	3	32	5	46	8
AD-1726092.1	32	5	71	9	82	7
AD-1726095.1	68	8	73	9	79	12
AD-1728317.1	34	2	40	5	42	9
AD-1726096.1	16	2	24	4	24	5
AD-1728318.1	106	19	45	15	110	4
AD-1726097.1	17	4	28	6	38	4
AD-1730183.1	61	7	71	14	94	16
AD-1726098.1	54	3	69	10	90	9
AD-1730184.1	69	6	74	4	93	12
AD-1728320.1	48	9	73	12	94	4
AD-1726099.1	40	7	71	11	79	7
AD-1726103.1	70	12	83	11	73	5
AD-1728324.1	67	9	71	12	68	13
AD-1726113.1	51	7	74	3	88	8
AD-1726159.1	15	4	32	5	39	8
AD-1730256.1	35	6	42	7	56	6
AD-1726171.1	15	2	21	2	32	4
AD-1728405.1	30	7	42	5	67	9
AD-1726184.1	11	3	19	2	30	8
AD-1728408.1	17	1	39	8	63	9

Duplex Name	10nM Average mRNA remaining (%)	10nM STDEV	1nM Average mRNA remaining (%)	1nM STDEV	0.1nM Average mRNA remaining (%)	0.1nM STDEV
AD-1726187.1	11	2	22	5	39	11
AD-1728410.1	9	2	17	3	20	4
AD-1726189.1	7	2	14	1	17	4
AD-1728412.1	9	2	19	3	29	6
AD-1726191.1	9	1	18	3	26	10
AD-1726201.1	8	1	17	1	16	3
AD-1728422.1	12	3	20	6	23	5
AD-1730287.1	13	3	24	2	31	5
AD-1728423.1	15	3	30	5	37	4
AD-1726202.1	15	2	29	7	44	8
AD-1730288.1	12	1	25	6	41	7
AD-1726203.1	11	2	17	4	25	6
AD-1728427.1	16	4	36	4	56	14
AD-1726206.1	12	2	22	3	28	7
AD-1726207.1	4	1	10	1	11	5
AD-1730293.1	13	4	19	3	23	3
AD-1726208.1	6	2	16	2	20	5
AD-1726209.1	7	1	17	4	17	4
AD-1730476.1	22	5	25	3	17	6
AD-1730477.1	7	1	13	3	13	3
AD-1730478.1	21	3	36	7	50	11

Example 3. *In vitro* screening methods

A subset of the duplexes was also assessed by transfection and free uptake in primary human hepatocytes and primary cynomolgus hepatocytes.

Transfection and free uptake assays were carried out in primary human hepatocyte (PHH, BioIVT) and primary cynomolgus hepatocyte (PCH, BioIVT). Transfection was performed by adding of 5µl 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. 40µl of in Invitrogro CP media (BioIVT, Cat # Z99029) containing ~10 x10^3 cells were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Experiments were performed at 10nM, 1nM, 0.1nM and 0.01nM. Free uptake assay was performed similarly to transfection assay without using Liporectamine RNAimax and cells were incubated for 48 hours prior to the RNA purification. Experiments were performed at 200nM, 100nM, 10nM, 1nM.

RNA was isolated using an Highres Biosolution integration system using Dynabeads™ mRNA DIRECT™ Purification Kit (Invitrogen™, Catalog No. 61012). Briefly, 70 µL of

Lysis/Binding Buffer and 10 µL of lysis buffer containing 3 µL of magnetic beads were added to the plate with cells. Plates were incubated on an electromagnetic shaker for 10 minutes at room temperature and then magnetic beads were captured and the supernatant was removed. Bead-bound RNA was then washed 2 times with 90 µL Wash Buffer A and once with 90 µL Wash Buffer B. Beads were then washed with 90 µL Elution Buffer, re-captured, and supernatant was removed. Complementary DNA (cDNA) was synthesized using High-Capacity cDNA Reverse Transcription Kit with RNase Inhibitor (Applied Biosystems™, Catalog No. 4374967) according to the manufacturer's recommendations. A master mix containing 1 µL 10X Buffer, 0.4 µL 25X deoxyribonucleotide triphosphate, 1 µL 10X Random primers, 0.5 µL Reverse Transcriptase, 0.5 µL RNase inhibitor, and 6.6 µL of H_2O per reaction was added to RNA isolated above. The plates were sealed, mixed, and incubated on an electromagnetic shaker for 10 minutes at room temperature, followed by 2 hours incubation at 37°C.

CFB mRNA levels were quantified by performing RT-qPCR analysis. 2µl of cDNA were added to a master mix containing 0.5µl of human or cyno GAPDH TaqMan Probe, 0.5µl human or cyno CFB probe (Hs00156060_m1) and 5µl Lightcycler 480 probe master mix (Roche Cat # 04887301001) per well in a 384 well plates. Real time PCR was done in a LightCycler480 Real Time PCR system (Roche). To calculate relative fold change, real-time data were analyzed using the Delta-Delta Threshold Cycle (Relative Quantification) ($\Delta\Delta C_q$[RQ]) method [Schmittgen and Livak 2008] and were normalized to control assays performed using cells transfected with PBS. For all samples, CFB mRNA levels were first normalized to *GAPDH* as a reference gene. Data are expressed as percent of CFB mRNA remaining relative to average PBS control and error is expressed as standard deviation (SD), derived from the 4 transfection replicates.

The results of single dose transfection screens and free uptake screens in PHH and PCH cells are shown in Tables 5 and 6, respectively.

Table 5. In Vitro Single Dose Tranfection and Free Update Screens in Primary Human Hepatocytes

	Primary Human Hepatocytes Transfection								Primary Human Hepatocytes Free Uptake							
Duplex Name	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**	**0.1nM Avg**	**0.1nM Stdev**	**0.01nM Avg**	**0.01nM Stdev**	**200nM Avg**	**200nM Stdev**	**100nM Avg**	**100nM Stdev**	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**
AD-1724704.1	8	2	7	3	15	3	19	2	9	3	8	2	33	5	50	8
AD-1729137.1	8	2	12	3	20	5	25	3	32	2	30	3	53	1	87	11
AD-1725059.1	6	2	8	1	13	4	18	4	10	1	10	1	27	4	61	17
AD-1727392.1	9	2	12	4	20	4	27	5	27	4	62	18	54	4	32	3
AD-1725408.1	7	2	11	2	16	3	18	3	16	2	15	2	46	5	68	5
AD-1727703.1	9	1	15	1	21	4	23	2	31	3	33	6	63	4	74	7
AD-1725478.1	10	0	13	1	20	4	27	4	20	2	91	6	51	7	38	5
AD-1725759.1	13	2	19	3	25	3	33	5	30	5	29	6	69	7	86	3
AD-1725771.1	8	1	15	4	19	2	31	4	20	2	24	4	56	5	88	6
AD-1726051.1	16	2	16	3	21	4	18	2	17	5	24	2	59	7	79	9
AD-1726057.1	14	5	13	3	12	1	8	5	14	3	14	3	42	8	50	21
AD-1724693.1	8	2	8	2	22	0	29	3	22	1	22	2	43	2	39	16
AD-1724706.1	7	1	15	3	18	2	33	5	12	2	15	1	35	2	63	9
AD-1727288.1	8	4	11	2	24	5	24	5	16	4	20	2	46	2	69	7
AD-1725060.1	12	1	18	5	38	4	50	5	44	3	42	2	73	6	96	16
AD-1725192.1	15	2	20	2	16	10	44	6	38	2	41	5	50	10	78	10
AD-	7	1	8	1	16	4	18	2	19	3	17	5	46	7	65	16

	Primary Human Hepatocytes Transfection								Primary Human Hepatocytes Free Uptake							
Duplex Name	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**	**0.1nM Avg**	**0.1nM Stdev**	**0.01nM Avg**	**0.01nM Stdev**	**200nM Avg**	**200nM Stdev**	**100nM Avg**	**100nM Stdev**	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**
1725430.1																
AD-1725469.1	15	3	17	4	32	6	41	9	43	8	41	4	77	9	96	13
AD-1725535.1	8	1	13	3	22	2	21	7	18	3	21	2	51	5	75	13
AD-1727981.1	13	1	16	4	21	3	28	4	27	2	32	5	61	4	89	15
AD-1725772.1	10	1	16	3	22	6	31	8	20	4	25	2	54	19	107	31
AD-1728273.1	16	3	19	2	33	3	29	5	19	5	23	1	58	6	81	13
AD-1726058.1	7	2	15	2	15	3	18	6	13	5	16	2	50	7	61	21
AD-1728784.1	7	2	7	2	19	2	21	3	16	2	16	7	39	8	38	23
AD-1724708.1	9	2	12	2	24	5	26	4	12	4	15	1	43	9	69	6
AD-1725193.1	12	1	18	1	24	6	28	6	21	2	19	4	46	6	75	10
AD-1725460.1	14	4	19	4	31	5	40	4	70	9	61	3	94	6	95	11
AD-1729555.1	10	2	14	3	33	7	31	8	27	8	26	1	68	7	99	28
AD-1725643.1	10	1	19	5	32	9	23	7	26	3	26	3	59	2	83	5
AD-1726052.1	14	2	17	5	26	6	28	5	15	2	20	1	51	3	85	3
AD-1726062.1	4	1	17	1	23	11	26	8	15	5	18	3	45	9	48	15
AD-1726936.1	5	2	7	3	19	4	28	2	15	5	13	7	30	13	35	21
AD-1724715.1	11	3	18	5	26	6	46	11	22	4	25	3	45	11	66	11
AD-	5	2	8	2	20	2	21	5	17	2	20	1	47	2	74	6

	Primary Human Hepatocytes Transfection								Primary Human Hepatocytes Free Uptake							
Duplex Name	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**	**0.1nM Avg**	**0.1nM Stdev**	**0.01nM Avg**	**0.01nM Stdev**	**200nM Avg**	**200nM Stdev**	**100nM Avg**	**100nM Stdev**	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**
1725055.1																
AD-1725061.1	14	2	18	4	35	7	34	4	33	1	30	2	73	6	85	9
AD-1725194.1	13	3	14	2	26	6	23	5	16	2	16	2	40	6	62	11
AD-1725462.1	13	2	14	3	34	7	36	6	46	4	29	3	69	13	80	20
AD-1725472.1	10	3	17	1	28	6	27	3	32	5	102	7	60	5	103	16
AD-1725644.1	13	2	21	6	31	9	31	2	38	4	35	8	68	13	89	18
AD-1725761.1	10	1	17	3	31	5	27	5	29	3	37	3	81	10	112	8
AD-1725773.1	12	1	19	3	27	4	38	7	31	7	34	5	75	11	110	25
AD-1726053.1	14	2	19	2	22	2	23	4	14	4	17	0	45	4	73	12
AD-1728302.1	10	2	14	3	25	8	25	8	12	3	19	4	47	9	76	17
AD-1728786.1	7	2	9	1	16	3	19	4	16	1	19	4	38	17	47	4
AD-1724718.1	11	1	19	4	27	4	30	5	14	3	22	2	52	2	71	5
AD-1729141.1	15	4	17	2	30	5	28	5	31	7	34	4	57	5	107	19
AD-1725075.1	20	5	19	3	25	4	34	3	25	4	26	5	60	10	86	14
AD-1727432.1	14	2	17	2	23	3	31	5	24	5	104	10	56	6	82	12
AD-1729548.1	14	2	20	4	31	2	36	8	43	7	42	5	80	9	100	9
AD-1725476.1	11	2	19	2	32	8	28	8	24	4	35	1	83	7	111	8
AD-	13	1	21	4	29	6	25	6	36	8	41	3	74	2	111	16

	Primary Human Hepatocytes Transfection								Primary Human Hepatocytes Free Uptake							
Duplex Name	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**	**0.1nM Avg**	**0.1nM Stdev**	**0.01nM Avg**	**0.01nM Stdev**	**200nM Avg**	**200nM Stdev**	**100nM Avg**	**100nM Stdev**	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**
1729841.1																
AD-1725763.1	8	1	16	4	31	8	37	5	20	4	25	2	60	2	97	10
AD-1725777.1	14	4	18	4	18	1	21	6	24	7	27	5	65	8	90	22
AD-1728276.1	15	1	23	2	34	16	29	8	18	5	22	3	44	11	94	25
AD-1730167.1	10	2	14	2	16	8	20	5	7	4	15	4	35	8	50	15
AD-1726937.1	6	1	9	2	8	2	20	3	11	2	11	1	33	2	44	9
AD-1724725.1	9	1	14	2	22	1	25	4	15	3	19	1	41	5	59	12
AD-1727292.1	11	1	14	2	24	4	31	6	21	3	25	1	49	7	79	13
AD-1725095.1	12	2	13	1	21	4	27	5	15	2	15	1	39	4	66	6
AD-1725244.1	18	2	21	3	35	9	37	9	42	4	39	5	80	14	97	11
AD-1725463.1	8	2	13	3	22	8	26	9	21	3	23	3	57	9	80	10
AD-1729562.1	11	2	14	2	26	5	19	4	18	3	16	3	43	3	71	7
AD-1725756.1	10	2	12	2	23	5	24	2	24	2	26	3	58	5	87	10
AD-1725764.1	7	1	13	2	29	7	25	4	24	5	117	4	59	4	95	18
AD-1730001.1	16	2	25	11	22	5	32	7	29	5	107	15	75	9	105	13
AD-1726056.1	14	2	20	2	30	9	25	3	12	2	15	2	43	7	79	17
AD-1726189.1	11	3	18	2	18	1	23	8	15	5	23	5	43	9	88	11
AD-	6	1	11	2	15	4	23	7	15	0	15	1	36	1	50	8

	Primary Human Hepatocytes Transfection								Primary Human Hepatocytes Free Uptake							
Duplex Name	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**	**0.1nM Avg**	**0.1nM Stdev**	**0.01nM Avg**	**0.01nM Stdev**	**200nM Avg**	**200nM Stdev**	**100nM Avg**	**100nM Stdev**	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**
1724702.1																
AD-1724910.1	9	2	13	2	22	3	23	2	21	3	16	2	38	4	60	7
AD-1727293.1	6	1	10	3	14	1	19	4	20	5	23	3	48	6	77	8
AD-1725096.1	11	3	16	2	30	6	34	5	22	3	25	2	55	11	81	14
AD-1729487.1	13	1	20	2	40	9	31	3	31	7	33	12	70	11	96	21
AD-1725464.1	9	3	14	4	26	7	27	5	21	3	28	1	64	8	91	12
AD-1727713.1	11	1	16	3	32	4	34	5	26	5	28	2	67	6	97	7
AD-1725757.1	10	1	14	2	26	3	28	7	21	1	22	3	51	1	93	5
AD-1727986.1	7	2	12	3	29	8	27	7	17	6	24	2	60	10	80	13
AD-1725916.1	8	1	12	4	22	7	24	3	16	4	21	3	55	7	85	22
AD-1728278.1	13	2	20	4	28	12	25	6	17	2	23	4	49	4	81	17
AD-1726207.1	9	1	19	5	28	6	28	3	19	5	27	6	49	9	59	7
AD-1726939.1	5	1	7	1	12	4	18	5	11	1	11	2	28	4	33	5
AD-1725044.1	4	1	8	2	16	4	22	7	19	3	20	2	43	9	46	10
AD-1725057.1	6	3	11	2	20	2	23	6	16	2	20	2	47	9	64	14
AD-1725125.1	13	2	20	2	37	11	40	7	49	4	63	12	85	13	90	12
AD-1725405.1	6	2	9	2	20	6	25	8	17	3	21	1	57	12	66	9
AD-	9	2	13	2	28	4	27	5	18	3	25	2	56	7	73	6

	Primary Human Hepatocytes Transfection								Primary Human Hepatocytes Free Uptake							
Duplex Name	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**	**0.1nM Avg**	**0.1nM Stdev**	**0.01nM Avg**	**0.01nM Stdev**	**200nM Avg**	**200nM Stdev**	**100nM Avg**	**100nM Stdev**	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**
1725477.1																
AD-1727980.1	11	2	15	2	24	3	25	4	18	3	25	3	55	1	79	17
AD-1725767.1	9	2	17	4	41	11	37	9	24	6	35	4	66	5	87	9
AD-1730068.1	18	8	18	5	11	6	26	5	30	10	43	2	77	5	92	29
AD-1730477.1	9	1	14	5	27	7	26	7	21	3	24	2	52	3	108	34

Table 6. In Vitro Single Dose Tranfection and Free Update Screens in Primary Cynomolgus Hepatocytes

	Primary Cyno Hepatocytes Transfection								Primary Cyno Hepatocytes Free Uptake							
Duplex Name	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**	**0.1nM Avg**	**0.1nM Stdev**	**0.01nM Avg**	**0.01nM Stdev**	**200nM Avg**	**200nM Stdev**	**100nM Avg**	**100nM Stdev**	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**
AD-1724704.1	2	1	6	1	11	2	12	3	16	1	20	2	41	2	62	5
AD-1729137.1	5	0	11	1	19	1	21	1	58	1	59	6	72	2	91	6
AD-1725059.1	2	0	4	0	9	1	12	1	18	1	21	3	41	3	62	4
AD-1727392.1	12	1	25	2	42	1	53	3	56	2	56	4	80	4	93	4
AD-1725408.1	2	0	7	1	11	1	15	1	26	2	28	4	47	3	68	3
AD-1727703.1	5	1	11	0	18	1	24	2	50	7	49	4	76	2	89	1
AD-1725478.1	3	0	7	1	12	1	17	1	28	2	33	4	56	2	72	5
AD-1725759.1	9	5	12	1	19	1	24	1	43	1	44	1	66	4	83	4
AD-1725771.1	4	1	10	2	17	1	23	1	31	2	33	1	56	1	75	2

	Primary Cyno Hepatocytes Transfection							Primary Cyno Hepatocytes Free Uptake						
Duplex Name	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**	**0.1nM Avg**	**0.1nM Stdev**	**0.01nM Avg**	**0.01nM Stdev**	**200nM Avg**	**200nM Stdev**	**100nM Avg**	**100nM Stdev**	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**
AD-1726051.1	6	1	11	1	16	1	23	2	41	3	44	3	70	4	87	2
AD-1726057.1	4	1	12	2	15	1	21	1	33	1	43	2	72	4	91	2
AD-1724693.1	5	1	11	1	22	2	30	3	36	3	37	2	59	3	79	4
AD-1724706.1	2	0	6	1	11	1	16	2	15	0	20	1	38	1	57	2
AD-1727288.1	3	1	7	1	13	1	17	1	34	2	35	1	48	9	70	4
AD-1725060.1	6	1	16	1	29	3	37	2	46	1	48	3	69	4	81	1
AD-1725192.1	4	1	11	1	19	2	24	2	48	3	49	4	70	8	79	3
AD-1725430.1	3	1	5	1	8	1	12	1	21	1	21	1	39	2	60	3
AD-1725469.1	5	1	13	2	21	2	28	3	45	2	45	2	67	4	83	6
AD-1725535.1	2	0	6	1	9	1	12	1	21	2	23	0	45	2	67	4
AD-1727981.1	4	1	8	1	15	2	19	1	33	2	36	3	57	2	73	7
AD-1725772.1	4	1	9	2	14	2	22	3	34	4	32	2	52	2	74	4
AD-1728273.1	6	1	11	1	17	2	22	2	42	10	39	3	63	4	81	6
AD-1726058.1	4	1	7	1	11	1	16	1	29	3	32	2	54	2	73	2
AD-1728784.1	4	0	9	1	19	2	24	5	31	11	38	2	61	2	79	3
AD-1724708.1	3	0	8	1	13	1	17	1	20	1	21	0	44	1	62	1
AD-1725193.1	3	0	6	0	12	1	19	2	31	1	32	2	53	6	72	2

	Primary Cyno Hepatocytes Transfection							Primary Cyno Hepatocytes Free Uptake						
Duplex Name	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**	**0.1nM Avg**	**0.1nM Stdev**	**0.01nM Avg**	**0.01nM Stdev**	**200nM Avg**	**200nM Stdev**	**100nM Avg**	**100nM Stdev**	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**
AD-1725460.1	5	0	12	0	22	3	29	2	68	2	63	4	74	5	83	3
AD-1729555.1	3	0	9	1	15	1	20	2	32	1	33	1	56	4	74	1
AD-1725643.1	5	1	11	1	17	2	21	1	24	1	26	0	48	2	71	5
AD-1726052.1	5	1	10	1	16	2	19	1	32	1	37	2	60	4	78	3
AD-1726062.1	4	1	9	1	15	1	20	1	33	1	37	1	60	2	81	3
AD-1726936.1	3	0	10	1	16	0	22	1	34	3	30	3	52	3	73	3
AD-1724715.1	3	0	10	1	19	2	26	0	26	1	27	2	50	2	68	1
AD-1725055.1	3	1	6	1	11	1	15	1	29	1	30	0	50	3	66	4
AD-1725061.1	4	0	9	1	17	1	25	1	31	2	32	2	51	2	69	5
AD-1725194.1	2	0	5	0	8	1	13	2	21	1	22	2	41	3	59	2
AD-1725462.1	4	1	10	1	18	2	24	1	36	2	36	2	55	3	74	4
AD-1725472.1	3	1	8	1	14	1	18	2	33	1	33	1	49	3	66	2
AD-1725644.1	6	1	13	1	21	1	24	2	40	2	40	1	60	3	78	4
AD-1725761.1	4	1	8	1	15	3	19	1	33	2	33	2	55	2	70	2
AD-1725773.1	6	2	12	1	22	2	25	3	36	3	37	3	58	2	77	4
AD-1726053.1	4	1	7	1	12	1	13	1	25	1	29	3	48	4	68	3
AD-1728302.1	4	1	9	1	15	2	18	2	29	2	34	2	59	3	78	3

	Primary Cyno Hepatocytes Transfection							Primary Cyno Hepatocytes Free Uptake						
Duplex Name	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**	**0.1nM Avg**	**0.1nM Stdev**	**0.01nM Avg**	**0.01nM Stdev**	**200nM Avg**	**200nM Stdev**	**100nM Avg**	**100nM Stdev**	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**
AD-1728786.1	4	1	11	2	16	0	21	1	38	1	38	2	61	4	81	3
AD-1724718.1	3	1	11	1	18	1	24	2	26	1	31	3	55	4	73	2
AD-1729141.1	6	0	12	2	22	3	27	1	44	2	48	3	69	4	82	5
AD-1725075.1	3	0	9	1	14	1	19	2	27	1	30	3	53	5	70	2
AD-1727432.1	3	0	7	0	14	2	18	1	27	2	29	2	49	4	78	10
AD-1729548.1	4	1	11	1	21	1	29	2	36	2	37	2	61	4	75	5
AD-1725476.1	4	1	9	1	13	2	18	0	33	1	34	0	57	3	70	2
AD-1729841.1	4	1	10	1	15	2	19	1	40	3	40	2	62	4	74	6
AD-1725763.1	2	1	7	0	12	2	14	2	16	1	18	1	33	2	57	3
AD-1725777.1	4	1	9	1	17	2	21	2	29	3	35	1	58	2	71	3
AD-1728276.1	4	0	8	1	13	1	16	0	24	1	27	0	49	2	70	8
AD-1730167.1	3	1	8	1	13	1	17	1	25	1	29	2	50	1	75	6
AD-1726937.1	2	1	7	1	11	2	17	1	21	1	24	1	47	3	73	4
AD-1724725.1	3	0	8	1	15	2	21	2	23	1	28	1	51	1	73	3
AD-1727292.1	3	0	6	1	12	2	16	1	29	0	31	2	49	2	69	3
AD-1725095.1	2	0	5	0	9	1	13	0	17	1	19	1	39	2	60	4
AD-1725244.1	4	1	10	1	17	1	21	2	36	3	37	2	59	3	78	3

	Primary Cyno Hepatocytes Transfection							Primary Cyno Hepatocytes Free Uptake						
Duplex Name	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**	**0.1nM Avg**	**0.1nM Stdev**	**0.01nM Avg**	**0.01nM Stdev**	**200nM Avg**	**200nM Stdev**	**100nM Avg**	**100nM Stdev**	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**
AD-1725463.1	3	1	6	2	11	2	14	2	22	1	23	1	43	2	64	3
AD-1729562.1	2	0	5	1	8	1	11	1	25	1	26	1	41	3	63	5
AD-1725756.1	3	1	6	1	11	2	14	2	26	3	27	1	47	2	65	5
AD-1725764.1	2	0	6	1	12	2	16	2	25	1	26	2	44	3	64	5
AD-1730001.1	5	1	12	1	22	2	24	3	30	1	35	2	58	3	73	4
AD-1726056.1	4	1	8	1	13	2	14	1	24	1	28	2	50	4	70	3
AD-1726189.1	7	1	18	3	24	1	30	2	53	3	58	3	79	4	94	6
AD-1724702.1	4	0	10	1	16	2	22	2	31	2	33	2	57	1	77	4
AD-1724910.1	3	1	8	1	12	1	15	1	32	1	31	1	52	1	70	4
AD-1727293.1	4	1	8	0	16	2	22	3	40	1	43	2	66	5	80	3
AD-1725096.1	3	1	7	1	14	1	20	2	22	1	24	1	45	2	71	3
AD-1729487.1	7	1	13	1	24	4	33	6	47	1	49	3	70	4	85	4
AD-1725464.1	2	0	6	1	13	2	19	2	23	1	25	2	44	4	64	2
AD-1727713.1	3	1	7	1	13	1	18	1	30	1	33	2	57	1	77	2
AD-1725757.1	3	0	6	1	10	2	14	1	24	2	24	1	46	1	65	3
AD-1727986.1	3	1	6	1	14	1	17	2	24	1	27	2	47	4	65	4
AD-1725916.1	3	1	7	1	12	1	14	0	21	1	24	1	47	4	67	6

	Primary Cyno Hepatocytes Transfection							Primary Cyno Hepatocytes Free Uptake						
Duplex Name	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**	**0.1nM Avg**	**0.1nM Stdev**	**0.01nM Avg**	**0.01nM Stdev**	**200nM Avg**	**200nM Stdev**	**100nM Avg**	**100nM Stdev**	**10nM Avg**	**10nM Stdev**	**1nM Avg**	**1nM Stdev**
AD-1728278.1	3	0	8	1	12	2	14	1	25	2	30	2	54	2	72	5
AD-1726207.1	4	1	10	1	19	3	25	2	25	1	30	2	53	3	76	5
AD-1726939.1	3	1	6	0	12	2	17	0	21	1	23	1	46	4	74	5
AD-1725044.1	3	0	7	2	14	1	16	5	36	2	32	1	50	2	75	3
AD-1725057.1	3	0	7	1	14	2	20	1	42	3	38	1	60	4	80	3
AD-1725125.1	8	1	23	3	39	5	53	5	61	2	62	2	82	3	98	4
AD-1725405.1	2	1	7	1	13	1	19	2	22	2	23	1	43	1	71	4
AD-1725477.1	3	0	7	1	11	4	18	2	32	3	34	1	56	2	77	4
AD-1727980.1	4	1	9	0	16	1	20	3	29	2	31	3	51	3	74	7
AD-1725767.1	6	1	12	1	23	2	27	1	41	1	42	2	64	7	87	4
AD-1730068.1	5	1	11	0	18	2	19	2	35	2	36	2	63	5	84	6
AD-1730477.1	3	0	10	2	13	2	18	1	32	3	33	1	51	3	77	7

Example 4. *In vivo* screening of dsRNA Duplexes

Single Dose Study (1mg/kg)

Duplexes of interest, identified from the above *in vitro* studies, were evaluated *in vivo*. In particular, at pre-dose day -21 wild-type mice (C57BL/6) were transduced with 2 x 10^{11} viral particles of an adeno-associated virus 8 (AAV8) vector encoding human CFB intravenously *via* retro-orbital delivery. In particular, mice were administered an AAV8 encoding a portion of human CFB mRNA encoding the open reading frame and 3' UTR of human CFB mRNA referenced as NM_001710.5, referred to as VCAV–07851.AAV8.HsCFB.

At day 0, groups of three mice were subcutaneously administered a single 1 mg/kg dose of the duplexes of interest or phosphate-buffered saline (PBS). **Table 7** provides the treatment design and provides the duplexes of interest. On day 0 predose and day 7 post-dose, K_2EDTA plasma were collected and samples were analyzed for human CFB protein by ELISA (Assay Pro # EF7001). All plasma samples were diluted 1:1000 in 1x diluent and ELISA was conducted according to manufacturer's protocol. Data was interpolated using a 4-parameter logistic curve using GraphPad Prism software.

For all samples, human CFB protein levels were normalized to individual animals' day 0 level to calculate relative % human CFB protein remaining. For each group, the mean % CFB protein remaining was calculated (±standard deviation [SD]).

The data were expressed as percent of baseline value and presented as mean plus standard deviation. The results, listed in **Table 8** and shown in **Figure 2**, demonstrate that the exemplary duplex agents tested effectively reduce the level of the human CFB protein *in vivo*.

Table 7. Treatment Groups

Group	Treatment	# of animals	Dose (mpk)	Target region
1	PBS	3	NA	
2	AD-1726057.3	3	1	2242-2264
3	AD-1725763.3	3	1	1828-1850
4	AD-1725777.3	3	1	1842-1864
5	AD-1725057.3	3	1	995-1017
6	AD-1725096.3	3	1	1034-1056
7	AD-1728786.3	3	1	641-663
8	AD-1725059.3	3	1	997-1019
9	AD-1728276.3	3	1	2391-2413
10	AD-1728278.3	3	1	2393-2415
11	AD-1726936.3	3	1	640-662
12	AD-1725472.3	3	1	1473-1495
13	AD-1724715.3	3	1	504-526
14	AD-1727292.3	3	1	1145-1167
15	AD-1730477.3	3	1	2453-2475

17	AD-1727288.3	3	1	1141-1163
18	AD-1730167.3	3	1	2438-2460
19	AD-1725408.3	3	1	1389-1411
20	AD-1725761.3	3	1	1826-1848

Table 8. ***In Vivo*** **Screen**

Group	Treatment	% CFB remaining (Individual animals)			Group Mean	STDEV
1	PBS	100.01	106.18	98.65	101.61	4.01
2	AD-1726057.3	67.11	72.07	68.00	69.06	2.64
3	AD-1725763.3	35.75	44.82	31.92	37.50	6.63
4	AD-1725777.3	80.87	67.57	72.06	73.50	6.77
5	AD-1725057.3	60.58	72.93	70.28	67.93	6.50
6	AD-1725096.3	68.25	57.34	65.02	63.54	5.61
7	AD-1728786.3	68.9	65.6	69.2	67.91	1.99
8	AD-1725059.3	62.9	62.2	64.2	63.10	0.99
9	AD-1728276.3	49.2	26.3	38.7	38.06	11.43
10	AD-1728278.3	60.5	56.1	58.1	58.24	2.16
11	AD-1726936.3	38.4	62.2	50.0	50.21	11.92
12	AD-1725472.3	47.5	76.4	64.5	62.78	14.53
13	AD-1724715.3	51.69	47.15	66.83	55.23	10.30
14	AD-1727292.3	43.51	50.53	53.90	49.31	5.30
15	AD-1730477.3	50.08	50.96	ND	50.52	0.62
17	AD-1727288.3	67.03	56.42	42.49	55.31	12.31
18	AD-1730167.3	54.47	56.24	52.30	54.34	1.97
19	AD-1725408.3	56.03	39.87	58.80	51.56	10.22
20	AD-1725761.3	71.73	75.44	52.36	66.51	12.39

EQUIVALENTS

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

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Informal Sequence Listing

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SEQ ID NO:4
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SEQ ID NO:5
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SEQ ID NO:7
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SEQ ID NO:8
Reverse Complement of SEQ ID NO:1
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SEQ ID NO:9

Reverse Complement of SEQ ID NO:2

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SEQ ID NO:10
Reverse Complement of SEQ ID NO:3

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SEQ ID NO:11
Reverse Complement of SEQ ID NO:4

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SEQ ID NO:12
Reverse Complement of SEQ ID NO:5
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SEQ ID NO:13
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SEQ ID NO:14
Reverse Complement of SEQ ID NO:7
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CAGACCACCCACTTAGGGACCAGAAAT

We claim:

1. A double stranded ribonucleic acid (dsRNA) for inhibiting expression of complement factor B (CFB) in a cell, wherein the dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding CFB, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-3.

2. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising any of the sense nucleotide sequences in any one of Tables 2-3.

3. The dsRNA agent of claim 1, wherein the dsRNA agent comprises an antisense strand comprising any of the antisense nucleotide sequences in any one of Tables 2-3.

4. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising any of the sense nucleotide sequences in any one of Tables 2-3 and an antisense strand comprising any of the antisense nucleotide sequences in any one of Tables 2-3.

5. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising a nucleotide sequence which differs by no more than 4 nucleotides from any of the sense nucleotide sequences in any one of Tables 2-3 and an antisense strand comprising a nucleotide sequence which differs by no more than 4 nucleotides from any of the antisense nucleotide sequences in any one of Tables 2-3.

6. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising a nucleotide sequence which differs by no more than 3 nucleotides from any of the sense nucleotide sequences in any one of Tables 2-3 and an antisense strand comprising a nucleotide sequence which differs by no more than 3 nucleotides from any of the antisense nucleotide sequences in any one of Tables 2-3.

7. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising a nucleotide sequence which differs by no more than 2 nucleotides from any of the sense nucleotide sequences in any one of Tables 2-3 and an antisense strand comprising a nucleotide sequence which differs by no more than 2 nucleotides from any of the antisense nucleotide sequences in any one of Tables 2-3.

8. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand comprising a nucleotide sequence which differs by no more than 1 nucleotide from any of the sense nucleotide sequences in any one of Tables 2-3 and an antisense strand comprising a nucleotide sequence which differs by no more than 1 nucleotide from any of the antisense nucleotide sequences in any one of Tables 2-3.

9. A double stranded ribonucleic acid (dsRNA) for inhibiting expression of complement factor B (CFB) in a cell, wherein the dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 504-526, 640-662, 641-663, 995-1017, 997-1019, 1034-1056, 1141-1163, 1145-1167, 1389-1411, 1473-1495, 1826-1848, 1828-1850, 1842-1864, 2242-2264, 2391-2413, 2393-2415, 2438-2460, or 2453-2475 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from the corresponding nucleotide sequence of SEQ ID NO:8.

10. The dsRNA agent of any one of claims 1-9, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than four nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1726057; AD-1725763; AD-1725777; AD-1725057; AD-1725096; AD-1728786; AD-1725059; AD-1728276; AD-1728278; AD-1726936; AD-1725472; AD-1724715; AD-1727292; AD-1730477; AD-1727288; AD-1730167; AD-1725408; and AD-1725761.

11. The dsRNA agent of any one of claims 1-10, wherein the sense strand and the antisense strand comprise at least 15 contiguous nucleotides differing by no more than four nucleotides from any one of the sense strand and the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1726057; AD-1725763; AD-1725777; AD-1725057; AD-1725096; AD-1728786; AD-1725059; AD-1728276; AD-1728278; AD-1726936; AD-1725472; AD-1724715; AD-1727292; AD-1730477; AD-1727288; AD-1730167; AD-1725408; and AD-1725761

12. The dsRNA agent of any one of claims 1-11, wherein the sense strand and the antisense strand comprise at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the sense strand and the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1726057; AD-1725763; AD-1725777; AD-1725057; AD-1725096; AD-1728786; AD-1725059; AD-1728276; AD-1728278; AD-1726936; AD-1725472; AD-1724715; AD-1727292; AD-1730477; AD-1727288; AD-1730167; AD-1725408; and AD-1725761.

13. The dsRNA agent of any one of claims 1-12, wherein the sense strand and the antisense strand comprise at least 15 contiguous nucleotides differing by no more than two nucleotides from any one of the sense strand and the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1726057; AD-1725763; AD-1725777; AD-1725057; AD-1725096; AD-1728786; AD-1725059; AD-1728276; AD-1728278; AD-1726936; AD-1725472; AD-1724715; AD-1727292; AD-1730477; AD-1727288; AD-1730167; AD-1725408; and AD-1725761.

14. The dsRNA agent of any one of claims 1-13, wherein the sense strand and the antisense strand comprise at least 15 contiguous nucleotides differing by no more than one nucleotide from any one of the sense strand and the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1726057; AD-1725763; AD-1725777; AD-1725057; AD-1725096; AD-1728786; AD-1725059; AD-1728276; AD-1728278; AD-1726936; AD-1725472; AD-1724715; AD-1727292; AD-1730477; AD-1727288; AD-1730167; AD-1725408; and AD-1725761.

15. The dsRNA agent of any one of claims 1-14, wherein the sense strand and the antisense strand comprise the sense strand and the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1726057; AD-1725763; AD-1725777; AD-1725057; AD-1725096; AD-1728786; AD-1725059; AD-1728276; AD-1728278; AD-1726936; AD-1725472; AD-1724715; AD-1727292; AD-1730477; AD-1727288; AD-1730167; AD-1725408; and AD-1725761.

16. The dsRNA agent of any one of claims 1-15, wherein the sense strand and the antisense strand consist of the sense strand and the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1726057; AD-1725763; AD-1725777; AD-1725057; AD-1725096; AD-1728786; AD-1725059; AD-1728276; AD-1728278; AD-1726936; AD-1725472; AD-1724715; AD-1727292; AD-1730477; AD-1727288; AD-1730167; AD-1725408; and AD-1725761.

17. The dsRNA agent of any one of claims 1-16, wherein the dsRNA agent comprises at least one modified nucleotide.

18. The dsRNA agent of any one of claims 1-17, wherein substantially all of the nucleotides of the sense strand; 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.

19. The dsRNA agent of any one of claims 1-18, 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.

20. The dsRNA agent of any one of claims 17-19, wherein at least one of the nucleotide modifications is selected from the group consisting of a deoxy-nucleotide modification, a 3'-terminal deoxythimidine (dT) nucleotide modification, a 2'-O-methyl nucleotide modification, a 2'-fluoro nucleotide modification, a 2'-deoxy- nucleotide modification, a locked nucleotide modification, an unlocked nucleotide modification, a conformationally restricted nu nucleotide modification cleotide, a constrained ethyl nucleotide modification, an abasic nucleotide modification, a 2'-amino nucleotide modification, a 2'-O-allyl- nucleotide modification, 2'-C-alkyl- nucleotide modification, a 2'-methoxyethyl nucleotide modification, a 2'-O-alkyl- nucleotide modification, a morpholino nucleotide modification, a phosphoramidate nucleotide modification, a non-natural base comprising nucleotide modification, a tetrahydropyran nucleotide modification, a 1,5-anhydrohexitol nucleotide modification, a cyclohexenyl nucleotide modification, a nucleotide comprising a phosphorothioate group nucleotide modification, a nucleotide comprising a methylphosphonate group nucleotide modification, a nucleotide comprising a 2'-phosphate nucleotide modification, a nucleotide comprising a 5'-phosphate nucleotide modification, a nucleotide comprising a 5'-phosphate mimic nucleotide modification, a thermally destabilizing nucleotide modification, a glycol modified nucleotide (GNA) nucleotide modification, and a 2-O-(N-methylacetamide) nucleotide modification; and combinations thereof.

21. The dsRNA agent of any one of claims 17-19, wherein the nucleotide modifications are selected from the group consisting of LNA, HNA, CeNA, 2′-methoxyethyl, 2′-O-alkyl, 2′-O-allyl, 2′-C- allyl, 2′-fluoro, 2′-deoxy, 2'-hydroxyl, and a glycol modified nucleotide (GNA); and combinations thereof.

22. The dsRNA agent of any one of claims 17-19, wherein at least one of the nucleotide nucleotide modifications is selected from the group consisting of a deoxy-nucleotide nucleotide modification, a 2'-O-methyl nucleotide modification, a 2'-fluoro nucleotide modification, a 2'-deoxy-nucleotide modification, a glycol (GNA) nucleotide modification, a nucleotide comrprising a 2'-phosphate nucleotide modification, a vinyl-phosphonate nucleotide modification, and 2'-O hexadecyl nucleotide modification; and combinations thereof.

23. The dsRNA agent of any one of claims 17-19, wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification.

24. The dsRNA agent of claim 23, wherein the thermally destabilizing nucleotide modification is selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; and destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an unlocked nucleic acids (UNA), and a glycol modified nucleic acid (GNA).

25. The dsRNA agent of any one of claims 1-24, wherein the double stranded region is 19-30 nucleotide pairs in length.

26. The dsRNA agent of claim 25, wherein the double stranded region is 19-25 nucleotide pairs in length.

27. The dsRNA agent of claim 25, wherein the double stranded region is 19-23 nucleotide pairs in length.

28. The dsRNA agent of claim 25, wherein the double stranded region is 23-27 nucleotide pairs in length.

29. The dsRNA agent of claim 25, wherein the double stranded region is 21-23 nucleotide pairs in length.

30. The dsRNA agent of any one of claims 1-29, wherein each strand is independently no more than 30 nucleotides in length.

31. The dsRNA agent of any one of claims 1-30, wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.

32. The dsRNA agent of any one of claims 1-31, wherein the region of complementarity is at least 17 nucleotides in length.

33. The dsRNA agent of any one of claims 1-32, wherein the region of complementarity is 19-23 nucleotides in length.

34. The dsRNA agent of any one of claims 1-33, wherein the region of complementarity is 19-21 nucleotides in length.

35. The dsRNA agent of any one of claims 1-34, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

36. The dsRNA agent of any one of claims 1-35, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

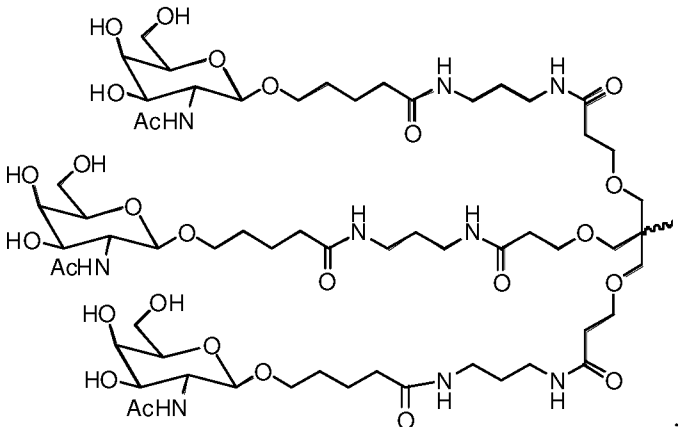
37. The dsRNA agent of any one of claims 1-36, further comprising a ligand.

38. The dsRNA agent of claim 37, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

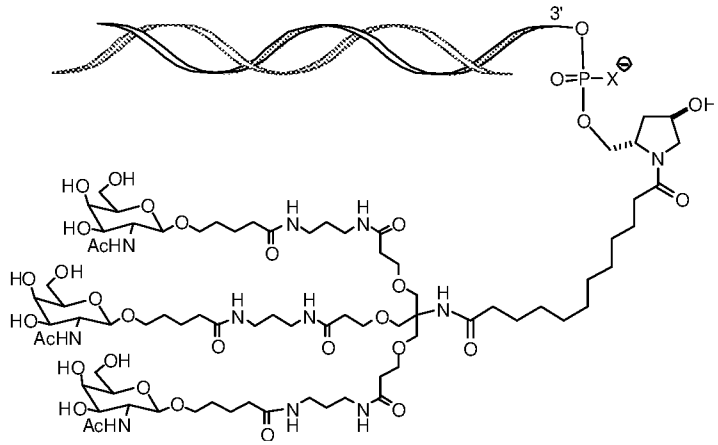
39. The dsRNA agent of claim 37 or 38, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

40. The dsRNA agent of any one of claims 37-39, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

41. The dsRNA agent of claim 39 or 40, wherein the ligand is



42. The dsRNA agent of claim 41, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

43. The dsRNA agent of claim 42, wherein the X is O.

44. The dsRNA agent of any one of claims 1-43, wherein the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

45. The dsRNA agent of claim 44, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

46. The dsRNA agent of claim 45, wherein the strand is the antisense strand.

47. The dsRNA agent of claim 45, wherein the strand is the sense strand.

48. The dsRNA agent of claim 44, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand.

49. The dsRNA agent of claim 48, wherein the strand is the antisense strand.

50. The dsRNA agent of claim 48, wherein the strand is the sense strand.

51. The dsRNA agent of claim 42, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand.

52. The dsRNA agent of claim 50, wherein the strand is the antisense strand.

53. The dsRNA agent of any one of claims 1-52, wherein the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

54. A cell containing the dsRNA agent of any one of claims 1-53.

55. A pharmaceutical composition for inhibiting expression of a gene encoding complement factor B (CFB) comprising the dsRNA agent of any one of claims 1-53.

56. The pharmaceutical composition of claim 55, wherein dsRNA agent is in an unbuffered solution.

57. The pharmaceutical composition of claim 56, wherein the unbuffered solution is saline or water.

58. The pharmaceutical composition of claim 55, wherein said dsRNA agent is in a buffer solution.

59. The pharmaceutical composition of claim 58, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

60. The pharmaceutical composition of claim 59, wherein the buffer solution is phosphate buffered saline (PBS).

61. A method of inhibiting expression of a complement factor B (CFB) gene in a cell, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-53, or the pharmaceutical composition of any one of claims 55-60, thereby inhibiting expression of the CFB gene in the cell.

62. The method of claim 61, wherein the cell is within a subject.

63. The method of claim 62, wherein the subject is a human.

64. The method of claim 62, wherein the subject has a complement factor B- (CFB)-associated disorder.

65. The method of any one of claims 61-64, wherein contacting the cell with the dsRNA agent inhibits the expression of complement factor B by at least 50%, 60%, 70%, 80%, 90%, or 95%.

66. The method of any one of claims 61-65, wherein inhibiting expression of complement factor B decreases complement factor B protein level in serum of the subject by at least 50%, 60%, 70%, 80%, 90%, or 95%.

67. A method of treating a subject having a disorder that would benefit from reduction in complement factor B expression, comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-53, or the pharmaceutical composition of any one of claims 55-60, thereby treating the subject having the disorder that would benefit from reduction in complement factor B expression.

68. A method of preventing at least one symptom in a subject having a disorder that would benefit from reduction in complement factor B expression, comprising administering to the subject a prophylactically effective amount of the dsRNA agent of any one of claims 1-53, or the

pharmaceutical composition of any one of claims 55-60, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in complement factor B expression.

69. The method of claim 67 or 68, wherein the disorder is a complement factor B-associated disorder.

70. The method of claim 69, wherein the complement factor B-associated disease is selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), asthma, rheumatoid arthritis (RA); antiphospholipid antibody syndrome; lupus nephritis; ischemia-reperfusion injury; typical or infectious hemolytic uremic syndrome (tHUS); dense deposit disease (DDD); neuromyelitis optica (NMO); multifocal motor neuropathy (MMN); multiple sclerosis (MS); macular degeneration (e.g., age-related macular degeneration (AMD)); hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP); spontaneous fetal loss; Pauci-immune vasculitis; epidermolysis bullosa; recurrent fetal loss; pre-eclampsia, traumatic brain injury, myasthenia gravis, cold agglutinin disease, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, C3 neuropathy, anti-neutrophil cytoplasmic antibody-associated vasculitis (e.g., granulomatosis with polyangiitis (previously known as Wegener granulomatosis), Churg-Strauss syndrome, and microscopic polyangiitis), humoral and vascular transplant rejection, graft dysfunction, myocardial infarction (*e.g.*, tissue damage and ischemia in myocardial infarction), an allogenic transplant, sepsis (*e.g.*, poor outcome in sepsis), Coronary artery disease, dermatomyositis, Graves' disease, atherosclerosis, Alzheimer's disease, systemic inflammatory response sepsis, septic shock, spinal cord injury, glomerulonephritis, Hashimoto's thyroiditis, type I diabetes, psoriasis, pemphigus, autoimmune hemolytic anemia (AIHA), ITP, Goodpasture syndrome, Degos disease, antiphospholipid syndrome (APS), catastrophic APS (CAPS), a cardiovascular disorder, myocarditis, a cerebrovascular disorder, a peripheral (e.g., musculoskeletal) vascular disorder, a renovascular disorder, a mesenteric/enteric vascular disorder, vasculitis, Henoch-Schönlein purpura nephritis, systemic lupus erythematosus-associated vasculitis, vasculitis associated with rheumatoid arthritis, immune complex vasculitis, Takayasu's disease, dilated cardiomyopathy, diabetic angiopathy, Kawasaki's disease (arteritis), venous gas embolus (VGE), and restenosis following stent placement, rotational atherectomy, and percutaneous transluminal coronary angioplasty (PTCA).

71. The method of claim 69, wherein the complement factor B-associated disease is selected from the group consisting of C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration, atypical hemolytic uremic syndrome, thrombotic microangiopathy, myasthenia gravis, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria, and rheumatoid arthritis.

72. The method of claim 69, wherein the complement factor B-associated disease is selected from the group consisting of C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.*, Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease.

73. The method of any one of claims 67-72, wherein the subject is human.

74. The method of any one of claims 67-73, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to 50 mg/kg or at a dose of about 5 mg or 1000 mg.

75. The method of any one of claims 67-74, wherein the dsRNA agent is administered to the subject subcutaneously.

76. The method of any one of claims 67-75, further comprising administering to the subject an agent for the treatment of a CFB-associated disease.

77. The method of any one of claims 67-75, further comprising administering to the subject an iRNA agent targeting complement component C5 or an iRNA agent targeting complement component C3.

78. The method of any one of claims 59-69, further comprising determining the level of complement factor B in a sample(s) from the subject.

79. The method of claim 78, wherein the level of complement factor B in the subject sample(s) is a complement factor B protein level in a blood or serum sample(s).

80. A kit comprising the dsRNA agent of any one of claims 1-53 or the pharmaceutical composition of any one of claims 55-60.

81. A vial comprising the dsRNA agent of any one of claims 1-53 or the pharmaceutical composition of any one of claims 55-60.

82. A syringe comprising the dsRNA agent of any one of claims 1-53 or the pharmaceutical composition of any one of claims 55-60.

83. An RNA-induced silencing complex (RISC) comprising an antisense strand of any of the dsRNA agents of any one of claims 1-53.