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

(57) Abstract: The present invention relates to RNAi agents, e.g., dsRNA agents, targeting the complement fator B (CFB) gene. The invention also relates to methods of using such RNAi agents to inhibit expression of a CFB gene and to methods of treating or preventing a CFB-associated disease in a subject.

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

Related Applications

This application claims the benefit of priority to U.S. Provisional Application No. 63/017,725, filed on April 30, 2020, U.S. Provisional Application No. 63/119,009, filed on November 30, 2020, and U.S. Provisional Application No. 63/157,899, filed on March 8, 2021. The entire contents of each of the foregoing applications are incorporated herein by reference.

Sequence Listing

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on April 23, 2021, is named 121301_11420_SL.txt and is 436,429 bytes in size.

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 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 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:8. In certain embodiments, the sense strand comprises at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:8. In certain embodiments, the sense strand comprises at least 17 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 17 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:8. In certain embodiments, the sense strand comprises at least 19 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 19 contiguous nucleotides 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 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-7, 13, 16, 19 and 20. In certain embodiments, the region of complementarity comprises at least 15 contiguous nucleotides of any one of the antisense nucleotide sequences in any one of Tables 2-7, 13, 16, 19 and 20. In certain embodiments, the region of complementarity comprises at least 17 contiguous nucleotides of any one of the antisense nucleotide sequences in any one of Tables 2-7, 13, 16, 19 and 20. In certain embodiments, the region of complementarity comprises at least 19 contiguous nucleotides of any one of the antisense nucleotide sequences in any one of Tables 2-7, 13, 16, 19 and 20. In certain embodiments, the region of complementarity comprises at least 20 contiguous nucleotides of any one of the antisense nucleotide sequences in any one of Tables 2-7, 13, 16, 19 and 20. In certain embodiments, the region of complementarity comprises at least 21 contiguous nucleotides of any one of the antisense nucleotide sequences in any one of Tables 2-7, 13, 16, 19 and 20.

In one 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 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 633-665, 1133-1185, 1133-1173, 1133-1167, 1143-1173, 1540-1563, 1976-2002, 2386-2438, 2386-2418, 2386-2413, and 2389-1418 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:8, where a substitution of a T with a U in either SEQ ID NO: 1 or SEQ ID NO: 8 does not count as a difference.

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 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides *e.g.,* at least 15 nucleotides, at least 17 nucleotides, at least 19 nucleotides, or at least 20 nucleotides, from any one of the nucleotide sequence of nucleotides 633-655, 643-665, 928-950, 1133-1155, 1140-1162, 1141-1163, 1143-1165, 1145-1167, 1148-1170, 1150-1172, 1151-1173, 1185-1207, 1306-1328, 1534-1556, 1540-1562, 1541-1563, 1976-1998, 1979-2001, 1980-2002, 2078-2100, 2386-2408, 2388-2410, 2389-2411, 2391-2413, 2393-2415, 2395-2417, 2396-2418, 2438-2460, 2602-2624 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides, , *e.g.,* at least 15 nucleotides, at least 17 nucleotides, at least 19 nucleotides, or at least 20 nucleotides, from the corresponding nucleotide sequence of SEQ ID NO:8, where a substitution of a T with a U in either SEQ ID NO: 1 or SEQ ID NO: 8 does not count as a difference.

In one embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-560018, AD-559375, AD-559160, AD-559374, AD-559060, AD-559721, AD-559026, AD-558225, AD-557069, AD-558068, AD-557422, AD-558063, AD-558066, AD-556701, AD-558657, AD-559020, AD-559023, AD-558860, AD-560019, AD-560016, AD-559008, AD-559717, AD-557072, AD-558097, AD-557774, AD-557070, AD-558065, AD-557853, and AD-557079. In certain embodiments, the antisense strand comprises at least 15 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the antisense strand comprises at least 17 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the antisense strand comprises at least 19 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the antisense strand comprises at least 20 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the antisense strand comprises at least 21 contiguous nucleotides of any one of the selsected duplexes.

In one embodiment, the sense strand comprises at least 15 contiguous nucleotides differing by nor more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-560018, AD-559375, AD-559160, AD-559374, AD-559060, AD-559721, AD-559026, AD-558225, AD-557069, AD-558068, AD-557422, AD-558063, AD-558066, AD-556701, AD-558657, AD-559020, AD-559023, AD-558860, AD-560019, AD-560016, AD-559008, AD-559717, AD-557072, AD-558097, AD-557774, AD-557070, AD-558065, AD-557853, and AD-557079. In certain embodiments, the sense strand comprises at least 15 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the sense strand comprises at least 17 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the sense strand comprises at least 19 contiguous nucleotides of any one of the

selsected duplexes. In certain embodiments, the sense strand comprises at least 20 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the sense strand comprises at least 21 contiguous nucleotides of any one of the selsected duplexes.

In one 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 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides *e.g.,* at least 15 nucleotides, at least 17 nucleotides, at least 19 nucleotides, or at least 20 nucleotides, from any one of the nucleotide sequence of nucleotides 153-175; 202-224; 219-241; 254-276; 304-326; 321-343; 347-369; 402-424; 418-440; 447-469; 491-513; 528-550; 549-571; 566-588; 591-613; 792-814; 819-841; 967-989; 1042-1064; 1234-1256; 1250-1272; 1269-1291; 1335-1357; 1354-1376; 1372-1394; 1422-1444; 1496-1518; 1670-1692; 1716-1738; 1757-1779; 1774-1796; 1793-1815; 1844-1866; 1871-1893; 1909-1931; 1924-1947; 1947-1969; 2161-2183; 2310-2332; 2330-2352; 2355-2377; 2494-2516; and 2527-2549 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides, , *e.g.,* at least 15 nucleotides, at least 17 nucleotides, at least 19 nucleotides, or at least 20 nucleotides, from the corresponding nucleotide sequence of SEQ ID NO:8, where a substitution of a T with a U in either SEQ ID NO: 1 or SEQ ID NO: 8 does not count as a difference.

In one embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-560132.1; AD-560099.1; AD-559998.1; AD-559993.1; AD-559973.1; AD-559882.1; AD-559706.1; AD-559704.1; AD-559688.1; AD-559668.1; AD-559641.1; AD-559609.1; AD-559590.1; AD-559573.1; AD-559532.1; AD-559486.1; AD-559330.1; AD-559274.1; AD-559226.1; AD-559208.1; AD-559189.1; AD-559124.1; AD-559105.1; AD-559089.1; AD-558935.1; AD-558879.1; AD-558777.1; AD-558750.1; AD-558637.1; AD-558612.1; AD-558595.1; AD-558574.1; AD-558555.1; AD-558511.1; AD-558482.1; AD-558466.1; AD-558450.1; AD-558424.1; AD-558407.1; AD-558393.1; AD-558378.1; AD-558361.1; AD-558312.1. In certain embodiments, the antisense strand comprises at least 15 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the antisense strand comprises at least 17 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the antisense strand comprises at least 19 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the antisense strand comprises at least 20 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the antisense strand comprises at least 21 contiguous nucleotides of any one of the selsected duplexes.

In one embodiment, the sense strand comprises at least 15 contiguous nucleotides differing by nor more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-560132.1; AD-560099.1; AD-559998.1; AD-559993.1; AD-559973.1; AD-559882.1; AD-559706.1; AD-559704.1; AD-559688.1; AD-559668.1; AD-

559641.1; AD-559609.1; AD-559590.1; AD-559573.1; AD-559532.1; AD-559486.1; AD-559330.1; AD-559274.1; AD-559226.1; AD-559208.1; AD-559189.1; AD-559124.1; AD-559105.1; AD-559089.1; AD-558935.1; AD-558879.1; AD-558777.1; AD-558750.1; AD-558637.1; AD-558612.1; AD-558595.1; AD-558574.1; AD-558555.1; AD-558511.1; AD-558482.1; AD-558466.1; AD-558450.1; AD-558424.1; AD-558407.1; AD-558393.1; AD-558378.1; AD-558361.1; AD-558312.1. In certain embodiments, the sense strand comprises at least 15 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the sense strand comprises at least 17 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the sense strand comprises at least 19 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the sense strand comprises at least 20 contiguous nucleotides of any one of the selsected duplexes. In certain embodiments, the sense strand comprises at least 21 contiguous nucleotides of any one of the selsected duplexes.

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.

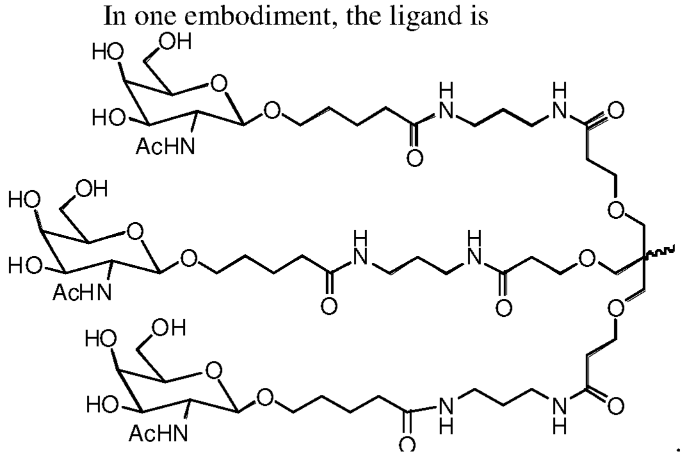
In one embodiment, the dsRNA agent further comprises a ligand.

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.

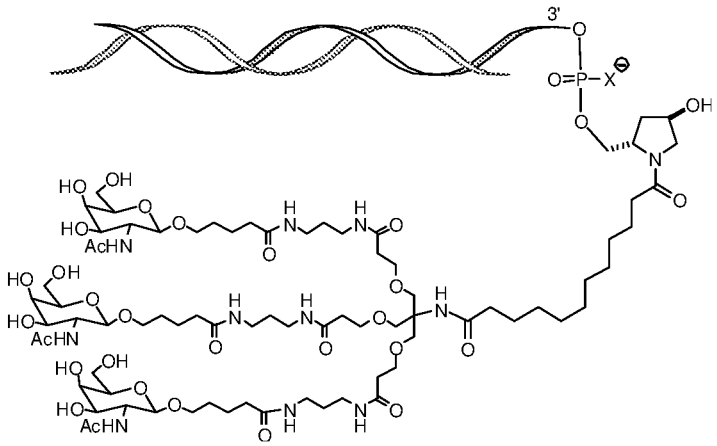
In one embodiment, the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In one embodiment, the ligand is



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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.

Brief Description of the Drawings

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

Figure 2A is a heatmap depicting the effect of dual targeting of C3 and CFB on alternative hemolytic activity in human sera *in vitro*.

Figure 2B is a heatmap depicting the effect of dual targeting of C3 and C5 on alternative hemolytic activity in human sera *in vitro*.

Figure 2C is a heatmap depicting the effect of dual targeting of C3 and C5 on classical hemolytic activity in human sera *in vitro*.

Figure 2D is a heatmap depicting the effect of dual targeting of C3 and C5 on classical hemolytic activity as determined by the Wieslab® Complement Classical Pathway (CCP) assay in human sera *in vitro*.

Figure 3A is a graph depicting the effect of administration of a single 6 mg/kg dose of a dsRNA agent targeting C3; or a dsRNA agent targeting CFB; or a dsRNA agent targeting C5; or a single 6 mg/kg dose of a dsRNA agent targeting C3 and a single 6 mg/kg dose of a dsRNA agent targeting CFB; or a single 6 mg/kg dose of a dsRNA agent targeting C3 and a single 6 mg/kg dose of a dsRNA agent targeting C5; or a single 6 mg/kg dose of a dsRNA agent targeting CFB and a single 6 mg/kg dose of a dsRNA agent targeting C5 on C3 protein levels, CFB protein levels or C5 protein levels in the sera of non-human primates.

Figure 3B is a graph depicting the effect of administration of a single 6 mg/kg dose of a dsRNA agent targeting C3; or a dsRNA agent targeting CFB; or a dsRNA agent targeting C5; or a single 6 mg/kg dose of a dsRNA agent targeting C3 and a single 6 mg/kg dose of a dsRNA agent targeting CFB; or a single 6 mg/kg dose of a dsRNA agent targeting C3 and a single 6 mg/kg dose of a dsRNA agent targeting C5; or a single 6 mg/kg dose of a dsRNA agent targeting CFB and a single 6 mg/kg dose of a dsRNA agent targeting C5 on alternative hemolytic activity in the sera of non-human primates.

Figure 3C is a graph depicting the effect of administration of a single 6 mg/kg dose of a dsRNA agent targeting C3; or a dsRNA agent targeting CFB; or a dsRNA agent targeting C5; or a single 6 mg/kg dose of a dsRNA agent targeting C3 and a single 6 mg/kg dose of a dsRNA agent targeting CFB; or a single 6 mg/kg dose of a dsRNA agent targeting C3 and a single 6 mg/kg dose of a dsRNA agent targeting C5; or a single 6 mg/kg dose of a dsRNA agent targeting CFB and a single 6 mg/kg dose of a dsRNA agent targeting C5 on classical hemolytic activity in the sera of non-human primates.

Figure 3D is a graph depicting the effect of administration of a single 6 mg/kg dose of a dsRNA agent targeting C3; or a dsRNA agent targeting CFB; or a dsRNA agent targeting C5; or a single 6 mg/kg dose of a dsRNA agent targeting C3 and a single 6 mg/kg dose of a dsRNA agent targeting CFB; or a single 6 mg/kg dose of a dsRNA agent targeting C3 and a single 6 mg/kg dose of a dsRNA agent targeting C5; or a single 6 mg/kg dose of a dsRNA agent targeting CFB and a single 6 mg/kg dose of a dsRNA agent targeting C5 on alternative hemolytic activity as determined by the Wieslab® Complement Alternative Pathway (CAP) assay in the sera of non-human primates.

Figure 3E is a graph depicting the effect of administration of a single 6 mg/kg dose of a dsRNA agent targeting C3; or a dsRNA agent targeting CFB; or a dsRNA agent targeting C5; or a single 6 mg/kg dose of a dsRNA agent targeting C3 and a single 6 mg/kg dose of a dsRNA agent targeting CFB; or a single 6 mg/kg dose of a dsRNA agent targeting C3 and a single 6 mg/kg dose of a dsRNA agent targeting C5; or a single 6 mg/kg dose of a dsRNA agent targeting CFB and a single 6 mg/kg dose of a dsRNA agent targeting C5 on alternative hemolytic activity as determined by the Wieslab® Complement Classical Pathway (CCP) assay in the sera of non-human primates.

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

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

21 nucleotide nucleic acid molecule" means that 19, 20, or 21 nucleotides have the indicated property. When at least is present before a series of numbers or a range, it is understood that "at least" can modify each of the numbers in the series or range.

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

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

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

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

As used herein, 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:189181756; 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, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33 or 35, or a fragment of any one of SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33 or 35, 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 943-965; 788-810; 734-756; 1016-1038; 1013-1035; 1207-1229; 1149-1171; 574-596; 1207-1229 or 828-850 of SEQ ID NO: 1, such as about 85%, about 90%, about 95%, or fully 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 153-175; 202-224; 219-241; 254-276; 304-326; 321-343; 347-369; 402-424; 418-440; 447-469; 491-513; 528-550; 549-571; 566-588; 591-613; 792-814; 819-841; 967-989; 1042-1064; 1234-1256; 1250-1272; 1269-1291; 1335-1357; 1354-1376; 1372-1394; 1422-

1444; 1496-1518; 1670-1692; 1716-1738; 1757-1779; 1774-1796; 1793-1815; 1844-1866; 1871-1893; 1909-1931; 1924-1947; 1947-1969; 2161-2183; 2310-2332; 2330-2352; 2355-2377; 2494-2516; and 2527-2549 of SEQ ID NO: 1, such as about 85%, about 90%, about 95%, or fully 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 2-7, 13, 16, 19 and 20, or a fragment of any one of the sense strand nucleotide sequences in any one of Tables 2-7, 13, 16, 19 and 20, 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: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34 or 36, or a fragment of any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34 or 36, 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 2-7, 13, 16, 19 and 20, or a fragment of any one of the antisense strand nucleotide sequences in any one of Tables 2-7, 13, 16, 19 and 20, such as about 85%, about 90%, about 95%, or fully complementary

In certain embodiments, the sense and antisense strands are selected from any one of the chemically modified duplexes AD-560018, AD-559375, AD-559160, AD-559374, AD-559060, AD-559721, AD-559026, AD-558225, AD-557069, AD-558068, AD-557422, AD-558063, AD-558066, AD-556701, AD-558657, AD-559020, AD-559023, AD-558860, AD-560019, AD-560016, AD-559008, AD-559717, AD-557072, AD-558097, AD-557774, AD-557070, AD-558065, AD-557853, AD-557079.

In certain embodiments, the sense and antisense strands are selected from any one of the chemically modified duplexes AD-560132.1; AD-560099.1; AD-559998.1; AD-559993.1; AD-559973.1; AD-559882.1; AD-559706.1; AD-559704.1; AD-559688.1; AD-559668.1; AD-559641.1; AD-559609.1; AD-559590.1; AD-559573.1; AD-559532.1; AD-559486.1; AD-559330.1; AD-559274.1; AD-559226.1; AD-559208.1; AD-559189.1; AD-559124.1; AD-559105.1; AD-559089.1; AD-558935.1; AD-558879.1; AD-558777.1; AD-558750.1; AD-558637.1; AD-558612.1; AD-558595.1; AD-558574.1; AD-558555.1; AD-558511.1; AD-558482.1; AD-558466.1; AD-558450.1; AD-558424.1; AD-558407.1; AD-558393.1; AD-558378.1; AD-558361.1; AD-558312.1

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, 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 2-7, 13, 16, 19 and 20, and the corresponding antisense strand of the sense strand is selected from the group of sequences of any one of Tables 2-7, 13, 16, 19 and 20. 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 2-7, 13, 16, 19 and 20, and the second oligonucleotide is described as the corresponding antisense strand of the sense strand in any one of Tables 2-7, 13, 16, 19 and 20.

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.

In certain embodiments, the sense or antisense strand is selected from the sense or antisense strand of any one of duplexes AD-560018, AD-559375, AD-559160, AD-559374, AD-559060, AD-559721, AD-559026, AD-558225, AD-557069, AD-558068, AD-557422, AD-558063, AD-558066, AD-556701, AD-558657, AD-559020, AD-559023, AD-558860, AD-560019, AD-560016, AD-559008, AD-559717, AD-557072, AD-558097, AD-557774, AD-557070, AD-558065, AD-557853, or AD-557079.

It will be understood that, although the sequences in Tables 2, 4, 6 and 19 are not described as modified or conjugated sequences, the RNA of the iRNA of the invention *e.g.*, a dsRNA of the invention, may comprise any one of the sequences set forth in any one of Tables 2-7, 13, 16, 19 and 20 that is un-modified, un-conjugated, or modified or conjugated differently than described therein. In other words, the invention encompasses dsRNA of Tables 2-7, 13, 16, 19 and 20 which are un-modified, un-conjugated, modified, or conjugated, as described herein.

The skilled person is well aware that dsRNAs having a duplex structure of about 20 to 23 base pairs, *e.g.,* 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir *et al.*, *EMBO* 2001, 20:6877-6888). However, others have found that shorter or longer RNA duplex structures can also be effective (Chu and Rana (2007) *RNA* 14:1714-1719; Kim *et al.* (2005) *Nat Biotech* 23:222-226). In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided in any one of Tables 2-7, 13, 16, 19 and 20, dsRNAs described herein can include at least one strand of a length of minimally 21 nucleotides. It can be reasonably expected that shorter duplexes having any one of the sequences in any one of Tables 2-7, 13, 16, 19 and 20 minus only a few nucleotides on one or both ends can be similarly effective as compared to the dsRNAs described above. Hence, dsRNAs having a sequence of at least 19, 20, or more contiguous nucleotides derived from any one of the sequences of any one of Tables 2-7, 13, 16, 19 and 20, 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 2-7, 13, 16, 19 and 20 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 2-7, 13, 16, 19 and 20 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.

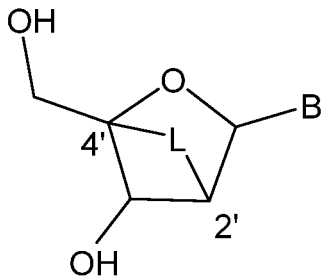
An iRNA can also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U). Modified 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'-0-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"- phosphate, inverted base dT(idT) and others. Disclosure of this modification can be found in WO2011/005861.

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 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):

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

$5'\ n_p\text{-}N_a\text{-}YYY\text{-}N_b\text{-}ZZZ\text{-}N_a\text{-}n_q\ 3'$ (Ib);

$5'\ n_p\text{-}N_a\text{-}XXX\text{-}N_b\text{-}YYY\text{-}N_a\text{-}n_q\ 3'$ (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.

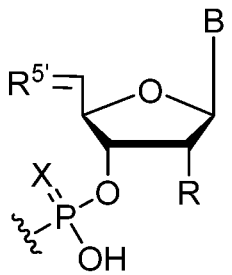
In certain embodiments, an RNAi agent of the invention may contain a low number of nucleotides containing a 2'-fluoro modification, *e.g.*, 10 or fewer nucleotides with 2'-fluoro

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.

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

Vinyl phosphate modifications are also contemplated for the compositions and methods of the instant disclosure. An exemplary vinyl phosphate 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

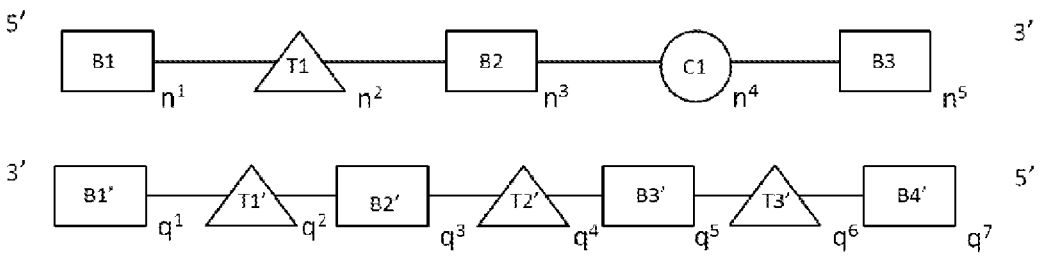
herein "seed region" means at positions 2-9 of the 5'-end of the referenced strand. For example, thermally destabilizing modifications can be incorporated in the seed region of the antisense strand to reduce or inhibit off-target gene silencing.

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 or acyclic nucleotide, e.g., unlocked nucleic acids (UNA) or glycol nucleic acid (GNA).

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

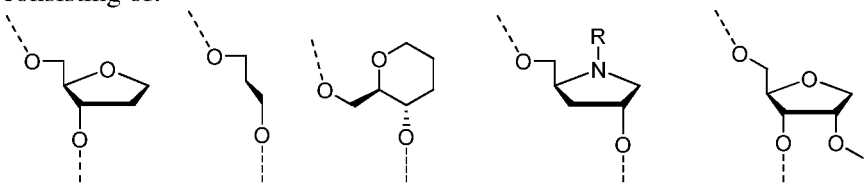


(L),

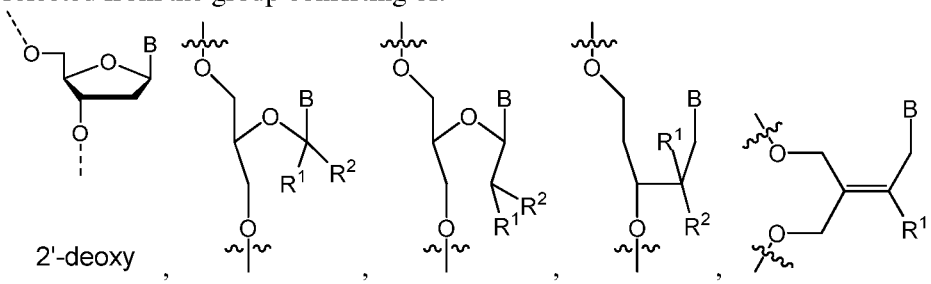
In formula (L), B1, B2, B3, B1', B2', B3', and B4' each are independently a nucleotide containing a modification selected from the group consisting of 2'-O-alkyl, 2'-substituted alkoxy, 2'-substituted alkyl, 2'-halo, ENA, and BNA/LNA. In one embodiment, B1, B2, B3, B1', B2', B3', and B4' each contain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

2'-OMe or 2'-F modifications. In one embodiment, at least one of B1, B2, B3, B1', B2', B3', and B4' contain 2'-O-N-methylacetamido (2'-O-NMA) modification.

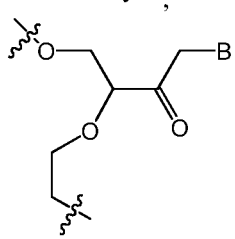
C1 is a thermally destabilizing nucleotide placed at a site opposite to the seed region of the antisense strand (*i.e.*, at positions 2-8 of the 5'-end of the antisense strand). For example, C1 is at a position of the sense strand that pairs with a nucleotide at positions 2-8 of the 5'-end of the antisense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

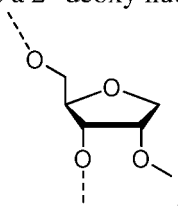


; and iii) sugar modification selected from the group consisting of:



2'-deoxy , , , , , 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).

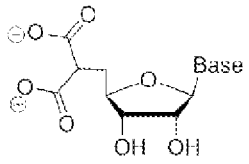
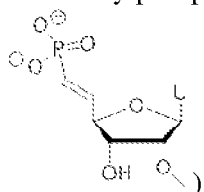
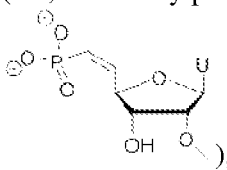
In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 5, T2' is 2'-F, q^4 is 1, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4' 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*-vinylphosphate, ), 5'-*Z*-VP isomer (*i.e.*, *cis*-vinylphosphate, ), or mixtures thereof.

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

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

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

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

In one embodiment, the RNAi agent comprises a 5'-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 2-7, 13, 16, 19 and 20. 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

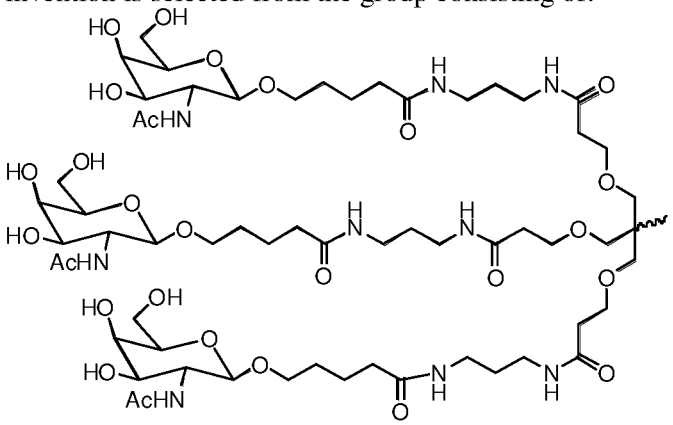
invention *via* a trivalent linker. In other embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a tetravalent linker.

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.

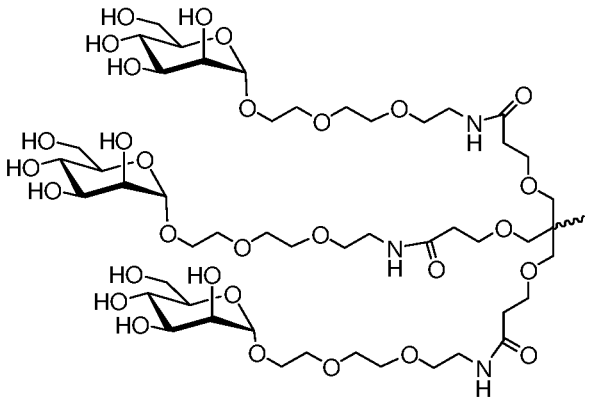
In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of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

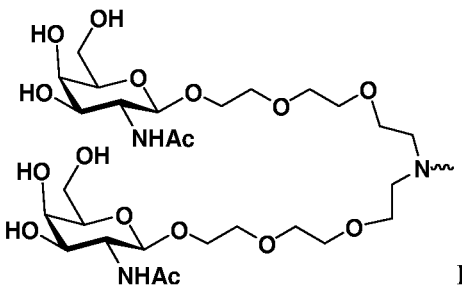
In one embodiment, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



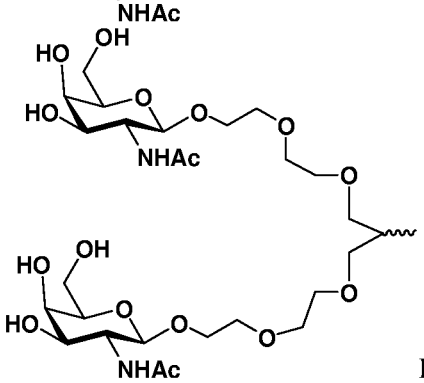
Formula II,



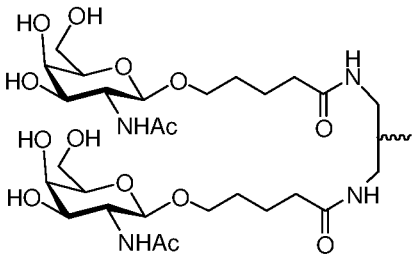
Formula III,



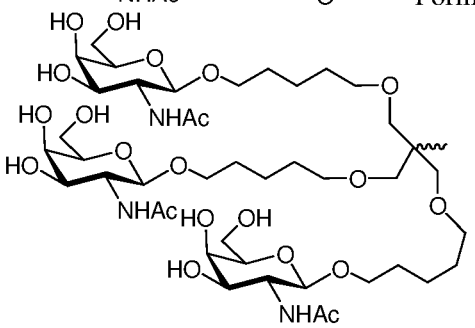
Formula IV,



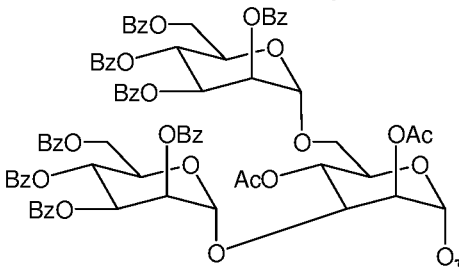
Formula V,



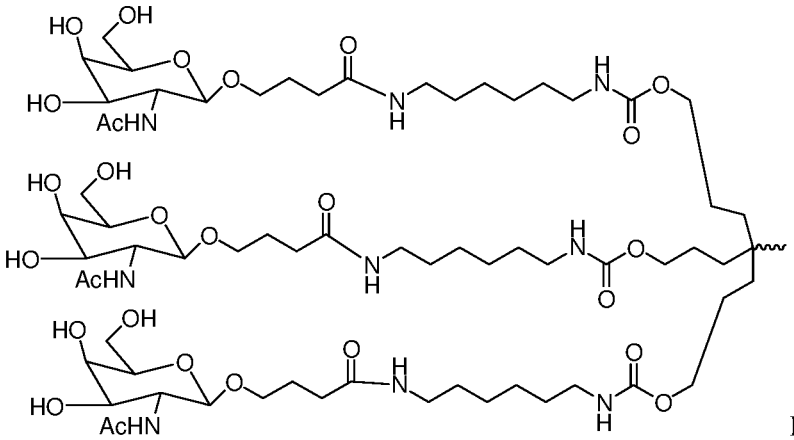
Formula VI,



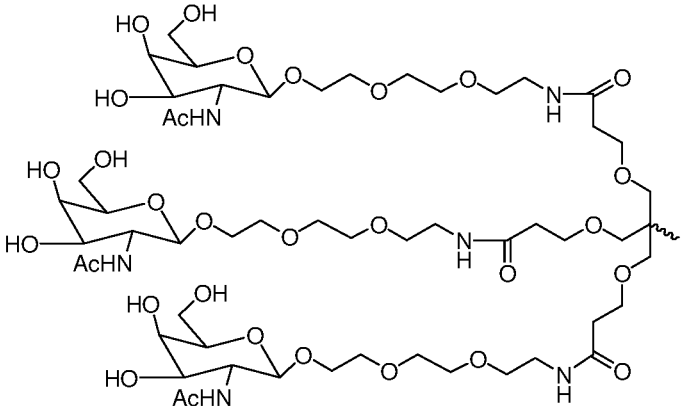
Formula VII,



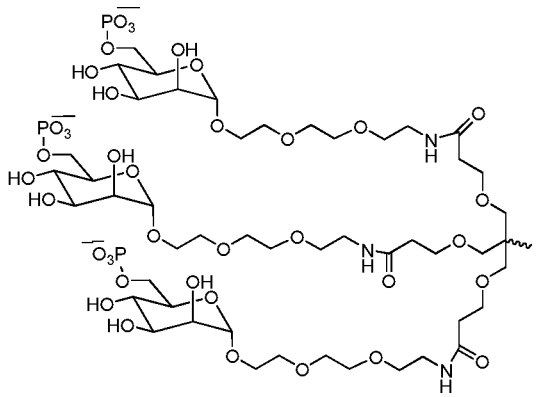
Formula VIII,



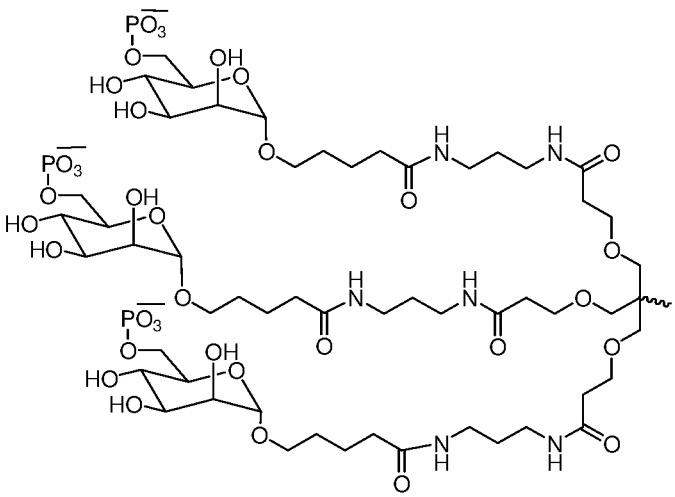
Formula IX,



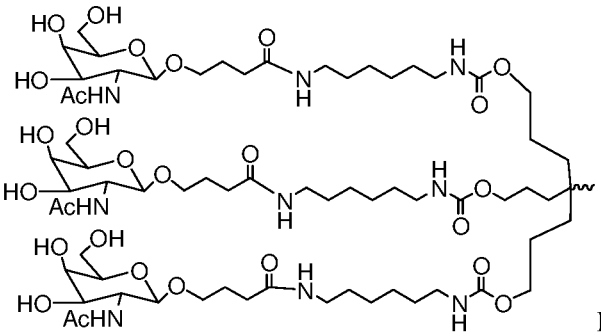
Formula X,



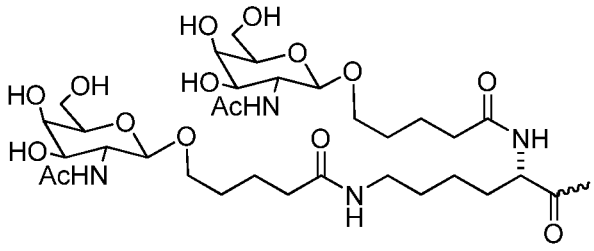
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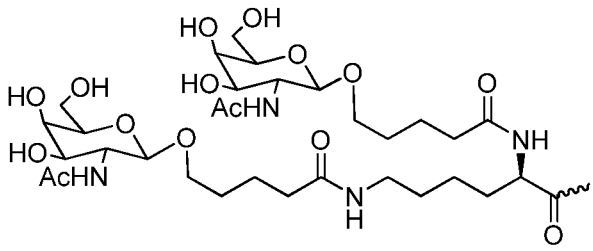
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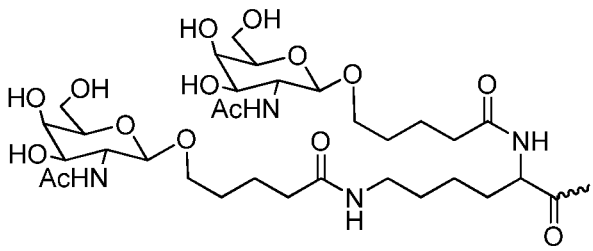
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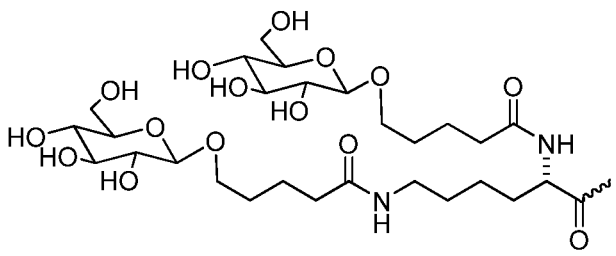
Formula XIV,



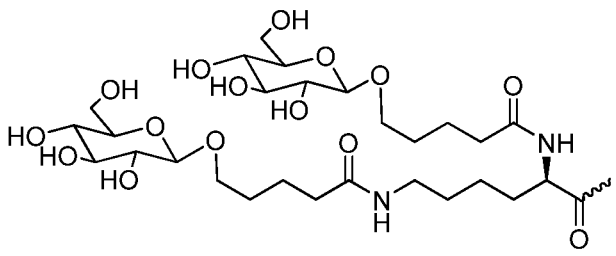
Formula XV,



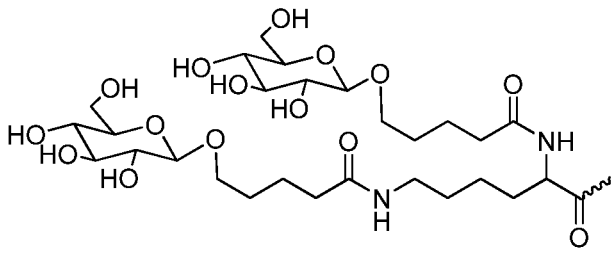
Formula XVI,



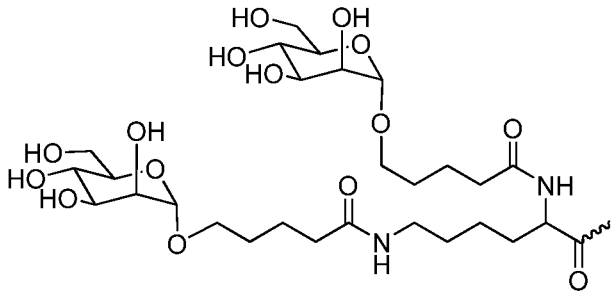
Formula XVII,



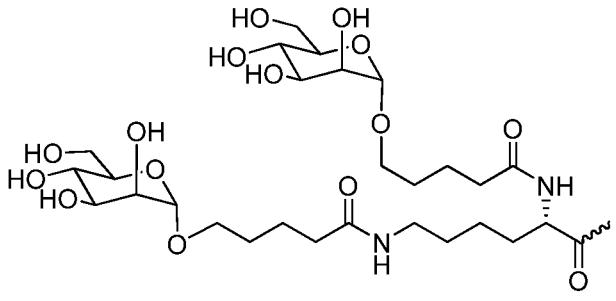
Formula XVIII,



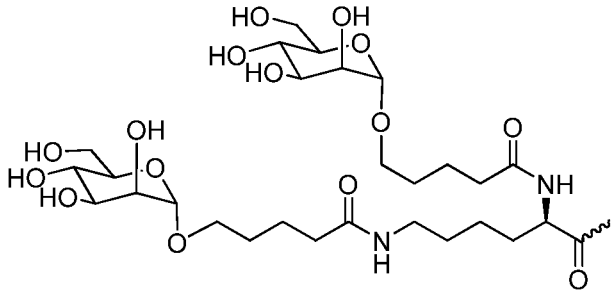
Formula XIX,



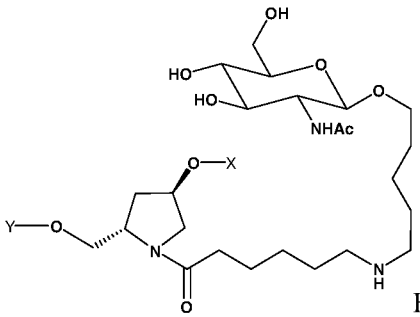
Formula XX,



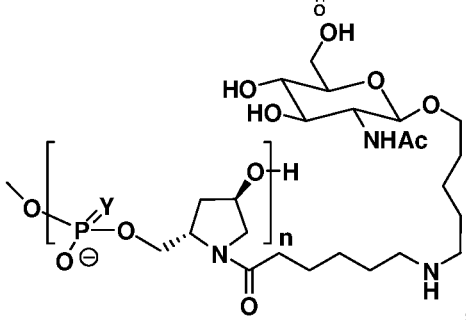
Formula XXI,



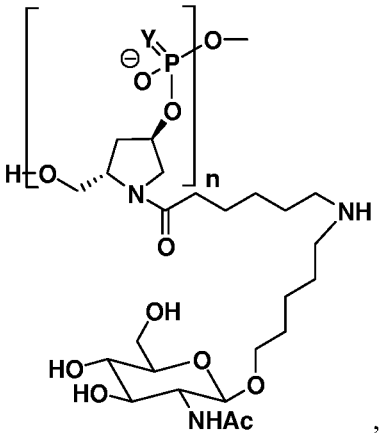
Formula XXII,



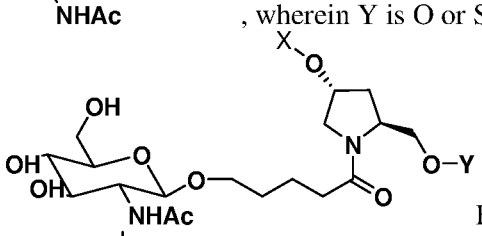
Formula XXIII;



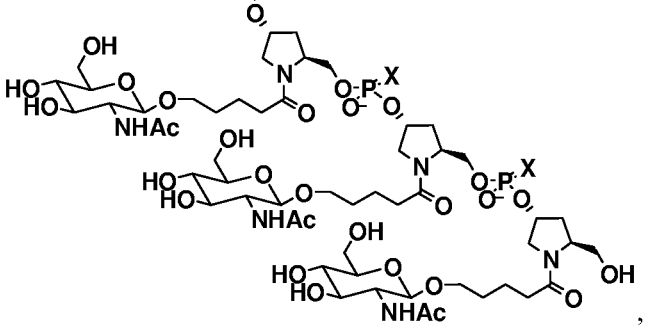
, wherein Y is O or S and n is 3 -6 (Formula XXIV);



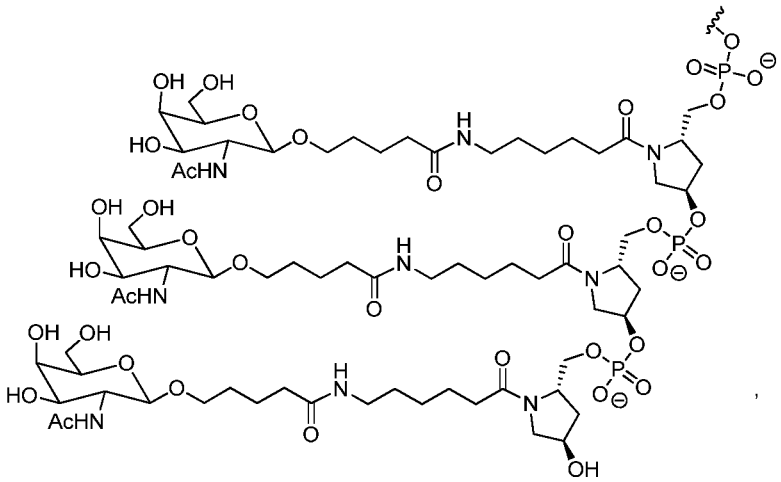
, wherein Y is O or S and n is 3-6 (Formula XXV);

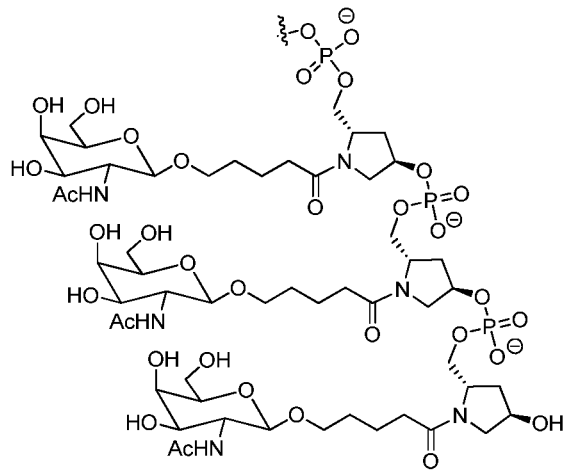


Formula XXVI;

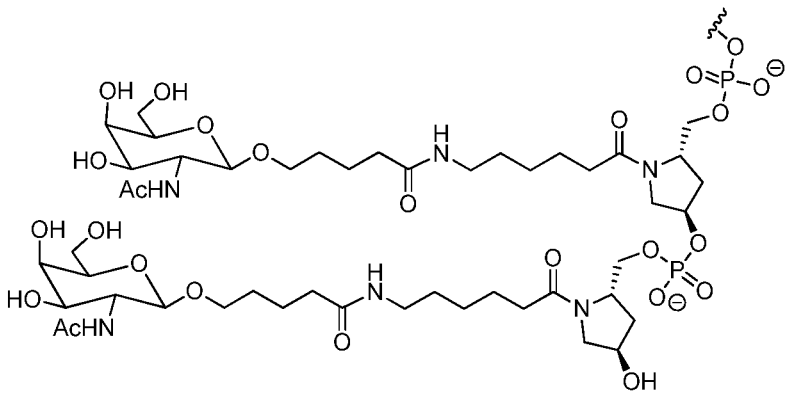


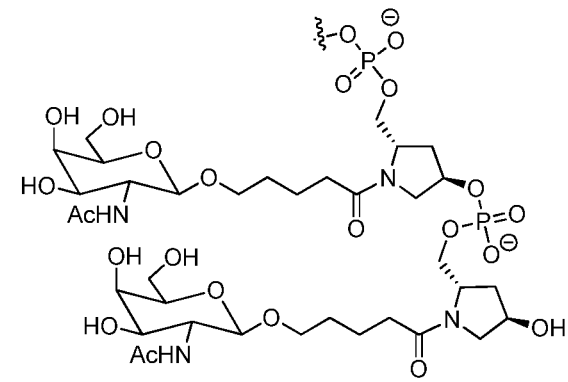
, wherein X is O or S (Formula XXVII);





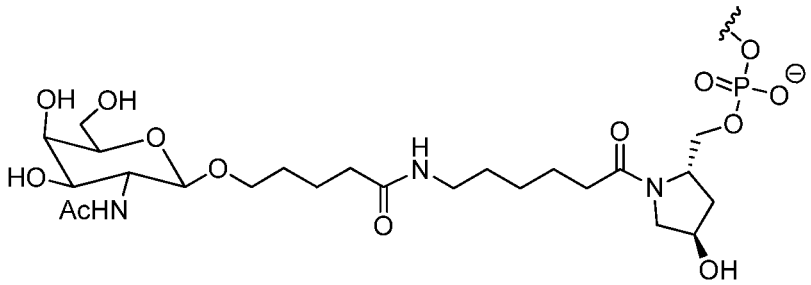
Formula XXVII; Formula XXIX;



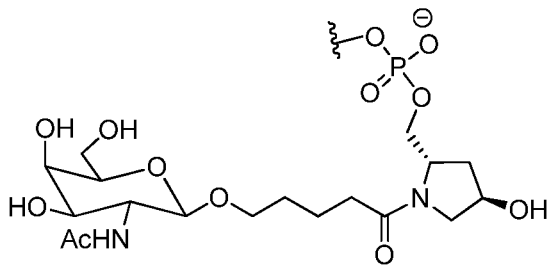


Formula XXX;

Formula XXXI;

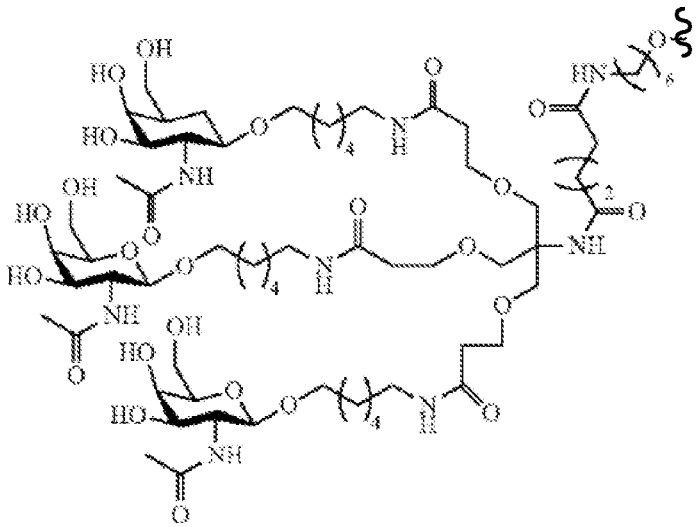


, and



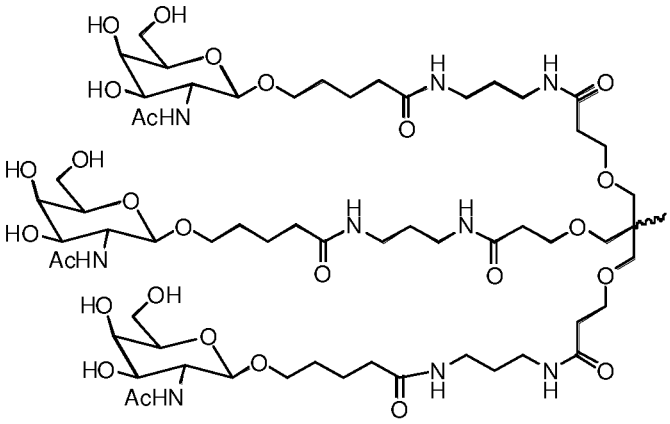
Formula XXXII;

Formula XXXIII.



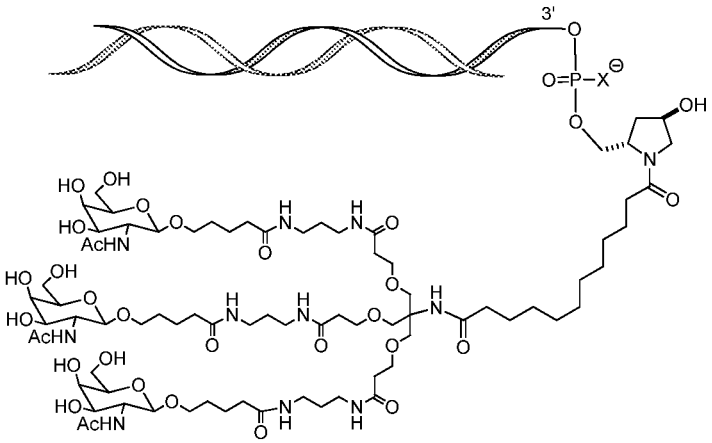
Formula XXXIV.

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

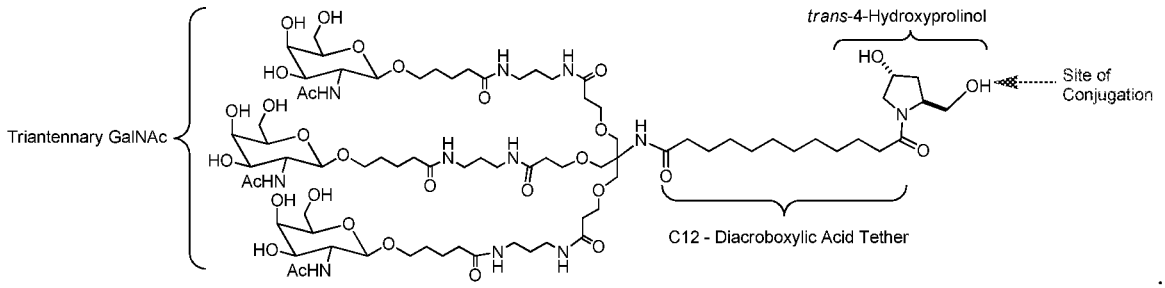


Formula II.

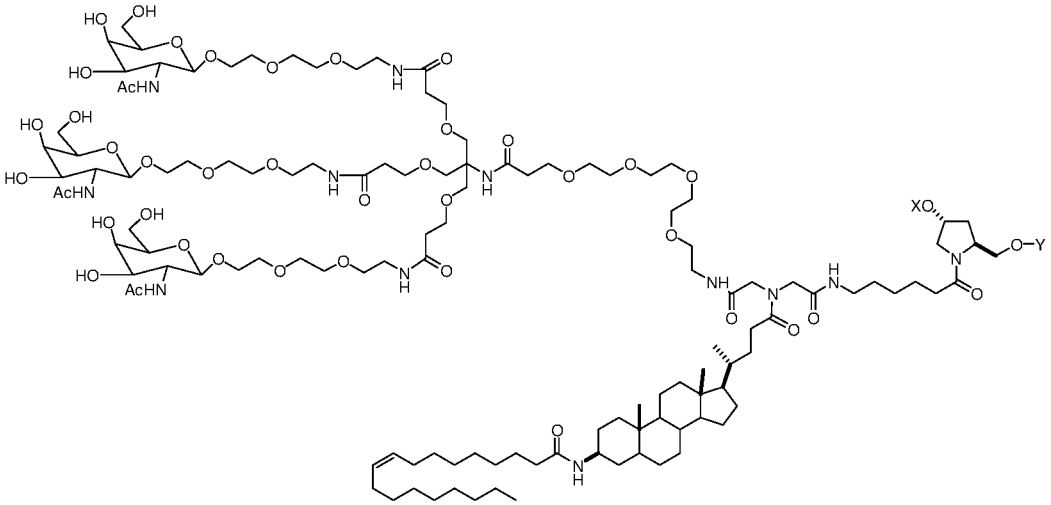
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate *via* a linker as shown in the following schematic, wherein X is O or S



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

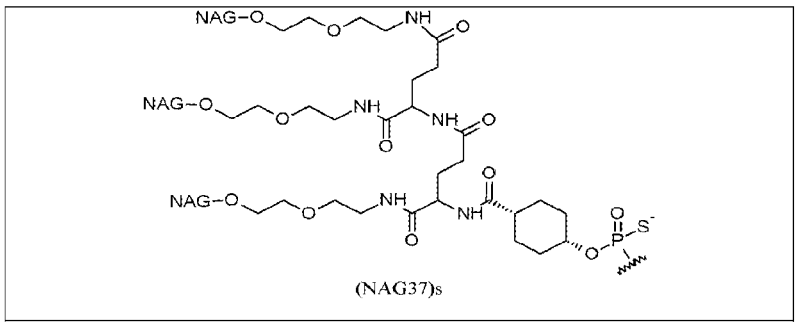


Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,



(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.

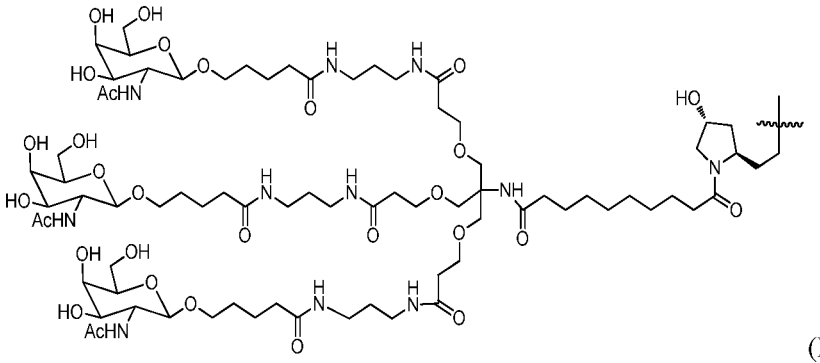
iv. Ester-based linking groups

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.

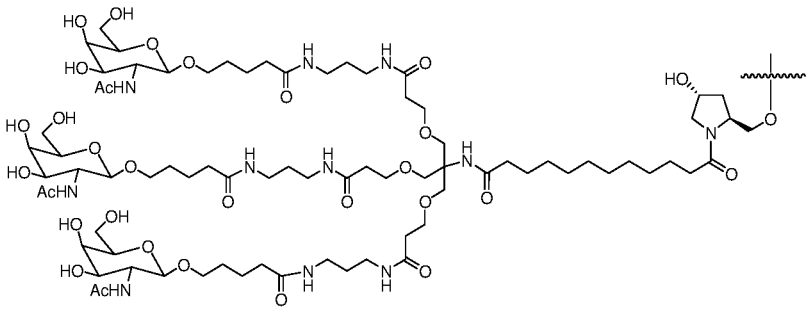
v. Peptide-based cleaving groups

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.

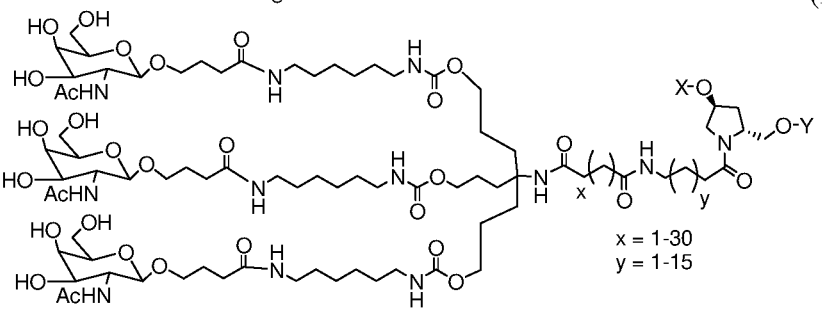
In some embodiments, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



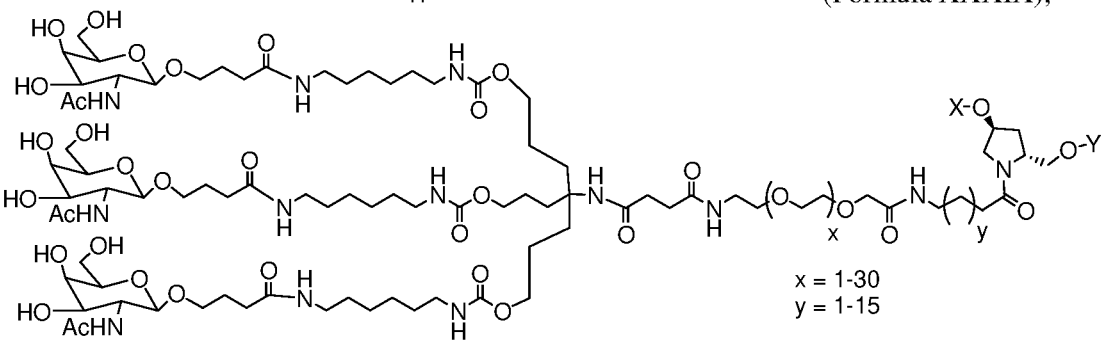
(Formula XXXVII),



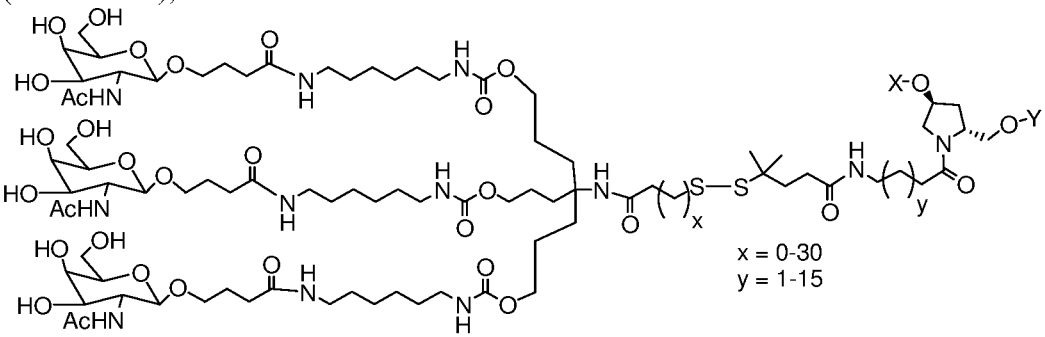
(Formula XXXVIII),



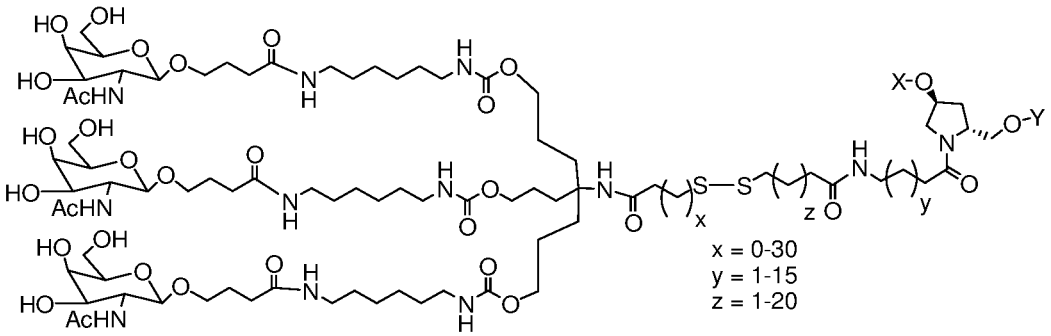
(Formula XXXIX),



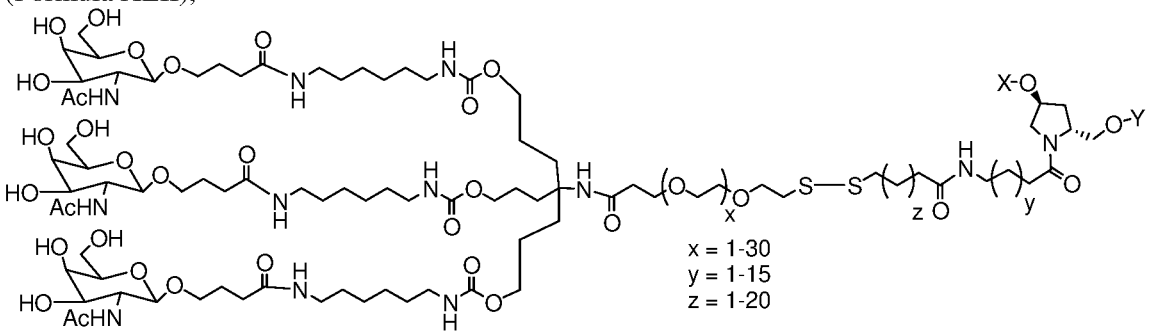
(Formula XL),



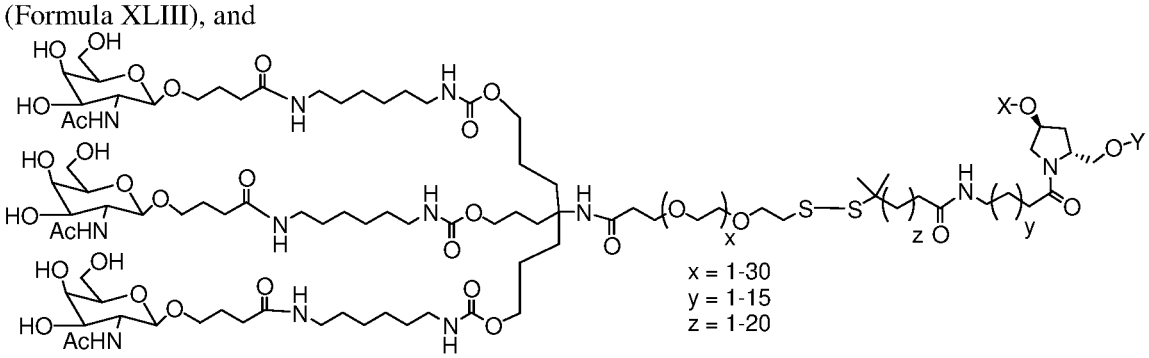
(Formula XLI),



(Formula XLII),



(Formula XLIII), and

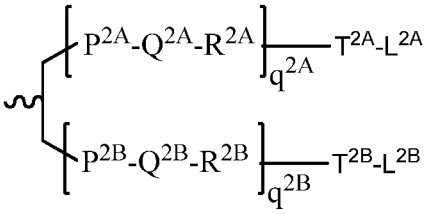


(Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

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.

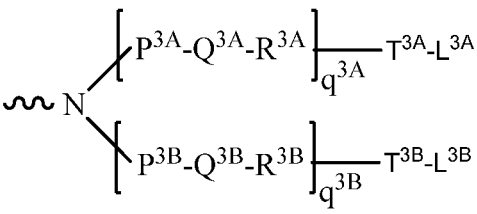
In one embodiment, a dsRNA of the invention is conjugated to a bivalent or trivalent branched linker selected from the group of structures shown in any of formula (XLV) – (XLVI):

Formula XXXXV

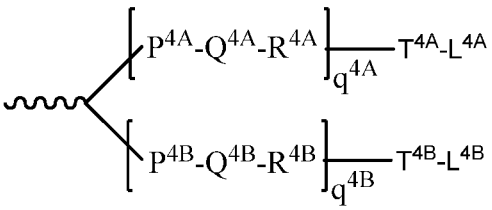


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Formula XLVI

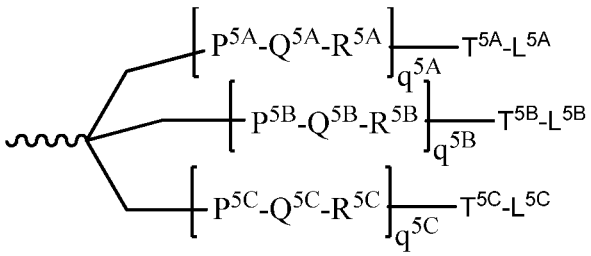


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Formula (VI)

,



Formula (VII)

;

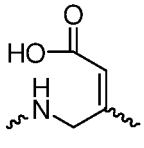
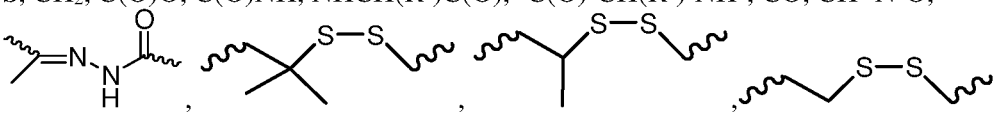
Formula XLVII Formula XLVIII

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;

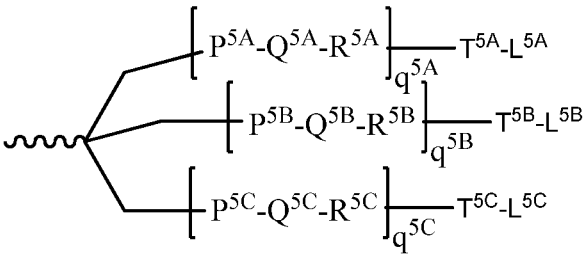
P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{4A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2, CH_2NH or CH_2O;

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) J*ournal 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 are 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_001710.5; NCBI GeneID: 629) was designed using custom R and Python scripts. The human NM_001710 REFSEQ mRNA, version 5, has a length of 2646 bases. Detailed lists of the unmodified

CFB sense and antisense strand nucleotide sequences are shown in Tables 2, 4, and 6. Detailed lists of the modified CFB sense and antisense strand nucleotide sequences are shown in Tables 3, 5, and 7.

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.

Example 2. *In vitro* screening methods

Cell culture and 384-well transfections

Hep3b cells (ATCC, Manassas, VA) were grown to near confluence at 37°C in an atmosphere of 5% CO_2 in Eagle's Minimum Essential Medium (Gibco) supplemented with 10% FBS (ATCC) before being released from the plate by trypsinization. Primary mouse hepatocytes (PMH) were freshly isolated less than 1 hour prior to transfections and grown in primary hepatocyte media. For both Hep3B and PMH, transfection was carried out by adding 5 µl of Opti-MEM plus 0.1 µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5 µl of each siRNA duplex to an individual well in a 384-well plate. The mixture was then incubated at room temperature for 15 minutes. Forty µl of Eagle's Minimum Essential Medium (ATCC Cat#30-2003) containing ~5 x10^3 Hep3B cells or PMH were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Single dose experiments were performed at 10 nM, 1 nM, and 0.1 nM.

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

RNA was isolated using an automated protocol on a BioTek-EL406 platform using DYNABEADs (Invitrogen, cat#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 150 µl Wash Buffer A and once with Wash Buffer B. Beads were then washed with 150 µl Elution Buffer, re-captured and supernatant removed.

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

A master mix of 1.2 µl 10X Buffer, 0.48 µl 25X dNTPs, 1.2 µl Random primers, 0.6 µl Reverse Transcriptase, 0.6 µl RNase inhibitor and 7.92 µl of H_2O per reaction were added per well. Plates were sealed, mixed, and then incubated on an electromagnetic shaker for 10 minutes at room temperature, followed by incubation at 37°C for 2 hours.

Real time PCR

Two µl of cDNA were added to a master mix containing 0.5µl of human GAPDH TaqMan Probe (4326317E), amd 0.5µl CFB human probe (Hs01071998_m1) and 5µl Lightcycler 480 probe master mix (Roche Cat # 04887301001) per well in a 384 well plates (Roche cat # 04887301001). Real time PCR was done in a LightCycler480 Real Time PCR system (Roche). Each duplex was tested at least two times and data were normalized to cells transfected with a non-targeting control siRNA. To calculate relative fold change, real time data were analyzed using the ΔΔCt method and normalized to assays performed with cells transfected with a non-targeting control siRNA.

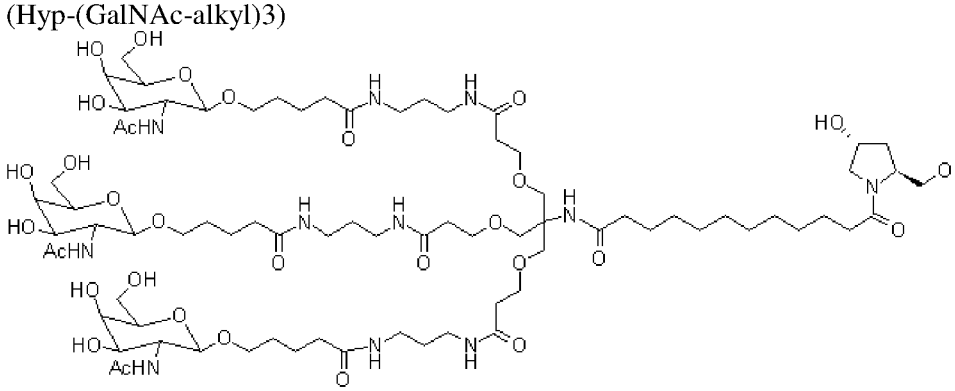
The results of the single dose screen of the dsRNA agents in Tables 2 are 3 in Hep3B cells are shown in Table 8. The results of the single dose screen of the dsRNA agents Tables 4 and 5 in Hep3B cells are shown in Table 9. The results of the single dose screen of the dsRNA agents Tables 4 and 5 in PMH cells are shown in Table 10. The results of the single dose screen of the dsRNA agents Tables 6 and 7 in PMH cells are shown in Table 11. The results of the single dose screen of the dsRNA agents Tables 6 and 7 in Hep3B cells are shown in Table 12.

ELISA Assay

Human CFB protein levels were determined using a quantitative sandwich enzyme immunoassay (Human Complement Factor B AssayMax ELISA Kit – AssayPro). Briefly, samples were diluted 1:1000 and 50 µl of sample was added to a well of a microtiter plate. Samples were incubated for two hours and subsequently washed. Fifty µl of biotinylated anti-CFB antibody was added to each well and incubated 1 hour. Samples were then washed and 50 µl of streptavidin-peroxidase conjugate was added to each well and incubated for 30 minutes. Following another wash, 50 µl of peroxidase enzyme substrate per well was added and samples were incubated for 15 minutes after which 50 µl of Stop Solution per well was added. Samples were read at 450 nm immediately and the amount of human CFB protein was determined by comparing the reading to a standard curve (0-280 ng of human CFB protein).

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).

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

Abbre*via*tion	**Nucleotide(s)**
C	cytidine-3’-phosphate
Cb	beta-L-cytidine-3`-phosphate
Cbs	beta-L-cytidine-3'-phosphorothioate
Cf	2’-fluorocytidine-3’-phosphate
Cfs	2’-fluorocytidine-3’-phosphorothioate
Cs	cytidine-3’-phosphorothioate
G	guanosine-3’-phosphate
Gb	beta-L-guanosine-3`-phosphate
Gbs	beta-L-guanosine-3`-phosphorothioate
Gf	2’-fluoroguanosine-3’-phosphate
Gfs	2’-fluoroguanosine-3’-phosphorothioate
Gs	guanosine-3’-phosphorothioate
T	5’-methyluridine-3’-phosphate
Tf	2’-fluoro-5-methyluridine-3’-phosphate
Tfs	2’-fluoro-5-methyluridine-3’-phosphorothioate
Ts	5-methyluridine-3’-phosphorothioate
U	Uridine-3’-phosphate
Uf	2’-fluorouridine-3’-phosphate
Ufs	2’-fluorouridine -3’-phosphorothioate
Us	uridine -3’-phosphorothioate
N	any nucleotide, modified or unmodified
a	2'-O-methyladenosine-3’-phosphate
as	2'-O-methyladenosine-3’- phosphorothioate
c	2'-O-methylcytidine-3’-phosphate
cs	2'-O-methylcytidine-3’- phosphorothioate
g	2'-O-methylguanosine-3’-phosphate
gs	2'-O-methylguanosine-3’- phosphorothioate
t	2’-O-methyl-5-methyluridine-3’-phosphate
ts	2’-O-methyl-5-methyluridine-3’-phosphorothioate
u	2'-O-methyluridine-3’-phosphate
us	2'-O-methyluridine-3’-phosphorothioate
s	phosphorothioate linkage
L10	N-(cholesterylcarboxamidocaproyl)-4-hydroxyprolinol (Hyp-C6-Chol)
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol (Hyp-(GalNAc-alkyl)3) 
Y34	2-hydroxymethyl-tetrahydrofurane-4-methoxy-3-phosphate (abasic 2'-OMe furanose)
Y44	inverted abasic DNA (2-hydroxymethyl-tetrahydrofurane-5-phosphate)
(Agn)	Adenosine-glycol nucleic acid (GNA)
(Cgn)	Cytidine-glycol nucleic acid (GNA)
(Ggn)	Guanosine-glycol nucleic acid (GNA)

Abbre*via*tion	**Nucleotide(s)**
(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
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(Ghd)	2'-O-hexadecyl-guanosine-3'-phosphate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate

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

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range (NM_001710.5)	Antiense Sequence 5' to 3'	SEQ ID NO:	Range (NM_001710.5)
AD-557072.1	CAAAAAGUGUCUAGUCAACUU	19	1145-1165	AAGUUGACUAGACACUUUUUGGC	105	1143-1165
AD-558097.1	UAGUGGAUGUCUGCAAAAACU	20	2440-2460	AGUUUUTGCAGACAUCCACUACU	106	2438-2460
AD-557774.1	GAAUUCCUGAAUUUUAUGACU	21	1981-2001	AGUCAUAAAAUUCAGGAAUUCCU	107	1979-2001
AD-557070.1	GCCAAAAAGUGUCUAGUCAAU	22	1143-1163	AUUGACTAGACACUUUUUGGCUC	108	1141-1163
AD-558068.1	UCACAAGAGAAGUCGUUUCAU	23	2393-2413	AUGAAACGACUUCUCUUGUGAAC	109	2391-2413
AD-557068.1	GAGCCAAAAAGUGUCUAGUCU	24	1141-1161	AGACUAGACACUUUUUGGCUCCU	110	1139-1161
AD-556701.1	CUACUACAAUGUGAGUGAUGU	25	635-655	ACAUCACUCACAUUGUAGUAGGG	111	633-655
AD-558076.1	GAAGUCGUUUCAUUCAAGUUU	26	2401-2421	AAACUUGAAUGAAACGACUUCUC	112	2399-2421
AD-558065.1	AGUUCACAAGAGAAGUCGUUU	27	2390-2410	AAACGACUUCUCUUGUGAACUAU	113	2388-2410
AD-557859.1	CAACUCGAGCUUUGAGGCUUU	28	2086-2106	AAAGCCTCAAAGCUCGAGUUGUU	114	2084-2106
AD-558096.1	GUAGUGGAUGUCUGCAAAAAU	29	2439-2459	AUUUUUGCAGACAUCCACUACUC	115	2437-2459
AD-557422.1	GAGGAUUAUCUGGAUGUCUAU	30	1536-1556	AUAGACAUCCAGAUAAUCCUCCC	116	1534-1556
AD-556919.1	AGACUCCUUCAUGUACGACAU	31	935-955	AUGUCGTACAUGAAGGAGUCUUG	117	933-955
AD-558069.1	CACAAGAGAAGUCGUUUCAUU	32	2394-2414	AAUGAAACGACUUCUCUUGUGAA	118	2392-2414
AD-558063.1	AUAGUUCACAAGAGAAGUCGU	33	2388-2408	ACGACUTCUCUUGUGAACUAUCA	119	2386-2408
AD-557069.1	AGCCAAAAAGUGUCUAGUCAU	34	1142-1162	AUGACUAGACACUUUUUGGCUCC	120	1140-1162
AD-558225.1	UGAAUUAAAACAGCUGCGACU	35	2604-2624	AGUCGCAGCUGUUUUAAUUCAAU	121	2602-2624
AD-557853.1	AGGGAACAACUCGAGCUUUGU	36	2080-2100	ACAAAGCUCGAGUUGUUCCCUCG	122	2078-2100
AD-558012.1	GACAAAGUCAAGGACAUCUCU	37	2277-2297	AGAGAUGUCCUUGACUUUGUCAU	123	2275-2297
AD-558061.1	UGAUAGUUCACAAGAGAAGUU	38	2386-2406	AACUUCTCUUGUGAACUAUCAAG	124	2384-2406
AD-557079.1	UGUCUAGUCAACUUAAUUGAU	39	1152-1172	AUCAAUTAAGUUGACUAGACACU	125	1150-1172
AD-558066.1	GUUCACAAGAGAAGUCGUUUU	40	2391-2411	AAAACGACUUCUCUUGUGAACUA	126	2389-2411
AD-557353.1	GACCCAAUUACUGUCAUUGAU	41	1467-1487	AUCAAUGACAGUAAUUGGGUCCC	127	1465-1487
AD-557782.1	GAAUUUUAUGACUAUGACGUU	42	1989-2009	AACGUCAUAGUCAUAAAAUUCAG	128	1987-2009
AD-556390.1	CUGGAGUUUCAGCUUGGACAU	43	179-199	AUGUCCAAGCUGAAACUCCAGAC	129	177-199
AD-557078.1	GUGUCUAGUCAACUUAAUUGU	44	1151-1171	ACAAUUAAGUUGACUAGACACUU	130	1149-1171
AD-557475.1	UUCCAAGAAAGACAAUGAGCU	45	1607-1627	AGCUCATUGUCUUUCUUGGAAGC	131	1605-1627
AD-556734.1	CUGCUAUGACGGUUACACUCU	46	668-688	AGAGUGTAACCGUCAUAGCAGUG	132	666-688
AD-557084.1	AGUCAACUUAAUUGAGAAGGU	47	1157-1177	ACCUUCTCAAUUAAGUUGACUAG	133	1155-1177
AD-557498.1	AUGUGUUCAAAGUCAAGGAUU	48	1630-1650	AAUCCUTGACUUUGAACACAUGU	134	1628-1650
AD-556788.1	GACAGCGAUCUGUGACAACGU	49	740-760	ACGUUGTCACAGAUCGCUGUCUG	135	738-760
AD-557067.1	GGAGCCAAAAAGUGUCUAGUU	50	1140-1160	AACUAGACACUUUUUGGCUCCUG	136	1138-1160
AD-557852.1	GAGGGAACAACUCGAGCUUUU	51	2079-2099	AAAAGCTCGAGUUGUUCCCUCGG	137	2077-2099

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range (NM_001710.5)	Antiense Sequence 5' to 3'	SEQ ID NO:	Range (NM_001710.5)
AD-556733.1	ACUGCUAUGACGGUUACACUU	52	667-687	AAGUGUAACCGUCAUAGCAGUGG	138	665-687
AD-556725.1	CUCUUUCCACUGCUAUGACGU	53	659-679	ACGUCATAGCAGUGGAAAGAGAU	139	657-679
AD-557860.1	AACUCGAGCUUUGAGGCUUCU	54	2087-2107	AGAAGCCUCAAAGCUCGAGUUGU	140	2085-2107
AD-556786.1	CAGACAGCGAUCUGUGACAAU	55	738-758	AUUGUCACAGAUCGCUGUCUGCC	141	736-758
AD-556581.1	CCUUCUGGCUUCUACCCGUAU	56	465-485	AUACGGGUAGAAGCCAGAAGGAC	142	463-485
AD-556963.1	ACCAUAGAAGGAGUCGAUGCU	57	999-1019	AGCAUCGACUCCUUCUAUGGUCU	143	997-1019
AD-557450.1	ACCAAGUGAACAUCAAUGCUU	58	1582-1602	AAGCAUUGAUGUUCACUUGGUUC	144	1580-1602
AD-557204.1	UGAAAUCAAUUAUGAAGACCU	59	1298-1318	AGGUCUUCAUAAUUGAUUUCAUU	145	1296-1318
AD-558062.1	GAUAGUUCACAAGAGAAGUCU	60	2387-2407	AGACUUCUCUUGUGAACUAUCAA	146	2385-2407
AD-557602.1	AAGGGUACCGAUUACCACAAU	61	1734-1754	AUUGUGGUAAUCGGUACCCUUCC	147	1732-1754
AD-556917.1	CAAGACUCCUUCAUGUACGAU	62	933-953	AUCGUACAUGAAGGAGUCUUGGC	148	931-953
AD-557969.1	CUGACUCGGAAGGAGGUCUAU	63	2196-2216	AUAGACCUCCUUCCGAGUCAGCU	149	2194-2216
AD-558064.1	UAGUUCACAAGAGAAGUCGUU	64	2389-2409	AACGACTUCUCUUGUGAACUAUC	150	2387-2409
AD-558105.1	GUCUGCAAAAACCAGAAGCGU	65	2448-2468	ACGCUUCUGGUUUUUGCAGACAU	151	2446-2468
AD-556791.1	AGCGAUCUGUGACAACGGAGU	66	743-763	ACUCCGTUGUCACAGAUCGCUGU	152	741-763
AD-557972.1	ACUCGGAAGGAGGUCUACAUU	67	2199-2219	AAUGUAGACCUCCUUCCGAGUCA	153	2197-2219
AD-556920.1	GACUCCUUCAUGUACGACACU	68	936-956	AGUGUCGUACAUGAAGGAGUCUU	154	934-956
AD-558078.1	AGUCGUUUCAUUCAAGUUGGU	69	2403-2423	ACCAACTUGAAUGAAACGACUUC	155	2401-2423
AD-557861.1	ACUCGAGCUUUGAGGCUUCCU	70	2088-2108	AGGAAGCCUCAAAGCUCGAGUUG	156	2086-2108
AD-557856.1	GAACAACUCGAGCUUUGAGGU	71	2083-2103	ACCUCAAAGCUCGAGUUGUUCCC	157	2081-2103
AD-557041.1	UGGUGCUAGAUGGAUCAGACU	72	1096-1116	AGUCUGAUCCAUCUAGCACCAGG	158	1094-1116
AD-556874.1	GUGUCAGGAAGGUGGCUCUUU	73	890-910	AAAGAGCCACCUUCCUGACACGU	159	888-910
AD-557345.1	CUGAUGGAUUGCACAACAUGU	74	1441-1461	ACAUGUTGUGCAAUCCAUCAGUC	160	1439-1461
AD-557839.1	CAGACUAUCAGGCCCAUUUGU	75	2046-2066	ACAAAUGGGCCUGAUAGUCUGGC	161	2044-2066
AD-556962.1	GACCAUAGAAGGAGUCGAUGU	76	998-1018	ACAUCGACUCCUUCUAUGGUCUC	162	996-1018
AD-557066.1	AGGAGCCAAAAAGUGUCUAGU	77	1139-1159	ACUAGACACAUUUUUGGCUCCUGU	163	1137-1159
AD-556961.1	AGACCAUAGAAGGAGUCGAUU	78	997-1017	AAUCGACUCCUUCUAUGGUCUCU	164	995-1017
AD-557226.1	AAGUUGAAGUCAGGGACUAAU	79	1320-1340	AUUAGUCCCUGACUUCAACUUGU	165	1318-1340
AD-557865.1	GAGCUUUGAGGCUUCCUCCAU	80	2092-2112	AUGGAGGAAGCCUCAAAGCUCGA	166	2090-2112
AD-557209.1	UCAAUUAUGAAGACCACAAGU	81	1303-1323	ACUUGUGGGUCUUCAUAAUUGAUU	167	1301-1323
AD-556918.1	AAGACUCCUUCAUGUACGACU	82	934-954	AGUCGUACAUGAAGGAGUCUUGG	168	932-954
AD-557868.1	CUUUGAGGCUUCCUCCAACUU	83	2095-2115	AAGUUGGAGGAAGCCUCAAAGCU	169	2093-2115
AD-557873.1	AGGCUUCCUCCAACUACCACU	84	2100-2120	AGUGGUAGUUGGAGGAAGCCUCA	170	2098-2120
AD-556787.1	AGACAGCGAUCUGUGACAACU	85	739-759	AGUUGUCACAGAUCGCUGUCUGC	171	737-759

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range (NM_001710.5)	Antiense Sequence 5' to 3'	SEQ ID NO:	Range (NM_001710.5)
AD-558004.1	CAGGCUAUGACAAAGUCAAGU	86	2269-2289	ACUUGACUUUGUCAUAGCCUGGG	172	2267-2289
AD-557867.1	GCUUUGAGGCUUCCUCCAACU	87	2094-2114	AGUUGGAGGAAGCCUCAAAGCUC	173	2092-2114
AD-557788.1	UAUGACUAUGACGUUGCCCUU	88	1995-2015	AAGGGCAACGUCAUAGUCAUAAA	174	1993-2015
AD-558106.1	UCUGCAAAAACCAGAAGCGGU	89	2449-2469	ACCGCUTCUGGUUUUUGCAGACA	175	2447-2469
AD-556724.1	UCUCUUUCCACUGCUAUGACU	90	658-678	AGUCAUAGCAGUGGAAAGAGAUC	176	656-678
AD-556739.1	AUGACGGUUACACUCUCCGGU	91	673-693	ACCGGAGAGUGUAACCGUCAUAG	177	671-693
AD-557417.1	CAAGGGAGGAUUAUCUGGAUU	92	1531-1551	AAUCCAGAUAAUCCUCCCUUGGG	178	1529-1551
AD-556790.1	CAGCGAUCUGUGACAACGGAU	93	742-762	AUCCGUTGUCACAGAUCGCUGUC	179	740-762
AD-557872.1	GAGGCUUCCUCCAACUACCAU	94	2099-2119	AUGGUAGUUGGAGGAAGCCUCAA	180	2097-2119
AD-556738.1	UAUGACGGUUACACUCUCCGU	95	672-692	ACGGAGAGUGUAACCGUCAUAGC	181	670-692
AD-557857.1	AACAACUCGAGCUUUGAGGCU	96	2084-2104	AGCCUCAAAGCUCGAGUUGUUCC	182	2082-2104
AD-556726.1	UCUUUCCACUGCUAUGACGGU	97	660-680	ACCGUCAUAGCAGUGGAAAGAGA	183	658-680
AD-557495.1	AACAUGUGUUCAAAGUCAAGU	98	1627-1647	ACUUGACUUUGAACACAUGUUGC	184	1625-1647
AD-557016.1	CCUUCAGGCUCCAUGAACAUU	99	1071-1091	AAUGUUCAUGGAGCCUGAAGGGU	185	1069-1091
AD-558074.1	GAGAAGUCGUUUCAUUCAAGU	100	2399-2419	ACUUGAAUGAAACGACUUCUCUU	186	2397-2419
AD-557604.1	GGGUACCGAUUACCACAAGCU	101	1736-1756	AGCUUGTGGUAAUCGGUACCCUU	187	1734-1756
AD-557346.1	UGAUGGAUUGCACAACAUGGU	102	1442-1462	ACCAUGTUGUGCAAUCCAUCAGU	188	1440-1462
AD-557851.1	CGAGGGAACAACUCGAGCUUU	103	2078-2098	AAAGCUCGAGUUGUUCCCUCGGU	189	2076-2098
AD-557786.1	UUUAUGACUAUGACGUUGCCU	104	1993-2013	AGGCAACGUCAUAGUCAUAAAAU	190	1991-2013

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

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-557072.1	csasaaaaGfuGfUfCfuagucaacuuL96	191	asAfsguug(Agn)cuagacAfcUfuuuugsgsc	277	GCCAAAAAGUGUCUAGUCAACUU	363
AD-558097.1	usasguggAfuGfUfCfugcaaaaacuL96	192	asGfsuuuu(Tgn)gcagacAfuCfcacuascsu	278	AGUAGUGGAUGUCUGCAAAAACC	364
AD-557774.1	gsasauucCfuGfAfAfuuuuaugacuL96	193	asGfsucau(Agn)aaauucAfgGfaauucscsu	279	AGGAAUUCCUGAAUUUUAUGACU	365
AD-557070.1	gscscaaaAfaGfUfGfucuagucaauL96	194	asUfsugac(Tgn)agacacUfuUfuuggcsusc	280	GAGCCAAAAAGUGUCUAGUCAAC	366
AD-558068.1	uscsacaaGfaGfAfAfgucguuucauL96	195	asUfsgaaa(Cgn)gacuucUfcUfugugasasc	281	GUUCACAAGAGAAGUCGUUUCAU	367
AD-557068.1	gsasgccaAfaAfAfGfugucuagucuL96	196	asGfsacua(Ggn)acacuuUfuUfggcucscsu	282	AGGAGCCAAAAAGUGUCUAGUCA	368
AD-556701.1	csusacuaCfaAfUfGfugagugauguL96	197	asCfsauca(Cgn)ucacauUfgUfaguagsgsg	283	CCCUACUACAAUGUGAGUGAUGA	369
AD-558076.1	gsasagucGfuUfUfCfauucaaguuuL96	198	asAfsacuu(Ggn)aaugaaAfcGfacuucsusc	284	GAGAAGUCGUUUCAUUCAAGUUG	370
AD-558065.1	asgsuucaCfaAfGfAfgaagucguuuL96	199	asAfsacga(Cgn)uucucuUfgUfgaacusasu	285	AUAGUUCACAAGAGAAGUCGUUU	371

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-557859.1	csasacucGfaGfCfUfuugaggcuuuL96	200	asAfsagcc(Tgn)caaagcUfcGfaguugsusu	286	AACAACUCGAGCUUUGAGGCUUC	372
AD-558096.1	gsusagugGfaUfGfUfcugcaaaaauL96	201	asUfsuuuu(Ggn)cagacaUfcCfacuacsusc	287	GAGUAGUGGAUGUCUGCAAAAAC	373
AD-557422.1	gsasggauUfaUfCfUfggaugucuauL96	202	asUfsagac(Agn)uccagaUfaAfuccucscsc	288	GGGAGGAUUAUCUGGAUGUCUAU	374
AD-556919.1	asgsacucCfuUfCfAfuguacgacauL96	203	asUfsgucg(Tgn)acaugaAfgGfagucususg	289	CAAGACUCCUUCAUGUACGACAC	375
AD-558069.1	csascaagAfgAfAfGfucguuucauuL96	204	asAfsugaa(Agn)cgacuuCfuCfuugugsasa	290	UUCACAAGAGAAGUCGUUUCAUU	376
AD-558063.1	asusaguuCfaCfAfAfgagaagucguL96	205	asCfsgacu(Tgn)cucuugUfgAfacuauscsa	291	UGAUAGUUCACAAGAGAAGUCGU	377
AD-557069.1	asgsccaaAfaAfGfUfgucuagucauL96	206	asUfsgacu(Agn)gacacuUfuUfuggcuscsc	292	GGAGCCAAAAAGUGUCUAGUCAA	378
AD-558225.1	usgsaauuAfaAfAfCfagcugcgacuL96	207	asGfsucgc(Agn)gcuguuUfuAfauucasasu	293	AUUGAAUUAAAACAGCUGCGACA	379
AD-557853.1	asgsggaaCfaAfCfUfcgagcuuuguL96	208	asCfsaaag(Cgn)ucgaguUfgUfucccuscsg	294	CGAGGGAACAACUCGAGCUUUGA	380
AD-558012.1	gsascaaaGfuCfAfAfggacaucucuL96	209	asGfsagau(Ggn)uccuugAfcUfuugucsasu	295	AUGACAAAGUCAAGGACAUCUCA	381
AD-558061.1	usgsauagUfuCfAfCfaagagaaguuL96	210	asAfscuuc(Tgn)cuugugAfaCfuaucasasg	296	CUUGAUAGUUCACAAGAGAAGUC	382
AD-557079.1	usgsucuaGfuCfAfAfcuuaauugauL96	211	asUfscaau(Tgn)aaguugAfcUfagacascsu	297	AGUGUCUAGUCAACUUAAUUGAG	383
AD-558066.1	gsusucacAfaGfAfGfaagucguuuuL96	212	asAfsaacg(Agn)cuucucUfuGfugaacsusa	298	UAGUUCACAAGAGAAGUCGUUUC	384
AD-557353.1	gsascccaAfuUfAfCfugucauugauL96	213	asUfscaau(Ggn)acaguaAfuUfgggucscsc	299	GGGACCCAAUUACUGUCAUUGAU	385
AD-557782.1	gsasauuuUfaUfGfAfcuaugacguuL96	214	asAfscguc(Agn)uagucaUfaAfaauucsasg	300	CUGAAUUUUAUGACUAUGACGUU	386
AD-556390.1	csusggagUfuUfCfAfgcuuggacauL96	215	asUfsgucc(Agn)agcugaAfaCfuccagsasc	301	GUCUGGAGUUUCAGCUUGGACAC	387
AD-557078.1	gsusgucuAfgUfCfAfacuuaauuguL96	216	asCfsaauu(Agn)aguugaCfuAfgacacsusu	302	AAGUGUCUAGUCAACUUAAUUGA	388
AD-557475.1	ususccaaGfaAfAfGfacaaugagcuL96	217	asGfscuca(Tgn)ugucuuUfcUfuggaasgsc	303	GCUUCCAAGAAAGACAAUGAGCA	389
AD-556734.1	csusgcuaUfgAfCfGfguuacacucuL96	218	asGfsagug(Tgn)aaccguCfaUfagcagsusg	304	CACUGCUAUGACGGUUACACUCU	390
AD-557084.1	asgsucaaCfuUfAfAfuugagaagguL96	219	asCfscuuc(Tgn)caauuaAfgUfugacusasg	305	CUAGUCAACUUAAUUGAGAAGGU	391
AD-557498.1	asusguguUfcAfAfAfgucaaggauuL96	220	asAfsuccu(Tgn)gacuuuGfaAfcacausgsu	306	ACAUGUGUUCAAAGUCAAGGAUA	392
AD-556788.1	gsascagcGfaUfCfUfgugacaacguL96	221	asCfsguug(Tgn)cacagaUfcGfcugucsusg	307	CAGACAGCGAUCUGUGACAACGG	393
AD-557067.1	gsgsagccAfaAfAfAfgugucuaguuL96	222	asAfscuag(Agn)cacuuuUfuGfgcuccsusg	308	CAGGAGCCAAAAAGUGUCUAGUC	394
AD-557852.1	gsasgggaAfcAfAfCfucgagcuuuuL96	223	asAfsaagc(Tgn)cgaguuGfuUfcccucsgsg	309	CCGAGGGAACAACUCGAGCUUUG	395
AD-556733.1	ascsugcuAfuGfAfCfgguuacacuuL96	224	asAfsgugu(Agn)accgucAfuAfgcagusgsg	310	CCACUGCUAUGACGGUUACACUC	396
AD-556725.1	csuscuuuCfcAfCfUfgcuaugacguL96	225	asCfsguca(Tgn)agcaguGfgAfaagagsasu	311	AUCUCUUUCCACUGCUAUGACGG	397
AD-557860.1	asascucgAfgCfUfUfugaggcuucuL96	226	asGfsaagc(Cgn)ucaaagCfuCfgaguusgsu	312	ACAACUCGAGCUUUGAGGCUUCC	398
AD-556786.1	csasgacaGfcGfAfUfcugugacaauL96	227	asUfsuguc(Agn)cagaucGfcUfgucugscsc	313	GGCAGACAGCGAUCUGUGACAAC	399
AD-556581.1	cscsuucuGfgCfUfUfcuacccguauL96	228	asUfsacgg(Ggn)uagaagCfcAfgaaggsasc	314	GUCCUUCUGGCUUCUACCCGUAC	400
AD-556963.1	ascscauaGfaAfGfGfagucgaugcuL96	229	asGfscauc(Ggn)acuccuUfcUfaugguscsu	315	AGACCAUAGAAGGAGUCGAUGCU	401
AD-557450.1	ascscaagUfgAfAfCfaucaaugcuuL96	230	asAfsgcau(Tgn)gauguuCfaCfuuggususc	316	GAACCAAGUGAACAUCAAUGCUU	402
AD-557204.1	usgsaaauCfaAfUfUfaugaagaccuL96	231	asGfsgucu(Tgn)cauaauUfgAfuuucasusu	317	AAUGAAAUCAAUUAUGAAGACCA	403
AD-558062.1	gsasuaguUfcAfCfAfagagaagucuL96	232	asGfsacuu(Cgn)ucuuguGfaAfcuaucsasa	318	UUGAUAGUUCACAAGAGAAGUCG	404
AD-557602.1	asasggguAfcCfGfAfuuaccacaauL96	233	asUfsugug(Ggn)uaaucgGfuAfcccuuscsc	319	GGAAGGGUACCGAUUACCACAAG	405

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-556917.1	csasagacUfcCfUfUfcauguacgauL96	234	asUfscgua(Cgn)augaagGfaGfucuugsgsc	320	GCCAAGACUCCUUCAUGUACGAC	406
AD-557969.1	csusgacuCfgGfAfAfggaggucuauL96	235	asUfsagac(Cgn)uccuucCfgAfgucagscsu	321	AGCUGACUCGGAAGGAGGUCUAC	407
AD-558064.1	usasguucAfcAfAfGfagaagucguuL96	236	asAfscgac(Tgn)ucucuuGfuGfaacuasusc	322	GAUAGUUCACAAGAGAAGUCGUU	408
AD-558105.1	gsuscugcAfaAfAfAfccagaagcguL96	237	asCfsgcuu(Cgn)ugguuuUfuGfcagacsasu	323	AUGUCUGCAAAAACCAGAAGCGG	409
AD-556791.1	asgscgauCfuGfUfGfacaacggaguL96	238	asCfsuccg(Tgn)ugucacAfgAfucgcusgsu	324	ACAGCGAUCUGUGACAACGGAGC	410
AD-557972.1	ascsucggAfaGfGfAfggucuacauuL96	239	asAfsugua(Ggn)accuccUfuCfcgaguscsa	325	UGACUCGGAAGGAGGUCUACAUC	411
AD-556920.1	gsascuccUfuCfAfUfguacgacacuL96	240	asGfsuguc(Ggn)uacaugAfaGfgagucsusu	326	AAGACUCCUUCAUGUACGACACC	412
AD-558078.1	asgsucguUfuCfAfUfucaaguugguL96	241	asCfscaac(Tgn)ugaaugAfaAfcgacususc	327	GAAGUCGUUUCAUUCAAGUUGGU	413
AD-557861.1	ascsucgaGfcUfUfUfgaggcuuccuL96	242	asGfsgaag(Cgn)cucaaaGfcUfcgagususg	328	CAACUCGAGCUUUGAGGCUUCCU	414
AD-557856.1	gsasacaaCfuCfGfAfgcuuugagguL96	243	asCfscuca(Agn)agcucgAfgUfuguucscsc	329	GGGAACAACUCGAGCUUUGAGGC	415
AD-557041.1	usgsgugcUfaGfAfUfggaucagacuL96	244	asGfsucug(Agn)uccaucUfaGfcaccasgsg	330	CCUGGUGCUAGAUGGAUCAGACA	416
AD-556874.1	gsusgucaGfgAfAfGfguggcucuuuL96	245	asAfsagag(Cgn)caccuuCfcUfgacacsgsu	331	ACGUGUCAGGAAGGUGGCUCUUG	417
AD-557345.1	csusgaugGfaUfUfGfcacaacauguL96	246	asCfsaugu(Tgn)gugcaaUfcCfaucagsusc	332	GACUGAUGGAUUGCACAACAUGG	418
AD-557839.1	csasgacuAfuCfAfGfgcccauuuguL96	247	asCfsaaau(Ggn)ggccugAfuAfgucugsgsc	333	GCCAGACUAUCAGGCCCAUUUGU	419
AD-556962.1	gsasccauAfgAfAfGfgagucgauguL96	248	asCfsaucg(Agn)cuccuuCfuAfuggucsusc	334	GAGACCAUAGAAGGAGUCGAUGC	420
AD-557066.1	asgsgagcCfaAfAfAfagugucuaguL96	249	asCfsuaga(Cgn)acuuuuUfgGfcuccusgsu	335	ACAGGAGCCAAAAAGUGUCUAGU	421
AD-556961.1	asgsaccaUfaGfAfAfggagucgauuL96	250	asAfsucga(Cgn)uccuucUfaUfggucuscsu	336	AGAGACCAUAGAAGGAGUCGAUG	422
AD-557226.1	asasguugAfaGfUfCfagggacuaauL96	251	asUfsuagu(Cgn)ccugacUfuCfaacuusgsu	337	ACAAGUUGAAGUCAGGGACUAAC	423
AD-557865.1	gsasgcuuUfgAfGfGfcuuccuccauL96	252	asUfsggag(Ggn)aagccuCfaAfagcucsgsa	338	UCGAGCUUUGAGGCUUCCUCCAA	424
AD-557209.1	uscsaauuAfuGfAfAfgaccacaaguL96	253	asCfsuugu(Ggn)gucuucAfuAfauugasusu	339	AAUCAAUUAUGAAGACCACAAGU	425
AD-556918.1	asasgacuCfcUfUfCfauguacgacuL96	254	asGfsucgu(Agn)caugaaGfgAfgucuusgsg	340	CCAAGACUCCUUCAUGUACGACA	426
AD-557868.1	csusuugaGfgCfUfUfccuccaacuuL96	255	asAfsguug(Ggn)aggaagCfcUfcaaagscsu	341	AGCUUUGAGGCUUCCUCCAACUA	427
AD-557873.1	asgsgcuuCfcUfCfCfaacuaccacuL96	256	asGfsuggu(Agn)guuggaGfgAfagccuscsa	342	UGAGGCUUCCUCCAACUACCACU	428
AD-556787.1	asgsacagCfgAfUfCfugugacaacuL96	257	asGfsuugu(Cgn)acagauCfgCfugucusgsc	343	GCAGACAGCGAUCUGUGACAACG	429
AD-558004.1	csasggcuAfuGfAfCfaaagucaaguL96	258	asCfsuuga(Cgn)uuugucAfuAfgccugsgsg	344	CCCAGGCUAUGACAAAGUCAAGG	430
AD-557867.1	gscsuuugAfgGfCfUfuccuccaacuL96	259	asGfsuugg(Agn)ggaagcCfuCfaaagcsusc	345	GAGCUUUGAGGCUUCCUCCAACU	431
AD-557788.1	usasugacUfaUfGfAfcguugcccuuL96	260	asAfsgggc(Agn)acgucaUfaGfucauasasa	346	UUUAUGACUAUGACGUUGCCCUG	432
AD-558106.1	uscsugcaAfaAfAfCfcagaagcgguL96	261	asCfscgcu(Tgn)cugguuUfuUfgcagascsa	347	UGUCUGCAAAAACCAGAAGCGGC	433
AD-556724.1	uscsucuuUfcCfAfCfugcuaugacuL96	262	asGfsucau(Agn)gcagugGfaAfagagasusc	348	GAUCUCUUUCCACUGCUAUGACG	434
AD-556739.1	asusgacgGfuUfAfCfacucuccgguL96	263	asCfscgga(Ggn)aguguaAfcCfgucausasg	349	CUAUGACGGUUACACUCUCCGGG	435
AD-557417.1	csasagggAfgGfAfUfuaucuggauuL96	264	asAfsucca(Ggn)auaaucCfuCfccuugsgsg	350	CCCAAGGGAGGAUUAUCUGGAUG	436
AD-556790.1	csasgcgaUfcUfGfUfgacaacggauL96	265	asUfsccgu(Tgn)gucacaGfaUfcgcugsusc	351	GACAGCGAUCUGUGACAACGGAG	437
AD-557872.1	gsasggcuUfcCfUfCfcaacuaccauL96	266	asUfsggua(Ggn)uuggagGfaAfgccucsasa	352	UUGAGGCUUCCUCCAACUACCAC	438
AD-556738.1	usasugacGfgUfUfAfcacucuccguL96	267	asCfsggag(Agn)guguaaCfcGfucauasgsc	353	GCUAUGACGGUUACACUCUCCGG	439

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-557857.1	asascaacUfcGfAfGfcuuugaggcuL96	268	asGfsccuc(Agn)aagcucGfaGfuuguuscsc	354	GGAACAACUCGAGCUUUGAGGCU	440
AD-556726.1	uscsuuucCfaCfUfGfcuaugacgguL96	269	asCfscguc(Agn)uagcagUfgGfaaagasgsa	355	UCUCUUUCCACUGCUAUGACGGU	441
AD-557495.1	asascaugUfgUfUfCfaaagucaaguL96	270	asCfsuuga(Cgn)uuugaaCfaCfauguusgsc	356	GCAACAUGUGUUCAAAGUCAAGG	442
AD-557016.1	cscsuucaGfgCfUfCfcaugaacauuL96	271	asAfsuguu(Cgn)auggagCfcUfgaaggsgsu	357	ACCCUUCAGGCUCCAUGAACAUC	443
AD-558074.1	gsasgaagUfcGfUfUfucauucaaguL96	272	asCfsuuga(Agn)ugaaacGfaCfuucucsusu	358	AAGAGAAGUCGUUUCAUUCAAGU	444
AD-557604.1	gsgsguacCfgAfUfUfaccacaagcuL96	273	asGfscuug(Tgn)gguaauCfgGfuacccsusu	359	AAGGGUACCGAUUACCACAAGCA	445
AD-557346.1	usgsauggAfuUfGfCfacaacaugguL96	274	asCfscaug(Tgn)ugugcaAfuCfcaucasgsu	360	ACUGAUGGAUUGCACAACAUGGG	446
AD-557851.1	csgsagggAfaCfAfAfcucgagcuuuL96	275	asAfsagcu(Cgn)gaguugUfuCfccucgsgsu	361	ACCGAGGGAACAACUCGAGCUUU	447
AD-557786.1	ususuaugAfcUfAfUfgacguugccuL96	276	asGfsgcaa(Cgn)gucauaGfuCfauaaasasu	362	AUUUUAUGACUAUGACGUUGCCC	448

Table 4. Unmodified Sense and Antisense Strand Sequences of Complement Factor B dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range (NM_001710.5)	Antiense Sequence 5' to 3'	SEQ ID NO:	Range (NM_001710.5)
AD-558860.1	UGCCAAGACUCCUUCAUGUAU	449	930-950	AUACAUGAAGGAGUCUUGGCAGG	520	928-950
AD-560018.1	AAGAGAAGUCGUUUCAUUCAU	450	2397-2417	AUGAAUGAAACGACUUCUCUUGU	521	2395-2417
AD-560019.1	AGAGAAGUCGUUUCAUUCAAU	451	2398-2418	AUUGAAUGAAACGACUUCUCUUG	522	2396-2418
AD-559160.1	UAUGAAGACCACAAGUUGAAU	452	1308-1328	AUUCAACUUGUGGUCUUCAUAAU	523	1306-1328
AD-559921.1	CGGAAGGAGGUCUACAUCAAU	453	2202-2222	AUUGAUGUAGACCUCCUUCCGAG	524	2200-2222
AD-559755.1	AUCAAGCUCAAGAAUAAGCUU	454	2016-2036	AAGCUUAUUCUUGAGCUUGAUCA	525	2014-2036
AD-560017.1	CAAGAGAAGUCGUUUCAUUCU	455	2396-2416	AGAAUGAAACGACUUCUCUUGUG	526	2394-2416
AD-559614.1	CUGUGGUGUCUGAGUACUUUU	456	1819-1839	AAAAGUACUCAGACACCACAGCC	527	1817-1839
AD-559435.1	AUGAGCAACAUGUGUUCAAAU	457	1621-1641	AUUUGAACACAUGUUGCUCAUUG	528	1619-1641
AD-560016.1	ACAAGAGAAGUCGUUUCAUUU	458	2395-2415	AAAUGAAACGACUUCUCUUGUGA	529	2393-2415
AD-559451.1	CAAAGUCAAGGAUAUGGAAAU	459	1637-1657	AUUUCCAUAUCCUUGACUUUGAA	530	1635-1657
AD-559617.1	UGGUGUCUGAGUACUUUGUGU	460	1822-1842	ACACAAAGUACUCAGACACCACA	531	1820-1842
AD-560021.1	AGAAGUCGUUUCAUUCAAGUU	461	2400-2420	AACUUGAAUGAAACGACUUCUCU	532	2398-2420
AD-559449.1	UUCAAAGUCAAGGAUAUGGAU	462	1635-1655	AUCCAUAUCCUUGACUUUGAACA	533	1633-1655
AD-559450.1	UCAAAGUCAAGGAUAUGGAAU	463	1636-1656	AUUCCAUAUCCUUGACUUUGAAC	534	1634-1656
AD-559925.1	AGGAGGUCUACAUCAAGAAUU	464	2206-2226	AAUUCUUGAUGUAGACCUCCUUC	535	2204-2226
AD-559440.1	CAACAUGUGUUCAAAGUCAAU	465	1626-1646	AUUGACUUUGAACACAUGUUGCU	536	1624-1646
AD-559788.1	ACUAUCAGGCCCAUUUGUCUU	466	2049-2069	AAGACAAAUGGGCCUGAUAGUCU	537	2047-2069
AD-559437.1	GAGCAACAUGUGUUCAAAGUU	467	1623-1643	AACUUUGAACACAUGUUGCUCAU	538	1621-1643

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range (NM_001710.5)	Antiense Sequence 5' to 3'	SEQ ID NO:	Range (NM_001710.5)
AD-559369.1	AGGAUUAUCUGGAUGUCUAUU	468	1537-1557	AAUAGACAUCCAGAUAAUCCUCC	539	1535-1557
AD-559446.1	GUGUUCAAAGUCAAGGAUAUU	469	1632-1652	AAUAUCCUUGACUUUGAACACAU	540	1630-1652
AD-559924.1	AAGGAGGUCUACAUCAAGAAU	470	2205-2225	AUUCUUGAUGUAGACCUCCUUCC	541	2203-2225
AD-558965.1	UCAGGCUCCAUGAACAUCUAU	471	1074-1094	AUAGAUGUUCAUGGAGCCUGAAG	542	1072-1094
AD-560045.1	GUGGAUGUCUGCAAAAACCAU	472	2442-2462	AUGGUUUUUGCAGACAUCCACUA	543	2440-2462
AD-559946.1	GUGAGAGAGAUGCUCAAUAUU	473	2245-2265	AAUAUUGAGCAUCUCUCUCACAG	544	2243-2265
AD-558697.1	AUCGCACCUGCCAAGUGAAUU	474	703-723	AAUUCACUUGGCAGGUGCGAUUG	545	701-723
AD-559008.1	UCACAGGAGCCAAAAAGUGUU	475	1135-1155	AACACUUUUUGGCUCCUGUGAAG	546	1133-1155
AD-559357.1	AAAACCCAAGGGAGGAUUAUU	476	1525-1545	AAUAAUCCUCCCUUGGGUUUUUG	547	1523-1545
AD-559020.1	AAAAGUGUCUAGUCAACUUAU	477	1147-1167	AUAAGUUGACUAGACACUUUUUG	548	1145-1167
AD-559143.1	CAGCUCAAUGAAAUCAAUUAU	478	1290-1310	AUAAUUGAUUUCAUUGAGCUGCU	549	1288-1310
AD-559374.1	UAUCUGGAUGUCUAUGUGUUU	479	1542-1562	AAACACAUAGACAUCCAGAUAAU	550	1540-1562
AD-560161.1	GGCGUGGGAUUGAAUUAAAAU	480	2594-2614	AUUUUAAUUCAAUCCCACGCCCC	551	2592-2614
AD-559947.1	UGAGAGAGAUGCUCAAUAUGU	481	2246-2266	ACAUAUUGAGCAUCUCUCUCACA	552	2244-2266
AD-559616.1	GUGGUGUCUGAGUACUUUGUU	482	1821-1841	AACAAAGUACUCAGACACCACAG	553	1819-1841
AD-559142.1	GCAGCUCAAUGAAAUCAAUUU	483	1289-1309	AAAUUGAUUUCAUUGAGCUGCUU	554	1287-1309
AD-558639.1	CGGUCUCCCUACUACAAUGUU	484	627-647	AACAUUGUAGUAGGGAGACCGGG	555	625-647
AD-560166.1	GGGAUUGAAUUAAAACAGCUU	485	2599-2619	AAGCUGUUUUAAUUCAAUCCCAC	556	2597-2619
AD-559359.1	AACCCAAGGGAGGAUUAUCUU	486	1527-1547	AAGAUAAUCCUCCCUUGGGUUUU	557	1525-1547
AD-558657.1	GUGAGUGAUGAGAUCUCUUUU	487	645-665	AAAAGAGAUCUCAUCACUCACAU	558	643-665
AD-559442.1	ACAUGUGUUCAAAGUCAAGGU	488	1628-1648	ACCUUGACUUUGAACACAUGUUG	559	1626-1648
AD-559023.1	AGUGUCUAGUCAACUUAAUUU	489	1150-1170	AAAUUAAGUUGACUAGACACUUU	560	1148-1170
AD-560160.1	GGGCGUGGGAUUGAAUUAAAU	490	2593-2613	AUUUAAUUCAAUCCCACGCCCCU	561	2591-2613
AD-559398.1	CAAGUGAACAUCAAUGCUUUU	491	1584-1604	AAAAGCAUUGAUGUUCACUUGGU	562	1582-1604
AD-559722.1	AUUCCUGAAUUUUAUGACUAU	492	1983-2003	AUAGUCAUAAAAAUUCAGGAAUUC	563	1981-2003
AD-559146.1	CUCAAUGAAAUCAAUUAUGAU	493	1293-1313	AUCAUAAUUGAUUUCAUUGAGCU	564	1291-1313
AD-558267.1	GGAUGUUCCGGGAAAGUGAUU	494	55-75	AAUCACUUUCCCGGAACAUCCAA	565	53-75
AD-559074.1	GAUAUGGUCUAGUGACAUAUU	495	1201-1221	AAUAUGUCACUAGACCAUAUCUU	566	1199-1221
AD-560162.1	GCGUGGGAUUGAAUUAAAACU	496	2595-2615	AGUUUUAAUUCAAUCCCACGCCC	567	2593-2615
AD-559021.1	AAAGUGUCUAGUCAACUUAAU	497	1148-1168	AUUAAGUUGACUAGACACUUUUU	568	1146-1168
AD-559144.1	AGCUCAAUGAAAUCAAUUAUU	498	1291-1311	AAUAAUUGAUUUCAUUGAGCUGC	569	1289-1311
AD-559147.1	CAAUGAAAUCAAUUAUGAAGU	499	1295-1315	ACUUCAUAAUUGAUUUCAUUGAG	570	1293-1315
AD-560164.1	GUGGGAUUGAAUUAAAACAGU	500	2597-2617	ACUGUUUUAAUUCAAUCCCACGC	571	2595-2617
AD-559714.1	AAGCAGGAAUUCCUGAAUUUU	501	1975-1995	AAAAUUCAGGAAUUCCUGCUUCU	572	1973-1995

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range (NM_001710.5)	Antiense Sequence 5' to 3'	SEQ ID NO:	Range (NM_001710.5)
AD-560165.1	UGGGAUUGAAUUAAAACAGCU	502	2598-2618	AGCUGUUUUAAUUCAAUCCCACG	573	2596-2618
AD-559300.1	ACCCAAUUACUGUCAUUGAUU	503	1468-1488	AAUCAAUGACAGUAAUUGGGUCC	574	1466-1488
AD-559866.1	CCCUGCACAGGAUAUCAAAGU	504	2147-2167	ACUUUGAUAUCCUGUGCAGGGAG	575	2145-2167
AD-559302.1	CCAAUUACUGUCAUUGAUGAU	505	1470-1490	AUCAUCAAUGACAGUAAUUGGGU	576	1468-1490
AD-560163.1	CGUGGGAUUGAAUUAAAACAU	506	2596-2616	AUGUUUUAAUUCAAUCCCACGCC	577	2594-2616
AD-559718.1	AGGAAUUCCUGAAUUUUAUGU	507	1979-1999	ACAUAAAAUUCAGGAAUUCCUGC	578	1977-1999
AD-559721.1	AAUUCCUGAAUUUUAUGACUU	508	1982-2002	AAGUCAUAAAAUUCAGGAAUUCC	579	1980-2002
AD-559026.1	GUCUAGUCAACUUAAUUGAGU	509	1153-1173	ACUCAAUUAAGUUGACUAGACAC	580	1151-1173
AD-559719.1	GGAAUUCCUGAAUUUUAUGAU	510	1980-2000	AUCAUAAAAUUCAGGAAUUCCUG	581	1978-2000
AD-559060.1	UGGUGUGAAGCCAAGAUAUGU	511	1187-1207	ACAUAUCUUGGCUUCACACCAUA	582	1185-1207
AD-559864.1	CUCCCUGCACAGGAUAUCAAU	512	2145-2165	AUUGAUAUCCUGUGCAGGGAGCA	583	2143-2165
AD-559059.1	AUGGUGUGAAGCCAAGAUAUU	513	1186-1206	AAUAUCUUGGCUUCACACCAUAA	584	1184-1206
AD-559865.1	UCCCUGCACAGGAUAUCAAAU	514	2146-2166	AUUUGAUAUCCUGUGCAGGGAGC	585	2144-2166
AD-559148.1	AAUGAAAUCAAUUAUGAAGAU	515	1296-1316	AUCUUCAUAAUUGAUUUCAUUGA	586	1294-1316
AD-559375.1	AUCUGGAUGUCUAUGUGUUUU	516	1543-1563	AAAACACAUAGACAUCCAGAUAA	587	1541-1563
AD-559393.1	UGAACCAAGUGAACAUCAAUU	517	1579-1599	AAUUGAUGUUCACUUGGUUCACC	588	1577-1599
AD-559717.1	CAGGAAUUCCUGAAUUUUAUU	518	1978-1998	AAUAAAAUUCAGGAAUUCCUGCU	589	1976-1998
AD-559392.1	GUGAACCAAGUGAACAUCAAU	519	1578-1598	AUUGAUGUUCACUUGGUUCACCA	590	1576-1598

Table 5. Modified Sense and Antisense Strand Sequences of Complement Factor B dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-558860.1	usgsccaaGfaCfUfCfcuucauguauL96	591	asUfsacaUfgAfAfggagUfcUfuggcasgsg	662	CCUGCCAAGACUCCUUCAUGUAC	733
AD-560018.1	asasgagaAfgUfCfGfuuucauucauL96	592	asUfsgaaUfgAfAfacgaCfuUfcucuusgsu	663	ACAAGAGAAGUCGUUUCAUUCAA	734
AD-560019.1	asgsagaaGfuCfGfUfuucauucaauL96	593	asUfsugaAfuGfAfaacgAfcUfucucususg	664	CAAGAGAAGUCGUUUCAUUCAAG	735
AD-559160.1	usasugaaGfaCfCfAfcaaguugaauL96	594	asUfsucaAfcUfUfguggUfcUfucauasasu	665	AUUAUGAAGACCACAAGUUGAAG	736
AD-559921.1	csgsgaagGfaGfGfUfcuacaucaauL96	595	asUfsugaUfgUfAfgaccUfcCfuuccgsasg	666	CUCGGAAGGAGGUCUACAUCAAG	737
AD-559755.1	asuscaagCfuCfAfAfgaauaagcuuL96	596	asAfsgcuUfaUfUfcuugAfgCfuugauscsa	667	UGAUCAAGCUCAAGAAUAAGCUG	738
AD-560017.1	csasagagAfaGfUfCfguuucauucuL96	597	asGfsaauGfaAfAfcgacUfuCfucuugsusg	668	CACAAGAGAAGUCGUUUCAUUCA	739
AD-559614.1	csusguggUfgUfCfUfgaguacuuuuL96	598	asAfsaagUfaCfUfcagaCfaCfcacagscsc	669	GGCUGUGGUGUCUGAGUACUUUG	740

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-559435.1	asusgagcAfaCfAfUfguguucaaauL96	599	asUfsuugAfaCfAfcaugUfuGfcucaususg	670	CAAUGAGCAACAUGUGUUCAAAG	741
AD-560016.1	ascsaagaGfaAfGfUfcguuucauuuL96	600	asAfsaugAfaAfCfgacuUfcUfcuugusgsa	671	UCACAAGAGAAGUCGUUUCAUUC	742
AD-559451.1	csasaaguCfaAfGfGfauauggaaauL96	601	asUfsuucCfaUfAfuccuUfgAfcuuugsasa	672	UUCAAAGUCAAGGAUAUGGAAAA	743
AD-559617.1	usgsguguCfuGfAfGfuacuuuguguL96	602	asCfsacaAfaGfUfacucAfgAfcaccascsa	673	UGUGGUGUCUGAGUACUUUGUGC	744
AD-560021.1	asgsaaguCfgUfUfUfcauucaaguuL96	603	asAfscuuGfaAfUfgaaaCfgAfcuucuscsu	674	AGAGAAGUCGUUUCAUUCAAGUU	745
AD-559449.1	ususcaaaGfuCfAfAfggauauggauL96	604	asUfsccaUfaUfCfcuugAfcUfuugaascsa	675	UGUUCAAAGUCAAGGAUAUGGAA	746
AD-559450.1	uscsaaagUfcAfAfGfgauauggaauL96	605	asUfsuccAfuAfUfccuuGfaCfuuugasasc	676	GUUCAAAGUCAAGGAUAUGGAAA	747
AD-559925.1	asgsgaggUfcUfAfCfaucaagaauuL96	606	asAfsuucUfuGfAfuguaGfaCfcuccususc	677	GAAGGAGGUCUACAUCAAGAAUG	748
AD-559440.1	csasacauGfuGfUfUfcaaagucaauL96	607	asUfsugaCfuUfUfgaacAfcAfuguugscsu	678	AGCAACAUGUGUUCAAAGUCAAG	749
AD-559788.1	ascsuaucAfgGfCfCfcauuugucuuL96	608	asAfsgacAfaAfUfgggcCfuGfauaguscsu	679	AGACUAUCAGGCCCAUUUGUCUC	750
AD-559437.1	gsasgcaaCfaUfGfUfguucaaaguuL96	609	asAfscuuUfgAfAfcacaUfgUfugcucsasu	680	AUGAGCAACAUGUGUUCAAAGUC	751
AD-559369.1	asgsgauuAfuCfUfGfgaugucuauuL96	610	asAfsuagAfcAfUfccagAfuAfauccuscsc	681	GGAGGAUUAUCUGGAUGUCUAUG	752
AD-559446.1	gsusguucAfaAfGfUfcaaggauauuL96	611	asAfsuauCfcUfUfgacuUfuGfaacacsasu	682	AUGUGUUCAAAGUCAAGGAUAUG	753
AD-559924.1	asasggagGfuCfUfAfcaucaagaauL96	612	asUfsucuUfgAfUfguagAfcCfuccuuscsc	683	GGAAGGAGGUCUACAUCAAGAAU	754
AD-558965.1	uscsaggcUfcCfAfUfgaacaucuauL96	613	asUfsagaUfgUfUfcaugGfaGfccugasasg	684	CUUCAGGCUCCAUGAACAUCUAC	755
AD-560045.1	gsusggauGfuCfUfGfcaaaaaccauL96	614	asUfsgguUfuUfUfgcagAfcAfuccacsusa	685	UAGUGGAUGUCUGCAAAAACCAG	756
AD-559946.1	gsusgagaGfaGfAfUfgcucaauauuL96	615	asAfsuauUfgAfGfcaucUfcUfcucacsasg	686	CUGUGAGAGAGAUGCUCAAUAUG	757
AD-558697.1	asuscgcaCfcUfGfCfcaagugaauuL96	616	asAfsuucAfcUfUfggcaGfgUfgcgaususg	687	CAAUCGCACCUGCCAAGUGAAUG	758
AD-559008.1	uscsacagGfaGfCfCfcaaaaaguguuL96	617	asAfscacUfuUfUfuggcUfcCfugugasasg	688	CUUCACAGGAGCCAAAAAGUGUC	759
AD-559357.1	asasaaccCfaAfGfGfgaggauuauuL96	618	asAfsuaaUfcCfUfcccuUfgGfguuuususg	689	CAAAAACCCAAGGGAGGAUUAUC	760
AD-559020.1	asasaaguGfuCfUfAfgucaacuuauL96	619	asUfsaagUfuGfAfcuagAfcAfcuuuususg	690	CAAAAAGUGUCUAGUCAACUUAA	761
AD-559143.1	csasgcucAfaUfGfAfaaucaauuauL96	620	asUfsaauUfgAfUfuucaUfuGfagcugscsu	691	AGCAGCUCAAUGAAAUCAAUUAU	762
AD-559374.1	usasucugGfaUfGfUfcuauguguuuL96	621	asAfsacaCfaUfAfgacaUfcCfagauasasu	692	AUUAUCUGGAUGUCUAUGUGUUU	763
AD-560161.1	gsgscgugGfgAfUfUfgaauuaaaauL96	622	asUfsuuuAfaUfUfcaauCfcCfacgccscsc	693	GGGGCGUGGGAUUGAAUUAAAAC	764
AD-559947.1	usgsagagAfgAfUfGfcucaauauguL96	623	asCfsauaUfuGfAfgcauCfuCfucucascsa	694	UGUGAGAGAGAUGCUCAAUAUGC	765
AD-559616.1	gsusggugUfcUfGfAfguacuuuguuL96	624	asAfscaaAfgUfAfcucaGfaCfaccacsasg	695	CUGUGGUGUCUGAGUACUUUGUG	766
AD-559142.1	gscsagcuCfaAfUfGfaaaucaauuuL96	625	asAfsauuGfaUfUfucauUfgAfgcugcsusu	696	AAGCAGCUCAAUGAAAUCAAUUA	767
AD-558639.1	csgsgucuCfcCfUfAfcuacaauguuL96	626	asAfscauUfgUfAfguagGfgAfgaccgsgsg	697	CCCGGUCUCCCUACUACAAUGUG	768
AD-560166.1	gsgsgauuGfaAfUfUfaaaacagcuuL96	627	asAfsgcuGfuUfUfuaauUfcAfaucccsasc	698	GUGGGAUUGAAUUAAAACAGCUG	769
AD-559359.1	asascccaAfgGfGfAfggauuaucuuL96	628	asAfsgauAfaUfCfcuccCfuUfggguususu	699	AAAACCCAAGGGAGGAUUAUCUG	770
AD-558657.1	gsusgaguGfaUfGfAfgaucucuuuuL96	629	asAfsaagAfgAfUfcucaUfcAfcucacsasu	700	AUGUGAGUGAUGAGAUCUCUUUC	771
AD-559442.1	ascsauguGfuUfCfAfaagucaagguL96	630	asCfscuuGfaCfUfuugaAfcAfcaugususg	701	CAACAUGUGUUCAAAGUCAAGGA	772
AD-559023.1	asgsugucUfaGfUfCfaacuuaauuuL96	631	asAfsauuAfaGfUfugacUfaGfacacususu	702	AAAGUGUCUAGUCAACUUAAUUG	773
AD-560160.1	gsgsgcguGfgGfAfUfugaauuaaauL96	632	asUfsuuaAfuUfCfaaucCfcAfcgcccscsu	703	AGGGGCGUGGGAUUGAAUUAAAA	774

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-559398.1	csasagugAfaCfAfUfcaaugcuuuuL96	633	asAfsaagCfaUfUfgaugUfuCfacuugsgsu	704	ACCAAGUGAACAUCAAUGCUUUG	775
AD-559722.1	asusuccuGfaAfUfUfuuaugacuauL96	634	asUfsaguCfaUfAfaaauUfcAfggaaususc	705	GAAUUCCUGAAUUUUAUGACUAU	776
AD-559146.1	csuscaauGfaAfaAfUfcaauuaugauL96	635	asUfscauAfaUfUfgauuUfcAfuugagscsu	706	AGCUCAAUGAAAUCAAUUAUGAA	777
AD-558267.1	gsgsauguUfcCfGfUfgaaagugauuL96	636	asAfsucaCfuUfUfcccgGfaAfcauccsasa	707	UUGGAUGUUCCGGGAAAGUGAUG	778
AD-559074.1	gsasuaugGfuCfUfAfgugacauauuL96	637	asAfsuauGfuCfAfcuagAfcCfauaucsusu	708	AAGAUAUGGUCUAGUGACAUAUG	779
AD-560162.1	gscsguggGfaUfUfGfaauuaaaacuL96	638	asGfsuuuUfaAfUfucaaUfcCfcacgcscsc	709	GGGCGUGGGAUUGAAUUAAAACA	780
AD-559021.1	asasagugUfcUfAfGfucaacuuaauL96	639	asUfsuaaGfuUfGfacuaGfaCfacuuususu	710	AAAAAGUGUCUAGUCAACUUAAU	781
AD-559144.1	asgscucaAfuGfAfAfaucaauuauuL96	640	asAfsuaaUfuGfUfAfuuucAfuUfgagcusgsc	711	GCAGCUCAAUGAAAUCAAUUAUG	782
AD-559147.1	csasaugaAfaUfCfAfauuaugaaguL96	641	asCfsuucAfuAfAfuugaUfuUfcauugsasg	712	CUCAAUGAAAUCAAUUAUGAAGA	783
AD-560164.1	gsusgggaUfuGfAfAfuuaaaacaguL96	642	asCfsuguUfuUfAfauucAfaUfcccacsgsc	713	GCGUGGGAUUGAAUUAAAACAGC	784
AD-559714.1	asasgcagGfaAfUfUfccugaauuuuL96	643	asAfsaauUfcAfGfgaauUfcCfugcuuscsu	714	AGAAGCAGGAAUUCCUGAAUUUU	785
AD-560165.1	usgsggauUfgAfAfUfuaaaacagcuL96	644	asGfscugUfuUfUfaauuCfaAfucccascsg	715	CGUGGGAUUGAAUUAAAACAGCU	786
AD-559300.1	ascsccaaUfuAfCfUfgucauugauuL96	645	asAfsucaAfuGfAfcaguAfaUfuggguscsc	716	GGACCCAAUUACUGUCAUUGAUG	787
AD-559866.1	cscscugcAfcAfGfGfauaucaaaguL96	646	asCfsuuuGfaUfAfuccuGfuGfcagggsasg	717	CUCCCUGCACAGGAUAUCAAAGC	788
AD-559302.1	cscsaauuAfcUfGfUfcauugaugauL96	647	asUfscauCfaAfUfgacaGfuAfauugggsgsu	718	ACCCAAUUACUGUCAUUGAUGAG	789
AD-560163.1	csgsugggAfuUfGfAfauuaaaacauL96	648	asUfsguuUfuAfAfuucaAfuCfccacgscsc	719	GGCGUGGGAUUGAAUUAAAACAG	790
AD-559718.1	asgsgaauUfcCfUfGfaauuuuauguL96	649	asCfsauaAfaAfUfucagGfaAfuuccusgsc	720	GCAGGAAUUCCUGAAUUUUAUGA	791
AD-559721.1	asasuuccUfgAfAfUfuuaugacuuL96	650	asAfsgucAfuAfAfaauuCfaGfgaauuscsc	721	GGAAUUCCUGAAUUUUAUGACUA	792
AD-559026.1	gsuscuagUfcAfAfCfuuaauugaguL96	651	asCfsucaAfuUfAfaguuGfaCfuagacsasc	722	GUGUCUAGUCAACUUAAUUGAGA	793
AD-559719.1	gsgsaauuCfcUfGfAfauuuuauguL96	652	asUfscauAfaAfAfuucaGfgAfauuccsusg	723	CAGGAAUUCCUGAAUUUUAUGAC	794
AD-559060.1	usgsguguGfaAfGfCfcaagauaugL96	653	asCfsauaUfcUfUfggcuUfcAfcaccasusa	724	UAUGGUGUGAAGCCAAGAUAUGG	795
AD-559864.1	csuscccuGfcAfCfAfggauaucaauL96	654	asUfsugaUfaUfCfcuguGfcAfgggagscsa	725	UGCUCCCUGCACAGGAUAUCAAA	796
AD-559059.1	asusggguUfgAfAfGfccaagauauuL96	655	asAfsuauCfuUfGfgcuuCfaCfaccausasa	726	UUAUGGUGUGAAGCCAAGAUAUG	797
AD-559865.1	uscscccuGfaCfAfGfgauaucaaauL96	656	asUfsuugAfuAfUfccugUfgCfagggasgsc	727	GCUCCCUGCACAGGAUAUCAAAG	798
AD-559148.1	asasugaaAfuCfAfAfuuaugaagauL96	657	asUfscuuCfaUfAfauugAfuUfucauusgsa	728	UCAAUGAAAUCAAUUAUGAAGAC	799
AD-559375.1	asuscuggAfuGfUfCfuauguguuuuL96	658	asAfsaacAfcAfUfagacAfuCfcagausasa	729	UUAUCUGGAUGUCUAUGUGUUUG	800
AD-559393.1	usgsaaccAfaGfUfGfaacaucaauuL96	659	asAfsuugAfuGfUfucacUfuGfguucascsc	730	GGUGAACCAAGUGAACAUCAAUG	801
AD-559717.1	csasggaaUfuCfCfUfgaauuuuauuL96	660	asAfsuaaAfaUfUfcaggAfaUfuccugscsu	731	AGCAGGAAUUCCUGAAUUUUAUG	802
AD-559392.1	gsusgaacCfaAfGfUfgaacaucaauL96	661	asUfsugaUfgUfUfcacuUfgGfuucacscsa	732	UGGUGAACCAAGUGAACAUCAAU	803

Table 6. Unmodified Sense and Antisense Strand Sequences of Complement Factor B dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Source Name	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Source Name
AD-560969.1	UGCCAAGAUUCCUUCAUGUAU	804	NM_008198.2_1051-1071_s	AUACAUGAAGGAAUCUUGGCAGG	849	NM_008198.2_1049-1071_as
AD-561537.1	AUGUGUUUAAAGUCAAGGAUU	805	NM_008198.2_1751-1771_A21U_s	AAUCCUTGACUUUAAACACAUGA	850	NM_008198.2_1749-1771_U1A_as
AD-562262.1	AAAGAUGAGGAUUUGGGUUUU	806	NM_008198.2_2668-2688_s	AAAACCCAAAUCCUCAUCUUUGA	851	NM_008198.2_2666-2688_as
AD-561960.1	AAGGAUGUCAAAGCUCUGUUU	807	NM_008198.2_2275-2295_s	AAACAGAGCUUUGACAUCCUUCA	852	NM_008198.2_2273-2295_as
AD-561580.1	CUACCAAAUGAUUGAUGAAAU	808	NM_008198.2_1794-1814_C21U_s	AUUUCATCAAUCAUUUGGUAGAA	853	NM_008198.2_1792-1814_G1A_as
AD-561254.1	AUCAGUUAUGAAGACCACAAU	809	NM_008198.2_1423-1443_G21U_s	AUUGUGGUCUUCAUAACUGAUUU	854	NM_008198.2_1421-1443_C1A_as
AD-561578.1	UUCUACCAAAUGAUUGAUGAU	810	NM_008198.2_1792-1812_A21U_s	AUCAUCAAUCAUUUGGUAGAAAA	855	NM_008198.2_1790-1812_U1A_as
AD-561538.1	UGUGUUUAAAGUCAAGGAUAU	811	NM_008198.2_1752-1772_s	AUAUCCTUGACUUUAAACACAUG	856	NM_008198.2_1750-1772_as
AD-561252.1	AAAUCAGUUAUGAAGACCACU	812	NM_008198.2_1421-1441_A21U_s	AGUGGUCUUCAUAACUGAUUUGG	857	NM_008198.2_1419-1441_U1A_as
AD-561963.1	GAUGUCAAAGCUCUGUUUGUU	813	NM_008198.2_2278-2298_A21U_s	AACAAACAGAGCUUUGACAUCCU	858	NM_008198.2_2276-2298_U1A_as
AD-562027.1	CCAGUUGUGAGAGAGAUGCUU	814	NM_008198.2_2360-2380_A21U_s	AAGCAUCUCUCUCACAACUGGCU	859	NM_008198.2_2358-2380_U1A_as
AD-561653.1	AGCCAAGAUCUCAGUCACUCU	815	NM_008198.2_1887-1907_G21U_s	AGAGUGACUGAGAUCUUGGCUUG	860	NM_008198.2_1885-1907_C1A_as
AD-562137.1	CGCUUCAUUCAAGUUGGUGUU	816	NM_008198.2_2527-2547_G21U_s	AACACCAACUUGAAUGAAGCGGC	861	NM_008198.2_2525-2547_C1A_as
AD-561536.1	CAUGUGUUUAAAGUCAAGGAU	817	NM_008198.2_1750-1770_s	AUCCUUGACUUUAAACACAUGAU	862	NM_008198.2_1748-1770_as
AD-561253.1	AAUCAGUUAUGAAGACCACAU	818	NM_008198.2_1422-1442_A21U_s	AUGUGGTCUUCAUAACUGAUUUG	863	NM_008198.2_1420-1442_U1A_as
AD-561959.1	GAAGGAUGUCAAAGCUCUGUU	819	NM_008198.2_2274-2294_s	AACAGAGCUUUGACAUCCUUCAC	864	NM_008198.2_2272-2294_as
AD-	AUGUUUUCUACCAAAUGA	820	NM_008198.2_1787-	AAAUCATUUGGUAGAAAAC	865	NM_008198.2_1785-

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Source Name	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Source Name
561573.1	UUU		1807_G21U_s	AUUC		1807_C1A_as
AD-561651.1	CAAGCCAAGAUCUCAGUCACU	821	NM_008198.2_1885-1905_s	AGUGACTGAGAUCUUGGCUUGCC	866	NM_008198.2_1883-1905_as
AD-561148.1	ACCAACUUGAUUGAGAAGGUU	822	NM_008198.2_1279-1299_G21U_s	AACCUUCUCAAUCAAGUUGGUGA	867	NM_008198.2_1277-1299_C1A_as
AD-561962.1	GGAUGUCAAAGCUCUGUUUGU	823	NM_008198.2_2277-2297_s	ACAAACAGAGCUUUGACAUCCUU	868	NM_008198.2_2275-2297_as
AD-562237.1	AGAUGAGGAUUUGGGUUUUCU	824	NM_001710.5_2549-2569_s	AGAAAACCCAAAUCCUCAUCUUU	869	NM_008198.2_2668-2690_as
AD-561654.1	GCCAAGAUCUCAGUCACUCGU	825	NM_008198.2_1888-1908_C21U_s	ACGAGUGACUGAGAUCUUGGCUU	870	NM_008198.2_1886-1908_G1A_as
AD-562136.1	CCGCUUCAUUCAAGUUGGUGU	826	NM_008198.2_2526-2546_s	ACACCAACUUGAAUGAAGCGGCU	871	NM_008198.2_2524-2546_as
AD-562026.1	GCCAGUUGUGAGAGAGAUGCU	827	NM_008198.2_2359-2379_s	AGCAUCTCUCUCACAACUGGCUU	872	NM_008198.2_2357-2379_as
AD-561101.1	UCCAUGAAUAUCUACCUGGUU	828	NM_008198.2_1201-1221_G21U_s	AACCAGGUAGAUAUUCAUGGAGC	873	NM_008198.2_1199-1221_C1A_as
AD-561539.1	GUGUUUAAAGUCAAGGAUAUU	829	NM_008198.2_1753-1773_G21U_s	AAUAUCCUUGACUUUAAACACAU	874	NM_008198.2_1751-1773_C1A_as
AD-561961.1	AGGAUGUCAAAGCUCUGUUUU	830	NM_008198.2_2276-2296_G21U_s	AAAACAGAGCUUUGACAUCCUUC	875	NM_008198.2_2274-2296_C1A_as
AD-561535.1	UCAUGUGUUUAAAGUCAAGGU	831	NM_008198.2_1749-1769_A21U_s	ACCUUGACUUUAAACACAUGAUG	876	NM_008198.2_1747-1769_U1A_as
AD-561652.1	AAGCCAAGAUCUCAGUCACUU	832	NM_008198.2_1886-1906_C21U_s	AAGUGACUGAGAUCUUGGCUUGC	877	NM_008198.2_1884-1906_G1A_as
AD-562260.1	UCAAAGAUGAGGAUUUUGGGUU	833	NM_008198.2_2666-2686_s	AACCCAAAUCCUCAUCUUUGAGC	878	NM_008198.2_2664-2686_as
AD-557041.2	UGGUGCUAGAUGGAUCAGACU	72	NM_001710.5_1096-1116_A21U_s	AGUCUGAUCCAUCUAGCACCAGG	158	NM_001710.5_1094-1116_U1A_as
AD-561655.1	CCAAGAUCUCAGUCACUCGCU	834	NM_008198.2_1889-1909_C21U_s	AGCGAGTGACUGAGAUCUUGGCU	879	NM_008198.2_1887-1909_G1A_as
AD-557043.1	GUGCUAGAUGGAUCAGACAGU	835	NM_001710.5_1098-1118_C21U_s	ACUGUCTGAUCCAUCUAGCACCA	880	NM_001710.5_1096-1118_G1A_as
AD-561603.1	CAAAUCUCUGAGUCUCUGUGU	836	NM_008198.2_1815-1835_G21U_s	ACACAGAGACUCAGAGAUUUGGU	881	NM_008198.2_1813-1835_C1A_as

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Sense Source Name	Antisense Sequence 5' to 3'	SEQ ID NO:	Antisense Source Name
AD-557044.1	UGCUAGAUGGAUCAGACAGCU	837	NM_001710.5_1099-1119_A21U_s	AGCUGUCUGAUCCAUCUAGCACC	882	NM_001710.5_1097-1119_U1A_as
AD-561266.1	GACCACAAGCUGAAGUCAGGU	838	NM_008198.2_1435-1455_G21U_s	ACCUGACUUCAGCUUGUGGUCUU	883	NM_008198.2_1433-1455_C1A_as
AD-561541.1	GUUUAAAGUCAAGGAUAUGGU	839	NM_008198.2_1755-1775_A21U_s	ACCAUATCCUUGACUUUAAACAC	884	NM_008198.2_1753-1775_U1A_as
AD-562257.1	AGCUCAAAGAUGAGGAUUUGU	840	NM_008198.2_2663-2683_G21U_s	ACAAAUCCUCAUCUUUGAGCUUG	885	NM_008198.2_2661-2683_C1A_as
AD-560538.1	GAGGGAGUAGAGAUCAAAGGU	841	NM_008198.2_517-537_C21U_s	ACCUUUGAUCUCUACUCCCUCCA	886	NM_008198.2_515-537_G1A_as
AD-561579.1	UCUACCAAAUGAUUGAUGAAU	842	NM_008198.2_1793-1813_A21U_s	AUUCAUCAAUCAUUUGGUAGAAA	887	NM_008198.2_1791-1813_U1A_as
AD-562259.1	CUCAAAGAUGAGGAUUUGGGU	843	NM_008198.2_2665-2685_s	ACCCAAAUCCUCAUCUUUGAGCU	888	NM_008198.2_2663-2685_as
AD-560968.1	CUGCCAAGAUUCCUUCAUGUU	844	NM_008198.2_1050-1070_A21U_s	AACAUGAAGGAAUCUUGGCAGGA	889	NM_008198.2_1048-1070_U1A_as
AD-561647.1	AUGGCAAGCCAAGAUCUCAGU	845	NM_008198.2_1881-1901_s	ACUGAGAUCUUGGCUUGCCAUGG	890	NM_008198.2_1879-1901_as
AD-561469.1	CCUGGAUGUGUAUGUGUUUGU	846	NM_008198.2_1665-1685_G21U_s	ACAAACACAUACACAUCCAGGUA	891	NM_008198.2_1663-1685_C1A_as
AD-561540.1	UGUUUAAAGUCAAGGAUAUGU	847	NM_008198.2_1754-1774_G21U_s	ACAUAUCCUUGACUUUAAACACA	892	NM_008198.2_1752-1774_C1A_as
AD-562135.1	GCCGCUUCAUUCAAGUUGGUU	848	NM_008198.2_2525-2545_G21U_s	AACCAACUUGAAUGAAGCGGCUU	893	NM_008198.2_2523-2545_C1A_as

Table 7. Modified Sense and Antisense Strand Sequences of Complement Factor B dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-560969.1	usgsccaaGfaUfUfUfCfcuucauguauL96	894	asUfsacau(Ggn)aaggaaUfcUfuggcasgsg	939	CCUGCCAAGAUUCCUUCAUGUAU	984
AD-561537.1	asusguguUfuAfAfAfgucaaggauuL96	895	asAfsuccu(Tgn)gacuuuAfaAfcacausgsa	940	UCAUGUGUUUAAAGUCAAGGAUA	985
AD-562262.1	asasagauGfaGfGfAfuuuggguuuuL96	896	asAfsaacc(Cgn)aaauccUfcAfucuuusgsa	941	UCAAAGAUGAGGAUUUGGGUUUU	986
AD-561960.1	asasggauGfuCfAfAfagcucuguuuL96	897	asAfsacag(Agn)gcuuugAfcAfuccuuscsa	942	UGAAGGAUGUCAAAGCUCUGUUU	987
AD-561580.1	csusaccaAfaUfGfAfuugaugaaauL96	898	asUfsuuca(Tgn)caaucaUfuUfgguagsasa	943	UUCUACCAAAUGAUUGAUGAAAC	988

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-561254.1	asuscaguUfaUfGfAfagaccacaauL96	899	asUfsugug(Ggn)ucuucaUfaAfcugaususu	944	AAAUCAGUUAUGAAGACCACAAG	989
AD-561578.1	ususcuacCfaAfAfUfgauugaugauL96	900	asUfscauc(Agn)aucauuUfgGfuagaasasa	945	UUUUCUACCAAAUGAUUGAUGAA	990
AD-561538.1	usgsuguuUfaAfAfGfucaaggauauL96	901	asUfsaucc(Tgn)ugacuuUfaAfacacasusg	946	CAUGUGUUUAAAGUCAAGGAUAU	991
AD-561252.1	asasaucaGfuUfAfUfgaagaccacuL96	902	asGfsuggu(Cgn)uucauaAfcUfgauuusgsg	947	CCAAAUCAGUUAUGAAGACCACA	992
AD-561963.1	gsasugucAfaAfGfCfucuguuuguuL96	903	asAfscaaa(Cgn)agagcuUfuGfacaucscsu	948	AGGAUGUCAAAGCUCUGUUUGUA	993
AD-562027.1	cscsaguuGfuGfAfGfagagaugcuuL96	904	asAfsgcau(Cgn)ucucucAfcAfacuggcsu	949	AGCCAGUUGUGAGAGAGAUGCUA	994
AD-561653.1	asgsccaaGfaUfCfUfcagucacucuL96	905	asGfsagug(Agn)cugagaUfcUfuggcususg	950	CAAGCCAAGAUCUCAGUCACUCG	995
AD-562137.1	csgscuucAfuUfCfAfaguugguguuL96	906	asAfscacc(Agn)acuugaAfuGfaagcgsgsc	951	GCCGCUUCAUUCAAGUUGGUGUG	996
AD-561536.1	csasugugUfuUfAfAfagucaaggauL96	907	asUfsccuu(Ggn)acuuuaAfaCfacaugsasu	952	AUCAUGUGUUUAAAGUCAAGGAU	997
AD-561253.1	asasucagUfuAfUfGfaagaccacauL96	908	asUfsgugg(Tgn)cuucauAfaCfugauususg	953	CAAAUCAGUUAUGAAGACCACAA	998
AD-561959.1	gsasaggaUfgUfCfAfaagcucuguuL96	909	asAfscaga(Ggn)cuuugaCfaUfccuucsasc	954	GUGAAGGAUGUCAAAGCUCUGUU	999
AD-561573.1	asusguuuUfcUfAfCfcaaaugauuuL96	910	asAfsauca(Tgn)uugguaGfaAfaacaususc	955	GAAUGUUUUCUACCAAAUGAUUG	1000
AD-561651.1	csasagccAfaGfAfUfcucagucacuL96	911	asGfsugac(Tgn)gagaucUfuGfgcuugcsc	956	GGCAAGCCAAGAUCUCAGUCACU	1001
AD-561148.1	ascscaacUfuGfAfUfugagaagguuL96	912	asAfsccuu(Cgn)ucaaucAfaGfuuggusgsa	957	UCACCAACUUGAUUGAGAAGGUG	1002
AD-561962.1	gsgsauguCfaAfAfGfcucuguuuguL96	913	asCfsaaac(Agn)gagcuuUfgAfcauccsusu	958	AAGGAUGUCAAAGCUCUGUUUGU	1003
AD-562237.1	asgsaugaGfgAfUfUfuggguuuucuL96	914	asGfsaaaa(Cgn)ccaaauCfcUfcaucususu	959	AAGAUGAGGAUUUGGGUUUUCU	1004
AD-561654.1	gscscaagAfuCfUfCfagucacucguL96	915	asCfsgagu(Ggn)acugagAfuCfuuggcsusu	960	AAGCCAAGAUCUCAGUCACUCGC	1005
AD-562136.1	cscsgcuuCfaUfUfCfaaguugguguL96	916	asCfsacca(Agn)cuugaaUfgAfagcggscsu	961	AGCCGCUUCAUUCAAGUUGGUGU	1006
AD-562026.1	gscscaguUfgUfGfAfgagagaugcuL96	917	asGfscauc(Tgn)cucucaCfaAfcuggcsusu	962	AAGCCAGUUGUGAGAGAGAUGCU	1007
AD-561101.1	uscscaugAfaUfAfUfcuaccugguuL96	918	asAfsccag(Ggn)uagauaUfuCfauggasgsc	963	GCUCCAUGAAUAUCUACCUGGUG	1008
AD-561539.1	gsusguuuAfaAfGfUfcaaggauauuL96	919	asAfsuauc(Cgn)uugacuUfuAfaacacsasu	964	AUGUGUUUAAAGUCAAGGAUAUG	1009
AD-561961.1	asgsgaugUfcAfAfAfgcucuguuuuL96	920	asAfsaaca(Ggn)agcuuuGfaCfauccususc	965	GAAGGAUGUCAAAGCUCUGUUUG	1010
AD-561535.1	uscsauguGfuUfUfAfaagucaagguL96	921	asCfscuug(Agn)cuuuaaAfcAfcaugasusg	966	CAUCAUGUGUUUAAAGUCAAGGA	1011
AD-561652.1	asasgccaAfgAfUfCfucagucacuuL96	922	asAfsguga(Cgn)ugagauCfuUfggcuusgsc	967	GCAAGCCAAGAUCUCAGUCACUC	1012
AD-562260.1	uscsaaagAfuGfAfGfgauuuggguuL96	923	asAfsccca(Agn)auccucAfuCfuuugasgsc	968	GCUCAAAGAUGAGGAUUUGGGUU	1013
AD-557041.2	usgsgugcUfaGfAfUfggaucagacuL96	244	asGfsucug(Agn)uccaucUfaGfcaccasgsg	330	CCUGGUGCUAGAUGGAUCAGACA	416
AD-561655.1	cscsaagaUfcUfCfAfgucacucgcuL96	924	asGfscgag(Tgn)gacugaGfaUfcuuggcscsu	969	AGCCAAGAUCUCAGUCACUCGCC	1014
AD-557043.1	gsusgcuaGfaUfGfGfaucagacaguL96	925	asCfsuguc(Tgn)gauccaUfcUfagcacscsa	970	UGGUGCUAGAUGGAUCAGACAGC	1015
AD-561603.1	csasaaucUfcUfGfAfgucucuguguL96	926	asCfsacag(Agn)gacucaGfaGfauuugsgsu	971	ACCAAAUCUCUGAGUCUCUGUGG	1016
AD-557044.1	usgscuagAfuGfGfAfucagacagcuL96	927	asGfscugu(Cgn)ugauccAfuCfuagcascsc	972	GGUGCUAGAUGGAUCAGACAGCA	1017
AD-561266.1	gsasccacAfaGfCfUfgaagucagguL96	928	asCfscuga(Cgn)uucagcUfuGfuggucsusu	973	AAGACCACAAGCUGAAGUCAGGG	1018
AD-561541.1	gsusuuaaAfgUfCfAfaggauaugguL96	929	asCfscaua(Tgn)ccuugaCfuUfuaaacsasc	974	GUGUUUAAAGUCAAGGAUAUGGA	1019
AD-562257.1	asgscucaAfaGfAfUfgaggauuuguL96	930	asCfsaaau(Cgn)cucaucUfuUfgagcususg	975	CAAGCUCAAAGAUGAGGAUUUGG	1020
AD-560538.1	gsasgggaGfuAfGfAfgaucaaagguL96	931	asCfscuuu(Ggn)aucucuAfcUfcccucscsa	976	UGGAGGGAGUAGAGAUCAAAGGC	1021

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-561579.1	uscsuaccAfaAfUfGfauugaugaauL96	932	asUfsucau(Cgn)aaucauUfuGfguagasasa	977	UUUCUACCAAAUGAUUGAUGAAA	1022
AD-562259.1	csuscaaaGfaUfGfAfggauuuggguL96	933	asCfsccaa(Agn)uccucaUfcUfuugagscsu	978	AGCUCAAAGAUGAGGAUUUGGGU	1023
AD-560968.1	csusgccaAfgAfUfUfccuucauguuL96	934	asAfscaug(Agn)aggaauCfuUfggcagsgsa	979	UCCUGCCAAGAUUCCUUCAUGUA	1024
AD-561647.1	asusggcaAfgCfCfAfagaucucaguL96	935	asCfsugag(Agn)ucuuggCfuUfgccausgsg	980	CCAUGGCAAGCCAAGAUCUCAGU	1025
AD-561469.1	cscsuggaUfgUfGfUfaugguuuguL96	936	asCfsaaac(Agn)cauacaCfaUfccaggsusa	981	UACCUGGAUGUGUAUGUGUUUGG	1026
AD-561540.1	usgsuuuaAfaGfUfCfaaggauauguL96	937	asCfsauau(Cgn)cuugacUfuUfaaacascsa	982	UGUGUUUAAAGUCAAGGAUAUGG	1027
AD-562135.1	gscscgcuUfcAfUfUfcaaguuggguL96	938	asAfsccaa(Cgn)uugaauGfaAfgcggcsusu	983	AAGCCGCUUCAUUCAAGUUGGUG	1028

Table 8. Complement Factor B *In Vitro* Single Dose Screens in Hep3B cells

DuplexID	10 nM % of Message Remaining	1nM % of Message Remaining	0.1 nM % of Message Remaining
AD-557072.1	4.99	8.87	40.99
AD-558097.1	5.00	11.75	45.33
AD-557068.1	9.00	22.78	53.22
AD-557774.1	6.55	17.23	52.48
AD-557070.1	7.33	21.06	54.78
AD-558225.1	19.10	29.43	106.87
AD-558065.1	12.21	24.28	61.24
AD-557853.1	9.39	35.28	55.01
AD-556919.1	20.01	27.64	138.66
AD-557859.1	13.46	25.92	104.56
AD-557069.1	11.26	29.35	54.36
AD-558068.1	14.59	21.63	48.67
AD-557422.1	14.87	27.15	55.45
AD-558096.1	10.81	26.65	76.39
AD-557084.1	28.07	54.88	138.96
AD-558076.1	13.06	24.15	42.77
AD-558063.1	20.24	28.87	54.49
AD-558069.1	17.70	27.78	53.41
AD-558061.1	19.59	36.04	48.88
AD-558066.1	23.98	44.12	51.72
AD-556581.1	22.46	67.53	186.97
AD-557079.1	9.97	41.07	71.40
AD-558012.1	17.26	35.39	112.72
AD-556701.1	9.91	23.66	62.85
AD-557782.1	13.23	45.66	53.87
AD-557498.1	28.16	56.57	131.91
AD-556788.1	33.88	58.98	118.02
AD-557078.1	18.18	50.25	80.91
AD-557852.1	40.94	60.36	167.53
AD-557353.1	23.37	44.41	62.52
AD-557041.1	26.00	87.78	110.85
AD-556786.1	51.74	66.59	90.96
AD-556734.1	29.10	54.88	70.13
AD-557475.1	26.95	50.54	65.87
AD-557972.1	63.07	77.45	71.99
AD-556390.1	31.40	46.72	72.19
AD-556963.1	42.99	68.75	146.93
AD-558078.1	30.67	83.78	62.14
AD-557204.1	40.18	69.41	199.62
AD-556962.1	67.05	92.06	80.95

DuplexID	10 nM % of Message Remaining	1nM % of Message Remaining	0.1 nM % of Message Remaining
AD-556733.1	34.07	61.86	62.03
AD-556724.1	43.85	114.37	225.16
AD-557067.1	42.27	59.20	67.56
AD-557602.1	39.99	70.66	155.25
AD-557345.1	45.66	91.09	186.86
AD-557969.1	70.94	72.23	72.25
AD-557867.1	43.92	108.43	178.41
AD-557860.1	49.94	63.71	134.13
AD-557868.1	52.22	99.81	112.51
AD-558064.1	61.63	72.39	59.83
AD-556725.1	45.46	62.37	68.67
AD-556787.1	58.40	102.98	163.60
AD-558062.1	55.53	70.65	156.02
AD-556874.1	83.34	90.67	62.04
AD-557066.1	75.61	93.55	168.75
AD-556791.1	64.56	74.17	75.36
AD-557450.1	56.23	68.84	77.40
AD-557865.1	66.83	94.99	153.50
AD-556961.1	69.87	93.70	206.00
AD-556920.1	52.86	81.48	188.46
AD-558074.1	74.73	132.35	71.18
AD-556738.1	72.67	123.81	206.91
AD-558004.1	100.55	103.41	190.48
AD-556918.1	85.53	97.13	199.73
AD-557209.1	84.13	96.02	140.72
AD-557861.1	66.07	84.41	120.27
AD-557226.1	83.39	94.85	123.74
AD-557856.1	84.68	85.69	137.01
AD-557839.1	114.79	91.84	69.49
AD-557873.1	84.73	102.93	65.71
AD-557417.1	88.08	115.91	225.81
AD-558106.1	95.90	110.10	217.75
AD-557788.1	87.87	109.59	129.42
AD-556917.1	79.04	71.81	78.26
AD-556739.1	87.37	115.81	70.32
AD-556726.1	96.01	129.96	221.48
AD-556790.1	109.55	118.05	193.15
AD-557604.1	74.95	133.00	177.11
AD-557495.1	96.32	130.00	254.48
AD-557016.1	106.90	131.43	110.73
AD-558105.1	77.28	73.82	85.07
AD-557872.1	102.16	123.17	172.64

DuplexID	10 nM % of Message Remaining	1nM % of Message Remaining	0.1 nM % of Message Remaining
AD-557346.1	113.18	138.10	228.78
AD-557851.1	107.51	138.22	178.85
AD-557786.1	117.86	149.34	168.00
AD-557857.1	118.52	127.67	145.90

Table 9. Complement Factor B *In Vitro* Single Dose Screens in Hep3B cells

DuplexID	10 nM Dose % of Message Remaining	STDEV	1 nM Dose % of Message Remaining	STDEV	0.1 nM Dose %o f Message Remaining	STDEV
AD-558657.1	4.81	0.55	6.98	1.27	24.75	5.46
AD-559020.1	5.18	0.75	7.21	1.31	17.95	3.88
AD-559023.1	7.71	0.93	9.85	2.87	32.65	5.12
AD-558860.1	8.35	1.69	14.34	1.97	33.70	7.41
AD-559143.1	8.57	1.09	11.19	1.02	28.52	7.22
AD-559021.1	8.65	3.21	13.97	4.56	42.99	5.93
AD-559144.1	9.25	0.94	16.75	3.32	33.52	2.97
AD-559435.1	10.47	0.85	13.57	1.00	38.94	5.33
AD-560019.1	10.57	0.67	12.96	1.19	17.67	1.23
AD-559722.1	11.24	1.35	19.04	1.63	42.16	2.85
AD-560016.1	11.42	1.30	17.54	2.39	28.72	3.63
AD-559008.1	11.51	3.34	17.60	0.78	45.58	15.60
AD-560018.1	11.76	1.89	16.87	2.51	28.83	4.60
AD-560045.1	12.13	1.71	28.22	11.60	53.32	14.16
AD-559375.1	12.45	1.28	21.86	1.78	61.75	7.34
AD-559142.1	13.01	2.52	20.98	3.88	43.82	6.89
AD-559160.1	13.06	3.15	19.02	1.35	47.19	7.99
AD-559374.1	13.17	3.28	27.58	5.37	72.78	11.80
AD-559369.1	13.75	0.79	25.72	0.58	62.74	6.62
AD-559148.1	13.81	1.72	25.39	1.60	53.03	5.36
AD-560163.1	14.11	0.87	20.31	1.31	49.05	4.99
AD-559398.1	14.23	3.97	18.11	2.34	46.53	6.07
AD-559060.1	14.39	3.41	32.15	3.07	62.25	5.65
AD-559392.1	14.69	3.59	21.68	2.40	55.88	8.59
AD-559451.1	14.84	3.18	25.50	3.19	43.71	5.05
AD-559721.1	15.23	3.73	23.03	3.34	51.33	10.51
AD-559146.1	15.26	5.05	28.14	1.99	71.88	8.41
AD-560165.1	15.74	2.70	25.08	2.14	65.45	14.31
AD-559921.1	15.99	1.86	19.91	4.59	38.78	9.90
AD-560021.1	16.02	3.62	37.73	4.08	58.59	3.73
AD-560164.1	16.23	2.00	22.73	3.67	63.13	4.12
AD-559614.1	16.27	4.70	31.75	4.73	49.34	6.16

DuplexID	10 nM Dose % of Message Remaining	STDEV	1 nM Dose % of Message Remaining	STDEV	0.1 nM Dose %o f Message Remaining	STDEV
AD-559393.1	16.46	3.99	31.63	4.04	61.56	10.13
AD-559717.1	16.68	1.69	20.78	3.33	42.46	10.02
AD-560017.1	16.71	2.32	28.04	3.35	57.72	16.22
AD-559440.1	16.90	1.64	27.94	4.84	50.75	9.54
AD-560166.1	17.02	4.84	20.01	3.95	58.88	13.01
AD-559059.1	17.61	5.82	33.74	3.87	59.15	7.45
AD-559300.1	17.90	5.18	34.67	2.86	67.79	6.31
AD-559946.1	18.11	1.61	36.74	5.04	62.70	7.20
AD-559147.1	18.33	2.11	47.39	7.94	85.39	10.23
AD-559755.1	19.99	5.12	26.88	2.30	52.33	10.49
AD-559446.1	20.58	2.25	30.84	7.47	64.13	7.62
AD-559026.1	21.11	2.49	41.40	14.50	65.91	11.08
AD-559714.1	22.71	0.91	32.56	2.47	69.69	6.49
AD-560160.1	22.85	5.07	28.30	2.24	65.27	9.41
AD-559437.1	25.76	4.50	44.87	12.58	78.13	8.91
AD-560162.1	25.95	4.26	43.29	5.64	71.14	20.99
AD-560161.1	26.34	3.19	38.91	4.83	68.19	5.53
AD-559924.1	26.34	8.91	36.46	3.90	57.07	6.32
AD-559865.1	27.49	2.47	47.05	6.32	75.04	14.94
AD-559449.1	28.57	3.20	54.33	4.83	70.39	14.64
AD-559788.1	28.70	6.51	62.57	7.45	79.25	8.07
AD-559617.1	29.43	9.48	67.18	6.78	88.54	10.81
AD-559719.1	30.38	3.11	55.82	5.69	83.18	12.99
AD-559718.1	32.51	3.42	57.77	8.99	82.88	18.79
AD-558697.1	32.69	5.66	44.32	3.45	58.56	7.73
AD-559357.1	33.33	3.84	33.06	4.91	59.41	16.08
AD-558965.1	35.13	2.66	34.85	11.29	51.66	15.94
AD-558267.1	37.43	7.93	35.43	6.56	40.76	7.84
AD-558639.1	37.99	5.49	46.82	7.78	44.37	7.45
AD-559925.1	39.15	17.96	74.82	7.86	75.18	4.17
AD-559450.1	40.47	6.34	63.09	4.35	53.12	12.34
AD-559302.1	41.61	5.63	59.86	3.32	79.54	9.58
AD-559074.1	41.79	3.21	57.94	3.73	62.36	5.75
AD-559947.1	43.30	2.71	66.78	11.57	73.55	7.33
AD-559442.1	47.58	8.47	69.78	10.91	92.36	7.58
AD-559359.1	48.10	2.37	86.83	11.09	102.01	6.31
AD-559616.1	50.68	6.63	93.13	11.78	88.54	12.26
AD-559864.1	63.01	11.07	91.70	12.15	89.75	13.66
AD-559866.1	85.15	11.86	94.33	6.79	79.14	12.77

Table 10. Complement Factor B *In Vitro* Single Dose Screens in Primary Mouse Hepatocytes (PMH)

DuplexID	10 nM Dose % of Message Remaining	STDEV	1 nM Dose % of Message Remaining	STDEV	0.1 nM Dose % of Message Remaining	STDEV
AD-558860.1	10.33	2.38	40.10	5.03	94.64	11.07
AD-560018.1	13.28	3.25	64.35	11.23	114.97	8.99
AD-560019.1	18.44	3.65	75.46	18.65	118.42	14.85
AD-559160.1	19.42	3.01	47.55	4.18	125.03	7.48
AD-559921.1	20.12	3.89	67.51	6.36	123.87	9.76
AD-559755.1	20.65	5.45	77.24	11.02	117.00	9.54
AD-560017.1	22.11	5.43	82.72	11.41	123.23	4.98
AD-559614.1	23.18	7.36	67.15	7.61	123.18	19.54
AD-559435.1	25.13	3.68	66.19	8.46	118.78	11.85
AD-560016.1	25.40	5.70	91.81	22.08	128.76	16.87
AD-559451.1	27.47	9.44	71.89	12.25	137.27	20.14
AD-559617.1	29.70	10.00	84.66	4.39	140.37	6.69
AD-560021.1	32.74	4.65	91.51	4.21	126.40	12.31
AD-559449.1	37.90	5.63	82.95	9.33	130.52	19.04
AD-559450.1	38.55	8.96	87.87	22.39	129.90	7.64
AD-559925.1	38.62	3.39	90.35	10.90	104.75	5.55
AD-559440.1	39.15	5.87	82.63	10.21	124.84	7.74
AD-559788.1	42.67	7.18	114.25	12.73	138.37	4.54
AD-559437.1	45.26	10.40	94.10	7.91	130.12	11.84
AD-559369.1	47.64	10.56	83.98	9.74	136.96	5.52
AD-559446.1	49.32	10.27	104.76	13.05	141.33	23.45
AD-559924.1	56.47	10.68	101.50	14.50	131.17	5.61
AD-558965.1	58.30	14.89	94.61	10.27	109.17	5.25
AD-560045.1	68.96	6.99	94.93	5.17	98.24	5.15
AD-559946.1	74.67	7.51	116.30	7.12	108.08	6.00
AD-558697.1	79.21	8.58	103.00	11.53	141.24	23.63
AD-559008.1	79.41	8.78	103.11	8.12	103.48	5.21
AD-559357.1	81.03	4.45	95.92	5.13	110.83	8.24
AD-559020.1	82.26	11.63	98.50	12.69	102.20	4.21
AD-559143.1	82.37	15.28	97.44	5.47	104.94	5.93
AD-559374.1	85.24	7.46	89.59	3.03	130.94	10.46
AD-560161.1	85.46	17.44	91.49	7.11	106.52	4.01
AD-559947.1	86.06	13.19	115.94	7.06	118.65	5.89
AD-559616.1	86.75	7.61	115.52	9.47	134.57	3.86
AD-559142.1	87.22	10.07	88.47	5.77	96.92	5.92
AD-558639.1	87.64	13.26	99.95	4.27	122.33	12.04
AD-560166.1	88.71	22.04	104.01	13.19	97.42	5.90
AD-559359.1	89.05	14.80	104.69	7.55	123.70	6.43
AD-558657.1	89.59	11.42	95.66	6.61	109.56	9.31

DuplexID	10 nM Dose % of Message Remaining	STDEV	1 nM Dose % of Message Remaining	STDEV	0.1 nM Dose % of Message Remaining	STDEV
AD-559442.1	90.05	26.12	107.09	17.30	152.65	17.71
AD-559023.1	93.44	12.18	96.28	8.79	116.18	4.76
AD-560160.1	93.98	12.77	106.07	14.37	96.30	1.99
AD-559398.1	94.15	14.19	89.68	5.33	141.12	7.36
AD-559722.1	94.20	7.15	114.34	13.25	128.86	17.84
AD-559146.1	94.84	7.07	94.68	6.79	150.36	18.96
AD-558267.1	96.73	10.58	101.69	8.01	107.42	7.77
AD-559074.1	99.75	10.40	91.77	6.74	132.38	20.72
AD-560162.1	100.49	17.85	98.34	9.70	99.71	7.13
AD-559021.1	102.22	20.82	100.57	9.81	143.53	24.85
AD-559144.1	105.28	4.70	98.16	9.44	149.08	20.99
AD-559147.1	106.45	27.57	89.01	4.30	147.67	22.58
AD-560164.1	106.73	13.72	97.25	8.25	103.76	7.45
AD-559714.1	107.80	24.01	130.26	16.11	139.71	8.34
AD-560165.1	108.93	14.81	100.31	4.51	95.90	5.35
AD-559300.1	111.25	11.78	90.58	4.56	134.36	10.29
AD-559866.1	112.76	7.74	123.50	10.25	143.37	8.58
AD-559302.1	113.89	12.96	90.69	3.34	112.12	19.35
AD-560163.1	114.10	15.54	92.44	9.83	107.52	5.99
AD-559718.1	114.19	9.34	139.34	10.12	143.95	10.17
AD-559721.1	115.30	17.06	116.42	5.04	143.90	13.34
AD-559026.1	115.85	15.27	95.64	12.87	132.32	13.74
AD-559719.1	116.22	12.55	130.31	6.06	150.76	26.42
AD-559060.1	117.05	20.30	95.06	4.36	141.26	25.56
AD-559864.1	118.44	9.57	134.91	10.92	143.92	22.59
AD-559059.1	120.63	14.40	94.88	3.85	154.23	9.79
AD-559865.1	123.03	9.71	134.45	14.17	142.24	10.43
AD-559148.1	123.28	10.25	91.36	4.38	156.95	14.94
AD-559375.1	125.42	7.77	96.09	8.53	148.89	19.81
AD-559393.1	126.82	14.36	97.97	6.13	142.67	16.86
AD-559717.1	131.20	6.00	131.80	6.57	148.89	12.67
AD-559392.1	134.26	21.19	96.35	2.77	130.60	8.29

Table 11. Complement Factor B *In Vitro* Single Dose Screens in Primary Mouse Hepatocytes (PMH)

DuplexID	10 nM Dose % of Message Remaining	STDEV	1 nM Dose % of Message Remaining	STDEV	0.1 nM Dose %of Message Remaining	STDEV
AD-560969.1	1.76	0.44	12.85	2.32	72.08	7.11
AD-561537.1	1.97	0.30	13.11	1.38	57.66	1.85

DuplexID	10 nM Dose % of Message Remaining	STDEV	1 nM Dose % of Message Remaining	STDEV	0.1 nM Dose %of Message Remaining	STDEV
AD-562262.1	2.07	0.40	14.20	2.60	54.79	3.33
AD-561960.1	2.82	0.45	15.86	1.84	76.74	10.88
AD-561580.1	2.88	1.59	18.55	1.98	69.39	11.71
AD-561254.1	2.89	0.86	15.62	4.05	61.84	5.51
AD-561578.1	2.95	0.42	25.93	1.50	76.75	7.73
AD-561538.1	3.50	0.97	4.45	1.11	31.69	5.04
AD-561252.1	3.60	1.65	16.00	2.58	59.33	6.64
AD-561963.1	3.62	0.30	29.50	8.22	81.62	4.93
AD-562027.1	3.89	0.78	23.89	5.04	70.54	7.81
AD-561653.1	4.01	0.74	23.82	3.53	80.62	7.07
AD-562137.1	4.14	1.55	24.06	11.00	69.61	6.62
AD-561536.1	4.21	1.10	29.07	5.79	80.38	5.28
AD-561253.1	5.04	1.15	27.31	6.10	68.27	12.61
AD-561959.1	5.17	1.81	50.97	13.35	90.71	8.16
AD-561573.1	5.38	0.27	33.50	11.42	91.06	13.14
AD-561651.1	6.36	1.01	49.06	2.79	92.69	9.37
AD-561148.1	6.36	0.87	38.00	1.38	89.30	12.00
AD-561962.1	7.16	1.19	36.21	6.11	91.19	5.39
AD-562237.1	8.80	2.07	53.16	6.31	86.16	11.24
AD-561654.1	9.91	1.61	55.56	7.65	101.67	5.04
AD-562136.1	10.27	0.81	62.46	9.28	97.86	7.44
AD-562026.1	11.34	1.47	60.69	2.81	89.22	3.89
AD-561101.1	11.78	2.75	62.67	4.18	84.92	9.50
AD-561539.1	12.00	1.31	53.65	10.81	84.80	12.57
AD-561961.1	14.01	2.50	58.58	7.03	101.01	6.13
AD-561535.1	14.27	3.13	70.96	10.08	103.90	12.70
AD-561652.1	16.40	3.40	64.57	7.97	96.09	9.38
AD-562260.1	19.73	4.82	77.55	5.09	91.07	8.78
AD-557041.2	25.76	5.84	50.26	6.69	93.59	0.72
AD-561655.1	26.16	3.41	80.98	7.80	102.69	10.61
AD-557043.1	27.03	3.02	69.48	3.50	95.16	3.84
AD-561603.1	31.99	4.57	78.55	6.25	86.39	7.35
AD-557044.1	38.05	3.97	53.45	3.97	90.84	7.63
AD-561266.1	38.64	2.80	79.00	6.75	89.14	5.01
AD-561541.1	45.60	6.83	92.73	1.82	107.60	8.31
AD-562257.1	52.27	2.66	93.01	8.78	100.58	4.10
AD-560538.1	57.85	5.71	92.26	2.62	102.77	6.06
AD-561579.1	65.71	10.54	91.74	8.83	101.05	6.91
AD-562259.1	66.28	3.34	91.38	7.85	96.23	5.92
AD-560968.1	73.08	6.97	87.16	9.40	100.89	2.47
AD-561647.1	74.09	6.95	96.10	5.34	103.62	8.94

DuplexID	10 nM Dose % of Message Remaining	STDEV	1 nM Dose % of Message Remaining	STDEV	0.1 nM Dose %of Message Remaining	STDEV
AD-561469.1	78.98	10.38	91.17	7.11	102.25	6.72
AD-561540.1	84.14	6.35	95.72	4.13	104.96	9.90
AD-562135.1	87.86	10.90	102.43	11.38	102.47	11.43

Table 12. Complement Factor B *In Vitro* Single Dose Screens in Hep3B Cells

DuplexID	10 nM Dose % of Message Remaining	STDEV	1 nM Dose % of Message Remaining	STDEV	0.1 nM Dose % of Message Remaining	STDEV
AD-560969.1	29.34	1.71	71.22	4.40	88.98	14.10
AD-561537.1	86.96	7.93	84.92	6.56	97.67	11.01
AD-562262.1	19.99	1.52	43.30	9.67	77.20	2.33
AD-561960.1	101.89	7.12	93.06	6.78	86.95	11.28
AD-561580.1	77.04	4.88	72.79	13.33	99.51	7.87
AD-561254.1	47.27	3.23	59.31	9.89	80.05	5.60
AD-561578.1	17.62	1.52	54.39	5.50	86.17	9.50
AD-561538.1	14.90	6.97	24.45	3.87	42.19	9.11
AD-561252.1	93.27	11.00	96.17	6.74	78.24	13.72
AD-561963.1	40.07	4.40	63.17	10.68	84.66	8.57
AD-562027.1	77.41	4.07	84.74	1.64	95.86	11.49
AD-561653.1	44.48	8.74	68.46	11.39	101.86	10.10
AD-562137.1	12.14	2.49	35.01	5.57	63.19	12.92
AD-561536.1	81.78	6.45	107.20	6.41	72.90	5.20
AD-561253.1	83.43	9.54	84.78	15.70	70.37	8.01
AD-561959.1	78.06	6.19	70.68	2.99	89.62	9.10
AD-561573.1	62.25	8.08	74.47	7.81	69.74	13.65
AD-561651.1	65.86	6.99	94.78	14.92	86.37	10.00
AD-561148.1	85.70	6.64	93.17	12.36	96.96	10.73
AD-561962.1	73.24	4.15	104.85	7.06	105.02	11.38
AD-562237.1	35.58	3.42	62.94	2.85	82.87	12.89
AD-561654.1	68.27	6.59	84.86	8.20	88.86	16.82
AD-562136.1	43.50	5.85	96.79	6.07	97.96	8.53
AD-562026.1	78.57	11.58	92.78	9.79	100.53	12.79
AD-561101.1	80.42	8.87	88.94	8.58	78.42	5.79
AD-561539.1	73.75	9.48	70.46	13.02	81.45	11.45
AD-561961.1	93.29	14.09	102.04	3.89	82.92	14.39
AD-561535.1	90.31	7.87	100.89	9.09	89.58	10.53
AD-561652.1	99.83	14.12	86.03	11.59	99.32	15.07
AD-562260.1	72.75	4.48	93.46	5.11	91.71	18.08
AD-557041.2	18.62	0.85	50.98	12.96	78.19	10.26
AD-561655.1	81.07	2.83	92.73	6.74	73.97	11.80

DuplexID	10 nM Dose % of Message Remaining	STDEV	1 nM Dose % of Message Remaining	STDEV	0.1 nM Dose % of Message Remaining	STDEV
AD-557043.1	28.86	4.75	81.11	7.28	91.72	10.13
AD-561603.1	46.27	14.44	99.22	11.97	86.19	7.73
AD-557044.1	23.45	2.59	74.62	9.75	79.77	7.73
AD-561266.1	105.79	5.46	95.99	11.36	99.59	2.26
AD-561541.1	100.77	11.65	98.43	4.85	93.30	4.25
AD-562257.1	101.31	9.81	97.55	15.36	95.26	7.79
AD-560538.1	103.91	11.00	104.39	8.70	86.71	20.47
AD-561579.1	87.65	10.59	80.92	11.54	83.54	7.48
AD-562259.1	86.75	12.13	98.75	19.03	90.33	10.56
AD-560968.1	94.61	7.70	107.14	4.84	88.97	10.45
AD-561647.1	99.94	9.55	110.74	11.11	98.97	13.25
AD-561469.1	84.71	4.50	88.17	6.08	82.50	8.92
AD-561540.1	84.25	4.08	88.70	14.19	110.80	11.10
AD-562135.1	89.38	4.70	95.02	2.81	98.61	12.79

Example 3. *In vivo* screening of dsRNA Duplexes in Mice

Duplexes of interest, identified from the above *in vitro* studies, were evaluated *in vivo*.

In particular, 6-8-week old wild-type mice (C57BL/6) were administered 100 ml of a 2 x 10^{11} viral particles/ml solution of an adeno-associated virus 8 (AAV8) vector encoding human complement fator B (hCFB AAV) by intravenous tail vein injection at Day -14.

At day 0, mice were subcutaneously administered a single 2 mg/kg dose of a duplex of interest or PBS control (n=3/group). Table 13 provides the duplexes that were administered to the mice.

At day 0, 7, and 14 post dose, blood was collected and plasma was prepared for ELISA assay. At day14 post-dose, animals were sacrificed, liver samples were collected and snap-frozen in liquid nitrogen and tissue mRNA was extracted.

The level of human CFB protein was determined by quantitative sandwich enzyme immunoassay (AssayMax™, Human Complement Factor B ELISA Kit). Table 14 shows that the protein levels of human CFB were reduced upon treatment with a single dose of siRNA targeting hCFB at 2 mg/kg.

The level of human CFB expression was measured by RT-QPCR, as described above. Human CFB mRNA levels were compared to the mRNA level of the housekeeping gene GAPDH. The values were then normalized to the average of PBS vehicle control group. The data were expressed as percent of baseline value, and were presented as mean plus standard deviation. As shown in Table 15, human CFB mRNA levels were reduced upon treatment with a single dose of siRNA targeting hCFB at 2 mg/kg.

Table 13. dsRNA Duplexes for *In Vivo* Screening

Duplex ID	Oligo ID	Strand	Sequence 5' to 3'	SEQ ID NO:	Range in NM_001710.5
AD-558657.2	A-1072067.1	sense	gsusgaguGfaUfGfAfgaucucuuuuL96	629	643-665
	A-1075535.1	antis	asAfsaagAfgAfUfcucaUfcAfcucacsasu	700	
AD-559020.2	A-1072793.1	sense	asasaaguGfuCfUfAfgucaacuuauL96	619	1145-1167
	A-1075898.1	antis	asUfsaagUfuGfAfcuagAfcAfcuuuususg	690	
AD-559023.2	A-1072799.1	sense	asgsugucUfaGfUfCfaacuuaauuuL96	631	1148-1170
	A-1075901.1	antis	asAfsauuAfaGfUfugacUfaGfacacususu	702	
AD-558860.2	A-1072473.1	sense	usgsccaaGfaCfUfCfcuucauguauL96	591	928-950
	A-1075738.1	antis	asUfsacaUfgAfAfggagUfcUfuggcasgsg	662	
AD-560019.2	A-1074791.1	sense	asgsagaaGfuCfGfUfuucauucaauL96	593	2396-2418
	A-1076897.1	antis	asUfsugaAfuGfAfaacgAfcUfucucususg	664	
AD-560016.2	A-1074785.1	sense	ascsaagaGfaAfGfUfcguuucauuuL96	600	2393-2415
	A-1076894.1	antis	asAfsaugAfaAfCfgacuUfcUfcuugusgsa	671	
AD-559008.2	A-1072769.1	sense	uscsacagGfaGfCfCfaaaaaguguuL96	617	1133-1155
	A-1075886.1	antis	asAfscacUfuUfUfuggcUfcCfugugasasg	688	
AD-559717.2	A-1074187.1	sense	csasggaaUfuCfCfUfgaauuuuauuL96	660	1976-1998
	A-1076595.1	antis	asAfsuaaAfaUfUfcaggAfaUfuccugscsu	731	
AD-557072.2	A-1072789.1	sense	csasaaaaGfuGfUfCfuagucaacuuL96	191	1143-1165
	A-1072790.1	antis	asAfsguug(Agn)cuagacAfcUfuuuugsgsc	277	
AD-558097.2	A-1074839.1	sense	usasguggAfuGfUfCfugcaaaaacuL96	192	2438-2460
	A-1074840.1	antis	asGfsuuuu(Tgn)gcagacAfuCfcacuascsu	278	
AD-557774.2	A-1074193.1	sense	gsasauucCfuGfAfAfuuuuaugacuL96	193	1979-2001
	A-1074194.1	antis	asGfsucau(Agn)aaauucAfgGfaauucscsu	279	
AD-557070.2	A-1072785.1	sense	gscscaaaAfaGfUfGfucuagucaauL96	194	1141-1163
	A-1072786.1	antis	asUfsugac(Tgn)agacacUfuUfuuggcsusc	280	
AD-558065.2	A-1074775.1	sense	asgsuucaCfaAfGfAfgaagucguuuL96	199	2388-2410
	A-1074776.1	antis	asAfsacga(Cgn)uucucuUfgUfgaacusasu	285	
AD-557853.2	A-1074351.1	sense	asgsggaaCfaAfCfUfcgagcuuuguL96	208	2078-2100
	A-1074352.1	antis	asCfsaaag(Cgn)ucgaguUfgUfucccuscsg	294	
AD-557079.2	A-1072803.1	sense	usgsucuaGfuCfAfAfcuuaauugauL96	211	1150-1172
	A-1072804.1	antis	asUfscaau(Tgn)aaguugAfcUfagacascsu	297	

Table 14. Human CFB siRNA *In Vivo* Screening

	ELISA Results D7		ELISA Results D14	
	Avg hCFB Protein Remaining	SD	Avg hCFB Protein Remaining	SD
PBS	110.13	22.47	104.31	17.38
Naïve	96.75	21.00	92.31	6.54
AD-558657.2	29.32	8.38	24.76	5.08
AD-559020.2	24.26	4.07	25.05	1.22
AD-559023.2	28.56	7.34	26.35	3.44
AD-558860.2	52.69	4.25	50.31	17.27
AD-560019.2	26.68	8.43	20.07	6.59
AD-560016.2	44.06	2.59	45.94	2.69
AD-559008.2	46.07	6.47	34.55	5.26
AD-559717.2	57.72	11.41	51.14	13.28
AD-557072.2	34.29	8.88	22.19	6.45

	ELISA Results D7		ELISA Results D14	
	Avg hCFB Protein Remaining	SD	Avg hCFB Protein Remaining	SD
AD-558097.2	31.01	9.59	29.55	10.60
AD-557774.2	70.26	6.03	64.26	12.89
AD-557070.2	91.58	21.23	71.11	18.76
AD-558065.2	120.96	14.77	82.66	44.55
AD-557853.2	94.22	24.50	81.47	18.23
AD-557079.2	101.05	17.40	97.09	15.44

Table 15. Human CFB siRNA *In Vivo* Screening

qPCR Results D14		
	% message remaining	SD
PBS	100.19	7.12
Naïve	88.59	6.21
AD-558657.2	37.82	11.34
AD-559020.2	56.19	2.64
AD-559023.2	37.50	3.28
AD-558860.2	65.89	10.68
AD-560019.2	22.01	1.70
AD-560016.2	68.31	5.22
AD-559008.2	53.91	12.03
AD-559717.2	63.13	7.55
AD-557072.2	39.39	1.21
AD-558097.2	43.35	11.63
AD-557774.2	81.10	4.79
AD-557070.2	83.09	13.83
AD-558065.2	86.18	9.28
AD-557853.2	84.42	6.60
AD-557079.2	98.00	15.34

Example 4. *In vivo* screening of dsRNA Duplexes in Mice

Additional duplexes of interest, identified from the above *in vitro* studies, were evaluated *in vivo*.

In particular, 6-8-week old wild-type mice (C57BL/6) were administered 100 ml of a 2 x 10^{11} viral particles/ml solution of an adeno-associated virus 8 (AAV8) vector encoding human complement fator B (hCFB AAV) by intravenous tail vein injection at Day -14.

At day 0, mice were subcutaneously administered a single 2 mg/kg dose of a duplex of interest or PBS control (n=3/group). Table 16 provides the duplexes that were administered to the mice.

At day 0, 7, and 14 post dose, blood was collected and plasma was prepared for ELISA assay. At day14 post-dose, animals were sacrificed, liver samples were collected and snap-frozen in liquid nitrogen and tissue mRNA was extracted.

The level of human CFB protein was determined by quantitative sandwich enzyme immunoassay (AssayMax™, Human Complement Factor B ELISA Kit). Table 17 shows that the protein levels of human CFB were reduced upon treatment with a single dose of siRNA targeting hCFB at 2 mg/kg.

The level of human CFB expression was measured by RT-QPCR, as described above. Human CFB mRNA levels were compared to the mRNA level of the housekeeping gene GAPDH. The values were then normalized to the average of PBS vehicle control group. The data were expressed as percent of baseline value, and were presented as mean plus standard deviation. As shown in Table 18, human CFB mRNA levels were reduced upon treatment with a single dose of siRNA targeting hCFB at 2 mg/kg.

Table 16. dsRNA Duplexes for *In Vivo* Screening

DuplexID	OligoID	Strand	Sequence 5' to 3'	SEQ ID NO:	Range in NM_001710.5
AD-560018.2	A-1074789.1	sense	asasgagaAfgUfCfGfuuucauucauL96	592	2395-2417
	A-1076896.1	antis	asUfsgaaUfgAfAfacgaCfuUfcucuusgsu	663	
AD-559375.2	A-1073503.1	sense	asuscuggAfuGfUfCfuauguguuuuL96	658	1541-1563
	A-1076253.1	antis	asAfsaacAfcAfUfagacAfuCfcagausasa	729	
AD-559160.2	A-1073073.1	sense	usasugaaGfaCfCfAfcaaguugaauL96	594	1306-1328
	A-1076038.1	antis	asUfsucaAfcUfUfguggUfcUfucauasasu	665	
AD-559374.2	A-1073501.1	sense	usasucugGfaUfGfUfcuauguguuuL96	621	1540-1562
	A-1076252.1	antis	asAfsacaCfaUfAfgacaUfcCfagauasasu	692	
AD-559060.2	A-1072873.1	sense	usgsguguGfaAfGfCfcaagauauguL96	653	1185-1207
	A-1075938.1	antis	asCfsauaUfcUfUfggcuUfcAfcaccasusa	724	
AD-559721.2	A-1074195.1	sense	asasuuccUfgAfAfUfuuuaugacuuL96	650	1980-2002
	A-1076599.1	antis	asAfsgucAfuAfAfaauuCfaGfgaauuscsc	721	
AD-559026.2	A-1072805.1	sense	gsuscuagUfcAfAfCfuuaauugaguL96	651	1151-1173
	A-1075904.1	antis	asCfsucaAfuUfAfaguuGfaCfuagacsasc	722	
AD-558225.2	A-1075095.1	sense	usgsaauuAfaAfAfCfagcugcgacuL96	207	2602-2624
	A-1075096.1	antis	asGfsucgc(Agn)gcuguuUfuAfauucasasu	293	
AD-557069.2	A-1072783.1	sense	asgsccaaAfaAfGfUfgucuagucauL96	206	1140-1162
	A-1072784.1	antis	asUfsgacu(Agn)gacacuUfuUfuggcuscsc	292	
AD-558068.2	A-1074781.1	sense	uscsacaaGfaGfAfAfgucguuucauL96	195	2391-2413
	A-1074782.1	antis	asUfsgaaa(Cgn)gacuucUfcUfugugasasc	281	
AD-557422.2	A-1073489.1	sense	gsasggauUfaUfCfUfggaugucuauL96	202	1534-1556
	A-1073490.1	antis	asUfsagac(Agn)uccagaUfaAfuccucscsc	288	
AD-558063.2	A-1074771.1	sense	asusaguuCfaCfAfAfgagaagucguL96	205	2386-2408
	A-1074772.1	antis	asCfsgacu(Tgn)cucuugUfgAfacuauscsa	291	
AD-558066.2	A-1074777.1	sense	gsusucacAfaGfAfGfaagucguuuuL96	212	2389-2411
	A-1074778.1	antis	asAfsaacg(Agn)cuucucUfuGfugaacsusa	298	
AD-556701.2	A-1072047.1	sense	csusacuaCfaAfUfGfugagugauguL96	197	633-655
	A-1072048.1	antis	asCfsauca(Cgn)ucacauUfgUfaguagsgsg	283	

Table 17. Human CFB siRNA *In Vivo* Screening

	ELISA Results D7		ELISA Results D14	
	Avg hCFB Protein Remaining	SD	Avg hCFB Protein Remaining	SD
PBS	115.67	31.44	117.68	25.52
Naïve	110.11	4.46	108.16	15.25
AD-560018.2	16.29	2.97	15.23	4.63
AD-559375.2	42.43	8.09	44.31	14.32
AD-559160.2	39.66	10.78	49.87	3.52
AD-559374.2	43.88	10.14	41.19	9.12
AD-559060.2	63.43	15.73	50.37	6.51
AD-559721.2	30.89	2.80	28.32	5.76
AD-559026.2	70.20	7.55	53.71	3.75
AD-558225.2	42.06	1.30	41.12	6.52
AD-557069.2	94.78	13.32	71.48	6.01
AD-558068.2	94.83	9.22	97.31	20.15
AD-557422.2	74.07	1.97	63.49	9.48
AD-558063.2	77.64	3.66	81.77	4.84
AD-558066.2	76.19	5.77	65.77	8.00
AD-556701.2	69.44	3.28	62.51	21.07

Table 18. Human CFB siRNA *In Vivo* Screening

qPCR Results D14		
	% message remaining	SD
PBS	100.4	9.3
Naïve	77.4	13.2
AD-560018.2	20.0	1.7
AD-559375.2	66.4	10.1
AD-559160.2	60.4	6.4
AD-559374.2	38.3	12.3
AD-559060.2	67.7	4.4
AD-559721.2	38.6	7.2
AD-559026.2	69.5	22.8
AD-558225.2	58.7	12.7
AD-557069.2	74.2	20.7
AD-558068.2	56.4	18.2
AD-557422.2	92.5	10.5
AD-558063.2	91.9	26.6
AD-558066.2	62.3	8.2
AD-556701.2	58.4	3.2

Example 5. Design and Synthesis of Additional dsRNA Duplexes

Additional siRNAs were designed, synthesized and annealed using methods known in the art and described above in Example 1.

Detailed lists of the additional unmodified CFB sense and antisense strand nucleotide sequences are shown in Table 19. Detailed lists of the modified CFB sense and antisense strand nucleotide sequences are shown in Table 20.

In vitro and *in vivo* single dose screens of these agents in HepG2 cells were performed as described in the Examples above. Briely, HepG2 cells were transfected by adding 5 µl of Opti-MEM plus 0.25 µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5 µl of each siRNA duplex to an individual well in a 96-well plate. The mixture was then incubated at room temperature for 15 minutes. Forty µl of Eagle's Minimum Essential Medium (ATCC Cat#30-2003) containing ~2 $x10^4$ HepG2 cells were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Single dose experiments were performed at 10 nM. The assays were performed as quadruplicates.

The results of the single dose screens of the dsRNA agents listed in Tables 19 and 20 in HepG2 cells are shown in Table 21. The results are presented as the mean percentage of message remaining.

Table 19. Unmodified Sense and Antisense Strand Sequences of Complement Factor B dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antiense Sequence 5' to 3'	SEQ ID NO:	Start site in NM_001710.5	End site in NM_001710.5	Region	Exon
AD-558312	AAGGGAAUGUGACCAGGUCUU	1029	AAGACCUGGUCACAUUCCCUUCC	1121	153	175	5'UTR	1
AD-558336	CUGGAGUUUCAGCUUGGACAU	43	AUGUCCAAGCUGAAACUCCAGAC	129	177	199	5'UTR	1
AD-558361	CCAAGCAGACAAGCAAAGCAU	1030	AUGCUUUGCUUGUCUGCUUGGCU	1122	202	224	5'UTR	1
AD-558382	GCCAGGACACACCAUCCUGCU	1031	AGCAGGAUGGUGUGUCCUGGCUU	1123	223	245	5'UTR	1
AD-558389	CCAGCUUCUCUCCUGCCUUCU	1032	AGAAGGCAGGAGAGAAGCUGGGC	1124	250	272	5'UTR	1
AD-558407	UGCCUGAUGCCCUUUAUCUUU	1033	AAAGAUAAAGGGCAUCAGGCAGA	1125	304	326	CDS	1
AD-558426	UGGGCCUCUUGUCUGGAGGUU	1034	AACCUCCAGACAAGAGGCCCAAG	1126	323	345	CDS	1-2
AD-558450	CCACCACUCCAUGGUCUUUGU	1035	ACAAAGACCAUGGAGUGGUGGUC	1127	347	369	CDS	2
AD-558482	UCCUUCCGACUUCUCCAAGAU	1036	AUCUUGGAGAAGUCGGAAGGAGC	1128	418	440	CDS	2
AD-558507	AGGCACUGGAGUACGUGUGUU	1037	AACACACGUACUCCAGUGCCUGG	1129	443	465	CDS	2
AD-558522	UGUGUCCUUCUGGCUUCUACU	1038	AGUAGAAGCCAGAAGGACACACG	1130	458	480	CDS	2
AD-558539	UACCCGUACCCUGUGCAGACU	1039	AGUCUGCACAGGGUACGGGUAGA	1131	475	497	CDS	2
AD-558555	AGACACGUACCUGCAGAUCUU	1040	AAGAUCUGCAGGUACGUGUCUGC	1132	491	513	CDS	2
AD-558579	AGACUCAAGACCAAAAGACUU	1041	AAGUCUUUUGGUCUUGAGUCUUC	1133	533	555	CDS	2
AD-558612	AGUGCAGAGCAAUCCACUGUU	1042	AACAGUGGAUUGCUCUGCACUCU	1134	566	588	CDS	2-3
AD-558637	ACCACACGACUUCGAGAACGU	1043	ACGUUCUCGAAGUCGUGUGGUCU	1135	591	613	CDS	3
AD-558646	CCUACUACAAUGUGAGUGAUU	1044	AAUCACUCACAUUGUAGUAGGGA	1136	632	654	CDS	3
AD-558662	UGAUGAGAUCUCUUUCCACUU	1045	AAGUGGAAAGAGAUCUCAUCACU	1137	648	670	CDS	3
AD-558679	ACUGCUAUGACGGUUACACUU	52	AAGUGUAACCGUCAUAGCAGUGG	138	665	687	CDS	3
AD-558701	CACCUGCCAAGUGAAUGGCCU	1046	AGGCCAUUCACUUGGCAGGUGCG	1138	705	727	CDS	3
AD-558737	AGCGAUCUGUGACAACGGAGU	66	ACUCCGUUGUCACAGAUCGCUGU	1139	741	763	CDS	3-4
AD-558747	CAUUGGCACAAGGAAGGUGGU	1047	ACCACCUUCCUUGUGCCAAUGGG	1140	789	811	CDS	4
AD-558778	CGCCUUGAAGACAGCGUCACU	1048	AGUGACGCUGUCUUCAAGGCGGU	1141	820	842	CDS	4
AD-558813	GGCGAACGUGUCAGGAAGGUU	1049	AACCUUCCUGACACGUUCGCCGC	1142	881	903	CDS	4
AD-558859	CUGCCAAGACUCCUUCAUGUU	1050	AACAUGAAGGAGUCUUGGCAGGA	1143	927	949	CDS	4-5
AD-558879	GCCGAAGCUUUCCUGUCUUCU	1051	AGAAGACAGGAAAGCUUCGGCCA	1144	967	989	CDS	5
AD-558896	UUCCCUGACAGAGACCAUAGU	1052	ACUAUGGUCUCUGUCAGGGAAGA	1145	984	1006	CDS	5
AD-558918	GGAGUCGAUGCUGAGGAUGGU	1053	ACCAUCCUCAGCAUCGACUCCUU	1146	1006	1028	CDS	5
AD-558935	CAACAGAAGCGGAAGAUCGUU	1054	AACGAUCUUCCGCUUCUGUUGUU	1147	1042	1064	CDS	6
AD-558965	UCAGGCUCCAUGAACAUCUAU	471	AUAGAUGUUCAUGGAGCCUGAAG	542	1072	1094	CDS	6
AD-558993	UAGAUGGAUCAGACAGCAUUU	1055	AAAUGCUGUCUGAUCCAUCUAGC	1148	1100	1122	CDS	6
AD-558998	GCCAGCAACUUCACAGGAGCU	1056	AGCUCCUGUGAAGUUGCUGGCCC	1149	1123	1145	CDS	6

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antiense Sequence 5' to 3'	SEQ ID NO:	Start site in NM_0017 10.5	End site in NM_0017 10.5	Region	Exon
AD-559023	AGUGUCUAGUCAACUUAAUUU	489	AAAUUAAGUUGACUAGACACUUU	560	1148	1170	CDS	6
AD-559040	AUUGAGAAGGUGGCAAGUUAU	1057	AUAACUUGCCACCUUCUCAAUUA	1150	1165	1187	CDS	6-7
AD-559059	AUGGUGUGAAGCCAAGAUAUU	513	AAUAUCUUGGCUUCACACCAUAA	584	1184	1206	CDS	7
AD-559074	GAUAUGGUCUAGUGACAUAUU	495	AAUAUGUCACUAGACCAUAUCUU	566	1199	1221	CDS	7
AD-559089	AUUUGGGUCAAAGUGUCUGAU	1058	AUCAGACACUUUGACCCAAAUUU	1151	1234	1256	CDS	7
AD-559112	AGACAGCAGUAAUGCAGACUU	1059	AAGUCUGCAUUACUGCUGUCUGC	1152	1257	1279	CDS	7
AD-559143	CAGCUCAAUGAAAUCAAUUAU	478	AUAAUUGAUUUCAUUGAGCUGCU	549	1288	1310	CDS	7
AD-559163	GAAGACCACAAGUUGAAGUCU	1060	AGACUUCAACUUGUGGUCUUCAU	1153	1309	1331	CDS	7-8
AD-559184	GGGACUAACACCAAGAAGGCU	1061	AGCCUUCUUGGUGUUAGUCCCUG	1154	1330	1352	CDS	8
AD-559208	CAGGCAGUGUACAGCAUGAUU	1062	AAUCAUGCUGUACACUGCCUGGA	1155	1354	1376	CDS	8
AD-559233	GGCCAGAUGACGUCCCUCCUU	1063	AAGGAGGGACGUCAUCUGGCCAG	1156	1379	1401	CDS	8
AD-559274	UGUCAUCAUCCUCAUGACUGU	1064	ACAGUCAUGAGGAUGAUGACAUG	1157	1422	1444	CDS	8
AD-559290	ACUGAUGGAUUGCACAACAUU	1065	AAUGUUGUGCAAUCCAUCAGUCA	1158	1438	1460	CDS	8-9
AD-559306	UUACUGUCAUUGAUGAGAUCU	1066	AGAUCUCAUCAAUGACAGUAAUU	1159	1472	1494	CDS	9
AD-559329	GACUUGCUAUACAUUGGCAAU	1067	AUUGCCAAUGUAUAGCAAGUCCC	1160	1495	1517	CDS	9
AD-559359	AACCCAAGGGAGGAUUAUCUU	486	AAGAUAAUCCUCCCUUGGGUUUU	557	1525	1547	CDS	9
AD-559374	UAUCUGGAUGUCUAUGUGUUU	479	AAACACAUAGACAUCCAGAUAAU	550	1540	1562	CDS	9-10
AD-559383	GGGCCUUUGGUGAACCAAGUU	1068	AACUUGGUUCACCAAAGGCCCGA	1161	1567	1589	CDS	10
AD-559398	CAAGUGAACAUCAAUGCUUUU	491	AAAAGCAUUGAUGUUCACUUGGU	562	1582	1604	CDS	10
AD-559421	UUCCAAGAAAGACAAUGAGCU	45	AGCUCAUUGUCUUUCUUGGAAGC	1162	1605	1627	CDS	10
AD-559438	AGCAACAUGUGUUCAAAGUCU	1069	AGACUUUGAACACAUGUUGCUCA	1163	1622	1644	CDS	10
AD-559455	GUCAAGGAUAUGGAAAACCUU	1070	AAGGUUUUCCCAUAUCCUUGACUU	1164	1639	1661	CDS	10
AD-559476	GAAGAUGUUUUCUACCAAAUU	1071	AAUUUGGUAGAAAACAUCUUCCA	1165	1660	1682	CDS	10
AD-559497	AUCGAUGAAAGCCAGUCUCUU	1072	AAGAGACUGGCUUUCAUCGAUCA	1166	1681	1703	CDS	10-11
AD-559512	UCUCUGAGUCUCUGUGGCAUU	1073	AAUGCCACAGAGACUCAGAGACU	1167	1696	1718	CDS	11
AD-559536	UGGGAACACAGGAAGGGUACU	1074	AGUACCCUUCCUGUGUUCCCAAA	1168	1720	1742	CDS	11
AD-559556	CGAUUACCACAAGCAACCAUU	1075	AAUGGUUGCUUGUGGUAAUCGGU	1169	1740	1762	CDS	11
AD-559590	UCAGUCAUUCGCCCUUCAAAU	1076	AUUUGAAGGGCGAAUGACUGAGA	1170	1774	1796	CDS	11-12
AD-559610	GGGACACGAGAGCUGUAUGGU	1077	ACCAUACAGCUCUCGUGUCCCUU	1171	1794	1816	CDS	12
AD-559616	GUGGUGUCUGAGUACUUUGUU	482	AACAAAGUACUCAGACACCACAG	553	1819	1841	CDS	12
AD-559641	CAGCAGCACAUUGUUUCACUU	1078	AAGUGAAACAAUGUGCUGCUGUC	1172	1844	1866	CDS	12

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antiense Sequence 5' to 3'	SEQ ID NO:	Start site in NM_0017 10.5	End site in NM_0017 10.5	Region	Exon
AD-559670	AAGGAACACUCAAUCAAGGUU	1079	AACCUUGAUUGAGUGUUCCUUGU	1173	1873	1895	CDS	12
AD-559704	UAGAAGUAGUCCUAUUUCACU	1080	AGUGAAAUAGGACUACUUCUAUC	1174	1925	1947	CDS	13
AD-559706	CAACUACAACAUUAAUGGGAU	1081	AUCCCAUUAAUGUUGUAGUUGGG	1175	1947	1969	CDS	13
AD-559722	AUUCCUGAAUUUUAUGACUAU	492	AUAGUCAUAAAAUUCAGGAAUUC	563	1981	2003	CDS	13
AD-559740	UAUGACGUUGCCCUGAUCAAU	1082	AUUGAUCAGGGCAACGUCAUAGU	1176	1999	2021	CDS	13
AD-559760	GCUCAAGAAUAAGCUGAAAUU	1083	AAUUUCAGCUUAUUCUUGAGCUU	1177	2019	2041	CDS	13
AD-559788	ACUAUCAGGCCCAUUUGUCUU	466	AAGACAAAUGGGCCUGAUAGUCU	537	2047	2069	CDS	13-14
AD-559799	AGGGAACAACUCGAGCUUUGU	36	ACAAAGCUCGAGUUGUUCCCUCG	122	2078	2100	CDS	14
AD-559823	UUCCUCCAACUACCACUUGCU	1084	AGCAAGUGGUAGUUGGAGGAAGC	1178	2102	2124	CDS	14
AD-559838	CUUGCCAGCAACAAAAGGAAU	1085	AUUCCUUUUGUUGCUGGCAAGUG	1179	2117	2139	CDS	14-15
AD-559873	CAGGAUAUCAAAGCUCUGUUU	1086	AAACAGAGCUUUGAUAUCCUGUG	1180	2152	2174	CDS	15
AD-559892	UUGUGUCUGAGGAGGAGAAAU	1087	AUUUCUCCUCCUCAGACACAAAC	1181	2171	2193	CDS	15
AD-559926	GGAGGUCUACAUCAAGAAUGU	1088	ACAUUCUUGAUGUAGACCUCCUU	1182	2205	2227	CDS	15
AD-559946	GUGAGAGAGAUGCUCAAUAUU	473	AAUAUUGAGCAUCUCUCUCACAG	544	2243	2265	CDS	16
AD-559958	GACAAAGUCAAGGACAUCUCU	37	AGAGAUGUCCUUGACUUUGUCAU	123	2275	2297	CDS	16
AD-559973	UCGGUUCCUUUGUACUGGAGU	1089	ACUCCAGUACAAAGGAACCGAGG	1183	2310	2332	CDS	16
AD-559993	GAGUGAGUCCCUAUGCUGACU	1090	AGUCAGCAUAGGGACUCACUCCU	1184	2330	2352	CDS	16
AD-559998	UACUUGCAGAGGUGAUUCUGU	1091	ACAGAAUCACCUCUGCAAGUAUU	1185	2355	2377	CDS	16-17
AD-560011	AGUUCACAAGAGAAGUCGUUU	27	AAACGACUUCUCUUGUGAACUAU	113	2388	2410	CDS	17
AD-560031	UCAUUCAAGUUGGUGUAAUCU	1092	AGAUUACACCAACUUGAAUGAAA	1186	2408	2430	CDS	17-18
AD-560040	GAGUAGUGGAUGUCUGCAAAU	1093	AUUUGCAGACAUCCACUACUCCC	1187	2435	2457	CDS	18
AD-560060	AACCAGAAGCGGCAAAAGCAU	1094	AUGCUUUUGCCGCUUCUGGUUUU	1188	2455	2477	CDS	18
AD-560099	GACUUUCACAUCAACCUCUUU	1095	AAAGAGGUUGAUGUGAAAGUCUC	1189	2494	2516	CDS	18
AD-560114	CUCUUUCAAGUGCUGCCCUGU	1096	ACAGGGCAGCACUUGAAAGAGGU	1190	2509	2531	CDS	18
AD-560138	AAGGAGAAAACUCCAAGAUGAU	1097	AUCAUCUUGGAGUUUCUCCUUCA	1191	2533	2555	CDS	18
AD-560156	GAGGAUUUGGGUUUUCUAUAU	1098	AUAUAGAAAACCCAAAUCCUCAU	1192	2551	2573	CDS	18
AD-560163	CGUGGGAUUGAAUUAAAACAU	506	AUGUUUUAAUUCAAUCCCACGCC	577	2594	2616	3'UTR	18
AD-558378	GCAAGCCAGGACACACCAUCU	1099	AGAUGGUGUGUCCUGGCUUGCUU	1193	219	241		
AD-558393	CUUCUCUCCCUGCCUUCCAACU	1100	AGUUGGAAGGCAGGAGAGAAGCU	1194	254	276		

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antiense Sequence 5' to 3'	SEQ ID NO:	Start site in NM_0017 10.5	End site in NM_0017 10.5	Region	Exon
AD-558424	CUUGGGCCUCUUGUCUGGAGU	1101	ACUCCAGACAAGAGGCCCAAGAU	1195	321	343		
AD-558466	AGAGAUCAAAGGCGGCUCCUU	1102	AAGGAGCCGCCUUUGAUCUCUAC	1196	402	424		
AD-558511	ACUGGAGUACGUGUGUCCUUU	1103	AAAGGACACACGUACUCCAGUGC	1197	447	469		
AD-558574	CCUGAAGACUCAAGACCAAAU	1104	AUUUGGUCUUGAGUCUUCAGGGU	1198	528	550		
AD-558595	GACUGUCAGGAAGGCAGAGUU	1105	AACUCUGCCUUCCUGACAGUCUU	1199	549	571		
AD-558750	UGGCACAAGGAAGGUGGGCAU	1106	AUGCCCACCUUCCUUGUGCCAAU	1200	792	814		
AD-558777	CCGCCUUGAAGACAGCGUCAU	1107	AUGACGCUGUCUUCAAGGCGGUA	1201	819	841		
AD-559105	CUGAAGCAGACAGCAGUAAUU	1108	AAUUACUGCUGUCUGCUUCAGAC	1202	1250	1272		
AD-559124	UGCAGACUGGGUCACGAAGCU	1109	AGCUUCGUGACCCAGUCUGCAUU	1203	1269	1291		
AD-559189	UAACACCAAGAAGGCCCUCCU	1110	AGGAGGGCCUUCUUGGUGUUAGU	1204	1335	1357		
AD-559226	AUGAGCUGGCCAGAUGACGUU	1111	AACGUCAUCUGGCCAGCUCAUCA	1205	1372	1394		
AD-559330	ACUUGCUAUACAUUGGCAAGU	1112	ACUUGCCAAUGUAUAGCAAGUCC	1206	1496	1518		
AD-559486	UCUACCAAAUGAUCGAUGAAU	1113	AUUCAUCGAUCAUUUGGUAGAAA	1207	1670	1692		
AD-559532	GGUUUGGGAACACAGGAAGGU	1114	ACCUUCCUGUGUUCCCAAACCAU	1208	1716	1738		
AD-559573	CAUGGCAGGCCAAGAUCUCAU	1115	AUGAGAUCUUGGCCUGCCAUGGU	1209	1757	1779		
AD-559609	AGGGACACGAGAGCUGUAUGU	1116	ACAUACAGCUCUCGUGUCCCUUU	1210	1793	1815		
AD-559668	ACAAGGAACACUCAAUCAAGU	1117	ACUUGAUUGAGUGUUCCUUGUCA	1211	1871	1893		
AD-559688	AAGCGGGACCUGGAGAUAGAU	1118	AUCUAUCUCCAGGUCCCGCUUCU	1212	1909	1931		
AD-559882	AAAGCUCUGUUUGUGUCUGAU	1119	AUCAGACACAAACAGAGCUUUGA	1213	2161	2183		
AD-560132	UGGCUGAAGGAGAAACUCCAU	1120	AUGGAGUUUCUCCUUCAGCCAGG	1214	2527	2549		

Table 20. Modified Sense and Antisense Strand Sequences of Complement Factor B dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-558312	asasgggaAfuGfUfGfaccaggucuuL96	1215	asAfsgacCfuGfGfucacAfuUfcccuuscsc	1307	GGAAGGGAATGTGACCAGGTCTA	1406
AD-558336	csusggagUfuUfCfAfgcuuggacauL96	215	asUfsgucCfaAfGfcugaAfaCfuccagsasc	1308	GTCTGGAGTTTCAGCTTGGACAC	1407
AD-558361	cscsaagcAfgAfCfAfagcaaagcauL96	1216	asUfsgcuUfuGfCfuuguCfuGfcuuggscsu	1309	AGCCAAGCAGACAAGCAAAGCAA	1408
AD-558382	gscscaggAfcAfCfAfccauccugcuL96	1217	asGfscagGfaUfGfguguGfuCfcuggcsusu	1310	AAGCCAGGACACACCATCCTGCC	1409
AD-558389	cscsagcuUfcUfCfUfccugccuucuL96	1218	asGfsaagGfcAfGfgagaGfaAfgcuggsgsc	1311	GCCCAGCTTCTCTCCTGCCTTCC	1410
AD-558407	usgsccugAfuGfCfCfcuuuaucuuuL96	1219	asAfsagaUfaAfAfgggcAfuCfaggcasgsa	1312	TCTGCCTGATGCCCTTTATCTTG	1411
AD-558426	usgsggccUfcUfUfGfucuggagguuL96	1220	asAfsccuCfcAfGfacaaGfaGfgcccasasg	1313	CTTGGGCCTCTTGTCTGGAGGTG	1412

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-558450	cscsaccaCfuCfCfAfuggucuuuguL96	1221	asCfsaaaGfaCfCfauggAfgUfgguggsusc	1314	GACCACCACTCCATGGTCTTTGG	1413
AD-558482	uscscuucCfgAfCfUfucuccaagauL96	1222	asUfscuuGfgAfGfaaguCfgGfaaggasgsc	1315	GCTCCTTCCGACTTCTCCAAGAG	1414
AD-558507	asgsgcacUfgGfAfGfuacgugugguuL96	1223	asAfscacAfcGfUfacucCfaGfugccusgsg	1316	CCAGGCACTGGAGTACGTGTGTC	1415
AD-558522	usgsugucCfuUfCfUfggcuucuacuL96	1224	asGfsuagAfaGfCfcagaAfgGfacacascsg	1317	CGTGTGTCCTTCTGGCTTCTACC	1416
AD-558539	usascccgUfaCfCfCfugugcagacuL96	1225	asGfsucuGfcAfCfagggUfaCfggguasgsa	1318	TCTACCCGTACCCTGTGCAGACA	1417
AD-558555	asgsacacGfuAfCfCfugcagaucuuL96	1226	asAfsgauCfuGfCfagguAfcGfugucusgsc	1319	GCAGACACGTACCTGCAGATCTA	1418
AD-558579	asgsacucAfaGfAfCfcaaaagacuuL96	1227	asAfsgucUfuUfUfggucUfuGfagucususc	1320	GAAGACTCAAGACCAAAAGACTG	1419
AD-558612	asgsugcaGfaGfCfAfauccacuguuL96	1228	asAfscagUfgGfAfuugcUfcUfgcacuscsu	1321	AGAGTGCAGAGCAATCCACTGTC	1420
AD-558637	ascscacaCfgAfCfUfucgagaacguL96	1229	asCfsguuCfuCfGfaaguCfgUfgugguscsu	1322	AGACCACACGACTTCGAGAACGG	1421
AD-558646	cscsuacuAfcAfAfUfgugagugauuL96	1230	asAfsucaCfuCfAfcauuGfuAfguaggsgsa	1323	TCCCTACTACAATGTGAGTGATG	1422
AD-558662	usgsaugaGfaUfCfUfcuuuccacuuL96	1231	asAfsgugGfaAfAfgagaUfcUfcaucascsu	1324	AGTGATGAGATCTCTTTCCACTG	1423
AD-558679	ascsugcuAfuGfAfCfgguuacacuuL96	224	asAfsgugUfaAfCfcgucAfuAfgcagusgsg	1325	CCACTGCTATGACGGTTACACTC	1424
AD-558701	csasccugCfcAfAfGfugaauggccuL96	1232	asGfsgccAfuUfCfacuuGfgCfaggugscsg	1326	CGCACCTGCCAAGTGAATGGCCG	1425
AD-558737	asgscgauCfuGfUfGfacaacggaguL96	238	asCfsuccGfuUfGfucacAfgAfucgcusgsu	1327	ACAGCGATCTGTGACAACGGAGC	1426
AD-558747	csasuuggCfaCfAfAfggaaggugguL96	1233	asCfscacCfuUfCfcuugUfgCfcaaugsgsg	1328	CCCATTGGCACAAGGAAGGTGGG	1427
AD-558778	csgsccuuGfaAfGfAfcagcgucacuL96	1234	asGfsugaCfgCfUfgucuUfcAfaggcgsgsu	1329	ACCGCCTTGAAGACAGCGTCACC	1428
AD-558813	gsgscgaaCfgUfGfUfcaggaagguuL96	1235	asAfsccuUfcCfUfgacaCfgUfucgccsgsc	1330	GCGGCGAACGTGTCAGGAAGGTG	1429
AD-558859	csusgccaAfgAfCfUfccuucauguuL96	1236	asAfscauGfaAfGfgaguCfuUfggcagsgsa	1331	TCCTGCCAAGACTCCTTCATGTA	1430
AD-558879	gscscgaaGfcUfUfUfccugucuucuL96	1237	asGfsaagAfcAfGfgaaaGfcUfucggcscsa	1332	TGGCCGAAGCTTTCCTGTCTTCC	1431
AD-558896	ususcccuGfaCfAfGfagaccauaguL96	1238	asCfsuauGfgUfCfucugUfcAfgggaasgsa	1333	TCTTCCCTGACAGAGACCATAGA	1432
AD-558918	gsgsagucGfaUfGfCfugaggaugguL96	1239	asCfscauCfcUfCfagcaUfcGfacuccsusu	1334	AAGGAGTCGATGCTGAGGATGGG	1433
AD-558935	csasacagAfaGfCfCfgfgaagaucguuL96	1240	asAfscgaUfcUfUfccgcUfuCfuguugsusu	1335	AACAACAGAAGCGGAAGATCGTC	1434
AD-558965	uscsaggcUfcCfAfUfgaacaucuauL96	613	asUfsagaUfgUfUfcaugGfaGfccugasasg	684	CTTCAGGCTCCATGAACATCTAC	1435
AD-558993	usasgaugGfaUfCfAfgacagcauuuL96	1241	asAfsaugCfuGfUfcugaUfcCfaucuasgsc	1336	GCTAGATGGATCAGACAGCATTG	1436
AD-558998	gscscagcAfaCfUfUfcacaggagcuL96	1242	asGfscucCfuGfUfgaagUfuGfcuggcscsc	1337	GGGCCAGCAACTTCACAGGAGCC	1437
AD-559023	asgsugucUfaGfUfCfaacuuaauuuL96	631	asAfsauuAfaGfUfugacUfaGfacacususu	702	AAAGTGTCTAGTCAACTTAATTG	1438
AD-559040	asusugagAfaGfGfUfggcaaguuauL96	1243	asUfsaacUfuGfCfcaccUfuCfucaaususa	1338	TAATTGAGAAGGTGGCAAGTTAT	1439
AD-559059	asusggugUfgAfAfGfccaagauauuL96	655	asAfsuauCfuUfGfgcuuCfaCfaccausasa	726	TTATGGTGTGAAGCCAAGATATG	1440
AD-559074	gsasuaugGfuCfUfAfgugacauauuL96	637	asAfsuauGfuCfAfcuagAfcCfauaucsusu	708	AAGATATGGTCTAGTGACATATG	1441
AD-559089	asusuuggGfuCfAfAfagugucugauL96	1244	asUfscagAfcAfCfuuugAfcCfcaaaususu	1339	AAATTTGGGTCAAAGTGTCTGAA	1442
AD-559112	asgsacagCfaGfUfAfaugcagacuuL96	1245	asAfsgucUfgCfAfuuacUfgCfugucusgsc	1340	GCAGACAGCAGTAATGCAGACTG	1443
AD-559143	csasgcucAfaUfGfAfaaucaauuauL96	620	asUfsaauUfgAfUfuucaUfuGfagcugscsu	691	AGCAGCTCAATGAAATCAATTAT	1444
AD-559163	gsasagacCfaCfAfAfguugaagucuL96	1246	asGfsacuUfcAfAfcuugUfgGfucuucsasu	1341	ATGAAGACCACAAGTTGAAGTCA	1445
AD-559184	gsgsgacuAfaCfAfCfcaagaaggcuL96	1247	asGfsccuUfcUfUfggugUfuAfgucccsusg	1342	CAGGGACTAACACCAAGAAGGCC	1446

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-559208	csasggcaGfuGfUfAfcagcaugauuL96	1248	asAfsucaUfgCfUfguacAfcUfgccugsgsa	1343	TCCAGGCAGTGTACAGCATGATG	1447
AD-559233	gsgsccagAfuGfAfCfgucccuccuuL96	1249	asAfsggaGfgGfAfcgucAfuCfuggccsasg	1344	CTGGCCAGATGACGTCCCTCCTG	1448
AD-559274	usgsucauCfaUfCfCfucaugacuguL96	1250	asCfsaguCfaUfGfaggaUfgAfugacasusg	1345	CATGTCATCATCCTCATGACTGA	1449
AD-559290	ascsugauGfgAfUfUfgcacaacauuL96	1251	asAfsuguUfgUfGfcaauCfcAfucaguscsa	1346	TGACTGATGGATTGCACAACATG	1450
AD-559306	ususacugUfcAfUfUfgaugagaucuL96	1252	asGfsaucUfcAfUfcaauGfaCfaguaasusu	1347	AATTACTGTCATTGATGAGATCC	1451
AD-559329	gsascuugCfuAfUfAfcauuggcaauL96	1253	asUfsugcCfaAfUfguauAfgCfaagucscsc	1348	GGGACTTGCTATACATTGGCAAG	1452
AD-559359	asascccaAfgGfGfAfggauuaucuuL96	628	asAfsgauAfaUfCfcuccCfuUfggguususu	699	AAAACCCAAGGGAGGATTATCTG	1453
AD-559374	usasucugGfaUfGfUfcuauguguuuL96	621	asAfsacaCfaUfAfgacaUfcCfagauasasu	692	ATTATCTGGATGTCTATGTGTTT	1454
AD-559383	gsgsgccuUfuGfGfUfgaaccaaguuL96	1254	asAfscuuGfgUfUfcaccAfaAfggcccsgsa	1349	TCGGGCCTTTGGTGAACCAAGTG	1455
AD-559398	csasagugAfaCfAfUfcaaugcuuuuL96	633	asAfsaagCfaUfUfgaugUfuCfacuugsgsu	704	ACCAAGTGAACATCAATGCTTTG	1456
AD-559421	ususccaaGfaAfAfGfacaaugagcuL96	217	asGfscucAfuUfGfucuuUfcUfuggaasgsc	1350	GCTTCCAAGAAAGACAATGAGCA	1457
AD-559438	asgscaacAfuGfUfGfuucaaagucuL96	1255	asGfsacuUfuGfAfacacAfuGfuugcuscsa	1351	TGAGCAACATGTGTTCAAAGTCA	1458
AD-559455	gsuscaagGfaUfAfUfggaaaaccuuL96	1256	asAfsgguUfuUfCfcauaUfcCfuugacsusu	1352	AAGTCAAGGATATGGAAAACCTG	1459
AD-559476	gsasagauGfuUfUfUfcuaccaaauuL96	1257	asAfsuuuGfgUfAfgaaaAfcAfucuucscsa	1353	TGGAAGATGTTTTCTACCAAATG	1460
AD-559497	asuscgauGfaAfAfGfccagucucuuL96	1258	asAfsgagAfcUfGfgcuuUfcAfucgauscsa	1354	TGATCGATGAAAGCCAGTCTCTG	1461
AD-559512	uscsucugAfgUfCfUfcuguggcauuL96	1259	asAfsugcCfaCfAfgagaCfuCfagagascsu	1355	AGTCTCTGAGTCTCTGTGGCATG	1462
AD-559536	usgsggaaCfaCfAfGfgaaggguacuL96	1260	asGfsuacCfcUfUfccugUfgUfucccasasa	1356	TTTGGGAACACAGGAAGGGTACC	1463
AD-559556	csgsauuaCfcAfCfAfagcaaccauuL96	1261	asAfsuggUfuGfCfuuguGfgUfaaucgsgsu	1357	ACCGATTACCACAAGCAACCATG	1464
AD-559590	uscsagucAfuUfCfGfcccuucaaauL96	1262	asUfsuugAfaGfGfgcgaAfuGfacugasgsa	1358	TCTCAGTCATTCGCCCTTCAAAG	1465
AD-559610	gsgsgacaCfgAfGfAfgcuguaugguL96	1263	asCfscauAfcAfGfcucuCfgUfgucccsusu	1359	AAGGGACACGAGAGCTGTATGGG	1466
AD-559616	gsusggugUfcUfGfAfguacuuuguuL96	624	asAfscaaAfgUfAfcucaGfaCfaccacsasg	695	CTGTGGTGTCTGAGTACTTTGTG	1467
AD-559641	csasgcagCfaCfAfUfuguuucacuuL96	1264	asAfsgugAfaAfCfaaugUfgCfugcugsusc	1360	GACAGCAGCACATTGTTTCACTG	1468
AD-559670	asasggaaCfaCfUfCfaaucaagguuL96	1265	asAfsccuUfgAfUfugagUfgUfuccuusgsu	1361	ACAAGGAACACTCAATCAAGGTC	1469
AD-559704	usasgaagUfaGfUfCfcuauuucacuL96	1266	asGfsugaAfaUfAfggacUfaCfuucuasusc	1362	GATAGAAGTAGTCCTATTTCACC	1470
AD-559706	csasacuaCfaAfCfAfuuaaugggauL96	1267	asUfscccAfuUfAfauguUfgUfaguugsgsg	1363	CCCAACTACAACATTAATGGGAA	1471
AD-559722	asusuccuGfaAfUfUfuuaugacuauL96	634	asUfsaguCfaUfAfaaauUfcAfggaaususc	705	GAATTCCTGAATTTTATGACTAT	1472
AD-559740	usasugacGfuUfGfCfccugaucaauL96	1268	asUfsugaUfcAfGfggcaAfcGfucauasgsu	1364	ACTATGACGTTGCCCTGATCAAG	1473
AD-559760	gscsucaaGfaAfUfAfagcugaaauuL96	1269	asAfsuuuCfaGfCfuuauUfcUfugagcsusu	1365	AAGCTCAAGAATAAGCTGAAATA	1474
AD-559788	ascsuaucAfgGfCfCfcauuugucuuL96	608	asAfsgacAfaAfUfgggcCfuGfauagucscsu	679	AGACTATCAGGCCCATTTGTCTC	1475
AD-559799	asgsggaaCfaAfCfUfcgagcuuuguL96	208	asCfsaaaGfcUfCfgaguUfgUfucccuscsg	1366	CGAGGGAACAACTCGAGCTTTGA	1476
AD-559823	ususccucCfaAfCfUfaccacuugcuL96	1270	asGfscaaGfuGfGfuaguUfgGfaggaasgsc	1367	GCTTCCTCCAACTACCACTTGCC	1477
AD-559838	csusugccAfgCfAfAfcaaaggaauL96	1271	asUfsuccUfuUfUfguugCfuGfgcaagsusg	1368	CACTTGCCAGCAACAAAAGGAAG	1478
AD-559873	csasggauAfuCfAfAfagcucuguuuL96	1272	asAfsacaGfaGfCfuuugAfuAfuccugsusg	1369	CACAGGATATCAAAGCTCTGTTT	1479
AD-559892	ususguguCfuGfAfGfgaggagaaauL96	1273	asUfsuucUfcCfUfccucAfgAfcacaasasc	1370	GTTTGTGTCTGAGGAGGAGAAAA	1480

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-559926	gsgsagguCfuAfCfAfucaagaauguL96	1274	asCfsauuCfuUfGfauguAfgAfccuccsusu	1371	AAGGAGGTCTACATCAAGAATGG	1481
AD-559946	gsusgagaGfaGfAfUfgcucaauauuL96	615	asAfsuauUfgAfGfcaucUfcUfcucacsasg	686	CTGTGAGAGAGATGCTCAATATG	1482
AD-559958	gsascaaaGfuCfAfAfggacaucucuL96	209	asGfsagaUfgUfCfcuugAfcUfuugucsasu	1372	ATGACAAAGTCAAGGACATCTCA	1483
AD-559973	uscsgguuCfcUfUfUfguacuggaguL96	1275	asCfsuccAfgUfAfcaaaGfgAfaccgasgsg	1373	CCTCGGTTCCTTTGTACTGGAGG	1484
AD-559993	gsasgugaGfuCfCfCfuaugcugacuL96	1276	asGfsucaGfcAfUfagggAfcUfcacucscsu	1374	AGGAGTGAGTCCCTATGCTGACC	1485
AD-559998	usascuugCfaGfAfGfgugauucuguL96	1277	asCfsagaAfuCfAfccucUfgCfaaguasusu	1375	AATACTTGCAGAGGTGATTCTGG	1486
AD-560011	asgsuucaCfaAfGfAfgaagucguuuL96	199	asAfsacgAfcUfUfcucuUfgUfgaacusasu	1376	ATAGTTCACAAGAGAAGTCGTTT	1487
AD-560031	uscsauucAfaGfUfUfgguguaaucuL96	1278	asGfsauuAfcAfCfcaacUfuGfaaugasasa	1377	TTTCATTCAAGTTGGTGTAATCA	1488
AD-560040	gsasguagUfgGfAfUfgucugcaaauL96	1279	asUfsuugCfaGfAfcaucCfaCfuacucscsc	1378	GGGAGTAGTGGATGTCTGCAAAA	1489
AD-560060	asasccagAfaGfCfCfgfgcaaaagcauL96	1280	asUfsgcuUfuUfGfccgcUfuCfugguususu	1379	AAAACCAGAAGCGGCAAAAGCAG	1490
AD-560099	gsascuuuCfaCfAfUfcaaccucuuuL96	1281	asAfsagaGfgUfUfgaugUfgAfaagucsusc	1380	GAGACTTTCACATCAACCTCTTT	1491
AD-560114	csuscuuuCfaAfGfUfgcugcccuguL96	1282	asCfsaggGfcAfGfcacuUfgAfaagagsgsu	1381	ACCTCTTTCAAGTGCTGCCCTGG	1492
AD-560138	asasggagAfaAfCfUfccaagaugauL96	1283	asUfscauCfuUfGfgaguUfuCfuccuuscsa	1382	TGAAGGAGAAACTCCAAGATGAG	1493
AD-560156	gsasggauUfuGfGfGfuuuucuauauL96	1284	asUfsauaGfaAfAfacccAfaAfuccucsasu	1383	ATGAGGATTTGGGTTTTCTATAA	1494
AD-560163	csgsugggAfuUfGfAfauuaaaacauL96	648	asUfsguuUfuAfAfuucaAfuCfccacgscsc	719	GGCGTGGGATTGAATTAAAACAG	1495
AD-558378	gscsaagcCfaGfGfAfcacaccaucuL96	1285	asGfsaugGfuGfUfguccUfgGfcuugcsusu	1384	AAGCAAGCCAGGACACACCAUCC	1496
AD-558393	csusucucUfcCfUfGfccuuccaacuL96	1286	asGfsuugGfaAfGfgcagGfaGfagaagscsu	1385	AGCUUCUCUCCUGCCUUCCAACG	1497
AD-558424	csusugggCfcUfCfUfugucuggaguL96	1287	asCfsuccAfgAfCfaagaGfgCfccaagsasu	1386	AUCUUGGGCCUCUUGUCUGGAGG	1498
AD-558466	asgsagauCfaAfAfGfgcggcuccuuL96	1288	asAfsggaGfcCfGfccuuUfgAfucucusasc	1387	GUAGAGAUCAAAGGCGGCUCCUU	1499
AD-558511	ascsuggaGfuAfCfGfuguguccuuuL96	1289	asAfsaggAfcAfCfacguAfcUfccagusgsc	1388	GCACUGGAGUACGUGUGUCCUUC	1500
AD-558574	cscsugaaGfaCfUfCfaagaccaaauL96	1290	asUfsuugGfuCfUfugagUfcUfucaggsgsu	1389	ACCCUGAAGACUCAAGACCAAAA	1501
AD-558595	gsascuguCfaGfGfAfaggcagaguuL96	1291	asAfscucUfgCfCfuuccUfgAfcagucsusu	1390	AAGACUGUCAGGAAGGCAGAGUG	1502
AD-558750	usgsgcacAfaGfGfAfaggugggcauL96	1292	asUfsgccCfaCfCfuuccUfuGfugccasasu	1391	AUUGGCACAAGGAAGGUGGGCAG	1503
AD-558777	cscsgccuUfgAfAfGfacagcgucauL96	1293	asUfsgacGfcUfGfucuuCfaAfggcggsusa	1392	UACCGCCUUGAAGACAGCGUCAC	1504
AD-559105	csusgaagCfaGfAfCfagcaguaauuL96	1294	asAfsuuaCfuGfCfugucUfgCfuucagsasc	1393	GUCUGAAGCAGACAGCAGUAAUG	1505
AD-559124	usgscagaCfuGfGfGfucacgaagcuL96	1295	asGfscuuCfgUfGfacccAfgUfcugcasusu	1394	AAUGCAGACUGGGUCACGAAGCA	1506
AD-559189	usasacacCfaAfGfAfaggcccuccuL96	1296	asGfsgagGfgCfCfuucuUfgGfuguuasgsu	1395	ACUAACACCAAGAAGGCCCUCCA	1507
AD-559226	asusgagcUfgGfCfCfagaugacguuL96	1297	asAfscguCfaUfCfuggcCfaGfcucauscsa	1396	UGAUGAGCUGGCCAGAUGACGUC	1508
AD-559330	ascsuugcUfaUfAfCfauuggcaaguL96	1298	asCfsuugCfcAfAfuguaUfaGfcaaguscsc	1397	GGACUUGCUAUACAUUGGCAAGG	1509
AD-559486	uscsuaccAfaAfUfGfaucgaugaauL96	1299	asUfsucaUfcGfAfucauUfuGfguagasasa	1398	UUUCUACCAAAUGAUCGAUGAAA	1510
AD-559532	gsgsuuugGfgAfAfCfacaggaagguL96	1300	asCfscuuCfcUfGfuguuCfcCfaaaccsasu	1399	AUGGUUUGGGAACACAGGAAGGG	1511
AD-559573	csasuggcAfgGfCfCfaagaucucauL96	1301	asUfsgagAfuCfUfuggcCfuGfccaugsgsu	1400	ACCAUGGCAGGCCAAGAUCUCAG	1512
AD-559609	asgsggacAfcGfAfGfagcuguauguL96	1302	asCfsauaCfaGfCfucucGfuGfucccususu	1401	AAAGGGACACGAGAGCUGUAUGG	1513
AD-559668	ascsaaggAfaCfAfCfucaaucaaguL96	1303	asCfsuugAfuUfGfagugUfuCfcuuguscsa	1402	UGACAAGGAACACUCAAUCAAGG	1514

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-559688	asasgcggGfaCfCfUfggagauagauL96	1304	asUfscuaUfcUfCfcaggUfcCfcgcuuscsu	1403	AGAAGCGGGACCUGGAGAUAGAA	1515
AD-559882	asasagcuCfuGfUfUfugugucugauL96	1305	asUfscagAfcAfCfaaacAfgAfgcuuusgsa	1404	UCAAAGCUCUGUUUGUGUCUGAG	1516
AD-560132	usgsgcugAfaGfGfAfgaaacuccauL96	1306	asUfsggaGfuUfUfcuccUfuCfagccasgsg	1405	CCUGGCUGAAGGAGAAACUCCAA	1517

Table 21. In Vitro Single Dose Screen in HepG2 cells

Duplex Name	CFB/gapdh		
	10 nM		
	% average message remaining	SD	Target region in NM_001710.5
AD-560132.1	9.927	1.092	2527-2549
AD-560099.1	9.213	1.335	2494-2516
AD-559998.1	11.297	1.165	2355-2377
AD-559993.1	11.852	1.080	2330-2352
AD-559973.1	53.866	5.431	2310-2332
AD-559882.1	10.290	1.623	2161-2183
AD-559706.1	11.537	1.805	1947-1969
AD-559704.1	15.239	3.563	1924-1947
AD-559688.1	38.443	9.924	1909-1931
AD-559668.1	10.169	0.593	1871-1893
AD-559641.1	29.195	3.820	1844-1866
AD-559609.1	88.678	6.099	1793-1815
AD-559590.1	35.152	4.022	1774-1796
AD-559573.1	38.212	6.701	1757-1779
AD-559532.1	74.766	13.877	1716-1738
AD-559486.1	24.644	9.120	1670-1692
AD-559330.1	95.265	4.050	1496-1518
AD-559274.1	13.751	2.733	1422-1444
AD-559226.1	102.524	5.658	1372-1394
AD-559208.1	16.066	2.069	1354-1376
AD-559189.1	16.100	2.031	1335-1357
AD-559124.1	15.423	2.069	1269-1291
AD-559105.1	9.673	1.193	1250-1272
AD-559089.1	10.663	2.329	1234-1256
AD-558935.1	13.757	1.222	1042-1064
AD-558879.1	14.752	3.406	967-989
AD-558777.1	14.623	2.074	819-841
AD-558750.1	16.390	2.306	792-814
AD-558637.1	24.702	7.767	591-613
AD-558612.1	12.506	1.594	566-588
AD-558595.1	11.413	1.630	549-571
AD-558574.1	12.253	1.051	528-550
AD-558555.1	12.550	1.821	491-513
AD-558511.1	10.434	4.050	447-469
AD-558482.1	47.746	10.594	418-440
AD-558466.1	17.794	3.389	402-424
AD-558450.1	11.521	2.865	347-369
AD-558424.1	23.751	5.256	321-343
AD-558407.1	14.394	1.584	304-326
AD-558393.1	14.017	1.825	254-276

Duplex Name	CFB/gapdh		
	10 nM		
	% average message remaining	SD	Target region in NM_001710.5
AD-558378.1	18.296	0.945	219-241
AD-558361.1	15.926	1.921	202-224
AD-558312.1	27.703	7.359	153-175

Example 6. Combinations of dsRNA agents targeting combinations of complement components

In order to determine whether hemolytic activity can be strongly suppressed using a combination of a dsRNA agent targeting complement component C3 (C3) and a dsRNA agent targeting complement component C5 (C5) or a dsRNA agent targeting complement component factor B (CFB) as compared to use of a single dsRNA targeting C3, C5, or CFB alone, *in vitro* double reconstitution studies were performed.

Briefly, *in vitro* complement combination modeling was conducted using sera depleted of two complement components and adding individual proteins back at various concentrations. All reagents were purchased from Complement Technology (Tyler, Texas), unless otherwise stated. An Alternative Hemolysis (AH) assay was performed by reconstituting C3 and CFB Complement component depleted human sera with a range of concentrations of C3 and CFB protein. Ten percent reconstituted serum was added to GVBE and 5 mM MgEGTA with 25% rabbit erythrocytes (Er). Samples were incubated at 37°C for one hour, with shaking. Hemolysis was stopped with addition of GVBE at a 1:1 ratio to samples. Samples were centrifuged, supernatants were transferred, and absorbance measured at 541 nm. Hemolytic activity was calculated by subtracting negative control sample and normalizing to positive control samples, where negative control was buffer and Er only and positive control was water and Er only.

The results of dual targeting of C3 and CFB are depicted in Figure 2A. In particular, the hemolytic activity (alternative hemolysis, AH) in human sera depleted of C3 and CFB is shown as a heatmap with higher hemolysis levels being medium gray (top left corner, "normal range") and lower being darker gray. The concentration of C3 was plotted on the Y axis and the concentration of CFB on the X axis.

Normal levels of CFB and C3 yielded full hemolytic activity. Decreasing either C3 or CFB level decreased hemopytic activity. siRNA administration in non-humn promates showed that C3 levels could be suppressed to 200 µg/ml levels; a similar reduction is expected in human sera. Asumming 200 µg/ml as the initial level of C3, Figure 2A demosntrates that suppression of CFB to about 40 µg/ml (about 80% silencing) reduces hemolytic activity to levels below 10%. Therefore, dual targeting of C3 and CFB can achieve near-complete suppression of AH.

It should be noted that CFB suppression does not impact Classical Hemolysis (CH), therefore no combination data was generated for CH.

Figure 2B depicts the results of dual dose response of C3 and C5 in depleted serum reconstituted with varying levels of C3 and C5 and assayed for AH as described above. C3 was plotted on the Y-axis and C5 on the X-axis. Normal levels of both C3 and C5 produced high levels of hemolytic activity; decreasing C5 levels lowered the AH. A dose response for C3 was also observed. Although it is known that administration of a dsRNA agent targeting C5, cemdisiran, to human subjects can achieve C5 silencing down to the range of about 1 - 3 μg/ml, further decrease in hemolytic activity can be achieved by concurrently decreasing the level of C3 protein.

The effect of dual targeting C3 and C5 on classical hemolytic activity was also determined using a Classical Hemolysis (CH) assay. C3 and C5 depleted human sera was reconstituted with a range of concentrations of C3 and C5 proteins. Reconstituted serum (0.7%) was added to GVB^{++} with 13.4% antibody sensitized sheep erythrocytes (EA). Samples were incubated at 37°C for one hour, with shaking. Samples were centrifuged, supernatants were transferred, and absorbance measured at 541 nm Hemolytic activity was calculated by subtracting negative control sample and normalizing to positive control samples, where negative control was buffer and Er only and positive control was water and Er only.

Figure 2C depicts the results of C3 and C5 CH reconstitution experiments; it demonstrates that targeting both C3 and C5 resulted in benefit on CH. The observed effect of C3 suppression on CH activity when C5 is ≤ 3 μg/ml could not by resolved by determining the level of active C5b-9 formation to assess classical hemolysis activity using the Wieslab® Complement Classical Pathway (CCP) assay (Figure 2D). The CCP assay (Wieslab® COMPL CP310, IBL America) was conducted according to manufacturer's protocol. Briefly, in vitro complement combination modeling was conducted using sera depleted of two complement components and adding individual proteins back at various concentrations. C3 and C5 Complement component depleted human sera was reconstituted with a range of concentrations of C3 and C5 protein. Reconstituted depleted sera were diluted to a final sera concentration of 1:101. Samples were added to wells and incubated for 1 hour at 37°C. Plates were washed three times and then 100 μl of conjugate solution was added to each well. Plates were incubated for 30 minutes at room temperature then washed three times. Substrate solution (100 μl) was added to each well and incubated for 30 minutes at room temperature. Reaction was stopped with 100 μl of 5 mM EDTA and absorbance was read at 405 nm. Activity was calculated by subtracting blank control from all values and then normalizing to positive control.

The ability of a combination of a dsRNA agent targeting complement component C3 (C3) and a dsRNA agent targeting complement component C5 (C5) or complement component factor B (CFB) to further suppress hemolytic activity as compared to use of a single dsRNA targeting C3, C5, or CFB alone was also assessed *in vivo* in non-human primates (NHPs), cynomologus monkeys *(Macaca fascicularis)*.

Cynomologus monkeys were subcutaneously administered a single 6 mg/kg dose of a dsRNA agent targeting C3; or a dsRNA agent targeting CFB; or a dsRNA agent targeting C5; or a single 6

mg/kg dose of a dsRNA agent targeting C3 and 6 mg/kg dose of a dsRNA agent targeting CFB; or a single 6 mg/kg dose of a dsRNA agent targeting C3 and 6 mg/kg dose of a dsRNA agent targeting C5; or a single 6 mg/kg dose of a dsRNA agent targeting CFB and 6 mg/kg dose of a dsRNA agent targeting C5 on Day 1. The study design in depicted in the Table below.

Group	**Target(s)**	**Test Article**	**Dose Route**	**Dose (mg/kg)**	**Number of Male Animals**	**Dose Regimen**	**End of Study**
2	C3	AD-570714	SubQ	6	3	Day 1	Day 29
3	CFB	AD-560018	SubQ	6	3	Day 1	Day 29
4	C5	AD-61679	SubQ	6	3	Day 1	Day 29
5	C3 CFB	AD-570714 AD-560018	SubQ	6 6	3	Day 1	Day 29
6	C3 C5	AD-570714 AD-61679	SubQ	6 6	3	Day 1	Day 29
7	CFB C5	AD-560018 AD-61679	SubQ	6 6	3	Day 1	Day 29

On Day -6 , 1 pre-dose, and Days 8, 15, 22, and 29 post-dose, serum samples were obtained from the NHPs and the levels of C3, C5, and CFB protein and the alternative and classical hemolytic activities and the Wieslab® CAP and CCP activities were determined.

The level of C3 protein was determined by ELISA. Briefly, C3 protein was measured by a cynomolgus cross-reactive ELISA (C3 Human ELISA, Hycult HK366) according to the manufacturer's protocol. Serum was diluted by 1:40,000. C3 levels were normalized to individual animal's pre-dose levels to determine percent of C3 remaining.

The level of C5 protein was also determined by ELISA. Briefly, C5 was measured by a cynomolgus cross-reactive ELISA (Human Complement C5 ELISA Kit, Abcam ab125963) according to the manufacturer's protocol. Serum was diluted by 1:20,000 for pre-dose and day 8 samples and 1:5,000 for silenced samples days 12, 22, and 29. C5 levels were normalized to individual animal's pre-dose levels to determine % C5 remaining.

Serum CFB was measured at 1:20 dilution by quantitative analysis of western blot, using 4-12% Bis-Tris gels and imaged on Li-Cor Odyssey CLx. (1°: ProteinTech 10170-1-AP 1:50, 2°: Goat anti-Rabbit HRP).

The alternative and classical hemolytic activities were determined. The NHP alternative hemolysis was performed as briefly described. Serum (5.6%) was added to GVB° (Complement Technology, Tyler, Texas) and 5 mM MgEGTA with 25% rabbit erythrocytes (Er, Complement Technology, Tyler, Texas). Samples were incubated at 37°C for 1 hour, with shaking. Hemolysis was

stopped with addition of GVBE (Complement Technology, Tyler, Texas) at a 1:1 ratio to samples. Samples were centrifuged, supernatants were transferred, and absorbance measured at 541 nm. Hemolytic activity was calculated by subtracting negative control sample and normalizing to positive control samples, where negative control was buffer and Er only and positive control was water and Er only. Then individual animal samples were normalized to their average pre-dose samples. The NHP classical pathway hemolysis was preformed as briefly described. 1.77% serum was added to GVB++ (Complement Technology, Tyler, Texas) with 13.4% antibody sensitized sheep erythrocytes (EA, Complement Technology, Tyler, Texas). Samples were incubated at 37°C for 1 hour, with shaking. Samples were centrifuged, supernatants were transferred, and absorbance measured at 541 nm. Hemolytic activity was calculated by subtracting negative control sample and normalizing to positive control samples, where negative control was buffer and Er only and positive control was water and EA only. Then individual animal samples were normalized to their average pre-dose samples.

The level of active C5b-9 formation to assess alternative hemolysis activity and classical hemolysis activity was also determined using the Wieslab® Complement Classical Pathway (CCP) assay as described above and the Wieslab® Complement Alternative Pathway (CAP) assay. The CAP assay (COMPL AP330 RUO, IBL America) was conducted according to manufacturer's protocol. Sera were diluted to a final sera concentration of 1:18. Samples were added to wells and incubated for 1 hour at 37°C. Plates were washed 3 times and then 100 µl of conjugate solution was added to each well. Plates were incubated for 30 minutes at room temperature then washed 3 times. Substrate solution (100 µl) was added to each well and incubated for 30 minutes at room temperature. Reaction was stopped with 100 µl of 5mM EDTA and absorbance was read at 405 nm. Activity was calculated by subtracting blank control from all values and then normalizing to positive control. For both CAP and CCP activity values were then normalized to individual animals' average pre-dose.

The results of these assays are depicted in Figures 3A-3E. In particular, Figure 3A demonstrates that a single 6 mg/kg dose of a dsRNA agent targeting C3 suppressed C3 protein up to 90% (~110 µg/ml) in serum. As expected, silencing CFB with a dsRNA agent targeting CFB caused C3 protein levels to sligntly increase. Figure 3A also demonstrates that silencing C5 with a dsRNA agent targeting C5 left C3 protein levels unaffected and that neither a dsRNA agent targeting C3 nor a dsRNA agent targeting CFB affected C5 protein levels.

Figure 3B demonstrates that a single 6 mg/kg dose of a dsRNA agent targeting C3 or a single 6 mg/kg dose of a dsRNA agent targeting CFB showed similar suppression of alternative hemolysis (about 60% suppression) and the combination of a single 6 mg/kg dose of a dsRNA agent targeting C3 and a 6 mg/kg dose of a dsRNA agent targeting CFB suppressed alternative hemolysis by about 90%. Figure 3C demonstrates that the combination of a single 6 mg/kg dose of a dsRNA agent targeting C3 and 6 mg/kg dose of a dsRNA agent targeting C5 have the greatest impact on classical hemolysis.

As depicted in Figure 3D, using the Wieslab® Complement alternative Pathway (CAP) assay, silencing either CFB or C3 or silencing CFB and C3, CFB and C5, and C3 and C5 inhibited alternative pathway activity. Silencing C5 alone had an intermediate effect in the Wieslab® CAP assay.

Figure 3E demonstrates that C3 or CFB suppression did not confer a benefit on silencing classical pathway activity beyond that of C5 silencing.

In summary, the combination of a dsRNA agent targeting C3 and a dsRNA agent taregting CFB effectively suppressed alternative hemolysis activity to less than about 10%, while the combination of a dsRNA agent targeting C3 and a dsRNA agent targeting C5 effectively suppresses classical hemolysis activity.

EQUIVALENTS

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

5

We claim:

1. 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 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 2-7, 13, 16, 19 and 20.

2. 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 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 633-665, 1133-1185, 1133-1173, 1133-1167, 1143-1173, 1540-1563, 1976-2002, 2386-2438, 2386-2418, 2386-2413, and 2389-1418 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:8, where a substitution of a T with a U in either SEQ ID NO: 1 or SEQ ID NO: 8 does not count as a difference.

3. 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 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 633-655, 643-665, 928-950, 1133-1155, 1140-1162, 1141-1163, 1143-1165, 1145-1167, 1148-1170, 1150-1172, 1151-1173, 1185-1207, 1306-1328, 1534-1556, 1540-1562, 1541-1563, 1976-1998, 1979-2001, 1980-2002, 2078-2100, 2386-2408, 2388-2410, 2389-2411, 2391-2413, 2393-2415, 2395-2417, 2396-2418, 2438-2460, and 2602-2624 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:8, where a substitution of a T with a U in either SEQ ID NO: 1 or SEQ ID NO: 8 does not count as a difference.

4. The dsRNA agent of any one of claims 1-3, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-560018, AD-559375, AD-559160, AD-559374, AD-559060, AD-559721, AD-559026, AD-558225, AD-557069, AD-558068, AD-557422, AD-558063, AD-558066, AD-556701, AD-558657, AD-559020, AD-559023, AD-558860, AD-560019, AD-560016, AD-559008, AD-559717, AD-557072, AD-558097, AD-557774, AD-557070, AD-558065, AD-557853, AD-557079.

5. 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 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 153-175; 202-224; 219-241; 254-276; 304-326; 321-343; 347-369; 402-424; 418-440; 447-469; 491-513; 528-550; 549-571; 566-588; 591-613; 792-814; 819-841; 967-989; 1042-1064; 1234-1256; 1250-1272; 1269-1291; 1335-1357; 1354-1376; 1372-1394; 1422-1444; 1496-1518; 1670-1692; 1716-1738; 1757-1779; 1774-1796; 1793-1815; 1844-1866; 1871-1893; 1909-1931; 1924-1947; 1947-1969; 2161-2183; 2310-2332; 2330-2352; 2355-2377; 2494-2516; and 2527-2549 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:8, where a substitution of a T with a U in either SEQ ID NO: 1 or SEQ ID NO: 8 does not count as a difference.

6. The dsRNA agent of claim 1 or 5, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-560132.1; AD-560099.1; AD-559998.1; AD-559993.1; AD-559973.1; AD-559882.1; AD-559706.1; AD-559704.1; AD-559688.1; AD-559668.1; AD-559641.1; AD-559609.1; AD-559590.1; AD-559573.1; AD-559532.1; AD-559486.1; AD-559330.1; AD-559274.1; AD-559226.1; AD-559208.1; AD-559189.1; AD-559124.1; AD-559105.1; AD-559089.1; AD-558935.1; AD-558879.1; AD-558777.1; AD-558750.1; AD-558637.1; AD-558612.1; AD-558595.1; AD-558574.1; AD-558555.1; AD-558511.1; AD-558482.1; AD-558466.1; AD-558450.1; AD-558424.1; AD-558407.1; AD-558393.1; AD-558378.1; AD-558361.1; AD-558312.1.

7. The dsRNA agent of any one of claims 1-6, wherein the dsRNA agent comprises at least one modified nucleotide.

8. The dsRNA agent of any one of claims 1-7, 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.

9. The dsRNA agent of any one of claims 1-8, 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.

10. The dsRNA agent of any one of claims 7-9, wherein 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 2'-phosphate, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

11. The dsRNA agent of any one of claims 7-9, wherein 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 a glycol modified nucleotide (GNA); and combinations thereof.

12. The dsRNA of any one of claims 7-9, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), a nucleotide comrprising a 2'-phosphate, a vinyl-phosphonate nucleotide, and 2'-O hexadecyl nucleotide modifications; and combinations thereof.

13. The dsRNA of any one of claims 7-9, wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification.

14. The dsRNA of claim 13, 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).

15. The dsRNA agent of any one of claims 1-14, wherein the double stranded region is 19-30 nucleotide pairs in length.

16. The dsRNA agent of claim 15, wherein the double stranded region is 19-25 nucleotide pairs in length.

17. The dsRNA agent of claim 15, wherein the double stranded region is 19-23 nucleotide pairs in length.

18. The dsRNA agent of claim 15, wherein the double stranded region is 23-27 nucleotide pairs in length.

19. The dsRNA agent of claim 15, wherein the double stranded region is 21-23 nucleotide pairs in length.

20. The dsRNA agent of any one of claims 1-19, wherein each strand is independently no more than 30 nucleotides in length.

21. The dsRNA agent of any one of claims 1-20, wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.

22. The dsRNA agent of any one of claims 1-21, wherein the region of complementarity is at least 17 nucleotides in length.

23. The dsRNA agent of any one of claims 1-22, wherein the region of complementarity is 19-23 nucleotides in length.

24. The dsRNA agent of any one of claims 1-21, wherein the region of complementarity is 19-21 nucleotides in length.

25. The dsRNA agent of any one of claims 1-24, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

26. The dsRNA agent of any one of claims 1-24, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

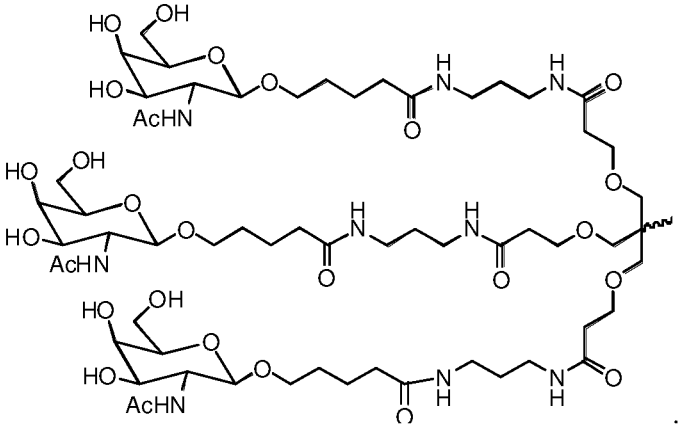
27. The dsRNA agent of any one of claims 1-26, further comprising a ligand.

28. The dsRNA agent of claim 27, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

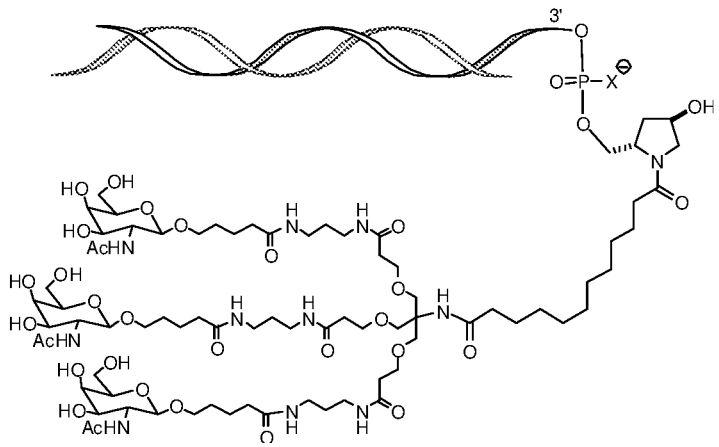
29. The dsRNA agent of claim 27 or 28, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

30. The dsRNA agent of any one of claims 27-29, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

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



32. The dsRNA agent of claim 31, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

33. The dsRNA agent of claim 32, wherein the X is O.

34. The dsRNA agent of any one of claims 1-33, wherein the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

35. The dsRNA agent of claim 34, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

36. The dsRNA agent of claim 35, wherein the strand is the antisense strand.

37. The dsRNA agent of claim 35, wherein the strand is the sense strand.

38. The dsRNA agent of claim 34, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand.

39. The dsRNA agent of claim 38, wherein the strand is the antisense strand.

40. The dsRNA agent of claim 38, wherein the strand is the sense strand.

41. The dsRNA agent of claim 34, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand.

42. The dsRNA agent of claim 41, wherein the strand is the antisense strand.

43. The dsRNA agent of any one of claims 1-42, wherein the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

44. A cell containing the dsRNA agent of any one of claims 1-43.

45. A pharmaceutical composition for inhibiting expression of a gene encoding complement factor B (CFB) comprising the dsRNA agent of any one of claims 1-43.

46. The pharmaceutical composition of claim 45, wherein dsRNA agent is in an unbuffered solution.

47. The pharmaceutical composition of claim 46, wherein the unbuffered solution is saline or water.

48. The pharmaceutical composition of claim 42, wherein said dsRNA agent is in a buffer solution.

49. The pharmaceutical composition of claim 48, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

50. The pharmaceutical composition of claim 49, wherein the buffer solution is phosphate buffered saline (PBS).

51. 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 1-43, or the pharmaceutical composition of any one of claims 45-50, thereby inhibiting expression of the CFB gene in the cell.

52. The method of claim 51, wherein the cell is within a subject.

53. The method of claim 52, wherein the subject is a human.

54. The method of claim 53, wherein the subject has a complement factor B- (CFB)-associated disorder.

55. The method of any one of claims 51-54, 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%.

56. The method of any one of claims 51-55, 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%.

57. 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 1-43, or the pharmaceutical composition of any one of claims 45-50, thereby treating the subject having the disorder that would benefit from reduction in complement factor B expression.

58. 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 1-43, or the pharmaceutical composition of any one of claims 45-50, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in complement factor B expression.

59. The method of claim 57 or 58, wherein the disorder is a complement factor B-associated disorder.

60. The method of claim 59, 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).

61. The method of claim 59, 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.

62. The method of claim 59, 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.

63. The method of any one of claims 57-62, wherein the subject is human.

64. The method of any one of claims 57-63, 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.

65. The method of any one of claims 57-64, wherein the dsRNA agent is administered to the subject subcutaneously.

66. The method of any one of claims 57-65, further comprising administering to the subject an agent for the treatment of a CFB-associated disease.

67. The method of any one of claims 57-65, further comprising administering to the subject an iRNA agent targeting complement component C5 or an iRNA agent targeting complement component C3.

68. The method of any one of claims 57-67, further comprising determining the level of complement factor B in a sample(s) from the subject.

69. The method of claim 68, 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).

70. A kit comprising the dsRNA agent of any one of claims 1-43 or the pharmaceutical composition of any one of claims 45-50.

71. A vial comprising the dsRNA agent of any one of claims 1-43 or the pharmaceutical composition of any one of claims 45-50.

72. A syringe comprising the dsRNA agent of any one of claims 1-43 or the pharmaceutical composition of any one of claims 45-50.

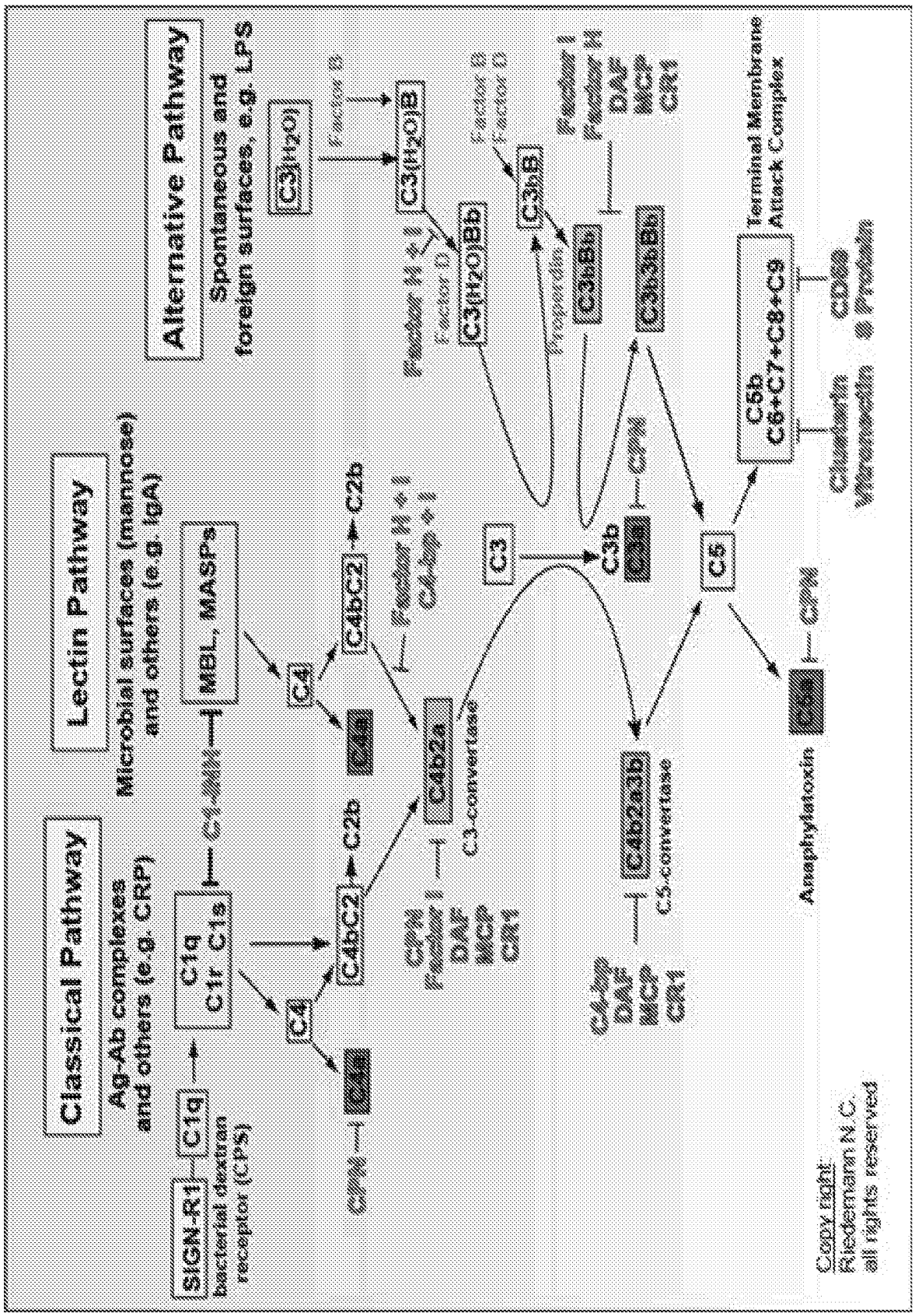

Classical Pathway
Lectin Pathway
Alternative Pathway
Ag-Ab complexes and others (e.g. CRP)
Microbial surfaces (mannose) and others (e.g. IgA)
Spontaneous and foreign surfaces, e.g. LPS
SIGN-R1
bacterial dextran receptor (CPS)
C1q
C1r C1s
MBL, MASPs
C4
C4bC2
C2b
C4a
C3
C3a
C3b
C3(H2O)
C3(H2O)B
C3(H2O)Bb
C3bB
C3bBb
C3b2Bb
C4b2a
C4b2a3b
C5
C5a
C5b
C6+C7+C8+C9
Terminal Membrane Attack Complex
Factor B
Factor D
Properdin
Factor I
Factor H
Factor H +I
C4bp +I
CPN
DAF
MCP
CR1
C5-convertase
Anaphylatoxin
Clusterin
CD59
Vitronectin
S Protein
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Figure 1

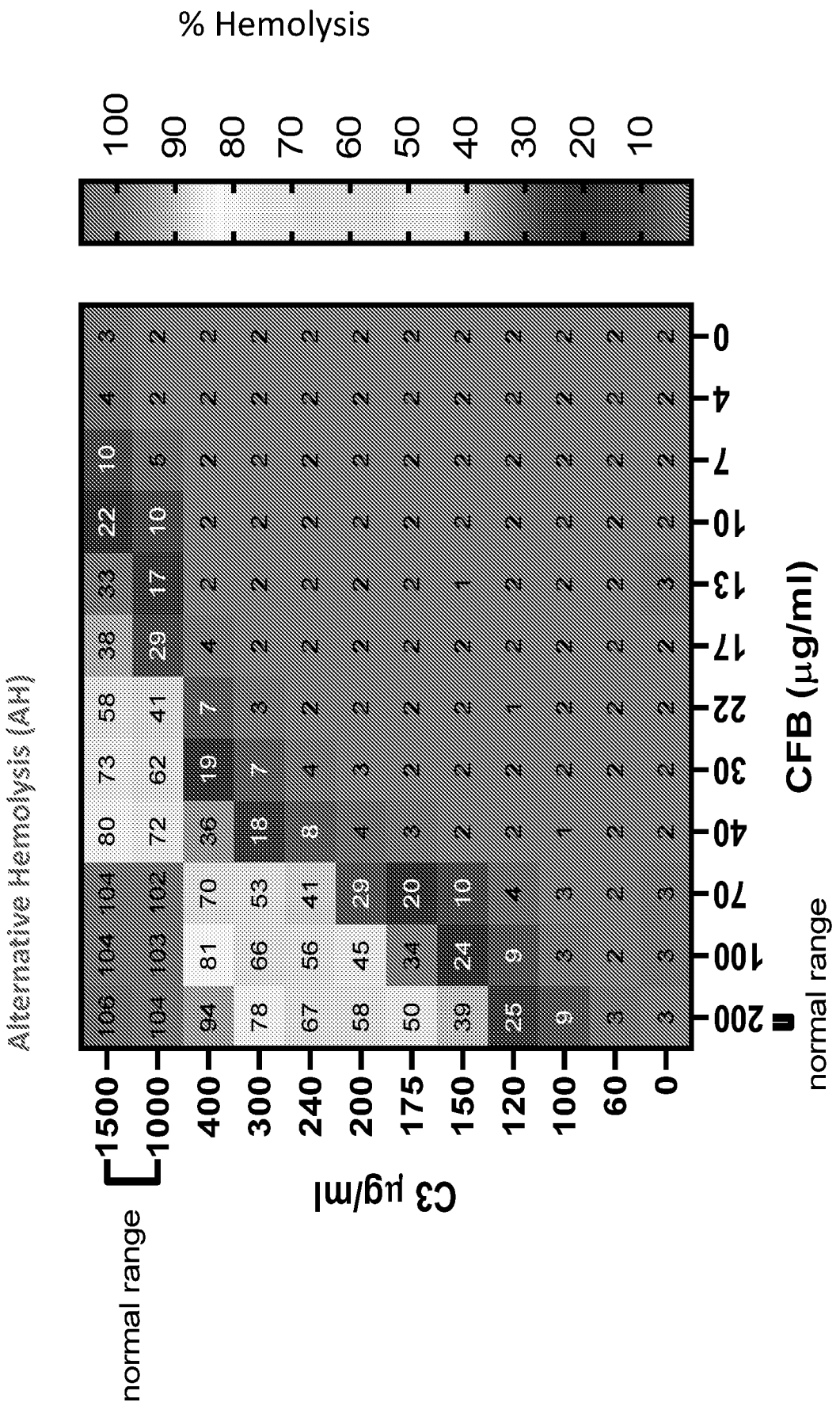

% Hemolysis
100
90
80
70
60
50
40
30
20
10
Alternative Hemolysis (AH)
C3 µg/ml
1500
1000
400
300
240
200
175
150
120
100
60
0
normal range
CFB (µg/ml)
0
4
7
10
13
17
22
30
40
70
100
200
normal range

Figure 2A

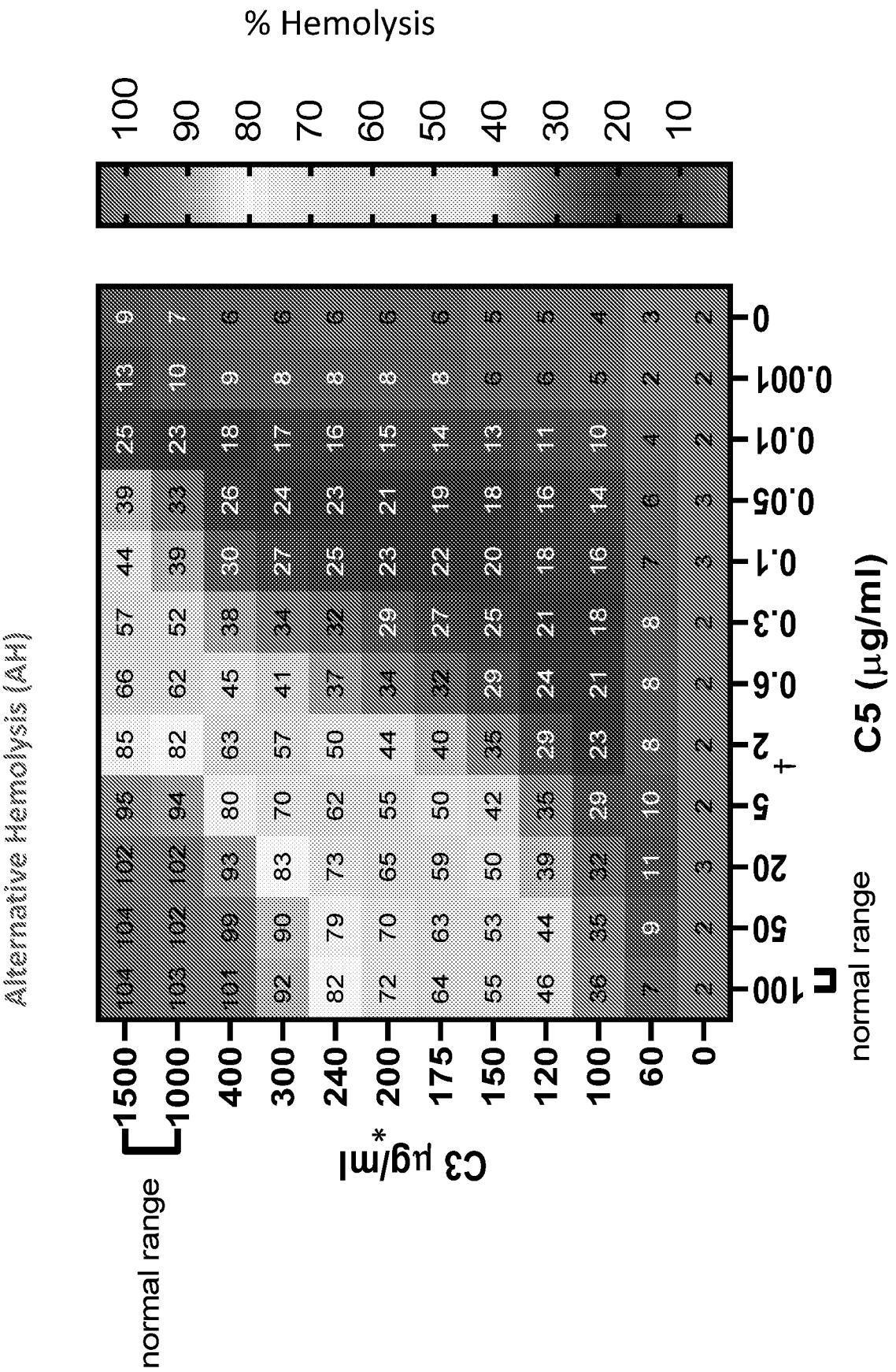

% Hemolysis
100
90
80
70
60
50
40
30
20
10
Alternative Hemolysis (AH)
C3 µg/ml*
1500
1000
400
300
240
200
175
150
120
100
60
0
normal range
n
100 50 20 5 2 1 0.6 0.3 0.1 0.05 0.01 0.001 0
C5 (µg/ml)
normal range

Figure 2B

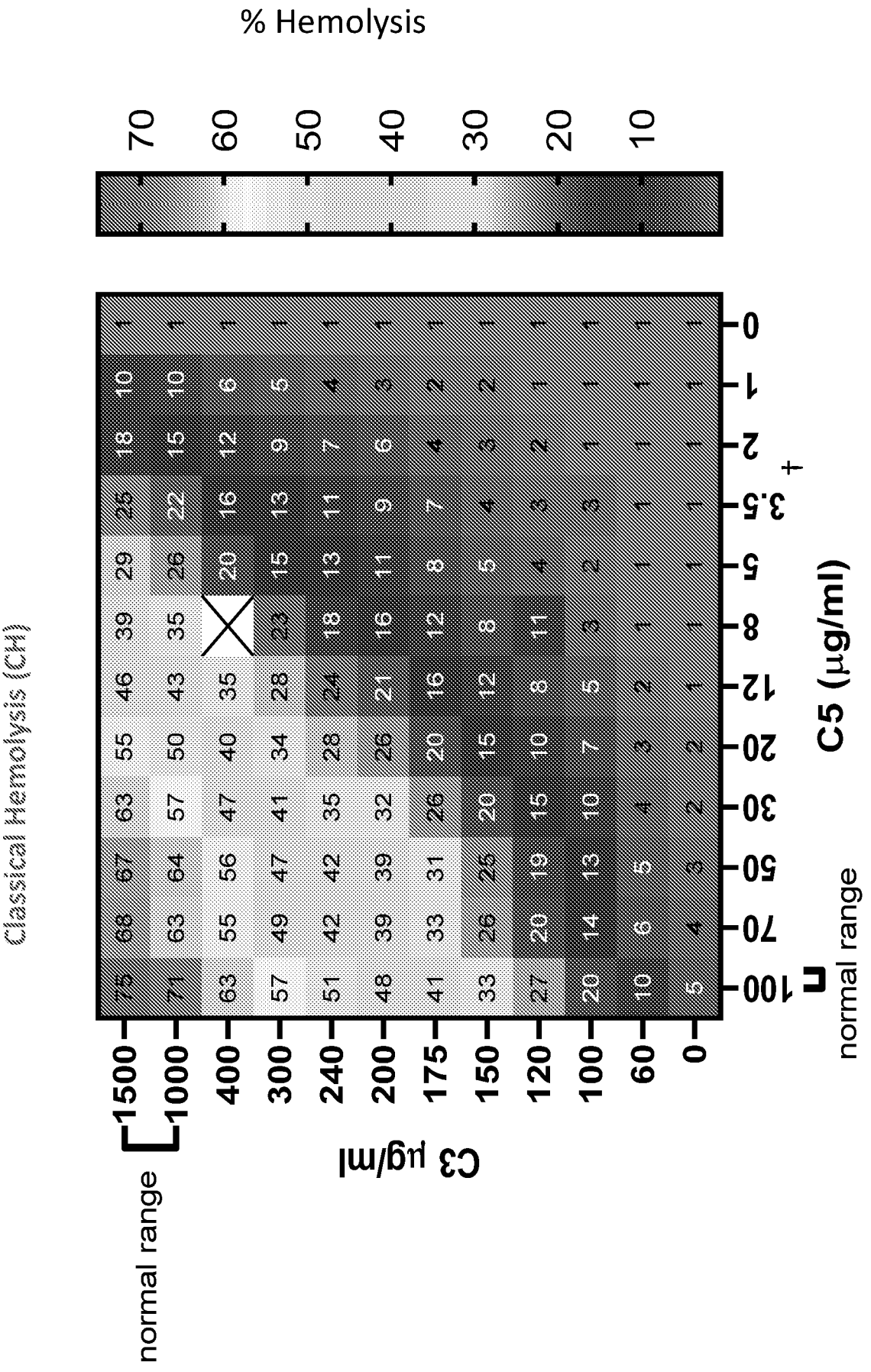

Classical Hemolysis (CH)
% Hemolysis
70
60
50
40
30
20
10
C3 µg/ml
normal range
1500
1000
400
300
240
200
175
150
120
100
60
0
100
70
50
30
20
12
8
5
3.5
2
1
0
C5 (µg/ml)
normal range

Figure 2C

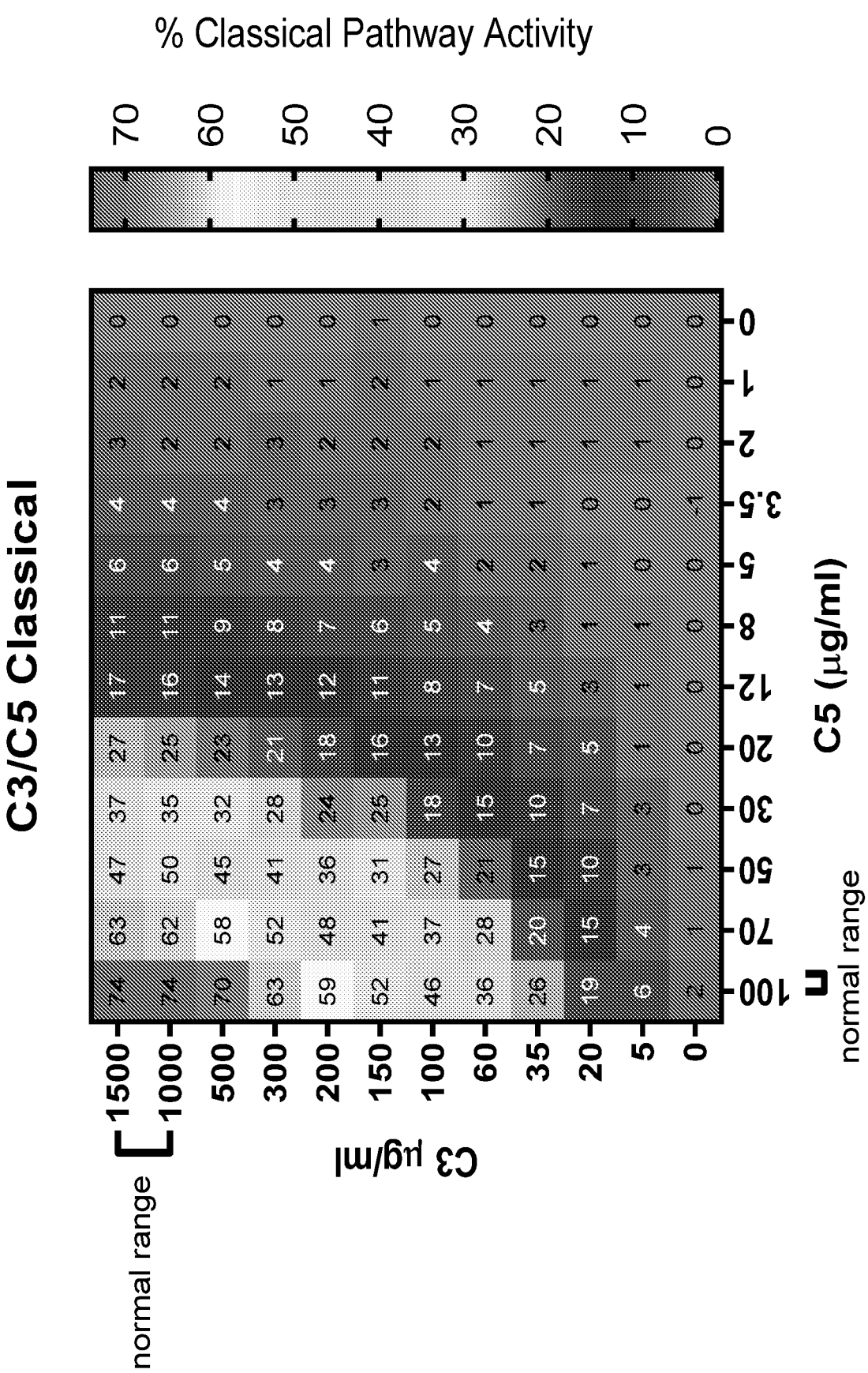

% Classical Pathway Activity
70
60
50
40
30
20
10
0
C3/C5 Classical
C3 µg/ml
normal range
1500
1000
500
300
200
150
100
60
35
20
5
0
C5 (µg/ml)
100
70
50
30
20
12
8
5
3.5
2
1
0
normal range

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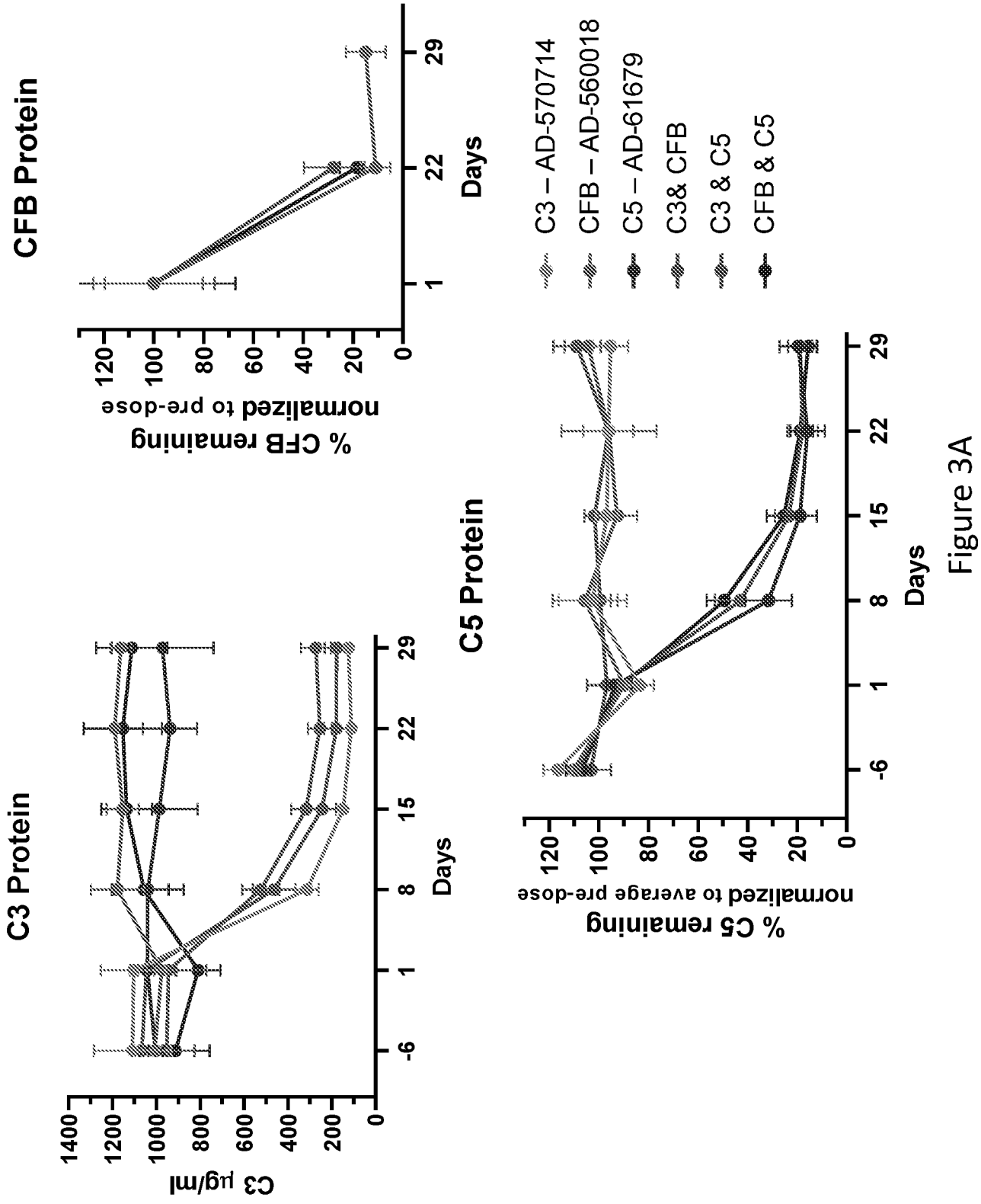

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Days
CFB Protein
% CFB remaining normalized to pre-dose
Days
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C3& CFB
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Figure 3A

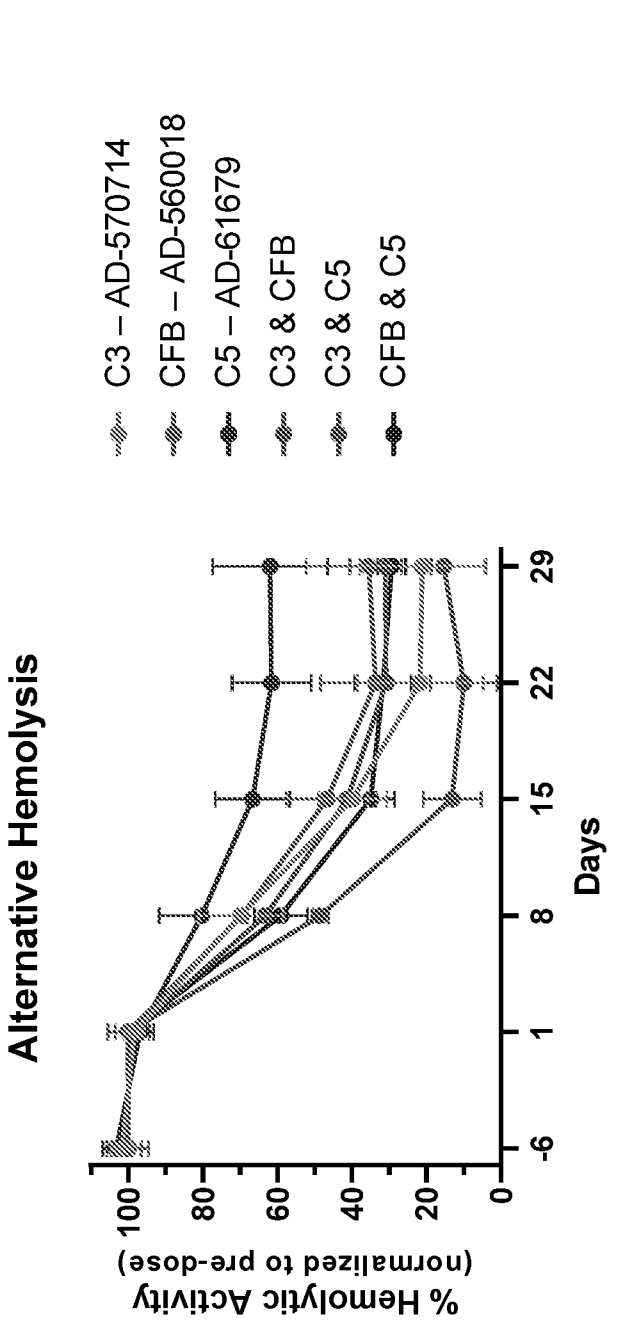


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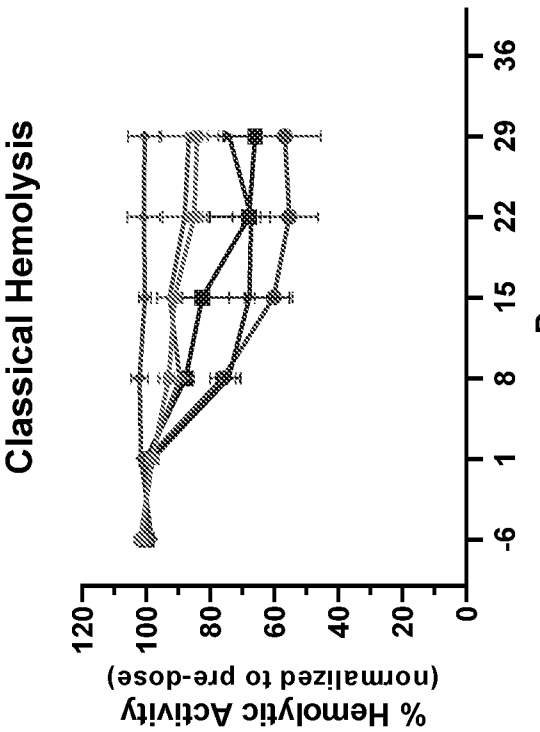


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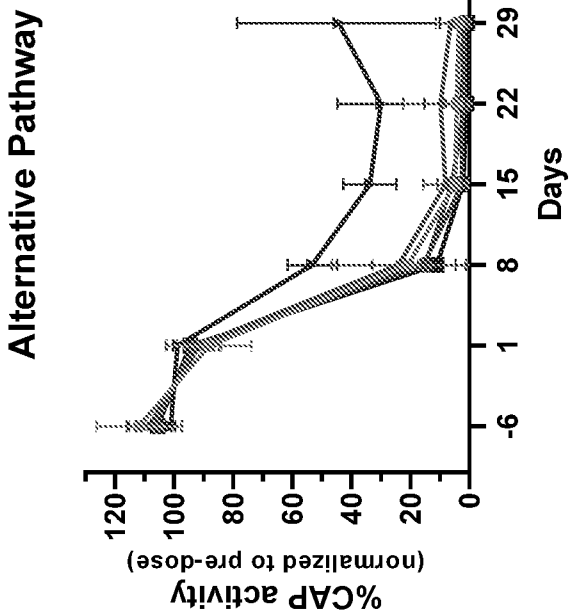


Figure 3D

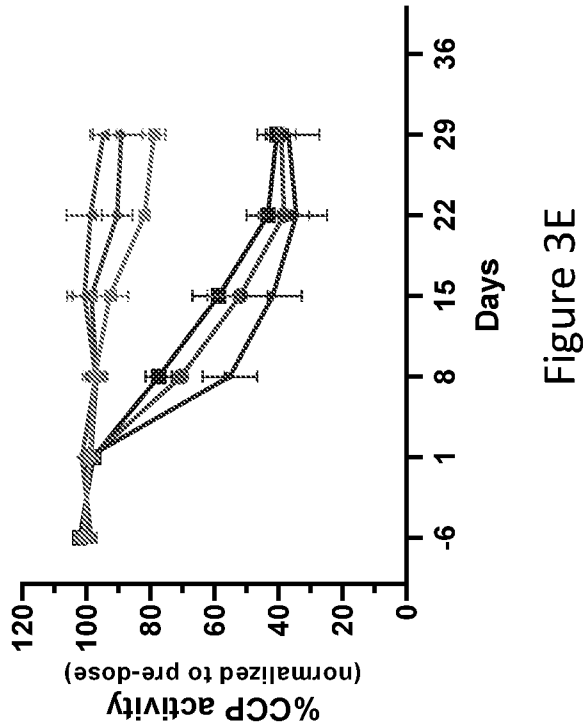


Figure 3E

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<213> Unknown

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<213> Unknown

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<210> 17
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<213> Human immunodeficiency virus

<400> 17
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<210> 18
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<400> 18
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<213> Unknown

<220>
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<223> /note="Description of Unknown:
Target sequence"

<400> 1423
agtgatgaga tctctttcca ctg 23

<210> 1424
<211> 23
<212> DNA
<213> Unknown

<220>
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<223> /note="Description of Unknown:
Target sequence"

<400> 1424
ccactgctat gacggttaca ctc 23

<210> 1425
<211> 23
<212> DNA
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<220>
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Target sequence"

<400> 1425
cgcacctgcc aagtgaatgg ccg 23

<210> 1426
<211> 23
<212> DNA

<213> Unknown

<220>
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<223> /note="Description of Unknown:
Target sequence"

<400> 1426
acagcgatct gtgacaacgg agc 23

<210> 1427
<211> 23
<212> DNA
<213> Unknown

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<223> /note="Description of Unknown:
Target sequence"

<400> 1427
cccattggca caaggaaggt ggg 23

<210> 1428
<211> 23
<212> DNA
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<220>
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<223> /note="Description of Unknown:
Target sequence"

<400> 1428
accgccttga agacagcgtc acc 23

<210> 1429
<211> 23
<212> DNA
<213> Unknown

<220>
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Target sequence"

<400> 1429
gcggcgaacg tgtcaggaag gtg 23

<210> 1430

<211> 23
<212> DNA
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<223> /note="Description of Unknown:
Target sequence"

<400> 1430
tcctgccaag actccttcat gta 23

<210> 1431
<211> 23
<212> DNA
<213> Unknown

<220>
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Target sequence"

<400> 1431
tggccgaagc tttcctgtct tcc 23

<210> 1432
<211> 23
<212> DNA
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<220>
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Target sequence"

<400> 1432
tcttccctga cagagaccat aga 23

<210> 1433
<211> 23
<212> DNA
<213> Unknown

<220>
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Target sequence"

<400> 1433
aaggagtcga tgctgaggat ggg 23

<210> 1434
<211> 23
<212> DNA
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<220>
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<223> /note="Description of Unknown:
Target sequence"

<400> 1434
aacaacagaa gcggaagatc gtc 23

<210> 1435
<211> 23
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<213> Unknown

<220>
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<223> /note="Description of Unknown:
Target sequence"

<400> 1435
cttcaggctc catgaacatc tac 23

<210> 1436
<211> 23
<212> DNA
<213> Unknown

<220>
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Target sequence"

<400> 1436
gctagatgga tcagacagca ttg 23

<210> 1437
<211> 23
<212> DNA
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<220>
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<223> /note="Description of Unknown:
Target sequence"

<400> 1437

gggccagcaa cttcacagga gcc 23

<210> 1438
<211> 23
<212> DNA
<213> Unknown

<220>
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Target sequence"

<400> 1438
aaagtgtcta gtcaacttaa ttg 23

<210> 1439
<211> 23
<212> DNA
<213> Unknown

<220>
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<223> /note="Description of Unknown:
Target sequence"

<400> 1439
taattgagaa ggtggcaagt tat 23

<210> 1440
<211> 23
<212> DNA
<213> Unknown

<220>
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Target sequence"

<400> 1440
ttatggtgtg aagccaagat atg 23

<210> 1441
<211> 23
<212> DNA
<213> Unknown

<220>
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Target sequence"

<400> 1441
aagatatggt ctagtgacat atg 23

<210> 1442
<211> 23
<212> DNA
<213> Unknown

<220>
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<223> /note="Description of Unknown:
Target sequence"

<400> 1442
aaatttgggt caaagtgtct gaa 23

<210> 1443
<211> 23
<212> DNA
<213> Unknown

<220>
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Target sequence"

<400> 1443
gcagacagca gtaatgcaga ctg 23

<210> 1444
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
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Target sequence"

<400> 1444
agcagctcaa tgaaatcaat tat 23

<210> 1445
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source

<223> /note="Description of Unknown:
Target sequence"

<400> 1445
atgaagacca caagttgaag tca 23

<210> 1446
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1446
cagggactaa caccaagaag gcc 23

<210> 1447
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1447
tccaggcagt gtacagcatg atg 23

<210> 1448
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1448
ctggccagat gacgtccctc ctg 23

<210> 1449
<211> 23
<212> DNA
<213> Unknown

<220>
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<223> /note="Description of Unknown:
Target sequence"

<400> 1449
catgtcatca tcctcatgac tga 23

<210> 1450
<211> 23
<212> DNA
<213> Unknown

<220>
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Target sequence"

<400> 1450
tgactgatgg attgcacaac atg 23

<210> 1451
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1451
aattactgtc attgatgaga tcc 23

<210> 1452
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1452
gggacttgct atacattggc aag 23

<210> 1453
<211> 23
<212> DNA

<213> Unknown

<220>
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Target sequence"

<400> 1453
aaaacccaag ggaggattat ctg 23

<210> 1454
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
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Target sequence"

<400> 1454
attatctgga tgtctatgtg ttt 23

<210> 1455
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
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Target sequence"

<400> 1455
tcgggccttt ggtgaaccaa gtg 23

<210> 1456
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
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Target sequence"

<400> 1456
accaagtgaa catcaatgct ttg 23

<210> 1457

<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
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Target sequence"

<400> 1457
gcttccaaga aagacaatga gca 23

<210> 1458
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
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Target sequence"

<400> 1458
tgagcaacat gtgttcaaag tca 23

<210> 1459
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1459
aagtcaagga tatggaaaac ctg 23

<210> 1460
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
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Target sequence"

<400> 1460
tggaagatgt tttctaccaa atg 23

<210> 1461
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1461
tgatcgatga aagccagtct ctg 23

<210> 1462
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
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Target sequence"

<400> 1462
agtctctgag tctctgtggc atg 23

<210> 1463
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
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Target sequence"

<400> 1463
tttgggaaca caggaagggt acc 23

<210> 1464
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
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Target sequence"

<400> 1464

accgattacc acaagcaacc atg 23

<210> 1465
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1465
tctcagtcat tcgcccttca aag 23

<210> 1466
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1466
aagggacacg agagctgtat ggg 23

<210> 1467
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1467
ctgtggtgtc tgagtacttt gtg 23

<210> 1468
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1468
gacagcagca cattgtttca ctg 23

<210> 1469
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1469
acaaggaaca ctcaatcaag gtc 23

<210> 1470
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1470
gatagaagta gtcctatttc acc 23

<210> 1471
<211> 23
<212> DNA
<213> Unknown

<220>
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Target sequence"

<400> 1471
cccaactaca acattaatgg gaa 23

<210> 1472
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source

<223> /note="Description of Unknown:
Target sequence"

<400> 1472
gaattcctga attttatgac tat 23

<210> 1473
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1473
actatgacgt tgccctgatc aag 23

<210> 1474
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1474
aagctcaaga ataagctgaa ata 23

<210> 1475
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1475
agactatcag gcccatttgt ctc 23

<210> 1476
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1476
cgagggaaca actcgagctt tga 23

<210> 1477
<211> 23
<212> DNA
<213> Unknown

<220>
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Target sequence"

<400> 1477
gcttcctcca actaccactt gcc 23

<210> 1478
<211> 23
<212> DNA
<213> Unknown

<220>
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Target sequence"

<400> 1478
cacttgccag caacaaaagg aag 23

<210> 1479
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
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Target sequence"

<400> 1479
cacaggatat caaagctctg ttt 23

<210> 1480
<211> 23
<212> DNA

<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1480
gtttgtgtct gaggaggaga aaa 23

<210> 1481
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1481
aaggaggtct acatcaagaa tgg 23

<210> 1482
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1482
ctgtgagaga gatgctcaat atg 23

<210> 1483
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1483
atgacaaagt caaggacatc tca 23

<210> 1484

<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1484
cctcggttcc tttgtactgg agg 23

<210> 1485
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1485
aggagtgagt ccctatgctg acc 23

<210> 1486
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1486
aatacttgca gaggtgattc tgg 23

<210> 1487
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1487
atagttcaca agagaagtcg ttt 23

<210> 1488
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1488
tttcattcaa gttggtgtaa tca 23

<210> 1489
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1489
gggagtagtg gatgtctgca aaa 23

<210> 1490
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1490
aaaaccagaa gcggcaaaag cag 23

<210> 1491
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1491

gagactttca catcaacctc ttt 23

<210> 1492
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1492
acctctttca agtgctgccc tgg 23

<210> 1493
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1493
tgaaggagaa actccaagat gag 23

<210> 1494
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1494
atgaggattt gggttttcta taa 23

<210> 1495
<211> 23
<212> DNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1495
ggcgtgggat tgaattaaaa cag 23

<210> 1496
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1496
aagcaagcca ggacacacca ucc 23

<210> 1497
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1497
agcuucucuc cugccuucca acg 23

<210> 1498
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1498
aucuugggcc ucuugucugg agg 23

<210> 1499
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source

<223> /note="Description of Unknown:
Target sequence"

<400> 1499
guagagauca aaggcggcuc cuu 23

<210> 1500
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1500
gcacuggagu acgugugucc uuc 23

<210> 1501
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1501
acccugaaga cucaagacca aaa 23

<210> 1502
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1502
aagacuguca ggaaggcaga gug 23

<210> 1503
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1503
auuggcacaa ggaagguggg cag 23

<210> 1504
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1504
uaccgccuug aagacagcgu cac 23

<210> 1505
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1505
gucugaagca gacagcagua aug 23

<210> 1506
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1506
aaugcagacu gggucacgaa gca 23

<210> 1507
<211> 23
<212> RNA

<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1507
acuaacacca agaaggcccu cca 23

<210> 1508
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1508
ugaugagcug gccagaugac guc 23

<210> 1509
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1509
ggacuugcua uacauuggca agg 23

<210> 1510
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1510
uuucuaccaa augaucgaug aaa 23

<210> 1511

<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1511
augguuuggg aacacaggaa ggg 23

<210> 1512
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1512
accauggcag gccaagaucu cag 23

<210> 1513
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1513
aaagggacac gagagcugua ugg 23

<210> 1514
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1514
ugacaaggaa cacucaauca agg 23

<210> 1515
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1515
agaagcggga ccuggagaua gaa 23

<210> 1516
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1516
ucaaagcucu guuugugucu gag 23

<210> 1517
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
Target sequence"

<400> 1517
ccuggcugaa ggagaaacuc caa 23