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(54) Title: COAGULATION FACTOR V (F5) iRNA COMPOSITIONS AND METHODS OF USE THEREOF

(57) Abstract: The present invention relates to RNAi agents, e.g., dsRNA agents, targeting the Coagulation Factor V (F5) gene. The invention also relates to methods of using such RNAi agents to inhibit expression of an F5 gene and to methods of treating or preventing an F5-associated disease, e.g., a disorder associated with thrombosis, in a subject.



WO 2022/103999 A1

COAGULATION FACTOR V (F5) iRNA COMPOSITIONS AND METHODS OF USE THEREOF

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application No. 63/113282, filed on November 13, 2020, U.S. Provisional Application No. 63/146115, filed on February 5, 2021, and U.S. Provisional Application No. 63/271872, filed on October 26, 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 November 5, 2021, is named 121301_13520_SL.txt and is 873,599 bytes in size.

BACKGROUND OF THE INVENTION

Coagulation Factor V (F5) is a plasma glycoprotein synthesized as a single-chain inactive precursor in the liver. Activation of F5 occurs via ordered proteolysis at three sites on the protein by thrombin. The proteolytically activated form of F5 (F5a) binds tightly to thrombin in the presence of ionic calcium and an anionic phospholipid surface to produce a potent procoagulant, *i.e.*, an activated thrombin. Activated thrombin, in turn, cleaves fibrinogen to form fibrin, which polymerizes to form the dense meshwork that makes up the majority of a clot. Activated protein C is a natural anticoagulant that acts to limit the extent of clotting by cleaving and degrading F5. F5 is also secreted from activated platelets, thus helping to localize thrombin activity to the site of vascular damage (see, *e.g.*, Figure 1).

As with thrombin, unregulated activation or activity of F5 may lead to generation of excess fibrin and excess clotting, thereby leading to the development of disorders associated with thrombosis.

Formation of excess clotting within a blood vessel results in thrombosis which prevents blood from flowing normally through the circulatory system. When a blood clot forms in the veins, it is known as venous thromboembolism such as deep vein thrombosis. If the venous clots break off, these clots can travel through the heart to the lung, where they block a pulmonary blood vessel and cause a pulmonary embolism. When a clot forms in the arteries, it is called atherothrombosis, which can lead to heart attack and stroke.

The common treatment for thrombosis is typically non-selective anti-coagulant therapy. Unfortunately, however, the lack of specificity of such therapies can lead to excessive bleeding.

Accordingly, there is a need in the art for more effective treatments for subjects suffering from or prone to suffering from thrombosis.

SUMMARY OF THE INVENTION

The present invention provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding coagulation Factor V (F5). The F5 may be within a cell, *e.g.*, a cell within a subject, such as a human subject.

5 Accordingly, in one aspect the invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of F5 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
10 nucleotides differing by no more than 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:2. 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:4. In certain embodiments, the sense strand comprises at least 17 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1 and the
15 antisense strand comprises at least 17 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:5. 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:5.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA)
20 for inhibiting expression of coagulation Factor V (F5) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding F5, 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, 3, 5, 6-8, 10
25 and 11. 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, 3, 5, 6-8, 10 and 11. 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, 3, 5, 6-8, 10 and 11. In certain embodiments, the region of complementarity comprises at least 19 contiguous
30 nucleotides of any one of the antisense nucleotide sequences in any one of Tables 2, 3, 5, 6-8, 10 and 11. 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, 3, 5, 6-8, 10 and 11. In certain embodiments, the region of complementarity comprises at least 21 contiguous
35 nucleotides of any one of the antisense nucleotide sequences in any one of Tables 2, 3, 5, 6-8, 10 and 11.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) for inhibiting expression of coagulation Factor V (F5) 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 640-668; 747-771; 755-784; 830-855; 1226-1262; 3351-3380; 5821-5858; 5874-5910; 6104-6149; and 6245-6277 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:5.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation Factor V (F5) 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 three nucleotides from any one of the nucleotide sequence of nucleotides 643-665; 645-667; 346-368; 5830-5852; 6104-6126; 6909-6931; and 1104-1126 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:5.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation Factor V (F5) 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 three nucleotides from any one of the nucleotide sequence of nucleotides 5830-5852; and 6909-6931 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:5.

In one embodiment, the antisense strand and the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, 3 or 4 nucleotides from any one of the antisense strand nucleotide sequences and the sense strand nucleotide sequences, respectively, of a duplex selected from the group consisting of AD-109630; AD-1465920; AD-1465922; AD-1615171; AD-1615234; AD-1615253; AD-1615278; and AD-1615312.

In one embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1615234; and AD-1615278.

In some embodiments, the dsRNA agent is selected from the group consisting of AD-109630; AD-1465920; AD-1465922; AD-1615171; AD-1615234; AD-1615253; AD-1615278; and AD-1615312,

wherein AD-109630 comprises a sense strand comprising the nucleotide sequence 5'-CAGGCUUACAUGACAUAUAAA-3' (SEQ ID NO: 9) and an antisense strand comprising the nucleotide sequence 5'-UUUAAUGUCAAGUAAGCCUGCA-3' (SEQ ID NO: 10);

wherein AD-1465920 comprises a sense strand comprising the nucleotide sequence 5'-GCCUCACACACAUCUAUUACU-3' (SEQ ID NO: 11) and an antisense strand comprising the nucleotide sequence 5'-AGUAAUAGAUGTGUGUGAGGCAU-3' (SEQ ID NO: 12);

wherein AD-1465922 comprises a sense strand comprising the nucleotide sequence 5'-CUCACACACAUCUAUUACUCU -3' (SEQ ID NO: 13) and an antisense strand comprising the nucleotide sequence 5'- AGAGTAAUAGATGUGUGUGAGGC -3' (SEQ ID NO: 14);

wherein AD-1615171 comprises a sense strand comprising the nucleotide sequence 5'-
 5 AGUAUGAACCAUAUUUUAAGU -3' (SEQ ID NO: 15) and an antisense strand comprising the nucleotide sequence 5'- ACUUA AAAUAUGGUUCAUACUCU -3' (SEQ ID NO: 16);

wherein AD-1615234 comprises a sense strand comprising the nucleotide sequence 5'-UGCAAACGCCAUUUCUUAUCU -3' (SEQ ID NO: 17) and an antisense strand comprising the nucleotide sequence 5'- AGAUAAGAAAUGGCGUUUGCAUC -3' (SEQ ID NO: 18);

10 wherein AD-1615253 comprises a sense strand comprising the nucleotide sequence 5'-CUGCUAUACCACAGAGUUCUU -3' (SEQ ID NO: 19) and an antisense strand comprising the nucleotide sequence 5'- AAGAACTCUGUGGUAUAGCAGGA -3' (SEQ ID NO: 20);

wherein AD-1615278 comprises a sense strand comprising the nucleotide sequence 5'-ACAGUUUCCACUAUUUCUCU -3' (SEQ ID NO: 21) and an antisense strand comprising the
 15 nucleotide sequence 5'- AGAGAAAUAGUGGAAAACUGUUA -3' (SEQ ID NO: 22); and

wherein AD-1615278 comprises a sense strand comprising the nucleotide sequence 5'-ACAGUUUCCACUAUUUCUCU -3' (SEQ ID NO: 21) and an antisense strand comprising the nucleotide sequence 5'- AGAGAAAUAGUGGAAAACUGUUA -3' (SEQ ID NO: 22); and

wherein AD-1615312 comprise a sense strand comprising the nucleotide sequence 5'-
 20 CAGGCUUACAUGAUUAUAAU -3' (SEQ ID NO: 23) and an antisense strand comprising the nucleotide sequence 5'- AUUAAUAUCA AUGUAAGCCUGCG -3' (SEQ ID NO: 24).

In some embodiments, the dsRNA agent is selected from the group consisting of AD-1615234; and AD-1615278,

wherein AD-1615234 comprises a sense strand comprising the nucleotide sequence 5'-
 25 UGCAAACGCCAUUUCUUAUCU -3' (SEQ ID NO: 17) and an antisense strand comprising the nucleotide sequence 5'- AGAUAAGAAAUGGCGUUUGCAUC -3' (SEQ ID NO: 18);

and wherein AD-1615278 comprises a sense strand comprising the nucleotide sequence 5'-ACAGUUUCCACUAUUUCUCU -3' (SEQ ID NO: 21) and an antisense strand comprising the nucleotide sequence 5'- AGAGAAAUAGUGGAAAACUGUUA -3' (SEQ ID NO: 22).

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

In one embodiment, substantially all of the nucleotides of the sense strand comprise a modification; substantially all of the nucleotides of the antisense strand comprise a modification; or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification.

35 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 deoxythymidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 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 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, 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; a 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.

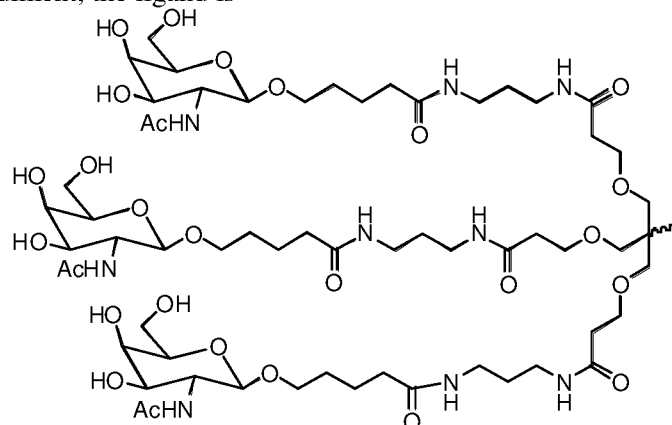
In one embodiment, the dsRNA agent further comprises a ligand.

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.

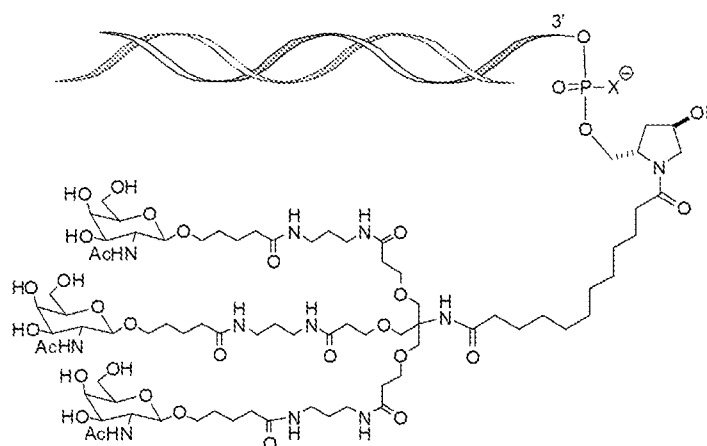
In one embodiment, the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In one embodiment, the ligand is



5

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



and, wherein X is O or S.

10 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.

15 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 both the 5'- and 3'-terminus of one strand, *e.g.*, the antisense strand or the sense strand. In one embodiment, the strand is the antisense strand.

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

In one aspect, the present invention provides a method of inhibiting expression of a coagulation Factor V (F5) gene in a cell. The method includes contacting the cell with any of the dsRNA agents of the invention or any of the pharmaceutical compositions of the invention, thereby inhibiting expression of the F5 gene in the cell.

In one embodiment, the cell is within a subject, *e.g.*, a human subject, *e.g.*, a subject having a coagulation Factor V-(F5)-associated disease. Such diseases are typically associated with excess formation of blood clots, *e.g.*, thrombosis. In certain embodiments, the F5-associated disease or disorder is a disease or disorder associated with thrombosis. Non-limiting examples of disorders or diseases associated with thrombosis include venous thrombosis, *e.g.*, deep vein thrombosis; genetic thrombophilia, *e.g.*, Factor V leiden and prothrombin thrombophilia; purpura fulminans; acquired thrombophilia, *e.g.*, antiphospholipid syndrome and systemic lupus erythematosus; drug induced thrombophilia; arterial thrombosis, *e.g.*, myocardial infarction and peripheral arterial disease; thromboembolic disease, *e.g.*, pulmonary embolus embolic and ischemic stroke; atrial fibrillation; post-surgery deep vein thrombosis; cancer thrombosis or infectious disease thrombosis.

In one embodiment, contacting the cell with the dsRNA agent inhibits the expression of F5 by at least 50%, 60%, 70%, 80%, 90%, or 95%.

In one embodiment, inhibiting expression of F5 decreases F5 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 coagulation Factor V (F5) expression. The method includes administering to the subject a therapeutically effective amount of any of the dsRNA agents 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 F5 expression.

In another aspect, the present invention provides a method of preventing development of a disorder that would benefit from reduction in coagulation Factor V (F5) 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 dsRNA agents of the invention or any of the pharmaceutical compositions of the invention, thereby preventing the subject from progressing to meet the diagnostic criteria of the disorder that would benefit from reduction in F5 expression.

In one embodiment, the disorder is a coagulation Factor V-(F5)-associated disorder. In certain embodiments, the F5-associated disorder is a disorder associated with thrombosis. Non-

limiting examples of disorders or diseases associated with thrombosis include venous thrombosis, *e.g.*, deep vein thrombosis; genetic thrombophilia, *e.g.*, Factor V leiden and prothrombin thrombophilia; plurpura fulminans; acquired thrombophilia, *e.g.*, antiphospholipid syndrome and systemic lupus erythematosus; drug induced thrombophilia; arterial thrombosis, *e.g.*, myocardial infarction and peripheral arterial disease; thromboembolic disease, *e.g.*, pulmonary embolus embolic and ischemic stroke; atrial fibrillation; post-surgery deep vein thrombosis; cancer thrombosis or infectious disease thrombosis.

In one embodiment, the subject is a 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 method further comprises determining the level of F5 in a sample from the subject. In one embodiment, the level of F5 in the subject sample(s) is an F5 protein level in a blood or serum sample(s).

In certain embodiments, the methods of the invention further comprise administering to the subject an additional therapeutic agent. In certain embodiments, the additional therapeutic agent is an anticoagulant. In some embodiments, the anticoagulant includes heparin, enoxaparin (Lovenox), dalteparin (Fragmin), fondaparinux (Arixtra), warfarin (Coumadin, Jantoven), dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa), argatroban or any combination thereof. In some embodiments, the additional therapeutic agent includes a thrombolytic. In certain embodiments, the thrombolytic includes antistreptase (Eminase), tissue plasminogen activator (tPA), urokinase-type plasminogen activator (uPA), or any combination thereof. In some embodiments, the additional therapeutic agent is an immunosuppressant. In certain embodiments, the immunosuppressant includes corticosteroid, azathioprine, cyclosporine A, or any combination thereof. In some embodiments, the additional therapeutic agent is hormone replacement therapy. In certain embodiments, the hormone replacement therapy includes estrogen, gestagen, androgen or any combination thereof. In some embodiments, the additional therapeutic agent is an antibiotic. In some embodiments, the additional therapeutic agent is an antihistamine agent. In some embodiments, the additional therapeutic agent is a mast cell stabilizer. In certain embodiments, the mast cell stabilizer includes cromoglicic acid (Cromolyn), lodoxamide (Alomide), or any combination thereof. In some embodiments, the additional therapeutic agent is an anti-proliferative agent. In some embodiments, the additional therapeutic agent is an oral contraceptive. In some embodiments, the additional therapeutic agent is a fresh frozen plasma or a plasminogen concentrate. In some embodiments, the additional therapeutic agent is hyaluronidase. In some embodiments, the additional therapeutic agent is alpha chymotrypsin. In certain embodiment, the additional therapeutic agent is a filter inserted into a large vein that prevents clots that break loose from lodging in the patient's lungs. In certain embodiments, the additional therapeutic agent is selected from the group consisting of an anticoagulant, an F5 inhibitor and a thrombin inhibitor.

The invention also provides uses of the dsRNA agents and the pharmaceutical compositions provided herein for treatment of an F5-associated disorder. In certain embodiments, the uses include any of the methods provided by the invention.

The invention provides kits or pharmaceutical compositions comprising a dsRNA agent of the invention. In certain embodiments, the invention provides kits for practicing a method of the invention.

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

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic of the coagulation cascade.

FIG. 2 is a graph depicting the effect of subcutaneous administration of a single 3 mg/kg or 20 mg/kg dose of the indicated duplexes on Factor V (FV) protein levels in the plasma of non-human primates. FV levels are shown as the percent of FV remaining relative to the average pre-dose levels of FV determined on pre-dose Days -14, -7 and 1).

FIG. 3 are graphs depicting the effect of subcutaneous administration of a single 3 mg/kg or 20 mg/kg dose of the indicated duplexes on absolute FV protein concentration in the plasma of non-human primates. FV levels are in $\mu\text{g/ml}$. The lower limit of quantification (LLOQ) is $0.69 \mu\text{g/ml}$ FV in plasma (represented as dashed line on the Y-axis).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides iRNA compositions which affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a coagulation Factor V (F5) 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 (coagulation Factor V gene) in mammals.

The iRNAs of the invention have been designed to target the human coagulation Factor V gene, including portions of the gene that are conserved in the coagulation Factor V 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 coagulation Factor V-associated disorder, disease, or condition, *e.g.*, a disorder, disease, or condition associated with thrombosis, *e.g.*, venous thrombosis, *e.g.*, deep vein thrombosis; genetic thrombophilia, *e.g.*, Factor V leiden and prothrombin thrombophilia; purpura fulminans; acquired thrombophilia, *e.g.*, antiphospholipid syndrome and systemic lupus erythematosus; drug induced thrombophilia; arterial thrombosis, *e.g.*, myocardial infarction and peripheral arterial disease;

thromboembolic disease, *e.g.*, pulmonary embolus embolic and ischemic stroke; atrial fibrillation; post-surgery deep vein thrombosis; cancer thrombosis or infectious disease thrombosis, using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a coagulation Factor V gene.

5 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 coagulation Factor V 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 coagulation Factor V gene.

10 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 coagulation Factor V 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.

20 The use of iRNAs of the invention enables the targeted degradation of mRNAs of the corresponding gene (coagulation Factor V gene) in mammals. Using *in vitro* and *in vivo* assays, the present inventors have demonstrated that iRNAs targeting a coagulation Factor V gene can potentially mediate RNAi, resulting in significant inhibition of expression of a coagulation Factor V gene. Thus, methods and compositions including these iRNAs are useful for treating a subject having a coagulation Factor V -associated disorder, *e.g.*, a disorder associated with thrombosis.

25 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 coagulation Factor V gene, *e.g.*, a coagulation Factor V-associated disease, *e.g.*, a disorder associated with thrombosis, using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an F5 gene.

30 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 coagulation Factor V gene, *e.g.*, a disorder associated with thrombosis.

35 The following detailed description discloses how to make and use compositions containing iRNAs to inhibit the expression of a coagulation Factor V gene as well as compositions, uses, and methods for treating subjects that would benefit from inhibition or reduction of the expression of a

coagulation Factor V gene, *e.g.*, subjects susceptible to or diagnosed with a coagulation Factor V-associated disorder, *e.g.*, a disorder associated with thrombosis.

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 than” 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 “coagulation Factor V,” used interchangeably with the term “F5,” refers to the well-known gene and polypeptide, also known in the art as Factor V leiden; activated protein C cofactor; coagulation Factor V jinjiang A2 domain; proaccelerin; labile factor; PCCF; RPRGL1; and THPH2.

The F5 gene encodes an essential cofactor of the blood coagulation cascade. This factor synthesis occurs primarily in the liver. This factor circulates in plasma, and is converted to the active form by the release of the activation peptide by thrombin during coagulation. This generates a heavy chain and a light chain which are held together by calcium ions. The activated protein is a cofactor that participates with activated coagulation factor X to activate prothrombin to thrombin.

The term “F5” includes human F5, the amino acid and nucleotide sequence of which may be found in, for example, GenBank Accession Nos. NM_000130.4 (SEQ ID NO: 1); mouse F5, the amino acid and nucleotide sequence of which may be found in, for example, GenBank Accession No. NM_007976.3 (SEQ ID NO:2); rat F5, the amino acid and nucleotide sequence of which may be found in, for example, GenBank Accession No. NM_001047878.1 (SEQ ID NO: 3); and *Macaca fascicularis* F5, the amino acid and nucleotide sequence of which may be found in, for example, GenBank Accession Nos. XM_005539935.2 (SEQ ID NO: 4). Additional examples of F5 mRNA sequences are readily available using, *e.g.*, GenBank, UniProt, OMIM, and the *Macaca* genome project web site.

Exemplary F5 nucleotide sequences may also be found in SEQ ID NOs:1-4. SEQ ID NOs:5-8 are the antisense sequences of SEQ ID NOs: 1-4, respectively.

The term “F5,” as used herein, also refers to naturally occurring DNA sequence variations of the F5 gene. The term “F5,” as used herein, also refers to single nucleotide polymorphisms in the F5 gene. Numerous sequence variations within the F5 gene have been identified and may be found at, for example, NCBI dbSNP and UniProt (see, *e.g.*, www.ncbi.nlm.nih.gov/snp?LinkName=gene_snp&from_uid=2153 (which is incorporated herein by reference as of the date of filing this application) which provide a list of SNPs in human F5). In some embodiments, such naturally occurring variants are included within the scope of the F5 gene sequence.

Further information on F5 can be found, for example, at www.ncbi.nlm.nih.gov/gene/2153 (which is incorporated herein by reference as of the date of filing this application).

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 coagulation Factor V 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 an F5 gene. In one embodiment, the target sequence is within the protein coding region of F5.

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
10 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
20 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
25 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
30 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 coagulation Factor V 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
35 interacts with a target RNA sequence, *e.g.*, a coagulation Factor V 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).

5 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 coagulation Factor V (F5) gene. Accordingly, the term “siRNA” is also used herein to refer to an iRNA as described above.

10 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-
15 894, 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,”
20 “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 coagulation Factor V (F5) gene. In some embodiments of the invention, a double stranded RNA (dsRNA) triggers the degradation of a target
25 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
30 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.

35 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 embodiments, 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, 16, 17, 18, 19, 20, 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 coagulation Factor V (F5) 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.*, an F5 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.*, an F5 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 coagulation Factor V 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 an F5 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 an F5 gene. Consideration of the efficacy of RNAi agents with mismatches in inhibiting expression of an F5 gene is important, especially if the particular region of complementarity in an F5 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" is intended to include dsRNA agents of the invention in which the sense and/or antisense strands 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 °C or 70 °C for 12-16 hours followed by washing (see, e.g., “Molecular Cloning: A Laboratory Manual, Sambrook, et al. (1989) Cold Spring Harbor Laboratory Press). Other conditions, such as physiologically relevant conditions as can be encountered inside an organism, can apply. The skilled person will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides.

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

“Complementary” sequences, as used herein, can also include, or be formed entirely from, non-Watson-Crick base pairs 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 coagulation Factor V gene). For example, a polynucleotide is complementary to at least a part of a coagulation Factor V mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding a coagulation Factor V gene.

Accordingly, in some embodiments, the antisense polynucleotides disclosed herein are fully complementary to the target F5 sequence.

In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target F5 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:1-4, or a fragment of any one of SEQ ID NOs:1-4, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target F5 sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the sense strand nucleotide sequences in any one of any one of Tables 2, 3, 5, 6-8, 10 and 11, or a fragment of any one of the sense strand nucleotide sequences in any one of Tables 2, 3, 5, 6-8, 10 and 11, such as about 85%, about 90%, about 95%, or fully complementary.

In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target F5 sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to a fragment of SEQ ID NO: 1 selected from the group of nucleotides 640-668; 747-771; 755-784; 830-855; 1226-1262; 3351-3380; 5821-5858; 5874-5910; 6104-6149; and 6245-6277 of SEQ ID NO: 1, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target F5 sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to a fragment of SEQ ID NO: 1 selected from the group of nucleotides 643-665; 645-667; 346-368; 5830-5852; 6104-6126; 6909-6931; and 1104-1126 of SEQ ID NO: 1, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In 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 F5 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: 5-8, or a fragment of any one of SEQ ID NOs: 5-8, 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 coagulation Factor V sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the antisense strand nucleotide sequences in any one of any one of Tables 2, 3, 5, 6-8, 10 and 11, or a fragment of any one of the antisense strand nucleotide sequences in any one of Tables 2, 3, 5, 6-8, 10 and 11, 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 duplexes AD-109630; AD-1465920; AD-1465922; AD-1615171; AD-1615234; AD-1615253; AD-1615278; and AD-1615312.

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 an F5 gene, is assessed by a reduction of the amount of F5 mRNA which can be isolated from or detected in a first cell or group

of cells in which an F5 gene is transcribed and which has or have been treated such that the expression of an F5 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 F5 expression; a human at risk for a disease or disorder that would benefit from reduction in F5 expression; a human

having a disease or disorder that would benefit from reduction in F5 expression; or human being treated for a disease or disorder that would benefit from reduction in F5 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 an F5-associated disorder in a subject. Treatment also includes a reduction of one or more sign or symptoms associated with unwanted F5 expression; diminishing the extent of unwanted F5 activation or stabilization; amelioration or palliation of unwanted F5 activation or stabilization. “Treatment” can also mean prolonging survival as compared to expected survival in the absence of treatment. In certain embodiments, the F5-associated disease or disorder is a disease or disorder associated with thrombosis. Non-limiting examples of disorders or diseases associated with thrombosis include venous thrombosis, *e.g.*, deep vein thrombosis; genetic thrombophilia, *e.g.*, Factor V leiden and prothrombin thrombophilia; purpura fulminans; acquired thrombophilia, *e.g.*, antiphospholipid syndrome and systemic lupus erythematosus; drug induced thrombophilia; arterial thrombosis, *e.g.*, myocardial infarction and peripheral arterial disease; thromboembolic disease, *e.g.*, pulmonary embolus embolic and ischemic stroke; atrial fibrillation; post-surgery deep vein thrombosis; cancer thrombosis or infectious disease thrombosis.

The term “lower” in the context of the level of F5 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 F5 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. 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 an F5-associated disease towards or to a level in a normal subject not suffering from an F5-associated disease.

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 an F5 gene or production of F5

protein, refers to preventing a subject who has at least one sign or symptom of a disease from developing further signs and symptoms 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 terms "coagulation Factor V-associated disease" or "F5-associated disease," include a disease, disorder or condition that would benefit from a decrease in F5 gene expression, replication, or protein activity. Such disorders are caused by, or associated with excessive blood clotting. In some embodiments, the F5-associated disease or disorder is a disease or disorder associated with thrombosis. Non-limiting examples of disorders or diseases associated with thrombosis include venous thrombosis, *e.g.*, deep vein thrombosis; genetic thrombophilia, *e.g.*, Factor V Leiden and prothrombin thrombophilia; purpura fulminans; acquired thrombophilia, *e.g.*, antiphospholipid syndrome and systemic lupus erythematosus; drug induced thrombophilia; arterial thrombosis, *e.g.*, myocardial infarction and peripheral arterial disease; thromboembolic disease, *e.g.*, pulmonary embolus embolic and ischemic stroke; atrial fibrillation; post-surgery deep vein thrombosis; cancer thrombosis or infectious disease thrombosis.

"Therapeutically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having an F5-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 an F5-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 coagulation Factor V gene. In certain embodiments, the iRNA includes double stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of an F5 gene in a cell, such as a cell within a subject, *e.g.*, a mammal, such as a human susceptible to developing a coagulation Factor V-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 an F5 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 F5 gene, the iRNA inhibits the expression of the F5 gene (*e.g.*, a human, a primate, a non-primate, or a rat F5 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 some 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 or cell line provided therein. In some embodiments, inhibition of expression *in vivo* is determined by knockdown of the human gene in a rodent expressing the human

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

A dsRNA includes two RNA strands that are complementary and hybridize to form a duplex structure under conditions in which the dsRNA will be used. One strand of a dsRNA (the antisense strand) includes a region of complementarity that is substantially complementary, and generally fully complementary, to a target sequence. The target sequence can be derived from the sequence of an mRNA formed during the expression of an F5 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 coagulation Factor V gene expression is not generated in the target cell by cleavage of a larger dsRNA.

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

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

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

In an aspect, a dsRNA of the invention includes at least two nucleotide sequences, a sense sequence and an anti-sense sequence. The sense strand is selected from the group of sequences provided in any one of Tables 2, 3, 5, 6-8, 10 and 11, and the corresponding antisense strand of the sense strand is selected from the group of sequences of any one of Tables 2, 3, 5, 6-8, 10 and 11. 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 coagulation Factor V gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand in any one of Tables 2, 3, 5, 6-8, 10 and 11, and the second oligonucleotide is described as the corresponding antisense strand of the sense strand in any one of Tables 2, 3, 5, 6-8, 10 and 11.

5 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 and antisense strand is selected from the sense or antisense strand of any one of duplexes AD-109630; AD-1465920; AD-1465922; AD-1615171; AD-1615234;
10 AD-1615253; AD-1615278; and AD-1615312.

It will be understood that, although the sequences in Tables 2, 5, 7 and 10 are not described as modified or conjugated sequences, the RNA of the iRNA of the invention *e.g.*, a dsRNA of the invention, may comprise any one of the sequences set forth in any one of Tables 2, 3, 5, 6-8, 10 and 11 that is un-modified, un-conjugated, or modified or conjugated differently than described therein.

15 In other words, the invention encompasses dsRNA of any one of Tables 2, 3, 5, 6-8, 10 and 11 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
20 duplex structures can also be effective (Chu and Rana (2007) *RNA* 14:1714-1719; Kim *et al.* (2005) *Nat Biotech* 23:222-226). In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided in any one of Tables 2, 3, 5, 6-8, 10 and 11, dsRNAs described herein can include at least one strand of a length of minimally 21 nucleotides. It can be reasonably expected that shorter duplexes having any one of the sequences in any one of Tables 2, 3, 5, 6-8, 10
25 and 11 minus only a few nucleotides on one or both ends can be similarly effective as compared to the dsRNAs described above. Hence, dsRNAs having a sequence of at least 19, 20, or more contiguous nucleotides derived from any one of the sequences of any one of Tables 2, 3, 5, 6-8, 10 and 11, and differing in their ability to inhibit the expression of a coagulation Factor V gene by not more than about 5, 10, 15, 20, 25, or 30 % inhibition from a dsRNA comprising the full sequence, are
30 contemplated to be within the scope of the present invention.

In addition, the RNAs provided in any one of Tables 2, 3, 5, 6-8, 10 and 11 identify a site(s) in a coagulation Factor V 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
35 the transcript anywhere within that particular site. Such an iRNA will generally include at least about 19 contiguous nucleotides from any one of the sequences provided in any one of Tables 2, 3, 5, 6-8, 10 and 11 coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in a coagulation Factor V 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 an F5 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 an F5 gene. Consideration of the efficacy of RNAi agents with mismatches in inhibiting expression of an F5 gene is important, especially if the particular region of complementarity in an F5 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 unmodified, and does not comprise, *e.g.*, chemical modifications or conjugations known in the art and described herein. In other embodiments, the RNA of an iRNA of the invention, *e.g.*, a dsRNA, is chemically modified to enhance stability or other beneficial characteristics. In certain embodiments of the invention, substantially all of the nucleotides of an iRNA of the invention are modified. In other embodiments of the invention, all of the nucleotides of an iRNA or substantially all of the nucleotides of an iRNA are modified, *i.e.*, not more than 5, 4, 3, 2, or 1 unmodified nucleotides are present in a strand of the iRNA.

The nucleic acids featured in the invention can be synthesized or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S.L. *et al.* (Edrs.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference. Modifications include, for example, end modifications, *e.g.*, 5'-end modifications (phosphorylation, conjugation, inverted linkages) or 3'-end modifications (conjugation, DNA nucleotides, inverted linkages, *etc.*); base modifications, *e.g.*, replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases; sugar modifications (*e.g.*, at the 2'-position or 4'-position) or replacement of the sugar; or backbone modifications, including modification or 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 phosphorothioate 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 phosphorothioate 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 CH₂ component parts.

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

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

Some embodiments featured in the invention include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular --CH₂--NH--CH₂--, --CH₂--N(CH₃)--O--CH₂--[known as a methylene (methylimino) or MMI backbone], --CH₂--O--N(CH₃)--CH₂--, --CH₂--N(CH₃)--N(CH₃)--CH₂-- and --N(CH₃)--CH₂--CH₂--[wherein the native phosphodiester backbone is represented as --O--P--O--CH₂--] of the above-referenced U.S. Patent No. 5,489,677, and the amide backbones of the above-referenced U.S. Patent No. 5,602,240. In some embodiments, the RNAs featured herein have morpholino backbone structures of the above-referenced U.S. Patent No. 5,034,506.

Modified RNAs can also contain one or more substituted sugar moieties. The iRNAs, *e.g.*, dsRNAs, featured herein can include one of the following at the 2'-position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Exemplary suitable modifications include O[(CH₂)_nO]_mCH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an iRNA, or a group for improving the pharmacodynamic properties of an iRNA, and other substituents having similar

properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminoethoxyethoxy, *i.e.*, a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH₂--O--CH₂--N(CH₂)₂. Further exemplary modifications include : 5'-Me-2'-F nucleotides, 5'-Me-2'-OMe nucleotides, 5'-Me-2'-deoxynucleotides, (both R and S isomers in these three families); 2'-alkoxyalkyl; and 2'-NMA (N-methylacetamide).

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

The RNA of an iRNA can also be modified to include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193).

In some embodiments, the RNA of an iRNA can also be modified to include one or more bicyclic sugar moieties. A "bicyclic sugar" is a furanosyl ring modified by the bridging of two atoms. A "bicyclic nucleoside" ("BNA") is a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4'-carbon and the 2'-carbon of the sugar ring. Thus, in some embodiments an agent of the invention may include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. In other words, an LNA is a nucleotide comprising a bicyclic sugar moiety comprising a 4'-CH₂-O-2' bridge. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193). Examples of bicyclic nucleosides for use in the polynucleotides of the invention include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, the antisense polynucleotide agents of the invention include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to 4'-(CH₂)—O-2' (LNA); 4'-(CH₂)—S-2'; 4'-(CH₂)₂—O-2' (ENA); 4'-CH(CH₃)—O-2'

(also referred to as “constrained ethyl” or “cEt”) and 4'-CH(CH₂OCH₃)—O-2' (and analogs thereof; see, *e.g.*, U.S. Patent No. 7,399,845); 4'-C(CH₃)(CH₃)—O-2' (and analogs thereof; see *e.g.*, U.S. Patent No. 8,278,283); 4'-CH₂—N(OCH₃)-2' (and analogs thereof; see *e.g.*, U.S. Patent No. 8,278,425); 4'-CH₂—O—N(CH₃)-2' (see, *e.g.*, U.S. Patent Publication No. 2004/0171570); 4'-CH₂—N(R)—O-2', wherein R is H, C1-C12 alkyl, or a protecting group (see, *e.g.*, U.S. Patent No. 7,427,672); 4'-CH₂—C(H)(CH₃)-2' (see, *e.g.*, Chattopadhyaya *et al.*, *J. Org. Chem.*, 2009, 74, 118-134); and 4'-CH₂—C(=CH₂)-2' (and analogs thereof; see, *e.g.*, U.S. Patent No. 8,278,426). 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).

The RNA of an iRNA can also be modified to include one or more constrained ethyl nucleotides. As used herein, a “constrained ethyl nucleotide” or “cEt” is a locked nucleic acid comprising a bicyclic sugar moiety comprising a 4'-CH(CH₃)-O-2' bridge. In one embodiment, a constrained ethyl nucleotide is in the S conformation referred to herein as “S-cEt.”

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

Representative publications that teach the preparation of certain of the above noted CRN include, but are not limited to, 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-
5 (acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-O-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"- phosphate, inverted base dT(idT) and others. Disclosure of this modification can be found in WO2011/005861.

Other modifications of the nucleotides of an iRNA of the invention include a 5' phosphate or
10 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

15 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. WO2013/075035 provides motifs of three identical modifications on three consecutive nucleotides 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
20 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
25 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.*, F5 gene) *in vivo*. The RNAi agent comprises a sense strand and an
30 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
35 ("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 not limited to 2'-sugar modified, such as, 2'-F, 2'-O-methyl, thymidine (T), 2'-O-methoxyethyl-5-methyluridine (Teo), 2'-O-methoxyethyladenosine (Aeo), 2'-O-methoxyethyl-5-methylcytidine (m5Ceo), and any combinations thereof.

For example, TT can be an overhang sequence for either end on either strand. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence.

The 5'- or 3'- overhangs at the sense strand, antisense strand, or both strands of the 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 dsRNAi agent may contain only a single overhang, which can strengthen the interference activity of the RNAi, without affecting its overall stability. For example, the single-stranded overhang may be located at the 3'- end of the sense strand or, alternatively, at the 3'-end of the antisense strand. The RNAi may also have a blunt end, located at the 5'-end of the antisense strand (or 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 ended bluntmer of 19 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 7, 8, 9 from the 5'end. The antisense strand contains at least one

motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5' end.

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

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

In 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, 11 from the 5' end; the antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5' end, wherein one end of the RNAi agent is blunt, while the other end comprises a 2 nucleotide overhang. In some embodiments, the 2 nucleotide overhang is at the 3' end of the antisense strand.

When the 2 nucleotide overhang is at the 3' end of the antisense strand, there may be two phosphorothioate internucleotide linkages between the terminal three nucleotides, wherein two of the three nucleotides are the overhang nucleotides, and the third nucleotide is a paired nucleotide next to the overhang nucleotide. In one embodiment, the RNAi agent additionally has two phosphorothioate internucleotide linkages between the terminal three nucleotides at both the 5' end of the sense strand and at the 5' end of the antisense strand. In certain embodiments, every nucleotide in the sense strand and the antisense strand of the dsRNAi agent, including the nucleotides that are part of the motifs are modified nucleotides. In certain embodiments each residue is independently modified with a 2'-O-methyl or 3'-fluoro, *e.g.*, in an alternating motif. Optionally, the dsRNAi agent further comprises a ligand (*e.g.*, 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, 13 from the 5' end; wherein the 3' end of the first strand and the 5' end of the second strand form a blunt end and the second strand is 1-4 nucleotides longer at its 3' end than the first strand, wherein the duplex region which is at least 25 nucleotides in length, and the second strand is sufficiently complementary to a target mRNA along at least 19 nucleotide of the second strand length to reduce target gene expression when the RNAi agent is introduced into a mammalian cell, and wherein Dicer cleavage of the dsRNAi agent results in an siRNA comprising the 3'-end of the second strand, thereby reducing expression of the target gene in the mammal. Optionally, the dsRNAi agent further comprises a ligand.

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

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

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

The sense strand of the dsRNAi agent may contain at least one motif of three identical modifications on three consecutive nucleotides at the cleavage site of the strand; and the antisense strand may have at least one motif of three identical modifications on three consecutive nucleotides at or near the cleavage site of the strand. When the sense strand and the antisense strand form a dsRNA

duplex, the sense strand and the antisense strand can be so aligned that one motif of the three nucleotides on the sense strand and one motif of the three nucleotides on the antisense strand have at least one nucleotide overlap, *i.e.*, at least one of the three nucleotides of the motif in the sense strand forms a base pair with at least one of the three nucleotides of the motif in the antisense strand.

5 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
10 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,
15 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
20 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.

25 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
30 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
35 an overlap of one, two or three nucleotides; two modifications one strand fall on each side of the lead motif, having an overlap of one, two or three nucleotides in the duplex region.

In some embodiments, every nucleotide in the sense strand and antisense strand of the dsRNAi agent, including the nucleotides that are part of the motifs, may be modified. Each

nucleotide may be modified with the same or different modification which can include one or more alteration of one or both of the non-linking phosphate oxygens or of one or more of the linking phosphate oxygens; alteration of a constituent of the ribose sugar, *e.g.*, of the 2'-hydroxyl on the ribose sugar; wholesale replacement of the phosphate moiety with "dephospho" linkers; modification or replacement of a naturally occurring base; and replacement or modification of the ribose-phosphate backbone.

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

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

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

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

In certain embodiments, the N_a or N_b comprise modifications of an alternating pattern. The term "alternating motif" as used herein refers to a motif having one or more modifications, each modification occurring on alternating nucleotides of one strand. The alternating nucleotide may refer to one per every other nucleotide or one per every three nucleotides, or a similar pattern. For

example, if A, B and C each represent one type of modification to the nucleotide, the alternating motif can be “ABABABABABAB...,” “AABBAABBAABB...,” “AABAABAABAAB...,” “AAABAAABAAB...,” “AAABBBAAABBB...,” or “ABCABCABCABC...,” *etc.*

The type of modifications contained in the alternating motif may be the same or different.

- 5 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.*

- 10 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.

- 20 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.

- 25 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.

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

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

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

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

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

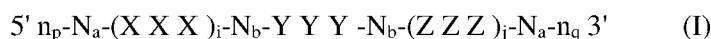
In one embodiment, the dsRNAi agent comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mismatch may occur in the overhang region or the duplex region. The base pair may be ranked on the basis of their propensity to promote dissociation or melting (*e.g.*, on the free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

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

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

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

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



wherein:

i and j are each independently 0 or 1;

p and q are each independently 0-6;

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

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

each n_p and n_q independently represent an overhang nucleotide;

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

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

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

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

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

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

10 5' n_p - N_a -XXX- N_b -YYY- N_a - n_q 3' (Ic); or

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

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

15 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.

20 When the sense strand is represented as formula (Id), each N_b independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2, or 0 modified nucleotides. In some embodiments, 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.

25 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.

30 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;

35 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.

5 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
 10 the first paired nucleotide within the duplex region, from the 5'-end. In some embodiments, the
 $Y'Y'Y'$ motif occurs at positions 11, 12, 13.

In 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:

15 $5' n_q'-N_a'-Z'Z'Z'-N_b'-Y'Y'Y'-N_a'-n_p', 3' \quad (\text{IIb});$

$5' n_q'-N_a'-Y'Y'Y'-N_b'-X'X'X'-n_p', 3' \quad (\text{IIc});$ or

$5' n_q'-N_a'-Z'Z'Z'-N_b'-Y'Y'Y'-N_b'-X'X'X'-N_a'-n_p', 3' \quad (\text{IId}).$

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'
 20 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
 25 nucleotides.

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

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

$5' n_p'-N_a'-Y'Y'Y'-N_a'-n_q', 3' \quad (\text{Ia}).$

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.

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

Each nucleotide of the sense strand and antisense strand may be independently modified with
 LNA, CRN, UNA, cEt, HNA, CeNA, 2'-methoxyethyl, 2'-O-methyl, 2'-O-allyl, 2'-C-allyl, 2'-
 hydroxyl, or 2'-fluoro. For example, each nucleotide of the sense strand and antisense strand is

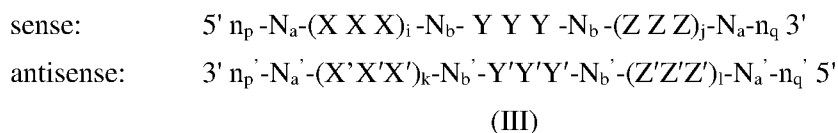
independently modified with 2'-O-methyl or 2'-fluoro. Each X, Y, Z, X', Y', and Z', in particular, may represent a 2'-O-methyl modification or a 2'-fluoro modification.

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

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

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

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



wherein:

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

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

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

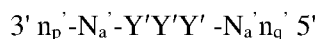
each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

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

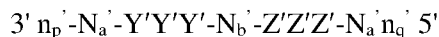
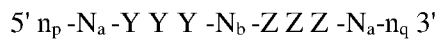
XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides.

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

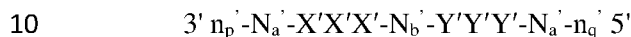
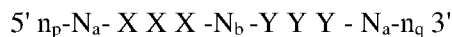
Exemplary combinations of the sense strand and antisense strand forming an iRNA duplex include the formulas below:



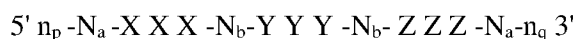
5 (IIIa)



(IIIb)



(IIIc)



(IIId)

15 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
20 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.

25 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.

30 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
35 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 *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.

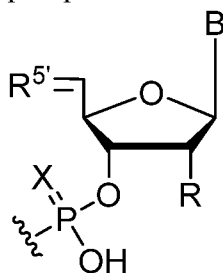
In one embodiment, two dsRNAi agents represented by at least one of formulas (III), (IIIa), (IIIb), (IIIc), and (IIId) are linked to each other at the 5' end, and one or both of the 3' ends, and are optionally conjugated to a ligand. Each of the agents can target the same gene or two different genes;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

Various publications describe multimeric 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 C1-20alkoxy (*e.g.*, methoxy or n-hexadecyloxy);

R5' is =C(H)-P(O)(OH)₂ and the double bond between the C5' carbon and R5' is in the E or Z orientation (*e.g.*, E orientation); and

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

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

Vinyl phosphonate modifications are also contemplated for the compositions and methods of the instant disclosure. An exemplary vinyl phosphonate structure includes the preceding structure, where 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 (such as, cyclic) carrier to which is attached a carbohydrate ligand. A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS). A cyclic carrier may be a carbocyclic ring system, i.e., all ring atoms are carbon atoms, or a heterocyclic ring system, i.e., one or more ring atoms may be a heteroatom, e.g., nitrogen, oxygen, sulfur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, e.g. fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds.

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

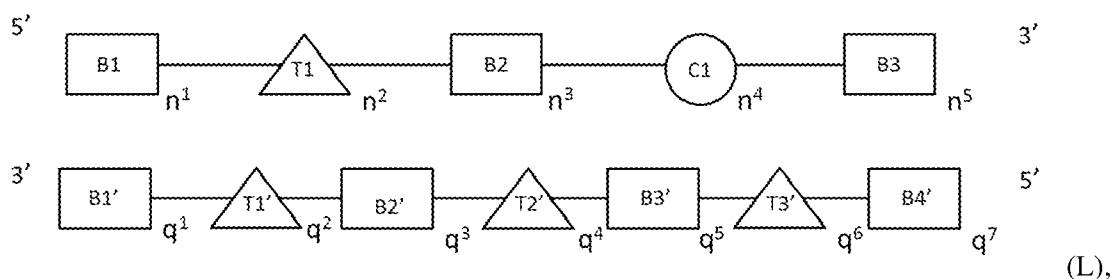
i. Thermally Destabilizing Modifications

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 (*i.e.*, at positions 2-9 of the 5'-end of the antisense strand or at positions 2-8 of the 5'-end of the antisense strand) to reduce or inhibit off-target gene silencing.

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

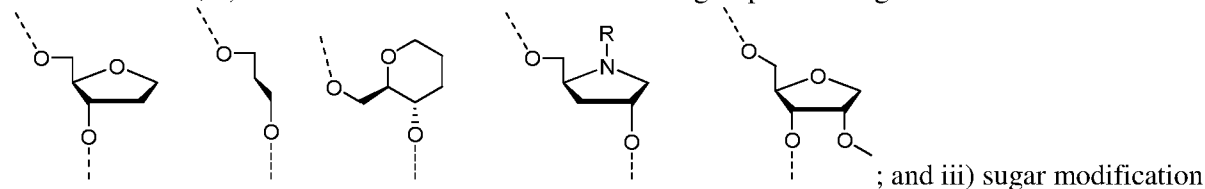
It has been discovered that dsRNAs with an antisense strand comprising at least one thermally destabilizing modification of the duplex within the first 9 nucleotide positions, counting from the 5' end, of the antisense strand have reduced off-target gene silencing activity. Accordingly, in some embodiments,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

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

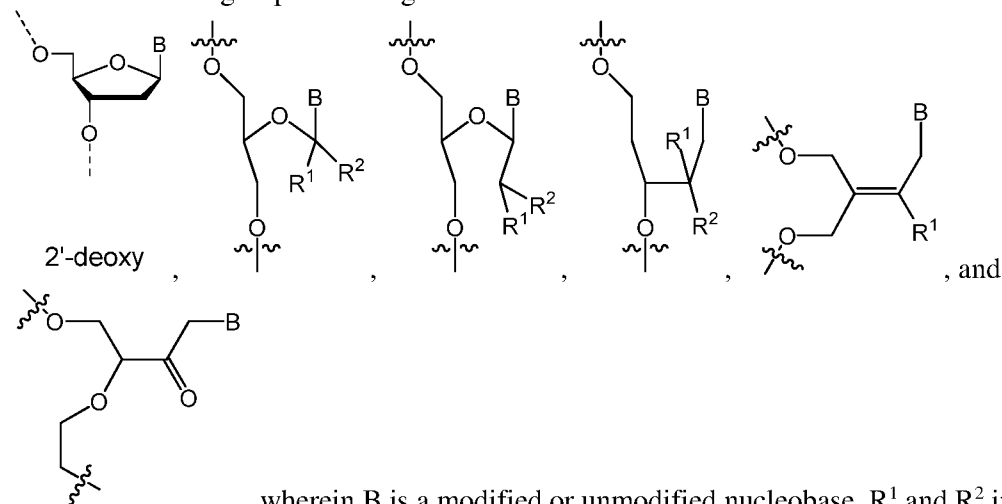


In formula (L), B1, B2, B3, B1', B2', B3', and B4' each are independently a nucleotide containing a modification selected from the group consisting of 2'-O-alkyl, 2'-substituted alkoxy, 2'-substituted alkyl, 2'-halo, ENA, and BNA/LNA. In one embodiment, B1, B2, B3, B1', B2', B3', and B4' each contain 2'-OMe modifications. In one embodiment, B1, B2, B3, B1', B2', B3', and B4' each contain 2'-OMe or 2'-F modifications. In one embodiment, at least one of B1, B2, B3, B1', B2', B3', and B4' contain 2'-O-N-methylacetamido (2'-O-NMA, 2'-O-CH₂C(O)N(Me)H) modification.

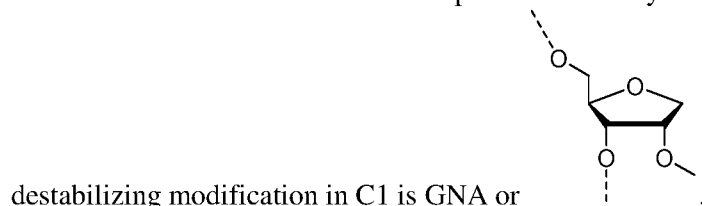
C1 is a thermally destabilizing nucleotide placed at a site opposite to the seed region of the antisense strand (*i.e.*, at positions 2-8 of the 5'-end of the antisense strand or at positions 2-9 of the 5'-end of the antisense strand). For example, C1 is at a position of the sense strand that pairs with a nucleotide at positions 2-8 of the 5'-end of the antisense strand. In one example, C1 is at position 15 from the 5'-end of the sense strand. C1 nucleotide bears the thermally destabilizing modification which can include abasic modification; mismatch with the opposing nucleotide in the duplex; and sugar modification such as 2'-deoxy modification or acyclic nucleotide *e.g.*, unlocked nucleic acids (UNA) 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:



selected from the group consisting of:



, 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.

5 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,

10 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
15 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,
20 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).

30 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
35 the 5'-end of the antisense strand).

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

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

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

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

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

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

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

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

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

optionally with at least 2 additional TT at the 3'-end of the antisense strand; with two phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand).

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

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

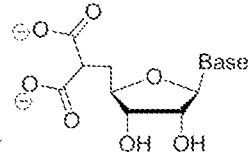
In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'-F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4'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

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

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

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

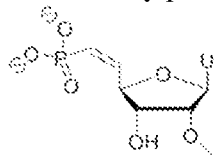
The RNAi agent can comprise a phosphorus-containing group at the 5'-end of the sense strand or antisense strand. The 5'-end phosphorus-containing group can be 5'-end phosphate (5'-P), 5'-end phosphorothioate (5'-PS), 5'-end phosphorodithioate (5'-PS₂), 5'-end vinylphosphonate (5'-

VP), 5'-end methylphosphonate (MePhos), or 5'-deoxy-5'-C-malonyl (). When the 5'-end phosphorus-containing group is 5'-end vinylphosphonate (5'-VP), the 5'-VP can be either

5'-*E*-VP isomer (*i.e.*, *trans*-vinylphosphonate,



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



vinylphosphonate, or mixtures thereof.

- 5 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.

- 10 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.

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

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

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

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

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

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'-PS₂.

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

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

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

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

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

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

two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-PS₂.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-OMe, and q⁷ is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

strand). The RNAi agent also comprises a 5'-PS₂ and a targeting ligand. In one embodiment, the 5'-PS₂ is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

In one embodiment, B1 is 2'-OMe or 2'-F, n¹ is 8, T1 is 2'-F, n² is 3, B2 is 2'-OMe, n³ is 7, n⁴ is 0, B3 is 2'-OMe, n⁵ is 3, B1' is 2'-OMe or 2'-F, q¹ is 9, T1' is 2'-F, q² is 1, B2' is 2'-OMe or 2'-F, q³ is 4, T2' is 2'-F, q⁴ is 2, B3' is 2'-OMe or 2'-F, q⁵ is 5, T3' is 2'-F, q⁶ is 1, B4' is 2'-OMe, and q⁷ is 1; with two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'-deoxy-5'-C-malonyl and a targeting ligand. In one embodiment, the 5'-deoxy-5'-C-malonyl is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

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

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

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

5'-E-VP, 5'-Z-VP, or combination thereof) and a targeting ligand. In one embodiment, the 5'-VP is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

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

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

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

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

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

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

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

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

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

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

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

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

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

- (a) a sense strand having:
- (i) a length of 21 nucleotides;
 - (ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker; and
 - (iii) 2'-F modifications at positions 1, 3, 5, 7, 9 to 11, 13, 17, 19, and 21, and 2'-OMe modifications at positions 2, 4, 6, 8, 12, 14 to 16, 18, and 20 (counting from the 5' end);

and

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

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

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

- (a) a sense strand having:
- (i) a length of 21 nucleotides;
 - (ii) an ASGPR ligand attached to the 3'-end, wherein said ASGPR ligand comprises three GalNAc derivatives attached through a trivalent branched linker;
 - (iii) 2'-F modifications at positions 1, 3, 5, 7, 9 to 11, 13, 15, 17, 19, and 21, and 2'-OMe modifications at positions 2, 4, 6, 8, 12, 14, 16, 18, and 20 (counting from the 5' end);
- and
- (iv) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3 (counting from the 5' end);

and

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 25 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 19 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 21 nucleotides;

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

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

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

In certain embodiments, the iRNA for use in the methods of the invention is an agent selected from agents listed in any one of Tables 2, 3, 5, 6-8, 10 and 11. 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. Acad. Sci. USA*, 1989, 86: 6553-6556). In other embodiments, the ligand is cholic acid (Manoharan *et al.*, *Biorg. Med. Chem. Lett.*, 1994, 4:1053-1060), a thioether, *e.g.*, beryl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660:306-309; Manoharan *et al.*, *Biorg. Med. Chem. Lett.*, 1993, 3:2765-2770), a thiocholesterol (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.*, dihexadecyl-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-carboxyloxycholesterol 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
 5 copolymer, poly(L-lactide-co-glycolide) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine,
 10 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,
 15 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,
 25 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),
 30 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-
 35 peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, or multivalent fucose. The ligand can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an activator of NF-κB.

The ligand can be a substance, *e.g.*, a drug, which can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.*, by disrupting the cell's microtubules, microfilaments, or intermediate filaments. The drug can be, for example, taxol, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide
5 A, indanocene, or myoservin.

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

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

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

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

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

standard phosphoramidites and non-standard phosphoramidites that are commercially available and routinely used in oligonucleotide synthesis.

A. Lipid Conjugates

5 In certain embodiments, the ligand or conjugate is a lipid or lipid-based molecule. 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
10 aspirin can be used. A lipid or lipid-based ligand can (a) increase resistance to degradation of the conjugate, (b) increase targeting or transport into a target cell or cell membrane, or (c) can be used to adjust binding to a serum protein, *e.g.*, HSA.

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

In certain embodiments, the lipid based ligand binds HSA. In some embodiments, 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
20 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,
25 *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 some embodiments, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopodia. If the agent is a peptide, it can be modified, including a peptidylmimetic,
35 invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. In some embodiments, the helical agent is an alpha-helical agent, which has a lipophilic and a lipophobic phase.

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

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: 25). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO:26) 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:27) and the Drosophila Antennapedia protein (RQIKIWFQNRRMKWKK (SEQ ID NO:28) 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 peptidomimetics may include D-amino acids, as well as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the integrin ligand, 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.

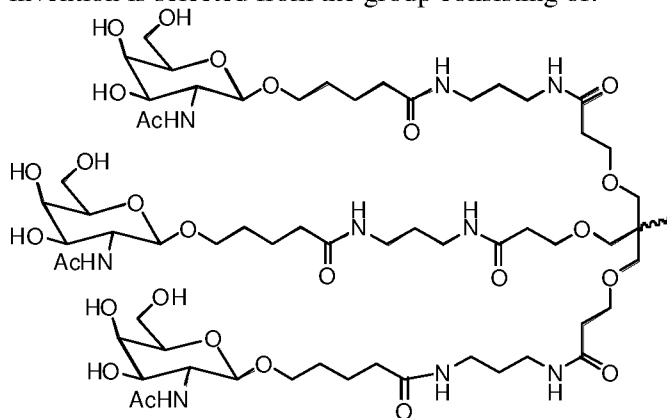
In certain embodiments, the double stranded RNAi agents of the invention comprise one GalNAc or GalNAc derivative attached to the iRNA agent. In certain embodiments, the double

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.

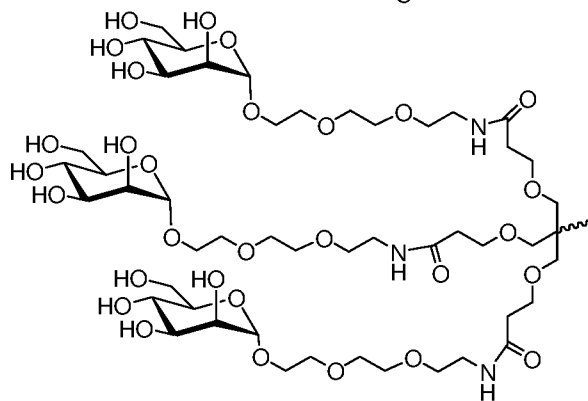
In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of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

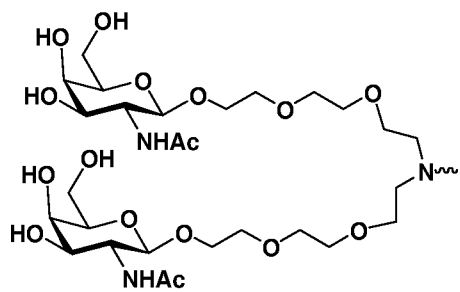
In one embodiment, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



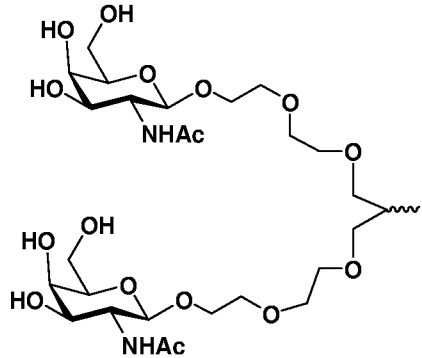
Formula II,



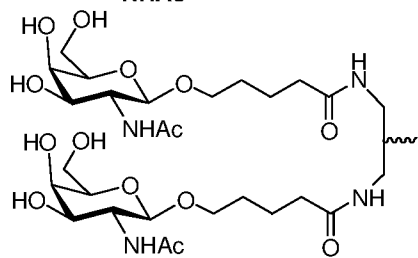
Formula III,



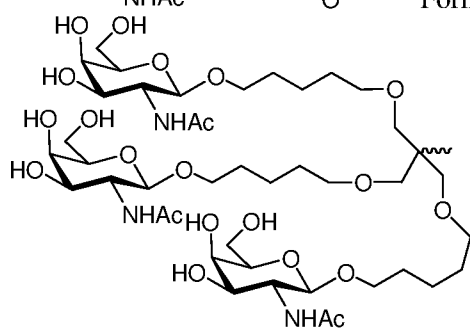
Formula IV,



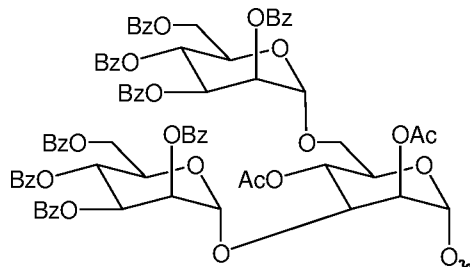
Formula V,



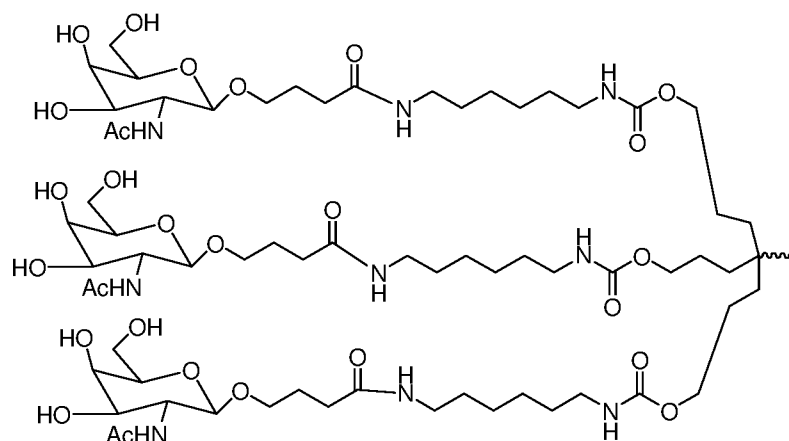
Formula VI,



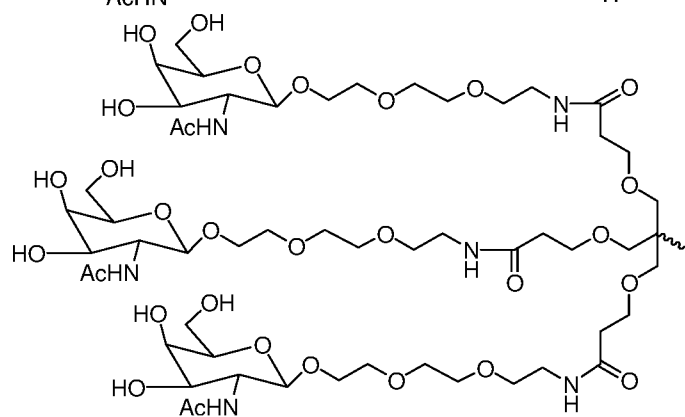
Formula VII,



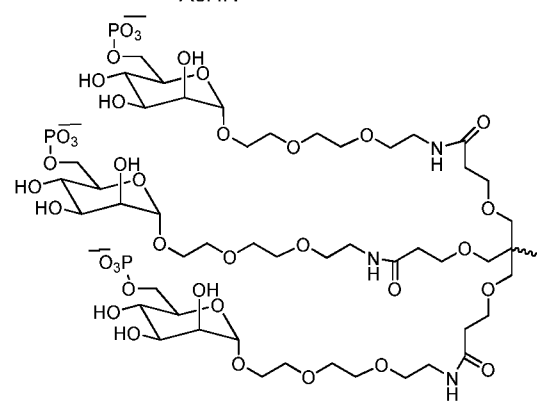
Formula VIII,



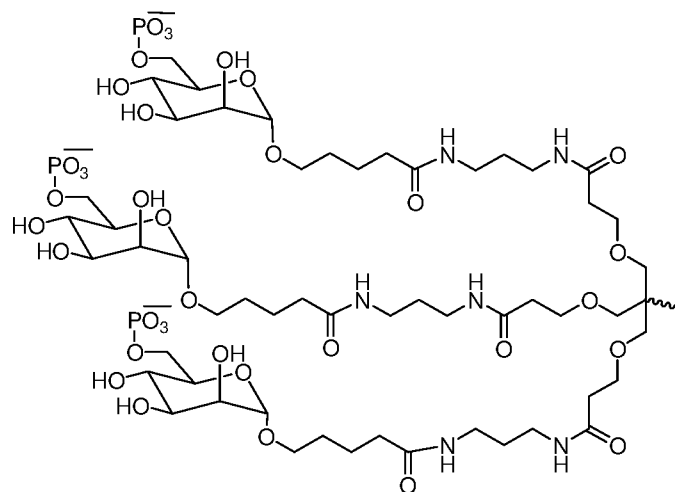
Formula IX,



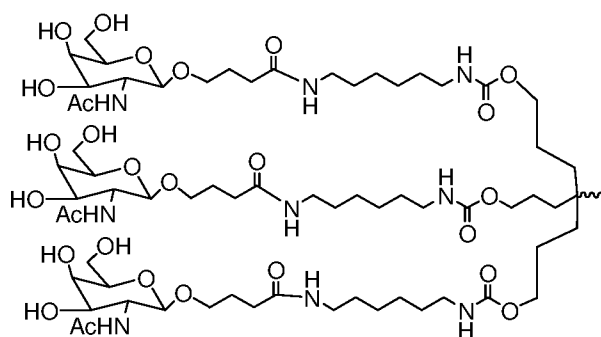
Formula X,



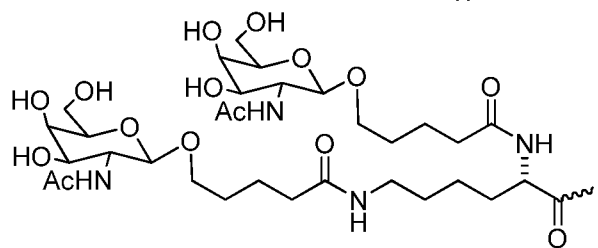
Formula XI,



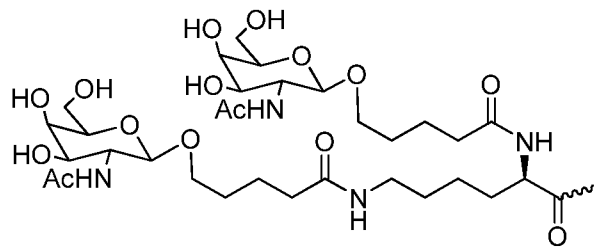
Formula XII,



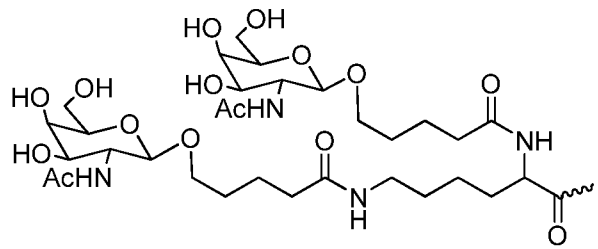
Formula XIII,



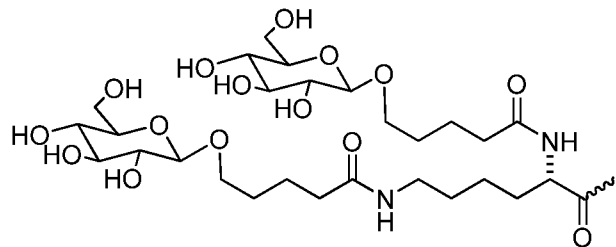
Formula XIV,



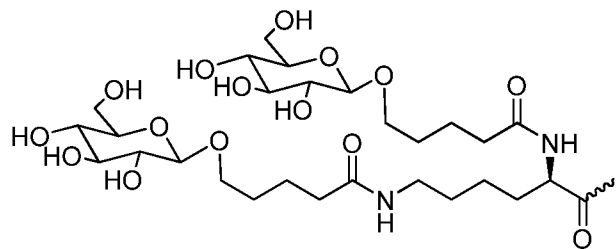
Formula XV,



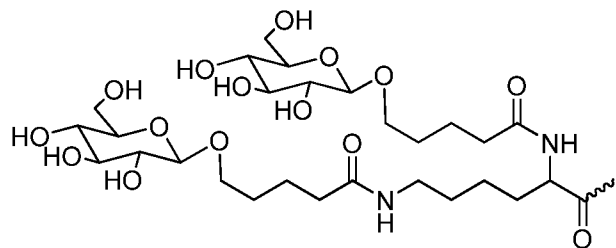
Formula XVI,



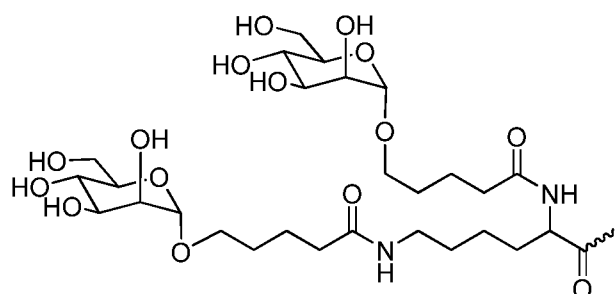
Formula XVII,



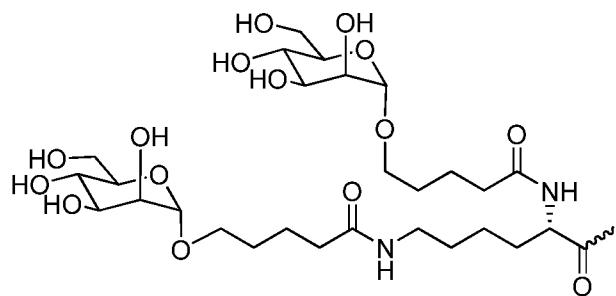
Formula XVIII,



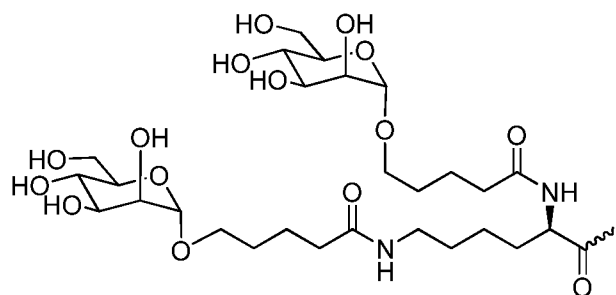
Formula XIX,



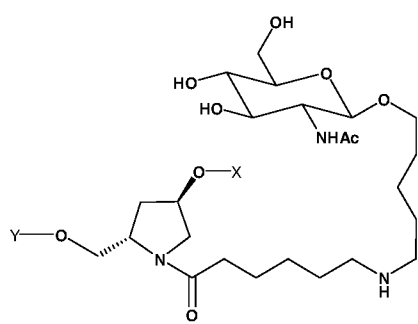
Formula XX,



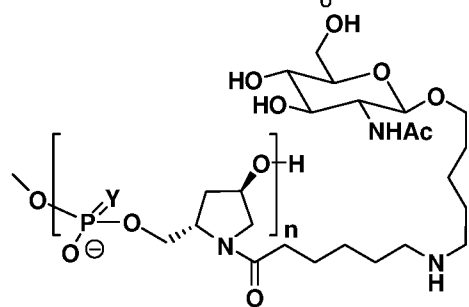
Formula XXI,



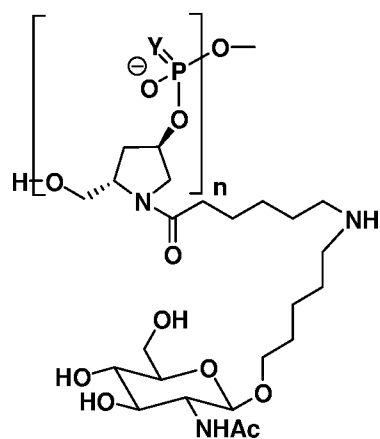
Formula XXII,



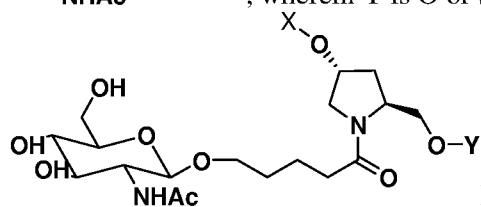
Formula XXIII;



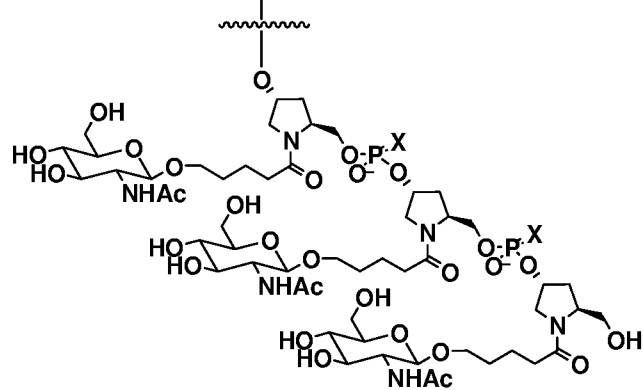
, wherein Y is O or S and n is 3 -6 (Formula XXIV);



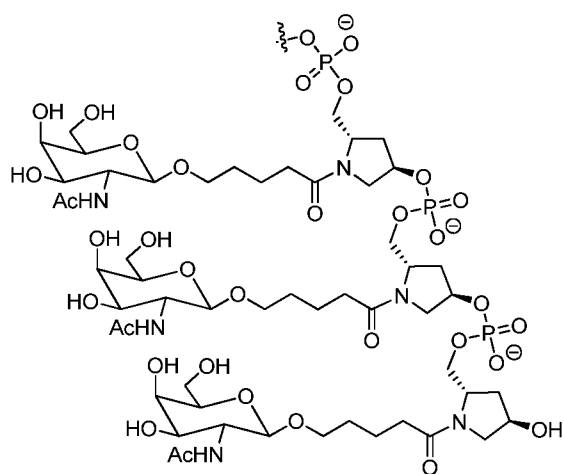
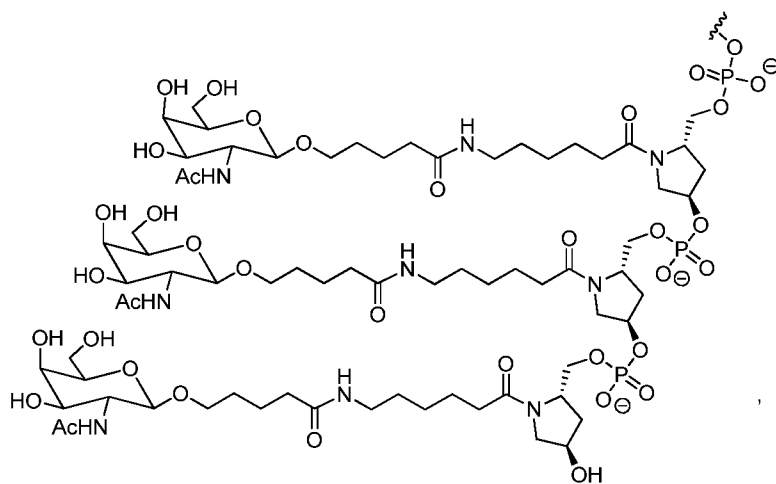
, wherein Y is O or S and n is 3-6 (Formula XXV);



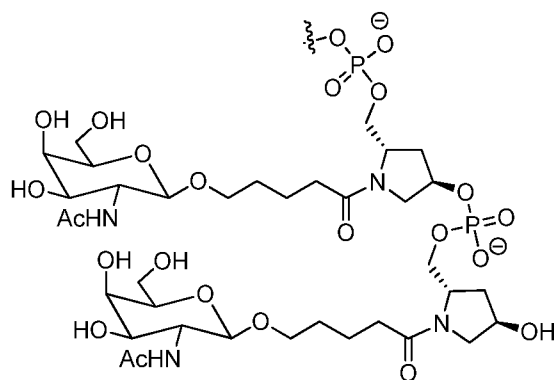
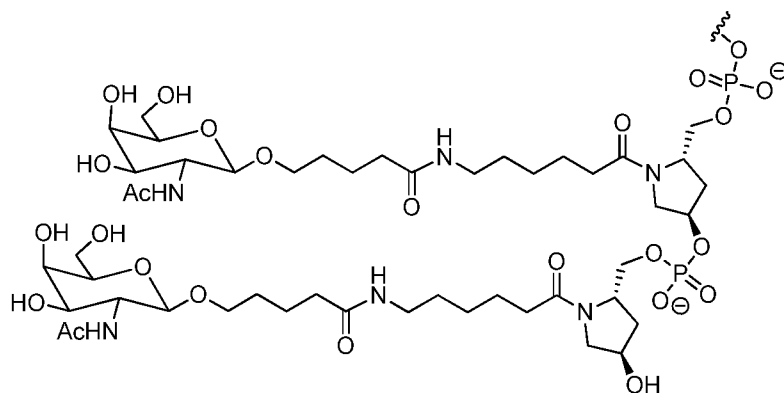
Formula XXVI;



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

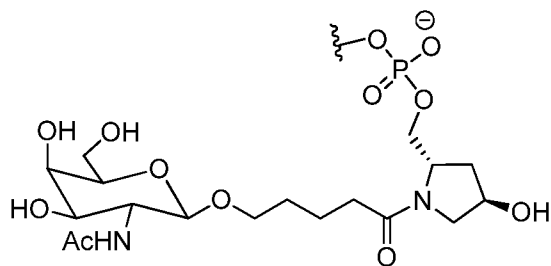
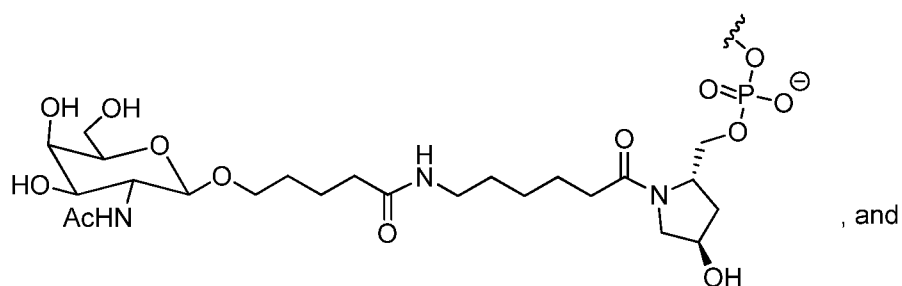


Formula XXVII; Formula XXIX;



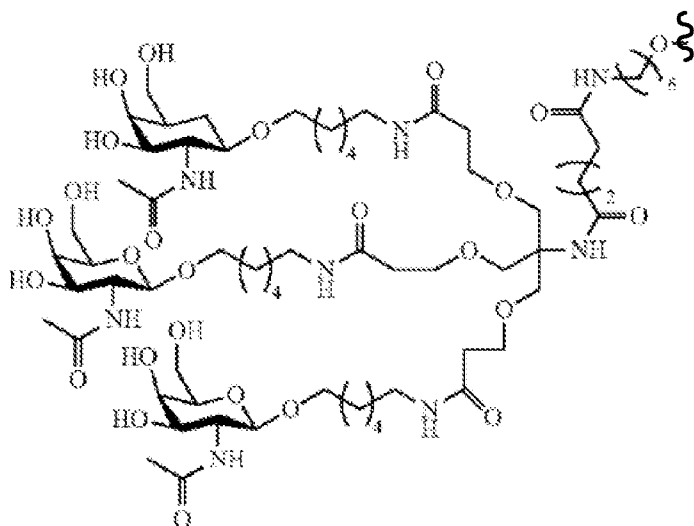
Formula XXX;

Formula XXXI;



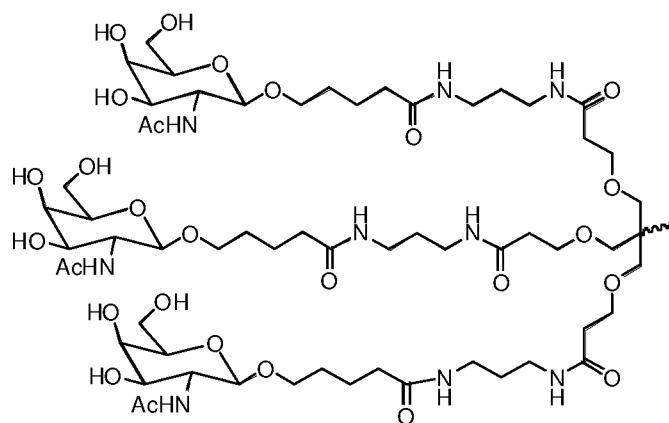
Formula XXXII;

Formula XXXIII.



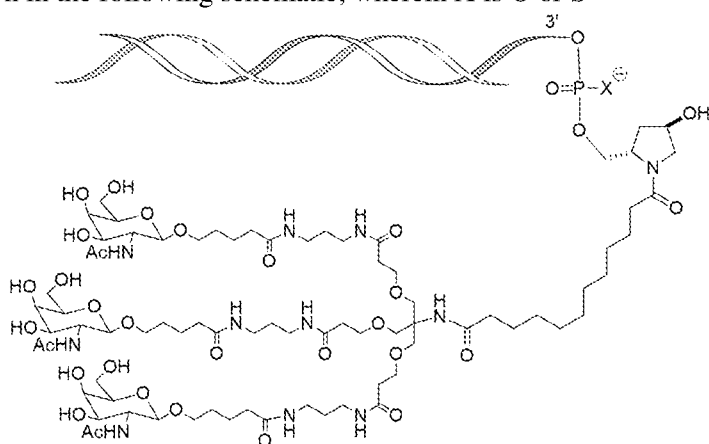
5 Formula XXXIV.

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

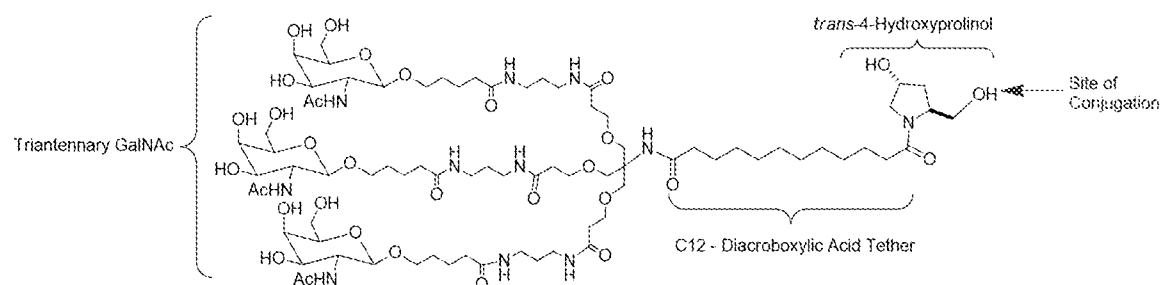


Formula II.

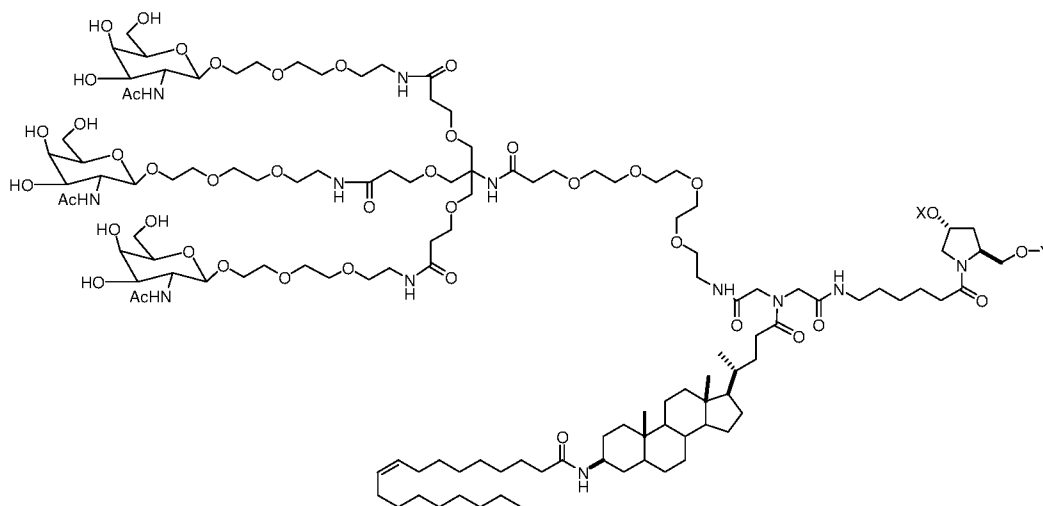
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate *via* a linker as shown in the following schematic, wherein X is O or S



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

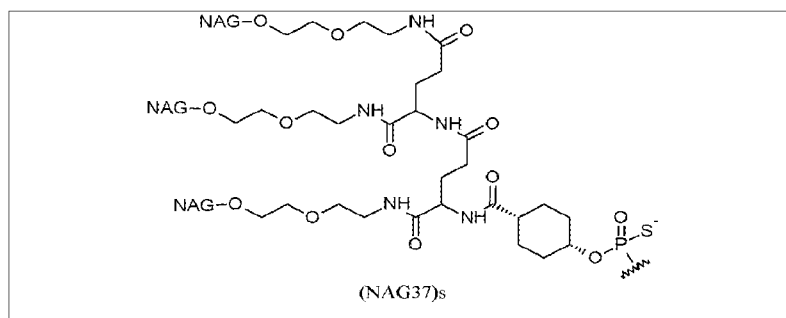


Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,



(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 antisense 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, SO₂, SO₂NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, aryl, heteroaryl, heterocycl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclalkyl, alkylheterocyclalkenyl, alkylheterocyclalkynyl, alkenylheterocyclalkyl, alkenylheterocyclalkenyl, alkenylheterocyclalkynyl, alkynylheterocyclalkyl, alkynylheterocyclalkenyl, alkynylheterocyclalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylheteroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO₂, N(R₈), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, 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).

5 *i. Redox cleavable linking groups*

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

ii. Phosphate-based cleavable linking groups

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

iii. Acid cleavable linking groups

In other embodiments, a cleavable linker comprises an acid cleavable linking group. An acid cleavable linking group is a linking group that is cleaved under acidic conditions. In certain

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

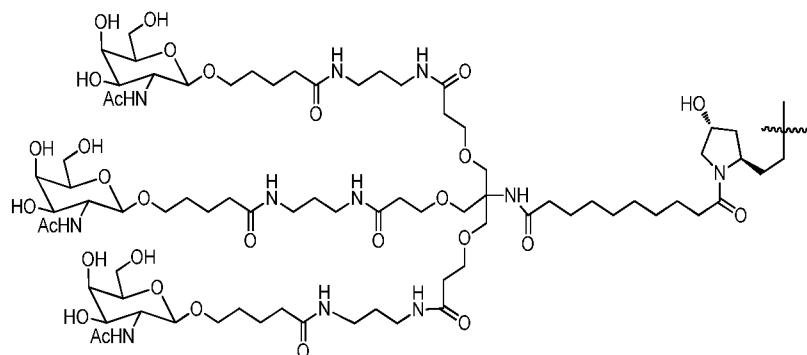
iv. Ester-based linking groups

In other embodiments, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include, but are not limited to, esters of alkylene, alkenylene and alkynylene groups. Ester cleavable linking groups have the general formula $-C(O)O-$, or $-OC(O)-$. These candidates can be evaluated using methods analogous to those described above.

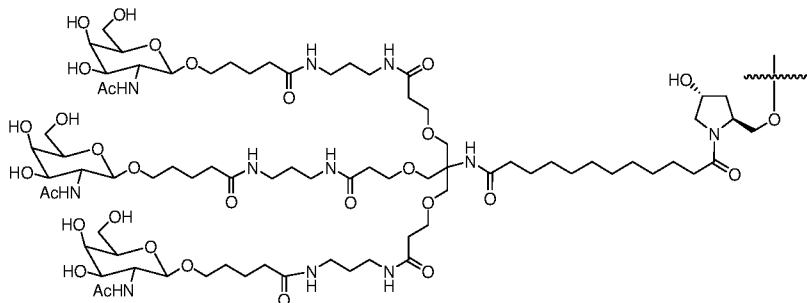
v. Peptide-based cleaving groups

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

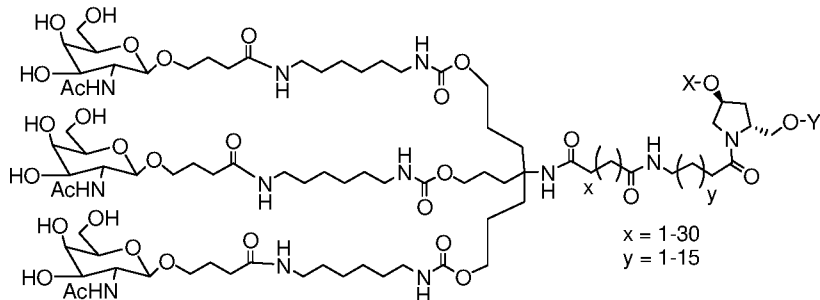
In some embodiments, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



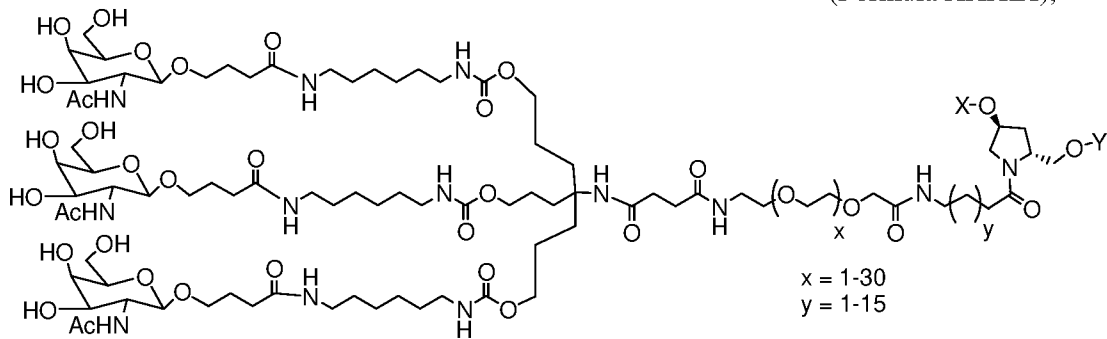
(Formula XXXVII),



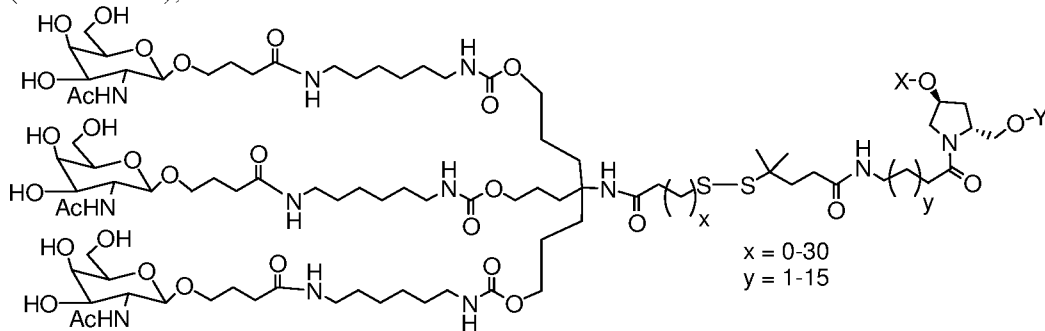
(Formula XXXVIII),



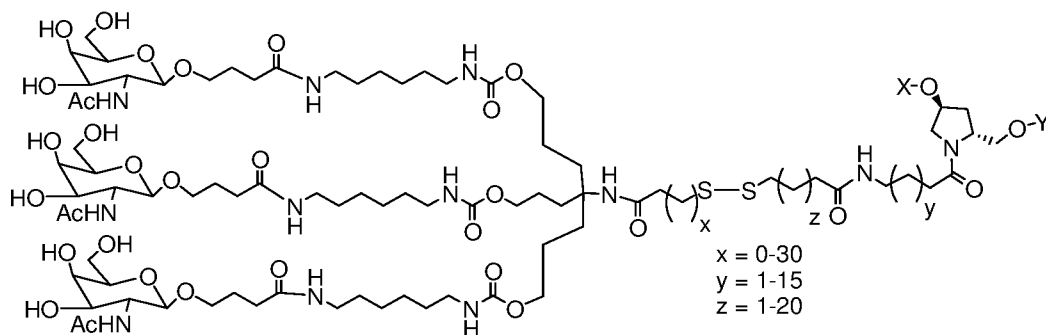
(Formula XXXIX),



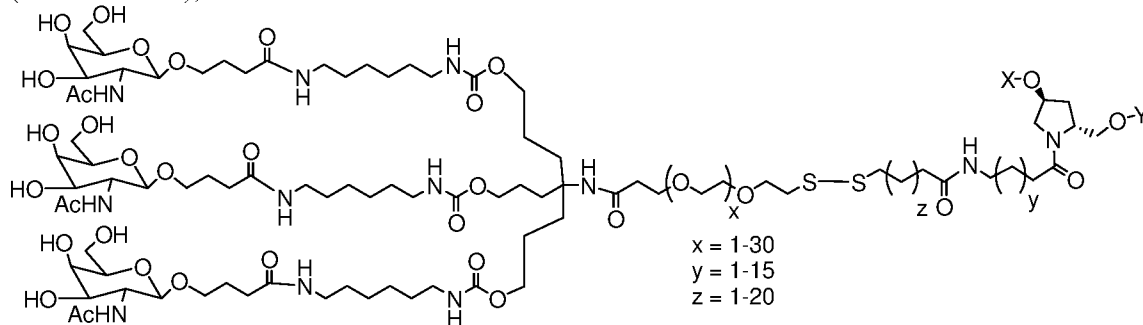
(Formula XL),



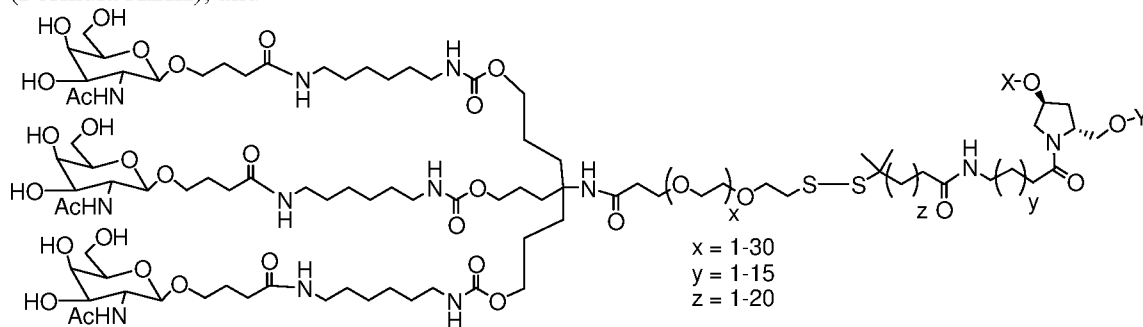
(Formula XLI),



(Formula XLII),



(Formula XLIII), and

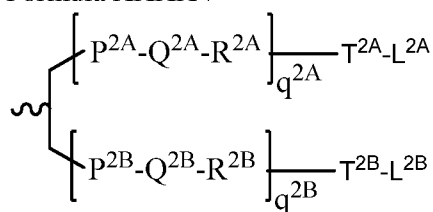


(Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

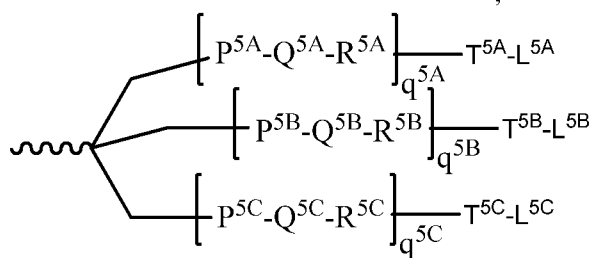
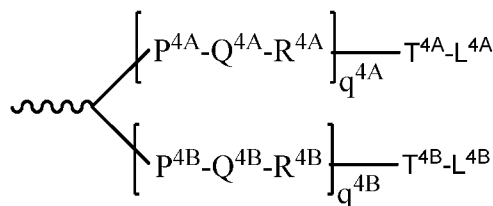
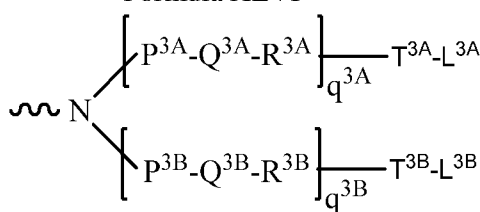
In certain embodiments of the compositions and methods of the invention, a ligand is one or more “GalNAc” (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

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 XXXV



Formula XLVI



, or

;

Formula XLVII

Formula XLVIII

5 wherein:

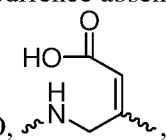
$\text{q}^{2\text{A}}$, $\text{q}^{2\text{B}}$, $\text{q}^{3\text{A}}$, $\text{q}^{3\text{B}}$, $\text{q}^{4\text{A}}$, $\text{q}^{4\text{B}}$, $\text{q}^{5\text{A}}$, $\text{q}^{5\text{B}}$ and $\text{q}^{5\text{C}}$ represent independently for each occurrence 0-20 and wherein the repeating unit can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

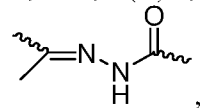
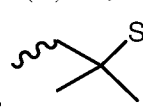
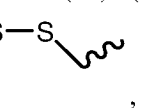
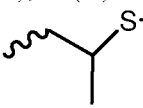
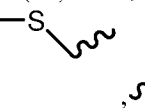
$\text{P}^{2\text{A}}$, $\text{P}^{2\text{B}}$, $\text{P}^{3\text{A}}$, $\text{P}^{3\text{B}}$, $\text{P}^{4\text{A}}$, $\text{P}^{4\text{B}}$, $\text{P}^{5\text{A}}$, $\text{P}^{5\text{B}}$, $\text{P}^{5\text{C}}$, $\text{T}^{2\text{A}}$, $\text{T}^{2\text{B}}$, $\text{T}^{3\text{A}}$, $\text{T}^{3\text{B}}$, $\text{T}^{4\text{A}}$, $\text{T}^{4\text{B}}$, $\text{T}^{5\text{A}}$, $\text{T}^{5\text{B}}$, $\text{T}^{5\text{C}}$ are each

independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2 , CH_2NH or CH_2O ;

10 $\text{Q}^{2\text{A}}$, $\text{Q}^{2\text{B}}$, $\text{Q}^{3\text{A}}$, $\text{Q}^{3\text{B}}$, $\text{Q}^{4\text{A}}$, $\text{Q}^{4\text{B}}$, $\text{Q}^{5\text{A}}$, $\text{Q}^{5\text{B}}$, $\text{Q}^{5\text{C}}$ 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 , $\text{N}(\text{R}^{\text{N}})$, $\text{C}(\text{R}')=\text{C}(\text{R}'')$, $\text{C}\equiv\text{C}$ or $\text{C}(\text{O})$;

$\text{R}^{2\text{A}}$, $\text{R}^{2\text{B}}$, $\text{R}^{3\text{A}}$, $\text{R}^{3\text{B}}$, $\text{R}^{4\text{A}}$, $\text{R}^{4\text{B}}$, $\text{R}^{5\text{A}}$, $\text{R}^{5\text{B}}$, $\text{R}^{5\text{C}}$ are each independently for each occurrence absent, NH, O,

S, CH_2 , $\text{C}(\text{O})\text{O}$, $\text{C}(\text{O})\text{NH}$, $\text{NHCH}(\text{R}^{\text{a}})\text{C}(\text{O})$, $-\text{C}(\text{O})-\text{CH}(\text{R}^{\text{a}})-\text{NH}-$, CO, $\text{CH}=\text{N}-\text{O}$, ,

15 , , , , , or heterocyclyl;

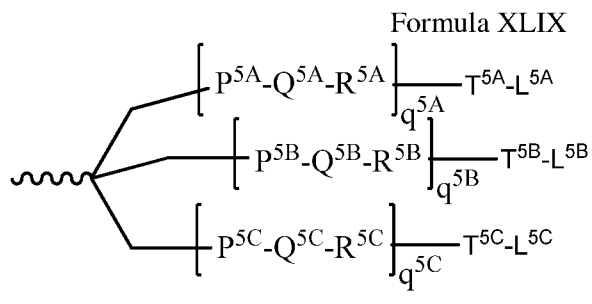
$\text{L}^{2\text{A}}$, $\text{L}^{2\text{B}}$, $\text{L}^{3\text{A}}$, $\text{L}^{3\text{B}}$, $\text{L}^{4\text{A}}$, $\text{L}^{4\text{B}}$, $\text{L}^{5\text{A}}$, $\text{L}^{5\text{B}}$ and $\text{L}^{5\text{C}}$ represent the ligand; *i.e.* each independently for each

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

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



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

5 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;
 10 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;
 15 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
 20 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
 25 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,
 30 therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of iRNA inhibition of gene expression. Consequently, comparable results can often be obtained with shorter iRNAs when chimeric dsRNAs are used, compared to phosphorothioate deoxy dsRNAs hybridizing to

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

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

IV. Delivery of an iRNA of the Invention

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

In general, any method of delivering a nucleic acid molecule (*in vitro* or *in vivo*) can be adapted for use with an iRNA of the invention (see *e.g.*, Akhtar S. and Julian RL. (1992) *Trends Cell. Biol.* 2(5):139-144 and WO94/02595, which are incorporated herein by reference in their entireties).

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

In an alternative embodiment, the iRNA can be delivered using drug delivery systems such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery systems facilitate binding of an iRNA molecule (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an iRNA by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an iRNA, or induced to form a vesicle or micelle (see *e.g.*, Kim SH, *et al.* (2008) *Journal of Controlled Release* 129(2):107-116) that encases an iRNA. The formation of vesicles or micelles further prevents degradation of the iRNA when administered systemically. Methods for making and administering cationic- iRNA complexes are well within the abilities of one skilled in the art (see *e.g.*, Sorensen, DR, *et al.* (2003) *J. Mol. Biol.* 327:761-766; Verma, UN, *et al.* (2003) *Clin. Cancer Res.* 9:1291-1300; Arnold, AS *et al.* (2007) *J. Hypertens.* 25:197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of iRNAs include DOTAP (Sorensen, DR., *et al.* (2003), *supra*; Verma, UN, *et al.* (2003), *supra*), "solid nucleic acid lipid particles" (Zimmermann, TS, *et al.* (2006) *Nature* 441:111-114), cardiolipin (Chien, PY, *et al.* (2005) *Cancer Gene Ther.* 12:321-328; Pal, A, *et al.* (2005) *Int J. Oncol.* 26:1087-1091), polyethyleneimine (Bonnet ME, *et al.* (2008) *Pharm. Res.* Aug 16 Epub ahead of print; Aigner, A. (2006) *J. Biomed. Biotechnol.* 71659), Arg-Gly-Asp (RGD) peptides (Liu, S. (2006) *Mol. Pharm.* 3:472-487), and polyamidoamines (Tomalia, DA, *et al.* (2007) *Biochem. Soc. Trans.* 35:61-67; Yoo, H., *et al.* (1999) *Pharm. Res.* 16:1799-1804). In some embodiments, an iRNA forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of iRNAs and cyclodextrins can be found in U.S. Patent No. 7,427,605, which is herein incorporated by reference in its entirety.

A. Vector encoded iRNAs of the Invention

iRNA targeting the coagulation Factor V 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 coagulation Factor V-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 coagulation Factor V 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 coagulation Factor V 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, about 0.3 mg/kg to 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

5 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
10 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;
15 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

20 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
25 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
30 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
35 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 coagulation Factor V-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 coagulation Factor V-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 Coagulation Factor V Expression

The present invention also provides methods of inhibiting expression of an F5 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 F5 in the cell, thereby inhibiting expression of F5 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.

5 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.

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

“Inhibiting expression of a coagulation Factor V gene” includes any level of inhibition of a coagulation Factor V gene, *e.g.*, at least partial suppression of the expression of a coagulation Factor V gene, such as a clinically relevant level of suppression. The expression of the coagulation Factor V
20 gene may be assessed based on the level, or the change in the level, of any variable associated with coagulation Factor V gene expression, *e.g.*, coagulation Factor V mRNA level or coagulation Factor V protein level. 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
25 that coagulation Factor V 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 coagulation Factor V 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
30 (such as, *e.g.*, buffer only control or inactive agent control).

In some embodiments of the methods of the invention, expression of a coagulation Factor V 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 coagulation Factor V gene is inhibited by at least 70%. It is further understood that inhibition of coagulation Factor V expression
35 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.*, coagulation Factor V), *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 coagulation Factor V 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 coagulation Factor V 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 coagulation Factor V 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, *e.g.*, 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 coagulation Factor V gene may be assessed in terms of a reduction of a parameter that is functionally linked to coagulation Factor V gene expression, *e.g.*, coagulation Factor V protein level in blood or serum from a subject. Coagulation Factor V gene silencing may be determined in any cell expressing coagulation Factor V, either endogenous or heterologous from an expression construct, and by any assay known in the art.

Inhibition of the expression of a coagulation Factor V protein may be manifested by a reduction in the level of the coagulation Factor V 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 coagulation Factor V 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 coagulation Factor V 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 coagulation Factor V in a sample is determined by detecting a transcribed polynucleotide, or portion thereof, *e.g.*, mRNA of the coagulation Factor V gene. RNA may be extracted from cells using RNA extraction techniques including, for example, using acid phenol/guanidine isothiocyanate extraction (RNAzol B; Biogenesis), RNeasyTM RNA preparation kits (Qiagen®) or PAXgeneTM (PreAnalytixTM, Switzerland). Typical assay formats utilizing ribonucleic acid hybridization include nuclear run-on assays, RT-PCR, RNase protection assays, northern blotting, *in situ* hybridization, and microarray analysis.

In some embodiments, the level of expression of coagulation Factor V 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 coagulation Factor V. 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 coagulation Factor V 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 coagulation Factor V mRNA.

An alternative method for determining the level of expression of coagulation Factor V 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 F5 is determined by quantitative fluorogenic RT-PCR (*i.e.*, the TaqMan™ System). In some embodiments, expression level is determined by the method provided in Example 2 using, *e.g.*, a 10nM siRNA concentration, in the species matched cell line.

The expression levels of coagulation Factor V 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 coagulation Factor V 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 F5 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 F5 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 coagulation Factor V may be assessed using measurements of the level or change in the level of coagulation Factor V mRNA or coagulation Factor V 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 coagulation Factor V, thereby preventing or treating a coagulation Factor V-associated disorder, *e.g.*, a disorder associated with thrombosis.

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 coagulation Factor V 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, coagulation Factor V 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 coagulation Factor V 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 F5, 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 coagulation Factor V gene in a mammal. The methods include administering to the mammal a composition comprising a dsRNA that targets a coagulation Factor V gene in a cell of the mammal

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

The present invention further provides methods of treatment in a subject in need thereof, *e.g.*, a subject diagnosed with a coagulation Factor V-associated disorder, such as, a disorder associated with thrombosis.

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 coagulation Factor V expression, in a prophylactically effective amount of an iRNA targeting a coagulation Factor V gene or a pharmaceutical composition comprising an iRNA targeting a coagulation Factor V gene.

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 coagulation Factor V expression are subjects susceptible to or diagnosed with an F5-associated disorder, *e.g.*, subjects susceptible to or diagnosed with, *e.g.*, a disorder associated with thrombosis. Non-limiting examples of disorders or diseases associated with thrombosis include venous thrombosis, *e.g.*, deep vein thrombosis; genetic thrombophilia, *e.g.*, Factor V leiden and prothrombin thrombophilia; purpura fulminans; acquired thrombophilia, *e.g.*, antiphospholipid syndrome and systemic lupus erythematosus; drug induced thrombophilia; arterial thrombosis, *e.g.*, myocardial infarction and peripheral arterial disease; thromboembolic disease, *e.g.*, pulmonary embolus embolic and ischemic stroke; atrial fibrillation; post-surgery deep vein thrombosis; cancer thrombosis or infectious disease thrombosis.

In an embodiment, the method includes administering a composition featured herein such that expression of the target coagulation Factor V 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 some embodiments, the iRNAs useful for the methods and compositions featured herein specifically target RNAs (primary or processed) of the target coagulation Factor V 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 coagulation Factor V-associated disorder, *e.g.*, a disorder associated with thrombosis. Non-limiting examples of disorders or diseases associated with thrombosis include venous thrombosis, *e.g.*, deep vein thrombosis; genetic thrombophilia, *e.g.*, Factor V leiden and prothrombin thrombophilia; purpura fulminans; acquired thrombophilia, *e.g.*, antiphospholipid syndrome and systemic lupus erythematosus; drug induced thrombophilia; arterial thrombosis, *e.g.*, myocardial infarction and peripheral arterial disease; thromboembolic disease, *e.g.*, pulmonary embolus embolic and ischemic stroke; atrial fibrillation; post-surgery deep vein thrombosis; cancer thrombosis or infectious disease thrombosis.

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 embodiments, 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 F5 gene expression, *e.g.*, a subject having an F5-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.

In certain embodiments, the additional therapeutic agent is an anticoagulant. In some embodiments, the anticoagulant includes heparin, enoxaparin (Lovenox), dalteparin (Fragmin), fondaparinux (Arixtra), warfarin (Coumadin, Jantoven), dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa), argatroban or any combination thereof. In some embodiments, the additional therapeutic agent includes a thrombolytic. In certain embodiments, the thrombolytic includes antistreptase (Eminase), tissue plasminogen activator (tPA), urokinase-type plasminogen activator (uPA), or any combination thereof. In some embodiments, the additional therapeutic agent is an immunosuppressant. In certain embodiments, the immunosuppressant includes corticosteroid, azathioprine, cyclosporine A, or any combination thereof. In some embodiments, the

additional therapeutic agent is hormone replacement therapy. In certain embodiments, the hormone replacement therapy includes estrogen, gestagen, androgen or any combination thereof. In some embodiments, the additional therapeutic agent is an antibiotic. In some embodiments, the additional therapeutic agent is an antihistamine agent. In some embodiments, the additional therapeutic agent is a mast cell stabilizer. In certain embodiments, the mast cell stabilizer includes cromoglicic acid (Cromolyn), lodoxamide (Alomide), or any combination thereof. In some embodiments, the additional therapeutic agent is an anti-proliferative agent. In some embodiments, the additional therapeutic agent is an oral contraceptive. In some embodiments, the additional therapeutic agent is a fresh frozen plasma or a plasminogen concentrate. In some embodiments, the additional therapeutic agent is hyaluronidase. In some embodiments, the additional therapeutic agent is alpha chymotrypsin. In certain embodiment, the additional therapeutic agent is a filter inserted into a large vein that prevents clots that break loose from lodging in the patient's lungs. In certain embodiments, the additional therapeutic agent is selected from the group consisting of an anticoagulant, an F5 inhibitor and a thrombin inhibitor.

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 is administered in combination with allopurinol. In one embodiment, the iRNA agent 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 and the additional therapeutic agent are administered at the same time.

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.

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 F5 (*e.g.*, means for measuring the inhibition of F5 mRNA, F5 protein, or F5 activity). Such means for measuring the inhibition of F5 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
5 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.*,
10 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.
15

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

EXAMPLES

Example 1. siRNA Synthesis

25 *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.

30 *siRNA Design*

siRNAs targeting the Coagulation Factor V (F5) gene, (human: NCBI refseqID NM_000130.4; NCBI GeneID: 2153) were designed using custom R and Python scripts. The human NM_000130.4 REFSEQ mRNA, version 4, has a length of 9719 bases.

A detailed list of the unmodified F5 sense and antisense strand nucleotide sequences are
35 shown in Table 2. A detailed list of the modified F5 sense and antisense strand nucleotide sequences are shown in Table 3.

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

5 *siRNA Synthesis*

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

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

Upon completion of the solid phase synthesis, solid-supported oligoribonucleotides were treated with 300 μ L of Methylamine (40% aqueous) at room temperature in 96 well plates for approximately 2 hours to afford cleavage from the solid support and subsequent removal of all additional base-labile protecting groups. For sequences containing any natural ribonucleotide linkages (2'-OH) protected with a tert-butyl dimethyl silyl (TBDMS) group, a second deprotection step was performed using TEA.3HF (triethylamine trihydrofluoride). To each oligonucleotide solution in aqueous methylamine was added 200 μ L of dimethyl sulfoxide (DMSO) and 300 μ L TEA.3HF and the solution was incubated for approximately 30 mins at 60 °C. After incubation, the plate was allowed to come to room temperature and crude oligonucleotides were precipitated by the addition of 1 mL of 9:1 acetonitrile:ethanol or 1:1 ethanol:isopropanol. The plates were then centrifuged at 4 °C for 45 mins and the supernatant carefully decanted with the aid of a multichannel pipette. The oligonucleotide pellet was resuspended in 20 mM NaOAc and subsequently desalted using a HiTrap size exclusion column (5 mL, GE Healthcare) on an Agilent LC system equipped with an autosampler, UV detector, conductivity meter, and fraction collector. Desalted samples were collected in 96 well plates and then analyzed by LC-MS and UV spectrometry to confirm identity and quantify the amount of material, respectively.

Duplexing of single strands was performed on a Tecan liquid handling robot. Sense and antisense single strands were combined in an equimolar ratio to a final concentration of 10 μ M in 1x

PBS in 96 well plates, the plate sealed, incubated at 100 °C for 10 minutes, and subsequently allowed to return slowly to room temperature over a period of 2-3 hours. The concentration and identity of each duplex was confirmed and then subsequently utilized for in vitro screening assays.

5 **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% CO₂ in Eagle's Minimum Essential Medium (Gibco) supplemented with 10% FBS (ATCC) before being released from the plate by trypsinization. Transfection of Hep3b cells was carried out by adding 14.8 µl of Opti-MEM plus 0.2 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. Eighty µl of complete growth media without antibiotic containing ~2 x10⁴ Hep3B cells was then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Single dose experiments are performed at 10 nM final duplex concentration.

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

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

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

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

Real time PCR

Two microlitre (µl) of cDNA were added to a master mix containing 0.5µl of human GAPDH TaqMan Probe (4326317E), 0.5µl human F5 probe, 2µl nuclease-free water and 5µl Lightcycler 480 probe master mix (Roche Cat # 04887301001) per well in a 384 well plates (Roche cat # 04887301001). Real time PCR was done in a LightCycler480 Real Time PCR system (Roche).

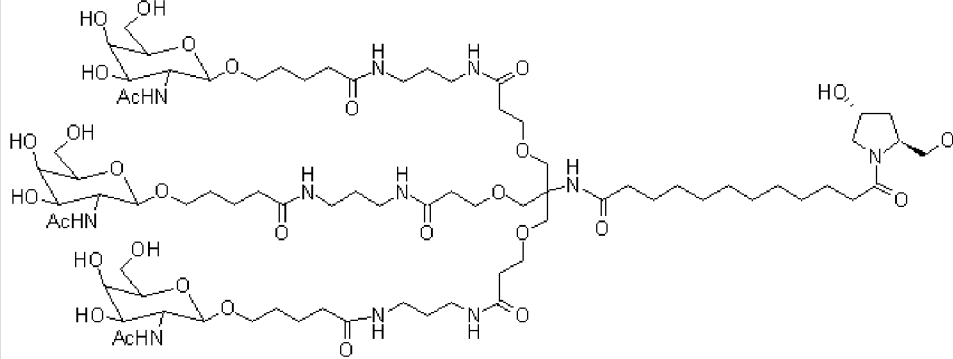
To calculate relative fold change, data were analyzed using the $\Delta\Delta C_t$ method and normalized to assays performed with cells transfected with 10nM AD-1955, or mock transfected cells. IC₅₀s were calculated using a 4 parameter fit model using XLFit and normalized to cells transfected with AD-1955 or mock-transfected. The sense and antisense sequences of AD-1955 are: sense:

- 5 cuuAcGcuGAGuAcuucGAdTsdT (SEQ ID NO: 29) and antisense
UCGAAGuACUcAGCGuAAGdTsdT (SEQ ID NO:30).

The results of the single dose screen of the agents in Tables 2 and 3 in Hep3b cells are shown in Table 4.

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

Abbreviation	Nucleotide(s)
A	Adenosine-3'-phosphate
Ab	beta-L-adenosine-3'-phosphate
Abs	beta-L-adenosine-3'-phosphorothioate
Af	2'-fluoroadenosine-3'-phosphate
Afs	2'-fluoroadenosine-3'-phosphorothioate
As	adenosine-3'-phosphorothioate
C	cytidine-3'-phosphate
Cb	beta-L-cytidine-3'-phosphate
Cbs	beta-L-cytidine-3'-phosphorothioate
Cf	2'-fluorocytidine-3'-phosphate
Cfs	2'-fluorocytidine-3'-phosphorothioate
Cs	cytidine-3'-phosphorothioate
G	guanosine-3'-phosphate
Gb	beta-L-guanosine-3'-phosphate
Gbs	beta-L-guanosine-3'-phosphorothioate
Gf	2'-fluoroguanosine-3'-phosphate
Gfs	2'-fluoroguanosine-3'-phosphorothioate
Gs	guanosine-3'-phosphorothioate
T	5'-methyluridine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate
Ts	5-methyluridine-3'-phosphorothioate
U	Uridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine-3'-phosphorothioate
Us	uridine-3'-phosphorothioate
N	any nucleotide, modified or unmodified
a	2'-O-methyladenosine-3'-phosphate
as	2'-O-methyladenosine-3'-phosphorothioate
c	2'-O-methylcytidine-3'-phosphate
cs	2'-O-methylcytidine-3'-phosphorothioate

Abbreviation	Nucleotide(s)
g	2'-O-methylguanosine-3'-phosphate
gs	2'-O-methylguanosine-3'-phosphorothioate
t	2'-O-methyl-5-methyluridine-3'-phosphate
ts	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u	2'-O-methyluridine-3'-phosphate
us	2'-O-methyluridine-3'-phosphorothioate
s	phosphorothioate linkage
L10	N-(cholesterylcarboxamidocaproyl)-4-hydroxyprolinol (Hyp-C6-Chol)
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl]-4-hydroxyprolinol (Hyp-(GalNAc-alkyl)3) 
Y34	2-hydroxymethyl-tetrahydrofuran-4-methoxy-3-phosphate (abasic 2'-OMe furanose)
Y44	inverted abasic DNA (2-hydroxymethyl-tetrahydrofuran-5-phosphate)
(Agn)	Adenosine-glycol nucleic acid (GNA)
(Cgn)	Cytidine-glycol nucleic acid (GNA)
(Ggn)	Guanosine-glycol nucleic acid (GNA)
(Tgn)	Thymidine-glycol nucleic acid (GNA) S-Isomer
P	Phosphate
VP	Vinyl-phosphonate
dA	2'-deoxyadenosine-3'-phosphate
dAs	2'-deoxyadenosine-3'-phosphorothioate
dC	2'-deoxycytidine-3'-phosphate
dCs	2'-deoxycytidine-3'-phosphorothioate
dG	2'-deoxyguanosine-3'-phosphate
dGs	2'-deoxyguanosine-3'-phosphorothioate
dT	2'-deoxythymidine-3'-phosphate
dTs	2'-deoxythymidine-3'-phosphorothioate
dU	2'-deoxyuridine
dUs	2'-deoxyuridine-3'-phosphorothioate
(C2p)	cytidine-2'-phosphate
(G2p)	guanosine-2'-phosphate
(U2p)	uridine-2'-phosphate
(A2p)	adenosine-2'-phosphate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(AhdS)	2'-O-hexadecyl-adenosine-3'-phosphorothioate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(ChdS)	2'-O-hexadecyl-cytidine-3'-phosphorothioate
(Ghd)	2'-O-hexadecyl-guanosine-3'-phosphate
(GhdS)	2'-O-hexadecyl-guanosine-3'-phosphorothioate

Abbreviation	Nucleotide(s)
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
(Uhds)	2'-O-hexadecyl-uridine-3'-phosphorothioate

Table 2. Unmodified Sense and Antisense Strand Sequences of Coagulation Factor V dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	R range in NM_000130.4
AD-109601	AAAGUGGAUCAUAUCUUCUCU	31	1057-1077	AGAGAAGAUAUGAUCCACUUUCC	162	1055-1077
AD-109799	UCAAACCAAAUUGGAAAACAU	32	1295-1315	AUGUUUCCAAUUUGGUUUGAGA	163	1293-1315
AD-110052	UAAGUGGAACAUCUUAAGAGUU	33	1594-1614	AACUCUAAGAUGUUCACUUAUA	164	1592-1614
AD-110281	GAGGACAACAUCACAAGUUU	34	1823-1843	AAACUUUGUUGAUUGUCCUCAA	165	1821-1843
AD-110370	GCAUAAACUACUCUUGGAUUCU	35	1932-1952	AGAAUCCAAGAGUAUUAUGCUC	166	1930-1952
AD-110518	UUGGAAACUUGGAUGUUAACUU	36	2118-2138	AAGUUAACAUCCAAGUUCACAA	167	2116-2138
AD-110787	GAAGAAAGAUUCAAUCUUAUCU	37	2387-2407	AGUAAAGAUUGAACUCUUCUUCU	168	2385-2407
AD-110844	UCAAACACAGAUUAUAUUGUU	38	2444-2464	AACAAUUAUAUCUGUUGUUUAG	169	2442-2464
AD-111287	AAGUAAACUACUAAAGAUAUUU	39	2953-2973	AAAUCUUAGAUGAGUUACUUUG	170	2951-2973
AD-111345	UAUGAAAUAAUCCAAGAUACU	40	3011-3031	AGUAUCUUGGAUUAUUUCAUAGC	171	3009-3031
AD-111483	ACUGAAGAAAAGCCAGUUUUCU	41	3202-3222	AGAAACUGGCUUUUUCUUCAGUCU	172	3200-3222
AD-112322	UCAUUGCUUCUUCAGAAUAUU	42	4559-4579	AAAUUCUUGAAGAAAGCAAUGACU	173	4557-4579
AD-112396	UACUCUCAAUGAUACUUUUUCU	43	4633-4653	AGAAAAGUAUCAUUGAGAGUAGG	174	4631-4653
AD-112618	AAACAGAAGAAAUUAUUACAU	44	4876-4896	AUGUAAAUUUUCUUCUGUUUCC	175	4874-4896
AD-112760	AGCACUUUUAACCAAACGUGAU	45	5021-5041	AUCACGUUUGGUAAAAGUGCUGU	176	5019-5041
AD-113137	GAGAGAAUUUGUCUUAUCUAUU	46	5443-5463	AAUAGUAAAGACAAAUAUCUCUCAU	177	5441-5463
AD-113331	GACAUUCACGUGGUUCACUUCU	47	5657-5677	AAAGUGAACCAACGUGAAUUGUCUU	178	5655-5677
AD-114455	CUGUGUUAUUAUUGUUAACAGUU	48	6896-6916	AACUGUUAACAUAUUUAACACAGCG	179	6894-6916
AD-114469	ACAGUUUCCACUAUUUCUCU	21	6911-6931	AGAGAAAUAGUGGAAAACUGUUA	22	6909-6931
AD-114478	CUUUCUUUUCUAUUAGUGAAU	49	6930-6950	AUUCACUAAUAGAAAAGAAAGAG	180	6928-6950
AD-114698	UUUCACAAACACAUAGAUUUUU	50	7211-7231	AAAAUUAUGUUGUUUGUGAAAGU	181	7209-7231
AD-114728	UACUUAAAAUAUCCUGUCUUU	51	7283-7303	AAAGACAGGAUAUUUUAAGUACU	182	7281-7303
AD-114746	UUUCCCAUAUAACAAUGAUUU	52	7301-7321	AAAUCAUUGUUAUUAUGGGAAGA	183	7299-7321
AD-115217	GUGUACAUUAUCAAUAUUGUU	53	7936-7956	AACAUAUUUGAUUAUUAUGUACACGU	184	7934-7956
AD-115235	CAACGAAAUUUAUUAACAAUUCU	54	7986-8006	AGAUUGUUAUAGAAUUAUUCGUUGAU	185	7984-8006

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-115563	GAAACUACCAGAGUUACCUGU	55	8322-8342	ACAGGUAAACUCUGGUAGUUUCUA	186	8320-8342
AD-115659	CUUUCUUUUCAGAUUCAUGU	56	8437-8457	ACAUGAAUCAUGAAAAGAAAGGA	187	8435-8457
AD-115814	CGCAUGCUAAAUUUAUGCUU	57	8612-8632	AAGCAUUAAAUUUAGCAUGCGGU	188	8610-8632
AD-115844	CCUCUUGAAAUCUUUAUUUU	58	8642-8662	AAAUAUAAAGGAUUUCAAAGGGU	189	8640-8662
AD-115919	UCUCUUGAUCUAGAAUUUACU	59	8755-8775	AGUAAAUUCUAGAUAAGAGAGA	190	8753-8775
AD-1410569	CCACAAACUCAGUUUUGAAUU	60	291-311	AAUUCAAACUUGAGUUUGGGC	191	289-311
AD-1410577	AUCUUUCUGUAAAUUCCUUU	61	309-329	AAAAGGAAGUACAGAAAAGAUUC	192	307-329
AD-1410605	AGUAUGAACCAUAUUUUAAGU	15	348-368	ACUUAUAAUUGGUUCAUACUCU	16	346-368
AD-1410628	CUACCAUUUCAGGACUUCUUU	62	384-404	AAAGAAAGUCCUGAAUUGGUAGAU	193	382-404
AD-1410662	CAUCAUAAAAGUUCACUUUAU	63	433-453	AUAAAGUGAAACUUUUAUGAUGUC	194	431-453
AD-1410700	UCAAGGAUUUAGGUACAGUAU	64	487-507	AUACUGUACCUAAUUCUUUGAGG	195	485-507
AD-1410725	UCUUAACUUUGACCACACAUUU	65	524-544	AAUUGUGUGUCAAGGUAAAGAAAG	196	522-544
AD-1410825	UCACACACAUUAUUACUCCU	66	648-668	AGGAGUAAUAGAUGUGUGAGG	197	646-668
AD-1410845	UCUGAUCGAGGAUUUCAAACUU	67	676-696	AAGUUGAAAUCCUCGACUACAGAUU	198	674-696
AD-1410880	GACAAGCAAAUCCGUCUACUU	68	767-787	AAGUAGCACGAUUUUGCUUUGUCA	199	765-787
AD-1410926	CCCUAAUGUACACAGUCAAUU	69	831-851	AAUUGACUGUGUACAUUAGGGAU	200	829-851
AD-1410994	AUUUUUCCUCCAUUCAUUUCAU	70	940-960	AUGAAAUGAAUGGAGAAUAAUUC	201	938-960
AD-1411107	CAGGCUUACAUUGACAUUAAU	71	1106-1126	AUUAAUGUCAUUGUAAAGCCUGCA	202	1104-1126
AD-1411138	CCAGGAAUCUUUAGAAAAUUAU	72	1143-1163	AUAUUUUCUUUAGAUUCCUGGUU	203	1141-1163
AD-1411226	UCAGCAUUUUGGAUAAUUUCUU	73	1276-1296	AAGAAAUAUUAUCCAAAUGCUGAGA	204	1274-1296
AD-1411270	UACGAAAGAUAGAGUCCUUCACU	74	1340-1360	AGUGAAGGACUCUUCUUCGUACU	205	1338-1360
AD-1411284	CACCAAAACAUACAGUGAAUUCU	75	1357-1377	AGAUUCACUGUAUGUUUUGGUGAA	206	1355-1377
AD-1411342	ACACUCAAAAUCGUGUUCAAU	76	1433-1453	AUUGAACACGAUUUUGAGUGUGU	207	1431-1453
AD-1411387	AUGAAGUCAACUCUUCUUUCU	77	1515-1535	AGAAAGAAGAUUUGACUUCUACU	208	1513-1535
AD-1411480	UAACAAAGACCAUACUACAGUU	78	1647-1667	AACUGUAGUAUGGUCUUGUUAAG	209	1645-1667
AD-1411521	AAUAGGACUACUUCUAAUUCUU	79	1702-1722	AAGAUUAGAAAGUAGUCCUUAUAG	210	1700-1722

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1411657	AAACAUC AUGAGCACUAUCAU	80	1894-1914	AUGAUAUGGUCUCAUGAUUUUGA	211	1892-1914
AD-1411743	CAUUCAUCAUUGGAAAGAGGU	81	2034-2054	ACCUCUUUCCCAUAGAUAAGAGAG	212	2032-2054
AD-1411798	UAACUUCCAUGAAUUCUAGUU	82	2133-2153	AACUAGAAUUCAUGGAAAGUUAAAC	213	2131-2153
AD-1411935	GACUAUGAUUACCAAGAACAGU	83	2312-2332	ACUGUUUCUGGUAUAUCAUAGUCAG	214	2310-2332
AD-1411972	CCGAAACUCAUCAUUGAAUCU	84	2362-2382	AGAUUCAUAGAUGAUUUUCGGAA	215	2360-2382
AD-1412021	ACUGAAUUCGUUUUCUCAAUU	85	2429-2449	AUUUGAAGAAACGAAUUUCAGUGC	216	2427-2449
AD-1412040	GUUGGUUCAAAUUAUUCUUCU	86	2462-2482	AGAAAGAAUAAUUUUAACCAACAA	217	2460-2482
AD-1412052	AGUUCACUGUCAAUUACCUUU	87	2499-2519	AAAGGUUAUUUGACAGUGAACUUA	218	2497-2519
AD-1412095	ACUCAGUUCUCAAUUCUUCU	88	2595-2615	AGGAAGAAUUUGAGAACUGAGUUC	219	2593-2615
AD-1412163	UACGUCUACUUUCACUUGGUU	89	2685-2705	AACCAAGUGAAAGUAGACGUUUC	220	2683-2705
AD-1412250	GGAUGAAUUACUAGCACAUU	90	2790-2810	AAUGGCUAGUAAUUUCAUCCAG	221	2788-2810
AD-1412364	GUUACUCUAAACAAAGUAU	91	2938-2958	AUACUUUGUUUAAAGAGUAAACAG	222	2936-2958
AD-1412429	CUGAUGAAGACACAGCUGUUU	92	3030-3050	AAACAGCUGUGUCUUCAUCAGUA	223	3028-3050
AD-1412482	CUAGAGUUAGACAUAAAUUU	93	3150-3170	AAGAUUUUUGUCUAAUCUCUAGGA	224	3148-3170
AD-1412497	CUCUACAAAGUAAGACAGGAU	94	3168-3188	AAUCCUGUCUUACUUUGUAGAGAU	225	3166-3188
AD-1412539	UUUCUCAUUUAAAGACACGAAU	95	3218-3238	AUUUCGUGUCUUAAUUGAGAAACU	226	3216-3238
AD-1412582	UGAAGCCUACAAACACAUUUUU	96	3304-3324	AAAAUUGUGUUUGUAGGCUUCACU	227	3302-3324
AD-1412622	AAUCCAAUGAAACAUCUCUUU	97	3360-3380	AAAGAGAUUUUCAUUGGAUUUA	228	3358-3380
AD-1412683	AUAAUACAGAAUUCUCAAUUU	98	3444-3464	AAUUUGAGGAAUUUCUGAUUAUGG	229	3442-3464
AD-1412721	AGGAACACUAUCAAACAUAUUU	99	3516-3536	AGAAUUUUUGAUAGUUGUCCUCU	230	3514-3536
AD-1412733	UCAAAUGCACUCUACUUCAGU	100	3553-3573	ACUGAAGUAGAGUGCAUUUUGAUC	231	3551-3573
AD-1412756	UCAGUGAAAUUGCUUGAGUAUU	101	3603-3623	AAUACUCAAGCAUUUCACUGAGC	232	3601-3623
AD-1412779	UCCUCAGAAACAUGAAGUCUGU	102	3671-3691	ACAGACUUCAUUGUUUCUGAGGAAG	233	3669-3691
AD-1412870	CUCAUUUCAGAGAAACCUUUUU	103	3794-3814	AGAAAGGUUUUCUCUGAAUUGAGUU	234	3792-3814
AD-1412963	ACAACCCUUUCUCUAGACUUU	104	3992-4012	AAAGUCUAGAGAAAGGUUGUAU	235	3990-4012
AD-1412982	CUCCAGAACUCAGUCAAACAUA	105	4164-4184	AUGUUUGACUGAGUUUCUGGAGAG	236	4162-4184

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1413036	UUGCAGAUUCAGUCAAAUUU	106	4326-4346	AAUUUUGACUGAGAUUCGCAAAAG	237	4324-4346
AD-1413128	GACCUUGAUCAGAUUUUCUAAU	107	4520-4540	AUAGAAAUUCUGAUAAGGUCUG	238	4518-4540
AD-1413143	UCUGAAUCUAGUCAGUCAUUU	108	4544-4564	AAUGACUGACUAGAUUCAGAAAG	239	4542-4564
AD-1413210	CUAUCAAAGGAUUUAAUCCU	109	4652-4672	AGGAUUAAAUUCCUUUGAUAGAA	240	4650-4672
AD-1413251	UACAUUGAGAUCAUUCCAAU	110	4709-4729	AUUUGGAUUGAUCUCAAUGUAAU	241	4707-4729
AD-1413286	ACU AUGCUGAAAUUGAUUUU	111	4755-4775	AAUAAUCAAUUUCAGCAUAGUCA	242	4753-4775
AD-1413311	UAGGACAAACAUCACUCCUU	112	4807-4827	AAGGAGUUGAUGUUUGUCCUAAAC	243	4805-4827
AD-1413488	UCGGAAUUCUUUGGUCCUAAUUU	113	5067-5087	AAUAGGACCAAGAAUUCGCGAGA	244	5065-5087
AD-1413517	UU AUCCAAGUUCGUUUUAAAU	114	5109-5129	AUUUAAACGAACUUGGAUAAACA	245	5107-5129
AD-1413605	AUGCUGUUCAGGCCAAAUAGCU	115	5238-5258	AGCUAUUUGGCUGAACAGCAUUA	246	5236-5258
AD-1413615	UAGCAGUUUAUACCUACGUUUU	116	5254-5274	AAUACGUAGGUUAUACUGCUUUU	247	5252-5274
AD-1413936	CUGGUUCAUUUAAAACUCUUU	117	5742-5762	AAAGAGUUUUAAAUGAACCAAGGC	248	5740-5762
AD-1414009	UGCAAACGCCAUUUUCUUAUCU	17	5832-5852	AGAUAAAGAAUUGGCGUUUUGCAUC	18	5830-5852
AD-1414059	AUAUCUGAUUCACAGAUCAAU	118	5897-5917	AUUGAUCUGUGAAUUCAGAUUGA	249	5895-5917
AD-1414074	UCAGAGUUUCUGGGUUUACUGU	119	5921-5941	ACAGUAAACCCAGAAAACUCUGAAG	250	5919-5941
AD-1414139	AGAAUUUGCCUCUAAACCUUU	120	6010-6030	AAAGGUUUAGAGGCAAAUUCUGC	251	6008-6030
AD-1414232	AUGUAGCUUACAGUUCCAAACU	121	6126-6146	AGUUGGAACUGUAAAGCUACAUAAG	252	6124-6146
AD-1414275	GAUGUGAUGUAUUUUAUUGU	122	6184-6204	ACAUUAAAUACAUCACAUAUCCU	253	6182-6204
AD-1414328	UAGAUUAUUUAGGAUCUCUCU	123	6259-6279	AGAGAGAUCCUAAUUAUUCUAGC	254	6257-6279
AD-1414410	UCACAGCUUCUUCGUUUUAAAGU	124	6390-6410	ACUUAAACGAAAGAGCUGUGAUU	255	6388-6410
AD-1414498	AUUGAUCUACUCAAGAUCAAU	125	6518-6538	AUUGAUCUUGAGUAGAUCAAUUU	256	6516-6538
AD-1414544	CCUCUGAAAUUGUAUUGUAAAAGU	126	6579-6599	ACUUUAACAUAUAUUUCAGAGGAC	257	6577-6599
AD-1414625	AAGGAAAUACUAAUACCAAU	127	6681-6701	AUUUGGUUUUAGUAUUUCCUUA	258	6679-6701
AD-1414662	CAUCCUAAAACAUGGAAUUCU	128	6754-6774	AGAUUCCAUUUUUAGGAAUUGAC	259	6752-6774
AD-1414713	AGACUCUUUAAGACCCUCAAU	129	6848-6868	AUUUGAGGUCUUUAAAGAGUCUCU	260	6846-6868
AD-1414786	AGAUAAUGGCUAUUACUUCUU	130	7003-7023	AAGAAGUAAUAGCCAUUAUCUUA	261	7001-7023

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1414796	UUUCGCAUUAAUUUUGAAUACU	131	7019-7039	AGUAUUCAAAUUAUAGCAGAAAGU	262	7017-7039
AD-1414831	AAGGGCUUAUCUUUUCUAAUU	132	7069-7089	AAUUAAGAAAGAUAAAGCCUUUU	263	7067-7089
AD-1414857	CUCUUUUAAAUCUUUACACU	133	7141-7161	AGUGUAAGGAUUUAAAAGAGUU	264	7139-7161
AD-1414871	CACUAGUAAAACAGAUUUUU	134	7160-7180	AUAAUAUCUGUUUUACUAGUGUG	265	7158-7180
AD-1414931	UUUCUGACUUUCCAUGAGUAAU	135	7321-7341	AUACUCAUGGAAAGUCAGAAAAA	266	7319-7341
AD-1415052	AAAACAUAUUUCACCUACUU	136	7532-7552	AAGUAGGUGAAAUUUGUUUUUGA	267	7530-7552
AD-1415096	CUGGUCUAAAUGCAGUUGUUU	137	7589-7609	AAACAACUGCAUUUAGACCAGCA	268	7587-7609
AD-1415166	UCUCUUUCCAGCAACUUCU	138	7696-7716	AGAAUUGCUGGAAAGAAAGAGAGA	269	7694-7716
AD-1415169	UUUCAUCUUCCUUUCCCUUGU	139	7719-7739	ACAGGGAAAGGAAUAGUAGAAAGG	270	7717-7739
AD-1415194	UUUAGACAUCUUUAAAUAU	140	7787-7807	AUGAUUUUAAAGGAUGUCUAAAGG	271	7785-7807
AD-1415243	UGAUUUAAUUAUCCUGUAACU	141	7916-7936	AGUUACAGGAUGAUUAAAUCAAAG	272	7914-7936
AD-1415314	GACUAAAGAAACUCACUCGAAU	142	8040-8060	AUUCGAGUGAGUUUCUUAGUCCU	273	8038-8060
AD-1415327	UCGAAACCACACAAACUACAUU	143	8055-8075	AAUGUAGUUUGUGGUUUUCGAGU	274	8053-8075
AD-1415412	ACAACAUACCAGAAUCUCUAAU	144	8170-8190	AUAGAGAUUCUGGUUAGUUGUCU	275	8168-8190
AD-1415439	GCAUUCUAAUUCGUUGUGAAACU	145	8213-8233	AGUUCACAAACGAAUAGAAUAGCAG	276	8211-8233
AD-1415466	GUUCGAAUUCAGUGUAGAAAGU	146	8248-8268	ACUUCUACACUGAAUUCGAGACUG	277	8246-8268
AD-1415563	AUCCACAAACAAUUGGCUUUU	147	8393-8413	AAAAGCCAAUUGUUUUGUGGAUGU	278	8391-8413
AD-1415578	CGUAUUUCCACUAUUUCCUUUU	148	8421-8441	AAAAGGAUAGUGGGGAUACGAA	279	8419-8441
AD-1415602	CAUCAACAUUUUCUAAAGAUUUU	149	8466-8486	AAAAUCUUAGAAAUGUUUGAUGGG	280	8464-8486
AD-1415633	AAAACAUUUUCUUUGUUUUUCUU	150	8527-8547	AAGAAAACAAAGAAUUGUUUUUCC	281	8525-8547
AD-1415663	GUGAUCUGUUCAGUUGCAAUU	151	8571-8591	AUUUGCAACUGAACAGAUACACAC	282	8569-8591
AD-1415714	AUUCGACAUUUCCAUUUUUUCU	152	8673-8693	AGAAAAAUGGAAAUGUCGAAUUC	283	8671-8693
AD-1415738	CUUCUCUACUCUGAAAUUGGU	153	8727-8747	ACCAUUUCAGAGUAGAGAGGCC	284	8725-8747
AD-1415798	GUUAUUUCUACUUUGAGAAAU	154	8857-8877	AUUUCUCAAGUAGAGAAUACCGA	285	8855-8877
AD-1415830	UGUUAGUGUCAGAAACUGAAAU	155	8920-8940	AUUUCAGUUCUGACACUAAACAAG	286	8918-8940
AD-1415857	UAUCCCUAGACUUUUUAGUCUU	156	8958-8978	AAGACUAAAAGUCUAGGGAUAUG	287	8956-8978

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	R range in NM_000130.4
AD-1415873	UCUUCCAUAAAUGAAACUUU	157	8984-9004	AAAGUUUCAUUUAUGGAAGAGA	288	8982-9004
AD-1415881	AUGUUUCUAAUCCAUUGCUCU	158	9007-9027	AGAGCAAUGGAUUAGAAACAUA	289	9005-9027
AD-1415899	GUAGACAUGAUAUUAAUUGU	159	9033-9053	ACAAUUAAUAUUAUGUCUACCU	290	9031-9053
AD-1415910	GAUCUGGAAAAUACUUGUUUU	160	9069-9089	AAAACAAGUAUUUUCAGAUCAA	291	9067-9089
AD-1415934	CUGUGUAGAAAAUUUAAAAACU	161	9124-9144	AGUUUUAAUAUUUCUACACAGCA	292	9122-9144

Table 3. Modified Sense and Antisense Strand Sequences of Coagulation Factor V 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-109601	asasagugGfaUfcAfAfuauuucucuuL96	293	asGfsagaAfgAfUfauaUfcCfacuunuscsc	427	GGAAAGUGGAUCAUAUCUUCU	561
AD-109799	uscsaaacCfaAfAfUfuggaaacauL96	294	asUfsguuUfuCfCfcauuUfgGfuuuagsga	428	UCUCAAAACCAAAUUGGAAAAC	562
AD-110052	usasagugGfaAfCfAfucuuagaguL96	295	asAfscucUfaAfGfaguUfcCfacuuaasusa	429	UAUAAAGUGGAACAUCUUAAGAG	563
AD-110281	gsasggacAfaCfAfUfcaacaaguuuL96	296	asAfscuUfgUfUfgaugUfuGfuccucsasa	430	UUGAGGACAAACAUCAACAAGU	564
AD-110370	gscsaauaCfuAfCfUfcuuggaauuL96	297	asGfsaauCfcAfAfagauAfgUfuauagsusc	431	GAGCAUAAACUACUCUUGGAUU	565
AD-110518	ususggaaCfuUfGfGfauuuuacuuL96	298	asAfsguuAfaCfAfuccaAfgUfuccaascsa	432	UGUUGGAACUUGGAUGUUUAAC	566
AD-110787	gsasagaaGfaGfUfUfcaauuuacuuL96	299	asGfsuaaGfaUfUfgaacUfcUfucuuucsusu	433	AAGAAGAAGAGUUCAAUUCUUA	567
AD-110844	uscsaaacAfcAfGfAfuaauuuuuL96	300	asAfscaaUfuAfUfauuUfcGfuuuugasasg	434	CUUCAAAACACAGAUUAUAAUUG	568
AD-111287	asasguaaCfuCfAfUfcauagauuuuL96	301	asAfsaauCfuUfAfgaugAfgUfuacuunusg	435	CAAAGUAAACUCAUCUAAAGAUA	569
AD-111345	usasugaaAfuAfAfUfccaauguauL96	302	asGfsuauCfuUfGfgaauAfuUfucuaagsgc	436	GCUAUGAAAUAAUCCAAAGAU	570

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-111483	asesugaaGfaAfaAfgcaguuuuL96	303	asGfsaaaCfuGfGfuuuUfcUfucagucsu	437	AGACUGAAGAAAAGCCAGUUU CU	571
AD-112322	uscsauugCfuUfCfUfucagaauuuL96	304	asAfsauuCfuUfGfagaAfgCfaugascsu	438	AGUCAUUGCUUUCUUCAGAAU UU	572
AD-112396	usascuucCfaAfuGfauuuuuuuL96	305	asGfsaaaAfgUfAfucauUfgAfgaguasgsg	439	CCUACUCUCAAAUGAUACUUUUC U	573
AD-112618	asasacagAfaGfaAfaauuuuuuuL96	306	asUfsguaAfuAfaAuuuUfcUfuuuuuscsc	440	GGAAACAGAAAGAAAUUAUUAC AU	574
AD-112760	asgscacuUfuUfAfcfaaacgugauL96	307	asUfscacGfuUfUfgguaAfaAfgucucsgsu	441	ACAGCACUUUUACCCAAACGUGA U	575
AD-113137	gsasgagaAfuUfUfGfuuuuuuuuL96	308	asAfsuagUfaAfgfaaaAfuUfcucucsasus	442	AUGAGAGAAUUUGUCUUACUA UU	576
AD-113331	gsascauuCfaCfGfUfgguuacuuuuL96	309	asAfsaguGfaAfcacagUfgAfaugucsu	443	AAGACAUUCACGUGGUUCACU UU	577
AD-114455	csusguguUfaAfaUfguuuacaguuL96	310	asAfsaugUfuAfaAuuuUfaAfcacagscsg	444	CGCUGUGUUAAAUGUUUAAACAG UU	578
AD-114469	asesaguuUfuCfCfAfcuaauuuuuL96	311	asGfsagaAfaUfAfguggAfaAfacugususa	445	UACAGUUUUUCCACUAUUUCUC U	579
AD-114478	csusuucuuUfuUfCfUfaauagugauL96	312	asUfsucaCfuAfaAuagaAfaAfgaaagsasg	446	CUCUUUCUUUUUCUAUUAGUGA AU	580
AD-114698	ususucacAfaAfaCfAfcaguuuuuuL96	313	asAfsaaaUfcAfuUfguguUfuGfugaagsgu	447	ACUUUCACAAACACAUGAUUU UU	581
AD-114728	usascuuuAfaAfuAfuuccugucuuuuL96	314	asAfsagaCfaGfGfaauUfuUfaaguascsu	448	AGUACUUAAAAUAUCCUGUCU UU	582
AD-114746	ususucccAfuAfuAfaaauguuuuL96	315	asAfsaucAfuUfGfuuuAfuGfggaagsga	449	UCUUUCCCAUAUAACAAUAGAU UU	583
AD-115217	gsusguacAfuAfuAfucaaaauguuL96	316	asAfscauUfuUfGfaauAfuGfuacacsgsu	450	ACGUGUACAUAUAUCAAAAUG UU	584
AD-115235	csasacgaAfaUfUfCfaaacaauuuL96	317	asGfsauuGfuUfAfuagaUfuUfcguugsasu	451	AUCAACGAAAUAUCAAAACAAU CU	585
AD-115563	gsasaacuAfcCfaAfgaguuaaccuguL96	318	asCfsaggUfaAfcfcucugGfuAfguuuucsusa	452	UAGAAAACUACCCAGAGUUUACCU GU	586
AD-115659	csusuucuuUfuUfCfAfuagaauuuuuL96	319	asCfsaugAfaUfCfaugaAfaAfgaaagsga	453	UCCUUUCUUUUUCAUGAUUCAU GU	587

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-115814	csgcaagCfuAfaAfuaaauuuuuL96	320	asAfsgeaUfuAfafaauuAfcCfaugcgsgsu	454	ACCGCAUGCUGCUAAAUUUAAUGC	588
AD-115844	cscsucuuGfaAfaUfcuuuuuuuuuuL96	321	asAfsaaUfaAfaGfgaauUfcAfaagagsgsu	455	ACCCUCUUUGAAAUCCUUUUUUU	589
AD-115919	uscucuuGfaUfcUfagaauuuuuuuL96	322	asGfsuaaAfuUfcfuagaUfcAfaagagsgsa	456	UCUCUCUUUGAUCUAGAAUUUA	590
AD-1410569	cscsacaaAfcUfcAfaaguuuuaauL96	323	asAfsuucAfaAfcfuagaGfuUfugggsgsc	457	GCCCACAAACUCAGUUUUUGAAU	591
AD-1410577	asuscuuuUfuUfcAfaucuuuuuuuuL96	324	asAfsaagGfaAfcfuuaaAfcAfaagaussc	458	GAAUCUUUCUGUAACUUUCCUU	592
AD-1410605	asgsuaugAfaCfcAfaaauuuuuuuuuL96	325	asCfsuuaAfaUfUfauggUfuCfaucusc	459	AGAGUAUGAACCAUAUUUUAA	593
AD-1410628	csusaccaUfuUfcAfaagacuuuuuuL96	326	asAfsagaAfgUfcfcugaAfaUfgguagsasu	460	AUCUACCAUUUUCAGGACUUCUU	594
AD-1410662	csasucaAfaAfaGfuaacuuuuuuL96	327	asUfsaaaGfuGfAfaauUfuAfaugaussc	461	GACAUCAUAAAAGUUUCACUUU	595
AD-1410700	uscsaaggAfaUfuUfAfgguacaguuuuL96	328	asUfsacuGfuAfcfcuaaUfuCfcuugagsg	462	CCUCAAGGAAUUAGGUACAGU	596
AD-1410725	uscsumacCfuUfGfAfcacacuuuuL96	329	asAfsaugUfgUfGfgucaAfcGfuaagagasg	463	CUUCUUACCUUGACCACACAUAU	597
AD-1410825	uscacacAfcAfuCfuauuuuuuuuuL96	330	asGfsagUfaAfuUfagaUfuGfugagsgsg	464	CCUCACACACAUCUAUUACUCC	598
AD-1410845	uscugauCfcAfcGfuaauuuuuuuuuL96	331	asAfsuuGfaAfaAfuuccUfcAfuagagasuu	465	AAUCUGAUCGAGGAUUUACAAC	599
AD-1410880	gsascaagCfaAfaUfcgugcuuuuuL96	332	asAfsuaGfcAfcfgaauUfcCfuugucsasa	466	UUGACAAGCAAAUUCGUGCUAC	600
AD-1410926	cscscuaaUfgUfAfcacaguuuuuuL96	333	asAfsuugAfcUfGfuguaCfaUfuaggggsasu	467	AUCCCUAAUGUACACAGUCAAU	601
AD-1410994	asusuaauCfuCfcAfuuaauuuuuuuL96	334	asUfsaaaAfuGfAfauggAfcAfaaauussc	468	GAAUUAUUCUCCAUUUAUUUC	602
AD-1411107	csasggcuUfaCfaUfugacuuuuuuuuL96	335	asUfsuaaUfgUfcfaugUfaAfcgccgsca	469	UGCAGGCUUACAUAUUGACAUA	603
AD-1411138	cscsaggaAfuCfuUfuaaguuuuuuuuL96	336	asUfsaauUfuCfuuaagAfuUfcuuggsusu	470	AACCAGGAUUCUUAAGAAAAAU	604

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-1411226	usesageaUfuUfGfGfaaauuuuuL96	337	asAfsгааAfuUfAfuccaAfaUfGfugagsa	471	UCUCAGCAUUUGGAUAAUUUC	605
AD-1411270	usascгааGfaUfGfAfguccuacuuL96	338	asGfsugaAfgGfAfucaUfcUfucguascu	472	AGUACGAAAGAUAGAGUCCUUA	606
AD-1411284	csasccaaAfcAfuAfcagugaauuuL96	339	asGfsauuCfaCfuUfguanGfuUfuggugsasa	473	UUCACCAAAACAUACAGUGAAUC	607
AD-1411342	asesacucAfaAfaUfGfuguaauL96	340	asUfsugaAfcAfcfgauuUfuGfagugsgsu	474	ACACACUCAAAAUCGUGUUCAA	608
AD-1411387	asusgaagUfcAfaCfucuuuuuuL96	341	asGfsaaaGfaAfgfaguGfaCfucauascu	475	AGAUGAAGUCAACUCUUCUUU	609
AD-1411480	usasacaaGfaCfCfAfuacuacaguL96	342	asAfsaugUfaGfUfauggUfcUfuguuasag	476	CUUAAACAAGACCAUACUACAGU	610
AD-1411521	asasuaggAfcUfaCfucuaauuuL96	343	asAfsauUfaGfAfaguaGfuCfcauuasag	477	CUAAUAGGACUACUUCUAAUC	611
AD-1411657	asasacuuCfaUfGfAfgcacuaauL96	344	asUfsauAfgUfGfcaUfGfaguuuusga	478	UCAAACAUCAUAGAGCACUAUCA	612
AD-1411743	csasuicaUfcUfaUfGfagaagguL96	345	asCfsuucUfuUfCfcauaGfaUfgaugsgag	479	CUCAUUCAUCUAUGGAAAGAG	613
AD-1411798	usasacuuCfcAfuGfauuuuaguuL96	346	asAfsuuaGfaAfuUfcauGfgAfguuasasc	480	GUUAAACUCCAUAGAAUUCUAG	614
AD-1411935	gsascuauGfaUfuAfcagacacaguL96	347	asCfsuguUfcUfGfguaaUfcAfuagucsgag	481	CUGACUAUGAUUACCAGAACAA	615
AD-1411972	csesgaaaCfuCfaUfcauugaauuuL96	348	asGfsauuCfaAfuUfgaugAfgUfuuagggsasa	482	UUCCGAAACUCAUCAUUUGAAUC	616
AD-1412021	asesugaaUfuCfGfUfucuuuauuuL96	349	asUfsuugAfaGfAfaacgAfaUfucagugsc	483	GCACUGAAUUCGUUUCUUCUCAA	617
AD-1412040	gsusugguUfcAfaAfaAfuuuuuuuuuL96	350	asGfsaagAfaUfAfauuuGfaAfcacaacsasa	484	UUGUUGGUUCAAAUAUUCUUU	618
AD-1412052	asgsuuaCfuGfuCfcauaaaccuuuL96	351	asAfsaggUfuAfuUfgacAfgUfgaacususa	485	UAAGUUCACUGUCAAAUAAACCU	619
AD-1412095	asesucagUfuCfuCfcauuuuuuuuL96	352	asGfsгааGfaAfuUfgagAfaCfugagustsc	486	GAACUCAGUUCUCAAAUUCUCC	620
AD-1412163	usascgucUfaCfuUfucacuuuguuL96	353	asAfscaaAfgUfGfaaagUfaGfaguasusc	487	GAUACGUCUACUUCACUUGG	621

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-1412250	gsgsaugAfaUfUfAfcuagcacauuL96	354	asAfsuguGfcUfAfguaaUfuUfcauccsag	488	CUGGAUGAAAAUACUAGCACA UA	622
AD-1412364	gsusuacuCfuUfAfafacaagaauL96	355	asUfsacuUfuGfUfuuuaAfgAfguaacsag	489	CUGUUACUCUUAAAAACAAAGU AA	623
AD-1412429	csusgaugAfaGfAfCfacagcuguuuL96	356	asAfsacaGfcUfGfugueUfuCfaucaagsusa	490	UACUGAUGAAGACACAGCUGU UA	624
AD-1412482	csusagagUfuAfGfAfcuaaauuuuL96	357	asAfsaguUfuUfUfgucuaAfaCfucuaagsga	491	UCCUAGAGUUAGACAUAAAUC UC	625
AD-1412497	csuscuacAfaGfUfAfagacaggaauL96	358	asAfsuucUfgUfCfuuaUfuGfuaagagsasu	492	AUCUCUACAAAGUAAGACAGGA UG	626
AD-1412539	ususucucAfuUfAfAfgacacgaauL96	359	asUfsuucGfuGfUfuuuaAfuGfagaacsu	493	AGUUUCUCAUUAAAGACACGAA AA	627
AD-1412582	usgsaagcCfuAfCfAfacacauuuuL96	360	asAfsaaaUfgUfGfuuguAfgGfucuaacsu	494	AGUGAAGCCUACAACACAUUU UC	628
AD-1412622	asasucaaAfuGfAfAfaucucuuuL96	361	asAfsagaGfaUfGfuuuuAfuUfgauususa	495	UAAAUCCAAUGAAACAUCUCU UC	629
AD-1412683	asusaauAfgAfuUfuccucaauuL96	362	asAfsuuuGfaGfGfaauCfuGfaunauusg	496	CCAUAAUCAGAAUCCCUCAAAU G	630
AD-1412721	asgsaaccAfcUfAfUfcaacaauuL96	363	asGfsaaUGfuUfUfgaauGfuGfuuccu	497	AGAGGAACACUAUCAAAACAUU CC	631
AD-1412733	uscsaaUGfcAfCfUfcauucaguL96	364	asCfsugaAfgUfAfgaguGfcAfuuuasusc	498	GAUCAAAUGCACUCUACUUCAG A	632
AD-1412756	uscsagugAfaAfUfGfcuugaguauuL96	365	asAfsuacUfcAfAfgcauUfuCfauagsgsc	499	GCUCAGUGAAAUGCUUUGAGUA UG	633
AD-1412779	uscsucaGfaAfCfAfugaagucuguL96	366	asCfsagaCfuUfCfauuUfuUfgagagsasg	500	CUUCCUCAGAACAUUGAAAGUCUG G	634
AD-1412870	csuscauuCfaGfAfGfaaaccuuuL96	367	asGfsaaaGfgUfUfucueUfgAfaugagsusu	501	AACUCAUUCAGAGAAACCUCUUC C	635
AD-1412963	asesaaccCfuUfUfCfucuaagacuuuL96	368	asAfsaguCfuAfAfgagaaAfgGfguuuagusu	502	AUACAACCCUUUUCUCUAGACUU C	636
AD-1412982	csusccagAfaCfUfCfagucuaaauL96	369	asUfsguuUfgAfCfugagUfuCfuggagsasg	503	CUCUCCAGAACUCACAGUCAACA A	637
AD-1413036	ususgcagAfuCfUfCfagucuaaauuL96	370	asAfsaauUfgAfCfugagAfuCfugcaasasg	504	CUUUGCAGAUUCUCAGUCAAAU UC	638

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-1413128	gsasccuuGfaUfCfAfgauuuuuL96	371	asUfsagaAfuAfUfcugaUfcAfaagucsuug	505	CAGACCUUGAUCAGAUUUCU	639
AD-1413143	uscsugaaUfcUfAfgfucagucuuuL96	372	asAfsaugAfcUfGfagaaGfaUfucagasaag	506	CUUCUGAAUCUAGUCAGUCAU	640
AD-1413210	csusaacaAfaGfGfAfauuuaucuuL96	373	asGfsgauUfaAfAfuiuccUfuUfgauagsasa	507	UUCUAUCAAAGGAAUUUAAUC	641
AD-1413251	usascuuGfaGfAfucauucaaaL96	374	asUfsuugGfaAfUfgaueUfcAfauguasasu	508	AUUACAUUGAGAUCAUUCCAA	642
AD-1413286	ascsuuagCfuGfAfAfaugauuuL96	375	asAfsuaaUfcAfAfuiuccAfgCfaugascsa	509	UGACUAUGCUGAAAAUUGAUUA	643
AD-1413311	usasggacAfaAfCfAfucacuccuuL96	376	asAfsaggGfuUfGfauuUfuGfuccuasasc	510	GUUAGGACAAACAUCAACUCCU	644
AD-1413488	uscsggaaUfuCfUfUfgguccuuuL96	377	asAfsauaGfgAfCfcaagAfaUfuccgagasa	511	UCUCGGAAUUCUUGGUCCUUA	645
AD-1413517	ususauccAfaGfUfUfgguuuuuL96	378	asUfsuuaAfaAfCfgaacUfuGfgauaascsa	512	UGUUAUCCAAGUUCGUUUUA	646
AD-1413605	asusgcugUfuCfAfGfccaaauagcuL96	379	asGfscuaUfuUfGfgcugAfaCfagcausua	513	UAAUGCUGUUUCAGCCAAAUAG	647
AD-1413615	usasgcagUfuAfUfAfccuacguuuL96	380	asAfsuacGfuAfGfgauuAfaCfugcuasusu	514	AAUAGCAGUUUAUACCUACGUA	648
AD-1413936	csusgguuCfaUfUfUfaaaacuuuL96	381	asAfsagaGfuUfUfuuaaUfgAfaacagsgsc	515	GCCUGGUUCAUUUAAAACUCU	649
AD-1414009	usgscaaaCfGfCfAfuuuuuuauL96	382	asGfsauaAfgAfAfauggCfGfuiugcausuc	516	GAUGCAAACGCCAUUUUCUUAUC	650
AD-1414059	asusaucuGfaUfUfCfagagaucuuL96	383	asUfsugaUfcUfGfugaaUfcAfgauausgsa	517	UCAUAUCUGAUUCACAGAUCA	651
AD-1414074	uscsagagUfuUfCfUfggguuuacugL96	384	asCfsaguAfaCfCfagaaAfaCfucugasaag	518	CUUCAGAGUUUCUGGGUUACU	652
AD-1414139	asgsaaauUfgCfCfUfcaaaacuuuL96	385	asAfsaggUfuUfAfgaggCfaAfaauucsgsc	519	GCAGAAUUUGCCUCUAAAACCUU	653
AD-1414232	asusguagCfuUfAfCfaguucaacuL96	386	asGfsuugGfaAfCfuguaAfgCfuacausaag	520	CUAUGUAGCUUACAGUUUCCAAC	654
AD-1414275	gsasauguGfaUfGfUfauuuuuuuL96	387	asCfsauuAfaAfAfuaaUfcAfaauucscsu	521	AGGAAUGUGAUGAUUUUUAAU	655

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-1414328	usasgaauUfaUfAfGgaucucucL96	388	asGfsagaGfaUfCfcuaaUfaUfaucuasgsc	522	GCUAGAUAAUAGGAUCUCU	656
AD-1414410	uscsacagCfuUfCfUfucguuaaaguL96	389	asCfsuuaAfaCfGfaagaAfgCfugugasusu	523	AAUCACAGCUUCUUCGUUUA	657
AD-1414498	asusugauCfuAfcUfcaagaucuaaL96	390	asUfsugaUfcUfUfgaguAfgAfucaaususu	524	AAAUUGAUCUACUCAAGAUA	658
AD-1414544	csesucugAfaUfGfuanguaaaguL96	391	asCfsuuaAfcAfuUfacauUfuCfagagsasc	525	GUCCUCUGAAAUGUAUGUAAA	659
AD-1414625	asasggaaAfuAfcUfaauaccuaaL96	392	asUfsuugGfuAfuUfuaaUfuUfuccuiscsa	526	UGAAGGAAAUACUAAUACCAA	660
AD-1414662	csasuuccUfaAfaAfcuaggaucuaL96	393	asGfsauuAfcAfuUfguuUfaGfgaugsasc	527	GUCAUUCUAAAACAUGGAAU	661
AD-1414713	asgsacucUfuUfAfAfgaccuaaL96	394	asUfsuugAfgGfuUfcuaaAfaGfagucscsu	528	AGAGACUCUUUAAAGACCUCAA	662
AD-1414786	asgsauaaUfgGfCfuauuacuaL96	395	asAfsagaGfuAfuUfuaaGfCfuauucusa	529	UAAGAUAAUGGCUAUUACUUC	663
AD-1414796	ususcugCfuUfAfAfuugaaucuaL96	396	asGfsuauUfcAfaUfaaUfaGfcaagaasgu	530	ACUUCUGCAUUAAUUUUGAAUA	664
AD-1414831	asasgggcUfuUfCfuuuuuuaaL96	397	asAfsuuaAfgAfaUfagaUfaGfcccuisusu	531	AAAAGGCUUAUCUUUUCUUA	665
AD-1414857	csuscuuuUfaAfaUfcccuaaL96	398	asGfsuugAfaAfgGgaUfaAfaagagsusu	532	AACUCUUUAAAUCUUUACAC	666
AD-1414871	csascuagUfaAfaAfcagaaauaL96	399	asUfsaauAfuCfuUfguuUfaCfuagugsusg	533	CACACUAGUAAAACAGAUUU	667
AD-1414931	ususucugAfcUfUfUfccaugaguL96	400	asUfsacuCfaUfGfgaaGfuCfagaasasa	534	UUUUUCUGACUUUCCAUAGAGU	668
AD-1415052	asasaacaUfaAfuUfucacuaaL96	401	asAfsuaGfgUfGfaaUfaUfguuuuusga	535	UCAAAAACAUAAUUUCACCUACU	669
AD-1415096	csusggucUfaAfaUfUfgcaguuuuL96	402	asAfsacaAfcUfGfcauUfaGfaccagscsa	536	UGCUGGUCUAAAUGCAGUUGU	670
AD-1415166	uscsuucCfuUfCfCfagcaacuL96	403	asGfsaagUfuGfCfuggaAfgAfaagagsga	537	UCUCUCUUCUCCAGCAACUUC	671
AD-1415169	ususucauCfaUfUfCfcuuuuccuL96	404	asCfsaggGfaAfaUfggaUfaUfgaagaasgsg	538	CCUUUCAUCAUUCCUUUCCUG	672

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-1415194	ususuagaCfaUfCfCfuuaaaucuuL96	405	asUfsgauUfuUfAfaggaUfgUfcaaaasgsg	539	CCUUUAGACAUCUUUAAAAUCA	673
AD-1415243	usgsauuuAfaUfCfAfuccuguaacuL96	406	asGfsuuaCfaGfGfauaUfuAfaucasasg	540	CUUGAUUUAAUCAUCCUGUAA	674
AD-1415314	gsascuaaGfaAfAfCficacucgaauL96	407	asUfsucgAfgUfGfaguuUfcUfuagucscsu	541	AGGACUAAAGAAACUCACUCGA	675
AD-1415327	uscsaaaCfcAfCfAfaacuaacuL96	408	asAfsuguAfgUfUfguguGfgUfucgagsgsu	542	ACUCGAAACCACACAACUACAU	676
AD-1415412	ascsaacaUfaCfCfAfgaauucuuL96	409	asUfsagaGfaUfUfcuggUfaUfguugscsu	543	AGACAACAUACCAGAAUCUCUA	677
AD-1415439	gscsaauUfaUfUfCfugungagaauL96	410	asGfsuucAfcAfAfagaaUfaGfaugcsasg	544	CUGCAUUCUAUUCGUUGUGAA	678
AD-1415466	gsusucgAfuUfCfAfugugaaguuL96	411	asCfsuucUfaCfAfugaaUfuCfagacsgsg	545	CAGUCUCGAUUCAGUGUAGAA	679
AD-1415563	asusccacAfaAfAfCfaunggcuuuL96	412	asAfsaagCfcAfAfuguuUfuGfugaugsgsu	546	ACAUCCACAAAAACAUUGGCUUU	680
AD-1415578	csgsuauuCfcCfAfCfuaauccuuuL96	413	asAfsaagGfaAfUfagugGfgAfaucgsasa	547	UUCGUAUUCCCCACUAUUCUUU	681
AD-1415602	csasucaaCfaUfUfUfcaagaauuuL96	414	asAfsaaUcfUfAfagaaUfgUfugaugsgsg	548	CCCAUCAACAUAUUUCUAAAGAUUU	682
AD-1415633	asasaacaUfuUfCfUfuguuuuuuL96	415	asAfsaaaAfaCfAfagaaAfaUfguuuuscsc	549	GGAAAACAUAUUUCUUUUGUUUUC	683
AD-1415663	gsusgaucUfgUfUfCfagugcaaaL96	416	asUfsuugCfaAfCfugaaCfaGfaucacsasc	550	GUGUGAUCUGUUCAGUUGCAA	684
AD-1415714	asusucgaCfaUfUfUfccaauuuuuL96	417	asGfsaaaAfaUfGfgaaaUfgUfcaaususc	551	GAAUUCGACAUAUUUCCAUAUUUU	685
AD-1415738	csusucucUfaCfUfCfugaauuuuuL96	418	asCfscaaUfuUfCfagagUfaGfagaagcsc	552	GGCUUCUCUACUCUGAAAUUG	686
AD-1415798	gsusuuuUcfUfAfcuugagaaaL96	419	asUfsuucUfcAfAfugaaUfgAfaaacgsa	553	UCGUUAUUCUCUACUUGAGAA	687
AD-1415830	usgsuuuagUfgUfCfAfgaacugaaaL96	420	asUfsuucAfgUfUfcaugaCfaCfaaacasag	554	CUUGUUAGUGUCAGAGAACUGAA	688
AD-1415857	usasuccUfaGfAfCfuuuuaguuuL96	421	asAfsagacUfaAfAfagucUfaGfggaauasg	555	CAUAUCCCUAGACUUUUUAGUCU	689

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-1415873	usesuuccAfuAfAfAfaugaaacuuuL96	422	asAfsaguUfuCfAfuuuuAfuGfgaagsgsa	556	UCUCUUCCAUAAAAAUGAAACU	690
AD-1415881	asusguuuCfuAfAfUfccauugcucuL96	423	asGfsagcAfaUfGfgauuAfgAfaacaususa	557	UAAUGUUUCUAAUCCAUUGCU	691
AD-1415899	gsusagacAfuGfAfAfuaauuuuuL96	424	asCfsaauUfaAfUfaauucAfuGfucuaacscsu	558	AGGUAGACAUGAAAUUUAAUU	692
AD-1415910	gsasucugGfaAfAfAfuaacuuuuuuL96	425	asAfsaacAfaGfUfauuuUfcCfagaucsasa	559	UUGAUCUGGAAAAUACUUGUU	693
AD-1415934	csusguguAfgAfAfAfuaauuuuuuuL96	426	asGfsuuuUfaAfUfauuuUfcAfcacagscsa	560	UGCUGUGUAGAAAUUUUAAAA	694

Table 4. Coagulation Factor V Single Dose Screens in Hep3b cells

Duplex Name	% mRNA FV/GAPDH	Std Dev.
AD-1415934.1	75.3	3.0
AD-1415910.1	85.0	11.7
AD-1415899.1	78.6	0.9
AD-1415881.1	85.2	2.8
AD-1415873.1	75.0	1.0
AD-1415857.1	83.3	2.6
AD-1415830.1	72.0	1.0
AD-1415798.1	83.5	1.5
AD-115919.1	90.2	9.2
AD-1415738.1	88.6	4.4
AD-1415714.1	97.7	17.7
AD-115844.1	89.0	5.6
AD-115814.1	76.5	2.7
AD-1415663.1	83.9	2.3
AD-1415633.1	84.2	7.8
AD-1415602.1	92.9	3.0
AD-115659.1	79.9	3.7
AD-1415578.1	89.4	3.4
AD-1415563.1	91.8	12.5
AD-115563.1	91.7	5.1
AD-1415466.1	89.5	4.1
AD-1415439.1	76.9	3.3
AD-1415412.1	84.4	3.7
AD-1415327.1	87.9	2.1
AD-1415314.1	91.6	2.8
AD-115235.1	87.6	2.6
AD-115217.1	89.8	1.9
AD-1415243.1	89.0	2.2
AD-1415194.1	91.2	1.7
AD-1415169.1	100.4	7.2
AD-1415166.1	85.1	5.7
AD-1415096.1	94.2	6.2
AD-1415052.1	101.4	4.7
AD-1414931.1	93.8	4.9
AD-114746.1	101.6	9.0
AD-114728.1	102.5	3.3
AD-114698.1	95.9	0.6
AD-1414871.1	94.1	2.1
AD-1414857.1	104.1	1.6
AD-1414831.1	87.3	3.6

Duplex Name	% mRNA FV/GAPDH	Std Dev.
AD-1414796.1	87.9	10.3
AD-1414786.1	89.5	6.4
AD-114478.1	22.9	4.0
AD-114469.1	15.8	0.9
AD-114455.1	18.4	1.9
AD-1414713.1	21.3	1.5
AD-1414662.1	22.3	3.7
AD-1414625.1	23.7	2.6
AD-1414544.1	18.8	2.8
AD-1414498.1	103.0	6.0
AD-1414410.1	16.0	1.6
AD-1414328.1	17.6	2.5
AD-1414275.1	16.7	1.6
AD-1414232.1	17.6	1.2
AD-1414139.1	20.5	1.0
AD-1414074.1	42.0	6.1
AD-1414059.1	26.1	2.1
AD-1414009.1	21.4	1.7
AD-1413936.1	17.4	2.8
AD-113331.1	28.2	2.2
AD-113137.1	16.1	3.0
AD-1413615.1	21.8	2.6
AD-1413605.1	21.7	2.9
AD-1413517.1	16.9	1.3
AD-1413488.1	24.3	2.9
AD-112760.1	20.0	2.6
AD-112618.1	17.0	1.7
AD-1413311.1	13.3	1.3
AD-1413286.1	13.3	1.9
AD-1413251.1	23.8	4.5
AD-1413210.1	17.5	3.1
AD-112396.1	10.3	1.3
AD-112322.1	14.1	1.5
AD-1413143.1	16.2	1.6
AD-1413128.1	11.9	3.4
AD-1413036.1	44.5	4.6
AD-1412982.1	12.9	1.1
AD-1412963.1	18.8	0.4
AD-1412870.1	24.9	1.8
AD-1412779.1	25.4	1.2
AD-1412756.1	21.0	2.9
AD-1412733.1	20.7	0.9
AD-1412721.1	17.7	3.6

Duplex Name	% mRNA FV/GAPDH	Std Dev.
AD-1412683.1	20.2	4.1
AD-1412622.1	29.9	5.5
AD-1412582.1	25.6	5.2
AD-1412539.1	28.2	4.8
AD-111483.1	18.5	2.8
AD-1412497.1	25.6	3.2
AD-1412482.1	22.8	3.7
AD-1412429.1	21.7	4.0
AD-111345.1	22.0	2.2
AD-111287.1	18.9	4.2
AD-1412364.1	19.2	3.9
AD-1412250.1	23.5	2.0
AD-1412163.1	23.4	1.4
AD-1412095.1	20.5	0.7
AD-1412052.1	17.3	1.7
AD-1412040.1	15.4	2.8
AD-110844.1	19.0	2.2
AD-1412021.1	20.2	4.7
AD-110787.1	20.5	1.0
AD-1411972.1	19.6	4.5
AD-1411935.1	24.3	1.3
AD-1411798.1	72.9	6.7
AD-110518.1	17.7	4.3
AD-1411743.1	75.4	7.7
AD-110370.1	20.5	1.2
AD-1411657.1	39.3	3.6
AD-110281.1	20.9	1.5
AD-1411521.1	18.7	1.7
AD-1411480.1	20.0	3.8
AD-110052.1	24.4	0.7
AD-1411387.1	20.1	1.4
AD-1411342.1	22.0	1.3
AD-1411284.1	32.5	5.8
AD-1411270.1	20.5	3.6
AD-109799.1	16.9	1.5
AD-1411226.1	19.5	3.8
AD-1411138.1	18.3	1.7
AD-1411107.1	13.0	1.7
AD-109601.1	24.8	5.9
AD-1410994.1	15.9	3.1
AD-1410926.1	22.6	1.7
AD-1410880.1	19.3	4.0
AD-1410845.1	20.6	4.4

Duplex Name	% mRNA FV/GAPDH	Std Dev.
AD-1410825.1	21.5	6.1
AD-1410725.1	31.8	4.2
AD-1410700.1	37.5	1.3
AD-1410662.1	18.0	3.5
AD-1410628.1	27.9	1.9
AD-1410605.1	29.3	3.0
AD-1410577.1	22.7	1.7
AD-1410569.1	22.2	5.2

Example 3. Additional Duplexes Targeting Coagulation Factor V

Human-cynomolgous cross-reactive agents targeting coagulation factor V gene were designed using custom R and Python scripts and synthesized as described above.

5 Detailed lists of the unmodified complement coagulation factor V sense and antisense strand nucleotide sequences are shown in Tables 5 and 7. Detailed lists of the modified coagulation factor V sense and antisense strand nucleotide sequences are shown in Tables 6 and 8.

Single dose screens of the additional agents were performed by free uptake.

10 For free uptake, experiments were performed by adding 2.5 μ L of siRNA duplexes in PBS per well into a 96 well plate. Complete growth media (47.5 μ L) containing about 1.5×10^4 primary human hepatocytes were then added to the siRNA. Cells were incubated for 48 hours prior to RNA purification and RT-qPCR. Single dose experiments were performed at 100nM, 10 nM, and 1 nM final duplex concentration.

15 Total RNA isolation was performed using DYNABEADS. Briefly, cells were lysed in 10 μ L of Lysis/Binding Buffer containing 3 μ L of beads per well were mixed for 10 minutes on an electrostatic shaker. The washing steps were automated on a Biotek EL406, using a magnetic plate support. Beads were washed (in 3 μ L) once in Buffer A, once in Buffer B, and twice in Buffer E, with aspiration steps in between. Following a final aspiration, complete 12 μ L RT mixture was added to each well, as described below.

20 For cDNA synthesis, a master mix of 1.5 μ L 10X Buffer, 0.6 μ L 10X dNTPs, 1.5 μ L Random primers, 0.75 μ L Reverse Transcriptase, 0.75 μ L RNase inhibitor and 9.9 μ L of H₂O per reaction was added per well. Plates were sealed, agitated for 10 minutes on an electrostatic shaker, and then incubated at 37 degrees C for 2 hours. Following this, the plates were agitated at 80 degrees C for 8 minutes.

25 RT-qPCR was performed as described above and relative fold change was calculated as described above. The results of the single dose screen of the agents in Tables 5 and 6 in primary human hepatocytes are shown in Table 9.

Table 5. Unmodified Sense and Antisense Strand Sequences of Coagulation Factor V dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1465901.1	CAGCUAAGGCAGUUCUACGUU	695	233-253	AACGTAGAACUGCCUUAGCUGUG	951	231-253
AD-1465902.1	AGGCAUCAGUUGGAGCUACU	696	261-281	AGUAGCTCCAAACUGAUGCCCUGA	952	259-281
AD-1465903.1	UCUACAGAGAGUAUGAACCAU	697	339-359	AUGGTUCAUACUCUCUGUAGACA	953	337-359
AD-1465904.1	UACAGAGAGUAUGAACCAU	698	341-361	AUAUGGTUCAUACUCUCUGUAGA	954	339-361
AD-1465905.1	ACAGAGAGUAUGAACCAU	699	342-362	AAUATGGUUCUAUCUCUCUGUAG	955	340-362
AD-1465906.1	UUCUUGGGCCUACUUUAU	700	399-419	AAUATAAGUAGGCCCAAGAAGU	956	397-419
AD-1465907.1	UACUUUAUUGCUGAAGUCGU	701	409-429	ACGACUTCAGCAUAUAAAGUAGG	957	407-429
AD-1465908.1	ACUUUAUUGCUGAAGUCGU	702	410-430	ACCGACTUCAGCAUAUAAAGUAG	958	408-430
AD-1465909.1	AGUAAAUAUCAGAGGUGCU	703	503-523	AGCACCTUCUGAUAAUUUACUGU	959	501-523
AD-1465910.1	AAAUUAUCAGAGGUGCUUCU	704	506-526	AGAAAGCACCUUCUGAUAAUUUAC	960	504-526
AD-1465911.1	AUCAGAGGUGCUUCUACCU	705	511-531	AGGUAAGAAGCACCUUCUGAUAA	961	509-531
AD-1465912.1	UCAGAGGUGCUUCUACCU	706	512-532	AAGGTAAGAAGCACCUUCUGAU	962	510-532
AD-1465913.1	CAGAGGUGCUUCUACCU	707	513-533	AAAGGUAAGAAGCACCUUCUGAU	963	511-533
AD-1465914.1	AUACACCUAUGAUGGAGUAU	708	586-606	AUACTCCAUAUAGGUGUAUUC	964	584-606
AD-1465915.1	ACCUAUGAUGGAGUAUCAGU	709	590-610	ACUGAUACUCCAUUUAUAGGUGU	965	588-610
AD-1465916.1	CCUAUGAUGGAGUAUCAGU	710	591-611	AACUGATACUCCAUUUAUAGGUG	966	589-611
AD-1465917.1	AUGAAUGGAGUAUCAGUGAGU	711	594-614	ACUCACCTGAUACUCCAUUUAUAG	967	592-614
AD-1465918.1	AUGCCUCACACACAUUUAU	712	643-663	AAAUAGAUGUGTGUGAGGCAUGG	968	641-663
AD-1465919.1	UGCCUCACACACAUUUAU	713	644-664	ATAATAGAUGUGUGUGAGGCAUG	969	642-664
AD-1465920.1	GCCUCACACACAUUUAU	11	645-665	AGUAAUAGAUGTGUGAGGCAU	12	643-665
AD-1465921.1	CCUCACACACAUUUAU	714	646-666	AAGUAATAGAUGUGUGAGGCA	970	644-666
AD-1465922.1	CUCACACACAUUUAU	13	647-667	AGAGTAUAAGATGUGUGAGGCG	14	645-667
AD-1465923.1	CACACACAUUUAUACUCCU	715	649-669	AGGGAGTAUAUAGAUGUGUGUGA	971	647-669
AD-1465924.1	ACAUCUAUACUCCCAUGAAU	716	654-674	AUUCAUUGGGAGUAUAGAUGUG	972	652-674
AD-1465925.1	GAAAGCGUUUGACAAAGCAAAU	717	757-777	AUUUGCTUGUCAAAACGUCUUCUG	973	755-777
AD-1465926.1	AGACGUUUUGACAAAGCAAAU	718	759-779	AGAUTUGCUUUGUCAACGUCUUC	974	757-779
AD-1465927.1	GACGUUUUGACAAAGCAAAU	719	760-780	ACGATUTGCUUUGUCAACGUCUUC	975	758-780
AD-1465928.1	GCCAGUCAUCAUCCCAU	720	819-839	ACAUTAGGGAUGAUGACUGGCUC	976	817-839
AD-1465929.1	GUCAUCAUCCCAU	721	823-843	AUGUACAUAUAGGGAUGAUGACU	977	821-843

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1465930.1	CAUCAUCCCUAAUGUACACAU	722	825-845	AUGUGACAUUAGGGAUGAUGA C	978	823-845
AD-1465931.1	AUCAUCCCUAAUGUACACAGU	723	826-846	ACUGTGTACAUUAGGGAUGAUGA	979	824-846
AD-1465932.1	AAUGUACACAGUCAUUGGAUU	724	835-855	AAUCCATUGACTGUGUACAUAUAG	980	833-855
AD-1465933.1	AUGUACACAGUCAUUGGAUU	725	836-856	AUAUCCAUAUGACUGUGUACAUAU	981	834-856
AD-1465934.1	AUGUGAAUGGACAAUGCCAU	726	855-875	AUGGCATUGUCCCAUUCACAUAU	982	853-875
AD-1465935.1	GCCAGAUUAACAGUUUGUGU	727	871-891	ACACAAACUGUTAUUUCUGGCAU	983	869-891
AD-1465936.1	CCAGAUUAACAGUUUGUGCU	728	872-892	AGCACAAACUGTUAUUCUGGCA	984	870-892
AD-1465937.1	GAGCAGAACCAUCAUAGGUU	729	974-994	AACCTUAUGAUGGUUCUGCUCCA	985	972-994
AD-1465938.1	CAGAACCAUCAUAGGUCUCU	730	977-997	AGAGACCUAUUGAUGGUUCUGCU	986	975-997
AD-1465939.1	AGAACCAUCAUAGGUCUCAU	731	978-998	AUGAGACCUUAUGAUGGUUCUGC	987	976-998
AD-1465940.1	AUCACCCUUGUCAGUGCUACU	732	1001-1021	AGUAGCACUGACAAAGGGUGAUGG	988	999-1021
AD-1465941.1	UUUCAGUGCUACAUCACAU	733	1008-1028	AAUGUGAUGUAGCACUGACAAGG	989	1006-1028
AD-1465942.1	CAUCCACUACCGCAAAUAUGU	734	1020-1040	ACAUAUTUGCGGUAGUGGAUGUA	990	1018-1040
AD-1465943.1	AAGCUGGGAUGCAGGCUUACU	735	1095-1115	AGUAAAGCCUGCAUCCAGCUUGC	991	1093-1115
AD-1465944.1	AGCUGGGAUGCAGGCUUACAU	736	1096-1116	AUGUAAAGCCUGCAUCCAGCUUG	992	1094-1116
AD-1465945.1	GCUGGGAUGCAGGCUUACAUU	737	1097-1117	AAUGTAAGCCUGCAUCCAGCUU	993	1095-1117
AD-1465946.1	CUGGGAUGCAGGCUUACAUUU	738	1098-1118	AAUGUAAAGCCTGCAUCCAGCU	994	1096-1118
AD-1465947.1	UGGGAUGCAGGCUUACAUUGU	739	1099-1119	ACAATGTAAAGCCUGCAUCCAGC	995	1097-1119
AD-1465948.1	GGGAUGCAGGCUUACAUUGAU	740	1100-1120	AUCAAUUGAAGCCUGCAUCCAG	996	1098-1120
AD-1465949.1	GGAUGCAGGCUUACAUUGACU	741	1101-1121	AGUCAATGUAAGCCUGCAUCCCA	997	1099-1121
AD-1465950.1	GAUGCAGGCUUACAUUGACAU	742	1102-1122	AUGUCAUUGAAGCCUGCAUCC	998	1100-1122
AD-1465951.1	AUGCAGGCUUACAUUGACAUU	743	1103-1123	AAUGTCAUUGAAGCCUGCAUCC	999	1101-1123
AD-1465952.1	UGCAGGCUUACAUUGACAUUU	744	1104-1124	AAUGUCAUUGAAGCCUGCAUC	1000	1102-1124
AD-1465953.1	GCAGGCUUACAUUGACAUUUU	745	1105-1125	AUAATGTCAAUGUAAGCCUGCAU	1001	1103-1125
AD-1465954.1	CAGGCUUACAUUGACAUUAAU	746	1106-1126	AUUAUUGUCAUUGUAAGCCUGCA	202	1104-1126
AD-1465955.1	AGGCUUACAUUGACAUUAAAU	747	1107-1127	ATUUAATGUCAAUGUAAGCCUGC	1002	1105-1127
AD-1465956.1	GGCUUACAUUGACAUUAAAAU	748	1108-1128	ATUUTAAUGUCAUUGUAAGCCUG	1003	1106-1128
AD-1465957.1	GCUUACAUUGACAUUAAAAU	749	1109-1129	ATUUTUAAUGUCAUUGUAAGCCU	1004	1107-1129
AD-1465958.1	CUUACAUUGACAUUAAAAACU	750	1110-1130	AGUUTUAAUGTCAAUGUAAGCC	1005	1108-1130
AD-1465959.1	UUACAUUGACAUUAAAAACUU	750	1111-1131	AAGUTUTUAAUGUCAUUGUAAGC	1006	1109-1131

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1465960.1	UACAUUGACAUUAAAAACUGU	751	1112-1132	ACAGTUTUUAAATGUCAAUGUAAAG	1007	1110-1132
AD-1465961.1	ACAUUGACAUUAAAAACUGCU	752	1113-1133	AGCAGUTUUUAAUGUCAAAUGUAA	1008	1111-1133
AD-1465962.1	CAUUGACAUUAAAAACUGCCU	753	1114-1134	AGGCAGTUUUAAUGUCAAUUGUA	1009	1112-1134
AD-1465963.1	AUUGACAUUAAAAACUGCCCU	754	1115-1135	AGGCAGUUUUUAAUGUCAAUUG U	1010	1113-1135
AD-1465964.1	UUUGACAUUAAAAACUGCCCAU	755	1116-1136	AUGGGCAGUUUUUAAUGUCAAU G	1011	1114-1136
AD-1465965.1	GGGAUAUCUUAUUGCUGCAU	756	1194-1214	AUGCAGCAAUGAAGUAUUCCCAC	1012	1192-1214
AD-1465966.1	AGUCAUUUGGACUAUGCACU	757	1219-1239	AGUGCATAGUCCCAAUGACUUC	1013	1217-1239
AD-1465967.1	GGGACUAUAGCACCUUGUAUUAU	758	1227-1247	AUAUTACAGGUGCAUAGUCCCAA	1014	1225-1247
AD-1465968.1	CACCUGUAAUACCCAGCGAAUU	759	1236-1256	AAUUCGUGGUAAUACAGGUGCA	1015	1234-1256
AD-1465969.1	UGUAAUACCCAGCGAAUUAUGGU	760	1240-1260	ACCATATUCGCTGGUAUUACAGG	1016	1238-1260
AD-1465970.1	GUAAUACCCAGCGAAUUAUGGAU	761	1241-1261	ATCCAUAAUUCGUGGUAAUACAG	1017	1239-1261
AD-1465971.1	AGGUCUCAGCAUUUGGAUAAU	762	1271-1291	AUUAATCCAAUAGCUGAGACCUGU	1018	1269-1291
AD-1465972.1	GUUAUGUACACACAGUACGAU	763	1325-1345	ATCGTACUGUGTGUAACAUAACUU	1019	1323-1345
AD-1465973.1	UUAUGUACACACAGUACGAU	764	1326-1346	ATUCGUACUGUGUGUAACAUAACU	1020	1324-1346
AD-1465974.1	AUGUACACACAGUACGAAGAU	765	1328-1348	AUCUTCGUACUGUGUGUAACAUA	1021	1326-1348
AD-1465975.1	UGUACACACAGUACGAAGAU	766	1329-1349	AAUCTUCGUACUGUGUGUAACAUA	1022	1327-1349
AD-1465976.1	GUACACACAGUACGAAGAU	767	1330-1350	ACAUCUTCGUACUGUGUGUAACA	1023	1328-1350
AD-1465977.1	AGUACGAAAGUAGAGUCCUUCU	768	1338-1358	AGAAGGACUCAUCUUCGUACUGU	1024	1336-1358
AD-1465978.1	GUACGAAAGUAGAGUCCUUCAU	769	1339-1359	AUGAAGGACUCAUCUUCGUACUG	1025	1337-1359
AD-1465979.1	GUGAUUCCTCAAUAUGAAAGAU	770	1370-1390	AUCUTUCAUAUUGGGAUUCACUG	1026	1368-1390
AD-1465980.1	ACCCUCAUGGAGUAGCCUUCU	771	1482-1502	AGAAGGTCACUCCAUAGAGGUA	1027	1480-1502
AD-1465981.1	GAACAACACCAUGAUCAGAGU	772	1546-1566	ACUCTGAUCAUGGUGUUGUUCU	1028	1544-1566
AD-1465982.1	CAACACCAUGAUCAGAGCAGU	773	1549-1569	ACUGCUCUGAUCUAGGUGUUGUU	1029	1547-1569
AD-1465983.1	CACCAUGAUCAGAGCAGUUCU	774	1552-1572	AGAACUGCUCUGAUCUAGGUGUU	1030	1550-1572
AD-1465984.1	CAUGAUCAGAGCAGUUCACCAU	775	1555-1575	AGUUGAACUGCUCUGAUCUAGGU	1031	1553-1575
AD-1465985.1	UGAUCAGAGCAGUUCACCAU	776	1557-1577	AUGGTUGAACUGCUCUGAUCUAG	1032	1555-1577
AD-1465986.1	AAACCUAAUCUUAUAAGUGGU	777	1581-1601	ACCACUTAAAGUAUAGGUUCC	1033	1579-1601
AD-1465987.1	AACCUAAUCUUAUAAGUGGAU	778	1582-1602	AUCCACTUAAAGUAUAGGUUUC	1034	1580-1602
AD-1465988.1	CUUAUAAGUGGAACAUCUUAU	779	1590-1610	AUAAGATGUUCCACUUAUAGUA	1035	1588-1610
AD-1465989.1	UCUAAUCUGUAAGAGCAGAUU	780	1714-1734	AAUCTGCUCUUAACAGAUUAGAA	1036	1712-1734

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1465990.1	AAUCUGUAAGAGCAGAUCCCU	781	1717-1737	AGGGAUCUGCUCUUACAGAUUAG	1037	1715-1737
AD-1465991.1	ACCUUGAGGACAAACAUCAACU	782	1818-1838	AGUUGATGUUGUCCUCAAGGUAC	1038	1816-1838
AD-1465992.1	AUGAAUCAAACAUCUAGAGCU	783	1887-1907	AGCUCATGAUGTUUGAUUCAUAA	1039	1885-1907
AD-1465993.1	GAAUCAAACAUCUAGAGCACU	784	1889-1909	AGUGCUCUAGAUUUGAUUUAU	1040	1887-1909
AD-1465994.1	UGAGCACUAUCAAUGGCUAUU	785	1902-1922	AAUAGCCAUUAGAUAGUGCUAUG	1041	1900-1922
AD-1465996.1	GAUUCUGCUUUGAUGACACUU	786	1947-1967	AAGUGUCAUCAAAGCAGAUCCA	1042	1945-1967
AD-1465997.1	CCAGUGGCACUUCUGUAGUGU	787	1969-1989	ACACTACAGAAUGGCCACUGGAC	1043	1967-1989
AD-1465998.1	AGUGGCACUUCUGUAGUGUGU	788	1971-1991	ACACACTACAGAAUGGCCACUGG	1044	1969-1991
AD-1465999.1	CUGGGCACUUAUCUUAU	789	2025-2045	AAUAGATGAUAGUGGCCACUGG	1045	2023-2045
AD-1466000.1	GUGACGGUCACAAUGGAUAAU	790	2096-2116	AUUATCCAUUUGUGACCGUCACAG	1046	2094-2116
AD-1466001.1	GGAAUUGGAUUGUUAACUUCU	791	2120-2140	AGAAGUTAACAUCUCAAAGUCCAA	1047	2118-2140
AD-1466002.1	UUAAUUCUUAAGAAUUCUAGU	792	2132-2152	ACUAGAAUUCATGGAAGUUAACA	1048	2130-2152
AD-1466003.1	AUGAUGAUGAAGACUCUAUU	793	2205-2225	AAUATGAGUCUUAUCUUAUCU	1049	2203-2225
AD-1466004.1	UGAUGAAGACUCUAUAGAGAU	794	2209-2229	ATCUCATAUGAGUCUUAUCAUC	1050	2207-2229
AD-1466005.1	AAACUCAUUAUUAUAGAGU	795	2365-2385	ACCUGATUCAATGAUGAGUUUCG	1051	2363-2385
AD-1466006.1	AAACACAGAUUAUUAUUGUUGU	796	2446-2466	ACAACAUAUAUCUGUGUUUGA	1052	2444-2466
AD-1466007.1	CACAGAUUAUAUUGUUGGUUU	797	2449-2469	AAACCAACAUAUAUCUGUGUUU	1053	2447-2469
AD-1466008.1	CAUAUUCUGAAGACCCUUAU	798	2634-2654	AUAUAGGGUUCUUCAGAAUAUGG	1054	2632-2654
AD-1466009.1	AUUCUGAAGACCCUUAUAGAGU	799	2637-2657	ACUCTATAGGGTCUUCAGAAUAU	1055	2635-2657
AD-1466010.1	CGUCUACUUCUACUUGGUGCU	800	2687-2707	AGCACCAAGUGAAAGUAGACGUA	1056	2685-2707
AD-1466011.1	AUGAAAUACUAGCACAUAAU	801	2792-2812	AUUATGTGCUAGUAAUUUCAUCC	1057	2790-2812
AD-1466012.1	AAUACUAGCACAUAAAGUUU	802	2796-2816	AAACTUTAUUGUGCUAGUAAUUUC	1058	2794-2816
AD-1466013.1	UACUAGCACAUAAAGUUGGU	803	2799-2819	ACCCAACUUUATGUGCUAGUAAU	1059	2797-2819
AD-1466014.1	GAGUUGGCAUUUGGUUUCUGU	804	2980-3000	ACAGAAAGCCAAUUGCCAUUCCU	1060	2978-3000
AD-1466015.1	GUAGCUAUGAAUUAUCCAAU	805	3006-3026	AUUGGATUAUUUCAUAGCUACCU	1061	3004-3026
AD-1466016.1	CAAGAUACUGAUGAAGACACU	806	3023-3043	AGUGTCTUCAUCAGUAUCUUUGGA	1062	3021-3043
AD-1466017.1	GAUACUGAUGAAGACACAGCU	807	3026-3046	AGCUGUGUCUUCUACAGUAUCUU	1063	3024-3046
AD-1466018.1	AAGACACAGCUGUUAACAAU	808	3036-3056	AAUUGUTAACAAGCUGUGUCUUA	1064	3034-3056
AD-1466019.1	AAGUUUCCUAGAGUUAGACAU	809	3143-3163	ATGUCUAAACUCTAGGAACUUUG	1065	3141-3163
AD-1466020.1	CCUAGAGUUAGACAUAAUUCU	810	3149-3169	AGAUTUAUGUCTAACUCUAGGAA	1066	3147-3169
AD-1466021.1	UACAAGUAAGACAGGAUGGAU	811	3171-3191	ATCCAUCUGUCUUAUCUUGAUA	1067	3169-3191

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1466022.1	GUUUCUCAUUAAGACACGAAU	812	3217-3237	AUUCGUGUCUUAAUAGAGAAACUG	1068	3215-3237
AD-1466023.1	CACCAUGCUCUUUAUCUCCU	813	3260-3280	AGGAGATAAAGGAGCAUGGUGUG	1069	3258-3280
AD-1466024.1	AGGACCUUUCACCCUCUAAGU	814	3281-3301	ACUAGAGGGUGAAAGGUCCUCG	1070	3279-3301
AD-1466025.1	GUGCUUCAUAAAUCCAAUGAU	815	3350-3370	AUCATUGGAUUUAUGAAGCACCA	1071	3348-3370
AD-1466026.1	UGCUCUAAAUAUCCAAUGAAU	816	3351-3371	ATUCAUTGGAUTUAUGAAGCACCC	1072	3349-3371
AD-1466027.1	CCAAUGAAACAUCUCUUCUU	817	3363-3383	AGGGAAGAGAUUUUCAUUGGA	1073	3361-3383
AD-1466028.1	ACUUCUGACCAUAAUCAGAU	818	3433-3453	AUCUGATUAUGGUCAGGAAGUGA	1074	3431-3453
AD-1466029.1	AAUUGCUUGAGUAUGACCGAU	819	3609-3629	AUCGGUCAUACUCAAGCAUUUCA	1075	3607-3629
AD-1466030.1	GCUUGAGUAUGACCGAAGUCU	820	3613-3633	AGACTUCGGUCAUACUCAAGCAU	1076	3611-3633
AD-1466031.1	GAGUAUGACCGAAGUCACAAU	821	3617-3637	AUUGTGACUUCGGUCAUACUCA	1077	3615-3637
AD-1466032.1	UAUGACCGAAGUCACAAAGUCU	822	3620-3640	AGACTUGUGACUUCGGUCAUACU	1078	3618-3640
AD-1466033.1	UGACCGAAGUCACAAAGUCCU	823	3622-3642	AAGGACTUGAGACUUCGGUCAU	1079	3620-3642
AD-1466034.1	GACCGAAGUCACAAAGUCCUU	824	3623-3643	AAAGGACUUGAGACUUCGGUCAU	1080	3621-3643
AD-1466035.1	ACCGAAGUCACAAAGUCCUUCU	825	3624-3644	AGAAGGACUUGAGACUUCGGUCA	1081	3622-3644
AD-1466036.1	UCUCCAGAACUCAGUCAGACU	826	3920-3940	AGUCTGACUGAGUUCUGGAGAGA	1082	3918-3940
AD-1466036.2	UCUCCAGAACUCAGUCAGACU	826	3920-3940	AGUCTGACUGAGUUCUGGAGAGA	1082	3918-3940
AD-1466036.3	UCUCCAGAACUCAGUCAGACU	826	3920-3940	AGUCTGACUGAGUUCUGGAGAGA	1082	3918-3940
AD-1466037.1	CUCCAGAACUCAGUCAGACAU	827	3921-3941	AUGUCUGACUGAGUUCUGGAGAG	1083	3919-3941
AD-1466037.2	CUCCAGAACUCAGUCAGACAU	827	3921-3941	AUGUCUGACUGAGUUCUGGAGAG	1083	3919-3941
AD-1466037.3	CUCCAGAACUCAGUCAGACAU	827	3921-3941	AUGUCUGACUGAGUUCUGGAGAG	1083	3919-3941
AD-1466038.1	CAGCCAGACAAACCUCUCUCU	828	3742-3762	AGAGAGAGGUUUUGUCUGGCUGA	1084	3740-3762
AD-1466038.2	CAGCCAGACAAACCUCUCUCU	828	3742-3762	AGAGAGAGGUUUUGUCUGGCUGA	1084	3740-3762
AD-1466039.1	UUCUACCCUUCUGAAUCUAGU	829	4535-4555	ACUAGATUCAGAAGGGUAGAAUA	1085	4533-4555
AD-1466040.1	CAUCUCCUACUCUCUCAAUGAUU	830	4626-4646	AAUCAUTGAGAGUAGGAGUAGAA	1086	4624-4646
AD-1466041.1	AUCAAGGAAUUUAAUCCACU	831	4654-4674	AGUGGATUAAAUUCCUUUUAUAG	1087	4652-4674
AD-1466042.1	AAGGAAUUUAAUCCACUGGUU	832	4658-4678	AACCAGTGGAAUAAAUUCCUUUG	1088	4656-4678
AD-1466043.1	UUUAAUCCACUGGUUAUAGUU	833	4664-4684	AACUAAUACCCAGUGGAUUAUAAU	1089	4662-4684
AD-1466044.1	UUAAUCCACUGGUUAUAGUGU	834	4665-4685	ACACTATAACCCAGUGGAUUAUAAU	1090	4663-4685
AD-1466045.1	AGAUGGUACAGAUUACAUUGU	835	4696-4716	ACAATGTAAUCUGUACCAUCUUU	1091	4694-4716

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1466046.1	AUGGUACAGAAUACAUGAGU	836	4698-4718	ACUCAATGUAATCUGUACCAUCU	1092	4696-4718
AD-1466047.1	ACUGAUGUUAGGACAAACAUAU	837	4799-4819	AAUGTUTGUCCTAACACUACAGUUU	1093	4797-4819
AD-1466048.1	CUGAUGUUAGGACAAACAUCU	838	4800-4820	AGAUGUTUGUCCUACAACUACAGUU	1094	4798-4820
AD-1466049.1	GAAAGAAUAUCCUGGAAUAU	839	4904-4924	AUAATCCAGGAUAUUUCUUCAG	1095	4902-4924
AD-1466050.1	UGAAGACUCUGAUGAAUAUUCU	840	4954-4974	AGAATATCAUCAGAGUCUUCUCAAU	1096	4952-4974
AD-1466051.1	GUUAGAAAGCAUCUCGGAUAU	841	5053-5073	ATUCCGAGUAGCUCUUCUACUC	1097	5051-5073
AD-1466052.1	AGAGCAUCUCGGAUAUUCUUGU	842	5059-5079	ACAAGAAUUCGAGAUUCUUC	1098	5057-5079
AD-1466053.1	UCGGAAUUCUUGGUCCUAUUU	113	5067-5087	AAUAGGACCAAGAAUUCGAGA	244	5065-5087
AD-1466054.1	CGGAAUUCUUGGUCCUAUUU	843	5068-5088	AUAATAGGACCAAGAAUUCGAG	1099	5066-5088
AD-1466055.1	AAUUCUUGGUCCUAUUUACAUAU	844	5071-5091	ATGATAAUAGGACCAAGAAUUCU	1100	5069-5091
AD-1466056.1	UCUUGGUCCUAUUUACAGAGU	845	5074-5094	ACUCTGAUAAUAGGACCAAGAAU	1101	5072-5094
AD-1466057.1	GUCCUAUUACAGAGCUGAAU	846	5079-5099	AUUCAGCUCUGAAUUAAGGACCA	1102	5077-5099
AD-1466058.1	UGAAGUGGAUGAUGUUAUCCU	847	5095-5115	AGGATAACAUCAUCCACUUCAGC	1103	5093-5115
AD-1466059.1	GAAUGGAGUAGUUAUCCAU	848	5096-5116	ATGGAUACAUCAUCCACUUCAG	1104	5094-5116
AD-1466060.1	AUCAGAGGGAAGACUUAUGU	849	5185-5205	ACAUAAUCUUTCCUUCUGAUGA	1105	5183-5205
AD-1466061.1	AGGGAAGACUUAUGAAGAUU	850	5190-5210	AAUCTUCAUAAAGUCUUUCCUUCU	1106	5188-5210
AD-1466062.1	AGCCAAUAGCAGUUAUACCU	851	5247-5267	AGGUAAACUGCUAAUUGGCUGA	1107	5245-5267
AD-1466063.1	AGCAGUUAUACCUACGUAGU	852	5255-5275	ACAUACGUAGGTAAUACUGCUAU	1108	5253-5275
AD-1466064.1	GAUAAUACUCACAGGCUUGAUU	853	5360-5380	AAUCAAGCCUGAGUAAUUCUUCU	1109	5358-5380
AD-1466065.1	GGAAUACUACAUAAGGACAGU	854	5405-5425	ACUGTCCUUAUGUAUUAUUCUUCU	1110	5403-5425
AD-1466066.1	CUACAUAAGGACAGCAACAUAU	855	5411-5431	AAUGTUGCUGUCCUUAUGUAGUA	1111	5409-5431
AD-1466067.1	ACAUAAGGACAGCAACAUGCU	856	5413-5433	AGCATGTUGCUGUCCUUAUGUAG	1112	5411-5433
AD-1466068.1	ACAUGAGAGAAUUUGUCUUAU	857	5439-5459	AUAAGACAAAUUCUCUCUACUCC	1113	5437-5459
AD-1466069.1	CAUGAGAGAAUUUGUCUUAU	858	5440-5460	AGUAAGACAAAUUCUCUCUACUCC	1114	5438-5460
AD-1466070.1	GAGAGAAUUUGUCUUAUUAU	46	5443-5463	AAUAGUAAGACAAAUUCUCUACU	177	5441-5463
AD-1466071.1	GACCUUUGAUGAAAGAAAGAU	859	5467-5487	AUCUTCTUUUCAUCAAAGGUCAU	1115	5465-5487
AD-1466072.1	ACCUUUGAUGAAAGAAAGAGU	860	5468-5488	ACUCTUCUUUUUCAUCAAAGGUCA	1116	5466-5488
AD-1466073.1	CCUUUGAUGAAAGAAAGAGCU	861	5469-5489	AGCUCUTCUUUUUUCAUCAAAGGU	1117	5467-5489
AD-1466074.1	CUUUUGAUGAAAGAAAGAGCUU	862	5470-5490	AAGCTCTUCUUUUUCAUCAAAGGU	1118	5468-5490
AD-1466075.1	UUUGAUGAAAGAAAGAGCUGU	863	5471-5491	ACAGCUCUCUUUUUCAUCAAAGG	1119	5469-5491
AD-1466076.1	UUUGAUGAAAGAAAGAGCUGGU	864	5472-5492	ACCAGCTCUCUUUUUCAUCAAAG	1120	5470-5492
AD-1466077.1	UGAUGAAAGAAAGAGCUGGUU	865	5473-5493	AACCAGCUCUCUUUUUCAUCAA	1121	5471-5493

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1466078.1	GAUGAAAAGAAAGAGCUGGUAAU	866	5474-5494	AUACCAAGCUCUUCUUUUCAUCA	1122	5472-5494
AD-1466079.1	AUGAAAAGAAAGAGCUGGUACU	867	5475-5495	AGUACCAAGCUCUUCUUUUCAUCA	1123	5473-5495
AD-1466080.1	UGAAAAGAAAGAGCUGGUACUU	868	5476-5496	AAGUACCAAGCUCUUCUUUUCAUC	1124	5474-5496
AD-1466081.1	GAAAAGAAAGAGCUGGUACUAAU	869	5477-5497	ATAGTACCAAGCUCUUCUUUUCAU	1125	5475-5497
AD-1466082.1	AAAAGAAAGAGCUGGUACUAAU	870	5478-5498	AAUAGUACCAAGCUCUUCUUUUCA	1126	5476-5498
AD-1466083.1	AAAGAAAGAGCUGGUACUAAU	871	5479-5499	ACAUAGTACCAAGCUCUUCUUUUUC	1127	5477-5499
AD-1466084.1	AAGAAGAGCUGGUACUAAU	872	5480-5500	AUCATAGUACCAAGCUCUUCUUUU	1128	5478-5500
AD-1466085.1	AGAAGAGCUGGUACUAAU	873	5481-5501	ATUCAUAGUACCAAGCUCUUCUUU	1129	5479-5501
AD-1466086.1	GAAAGAGCUGGUACUAAU	874	5482-5502	AUUUCATAGUACCAAGCUCUUCUU	1130	5480-5502
AD-1466087.1	AAGAGCUGGUACUAAU	875	5483-5503	AUUUTCAUAGUACCAAGCUCUUCU	1131	5481-5503
AD-1466088.1	AGAGCUGGUACUAAU	876	5484-5504	ACUUTUCAUAGUACCAAGCUCUUC	1132	5482-5504
AD-1466089.1	GAGCUGGUACUAAU	877	5485-5505	ATCUTUTCAUAGUACCAAGCUCUU	1133	5483-5505
AD-1466090.1	AGCUGGUACUAAU	878	5486-5506	AUUCTUTUCAUAGUACCAAGCUCU	1134	5484-5506
AD-1466091.1	GCUGGUACUAAU	879	5487-5507	ACUUCUTUUCATAGUACCAAGCUC	1135	5485-5507
AD-1466092.1	CUGGUACUAAU	880	5488-5508	AACUTCTUUCUAGUACCAAGCUCU	1136	5486-5508
AD-1466093.1	CCGAGUUCUUGGAGACUAAU	881	5509-5529	AUGAGUCUCCAAAGACUUCGGGA	1137	5507-5529
AD-1466094.1	GAAGUUCUUGGAGACUAAU	882	5511-5531	AUGUGAGUCUCCAAAGACUUCGG	1138	5509-5531
AD-1466095.1	UUUCACGCCAUUAAUUGGAAU	883	5558-5578	AAUCCCAUUAAATGGCGUGAAACU	1139	5556-5578
AD-1466096.1	AUUAAUUGGGAUUAUUAUUAU	884	5567-5587	ACUGTAGAUCAATCCCAUUAAUUGG	1140	5565-5587
AD-1466097.1	GCUCCCAAGACAUUACACGUGU	885	5649-5669	ACACGUGAAUUGTCUUUGGGAGCCG	1141	5647-5669
AD-1466098.1	CCAAGACAUUACACGUGGUUCU	886	5653-5673	AGAACCACGUGAAUUGUCUUGGGA	1142	5651-5673
AD-1466099.1	AUUCACGUGGUUACUUAUUAU	887	5660-5680	AUGAAAGUGAACCAAGCUGAAUUGU	1143	5658-5680
AD-1466100.1	AUGCAAACGCCAUUUAUUAUUAU	888	5831-5851	AAUAAAGAAUUGGCGUUUGCAUCC	1144	5829-5851
AD-1466101.1	GCAAACGCCAUUUAUUAUUAUUAU	889	5833-5853	ATGATAAGAAATGGCGUUUGCAU	1145	5831-5853
AD-1466102.1	UCUUAUCAUGGACAGAGACUUAU	890	5845-5865	AAGUCUCUGUCCUAGAUAAAGAA	1146	5843-5865
AD-1466103.1	UUUAUCAUGGACAGAGACUUAU	891	5847-5867	AACAGUCUCUGUCCUAGAUAAAGAA	1147	5845-5867
AD-1466104.1	UAAAGCACUGGUUAUUAUUAUUAU	892	5883-5903	AAGATATGAUACCAAGCUGCUUAU	1148	5881-5903
AD-1466105.1	UCAUAUCUGAUUACACAGAUUCU	893	5895-5915	AGAUCUGUGAAUACAGAUUAUGAU	1149	5893-5915
AD-1466106.1	AUAUCUGAUUACACAGAUCAAU	118	5897-5917	AUUGAUCUGUGAAUACAGAUUAUG	249	5895-5917
AD-1466107.1	UAAACAAUUGGUGGAUCUUAUUAU	894	5961-5981	AAUAAAGAUCCACCAUUGUUUAUUAU	1150	5959-5981

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1466108.1	AAACAAUGGUGGAUCUUAUAU	895	5962-5982	ATAAAGAUAUCCACCAUUGUUAA	1151	5960-5982
AD-1466109.1	CAUUGGUGGAUCUUAUAUAUGU	896	5965-5985	ACAUTATAAGATCCACCAUUGUU	1152	5963-5985
AD-1466110.1	GGUGGAUCUUAUAUAUGCUUGU	897	5969-5989	ACAAGCAUUAUAAGAUAUCCACCAU	1153	5967-5989
AD-1466111.1	AUCUUAUAUAUGCUUGGAGUGU	898	5974-5994	ACACTCCAAGCAUUAUAAGAUAUCC	1154	5972-5994
AD-1466112.1	CAAGGUGCCAACACUAACCUU	899	6080-6100	AAGGTAGUGUUUGGCACCUUGGG	1155	6078-6100
AD-1466113.1	CCUGCUUAUACCAACAGAGUUCU	900	6105-6125	AGAACUCUGUGGUUAUAGCAGGAC	1156	6103-6125
AD-1466114.1	CUGCUUAUACCAACAGAGUUCU	19	6106-6126	AAGAACTCUGUGGUUAUAGCAGGA	20	6104-6126
AD-1466115.1	UAUACCAACAGAGUUCUAUGUU	901	6110-6130	AACATAGAACUCUGUGGUUAUAGC	1157	6108-6130
AD-1466116.1	UACCACAGAGUUCUAUGUAGU	902	6112-6132	ACUACATAGAACUCUGUGGUUAUA	1158	6110-6132
AD-1466117.1	CCACAGAGUUCUAUGUAGCUU	903	6114-6134	AAGCTACAUAGAACUCUGUGGUA	1159	6112-6134
AD-1466118.1	CACAGAGUUCUAUGUAGCUU	904	6115-6135	AAAGCUACAUAAGAACUCUGUGGU	1160	6113-6135
AD-1466119.1	AGAGUUCUAUGUAGCUUAUACAU	905	6118-6138	AUGUAAGCUACAUAAGAACUCUGU	1161	6116-6138
AD-1466120.1	AGUUCUAUGUAGCUUAACAGUU	906	6120-6140	AACUGUAAGCUACAUAAGAACUCU	1162	6118-6140
AD-1466121.1	UCUAUGUAGCUUAACAGUUCU	907	6123-6143	AGGAAGTGUAAAGCUACAUAAGAAC	1163	6121-6143
AD-1466122.1	CAUUCAGAGUAGCCUCUAACAAU	908	6205-6225	AUUGTAGAGGCAUCUGAAUUGCC	1164	6203-6225
AD-1466123.1	AAUUCAGAUGCCUCUAACAAU	909	6206-6226	AAUUGUAGAGGCAUCUGAAUUGC	1165	6204-6226
AD-1466124.1	UUCAGAUGCCUCUAACAAUAAU	910	6208-6228	AUUATUGUAGAGGCAUCUGAAUUC	1166	6206-6228
AD-1466125.1	AUCAGUUUGACCCACCUAAUUU	911	6234-6254	AAUAAGGUGGGUCAACACUGAUUC	1167	6232-6254
AD-1466126.1	UCAGUUUGACCCACCUAAUUGU	912	6235-6255	ACAATAGGUGGGUCAACACUGAUU	1168	6233-6255
AD-1466127.1	CAGUUUGACCCACCUAAUUGUU	913	6236-6256	AACAAUAGGUGGGUCAACACUGAU	1169	6234-6256
AD-1466128.1	CUAUUGUGGCUAAGUAUAUUU	914	6249-6269	AAUAUAUCUAGCCACAAUAGGU	1170	6247-6269
AD-1466129.1	GGCUAGUAUAUUAGGAUCUU	915	6256-6276	AAGATCCUAAUAUUAUAGCCAC	1171	6254-6276
AD-1466130.1	GAUAUAUUAGGAUCUCUCCAU	916	6261-6281	AUGGAGAGAUCCUAUAUAUUCUA	1172	6259-6281
AD-1466131.1	AGCAAAUUCACAGCUUCUUCGU	917	6384-6404	ACGAAGAAGCUUGUAUUUGCUUG	1173	6382-6404
AD-1466132.1	AGUGGCUAGAAAUAUGAUCUUAU	918	6507-6527	AUAGAUCAAUUAUCUAGCCACUGC	1174	6505-6527
AD-1466133.1	AAAUUGAUCUACUCAAGAUCU	919	6516-6536	AGAUCUTGAGUAGAUCAAAUUCU	1175	6514-6536
AD-1466134.1	AUUGAUCUACUCAAGAUCAAU	125	6518-6538	AUUGAUCUUAGUAAGAUCAAUU		
AD-1466135.1	AAAUUGUAUGUAAAGAGCUAAU	920	6585-6605	AAUAGCTCUUUACAUAUUAUUA	256	6516-6538
AD-1466136.1	AUGUAAGAGCUUAUACCAUCU	921	6591-6611	AGAUGGTAUAGCUCUUUAUUAUAC	1176	6583-6605
AD-1466137.1	AAGAGCUUAUACCAUCCACUAU	922	6596-6616	AUAGTGGAUGGUUAUAGCUCUUUA	1177	6589-6611
AD-1466138.1	CUCCAUGGUGGACAGAUAUUU	923	6658-6678	AAATCTUGUCCACCAUGGAGGA	1178	6594-6616
					1179	6656-6678

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1466139.1	UCCAUGGUGGACAAAGAUUUUU	924	6659-6679	AAAAAUCUUUGUCCACCAUGGAGG	1180	6657-6679
AD-1466140.1	CCAUGGUGGACAAAGAUUUUUUU	925	6660-6680	AAAAAATCUUGTCCACCAUGGAG	1181	6658-6680
AD-1466141.1	CAUGGUGGACAAAGAUUUUUUGU	926	6661-6681	ACAAAAAUCUUGUCCACCAUGGA	1182	6659-6681
AD-1466142.1	AUGGUGGACAAAGAUUUUUUGAU	927	6662-6682	ATCAAAAUCUTGUGCCACCAUGG	1183	6660-6682
AD-1466143.1	UGGUGGACAAAGAUUUUUUGAAU	928	6663-6683	ATUCAAAAUCTGUGCCACCAUG	1184	6661-6683
AD-1466144.1	GGUGGACAAAGAUUUUUUGAAGU	929	6664-6684	ACUUCAAAAUCUUGUCCACCAU	1185	6662-6684
AD-1466145.1	GUGGACAAAGAUUUUUUGAAGGU	930	6665-6685	ACCUTC AAAATCUUGUCCACCA	1186	6663-6685
AD-1466146.1	UGGACAAAGAUUUUUUGAAGGAU	931	6666-6686	AUCCTUCAAAAUCUUGUCCACC	1187	6664-6686
AD-1466147.1	GGACAAAGAUUUUUUGAAGGAU	932	6667-6687	AUCCUTCAAAAUCUUGUCCAC	1188	6665-6687
AD-1466148.1	GACAAGAUUUUUUGAAGGAAU	933	6668-6688	AUUUCC TUCAAAAAUCUUGUCCA	1189	6666-6688
AD-1466149.1	ACAAGAUUUUUUGAAGGAAAU	934	6669-6689	AAUUTCCUUCAAAAAUCUUGUCC	1190	6667-6689
AD-1466150.1	CAAGAUUUUUUGAAGGAAAU	935	6670-6690	AUAUTUCCUUCAAAAAUCUUGUC	1191	6668-6690
AD-1466151.1	AAGAUUUUUUGAAGGAAAUACU	936	6671-6691	AGUATUTCCUUCAAAAAUCUUGU	1192	6669-6691
AD-1466152.1	AGAUAUUUUUGAAGGAAAUACUU	937	6672-6692	AAGUAUTUCCUTCAAAAUCUUG	1193	6670-6692
AD-1466153.1	GAUUAUUUUUGAAGGAAAUACU	938	6673-6693	ATAGTATUCCCTUCAAAAAUCUU	1194	6671-6693
AD-1466154.1	AUUUUUGAAGGAAAUACUAAU	939	6674-6694	AUUAGUAUUUCCUUCAAAAAUCU	1195	6672-6694
AD-1466155.1	UUUUUGAAGGAAAUACUAAU	940	6675-6695	AAUAGTAUUUCCUUCAAAAAUC	1196	6673-6695
AD-1466156.1	UUUUGAAGGAAAUACUAAU	941	6676-6696	AUAUTAGUAUUUCCUUCAAAAA	1197	6674-6696
AD-1466157.1	UUUGAAGGAAAUACUAAUACU	942	6677-6697	AGUATUAGUAUTUCCUUCAAAAA	1198	6675-6697
AD-1466158.1	UUUGAAGGAAAUACUAAUACCU	943	6678-6698	AGGUAUTAGUAUTUCCUUCAAAA	1199	6676-6698
AD-1466159.1	ACUAAUACCAAAAGGACAUGUU	944	6689-6709	AACATGTCCUUUGGUUUUAGUAU	1200	6687-6709
AD-1466160.1	CUAAUACCAAAAGGACAUGUGU	945	6690-6710	ACACAUGUCCUUGGUUUUAGUA	1201	6688-6710
AD-1466161.1	UAAUACCAAAAGGACAUGUGAU	946	6691-6711	ATCACATGUCCTUUGGUUUUAGU	1202	6689-6711
AD-1466162.1	CAAUCAUUUCCAGGUUUUACU	947	6729-6749	AGAUAAACCUGGAAAUAGAUUGG	1203	6727-6749
AD-1466163.1	AUCAUUUCCAGGUUUUACCGU	948	6731-6751	ACGGAUAAACCTGGAAAUGAUUG	1204	6729-6751
AD-1466164.1	AUGGAUUCAAAAGUAUUGCACU	949	6766-6786	AGUGCAAUACUUUGAUUCCAUUG	1205	6764-6786
AD-1466165.1	GCCUGGAACUCUUUUGGCUGUU	950	6789-6809	AACAGCCAAAAGAGUUCCAGGCGA	1206	6787-6809

Table 6. Modified Sense and Antisense Strand Sequences of Coagulation Factor V 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-1465901.1	csasgeuaagGfCfAfgnuacuauL96	1207	asdAscgdTadGaacudGcCfuagcugsug	1467	CACAGCUAAGGCAGUUCUACGUG	1731
AD-1465902.1	asgsggcaUfcAfGfUfuggagacuL96	1208	asGfsuadGc(Tgn)ccaacuGfaUfgccucgsa	1468	UCAGGGCAUCAGUUGGAGCUACC	1732
AD-1465903.1	uscsuacaGfaGfAfGfuaagaaccuL96	1209	asUfsggdTu(C2p)auacucUfcUfguagascsa	1469	UGUCUACAGAGAGUAUGAACCAU	1733
AD-1465904.1	uscsagaGfaGfUfAfugaaccuauL96	1210	asUfsaudGg(Tgn)ucauacUfcUfcuguasgsa	1470	UCUACAGAGAGUAUGAACCAU	1734
AD-1465905.1	ascsagagAfgUfAfUfgaaccuauL96	1211	asAfsuadTg(G2p)uucuaCfuCfuuguasgs	1471	CUACAGAGAGUAUGAACCAU	1735
AD-1465906.1	ususcungggCfCfUfaeuuuauuL96	1212	asdAsuadTadAaguadGgCfccaagaagsu	1472	ACUUCUUGGGCCUACUUAUUAUG	1736
AD-1465907.1	usascuuuuAfuUfGfugaagucguL96	1213	asdCsgradCudTcagcdAuAfaaagaugsag	1473	CCUACUUAUAUAGCUGAAGUCGG	1737
AD-1465908.1	ascsuuuauaUfGfCfugaagucguL96	1214	asdCscgdAcdTucagdCaUfaaagaugsag	1474	CUACUUAUAUAGCUGAAGUCGGA	1738
AD-1465909.1	asgsuaauuAfuUfCfagaagugcuL96	1215	asdGscadCcdTucugdAuAfaunuacugsu	1475	ACAGUAAUUAUCAGAAAGGUGCU	1739
AD-1465910.1	asasaauaUfcAfGfAfagugcuuL96	1216	asGfsaadGc(Agn)ccuucGfaUfaaunuasc	1476	GUAAAUAUCAGAAAGGUGCUUCU	1740
AD-1465911.1	asuscagaagGfUfGfucuuuaccuL96	1217	asdGsgudAadGaagcdAcCfuucugausasa	1477	UUUAUCAGAAAGGUGCUUCUACCU	1741
AD-1465912.1	uscsagaagUfGfCfucuuuaccuL96	1218	asdAsggdTadAgaagdCaCfucucugausa	1478	UAUCAGAAAGGUGCUUCUACCUU	1742
AD-1465913.1	csasgaagguGfCfUfucuuuaccuL96	1219	asdAsagdGudAgaadGcAfcuucugusas	1479	AUCAGAAAGGUGCUUCUACCUUG	1743
AD-1465914.1	asusacacCfuAfUfGfaagugaguL96	1220	asUfsacdTc(C2p)auuauAfgGfugauusnc	1480	GAAUACACCUAUGAAUGGAGUAU	1744
AD-1465915.1	ascsuauagaAfuUfGfagaucaguL96	1221	asdCsugdAudAcuccdAuUfcauagugsu	1481	ACACCUAUGAAUGGAGUAUCAGU	1745
AD-1465916.1	csesuauaaaUfGfGfagaucaguL96	1222	asdAscudGadTacedCaUfcauagugsu	1482	CACCUAUGAAUGGAGUAUCAGUG	1746
AD-	asusgauggAfGfUfaucaugaguL96	1223	asdCsucdAcdTgaudCuCfcauaucausag	1483	CUAUGAAUGGAGUAUCAGUGAG	1747

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1465917.1					G	
AD-1465918.1	asusgccuacCfAfCfacaucuaauuL96	1224	asdAsaudAgdAugudTgUfgaggcausgg	1484	CCAUGCCUCACACACAUCUAUUA	1748
AD-1465919.1	usgscuacAfCfAfaucuaauuL96	1225	asdTsaadTadGaugudGuGfugaggcasusg	1485	CAUGCCUCACACACAUCUAUUAUAC	1749
AD-1465920.1	gsescuacAfCfAfaucuaauuL96	1226	asdGsuadAudAgaudTgUfgugaggcsasu	1486	AUGCCUCACACACAUCUAUUAUACU	1750
AD-1465921.1	csesucacAfCfAfucauauuL96	1227	asdAsgudAadTagaudGuGfugaggcsa	1487	UGCCUCACACACAUCUAUUAUACUC	1751
AD-1465922.1	csuscacAfCfUfcauauuL96	1228	asdGsagdTadAuagadTgUfgugaggsgsc	1488	GCCUCACACACAUCUAUUAUACUCC	1752
AD-1465923.1	csascacAfCfUfcauauuL96	1229	asGfsggdAg(Tgn)aaugaUfgUfguggsasg	1489	CUCACACACAUCUAUUAUACUCCCA	1753
AD-1465924.1	ascsaucAfUfAfCfuuccaauL96	1230	asUfsudAu(G2p)ggaguaAfuAfgaugsgs	1490	ACACAUCUAUUAUACUCCCAUGAAA	1754
AD-1465925.1	gsasagacGfuUfUfGfacaagcaauL96	1231	asUfsudGc(Tgn)ugueaaAfcGfucucsusg	1491	CAGAAGACGUUUGACAAGCAAAU	1755
AD-1465926.1	asgsacguUfuGfAfCfaagcaauL96	1232	asGfsaudTu(G2p)cuugcAfaAfcgucusc	1492	GAAGACGUUUGACAAGCAAAUUCG	1756
AD-1465927.1	gsascguuugAfCfAfagcaauL96	1233	asdCsgadTudTgcundGuCfaaacgucsu	1493	AAGACGUUUGACAAGCAAAUUCGU	1757
AD-1465928.1	gsescagucaUfCfAfuuccuauL96	1234	asdCsaudTadGggandGaUfgacuggsusc	1494	GAGCCAGUCAUCAUCCCUAAUGU	1758
AD-1465929.1	gsuscaucAfUfCfCfuaanguacauL96	1235	asUfsgudAc(Agn)uuaggAfuGfaugacsus	1495	CAGUCAUCAUCCCUAAUGUACAC	1759
AD-1465930.1	csasucauCfcCfUfAfauguacauL96	1236	asUfsgudGu(Agn)cauugGfgAfugaugasac	1496	GUCAUCAUCCCUAAUGUACACAG	1760
AD-1465931.1	asuscaucCfeUfAfAfuaguacacagL96	1237	asCfsugdTg(Tgn)acaauaGfgGfaugausgsa	1497	UCAUCAUCCCUAAUGUACACAGU	1761
AD-1465932.1	asasuguacaCfAfGfucuaugauL96	1238	asdAsudCadTugadTgUfguacauusag	1498	CUAAUGUACACAGUCAAAUGGAUA	1762
AD-1465933.1	asusguacAfcAfGfUfcaauggauL96	1239	asUfsaudCc(Agn)uugacuGfuGfuacausa	1499	UAAUGUACACAGUCAAAUGGAUAU	1763
AD-	asusguagaAfuGfGfGfacaugccauL96	1240	asUfsggdCa(Tgn)ugueccAfuUfcaausasu	1500	AUAUGUAAUGGGACAAGCCAG	1764

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1465934.1						
AD-1465935.1	gscscaganaUfAfAfcaguuugugul96	1241	asdCsacdAadAcugudTtaUfaucuggcsasu	1501	AUGCCAGAUAAACAGUUUGUGC	1765
AD-1465936.1	csesagauauAfAfCfaguuugugul96	1242	asdGscadCadAacugdTtaUfaucuggcsa	1502	UGCCAGAUAAACAGUUUGUGC	1766
AD-1465937.1	gsasgcagaaCfCfAfuaaaggguul96	1243	asdAscddTudAugaudGgUfucugcscsa	1503	UGGAGCAGAACCAUCAUAAGGUC	1767
AD-1465938.1	csasgaacCfaUfCfAfuaaaggguul96	1244	asGfsagdAc(C2p)uuuugaUfgGfuucugscsu	1504	AGCAGAAACCAUCAUAAGGUCUCA	1768
AD-1465939.1	asgsaaccAfuCfAfUfaaggguucacul96	1245	asUfsgadGa(C2p)cuuugaAfuGfguucugsc	1505	GCAGAAACCAUCAUAAGGUCUCAG	1769
AD-1465940.1	asuscaccCfuUfGfUfcagugucacul96	1246	asGfsuadGc(Agn)cugacaAfgGfgugaugsug	1506	CCAUCACCCUUUGUCAGUGGCUACA	1770
AD-1465941.1	ususgucaGfuGfCfUfacaucacul96	1247	asAfsgudGg(Agn)uguagaAfcUfgacaugsug	1507	CCUUUGUCAGUGGCUACAUCACUA	1771
AD-1465942.1	csasuecacuAfCfCfagcaaaugul96	1248	asdCsaudAudTugcgdGuAfguggaugusua	1508	UACAUCCACUACCGCAAAUAUGA	1772
AD-1465943.1	asasgugGfgAfUfGfagggcuuacul96	1249	asGfsuadAg(C2p)cuageauCfcCfagcuusgsc	1509	GCAAGCUGGGAUGCAGGCUUACA	1773
AD-1465944.1	asgsuuggGfaUfGfCfagggcuuacul96	1250	asUfsgudAa(G2p)ccugcaUfcCfagcuusug	1510	CAAGCUGGGAUGCAGGCUUACA	1774
AD-1465945.1	gsesugggauGfCfAfggcuuacauul96	1251	asdAsugdTadAgccudGcAfucccagcsusu	1511	AAGCUGGGAUGCAGGCUUACA	1775
AD-1465946.1	csusgggaugCfAfGfgcuuacauul96	1252	asdAsaudGudAgagcdTgCfaucuccagcsu	1512	AGCUGGGAUGCAGGCUUACA	1776
AD-1465947.1	usgsuggaugCfAfGfgcuuacauul96	1253	asdCsaadTgdTaagcdCuGfaucuccagcsu	1513	GCUGGGAUGCAGGCUUACA	1777
AD-1465948.1	gsesgaugCfaGfGfCfuacauugul96	1254	asUfscadAu(G2p)uaagcdUfgCfaucuccagcsu	1514	CUGGGAUGCAGGCUUACA	1778
AD-1465949.1	gsesgaugcagGfCfUfuaaauugacul96	1255	asdGsuedAadTguaadGcCfugaucuccsa	1515	UGGGAUGCAGGCUUACA	1779
AD-1465950.1	gsasugcaGfgCfUfUfacaauugacul96	1256	asUfsgudCa(Agn)uguagaCfcUfgcaucuccsa	1516	GGAUGCAGGCUUACA	1780
AD-	asusgcaggcUfUfAfcauugacauul96	1257	asdAsugdTedAaugudAaGfcccugcaucsc	1517	GGAUGCAGGCUUACA	1781

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1465951.1						
AD-1465952.1	usgscaggCfuUfAfCfaugacauuuL96	1258	asAfsaudGu(C2p)aauguaAfgCfcgucasusc	1518	GAUGCAGGCUUACAUAUGACAUAUA	1782
AD-1465953.1	gscsaggeUfuAfCfAfuugacauuuL96	1259	asUfsaadTg(Tgn)caagnAfaGfcecugcsasu	1519	AUGCAGGCUUACAUAUGACAUAUA	1783
AD-1465954.1	csasggcuUfaCfAfUfugacauuuL96	335	asUfsuadAu(G2p)ucaagUfaAfgceugsesa	1520	UGCAGGCUUACAUAUGACAUAUAAA	603
AD-1465955.1	asgsgcuuacAfUfUfgacauuuL96	1260	asdTsuudAadTgucadAuGfuagaagceugsc	1521	GCAGGCUUACAUAUGACAUAUAAAA	1784
AD-1465956.1	gsgscuuacaUfUfGfacaauuuL96	1261	asdTsuudTadAuguedAaUfguaagccesug	1522	CAGGCUUACAUAUGACAUAUAAAA	1785
AD-1465957.1	gscsuuacauUfGfAfcuuuuL96	1262	asdTsuudTudAaugudCaAfuguaagcsesu	1523	AGGCUUACAUAUGACAUAUAAAAAC	1786
AD-1465958.1	csusuacauUGfAfCfauuuuL96	1263	asdGsuudTudTaaugdTcAfauguaagcsce	1524	GGCUUACAUAUGACAUAUAAAAACU	1787
AD-1465959.1	ususacauugAfCfAfuaaaaaL96	1264	asdAsgudTudTuaudGuCfaauguaagsc	1525	GUUACAUAUGACAUAUAAAAACUG	1788
AD-1465960.1	usascuugaCfAfUfuuaaaL96	1265	asdCsagdTudTuaadTgUfcaauguasag	1526	CUUACAUAUGACAUAUAAAAACUGC	1789
AD-1465961.1	ascsaugacAfUfUfaaaacugcuL96	1266	asdGscadGudTuuaadAuGfucaaugusasa	1527	UUACAUAUGACAUAUAAAAACUGCC	1790
AD-1465962.1	csasuuGaCfaUfUfaaaacugccuL96	1267	asGfsgcdAg(Tgn)uuuuuUfgUfcaaugsuma	1528	UACAUAUGACAUAUAAAAACUGCCCC	1791
AD-1465963.1	asusugacAfuUfAfAfaaacugcccuL96	1268	asGfsggdCa(G2p)uuuuuAfuGfucaaugsu	1529	ACAUUGACAUAUAAAAACUGCCCCA	1792
AD-1465964.1	ususgacaUfuAfAfAfaacugcccuL96	1269	asUfsggdGc(Agn)guuuuuAfaUfgucaasusg	1530	CAUUGACAUAUAAAAACUGCCCCAA	1793
AD-1465965.1	gsgsgaauAfeUfUfCfaugcugcauL96	1270	asUfsgcdAg(C2p)aaugaaGfuAftuueccsasc	1531	GUGGGAAUAACUUAUUGCUGCAG	1794
AD-1465966.1	asgsucauUfuGfGfGfacaugcacuL96	1271	asGfsugdCa(Tgn)agucccAfaAfugacustusc	1532	GAAGUCAUUUGGGGACUAUGCACC	1795
AD-1465967.1	gsgsgacuAfuGfCfAfecuguaauL96	1272	asUfsaudTa(C2p)aggugcAfuAfgueccsasa	1533	UUGGGACUAUGCACCUGUAAUAC	1796
AD-1465968.1	csascuguaUfUfAfecagcgaaL96	1273	asdAasuudCgdCuggudAuUfacagugcsesa	1534	UGCACCUGUAAUACCAGCGAAUA	1797

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1465968.1						
AD-1465969.1	usgsuaauacCfAfGfcgaauauguL96	1274	asdCscadTadTuegdTgGfuauuacsgsg	1535	CCUGUAAUACCAGCGAAUAUGGA	1798
AD-1465970.1	gsusaauaccAfGfCfgaauauggauL96	1275	asdTscddAudAuuugdCuGfguauuacsasg	1536	CUGUAAUACCAGCGAAUAUGGAC	1799
AD-1465971.1	asgsugucCfaGfCfAfuuggaauauL96	1276	asUfsuadTc(C2p)aaaugcUfgAfgaccusgsu	1537	ACAGGUCUCAGCAUUUGGAUAAU	1800
AD-1465972.1	gsusuauguaCfAfCfacagucgauL96	1277	asdTscgdTadCugugdTgUfacauaacsusu	1538	AAGUUAUGUACACACACAGUACGAA	1801
AD-1465973.1	ususauhuacAfCfAfcagucgaauL96	1278	asdTsucdGudAcugudGuGfuacauaacsu	1539	AGUUAUGUACACACACAGUACGAAAG	1802
AD-1465974.1	asusguacAfcAfCfAfguacgaagauL96	1279	asUfsuadTc(G2p)uacuguGfuGfuacausasa	1540	UUUAUGUACACACACAGUACGAAAGAU	1803
AD-1465975.1	usgsuacaCfaCfAfGfuacgaagaauL96	1280	asAfsuadTu(C2p)guacugUfgUfguacausa	1541	UAUGUACACACACAGUACGAAAGAU	1804
AD-1465976.1	gsusacacacAfGfUfacgaagaugauL96	1281	asdCsaudCudTcguadCuGfuguguacsasu	1542	AUGUACACACACAGUACGAAAGAU	1805
AD-1465977.1	asgsuacgAfaGfAfUfgaguccuucuuL96	1282	asGfsaadGg(Agn)cueaucUfuCfuguacugsu	1543	ACAGUACGAAAGAUAGAGUCCUUCAC	1806
AD-1465978.1	gsusacgaAfgAfUfGfaguccuucuuL96	1283	asUfsgadAg(G2p)acueauCfuUfuguacsusg	1544	CAGUACGAAAGAUAGAGUCCUUCAC	1807
AD-1465979.1	gsusgaauCfcCfAfAfuaugaagauL96	1284	asUfsuadTu(C2p)auauugGfgAfuaacsusg	1545	CAGUGAAUCCCCAAUAUGAAAGAA	1808
AD-1465980.1	ascsccucAfuGfGfAfgugaccuucuuL96	1285	asGfsaadGg(Tgn)cacuccAfuGfagggusasa	1546	UUACCCUCAUGGAGUGACCUUCU	1809
AD-1465981.1	gsasacaaCfaCfCfAfugaucagagauL96	1286	asCfsuadTg(Agn)uacuggUfgUfuguacsusu	1547	AGGAACAACACCAUGAUCAGAGAGC	1810
AD-1465982.1	csasacacCfaUfGfAfucagagagauL96	1287	asCfsuadCu(C2p)ugaucaUfgGfuguugsusu	1548	AACAACACCAUGAUCAGAGAGAGU	1811
AD-1465983.1	csasccauGfaUfCfAfagagagauuL96	1288	asGfsaadCu(G2p)cueugaUfcAfugguugsusu	1549	AACACCAUGAUCAGAGAGAGAGU	1812
AD-1465984.1	csasugauCfaGfAfGfagagaucaacuL96	1289	asGfsuadGa(Agn)cugcucUfgAfuaucugsu	1550	ACCAUGAUCAGAGAGAGAGAGU	1813
AD-1465985.1	usgsaucaGfaGfCfAfguacaccuL96	1290	asUfsggdTu(G2p)aacugcUfcUfguacsusg	1551	CAUGAUCAGAGAGAGAGAGAGAG	1814

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1465985.1						
AD-1465986.1	asasaccuauAfcUfuauaaagugguL96	1291	asdCscadCudTaaadGuAfiagguuuscsc	1552	GGAAACCUAUACUUAUAAAGUGGA	1815
AD-1465987.1	asasccuaUfaCfUfuauaaaguggauL96	1292	asUfsccdAc(Tgn)uauaagUfaUfagguuusuc	1553	GAAACCUAUACUUAUAAAGUGGAA	1816
AD-1465988.1	csusuaauAfgUfGfGfaacaucuuauL96	1293	asUfsaadGa(Tgn)guuuccaCfuUfauaagsusa	1554	UACUUAUAAAGUGGAACAUCUUAAG	1817
AD-1465989.1	usesuaauCfuGfUfAfaagagagaauL96	1294	asAfsuadTg(C2p)ucuuacAfgAfiuagagasag	1555	CUUCUAAUCUGUUAAGAGCAGAUCCU	1818
AD-1465990.1	asasucugUfaAfgAfgcagagaucuuL96	1295	asGfsggdAu(C2p)ugucucUfaCfagaauusag	1556	CUAAUCUGUUAAGAGCAGAUCCCU	1819
AD-1465991.1	ascsuugAfgGfAfcfaacaucuaauL96	1296	asGfsuudGa(Tgn)guugucCfuCfaagguusasc	1557	GUACCUUGAGGACAACAUCUAAACA	1820
AD-1465992.1	asusgaaucaAfaCfaucaugagcuL96	1297	asdGscudCadTgaugdTuUfgauucausasa	1558	UUAUGAAUCAAACAUCUAAAGAGCA	1821
AD-1465993.1	gsasaucAfaCfAfucaugagagcuL96	1298	asGfsugdCu(C2p)augaugUfuUfgauucasa	1559	AUGAAUCAAACAUCUAAAGAGCACU	1822
AD-1465994.1	usgsagcaCfuAfuCfauagguuauL96	1299	asAfsuadGc(C2p)auugauAfgUfgcucuasug	1560	CAUGAGCACUAUCAUAAUGGCUAUG	1823
AD-1465996.1	gsasuuuGfcUfuUfUfgaugagacuL96	1300	asAfsugdGu(C2p)aucaaaaGfcAfgaaucscsa	1561	UGGAUUCUGCUUUUGAUGACACUG	1824
AD-1465997.1	csesaguggcAfcUfuucuguaguguL96	1301	asdCsacdTadCagaadGuGfcccaggsasc	1562	GUCCAGUGGCACUUCUGUAGUGU	1825
AD-1465998.1	asgsuggcacUfuUfCfuguaguguguL96	1302	asdCsacdAcdTacagdAaGfugccacuasg	1563	CCAGUGGCACUUCUGUAGUGUGG	1826
AD-1465999.1	csusgggcacUfCfAfucaucuaauL96	1303	asdAsuadGadTgaandGaGfugcccaggsug	1564	CACUGGCACUCUUAUCUUAUG	1827
AD-1466000.1	gsusgacGfuCfAfcfaauggaaauL96	1304	asUfsuadTc(C2p)auugugAfcCfugcacsasg	1565	CUGUGACGGUCACAAUGGAUAAU	1828
AD-1466001.1	gsusaacuUfgGfAfuUfguaacuucuuL96	1305	asGfsaadGu(Tgn)aaacucCfaAfguuuacsasa	1566	UUGGAACUUGGAUGUUAAACUCC	1829
AD-1466002.1	ususaaucucCfAfuUfgaauucuauguL96	1306	asdCsuadGadAuucadTgGfaaguuuaacsasa	1567	UGUUAACUUCUCCAUUGAAUUCUAGU	1830
AD-	asusgaugAfuGfAfaagacuaauuL96	1307	asAfsuadTg(Agn)guuucAfuCfaucauscu	1568	AGAUGAUGAUGAAGACUCAUAAU	1831

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1466003.1					G	
AD-1466004.1	usgsauagAfcUfcauauagauL96	1308	asdTscudCadTaugadGuCfucaucasusc	1569	GAUGAUGAAGACUCAUAUGAGA	1832
AD-1466005.1	asasacucauCfAfUfugaauagguL96	1309	asdCscudGadTucaadTgAfugauuuncsg	1570	CGAAACUCAUCAUUGAAUACAGGA	1833
AD-1466006.1	asasacacagAfUfAfuaauugguL96	1310	asdCsaadCadAuuaudAuCfuguguuuugsa	1571	UCAAACACACAGAUAAAUUUGUUGG	1834
AD-1466007.1	csasacagauUfAfAfuaugguuuL96	1311	asdAsacdCadAcaudTaUfaucugugususu	1572	AACACAGAUAAAUUGUUGGUUC	1835
AD-1466008.1	csasuauuUfGfAfAfgaccuauauL96	1312	asUfsaudAg(G2p)gucuuCfAfauaugsgs	1573	CCCAUAUUCUGAAGACCCCUAUAG	1836
AD-1466009.1	asusucugaaGfAfCfcuauagagL96	1313	asdCsucdTadTagggdTcUfucagaauasasu	1574	AUAUUCUGAAGAGACCCCUAUAGAGG	1837
AD-1466010.1	csgsucuaUfUfCfauugggguL96	1314	asdGscadCedAagudAaAfguagacgsusa	1575	UACGUCUACUUUCACUUGGUGUCU	1838
AD-1466011.1	asusgaaaUfUfAfCfUfagcacauauL96	1315	asUfsuadTg(Tgn)geuaguAfaUfuaucasec	1576	GGAUGAAUUACUAGCACAUAAA	1839
AD-1466012.1	asasuuaUfGfAfcauaaaguuL96	1316	asdAsacdTudTaugudGcUfaguauuusu	1577	GAAAUUACUAGCACAUAAAGUUG	1840
AD-1466013.1	usasuagcaCfAfUfuaaagggguL96	1317	asdCsccdAadCuuaadTgUfgeuaguasasu	1578	AUUACUAGCACAUAAAGUUGGGA	1841
AD-1466014.1	gsasgauuggcAfUfUfuggcuuugguL96	1318	asdCsagdAadGccadAuGfccaucuescsc	1579	GGGAGAUGGCAUUUGGCUUCUGA	1842
AD-1466015.1	gsusagcuAfUfGfAfauaauccaauL96	1319	asUfsugdGa(Tgn)uauuucAfuAfgcuacscsu	1580	AGGUAGCUAUGAAAUAAUCCAAG	1843
AD-1466016.1	csasagauAfcUfGfAfugaagacacauL96	1320	asGfsugdTc(Tgn)ucaucaGfuAfuenuugsgsa	1581	UCCAAGAUACUGAUGAAGACACACA	1844
AD-1466017.1	gsasuacuGfAfUfGfAfagacacagcuL96	1321	asGfscudGu(G2p)uucuaUfcaAfguaucesusu	1582	AAGAUACUGAUGAAGACACACAGCU	1845
AD-1466018.1	asasgacaCfAfGfUfguuaacaauL96	1322	asAfsuudGu(Tgn)aacageUfGfugcuuuesasa	1583	UGAAGACACAGCUGUUAAACAAUU	1846
AD-1466019.1	asasguuuUfAfGfaguuagacauL96	1323	asdTsgudCudAacudTaGfgaaacuusug	1584	CAAAGUUUCCUAGAGUUAGACAU	1847
AD-1466020.1	csesuagaguUfAfGfacaauaaucL96	1324	asdGsaudTudAugudTaAfcuauaggsasa	1585	UUCUAGAGUUAGACAUAAAUUCU	1848

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1466020.1						
AD-1466021.1	usascaaguaAfGfAfcaggaggauL96	1325	asdTscddAudCcugndCuUfacuuguasgsa	1586	UCUACAAGUAAGACAGGAUGGAG	1849
AD-1466022.1	gsusuuCuCfaUfUfAfagacacgaauL96	1326	asUfsuedGu(G2p)ucuuuaUfgAfgaaacsug	1587	CAGUUUCUCAUUAAAGACACGAAA	1850
AD-1466023.1	csasceauGfeUfCfCfuuuauucuuL96	1327	asGfsgadGa(Tgn)aaagggaGfcAfuggugsug	1588	CACACCAUGCUCUUAUUCUCCG	1851
AD-1466024.1	asgsagacuuUfCfAfccecuuaagL96	1328	asdCsnuuAgdAgggudGaAfagguccucsg	1589	CGAGGACCUUUCACCCUCUUAAGA	1852
AD-1466025.1	gsusgcuuCfaUfAfAfaucacgaauL96	1329	asUfscadTu(G2p)gaunuaUfgAfagcacsca	1590	UGGUGCUUCAUAAAUCCAAUGAA	1853
AD-1466026.1	usgsuucuuAfAfAfucauagauL96	1330	asdTsuedAudTggandTuAfugaagcscsc	1591	GGUGCUUCAUAAAUCCAAUGAAA	1854
AD-1466027.1	csesaaugaaAfCfAfucuuuccuuL96	1331	asdGsggdAadGagandGuUfucuuuggsasu	1592	AUCCAAUGAAACAUCUCUUCUCCCA	1855
AD-1466028.1	asesuuuUfgAfCfCfauuaucagauL96	1332	asUfscudGa(Tgn)uagguCfaGfgaagugsa	1593	UCACUUCUUGACCAUAAUCAGAA	1856
AD-1466029.1	asasaugCfUfGfAfGfuauagacgaL96	1333	asUfscgdGu(C2p)auacUfGfcauuuessa	1594	UGAAAUGCUUGAGUAUGACCGAA	1857
AD-1466030.1	gsesuuuGfUfUfGfaccgaagucL96	1334	asGfsacdTu(C2p)ggucuuAfcUfcaagcsasu	1595	AUGCUUGAGUAUGACCGAAGUCA	1858
AD-1466031.1	gsasguuGfAfcCfGfagucacaaL96	1335	asUfsugdTg(Agn)cuueggUfcAfuaucsa	1596	UUAGUAUGACCGAAGUCACAAAG	1859
AD-1466032.1	usasugacCfGfAfAfGfucacaaucL96	1336	asGfsacdTu(G2p)ugacuuCfGfucuuascsu	1597	AGUAUGACCGAAGUCACAAAGUCC	1860
AD-1466033.1	usgsacgAfaGfUfCfacaaguccuuL96	1337	asAfsggdAc(Tgn)ugugcuUfuCfugucasusa	1598	UAUGACCGAAGUCACAAAGUCCUU	1861
AD-1466034.1	gsascegaagUfCfAfcacaguccuuL96	1338	asdAsagdGadCuugudGaCfuueggucsu	1599	AUGACCGAAGUCACAAAGUCCUUC	1862
AD-1466035.1	ascsesgaGfUfCfAfCfaaguccuuL96	1339	asGfsaadGg(Agn)cuugugAfcUfucggucsa	1600	UGACCGAAGUCACAAAGUCCUUC	1863
AD-1466036.1	uscsucaGfaAfCfUfcaagucagauL96	1340	asGfsudTg(Agn)cugaguUfcUfggagaggsa	1601	UCUCUCCAGAACUCAGUCAGACA	1864
AD-	uscsucaGfaAfCfUfcaagucagauL96	1340	asGfsudTg(Agn)cugaguUfcUfggagaggsa	1601	UCUCUCCAGAACUCAGUCAGACA	1864

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1466036.2						
AD-1466036.3	uscsuccaGfaAfCfUfcfagucagacauL96	1340	asGfsucdTg(Agn)cugaguUfcUfggaggsasg	1601	UCUCUCCAGAACUCAGUCAGACA	1864
AD-1466037.1	csusccagAfaCfUfCfagucagacauL96	1341	asUfsgudCu(G2p)acugagUfuCfuggagsasg	1602	CUCUCCAGAACUCAGUCAGACAA	1865
AD-1466037.2	csusccagAfaCfUfCfagucagacauL96	1341	asUfsgudCu(G2p)acugagUfuCfuggagsasg	1602	CUCUCCAGAACUCAGUCAGACAA	1865
AD-1466037.3	csusccagAfaCfUfCfagucagacauL96	1341	asUfsgudCu(G2p)acugagUfuCfuggagsasg	1602	CUCUCCAGAACUCAGUCAGACAA	1865
AD-1466038.1	csasgccaGfaCfAfAfaccucucueuL96	1342	asGfsagdAg(Agn)gguuugUfcUfggcugsas	1603	CUCAGCCAGACAAACCUCUCUCC	1866
AD-1466038.2	csasgccaGfaCfAfAfaccucucueuL96	1342	asGfsagdAg(Agn)gguuugUfcUfggcugsas	1603	CUCAGCCAGACAAACCUCUCUCC	1866
AD-1466039.1	ususcuaacceUfUfCfugaaucauL96	1343	asdCsuaadGadTucagAaGfgguagaasasa	1604	UAUUCUACCCUUCUCUGAAUUCUAGU	1867
AD-1466040.1	csasucuccuAfCfUfCfugaaucauL96	1344	asdAsucdAudTgagadGuAfggagauagsasa	1605	UUCAUCUCCUACUCUCUCAAUGAUA	1868
AD-1466041.1	asuscaaaGfgAfAfUfuaaauccauL96	1345	asGfsugdGa(Tgn)uaaauuCfcUfuugausag	1606	CUAUCAAAAGGAAUUUAAUCCACU	1869
AD-1466042.1	asasggaaUfuUfAfAfuaaauccauL96	1346	asAfscadAg(Tgn)ggauuaAfaUfuccuusug	1607	CAAAGGAUUUAAUCCACUGGUU	1870
AD-1466043.1	ususuuaaaccAfCfUfGfguuuauguL96	1347	asdAscudAudAaccadGuGfgauuaaasusu	1608	AAUUUAAUCCACUGGUUAAUAGUG	1871
AD-1466044.1	ususaauccaCfUfGfguuuauguL96	1348	asdCsacdTadTaaccdAgUfggaauaasusu	1609	AUUUAAUCCACUGGUUAAUAGUGG	1872
AD-1466045.1	asgsauggUfaCfAfGfaauuacauL96	1349	asCfsaadTg(Tgn)aaucugUfaCfcauciususu	1610	AAAGAUUGGUACAGAUUACAUAU	1873
AD-1466046.1	asusgguaacaGfAfUfuaaauuagauL96	1350	asdCsucdAadTguaadTcUfguaccuuesu	1611	AGAUGGUACAGAUUACAUAUAGAG	1874
AD-1466047.1	ascsugauuguUfAfGfgaacaauuL96	1351	asdAsugdTuadTguedTaAfaucacugususu	1612	AAACUGAUGUUAGGACAAACAUC	1875
AD-1466048.1	csusgaugUfuAfGfGfacaacaauL96	1352	asGfsaudGu(Tgn)uguccuAfaCfcauciususu	1613	AACUGAUGUUAGGACAAACAUC	1876
AD-	gsasagaaAfuAfUfCfCfugggauuauL96	1353	asUfsaadTc(C2p)caggauAfuUfuciuacsasg	1614	CUGAAGAAAUAUCCUGGGAUUAU	1877

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1466049.1						
AD-1466050.1	usgsaagacuCfUfGfaugauuauuL96	1354	asdGsaadTadTcaudAgAfgucmucasu	1615	AUUGAAGACUCUGAUGAUUUCC	1878
AD-1466051.1	gsusauaagAfGfCfaucucggaauL96	1355	asdTsuedCgdAgaugdCuCfuaucacusc	1616	GAGUAUGAAGAGCAUCUCGGAAU	1879
AD-1466052.1	asgsageaucUfCfGfgaauuauuL96	1356	asdCsaadGadAuuuccGfGfagucucusc	1617	GAAGAGCAUCUCGGAAUUCUUGG	1880
AD-1466053.1	uscsaggaaUfuCfUfUfggucuaauuL96	377	asAfsaudAg(G2p)accaagAfaUfuccgasa	1618	UCUCGGAUUUCUUGGUCUUAUA	645
AD-1466054.1	csagsaaUfuCfUfUfggucuaauuL96	1357	asUfsaadTa(G2p)gaccaaGfaAfuuccgsasg	1619	CUCGGAUUUCUUGGUCUUAUAU	1881
AD-1466055.1	asasuuuucgGfUfCfuaauuauL96	1358	asdTsagdTadAuaugdAcCfaagaauuscsc	1620	GGAAUUCUUGGUCUUAUAUCAG	1882
AD-1466056.1	uscsuugUfcCfUfAfuaucaagaguL96	1359	asCfsuedTg(Agn)uaauagGfaCfcaagasasu	1621	AUUCUUGGUCUUAUAUCAGAGC	1883
AD-1466057.1	gsuscuuUfuAfuCfagagcagaauL96	1360	asUfsuedAg(C2p)ucugauAfaUfaggacscsa	1622	UGGUCCUUAUAUCAGAGCUGAAG	1884
AD-1466058.1	usgsaagugGfUfGfaguuuauL96	1361	asdGsgadTadAcaudAuCfcaucucscsc	1623	GCUGAAGUGGAUGAUGUUUAUCCA	1885
AD-1466059.1	gsasagugGfUfGfaguuuauL96	1362	asdTsaggdAudAcaudCaUfccaucucscsc	1624	CUGAAGUGGAUGAUGUUUAUCCA	1886
AD-1466060.1	asusacagagGfAfaFagacuuauL96	1363	asdCsaudAadGucudTcCfucucgusa	1625	UCAUCAGAGGGAAGACUUAUGA	1887
AD-1466061.1	asgsaggaaAfgAfcUfuaagagaauL96	1364	asAfsuedTui(C2p)auaaguCfuUfuccucscsu	1626	AGAGGGAAGACUUAUGAAGAU G	1888
AD-1466062.1	asgsccaaauAfgCfaguuuauL96	1365	asdGsgudAudAacudCuAfuuugcucusa	1627	UCAGCCAAAUAGCAGUUAUACCU	1889
AD-1466063.1	asgsacaguuUfAfcfuaacgnaugL96	1366	asdCsaudAcdGuaggdTafuaucucscsu	1628	AUAGCAGUUAUACCUACGUUUGG	1890
AD-1466064.1	gsasuuuUfaCfUfCfagcuaauL96	1367	asAfsuedAa(G2p)ccugagUfgAfaauucscsu	1629	AAGAUUUCACUCACGGCUUGAU	1891
AD-1466065.1	gsgsaaUfaCfAfaaagacagL96	1368	asCfsugdTc(C2p)uuuauAfgUfaucucscsu	1630	AAGGAUAUCUACAUAAGGACAGC	1892
AD-1466066.1	csusaaUfaGfGfAfcagcaauL96	1369	asAfsugdTu(G2p)cuugccUfuAfuagcusa	1631	UACUACAUAAGGACAGCAACAUG	1893

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1466066.1						
AD-1466067.1	ascsaanaaGfgAfCfAfGcaacauL96	1370	asGfscadTg(Tgn)uGcguCfcUfuaugusag	1632	CUACAUAAAGGACAGCAACAUGCC	1894
AD-1466068.1	ascsaugaGfaGfAfAfuugucuuauL96	1371	asUfsaadGa(C2p)aaaucUfcUfcauguscsc	1633	GGACAUGAGAGAAUUUGUCUUAC	1895
AD-1466069.1	csasugagAfgAfAfUfuugucuuacuL96	1372	asGfsuadAg(Agn)caaaucCfuCfcauguscsc	1634	GACAUGAGAGAAUUUGUCUUACU	1896
AD-1466070.1	gsasgagaUfUfGfucuuacuauL96	1373	asdAsuadGudAagacdAaAfuucucucsas	1635	AUGAGAGAAUUUGUCUUACU	576
AD-1466071.1	gsasccuuUfgAfUfGfaaaagaagauL96	1374	asUfscudTc(Tgn)uuuauCfaAfaagucsas	1636	AUGACCUUUUGAUGAAAAAAGAAGA	1897
AD-1466072.1	ascscuuUfgAfUfGfaaaagaagauL96	1375	asCfsuadTu(C2p)uuuauCfaAfaagucscsa	1637	UGACCUUUUGAUGAAAAAAGAAGAGC	1898
AD-1466073.1	csesuugAfuGfAfAfaagaagagauL96	1376	asGfscudCu(Tgn)cuuuuAfuCfaaaggsusc	1638	GACCUUUUGAUGAAAAAAGAAGAGCU	1899
AD-1466074.1	csusuugaUfgAfAfAfaagaagagauL96	1377	asAfsgcdTc(Tgn)uuuuuAfuCfaaaggsu	1639	ACCUUUUGAUGAAAAAAGAAGAGCUG	1900
AD-1466075.1	ususugauGfaAfAfAfaagaagagauL96	1378	asCfsagdCu(C2p)uuuuuUfcAfuaaasgsg	1640	CCUUUGAUGAAAAAAGAAGAGCUGG	1901
AD-1466076.1	ususgaugAfaAfAfGfaagagcugguL96	1379	asCfscadGc(Tgn)cuuuuUfuCfaucasaasg	1641	CUUUGAUGAAAAAAGAAGAGCUGG	1902
AD-1466077.1	usgsauggAfaAfGfAfagagcugguL96	1380	asAfscadAg(C2p)uuuuuUfuUfcaucasasa	1642	UUUGAUGAAAAAAGAAGAGCUGGU	1903
AD-1466078.1	gsasugaaAfaGfAfAfgagcugguauL96	1381	asUfsaadCa(G2p)cuuuuUfuUfcaucasasa	1643	UUGAUGAAAAAAGAAGAGCUGGUA	1904
AD-1466079.1	asusgaagAfgAfAfGfagcugguacuL96	1382	asGfsuadCc(Agn)gcuuuUfuUfuaucasa	1644	UGAUGAAAAAAGAAGAGCUGGUA	1905
AD-1466080.1	usgsaagaaGfaAfGfAfagcugguacuL96	1383	asAfsgudAc(C2p)agcucUfcUfuucascsc	1645	GAUGAAAAAAGAAGAGCUGGUA	1906
AD-1466081.1	gsasaaagaaGfAfGfagcugguacuL96	1384	asdTsagdTadCcagdTcUfuuuuuucsas	1646	AUGAAAAAAGAAGAGCUGGUA	1907
AD-1466082.1	asasaagaAfgAfGfCfugguacuauL96	1385	asAfsuadGu(Agn)ccagcCfuUfuuuuucsa	1647	UGAAAAAAGAAGAGCUGGUA	1908
AD-1466083.1	asasaagaGfCfUfgguacuauL96	1386	asdCsaudAgtTaccadGcUfuuuuuuusc	1648	GAAAAAAGAAGAGCUGGUA	1909

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1466083.1					A	
AD-1466084.1	asasgaagAfgCfUfgGuacuaugauL96	1387	asUfscadTa(G2p)uaccagCfuCfuucuuusu	1649	AAAAGAAAGAGCUGGUACUAUGA	1910
AD-1466085.1	asgsaagagCfUfgGfGuacuaugauL96	1388	asdTsucdAudAguacdCaGfcucuuusu	1650	AAAGAAAGAGCUGGUACUAUGAA	1911
AD-1466086.1	gsasagagCfuGfGfUfacuaugaaauL96	1389	asUfsuudCa(Tgn)aguaccAfgCfucuuusu	1651	AAAGAGAGCUGGUACUAUGAAAA	1912
AD-1466087.1	asasgagCfUfgGfUfAfcuaugaaaaL96	1390	asUfsuudTc(Agn)uaguacCfaGfcucuuusc	1652	AGAAGAGCUGGUACUAUGAAAA	1913
AD-1466088.1	asgsagagCfUfgGfUfAfcuaugaaaaL96	1391	asCfsuudTu(C2p)auaguaCfcAfgcucuuusc	1653	GAGAGCUGGUACUAUGAAAAAG	1914
AD-1466089.1	gsasgcugguAfCfUfauugaaaagauL96	1392	asdTsucdTudTcauadGuAfcagcucuuusu	1654	AAAGAGCUGGUACUAUGAAAAAGA	1915
AD-1466090.1	asgsucggUfaCfUfAfguaaaagauL96	1393	asUfsuudTc(Tgn)ucauagUfaCfcagcucuuusu	1655	AGAGCUGGUACUAUGAAAAAGAA	1916
AD-1466091.1	gsesugguacUfAfUfgaaagaaagauL96	1394	asdCsuudCudTuucadTaGfuaccagcusc	1656	GAGCUGGUACUAUGAAAAAGAA	1917
AD-1466092.1	csusgguaCfuAfUfgfaaaagaaagauL96	1395	asAfscudTc(Tgn)uuuauAfgUfaccagcusc	1657	AGCUGGUACUAUGAAAAAGAAAGUC	1918
AD-1466093.1	csesgaagUfuCfUfUfggagacucacauL96	1396	asUfsgadGu(C2p)uccaagAfaCfuueggsgsa	1658	UCCCGAAGUUCUUGGAGACUCAC	1919
AD-1466094.1	gsasaguuCfuUfgGfGfagacucacauL96	1397	asUfsgudGa(G2p)ucuccaAfgAfacuucsgsg	1659	CCGAAGUUCUUGGAGACUCACAU	1920
AD-1466095.1	usuuacacgcCfAfUfuaaugggaauL96	1398	asdAsuudCedAuuuadTgGfcgugaascsu	1660	AGUUUCACGCCCAUUAUUGGGAUG	1921
AD-1466096.1	asuuuauggGfAfUfgauucacacauL96	1399	asdCsugdTadGaucadTcCfaauuaausgsg	1661	CCAUUAAUUGGGAUGAUUCUACAGC	1922
AD-1466097.1	gsesueccaaGfAfCfaauucacgugauL96	1400	asdCsacdGudGaaugdTcUfuggagcscsg	1662	CGGCUCCCAAGACAUUCACGUGG	1923
AD-1466098.1	csesaaagaCfaUfUfCfacguguuuL96	1401	asGfsaadCc(Agn)cgugaaUfgUfuuuggsgsa	1663	UCCCAAGACAUUCACGUGGUUCA	1924
AD-1466099.1	asusucacGfuGfGfUfucacuuuL96	1402	asUfsgadAa(G2p)ugaaccAfcGfugaugsu	1664	ACAUUCACGUGGUUCACUUCAC	1925
AD-	asusgcaaacGfCfCfauuuucuuuL96	1403	asdAsuadAgaAaaugGcGfuuuugcausc	1665	GGAUGCAAACGCCCAUUCUUCUAC	1926

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1466100.1						
AD-1466101.1	gscsaacgcCfAfUfucuaucanL96	1404	asdTsgadTadAgaadTgGfgcuuucsasu	1666	AUGCAAACGCCAUUUCUUAUCAU	1927
AD-1466102.1	usesuuauCfaUfGfGfacagagacuL96	1405	asAfsudCu(C2p)uguccaUfgAfuaagasasa	1667	UUUCUUUAUCAUGGACACAGAGACUG	1928
AD-1466103.1	ususaucaUfgGfAfCfagagacuguuL96	1406	asAfsadCu(C2p)ucugucCfaUfgauaasgsa	1668	UCUUUAUCAUGGACACAGAGACUGUA	1929
AD-1466104.1	usasagcacuGfGfUfaucuaucuuL96	1407	asdAsgadTadTgauadCcAfgugcuuasgsu	1669	ACUAAAGCACUGGUAUCAUAUCUG	1930
AD-1466105.1	usesauauCfuGfAfUfucacagacuL96	1408	asGfsaudCu(G2p)ugaaucAfgAfuaugasusa	1670	UAUCAUAUCUGAUUCACAGAUCA	1931
AD-1466106.1	asusaucuGfaUfUfCfacagaucaanL96	383	asUfsugdAu(C2p)ugugaaUfcAfgauaasgsa	1671	UCAUAUCUGAUUCACAGAUCAAG	651
AD-1466107.1	usasacaAfuGfGfUfggaucuuauuL96	1409	asAfsuadAg(Agn)uccaccAfuUfguuuasasu	1672	AUUAACAAUGGUGGAUCUUAU	1932
AD-1466108.1	asasacaangGfUfGfgaucuuauuL96	1410	asdTsaudAadGaucedAcCfauguuuusasa	1673	UUAAACA AUGGUGGAUCUUAUA	1933
AD-1466109.1	csasaugugGfAfUfucuaaauuL96	1411	asdCsaudTadTaagadTcCfaccuuggsusu	1674	AACAAUGGUGGAUCUUAUAAUGC	1934
AD-1466110.1	gsgsuggaucUfUfAfuaaagcuuL96	1412	asdCsadGedAuuuadAaGfauccacesasu	1675	AUGGUGGAUCUUAUAAUGCUUG	1935
AD-1466111.1	asuscuuauaAfUfGfucuuagcuuL96	1413	asdCsadTcdCaagedAuUfauaagauscsc	1676	GGAUCUUUAUAUGCUUGGAGUG	1936
AD-1466112.1	csasagguGfcCfAfafacacuaccuuL96	1414	asAfsugdTa(G2p)uguuugGfcAfcuugsgsg	1677	CCCAAGGUGCCAAACACUACCUG	1937
AD-1466113.1	csesugcuAfUfAfCfCfacagaguuuL96	1415	asGfsaadCu(C2p)ugugguAfuAfgcagsasc	1678	GUCCUGCUUAUACCACAGAGUUCU	1938
AD-1466114.1	csusgeuaUfaCfCfAfcagaguuuL96	1416	asAfsgadAc(Tgn)cuugguUfaUfageagsgsa	1679	UCCUGCUUAUACCACAGAGUUCUA	1939
AD-1466115.1	usasuaaccacAfGfAfguuauuL96	1417	asdAscadTadGaacudCuGfugguuauasgsc	1680	GCUAUACCACAGAGUUCUUAUGUA	1940
AD-1466116.1	usascacagAfGfUfucuauguaguL96	1418	asdCsuaadCadTagaadCuCfugugguuasusa	1681	UAUACCACAGAGUUCUUAUGUAGC	1941
AD-	csesacagAfGfUfCfuauguagcuuL96	1419	asAfsgcdTa(C2p)auaagaaCfuCfuguggsusa	1682	UACCACAGAGUUCUUAUGUAGCUU	1942

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1466117.1						
AD-1466118.1	csascagagUfCfUfauguagcuuL96	1420	asdAsagdCudAcauadGaAfcucugugsgsu	1683	ACCACAGAGUUCUAUGUAGCUUA	1943
AD-1466119.1	asgsaguuCfuAfuGfuaagcuuacauL96	1421	asUfsgudAa(G2p)cuacauAfgAfcucugsgsu	1684	ACAGAGUUCUAUGUAGCUUACAG	1944
AD-1466120.1	asgsuucuanGfUfAfgcuuacaguuL96	1422	asdAscudGudAagcudAcAfuagaacusesu	1685	AGAGUUCUAUGUAGCUUACAGUU	1945
AD-1466121.1	usesuagUfaGfCfUfuacaguuccuL96	1423	asGfsgadAc(Tgn)guaagcUfaCfauagasc	1686	GUUCUAUGUAGCUUACAGUUCUA	1946
AD-1466122.1	csasauncAfgAfuGfcccucuaaauL96	1424	asUfsgudTa(G2p)aggcauCfuGfaauugscsc	1687	GGCAAUUCAGAGUAGCCUCUACAAU	1947
AD-1466123.1	asasauncaGfaUfGfCfcucuaaauL96	1425	asAfsuudGu(Agn)gaggaUfcUfgaauugsc	1688	GCAAUUCAGAGUAGCCUCUACAAU	1948
AD-1466124.1	ususagaUfgCfCfUfcuacaaauL96	1426	asUfsuadTu(G2p)uagaggCfaUfcugaasusu	1689	AAUUCAGAGUAGCCUCUACAAUAAA	1949
AD-1466125.1	asuscaguUfuGfAfcfcacuaauuL96	1427	asAfsaudAg(G2p)ugggucAfaAfcugaususc	1690	GAAUCAGUUUGACCCACCUAUUG	1950
AD-1466126.1	usesaguuugAfcCfCfcacuaauuL96	1428	asdCsaadTadGguggdGuCfaaacugasusu	1691	AAUCAGUUUGACCCACCUAUUGU	1951
AD-1466127.1	csasguuuugaCfCfCfcacuaauuL96	1429	asdAscudAudAggugdGgUfc-aaacugsas	1692	AUCAGUUUGACCCACCUAUUGUG	1952
AD-1466128.1	csusaauugGfCfUfagauauuuL96	1430	asdAsaudAudAucudGcCfacaauagsgsu	1693	ACCUAUUGUGGCUAGAUUAUUA	1953
AD-1466129.1	gsgscuagAfuAfuAfuaggaucuuL96	1431	asAfsagdTc(C2p)uaauauAfuCfuagccsasc	1694	GUGGCUAGAUUAUUAUAGGAUCUC	1954
AD-1466130.1	gsasuaauUfuAfgGfauucuccauL96	1432	asUfsggdAg(Agn)gaucuuAfaUfauaucusa	1695	UAGAUUAUUAUAGGAUCUCUCCAA	1955
AD-1466131.1	asgscaaaucAfcAfgcuuucuuL96	1433	asdCsagadAgdAagcudGuGfaauuugcusug	1696	CAAGCAAUUCACAGCUUCUUCGU	1956
AD-1466132.1	asgsuggcUfaGfAfaauugauuauL96	1434	asUfsagdAu(C2p)aaauucUfaGfcaacugsc	1697	GCAGUGGCUAGAAAUUGAUCUAC	1957
AD-1466133.1	asasaauuauCfuUfafcucaagaucuuL96	1435	asdGsaudCudTgagudAgAfucaauuucsu	1698	AGAAAUUGAUCUACUCAAGAUA	1958
AD-	asusugauCfuAfcUfcaagaauL96	390	asUfsugdAu(C2p)uugaguAfgAfucaaus	1699	AAAUUGAUCUACUCAAGAUAAG	658

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1466134.1			u			
AD-1466135.1	asasauguAfuGfUfAfaagagcuauL96	1436	asAfsuadGc(Tgn)cuuuacAfuAfcuuuscsa	1700	UGAAAAUGUAUGUAAAAGAGCUAU	1959
AD-1466136.1	asusguuaAfgAfGfCfuauaccauL96	1437	asGfsaudGg(Tgn)auagcuCfuUfucausasc	1701	GU AUGUAAAAGAGCUAUACCAUCC	1960
AD-1466137.1	asasgagcUfaUfAfCfauccacuauL96	1438	asUfsagdTg(G2p)augguaUfaGfcucuususa	1702	UAAAGAGCUAUACCAUCCACUAC	1961
AD-1466138.1	csusceauGfgUfGfGfacaagauuuuL96	1439	asAfsaadTc(Tgn)uguccaCfcAfuggagsgsa	1703	UCCUCCAUGGUGGACAAAGAUUUUU	1962
AD-1466139.1	uscscaugguGfGfAfcaagaauuuuuL96	1440	asdAsaadAudCuugudCcAfccauggasgsg	1704	CCUCCAUGGUGGACAAAGAUUUUUU	1963
AD-1466140.1	cscaugguGfGfAfCfaagaauuuuuL96	1441	asdAsaadAadTcuugdTcCfaccauggsasg	1705	CUCCAUGGUGGACAAAGAUUUUUUG	1964
AD-1466141.1	csasugguGfGfAfafagaauuuuuL96	1442	asdCsaadAadAauudGuCfaccauggsa	1706	UCCAUGGUGGACAAAGAUUUUUUGA	1965
AD-1466142.1	asusgguggaCfAfAfgaauuuuuL96	1443	asdTscadAadAauudTgUfccaccausgsg	1707	CCAUGGUGGACAAAGAUUUUUUGAA	1966
AD-1466143.1	usgsuggacAfAfGfaauuuuuL96	1444	asdTsuedAadAauudTgUfuccaccasusg	1708	CAUGGUGGACAAAGAUUUUUUGAA	1967
AD-1466144.1	gsgsuggacaAfGfAfuuuuuL96	1445	asdCsuedCadAaaudCuUfuccaccasasu	1709	AUGGUGGACAAAGAUUUUUUGAAG	1968
AD-1466145.1	gsusggacaaGfAfUfuuuuL96	1446	asdCscudTedAaaadTcUfuccaccascsa	1710	UGGUGGACAAAGAUUUUUUGAAGG	1969
AD-1466146.1	usgsagacaAfgAfUfuuuL96	1447	asUfscedTu(C2p)aaaaaCfuUfuccascsc	1711	GGUGGACAAAGAUUUUUUGAAGGA	1970
AD-1466147.1	ggsacaaGfaUfUfuuuL96	1448	asUfsuedCu(Tgn)caaaaaUfcUfuccascsc	1712	GUGGACAAAGAUUUUUUGAAGGA	1971
AD-1466148.1	gsascaagAfuUfUfuuuL96	1449	asUfsuudCc(Tgn)ucaaaaaAfuCfuugucscsa	1713	UGGACAAAGAUUUUUUGAAGGAAA	1972
AD-1466149.1	ascsaagaUfuUfUfuuuL96	1450	asAfsuudTc(C2p)uucaaaaAfaUfcuuguscsc	1714	GGACAAAGAUUUUUUGAAGGAAA	1973
AD-1466150.1	csasagauUfuUfUfuuuL96	1451	asUfsaudTu(C2p)cuucaaAfaAfuuuuguscsc	1715	GACAAGAUUUUUUGAAGGAAAUA	1974
AD-	asasgaauUfuUfUfuuuL96	1452	asGfsuadTu(Tgn)ccucaaAfaAfaucuuugsu	1716	ACAAGAUUUUUUGAAGGAAAUA	1975

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
1466151.1					U	
AD-1466152.1	asgsauuuuGfAfAfgaaauacuL96	1453	asdAsgudAudTuccudTcAfaaaucusug	1717	CAAGAUUUUUGAAGGAAAUACU	1976
AD-1466153.1	gsasuuuuuGfAfGfgaaauacuL96	1454	asdTsagdTadTuuccdTcCfaaaucusuu	1718	AAGAUUUUUGAAGGAAAUACUA	1977
AD-1466154.1	asusuuuuGfAfGfgfaaaauacuL96	1455	asUfsuadGu(Agn)uuuuccUfcAfaaaucsu	1719	AGAUUUUUGAAGGAAAUACUAA	1978
AD-1466155.1	ususuuuuGfAfAfaauacuauuL96	1456	asAfsuudAg(Tgn)uuuuccUfcAfaaaucsu	1720	GAUUUUUUGAAGGAAAUACUAAU	1979
AD-1466156.1	ususuuuuGfAfAfaauacuauuL96	1457	asUfsuudTa(G2p)uuuuccUfcAfaaaucsu	1721	AUUUUUGAAGGAAAUACUAAUA	1980
AD-1466157.1	ususuuuuGfAfAfaauacuauuL96	1458	asdGsaudTudAguuadTuCfcuucaasasa	1722	UUUUUGAAGGAAAUACUAAUACC	1981
AD-1466158.1	ususuuuuGfAfAfaauacuauuL96	1459	asdGsaudAudTaguadTuUfcuucaasasa	1723	UUUUUGAAGGAAAUACUAAUACCA	1982
AD-1466159.1	ascsuuuuAfcCfAfAfgagacuguuL96	1460	asAfsuadTg(Tgn)uuuuccUfcAfaaaucsu	1724	AUACUAAUACCAAAAGGACAUGUG	1983
AD-1466160.1	csusaauaccAfAfAfgagacuguuL96	1461	asdCsaudAudGuuadTuGfguuuuuagusa	1725	UACUAAUACCAAAAGGACAUGUGA	1984
AD-1466161.1	usasaauaccAfAfAfgagacuguuL96	1462	asdTsaudCadTguuadTuUfguuuuuagusa	1726	ACUAAUACCAAAAGGACAUGUGAA	1985
AD-1466162.1	csasaauuuUfcCfAfgagacuguuL96	1463	asdGsaudAadAccuadGaAfaugauuagsg	1727	CCCAAUCAUUUCCAGGUUUUAUCC	1986
AD-1466163.1	asusaauuuCfAfGfguuuuuaccguL96	1464	asdCsaudAudAaaccdTgGfaaaugausug	1728	CAUCAUUUCCAGGUUUUAUCCGU	1987
AD-1466164.1	asusuuuuUfcAfAfAfgagacuguuL96	1465	asGfsuadCa(Agn)uuuuccUfcAfaaaucsu	1729	ACAUGGAAUCAAAGUAUUGCACU	1988
AD-1466165.1	gsasuuuuGfAfAfaauacuauuL96	1466	asAfsuadGc(C2p)uuuuccUfcAfaaaucsu	1730	UCGCCUGGAACUCUUGGCGUGUG	1989

Table 7. Unmodified Sense and Antisense Strand Sequences of Coagulation Factor V dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1410569	CCACAAACUCACAGUUUUGAAUU	60	291-311	AAUUCACACUUAGUUUGGGC	191	289-311
AD-1410577	AUCUUUCUGUAAACUUCUUUU	61	309-329	AAAAGGAAGUUACAGAAAAGAUUC	192	307-329
AD-1410605	AGUAUGAACCAUAUUUUAAAGU	15	348-368	ACUUAUUUUUAGUUUUAACUCU	16	346-368
AD-1410628	CUACCAUUUCAGGACUUCUUU	62	384-404	AAAGAAUCCUGAAAUGGUAGAU	193	382-404
AD-109252	CAUGCCUCACACACACUUAUU	1990	642-662	AAUAGAUGUGUGAGGCAUGGA	2050	640-662
AD-1410821	AUGCCUCACACACACUUAUU	712	643-663	AAUAGAUGUGUGAGGCAUGG	2051	641-663
AD-1410822	UGCCUCACACACACUUAUU	713	644-664	AUAUAAGAUGUGUGAGGCAUG	2052	642-664
AD-109255	GCCUCACACACACUUAUU	11	645-665	AGUAAUAAGAUGUGAGGCAU	2053	643-665
AD-1410823	CCUCACACACACUUAUU	714	646-666	AAGUAAUAAGAUGUGAGGCA	2054	644-666
AD-1410824	CUCACACACACUUAUU	13	647-667	AGAGUAAUAAGAUGUGAGGCA	2055	645-667
AD-1410825	UCACACACACUUAUU	66	648-668	AGGAGUAAUAAGAUGUGAGG	197	646-668
AD-1410831	CAUCUUAUACUCCCAUGAAU	1991	655-675	AUUUCAUGGGAGUAAUAAGAUG	2056	653-675
AD-1410845	UCUGAUCGAGGAUUUACAUCU	67	676-696	AAGUUGAAAUCUCCGACAGAUU	198	674-696
AD-1410866	GGGACACAGAAAGACGUUUUGAU	1992	749-769	AUCAACGUCUUUCUGUCCAC	2057	747-769
AD-1410867	GGACACAGAAAGACGUUUUGACU	1993	750-770	AGUCAACGUCUUUCUGUCCCA	2058	748-770
AD-1410868	GACACAGAAAGACGUUUUGACAU	1994	751-771	AUGUCAACGUCUUUCUGUCCC	2059	749-771
AD-109319	GAAGACGUUUUGACAAAGCAAAU	717	757-777	AUUUGCUUUGUCAACGUCUUCUG	2060	755-777
AD-109322	GACGUUUUGACAAAGCAAAUCGU	719	760-780	ACGAUUUGCUUUGUCAACGUCU	2061	758-780
AD-1410876	ACGUUUUGACAAAGCAAAUCGUU	1995	761-781	AACGAUUUGCUUUGUCAACGUCU	2062	759-781
AD-1410877	CGUUUGACAAAGCAAAUCGUGU	1996	762-782	ACACGAUUUGCUUUGUCAACGUC	2063	760-782
AD-109325	GUUUUGACAAAGCAAAUCGUGCU	1997	763-783	AGCACGAUUUGCUUUGUCAACGUC	2064	761-783
AD-1410878	UUUGACAAAGCAAAUCGUGCUU	1998	764-784	AAGCACGAUUUGCUUUGUCAACG	2065	762-784
AD-1410927	CCUAAUGUACACAGUCAAUUGU	1999	832-852	ACAUAUGACUGUACAUAUAGGGA	2066	830-852
AD-1410928	CUAAUGUACACAGUCAAUUGGU	2000	833-853	ACCAUUGACUGUGUACAUAUAGGG	2067	831-853

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-109396	UAAUGUACACAGUCAAUUGGAU	2001	834-854	AUCCAUAUGACUGUGUACAUAUAGG	2068	832-854
AD-1410929	AAUGUACACAGUCAAUUGGAUU	724	835-855	AAUCCAUAUGACUGUGUACAUAUAG	2069	833-855
AD-1410994	AUAUAUUCUCCAUAUUAUUAU	70	940-960	AUGAAUAUGAAUUGGAGAAUAUUAU	201	938-960
AD-109601	AAAGUGGAUCAUAUCUUCUCU	31	1057-1077	AGAGAAGUAUAUGAUCCACUUAUCC	162	1055-1077
AD-1411138	CCAGGAAUUCUUAAGAAUAU	72	1143-1163	AUAUUUUUUUAAGAUUCCUGGUU	203	1141-1163
AD-1411203	GGACUAUGCACCUUGUAUAUACU	2002	1228-1248	AGUAUAUACAGGUGCAUAGUCCCA	2070	1226-1248
AD-1411204	GACUAUGCACCUUGUAUAUACCU	2003	1229-1249	AGGUAUAUACAGGUGCAUAGUCC	2071	1227-1249
AD-1411205	ACUAUGCACCUUGUAUAUACCAU	2004	1230-1250	AUGGUAUAUACAGGUGCAUAGUCC	2072	1228-1250
AD-1411206	CUAUGCACCUUGUAUAUACCAU	2005	1231-1251	ACUGGUAUAUACAGGUGCAUAGUC	2073	1229-1251
AD-109757	GCACCUGUAUAUACCGCGAAU	2006	1235-1255	AUUCGCGUGUAUAUACAGGUGCAU	2074	1233-1255
AD-1411210	CACCUGUAUAUACCGCGAAU	759	1236-1256	AAUUCGCGUGUAUAUACAGGUGCA	1015	1234-1256
AD-109759	ACCUGUAUAUACCGCGAAU	2007	1237-1257	AUAUUCGCGUGUAUAUACAGGUGC	2075	1235-1257
AD-1411211	CCUGUAUAUACCGCGAAU	2008	1238-1258	AAUAUUCGCGUGUAUAUACAGGUG	2076	1236-1258
AD-1411212	CUGUAUAUACCGCGAAU	2009	1239-1259	ACAUAUUCGCGUGUAUAUACAGGU	2077	1237-1259
AD-1411213	UGUAUAUACCGCGAAU	760	1240-1260	ACCAUAUUCGCGUGUAUAUACAGG	2078	1238-1260
AD-1411214	GUAAUAUACCGCGAAU	761	1241-1261	AUCCAUAUUCGCGUGUAUAUACAG	2079	1239-1261
AD-1411215	UAAUAUACCGCGAAU	2010	1242-1262	AGUCCAUAUUCGCGUGUAUAUACA	2080	1240-1262
AD-1411226	UCAGCAUUUUGGAUAUUAUUCUU	73	1276-1296	AAGAAUAUAUCCAAUUGCUGAGA	204	1274-1296
AD-1411342	ACACUCAAAUAUCGUGUCAAU	76	1433-1453	AUUGAACACGAAUUUUGAGUGUGU	207	1431-1453
AD-110052	UAAGUGGAACAUCUUAAGAGUU	33	1594-1614	AACUCUAAGAUGUUUCCACUUAUA	164	1592-1614
AD-1411480	UAACAAGACCAUAUCUACAGUU	78	1647-1667	AACUGUAGUAUGGUCUUGUUAAG	209	1645-1667
AD-1411743	CAUUCACUAUUGGAAAGAGGU	81	2034-2054	ACCUCUUUCCAUAAGAUGAAUAGAG	212	2032-2054
AD-110518	UUGGAACUUGGAUGUUAACUU	36	2118-2138	AAGUUAACAUAUCCAAGUUAUACA	167	2116-2138
AD-1411798	UAACUCCCAUGAAUUCUAGUU	82	2133-2153	AACUAGAUAUUAUGGAAGUUAAC	213	2131-2153
AD-1411972	CCGAAACUCACUAUUGAAUUCU	84	2362-2382	AGAUAUAUUGAGUUUUCGGAA	215	2360-2382
AD-110844	UCAAAACACAGUAUAUUAUUGUU	38	2444-2464	AACAAUAUAUUCUGUGUUUGAAG	169	2442-2464

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1412040	GUUGGUUCAAUUUAAUUCUUCU	86	2462-2482	AGAAAGAAUAAUUUGAACCAACAA	217	2460-2482
AD-1412095	ACUCAGUUCUCAAUUCUUCU	88	2595-2615	AGGAAGAAUUUGAGAACUGAGUUC	219	2593-2615
AD-1412163	UACGUCUACUUUCACUUGGUU	89	2685-2705	AACCAAGUGAAAGUAGACGUUUC	220	2683-2705
AD-111287	AAGUAAUCUACUCUAAAGAUUUU	39	2953-2973	AAAUCUUAGAUAGAUUACUUUG	170	2951-2973
AD-1412482	CUAGAGUUAGACAUAAAUUCU	93	3150-3170	AAGAUUUUUGUCUAAACUCUAGGA	224	3148-3170
AD-1412539	UUUCUCAUUUAGACACGAAAU	95	3218-3238	AUUUCGUGUCUUUAAUGAGAAACU	226	3216-3238
AD-1412582	UGAAGCCUACAACACAUUUUU	96	3304-3324	AAAAGUGUUUGUAGGCUUCACU	227	3302-3324
AD-1412622	AAUCCAAUGAAACAUCUCUUU	97	3360-3380	AAAGAGAUUUUUCAUUGGAUUUA	228	3358-3380
AD-1412733	UCAAUUGCACUCUACUUCAGU	100	3553-3573	ACUGAAGUAGAGUGCAUUUGAUC	231	3551-3573
AD-112396	UACUCUCAUAGAUACUUUUCU	43	4633-4653	AGAAAAGUAUCAUUUGAGAGUAGG	174	4631-4653
AD-1413210	CUAUCAAAGGAAUUUAAUCCU	109	4652-4672	AGGAUUAAAUUCCUUUUGAUAGAA	240	4650-4672
AD-1413286	ACUAUGCUGAAAUUGAUUAUU	111	4755-4775	AAUAAUCAUUUCAGCAUAGUCA	242	4753-4775
AD-112618	AAACAGAAAGAAUUUAAUUAU	44	4876-4896	AUGUAAUAAUUUCUUCUGUUUCC	175	4874-4896
AD-112760	AGCACUUUUACCAAAACGUGAU	45	5021-5041	AUCACGUUUGGUAAAAGUGCUGU	176	5019-5041
AD-1413517	UUAUCCAAAGUUCGUUUUAAAU	114	5109-5129	AUUUAAAACGAACUUUGGAUAAAC	245	5107-5129
AD-1413605	AUGCUGUUCAGCCAAAUAGCU	115	5238-5258	AGCUAUUUUGGCUGAACAGCAUUA	246	5236-5258
AD-1413615	UAGCAGUUUAUACCUACGUUUU	116	5254-5274	AAUACGUAGGUUAUAAACUGCUAUU	247	5252-5274
AD-113137	GAGAGAAUUUGUCUUAUUAUU	46	5443-5463	AAUAGUAAGACAAAUAUUCUCUUAU	177	5441-5463
AD-113331	GACAUUCACGUGGUUUCACUUU	47	5657-5677	AAAGUGAACCAACGUGAAUUGUCUU	178	5655-5677
AD-1413936	CUGGUUCAUUUAAAACUCUUU	117	5742-5762	AAAGAGUUUUAAAUGAACCCAGGC	248	5740-5762
AD-113467	GAGCAGGGAUGCAAACGCCAU	2011	5823-5843	AUGGCGUUUGCAUCCUCCUGCUCU	2081	5821-5843
AD-113468	AGCAGGGAUGCAAACGCCAUU	2012	5824-5844	AAUGGCGUUUGCAUCCUCCUGCUCU	2082	5822-5844
AD-113471	AGGGAUGCAAACGCCAUUUUCU	2013	5827-5847	AGAAAUGGCGUUUGCAUCCUCCUGC	2083	5825-5847
AD-113472	GGGAUGCAAACGCCAUUUUCU	2014	5828-5848	AAGAAAUGGCGUUUGCAUCCUCCUG	2084	5826-5848
AD-1414007	GGAUGCAAACGCCAUUUUCU	2015	5829-5849	AAAGAAAUGGCGUUUGCAUCCUCCU	2085	5827-5849
AD-113474	GAUGCAAACGCCAUUUUCUUAU	2016	5830-5850	AUAAGAAAUGGCGUUUGCAUCCUCC	2086	5828-5850

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1414008	AUGCAAACGCCAUUUCUUAUU	888	5831-5851	AAUAAAGAAUUGGCGUUUGCAUCC	1144	5829-5851
AD-1414009	UGCAAACGCCAUUUCUUAUCU	17	5832-5852	AGAUAAGAAUUGGCGUUUGCAUC	18	5830-5852
AD-113477	GCAAACGCCAUUUCUUAUCAU	889	5833-5853	AUGAUAAGAAUUGGCGUUUGCAU	2087	5831-5853
AD-1414010	CAAACGCCAUUUCUUAUCAUU	2017	5834-5854	AAUGAUAAGAAUUGGCGUUUGCA	2088	5832-5854
AD-1414011	AAACGCCAUUUCUUAUCAUGU	2018	5835-5855	ACAUGAUAAGAAUUGGCGUUUGC	2089	5833-5855
AD-1414012	AACGCCAUUUCUUAUCAUGGU	2019	5836-5856	ACCAUGAUAAGAAUUGGCGUUUG	2090	5834-5856
AD-1414013	ACGCCAUUUCUUAUCAUGGAU	2020	5837-5857	AUCCAUGAUAAGAAUUGGCGUUU	2091	5835-5857
AD-1414014	CGCCAUUUCUUAUCAUGGACU	2021	5838-5858	AGUCCAUGAUAAGAAUUGGCGUU	2092	5836-5858
AD-1414044	AUGGGACUAAGCACUGGUAUU	2022	5876-5896	AAUACCAUGUGCUUAGUCCCAUUG	2093	5874-5896
AD-1414045	UGGGACUAAGCACUGGUAUCU	2023	5877-5897	AGAUAACCAUGUGCUUAGUCCCAU	2094	5875-5897
AD-113522	GGGACUAAGCACUGGUAUCAU	2024	5878-5898	AUGAUAACCAUGUGCUUAGUCCCAU	2095	5876-5898
AD-1414046	GGACUAAGCACUGGUAUCAUU	2025	5879-5899	AAUGAUAACCAUGUGCUUAGUCCCA	2096	5877-5899
AD-113526	CUAAGCACUGGUAUCAUAUCU	2026	5882-5902	AGAUAUGAUAACCAUGUGCUUAGUC	2097	5880-5902
AD-1414048	UAAGCACUGGUAUCAUAUCUU	892	5883-5903	AAGAUAUGAUAACCAUGUGCUUAGU	2098	5881-5903
AD-1414049	AAGCACUGGUAUCAUAUCUGU	2027	5884-5904	ACAGAUAUGAUAACCAUGUGCUUAG	2099	5882-5904
AD-113529	AGCACUGGUAUCAUAUCUGAU	2028	5885-5905	AUCAGAUAUGAUAACCAUGUGCUUA	2100	5883-5905
AD-113530	GCACUGGUAUCAUAUCUGAUU	2029	5886-5906	AAUCAGAUAUGAUAACCAUGUGCUU	2101	5884-5906
AD-1414050	CACUGGUAUCAUAUCUGAUUU	2030	5887-5907	AAAUCAGAUAUGAUAACCAUGUGCU	2102	5885-5907
AD-1414053	UGGUAUCAUAUCUGAUUUCACU	2031	5890-5910	AGUGAAUCAGAUAUGAUAACCAUGU	2103	5888-5910
AD-1414074	UCAGAGUUUCUGGGUUACUGU	119	5921-5941	ACAGUAACCCAGAGAAACUCUGAAG	250	5919-5941
AD-1414139	AGAAUUUGCCUCUAAACCUUU	120	6010-6030	AAAGGUUUAGAGGCAAAUUCUGC	251	6008-6030
AD-1414213	CUGAAGUCCUGCUAUACCCACU	2032	6098-6118	AGUGGUUAUAGCAGGACUUCAGGU	2104	6096-6118
AD-1414218	CUGCUAUUACCCACAGAGUUUCU	19	6106-6126	AAGAACUCUGUGGUUAUAGCAGGA	2105	6104-6126
AD-113751	UGCUAUACCCACAGAGUUUCUAU	2033	6107-6127	AUAGAACUCUGUGGUUAUAGCAGG	2106	6105-6127
AD-1414219	GCUAUACCCACAGAGUUUCUAUU	2034	6108-6128	AAUAGAACUCUGUGGUUAUAGCAG	2107	6106-6128
AD-113753	CUAUACCCACAGAGUUUCUAUGU	2035	6109-6129	ACAUAGAACUCUGUGGUUAUAGCA	2108	6107-6129

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1414220	UAUACACACAGAGUUCUAUGUU	901	6110-6130	AACAUAGAACUCUGUGGUUAUAGC	2109	6108-6130
AD-1414221	AUACCACAGAGUUCUAUGUAAU	2036	6111-6131	AUACAUAGAACUCUGUGGUUAUAG	2110	6109-6131
AD-1414222	UACCACAGAGUUCUAUGUAGU	902	6112-6132	ACUACAUAGAACUCUGUGGUUAUA	2111	6110-6132
AD-113757	ACCACAGAGUUCUAUGUAGCU	2037	6113-6133	AGCUACAUAGAACUCUGUGGUUAU	2112	6111-6133
AD-113758	CCACAGAGUUCUAUGUAGCUU	903	6114-6134	AAGCUACAUAGAACUCUGUGGUUA	2113	6112-6134
AD-1414223	CACAGAGUUCUAUGUAGCUUU	904	6115-6135	AAAGCUACAUAGAACUCUGUGGUU	1160	6113-6135
AD-1414226	AGAGUUCUAUGUAGCUUACAU	905	6118-6138	AUGUAAGCUACAUAGAACUCUGU	1161	6116-6138
AD-113763	GAGUUCUAUGUAGCUUACAGU	2038	6119-6139	ACUGUAAGCUACAUAGAACUCUG	2114	6117-6139
AD-113764	AGUUCUAUGUAGCUUACAGUU	906	6120-6140	AACUGUAAGCUACAUAGAACUCU	1162	6118-6140
AD-1414229	UCUAUGUAGCUUACAGUUCUU	907	6123-6143	AGGAACUGUAAGCUACAUAGAAC	2115	6121-6143
AD-1414230	CUAUGUAGCUUACAGUUCUCCAU	2039	6124-6144	AUGGAACUGUAAGCUACAUAGA	2116	6122-6144
AD-1414231	UAUGUAGCUUACAGUUCUCCAAU	2040	6125-6145	AUUGGAACUGUAAGCUACAUAGA	2117	6123-6145
AD-1414235	UAGCUUACAGUUCUCCAACCCAGU	2041	6129-6149	ACUGGUUGGAACUGUAAGCUACA	2118	6127-6149
AD-1414275	GAAUGUGAUGUAUUUUAAUGU	122	6184-6204	ACAUAUAAAUACAUCACAUUCCU	253	6182-6204
AD-113890	ACCUAUUGUGGCUAGAUUAUUAU	2042	6247-6267	AUAUAUCUAGCCACAAUAGGUGG	2119	6245-6267
AD-113891	CCUAUUGUGGCUAGAUUAUUAU	2043	6248-6268	AAUAUAUCUAGCCACAAUAGGUG	2120	6246-6268
AD-1414321	CUAUUGUGGCUAGAUUAUUAU	914	6249-6269	AAUAUAUCUAGCCACAAUAGGU	1170	6247-6269
AD-1414322	UAUUUGUGGCUAGAUUAUUAU	2044	6250-6270	AUAUAUAUCUAGCCACAAUAGG	2121	6248-6270
AD-1414323	AUUUGGCUAGAUUAUUAUAGU	2045	6251-6271	ACUAUAUAUCUAGCCACAAUAG	2122	6249-6271
AD-1414324	UUGUGGCUAGAUUAUUAUAGGU	2046	6252-6272	ACCUAUAUAUCUAGCCACAAUA	2123	6250-6272
AD-113896	UGUGGCUAGAUUAUUAUAGGAU	2047	6253-6273	AUCCUAUAUAUCUAGCCACAAU	2124	6251-6273
AD-1414325	GUGGCUAGAUUAUUAUAGGAU	2048	6254-6274	AAUCCUAUAUAUCUAGCCACAA	2125	6252-6274
AD-1414326	GGCUAGAUUAUUAUAGGAUCUU	915	6256-6276	AAGAUCUAAUAUAUCUAGCCAC	2126	6254-6276
AD-113900	GCUAGAUUAUUAUAGGAUCUCU	2049	6257-6277	AGAGAUCUAAUAUAUCUAGCCCA	2127	6255-6277
AD-1414544	CCUCUGAAAUUGUAUGUAAAGU	126	6579-6599	ACUUUACAUAUAUUUACAGAGGAC	257	6577-6599
AD-114455	CUGUGUUAUAUGUUAACAGUU	48	6896-6916	AACUGUUAACAUAUUUAACACAGCG	179	6894-6916

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-114469	ACAGUUUCCACUAUUUCUCU	21	6911-6931	AGAGAAUAGUGGAAACUGUUA	22	6909-6931

Table 8. Modified Sense and Antisense Strand Sequences of Coagulation Factor V dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO	mRNA target sequence 5' to 3'	SEQ ID NO:
AD-1410569	cscsacaaAfcUfcAfaguuugaauuL96	323	asAfsuucAfaAfCfuugaGfuUfugugsgsc	457	GCCCACAAACUCACAAAGUUUGAAUC	591
AD-1410577	asuscuuuCfuGfUfAfacuuccuuuL96	324	asAfsaagGfaAfGfuuacAfgAfaagausc	458	GAAUCUUUCUGUAAACUCCUUUA	592
AD-1410605	asgsuagAfaCfCfAfuaauuuuaguuL96	325	asCfsuuaAfaAfUfauggUfuCfaucusc	459	AGAGUAUGAACCACAAUUUUUAAAGA	593
AD-1410628	csusaccaUfuUfcAfagacuuccuuL96	326	asAfsagaAfgUfcfcugaAfaUfguaggsasu	460	AUCUACCAUUUCAGGACUUCUUG	594
AD-109252	csasugccUfcAfcAfcaucauuuL96	2128	asAfsuagAfuGfUfuguguGfaGfgcaugsgsa	2206	UCCAUGCCUUCACACACAUUAUU	2290
AD-1410821	asusgccuCfaCfAfcaucauuuL96	2129	asAfsauaGfaUfGfugugUfgAfggaugsgsg	2207	CCAUGCCUUCACACACAUUAUU	1748
AD-1410822	usgsccucAfcAfcAfcaucauuuL96	2130	asUfsaauAfgAfUfuguguGfuGfaggaucasug	2208	CAUGCCUUCACACACAUUAUUAC	1749
AD-109255	gsccscaCfaCfAfcaucauuuL96	2131	asGfsuaaUfaGfAfugugUfgUfgaggsasu	2209	AUGCCUUCACACACAUUAUUACU	1750
AD-1410823	cscsueacAfcAfcAfcaucauuuL96	2132	asAfsuaaUfaGfAfuguguGfuGfaggaugsgsa	2210	UGCCUUCACACACAUUAUUACUC	1751
AD-1410824	csusaccaCfaCfAfcaucauuuL96	2133	asGfsaguAfaUfAfgaugUfgUfgaggsugsc	2211	GCCUUCACACACAUUAUUACUCC	1752
AD-1410825	uscsacacAfcAfcAfcaucauuuL96	330	asGfsagUfaUfAfagauGfuGfugaggsugsg	464	CCUCACACACAUUAUUACUCCC	598
AD-1410831	csasueuaUfuAfcUfcfcccaugaauuL96	2134	asUfsuucAfuGfGfgaguAfaUfagaugsgsg	2212	CACAUCUAUUACUCCCAUGAAAA	2291

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO	mRNA target sequence 5' to 3'	SEQ ID NO:
AD-1410845	usesugauCfGfGfauuucaacuuL96	331	asAfsguuGfaAfAfuccuCfGfAfucagasusu	465	AAUCUGAUCGAGGAUUUCAAACUC	599
AD-1410866	gsgsgacaCfaGfAfagacguuugauL96	2135	asUfscaaAfcGfUfucuuUfgUfguccesasc	2213	GUGGGACACAGAAAGACGUUUGAC	2292
AD-1410867	gsgsacacAfcAfAfGfagcuuugacuL96	2136	asGfsucaAfaCfGfucuuCfuGfuguccscsa	2214	UGGGACACAGAAAGACGUUUGACA	2293
AD-1410868	gsasacaGfaAfGfAfguuugacuL96	2137	asUfsgucAfaAfCfugcuUfcUfguguccscsc	2215	GGGACACAGAAAGACGUUUGACAA	2294
AD-109319	gsasagacGfuUfGfacaagcaauL96	1231	asUfsgucCfuUfGfucuaAfcGfucuuucsg	2216	CAGAAGACGUUUGACAAAGCAAAU	1755
AD-109322	gsasaguuUfgAfCfAfcgcaauugauL96	2138	asCfsgauUfuGfCfuuguCfaAfcagucsu	2217	AAGACGUUUGACAAAGCAAAUUCGU	1757
AD-1410876	ascsuuuGfaCfAfAfcgcaauugauL96	2139	asAfscgaUfuUfGfucuuUfcAfaagucsu	2218	AGACGUUUGACAAAGCAAAUUCGUG	2295
AD-1410877	csgsuuugAfcAfAfGfcaauugcuL96	2140	asCfsagAfuUfUfgcuUfgUfcaagucsu	2219	GACGUUUGACAAAGCAAAUUCGUGC	2296
AD-109325	gsusuuGfaAfGfCfaaauugcuL96	2141	asGfscacGfaUfUfugcuUfgUfcaaacsgsu	2220	ACGUUUGACAAAGCAAAUUCGUGCU	2297
AD-1410878	ususugacAfaGfCfafaauugcuL96	2142	asAfsgcaCfGfAfUfugcuUfuGfucuaascsg	2221	CGUUUGACAAAGCAAAUUCGUGCUA	2298
AD-1410927	cscsuauGfuAfcAfAfcagcaauugauL96	2143	asCfsauuGfaCfUfguguAfcAfuuaagsgsa	2222	UCCCUAAUGUACACAGUCAAAUGG	2299
AD-1410928	csusaauGfaCfAfCfagcaauugcuL96	2144	asCfscuuUfgAfCfugugUfaCfaauagsgsg	2223	CCCUAAUGUACACAGUCAAAUGGA	2300
AD-109396	usasauGfaCfAfAfcgcaauugcuL96	2145	asUfscgaUfuGfAfcuguGfuAfcuaaagsgsg	2224	CCUAAUGUACACAGUCAAAUGGAU	2301
AD-1410929	asasuguaCfaCfAfGfcaauugcuL96	2146	asAfsuccAfuUfGfagcuUfgUfacaauasag	2225	CUAAUGUACACAGUCAAAUGGAU	1762
AD-1410994	asusuuuUfuCfCfAfuaauuucuuL96	334	asUfsgaaAfuGfAfaugGfAfaauaauusc	468	GAAUUAUUCUCCAUAUUAUUUCAA	602
AD-109601	asasagugGfaUfCfAfuaucuuucuuL96	293	asGfsagaAfcAfUfaugaUfcCfacaauuscsc	427	GGAAAGUGGAUCAUAUUAUUCUCU	561
AD-1411138	cscsaggaAfuCfUfafaagaaauuL96	336	asUfsauuUfuCfUfuaagAfuUfcuugsgsu	470	AACCAGGAUAUCUUAAGAAAAUAA	604

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO	mRNA target sequence 5' to 3'	SEQ ID NO:
AD-1411203	gsgsacuaUfgCfAfCfcuguaauacuL96	2147	asGfsuauUfaCfAfggugCfaUfaguccsa	2226	UGGGACUAUGCACCUGUAAUACC	2302
AD-1411204	gsascuaUGfcAfCfCfuguaauacuL96	2148	asGfsguaUfuAfCfaggUGfcAfaguccsc	2227	GGGACUAUGCACCUGUAAUACCA	2303
AD-1411205	ascsuauGfCfCfCfUfguaauaccuL96	2149	asUfsgguAfuUfAfCaggUfgCfauagusc	2228	GGACUAUGCACCUGUAAUACCCAG	2304
AD-1411206	csusaugcAfcCfUfGfuaauaccaguL96	2150	asCfsuggUfaUfUfacagGfuGfcauagsuc	2229	GACUAUGCACCUGUAAUACCAGC	2305
AD-109757	gscsaccUGfuAfAfUfacegcgaauL96	2151	asUfsucGfuGfGfuauuAfcAfggugcsau	2230	AUGCACCUGUAAUACCAGCGAAU	2306
AD-1411210	csasccugUfaAfUfAfccagcgaauL96	2152	asAfsuucGfcUfGfguauUfaCfaggugcsa	2231	UGCACCUGUAAUACCAGCGAAUA	1797
AD-109759	ascscuguAfaUfAfCfcagcgaauuL96	2153	asUfsauuCfGCUfGfguaUfuAfcaggugsc	2232	GCACCUGUAAUACCAGCGAAUAU	2307
AD-1411211	csesuguaAfuAfCfCfcagcgaauuL96	2154	asAfsuauUfcGfCfugguAfuUfacaggusg	2233	CACCUGUAAUACCAGCGAAUAUG	2308
AD-1411212	csusguuaUfaCfCfAfgcgaauuaguL96	2155	asCfsauaUfuCfGfuggUfaUfuacagsgsu	2234	ACCUGUAAUACCAGCGAAUAUGG	2309
AD-1411213	usgsuauAfcCfAfGfcgaauaugguL96	2156	asCfscauAfuUfCfgcugGfuAfuuacagsg	2235	CCUGUAAUACCAGCGAAUAUGGA	1798
AD-1411214	gsusaauaCfcAfGfCfgaauaugguL96	2157	asUfsecaUfaUfUfegcuGfgUfauuacsag	2236	CUGUAAUACCAGCGAAUAUGGAC	1799
AD-1411215	usasauacCfaGfCfGfaauauggacuL96	2158	asGfsuccAfuAfUfuegcUfgGfuauuacsca	2237	UGUAAUACCAGCGAAUAUGGACA	2310
AD-1411226	uscsagcaUfuUfGfGfaauuuuuuL96	337	asAfs_gaaAfuUfAfuccaAfaUfgcugagsga	471	UCUCAGCAUUUUGGAUAAUUUCUC	605
AD-1411342	ascsacucAfaAfAfUfCfuguuucaaL96	340	asUfslugAfcAfCf_gauuUfuGfagugusgsu	474	ACACACUCAAAAUCGUGUUCAAA	608
AD-110052	usasagugGfaAfCfAfucuuagaguL96	295	asAfsucUfaAfGfauuUfCfcauuasusa	429	UAUAAGUGGAACAUCUUAAGAGUU	563
AD-1411480	usasacaaGfaCfCfAfuaacuagguL96	342	asAfsucugUfaGfUfaugUfCfcauuasag	476	CUUAAACAAGACCAUACUACAGUG	610
AD-1411743	csasuucaUfcUfAfUfCfagaagagguL96	345	asCfscucUfuUfCfcauaGfaUfgaagsgsg	479	CUCAUUCAUUCUAUGGAAAGAGGC	613

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO	mRNA target sequence 5' to 3'	SEQ ID NO:
AD-110518	ususggaacCfuUfGfGfauguaacuuL96	298	asAfsuuAfaCfAfuccaAfgUfuccaascsa	432	UGUUGGAACUUGGAUGUUAACUU	566
AD-1411798	usasacuuCfcAfUfGfaauuacuuL96	346	asAfsuAfaCfAfufuauGfgAfaguuaasac	480	GUUAAUUUCCAUGAAUUCUAGUC	614
AD-1411972	cscsgaaaCfuCfAfUfcauugaauL96	348	asGfsauuAfaCfAfufgaugAfgUfuucggsasa	482	UUCCGAAAACUCAUAUUGAAUCA	616
AD-110844	uscsaaacAfcAfGfAfuaauuauuuL96	300	asAfscaaUfuAfuAfaucUfGfuuuagasag	434	CUUCAAAACACAGAUAAUUGUU	568
AD-1412040	gsusuguuUfcAfAfAfuauuauuuL96	350	asGfsaagAfaUfAfauuuGfaAfcacaasasa	484	UUUUGGUUCAAUUAUUCUCC	618
AD-1412095	ascsuagUfuCfuCfAfaauuauuuL96	352	asGfsaagAfaUfAfugagAfaCfugaguuusc	486	GAACUCAGUUCUCAUUCUCCA	620
AD-1412163	usasegucUfaCfuUfufacuuguuL96	353	asAfscaaAfgUfGfaaagUfaGfaguauusc	487	GAUACGUCUACUUUCACUUGGUG	621
AD-111287	asasguaaCfuCfAfUfcauagaauuuL96	301	asAfsaaCfuUfAfgaugAfgUfuauuuusc	435	CAAAGUAAACUCAUCUAAAGAUUUU	569
AD-1412482	csusagagUfuAfaGfAfaauuauuuL96	357	asAfsagUfuAfuUfaguAfaCfaguaggsa	491	UCCUAGAGUUAGACAUAAAUUCUC	625
AD-1412539	ususucucAfuUfAfAfgacacagaauL96	359	asUfsuucGfuGfUfcauaAfuGfagaauusc	493	AGUUUCUCAUUAAGACACGAAAA	627
AD-1412582	usgsaagCfuAfcAfAfacacauuuuuL96	360	asAfsaaUfgUfGfuuguAfgGfcuucasesu	494	AGUGAAGCCUACAACACAUUUUC	628
AD-1412622	asasucaAfuGfAfaacacuuuuL96	361	asAfsagaGfaUfGfuuuAfuUfagaauusa	495	UAAAUCCAUGAAACACAUUCUUC	629
AD-1412733	uscsaaauGfcAfCfuUfcauucuuL96	364	asCfsugaAfgUfAfgaguGfcAfuuuaguuusc	498	GAUCAAAUGCACUCUACUUCACAGA	632
AD-112396	usasucucCfaAfuGfauuauuuuuL96	305	asGfsaaaAfgUfAfucuuUfgAfgaguagsg	439	CCUACUCUCAUAGAUACUUUUUCU	573
AD-1413210	csusaucaAfaGfGfAfauuuauuuL96	373	asGfsagUfaAfaAfuuccUfuUfagauggsasa	507	UUUUAUCAAAAGGAUUUUAUCCA	641
AD-1413286	ascsuagCfuGfAfaAfaauuauuuL96	375	asAfsuaUfcAfAfuuuAfgCfauaguuusc	509	UGACUAUGCUGAAAUUGAUUAUG	643
AD-112618	asasacagAfaGfAfaauuauuuL96	306	asUfsguaAfuAfaAfuuuUfuCfuguuuusc	440	GGAAACAGAAAGAAAUUAUACAUC	574

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO	mRNA target sequence 5' to 3'	SEQ ID NO:
AD-112760	asgscacuUfuUfAfCfcaaacgugaulL96	307	asUfscacGfuUfuUfgguaAfaAfgugcugsu	441	ACAGCACUUUUACCAACGUGAU	575
AD-1413517	ususaucAfaGfUfUfguuuuuuuuL96	378	asUfsuuaAfaAfCfgaacUfuGfguaaascsa	512	UGUUAUCCAAGUUCGUUUUAAAA	646
AD-1413605	asusgcugUfuCfAfGfccaauagcuL96	379	asGfscuaUfuUfGfgcugAfaCfagcaususa	513	UAAUGCUGUUCAGCCAAAUAGCA	647
AD-1413615	usagcagUfuAfUfAfccuacguauuL96	380	asAfsuacGfuAfGfguaaAfaCfugcuasusu	514	AAUAGCAGUUUAUACCUACGU AUG	648
AD-113137	gsasgagaAfuUfUfGfucuaucuaauL96	308	asAfsuagUfaAfGfacaAfuUfucucsasusu	442	AUGAGAGAAUUUGUCUUACU AUU	576
AD-113331	gsascauuCfaCfGfUfguuuacuuuL96	309	asAfsaguGfaAfCfcagUfgAfaugcuscusu	443	AAGACAUUCACGUGGUUCACUUU	577
AD-1413936	csusgguuCfaUfUfUfaaaacuuuL96	381	asAfsagaGfuUfUfuuaaUfgAfaccagsgsc	515	GCCUGGUUCAUUUAAAAUCUCUUG	649
AD-113467	gsasgcagGfgAfUfGfcaaacgccauL96	2159	asUfsggcGfuUfUfgeauCfcCfugcuscusc	2238	GAGAGCAGGGAUGCAAACGCCAU	2311
AD-113468	asgscaggGfaUfGfCfaaacgccauuL96	2160	asAfsuggCfGfUfUfugcaUfcCfugcuscusu	2239	AGAGCAGGGAUGCAAACGCCAUU	2312
AD-113471	asgsggauGfcAfAfAfcccauuuL96	2161	asGfsaaaUfgGfCfguuuGfcAfucccuscsc	2240	GCAGGGAUGCAAACGCCAUUUUCU	2313
AD-113472	gsgsgaugCfaAfAfCfGfccaauuuL96	2162	asAfsaaaAfuGfGfGguUfgCfaucscscsu	2241	CAGGGAUGCAAACGCCAUUUUCU	2314
AD-1414007	gsgsaugCfaAfAfCfGfccaauuuL96	2163	asAfsagaAfaUfGfGcguUfuGfcaucscscsu	2242	AGGGAUGCAAACGCCAUUUUCUUA	2315
AD-113474	gsasugcaAfaCfGfCfcauuuuuuL96	2164	asUfsaagAfaAfUfGfgcgUfuUfgeaucscsc	2243	GGGAUGCAAACGCCAUUUUCU AUU	2316
AD-1414008	asusgcaaAfcGfCfCfauuuuuuuuL96	2165	asAfsuaaGfaAfAfuggcGfuUfugeaucscsc	2244	GGGAUGCAAACGCCAUUUUCU AUU	1926
AD-1414009	usgscaaaCfGfCfAfuuuuuuuL96	382	asGfsauaAfgAfAfauugCfGfufuugcaususc	516	GAUGCAAACGCCAUUUUCU AUU	650
AD-113477	gsascaacGfcCfAfUfucuuuuL96	2166	asUfsgauAfaGfAfauugGfcGfuuuugsasusu	2245	AUGCAAACGCCAUUUUCU AUU	1927
AD-1414010	csasaacGfcAfUfUfucuuuuL96	2167	asAfsugaUfaAfGfaaauGfGfuuuugsasca	2246	UGCAAACGCCAUUUUCU AUU	2317

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO	mRNA target sequence 5' to 3'	SEQ ID NO:
AD-1414011	asasacgcCfaUfUfUfcuaucauguL96	2168	asCfsaugAfuAfAfagaaaUfgGfgcuuusgsc	2247	GCAAAAGCCAUUUUCUUAUCAUGG	2318
AD-1414012	asascgccAfuUfUfCfuaucaugguL96	2169	asCfscauGfaUfAfafagaAfuGfgcguuusg	2248	CAAACGCCAUUUUCUUAUCAUGGA	2319
AD-1414013	asesgccAUfuUfCfufuaucaggauL96	2170	asUfsecaUfgAfuFufaagaAfaUfgggcususu	2249	AAACGCCAUUUUCUUAUCAUGGAC	2320
AD-1414014	csgsccauUfuCfuUfuaucaggacuL96	2171	asGfsuccAfuGfAfuaagAfaAfuggcgssusu	2250	AACGCCAUUUUCUUAUCAUGGACA	2321
AD-1414044	asusgggaCfuAfAfGfcacugguuuuL96	2172	asAfsuacCfaGfUfgcuuAfgUfcccousg	2251	CAAUGGGACUAAGCACUGGUUAUC	2322
AD-1414045	usgsggacUfaAfGfCfcacugguuuuL96	2173	asGfsauaCfcAfGfugcuUfaGfucecasusu	2252	AAUGGGACUAAGCACUGGUUAUCA	2323
AD-113522	gsgsgacuAfaGfCfAfcugguaucauL96	2174	asUfsgauAfcCfAfgugcUfuAfgucccsasu	2253	AUGGGACUAAGCACUGGUUAUCAU	2324
AD-1414046	gsgsacuaAfgCfAfCfugguaucauuL96	2175	asAfsugaUfaCfCfagugCfuUfaguccsesa	2254	UGGGACUAAGCACUGGUUAUCAUA	2325
AD-113526	csusaagcAfcUfGfGfuaucuuuL96	2176	asGfsauaUfgAFUfaceGfuGfcuuagsusc	2255	GACUAAGCACUGGUUAUCAUAUCU	2326
AD-1414048	usasageaCfuGfGfUfaucuuuL96	2177	asAfsgauAfuGFafuaccAfgUfgcuuasgsu	2256	ACUAAGCACUGGUUAUCAUAUCUG	1930
AD-1414049	asasgcacUfgGfUfafucauaucuguL96	2178	asCfsagaUfaUfGfauacCfaGfugcuunsasg	2257	CUAAGCACUGGUUAUCAUAUCUGA	2327
AD-113529	asgsacauGfgUfAfUfcauaucugauL96	2179	asUfscagAfuAFUfgauaCfcAfgugcususa	2258	UAAGCACUGGUUAUCAUAUCUGAU	2328
AD-113530	gscsacugGfuAfUfCfauaucugauuL96	2180	asAfsucaGfaUfAfugauAfcCfagugcsusu	2259	AAGCACUGGUUAUCAUAUCUGAUU	2329
AD-1414050	csascuggUfaUfCfAfuaucugauuuL96	2181	asAfsaucAfgAFUfanguUfaCfcagugsesu	2260	AGCACUGGUUAUCAUAUCUGAUUC	2330
AD-1414053	usgsguanCfaUfAfUfugauucacuL96	2182	asGfsguAfuCfAfagauUfgAfuaccasgsu	2261	ACUGGUUAUCAUAUCUGAUUCACA	2331
AD-1414074	usesagagUfuUfCfUfvgguuacugnuL96	384	asCfsaguAfaCfCfcagaAfaCfucuggasasg	518	CUUCAGAUUUUCUGGGUUACUGG	652
AD-1414139	asgsaaunuUfgCfCfUfcauaaacuuuL96	385	asAfsaggUfuUfAfgaggCfaAfaunueusgsc	519	GCAGAAUUUGCCUCUAAACC UU G	653

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO	mRNA target sequence 5' to 3'	SEQ ID NO:
AD-1414213	csusgaagUfaCfUfGfcauaccacaulL96	2183	asGfsuggUfaUfaGfcagGfaCfuucagsgsu	2262	ACCUGAAGUCCUGCUAUUACCACA	2332
AD-1414218	csusgcuUfaCfCfAfcagaguuuL96	1416	asAfsaaCfuCfUfguggUfaUfagcagsgsa	2263	UCCUGCUAUUACCACAGAGUUUCUA	1939
AD-113751	usgsuauAfcCfAfcfagaguuuL96	2184	asUfsagaAfcUfCfugugGfuAfuagcagsg	2264	CCUGCUAUUACCACAGAGUUUCUAU	2333
AD-1414219	gsesuauAfcCfAfcfagaguuuL96	2185	asAfsuaGfaCfUfcuugGfuUfaugcsag	2265	CUGCUAUUACCACAGAGUUUCUAUG	2334
AD-113753	csusauacCfaCfAfcfagaguuuL96	2186	asCfsauGfaAfcUfcuugGfuUfaugcsa	2266	UGCUAUACCACAGAGUUUCUAUGU	2335
AD-1414220	usasuaccAfcAfcfagaguuuL96	2187	asAfsauAfcAfcUfcuugGfuUfaugsc	2267	GCUAUUACCACAGAGUUUCUAUGUA	1940
AD-1414221	asusaccaCfaCfAfcfagaguuuL96	2188	asUfsacaUfaGfAfcuugGfuUfaugsa	2268	CUAUUACCACAGAGUUUCUAUGUAG	2336
AD-1414222	usascacAfcAfcfagaguuuL96	2189	asCfsuacAfuAfcfagaguuuL96	2269	UAUACCACAGAGUUUCUAUGUAGC	1941
AD-113757	ascscacaGfaGfuUfcauaguuL96	2190	asGfsucaCfaUfaGfagaaUfcUfguggusasu	2270	AUACCACAGAGUUUCUAUGUAGCU	2337
AD-113758	csesacagAfcUfUfcauaguuL96	1419	asAfsuacAfcAfcfagaguuuL96	2271	UACCACAGAGUUUCUAUGUAGCUU	1942
AD-1414223	csascagaGfuUfCfUfaugaguuL96	2191	asAfsagaUfaCfAfuagaAfcUfcuugsgsu	2272	ACCACAGAGUUUCUAUGUAGCUUA	1943
AD-1414226	asgsaguUcfaUfUfcauaguuL96	1421	asUfsuagAfcCfUfcauAfcUfcaucugsu	2273	ACAGAGUUUCUAUGUAGCUUACAG	1944
AD-113763	gsasguucUfaUfGfUfagaguuL96	2192	asCfsuagAfaGfCfuacaUfaGfaucucsg	2274	CAGAGUUUCUAUGUAGCUUACAGU	2338
AD-113764	asgsuucUfaUfUfcauaguuL96	2193	asAfsuagUfaUfGfcauAfcUfcaucucsu	2275	AGAGUUUCUAUGUAGCUUACAGUU	1945
AD-1414229	uscsuagUfaGfCfUfcauaguuL96	1423	asGfsuagAfcUfGfcauAfcUfcauagasa	2276	GUUCUAUGUAGCUUACAGUUCCA	1946
AD-1414230	csusanguAfcCfUfcauaguuL96	2194	asUfsggaAfcUfGfcauAfcUfcauagasa	2277	UUCUAUGUAGCUUACAGUUCCA	2339
AD-1414231	usasuagaGfcUfUfcauaguuL96	2195	asUfsggaAfcUfGfcauAfcUfcauagasa	2278	UCUAUGUAGCUUACAGUUCCAAC	2340

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO	mRNA target sequence 5' to 3'	SEQ ID NO:
AD-1414235	usagsuuAfeAfGfUfuuccaaccaguuL96	2196	asCfsuggUfuGfGfaacuGfuAfagcuacsca	2279	UGUAGCUUACAGUUCACCAACCAGA	2341
AD-1414275	gsasauuGfaUfGfUfauuuuuauuuL96	387	asCfsauuAfaAfAfuaaUfcAfaauucscsu	521	AGGAAUGUGAUGUAUUUUAUUGG	655
AD-113890	ascscuuUfgUfGfGfuaagauuuuuL96	2197	asUfsauuUfcUfAfGCCAfaAfuaagsgsg	2280	CCACCUAUUGUGGCCUAGAUUAU	2342
AD-113891	cscsuuuGfuGfGfCfuagauuuuuL96	2198	asAfsuuuAfuCfUfagccAfcAfaagsgsg	2281	CACCUAUUGUGGCCUAGAUUAU	2343
AD-1414321	csusuugUfgGfCfUfagauuuuuL96	2199	asAfsauuUfaUfCfuagCfcCfaauagsgsu	2282	ACCUAUUGUGGCCUAGAUUAUUA	1953
AD-1414322	usasuugUfgGfCfUfAfgauuuuuL96	2200	asUfsauuAfuAfUfcuagCfcAfaauagsgsg	2283	CCUUAUUGUGGCCUAGAUUAUUA	2344
AD-1414323	asusugugGfcUfAfGfauuuuuuuL96	2201	asCfsuuuUfaUfAfuaaUfcCfacaauasag	2284	CUAUUGUGGCCUAGAUUAUUAUAGG	2345
AD-1414324	ususugugCfuAfGfAfuaauuuuuL96	2202	asCfsuuuAfuAfUfaucUfGfacaauasusa	2285	UAUUGUGGCCUAGAUUAUUAUAGGA	2346
AD-113896	usgsugugUfaGfAfUfauuuuuuuuL96	2203	asUfscuuAfaUfAfuaaUfcGfcaacasasu	2286	AUUGUGGCCUAGAUUAUUAUAGGAU	2347
AD-1414325	gsusggcuAfgAfUfAfuaauuuuuuuL96	2204	asAfsuuuUfaUfAfuaaUfcUfagccacsasa	2287	UUUGUGGCCUAGAUUAUUAUAGGAUC	2348
AD-1414326	gsuscuagAfuAfUfAfuaaggaucuuL96	1431	asAfsuuuUfcUfAfuaaUfcUfagccacsasa	2288	GUGGCCUAGAUUAUUAUAGGAUCUC	1954
AD-113900	gsusuagaUfaUfAfUfuaaggaucuuL96	2205	asGfsagaUfcCfUfuaaUfcUfagccacsasa	2289	UGGCCUAGAUUAUUAUAGGAUCUCU	2349
AD-1414544	cscsucugAfaUfGfGfuaaggaauuuL96	391	asCfsuuuAfcAfuUfuaaUfcUfagccacsasa	525	GUCCUCUGAAAUGUAUGUAAAGA	659
AD-114455	csusugugUfaAfAfUfuaaaggaauuuL96	310	asAfsuuuUfcAfuUfuaaUfcUfagccacsasa	444	CGCUGUGUUAAAUGUAUGUAAAGA	578
AD-114469	ascsaguuUfuCfCfAfcuaauuuuuuuL96	311	asGfsagaAfaUfAfuaaUfcUfagccacsasa	445	UACAGUUUUUCCACUAUUUUUCUCU	579

Table 9. Coagulation Factor V Single Dose Screens in Primary Human Hepatocytes

Duplex	100 nM		10 nM		1 nM	
	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1465906.1	29.83	4.34	26.18	3.53	54.99	18.44
AD-1465908.1	59.18	12.74	74.88	11.96	74.90	17.45
AD-1465913.1	47.70	1.65	69.93	11.45	129.22	44.45
AD-1465918.1	35.23	4.46	65.53	10.38	93.25	25.68
AD-1465922.1	35.52	2.44	94.25	2.29	87.46	14.20
AD-1465928.1	60.78	12.66	122.14	35.25	100.35	16.69
AD-1465932.1	41.79	11.74	64.38	3.83	81.63	18.56
AD-1465937.1	48.83	6.44	124.91	13.19	110.81	14.87
AD-1465946.1	52.64	11.24	62.37	6.03	93.29	9.13
AD-1465951.1	40.09	8.54	99.58	21.83	104.92	22.08
AD-1465957.1	35.57	12.19	79.64	20.36	127.03	17.98
AD-1465960.1	30.07	2.92	56.45	5.43	92.21	3.19
AD-1465968.1	37.66	8.80	56.38	14.13	64.06	14.04
AD-1465973.1	48.33	2.94	52.38	16.25	113.50	17.56
AD-1465984.1	29.17	2.48	31.73	8.23	63.52	11.59
AD-1466007.1	21.09	6.59	47.97	9.50	50.25	11.81
AD-1466012.1	37.54	14.69	71.09	10.42	52.06	14.46
AD-1466022.1	38.58	4.19	69.33	25.75	84.13	23.97
AD-1466029.1	35.09	10.37	60.88	11.96	79.29	15.81
AD-1466031.1	37.70	7.26	50.53	12.10	72.60	19.92
AD-1466034.1	41.13	10.35	71.69	10.74	99.39	5.05
AD-1466036.1	29.61	11.15	32.21	2.39	64.99	4.40
AD-1466036.2	25.53	2.03	37.03	9.65	44.28	13.73
AD-1466036.3	33.97	10.46	38.07	13.12	70.11	14.74
AD-1466037.1	19.16	6.27	28.89	3.80	51.39	15.96
AD-1466037.2	22.98	2.00	41.43	6.68	57.10	11.24
AD-1466037.3	32.57	7.57	53.86	17.13	63.67	13.55
AD-1466039.1	42.09	5.62	62.04	7.76	71.60	16.01
AD-1466040.1	24.20	4.49	44.43	6.41	62.34	14.17
AD-1466050.1	54.83	10.50	64.87	14.11	80.99	11.86
AD-1466052.1	64.33	10.60	94.49	14.74	113.30	18.42
AD-1466053.1	32.55	2.44	63.88	12.42	85.39	13.49
AD-1466059.1	48.05	12.26	76.29	13.85	73.54	19.56
AD-1466066.1	35.30	4.41	42.33	4.75	78.36	21.73
AD-1466070.1	19.87	2.26	44.38	12.25	91.86	24.54
AD-1466078.1	20.58	5.99	67.33	18.33	56.91	18.27
AD-1466080.1	31.56	7.92	67.18	7.70	66.45	17.98
AD-1466082.1	36.38	11.56	74.65	19.53	71.90	13.54
AD-1466083.1	26.85	6.10	55.34	8.38	64.35	11.44
AD-1466085.1	61.43	10.38	60.17	8.76	80.75	3.17

	100 nM		10 nM		1 nM	
Duplex	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1466094.1	45.33	13.58	109.63	12.33	70.65	11.24
AD-1466098.1	57.19	11.12	112.82	21.23	70.86	10.04
AD-1466099.1	49.92	8.48	61.47	0.30	76.06	14.15
AD-1466100.1	66.18	17.53	64.33	18.17	47.91	3.99
AD-1466101.1	72.61	3.20	135.09	28.96	90.04	16.67
AD-1466102.1	68.75	14.03	126.84	1.24	86.34	19.49
AD-1466104.1	63.05	11.55	135.98	16.62	83.59	14.12
AD-1466109.1	56.62	7.50	77.86	23.34	86.34	18.30
AD-1466110.1	63.86	8.22	89.13	23.51	113.46	16.29
AD-1466114.1	29.08	6.64	68.45	15.00	64.11	14.88
AD-1466115.1	68.97	6.59	98.92	16.08	96.37	7.44
AD-1466118.1	41.23	5.82	66.23	14.57	85.04	22.51
AD-1466119.1	47.32	11.21	88.22	12.61	116.78	23.53
AD-1466121.1	35.13	11.94	53.02	9.03	92.73	23.97
AD-1466122.1	44.07	9.59	78.18	25.79	100.31	19.93
AD-1466123.1	54.48	12.25	70.01	21.25	122.02	12.65
AD-1466124.1	43.22	1.78	75.28	10.07	82.14	8.08
AD-1466127.1	52.50	15.95	75.27	16.90	94.42	24.31
AD-1466128.1	49.72	11.36	83.56	20.77	103.18	26.19
AD-1466129.1	40.62	6.09	48.16	5.32	103.49	24.33
AD-1466131.1	46.96	10.34	65.26	3.05	123.98	36.06
AD-1466135.1	64.01	14.24	40.27	8.20	111.27	31.75
AD-1466137.1	48.74	7.02	55.45	14.68	127.12	22.68
AD-1466139.1	36.06	2.25	64.10	10.32	84.71	11.45
AD-1466145.1	30.14	6.29	56.33	6.06	77.41	8.71
AD-1466147.1	30.89	6.23	38.65	10.28	90.85	19.90
AD-1466148.1	27.26	5.11	65.86	15.30	88.40	13.79
AD-1466149.1	29.84	3.30	48.08	7.86	75.66	12.50
AD-1466150.1	51.35	7.03	62.33	15.96	65.97	18.51
AD-1466151.1	24.29	5.94	48.65	6.55	98.02	1.92
AD-1466152.1	26.42	0.89	30.62	3.44	102.23	36.11
AD-1466157.1	25.73	8.82	51.23	10.09	102.04	32.17
AD-1466158.1	35.53	2.75	67.70	9.65	94.61	13.71
AD-1466159.1	33.02	7.52	52.84	4.51	120.51	11.21
AD-1466161.1	28.57	3.09	30.63		82.51	23.37
AD-1465901.1	57.87	9.04	53.64	13.38	88.39	22.15
AD-1465902.1	48.56	11.96	70.88	11.07	73.14	21.21
AD-1465903.1	44.34	9.85	47.75	8.77	67.42	11.36
AD-1465904.1	37.91	4.92	41.98	12.39	33.19	8.75
AD-1465905.1	50.62	5.95	44.70	11.89	60.39	9.15
AD-1465907.1	34.85	3.45	36.11	2.20	74.47	16.48

	100 nM		10 nM		1 nM	
Duplex	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1465909.1	58.91	8.10	62.94	3.57	104.51	15.20
AD-1465910.1	61.54	7.71	59.27	16.16	91.39	33.06
AD-1465911.1	59.52	15.38	132.87	32.57	100.84	39.39
AD-1465912.1	42.06	5.34	64.28	20.10	91.26	28.80
AD-1465914.1	105.46	11.10	92.12	24.35	106.32	18.69
AD-1465915.1	60.43	14.21	118.89	40.35	117.99	21.08
AD-1465916.1	45.27	10.91	106.59	11.06	119.82	15.00
AD-1465917.1	56.73	7.12	57.77	7.15	83.93	21.65
AD-1465919.1	43.92	6.66	66.21	19.27	116.81	15.98
AD-1465920.1	34.38	5.45	81.57	14.61	102.84	29.75
AD-1465921.1	52.78	11.57	110.77	30.64	88.13	33.52
AD-1465923.1	91.10	23.47	91.90	38.15	125.85	35.66
AD-1465924.1	41.76	1.90	68.53	10.44	94.54	17.38
AD-1465925.1	37.77	7.36	50.52	18.77	97.68	6.50
AD-1465926.1	62.24	7.15	99.17	38.42	130.35	18.97
AD-1465927.1	85.58	12.24	97.79	40.31	116.52	28.82
AD-1465929.1	36.85	9.84	103.71	44.60	93.92	6.32
AD-1465930.1	106.58	25.36	101.36	14.80	115.35	22.42
AD-1465931.1	74.08	10.84	110.75	26.50	92.45	19.87
AD-1465933.1	99.35	10.63	179.02	20.05	135.22	26.99
AD-1465934.1	85.52	12.99	140.24	46.25	145.52	25.19
AD-1465935.1	86.84	19.96	150.01	35.71	163.34	19.15
AD-1465936.1	88.64	13.40	162.30	34.76	156.28	25.44
AD-1465938.1	38.79	10.19	73.28	10.42	144.90	17.54
AD-1465939.1	73.88	4.07	85.75	19.22	101.88	24.06
AD-1465940.1	78.26	20.95	112.58	21.71	129.16	38.03
AD-1465941.1	54.44	15.96	123.89	9.08	121.39	14.29
AD-1465942.1	79.95	11.45	137.88	17.29	132.23	45.30
AD-1465943.1	75.70	6.40	115.27	20.52	162.27	43.22
AD-1465944.1	68.77	4.05	118.76	19.53	127.42	35.67
AD-1465945.1	57.12	16.44	103.63	24.90	115.73	33.37
AD-1465947.1	86.40	25.59	126.21	20.04	123.51	11.25
AD-1465948.1	43.10	10.20	98.00	22.83	103.47	19.59
AD-1465949.1	53.60	6.86	70.00	13.31	112.30	7.85
AD-1465950.1	116.16	31.53	147.58	22.51	104.47	7.33
AD-1465952.1	70.70	16.02	95.96	13.24	109.50	4.85
AD-1465953.1	37.01	11.62	68.81	9.98	95.21	18.03
AD-1465954.1	33.97	4.72	42.53	3.83	74.95	6.30
AD-1465955.1	63.93	12.79	54.90	7.80	99.36	37.08
AD-1465956.1	59.44	6.11	86.80	11.20	120.03	36.59
AD-1465958.1	40.12	4.18	65.27	11.85	100.13	21.77

	100 nM		10 nM		1 nM	
Duplex	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1465959.1	48.70	11.56	83.42	15.03	101.42	7.48
AD-1465961.1	78.95	22.73	87.27	8.89	104.09	16.54
AD-1465962.1	83.70	11.84	86.95	7.94	103.75	16.84
AD-1465963.1	67.50	10.82	86.53	6.10	119.68	27.60
AD-1465964.1	59.74	10.20	98.07	20.04	99.23	16.27
AD-1465965.1	113.61	11.17	117.85	19.19	108.54	31.57
AD-1465966.1	64.91	7.73	65.19	12.61	107.27	11.60
AD-1465967.1	41.57	9.28	51.46	13.83	100.10	3.83
AD-1465969.1	50.71	8.91	64.40	13.47	72.75	10.06
AD-1465970.1	81.09	11.19	52.52	9.13	70.49	5.26
AD-1465971.1	27.45	6.04	29.49	3.75	62.10	13.56
AD-1465972.1	71.55	12.55	54.61	7.95	102.37	16.29
AD-1465974.1	44.84	8.01	63.89	17.20	93.46	23.95
AD-1465975.1	41.96	3.12	53.23	11.24	74.50	17.09
AD-1465976.1	48.14	8.42	61.24	6.02	85.16	11.99
AD-1465977.1	33.43	4.92	45.13	5.79	62.44	14.14
AD-1465978.1	59.62	7.77	58.25	6.39	75.72	9.49
AD-1465979.1	71.02	11.11	62.45	7.83	89.18	10.38
AD-1465980.1	59.01	8.17	66.45	9.74	72.88	5.97
AD-1465981.1	60.22	9.89	85.34	11.41	88.80	4.48
AD-1465982.1	54.81	11.89	53.42	11.85	87.46	14.50
AD-1465983.1	45.97	4.25	56.23	10.22	82.52	11.05
AD-1465985.1	47.12	7.15	35.50	7.84	51.28	10.28
AD-1465986.1	47.40	10.35	39.85	6.57	49.36	2.74
AD-1465987.1	62.96	6.64	49.11	5.09	48.64	3.79
AD-1465988.1	59.81	10.49	50.67	11.49	71.18	8.19
AD-1465989.1	64.45	5.90	61.88	7.82	84.13	18.88
AD-1465990.1	59.90	11.33	58.08	11.01	88.46	6.32
AD-1465991.1	75.38	16.14	70.27	24.74	71.33	14.52
AD-1465992.1	64.73	24.05	69.13	12.11	64.30	7.18
AD-1465993.1	60.60	17.66	98.27	27.45	67.95	6.11
AD-1465994.1	68.62	13.30	82.83	21.82	80.85	13.41
AD-1465996.1	67.28	21.13	91.12	6.94	61.60	16.47
AD-1465997.1	89.75	29.13	88.27	21.51	60.90	20.08
AD-1465998.1	87.60	23.94	87.44	25.55	74.38	18.86
AD-1465999.1	56.54	12.64	57.84	16.37	67.44	10.28
AD-1466000.1	82.44	24.18	104.92	25.71	99.70	31.14
AD-1466001.1	105.11	43.76	83.07	15.38	74.33	21.86
AD-1466002.1	56.87	10.92	57.97	8.77	55.40	9.05
AD-1466003.1	42.28	13.90	73.58	14.86	40.71	
AD-1466004.1	47.70	18.67	105.81	30.23	71.40	20.88

	100 nM		10 nM		1 nM	
Duplex	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1466005.1	60.76	13.00	98.19	29.88	62.92	12.68
AD-1466006.1	28.82	11.04	48.39	4.26	57.30	17.12
AD-1466008.1	56.29	22.03	105.21	41.23	76.33	27.09
AD-1466009.1	56.96	24.47	84.33	32.80	87.94	19.64
AD-1466010.1	95.51	15.15	103.78	11.17	112.01	9.71
AD-1466011.1	48.01	12.24	104.28	26.32	97.24	19.93
AD-1466013.1	86.65	36.27	82.60	26.05	106.36	14.76
AD-1466014.1	76.11	31.62	73.81	20.04	99.35	20.06
AD-1466015.1	88.60	6.94	101.65	28.36	90.70	25.17
AD-1466016.1	41.80	6.21	84.88	10.65	77.06	11.10
AD-1466017.1	114.13	21.51	111.35	7.81	123.33	31.68
AD-1466018.1	41.91	14.58	89.62	15.03	62.42	8.54
AD-1466019.1	58.32	16.29	81.23	1.59	78.71	24.66
AD-1466020.1	57.28	15.09	76.81	15.12	100.96	15.84
AD-1466021.1	94.35	36.44	102.55	34.16	99.28	10.34
AD-1466023.1	66.44	2.00	100.54	31.58	142.84	31.71
AD-1466024.1	36.59	2.51	75.40	15.34	95.78	14.34
AD-1466025.1	60.70	16.18	115.36	12.71	105.95	18.13
AD-1466026.1	104.06	24.81	125.42	7.29	101.77	30.88
AD-1466027.1	39.35	5.77	92.58	31.80	89.93	17.29
AD-1466028.1	104.65	22.43	66.19	25.31	114.29	36.62
AD-1466030.1	64.67	12.81	79.17	21.83	81.64	21.69
AD-1466032.1	45.24	17.23	54.29	13.42	76.83	21.77
AD-1466033.1	101.69	43.70	98.93	11.01	105.73	31.15
AD-1466035.1	73.47	18.47	71.67	25.03	78.26	6.28
AD-1466038.1	54.56	21.49	58.15	12.05	63.76	20.55
AD-1466038.2	39.16	10.66	63.09	11.25	74.43	2.92
AD-1466041.1	83.08	34.14	78.60	18.18	106.28	34.28
AD-1466042.1	30.88	3.77	57.64	16.36	79.82	22.98
AD-1466043.1	75.44	24.75	82.03	14.68	96.69	5.38
AD-1466044.1	97.38	34.01	94.90	8.54	85.34	25.08
AD-1466045.1	84.99	15.95	105.86	17.24	128.01	35.31
AD-1466046.1	31.62	6.34	53.62	20.02	63.14	8.80
AD-1466047.1	81.68	11.74	95.14	14.68	93.03	12.69
AD-1466048.1	101.41	3.69	79.51	26.36	96.47	16.49
AD-1466049.1	42.71	6.67	34.75	4.16	74.14	18.97
AD-1466051.1	67.30	12.16	81.93	28.58	65.43	8.43
AD-1466054.1	47.15	10.50	55.95	18.32	65.02	10.28
AD-1466055.1	40.78	7.93	47.75	11.42	71.83	13.32
AD-1466056.1	82.16	5.10	68.00	16.82	70.89	1.69
AD-1466057.1	43.73	2.64	58.47	13.65	75.99	2.30

	100 nM		10 nM		1 nM	
Duplex	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1466058.1	67.88	12.93	48.60	13.63	82.28	16.65
AD-1466060.1	46.93	8.22	84.13	6.62	98.85	18.70
AD-1466061.1	37.29	2.34	59.22	16.11	82.67	19.04
AD-1466062.1	42.42	8.99	45.53	12.99	82.34	24.16
AD-1466063.1	36.92	4.46	43.96	5.72	68.18	11.18
AD-1466064.1	50.47	2.67	56.79	4.95	55.87	6.39
AD-1466065.1	56.87	6.13	44.29	0.65	72.16	15.36
AD-1466067.1	80.41	3.64	87.92	45.06	89.46	10.80
AD-1466068.1	34.25	5.13	53.77	9.75	72.16	10.06
AD-1466069.1	26.35	5.80	58.83	14.76	53.01	11.09
AD-1466071.1	58.38	12.97	69.88	8.08	80.06	22.67
AD-1466072.1	49.39	15.05	59.21	11.28	77.01	20.01
AD-1466073.1	43.42	10.64	68.96	15.38	75.63	19.26
AD-1466074.1	43.52	14.32	74.41	24.01	104.67	14.16
AD-1466075.1	40.34	4.13	57.67	15.37	103.19	25.57
AD-1466076.1	68.93	6.16	82.38	20.38	62.90	6.19
AD-1466077.1	40.23	5.52	84.02	10.68	65.11	
AD-1466079.1	24.56	0.48	93.85	27.49	60.02	4.02
AD-1466081.1	28.87	5.52	68.78	8.22	50.99	14.55
AD-1466084.1	50.97	8.36	69.55	9.88	60.83	9.90
AD-1466086.1	51.13	14.03	70.54	15.08	61.27	10.42
AD-1466087.1	72.70	25.94	89.10	12.79	53.69	11.01
AD-1466088.1	54.34	4.45	111.52	10.09	72.95	2.54
AD-1466089.1	62.03	15.02	112.74		61.34	5.51
AD-1466090.1	88.96	8.10	63.90	3.13	59.15	3.28
AD-1466091.1	86.10	18.26	117.43	12.07	80.71	18.82
AD-1466092.1	94.27	26.22	86.63	20.19	91.84	18.93
AD-1466093.1	51.55	7.27	69.49	9.12	84.20	7.86
AD-1466095.1	59.33	16.95	117.43	16.19	101.92	22.49
AD-1466096.1	67.52	3.97	115.48	24.10	91.18	30.26
AD-1466097.1	60.52	11.34	121.05	8.93	103.98	24.00
AD-1466103.1	128.42	29.78	73.87		122.30	13.53
AD-1466105.1	137.72	25.36	76.93	15.05	88.61	19.32
AD-1466106.1	45.30	1.18	73.74	17.90	61.05	12.02
AD-1466107.1	126.05	19.72	105.92	25.37	92.98	21.53
AD-1466108.1	101.05	14.68	110.20	25.25	106.89	22.80
AD-1466111.1	85.40	15.20	119.33	18.31	117.48	32.63
AD-1466112.1	98.27	20.07	108.15		130.61	29.03
AD-1466113.1	56.68	15.37	90.17	21.81	87.08	20.81
AD-1466116.1	72.73	19.52	108.86	17.51	111.94	17.51
AD-1466117.1	53.48	21.90	106.25	17.80	68.87	14.41

	100 nM		10 nM		1 nM	
Duplex	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1466120.1	68.55	12.11	71.46	13.06	126.78	19.42
AD-1466125.1	58.06	11.60	127.17	18.95	88.42	21.93
AD-1466126.1	87.08	19.79	85.32	22.55	104.98	14.78
AD-1466130.1	75.72	15.95	85.62	16.45	102.83	19.26
AD-1466132.1	68.29	5.25	83.42	14.04	88.45	19.49
AD-1466133.1	124.22	16.04	87.72	25.76	118.84	22.29
AD-1466134.1	122.00	18.11	135.48	9.25	114.08	23.01
AD-1466136.1	64.94	14.73	102.40	13.36	137.35	20.92
AD-1466138.1	52.11	6.59	85.51	26.78	117.79	32.30
AD-1466140.1	56.37	4.76	84.55	13.11	101.13	24.61
AD-1466141.1	43.17	3.72	68.32	15.93	91.57	19.50
AD-1466142.1	37.91	0.40	55.80	15.75	90.41	14.67
AD-1466143.1	49.82	2.12	41.70	8.52	84.60	12.40
AD-1466144.1	31.90	5.95	41.75	10.52	85.26	5.85
AD-1466146.1	56.26	11.10	70.57	7.60	86.64	5.46
AD-1466153.1	43.97	5.29	64.27	17.14	78.55	21.81
AD-1466154.1	38.09	8.31	46.35	9.11	108.60	28.64
AD-1466155.1	55.36	6.79	59.63	9.90	87.88	21.13
AD-1466156.1	70.04	14.74	92.49	4.18	102.37	24.04
AD-1466160.1	27.56	1.45	44.01	3.35	89.01	22.70
AD-1466162.1	27.16	2.05	47.00	6.89	108.14	13.91
AD-1466163.1	59.34	8.87	89.12	17.16	116.26	16.86
AD-1466164.1	62.57	8.31	70.35	13.88	97.88	12.84
AD-1466165.1	43.49	5.88	56.26	15.42	106.92	37.94

Example 4. Additional Duplexes Targeting Coagulation Factor V

Additional agents targeting coagulation factor V gene were designed using custom R and Python scripts and synthesized as described above.

A detailed list of the unmodified complement coagulation factor V sense and antisense strand nucleotide sequences is shown in Table 10. A detailed list of the modified coagulation factor V sense and antisense strand nucleotide sequences is shown in Table 11.

For transfections, 7.5 μ l of Opti-MEM plus 0.1 μ l of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) was added to 2.5 μ l 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 μ l of complete growth media without antibiotic containing $\sim 1.5 \times 10^4$ cells was then added to the siRNA mixture. Cells are incubated for 24 hours prior to RNA purification. Single dose experiments were performed at 10 nM, 1 nM, and 0.1 nM final duplex concentration.

Total RNA isolation was performed using DYNABEADS. Briefly, cells were lysed in 10µl of Lysis/Binding Buffer containing 3 µL of beads per well were mixed for 10 minutes on an electrostatic shaker. The washing steps were automated on a Biotek EL406, using a magnetic plate support. Beads were washed (in 3µL) once in Buffer A, once in Buffer B, and twice in Buffer E, with aspiration steps in between. Following a final aspiration, complete 12µL RT mixture was added to each well, as described below.

For cDNA synthesis, a master mix of 1.5µl 10X Buffer, 0.6µl 10X dNTPs, 1.5µl Random primers, 0.75µl Reverse Transcriptase, 0.75µl RNase inhibitor and 9.9µl of H₂O per reaction was added per well. Plates were sealed, agitated for 10 minutes on an electrostatic shaker, and then incubated at 37 degrees C for 2 hours. Following this, the plates were agitated at 80 degrees C for 8 minutes.

RT-qPCR was performed as described above and relative fold change was calculated as described above. The results of the single dose screen of the agents in Tables 10 and 11 in primary human hepatocytes are shown in Table 12.

Table 10. Unmodified Sense and Antisense Strand Sequences of Coagulation Factor V dsRNA Agents

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-110532.1	UUAAUUCCAUAGAAUUCUAGU	792	2132-2152	ACUAGAAUUCAUAGGAAGUUAACA	2425	2130-2152
AD-110931.1	AGAAUCUCAGUUCUCAAUUCUU	2350	2592-2612	AAGAAUUGAGAAACUGAGUUCUUG	2426	2590-2612
AD-112393.1	UCCUACUCUCAAGAUACUUU	2351	4630-4650	AAAGUAUCAUUGAGAGUAGGAGA	2427	4628-4650
AD-114469.2	ACAGUUUCCACUAUUUCUCU	21	6911-6931	AGAGAAUAGUGGAAAACUGUUA	22	6909-6931
AD-1410823.1	CCUCACACACAUUAUACUU	714	646-666	AAGUAAUAGAUGUGUGAGGCA	2054	644-666
AD-1411340.1	ACACACUCAAAUUCGUGUUCU	2352	1431-1451	AGAACACGAUUUUGAGUGUUCU	2428	1429-1451
AD-1411342.2	ACACUCAAAUUCGUGUUCAAU	76	1433-1453	AUUGAACACGAUUUUGAGUGUGU	207	1431-1453
AD-1411797.1	GUUAAUUCCAUAGAAUUCUUAU	2353	2131-2151	AUAGAAUUCAUAGGAAGUUAACA	2429	2129-2151
AD-1411798.2	UAAUUCCAUAGAAUUCUAGUU	82	2133-2153	AACUAGAAUUCAUAGGAAGUUAAC	213	2131-2153
AD-1412539.2	UUUCUCAUUAAGACACGAAAU	95	3218-3238	AUUUCGUGUCUUAUUGAGAAACU	226	3216-3238
AD-1413196.1	CUACUCUCAUAGAUACUUUUU	2354	4632-4652	AAAAAGUAUCAUUGAGAGUAGGA	2430	4630-4652
AD-1414748.1	AACAGUUUCCACUAUUUCUU	2355	6910-6930	AAGAAUAGUGGAAAACUGUUAA	2431	6908-6930
AD-1452126.1	AUAUGUCUUUCAUGAUUCUUGU	2356	8748-8768	ACAAGAUCAUAGAAAGACAUUAG	2432	8746-8768
AD-1452209.1	ACCAUCAAGGUUCACUUUAGU	2357	434-454	ACUAAAGUGAACCUUGAUGGUGU	2433	432-454
AD-1452212.1	AUCAAGGUUCACUUUAGAAAU	2358	437-457	AUUUCUAAAAGUGAACCUUGAUGG	2434	435-457
AD-1452985.1	GUUUUCUAUUCACUUCAACGU	2359	943-963	ACGUUGAAAGUGAAUAGAAAACA	2435	941-963
AD-1453516.1	UGUCACAUACAGUUCUACAAAGU	2360	1558-1578	ACUUGUAGAACUGAUGUGACAGC	2436	1556-1578
AD-1453784.1	CAUCAUGAACACUAUCAAUGU	2361	1897-1917	ACAUUGAUAGUGUUCUAGAUUUU	2437	1895-1917
AD-1454175.1	GACUCAUAGAGAUUUUAUCAU	2362	2216-2236	AUGAUAAAUCUCAUAGAGUUCU	2438	2214-2236
AD-1454221.1	CUCGGAAAUAUUGAUUUUCUU	2363	2262-2282	AAGAAUCAUGAAUUUUCCGAGUU	2439	2260-2282
AD-1454350.1	UCUAAUUCGAGGAUUUCAACUU	2364	676-696	AAGUUGAAAUCCUCUGAUUAGAUU	2440	674-696
AD-1454529.1	CAAAAUCCUCAAGAAACCUUU	2365	2048-2068	AAAGUUUUUCUUGAGGAUUUUUGAG	2441	2046-2068
AD-1454534.1	UCCUCAAGAAACCUUAGUAAU	2366	2480-2500	AUUACUAAAGGUUUCUUGAGGAUU	2442	2478-2500
AD-1454719.1	ACCCUUAACACAGAAUAUCAUU	2367	1817-1837	AAUGAUUUUCUGUUUGAAGGGUUG	2443	1815-1837
AD-1454720.1	CCCUUCAAACAGAAUAUCAUUU	2368	2608-2628	AAAUGAUUUUCUGUUGAAGGGUUG	2444	2606-2628

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-145491.1	AAAUCCAAAGAAUACUUCUUU	2369	9068-9088	AAAGAAUAUUCUUUGGAUUUGA	2445	9066-9088
AD-1455310.1	AAAGACUACUCAAUUAUUAU	2370	2020-2040	AUGAAUGAUUGAGUAGUCUUUC	2446	2018-2040
AD-1455313.1	AGACUACUCAAUUAUUAUUAU	2371	2022-2042	AAAUGAAUGAUUGAGUAGUCUUU	2447	2020-2042
AD-1455314.1	GACUACUCAAUUAUUAUUAU	2372	4754-4774	AUAAUGAAUGAUUGAGUAGUCUU	2448	4752-4774
AD-1455522.1	AACACUCUCCAAUUAUUAUUAU	2373	4614-4634	AAGGAAUUGUUGGAGAGUUGCC	2449	4612-4634
AD-1455659.1	GAUGAAGUCAACUCUACUUUU	2374	1514-1534	AAAAGUAGAUUGAGUAGUUAUUAU	2450	1512-1534
AD-1455664.1	AGUCAACUCUACUUUAUUAUUAU	2375	1519-1539	AAGGUGAAAGUAGAGUUAUUAUUAU	2451	1517-1539
AD-1455701.1	GACAUUAGUCAAAUUAUUAUUAU	2376	7342-7362	AAAAGAUUUUGAGUUAUUAUUAUUAU	2452	7340-7362
AD-1455771.1	CCUCCUCAGACUUAUUAUUAUUAU	2377	3150-3170	AAGAUUUAAGUCUGAGGAAGGA	2453	3148-3170
AD-1455780.1	UCAGACUUAUUAUUAUUAUUAUUAU	2378	3156-3176	AGUAAAGAGAUUAUUAUUAUUAUUAU	2454	3154-3176
AD-1455807.1	GAAUUGGAUCAAAUUAUUAUUAU	2379	7300-7320	AUAAUUGUUAUUAUUAUUAUUAUUAU	2455	7298-7320
AD-1457108.1	AUUAGGUCUUAUUAUUAUUAUUAU	2380	2351-2371	AGAGUUUCUGAAUUAUUAUUAUUAUUAU	2456	2349-2371
AD-1457130.1	GAAAGAGAGUACAAUUAUUAUUAU	2381	2387-2407	AGUAAAGAUUAUUAUUAUUAUUAUUAU	2457	2385-2407
AD-1457237.1	UUCGAAACACAGAUUAUUAUUAUUAU	2382	2443-2463	ACAAUUAUUAUUAUUAUUAUUAUUAUUAU	2458	2441-2463
AD-1458307.1	AAGCAAUUUAUUAUUAUUAUUAUUAU	2383	6383-6403	AGAAGAUUGCAGUAAUUAUUAUUAUUAU	2459	6381-6403
AD-1458619.1	UCAUUGUUGCUUAUUAUUAUUAUUAU	2384	3344-3364	AGAUUUAUUAUUAUUAUUAUUAUUAUUAU	2460	3342-3364
AD-1458724.1	UAAUCAGAAUUAUUAUUAUUAUUAUUAU	2385	3445-3465	ACAUUCGAGGAUUAUUAUUAUUAUUAUUAU	2461	3443-3465
AD-1459277.1	UCUGAAUUCUAGUCAGUUAUUAUUAU	2386	4544-4564	AAAUAAUUAUUAUUAUUAUUAUUAUUAUUAU	2462	4542-4564
AD-1459922.1	GAACUGAAUUAUUAUUAUUAUUAUUAUUAU	2387	6820-6840	AGGUUUUUAUUAUUAUUAUUAUUAUUAUUAU	2463	6818-6840
AD-1465918.3	AUGCCUCACACACAUUAUUAUUAUUAUUAU	712	643-663	AAAUAGAUUGUGTGUGAGGCAUUAUUAUUAU	968	641-663
AD-1465918.4	AUGCCUCACACACAUUAUUAUUAUUAUUAU	712	643-663	AAAUAGAUUGUGTGUGAGGCAUUAUUAUUAU	968	641-663
AD-1465919.2	UGCCUCACACACAUUAUUAUUAUUAUUAUUAU	713	644-664	ATAATAGAUUGUGTGUGAGGCAUUAUUAUUAU	969	642-664
AD-1465920.2	GCCUCACACACAUUAUUAUUAUUAUUAUUAU	11	645-665	AGUAAUAGAUUGTGUGAGGCAUUAUUAUUAUUAU	12	643-665
AD-1465921.2	CCUCACACACAUUAUUAUUAUUAUUAUUAUUAU	714	646-666	AAGUAAATAGAUUGUGTGUGAGGCAUUAUUAUUAU	970	644-666
AD-1465922.3	CUCACACACAUUAUUAUUAUUAUUAUUAUUAU	13	647-667	AGAGTAAUAGATGUGTGUGAGGCAUUAUUAUUAUUAU	14	645-667
AD-1465922.4	CUCACACACAUUAUUAUUAUUAUUAUUAUUAU	13	647-667	AGAGTAAUAGATGUGTGUGAGGCAUUAUUAUUAUUAU	14	645-667

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1465927.2	GACGUUUUGACAAGCAAAUUCGU	719	760-780	ACGATUTGCUUUGUCAAACGUCUU	975	758-780
AD-1465932.3	AAUGUACACAGUCAAUUGGAUU	724	835-855	AAUCCATUGACTGUGUACAUAUAG	980	833-855
AD-1465932.4	AAUGUACACAGUCAAUUGGAUU	724	835-855	AAUCCATUGACTGUGUACAUAUAG	980	833-855
AD-1465953.3	GCAGGCUUACAUAUGACAUAUU	745	1105-1125	AUAATGTCAAUGUAAGCCUGCAU	1001	1103-1125
AD-1465954.3	CAGGCUUACAUAUGACAUAUU	71	1106-1126	AUUAAGUGCAAUUGAAGCCUGCA	202	1104-1126
AD-1465960.3	UACAUAUGACAUAUAAAACUGU	751	1112-1132	ACAGTUTUUAATGUCAAUGUAAG	1007	1110-1132
AD-1465968.3	CACCUGUAAUACCGAGCGAAUU	759	1236-1256	AAUUCGUGGUAUUACAGGUGCA	1015	1234-1256
AD-1465968.4	CACCUGUAAUACCGAGCGAAUU	759	1236-1256	AAUUCGUGGUAUUACAGGUGCA	1015	1234-1256
AD-1465969.2	UGUAAUACCGAGCGAAUAUUGGU	760	1240-1260	ACCATATUCGCTGGUAUUACAGG	1016	1238-1260
AD-1465970.2	GUAAUACCGAGCGAAUAUUGGAU	761	1241-1261	ATCCAUAUUCGUGGUAUUACAG	1017	1239-1261
AD-1466053.3	UCGGAAUUCUUGGUCCUAUUU	113	5067-5087	AAUAGGACCAAGAAUUCGAGGA	244	5065-5087
AD-1466070.2	GAGAGAAUUUGUCUUACUAUU	46	5443-5463	AAUAGUAAAGACAAAUAUUCUCAU	177	5441-5463
AD-1466083.3	AAAGAGAGCGUGGUACUAUGU	871	5479-5499	ACAUAGTACCAAGCUCUUCUUUUC	1127	5477-5499
AD-1466100.4	AUGCAAACGCCAUUUCUUUAUU	888	5831-5851	AAUAAAGAAUUGGCGUUUGCAUCC	1144	5829-5851
AD-1466100.5	AUGCAAACGCCAUUUCUUUAUU	888	5831-5851	AAUAAAGAAUUGGCGUUUGCAUCC	1144	5829-5851
AD-1466101.2	GCAAACGCCAUUUCUUUAUCAU	889	5833-5853	ATGATAAGAAAATGGCGUUUUGCAU	1145	5831-5853
AD-1466104.3	UAAGCACUGGUAUCAUAUCUU	892	5883-5903	AAGATATGAUACCAAGUGGCUUAGU	1148	5881-5903
AD-1466104.4	UAAGCACUGGUAUCAUAUCUU	892	5883-5903	AAGATATGAUACCAAGUGGCUUAGU	1148	5881-5903
AD-1466114.4	CUGCUAUACCCACAGAGUUCUU	19	6106-6126	AAGAACTCUGUGGUAUAGCAGGA	20	6104-6126
AD-1466115.2	UAUACCCACAGAGUUCUAUUGUU	901	6110-6130	AACATAGAACUCUGUGGUAUAGC	1157	6108-6130
AD-1466116.2	UACCACAGAGUUCUAUUGUAU	902	6112-6132	ACUACATAGAACUCUGUGGUAUA	1158	6110-6132
AD-1466118.3	CACAGAGUUCUAUUGUAGCUUU	904	6115-6135	AAAGCUACAUAAGAACUCUGUGGU	1160	6113-6135
AD-1466119.3	AGAGUUCUAUUGUAGCUUAUCAU	905	6118-6138	AUGUAAGCUACAUAAGAACUCUGU	1161	6116-6138
AD-1466120.2	AGUUCUAUUGUAGCUUAACAGUU	906	6120-6140	AACUGUAAGCUACAUAAGAACUCU	1162	6118-6140
AD-1466121.3	UCUAUGUAGCUUAACAGUUCUU	907	6123-6143	AGGAACTGUAAGCUACAUAAGAAC	1163	6121-6143
AD-1466128.3	CUAUUUGGCUAGAUUAUUAUU	914	6249-6269	AAAUUAUUCUAGCCACAAUAGGU	1170	6247-6269

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1466128.4	CUAUUUGGGCUAGAUUAUUAUU	914	6249-6269	AAUUAUAUCUAGCCACAAUAGGU	1170	6247-6269
AD-1466139.3	UCCAUUGGUGGACAAAGAUUUUU	924	6659-6679	AAAAUUCUUUGUCCACCAUGGAGG	1180	6657-6679
AD-1466151.3	AAGAUUUUUUGAAGGAAAUACU	936	6671-6691	AGUATUTCCUUUACAAAACUUGU	1192	6669-6691
AD-1466152.3	AGAUUUUUUGAAGGAAAUACUU	937	6672-6692	AAGUAUTUCCUTCAAAAAUUCUUG	1193	6670-6692
AD-1615169.1	CCACAAACUCUAGUUUGAAUU	60	291-311	AAUCAAACUUUGAGUUUGUGGGC	191	289-311
AD-1615170.1	AUCUUUCUGUAACUUCUUUUU	61	309-329	AAAAGGAAUUAACAGAAAAGAUUC	192	307-329
AD-1615171.1	AGUAUGAACCACUUAUUUUAAGU	15	348-368	ACUUAAAAUAUGGUUUAUACUCU	16	346-368
AD-1615172.1	CUACCAUUUCAGGACUUCUUU	62	384-404	AAAGAAUCCUGAAAUGGUAGAU	193	382-404
AD-1615173.1	CAUGCCUCACACACACUUAUU	1990	642-662	AAUAGATGUGUGUGAGGCAUGGA	2464	640-662
AD-1615174.1	UCACACACACUUAUUACUCCU	66	648-668	AGGAGUAAUAGAUGUGUGAGG	197	646-668
AD-1615175.1	CAUCUAUUACUCCCAUGAAAU	1991	655-675	ATUUCATGGGAGUAAUAGAUGUG	2465	653-675
AD-1615176.1	UCUGAUCGAGGAUUUUAACUU	67	676-696	AAGUTGAAAUCCUCGACUACAGAUU	2466	674-696
AD-1615177.1	GGGACACAGAAGACGUUUUGAU	1992	749-769	ATCAAACGUCUTCUGUGUCCAC	2467	747-769
AD-1615178.1	GGACACAGAAGACGUUUUGACU	1993	750-770	AGUCAAACGUCTUCUGUGUCCCA	2468	748-770
AD-1615179.1	GACACAGAAGACGUUUUGACAU	1994	751-771	ATGUCAAACGUCUUCUGUGUCCC	2469	749-771
AD-1615180.1	GAAAGCGUUUGACAAAGCAAU	717	757-777	ATUUGCTUGUCAAACGUCUUCUG	2470	755-777
AD-1615181.1	ACGUUUUGACAAAGCAAUUCGUU	1995	761-781	AACGAUTUGCUTGUCAAAACGUCU	2471	759-781
AD-1615182.1	CGUUUGACAAGCAAUUCGUGU	1996	762-782	ACACGATUUGCTUGUCAAACGUC	2472	760-782
AD-1615183.1	GUUUUGACAAGCAAUUCGUGCU	1997	763-783	AGCAGAUUUUGCUUGUCAAAACG	2064	761-783
AD-1615184.1	UUUGACAAGCAAUUCGUGCUU	1998	764-784	AAGCAGAUUUUGCUUGUCAAAACG	2065	762-784
AD-1615185.1	CCUAAUGUACACAGUCAAAUGU	1999	832-852	ACAUTGACUGUGUACAUAAGGGA	2473	830-852
AD-1615186.1	CUAAUGUACACAGUCAAAUGGU	2000	833-853	ACCATUGACUGTGUACAUAAGGG	2474	831-853
AD-1615187.1	UAAUGUACACAGUCAAAUGGAU	2001	834-854	ATCCAUTGACUGUGUACAUAAGG	2475	832-854
AD-1615188.1	AUUUUAUCCAUUCAUUUUAU	70	940-960	ATGAAATGAAUGGAGAAUAAUUC	2476	938-960
AD-1615189.1	AAAGUGGAUCAUAUCUUCUCU	31	1057-1077	AGAGAAGAUAUGAUCCACUUC	162	1055-1077
AD-1615190.1	CCAGGAAUCUUAAAGAAAAUUAU	72	1143-1163	ATAUTUTCUUAAAGAUUCCUGGUU	2477	1141-1163

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1615191.1	GGACUAUGCACCUGUAAUACU	2002	1228-1248	AGUATUACAGGTGCAUAGUCCCA	2478	1226-1248
AD-1615192.1	GACUAUGCACCUGUAAUACCU	2003	1229-1249	AGGUAUTACAGGUGCAUAGUCCC	2479	1227-1249
AD-1615193.1	ACUAUGCACCUGUAAUACCAU	2004	1230-1250	ATGGTATUACAGGUGCAUAGUCC	2480	1228-1250
AD-1615194.1	CUAUGCACCUGUAAUACCAU	2005	1231-1251	ACUGGUUUACAGGUGCAUAGUC	2073	1229-1251
AD-1615195.1	GCACCCUGUAAUACCGCGAAU	2006	1235-1255	ATUCGCTGUATUACAGGUGCAU	2481	1233-1255
AD-1615196.1	ACCUGUAAUACCGCGAAUUAU	2007	1237-1257	ATAUTCGCUGGTAAUACAGGUGC	2482	1235-1257
AD-1615197.1	CCUGUAAUACCGCGAAUUAU	2008	1238-1258	AAUATUCGUGGUAAUACAGGUG	2483	1236-1258
AD-1615198.1	CUGUAAUACCGCGAAUUAUGU	2009	1239-1259	ACAUAUTCGCUGGUAAUACAGGU	2484	1237-1259
AD-1615199.1	UAAUACCGCGAAUUAUGGACU	2010	1242-1262	AGUCCATAUUCGUGGUAAUUAACA	2485	1240-1262
AD-1615200.1	UCAGCAUUUGGAUAAUUCUU	73	1276-1296	AAGAAATUAUCCAAUUGCUGAGA	2486	1274-1296
AD-1615201.1	ACACUCAAAUUCGUGUUCAAU	76	1433-1453	ATUGAACACGATUUUGAGUGUGU	2487	1431-1453
AD-1615202.1	UAAUGGGAACAUCUUAAGAGUU	33	1594-1614	AACUCUAAAGAUGUCCACUUAUA	164	1592-1614
AD-1615203.1	UAACAAGACCAUACUACAGUU	78	1647-1667	AACUGUAGUAUGGUCUUGUUAAG	209	1645-1667
AD-1615204.1	CAUUCAUUAUGGAAAGAGGU	81	2034-2054	ACCUCUTUCCATAGAUGAAUGAG	2488	2032-2054
AD-1615205.1	UUGGAACUUGGAUGUUAACUU	36	2118-2138	AAGUTAAACAUCCAAAGUCCACA	2489	2116-2138
AD-1615206.1	UAAUUCCAUUGAAUUCUAGUU	82	2133-2153	AACUAGAAUUAUGGAAGUUAAC	213	2131-2153
AD-1615207.1	CCGAAACUCAUCAUUGAAUUCU	84	2362-2382	AGAUTCAAUGATGAGUUUCGGAA	2490	2360-2382
AD-1615208.1	UCAAAACACAGAUAAUUAUUGUU	38	2444-2464	AACAAUTAUUUCUGUGUUUGAAG	2491	2442-2464
AD-1615209.1	GUUGGUUCAAUUAUUAUUCUUCU	86	2462-2482	AGAAGAAUAAUTUGAACCAACA	2492	2460-2482
AD-1615210.1	ACUCAGUUCUCAAUUCUUCUU	88	2595-2615	AGGAAGAAUUGAGAACUGAGUUC	219	2593-2615
AD-1615211.1	UACGUCUACUUUCACUUGGUU	89	2685-2705	AACCAAGUGAAAGUAGACGUUUC	220	2683-2705
AD-1615212.1	AAGUAAUCUCAUCUAAAGAUUUU	39	2953-2973	AAAATCTUAGATGAGUUACUUUG	2493	2951-2973
AD-1615213.1	CUAGAGUUAGACAUAAAUUCUU	93	3150-3170	AAGATUTAUUGUCUAAACUCUAGGA	2494	3148-3170
AD-1615214.1	UUUCUCAUUAAGACACGAAAU	95	3218-3238	ATUUCGTGUCUTAAUGAGAAACU	2495	3216-3238
AD-1615215.1	UGAAGCCUACAACACAUUUUUU	96	3304-3324	AAAAAUGUGUUGUAGGCUUCACU	227	3302-3324
AD-1615216.1	AAUCCAAUGAAACAUCUCUUU	97	3360-3380	AAAGAGAUUGUUTCAUUGGAUUUA	2496	3358-3380

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1615217.1	UCAAUUGCACUCUACUUCAGU	100	3553-3573	ACUGAAGUAGAGUGCAUUUGAUC	231	3551-3573
AD-1615218.1	UACUCUCAUAGUACUUUUUCU	43	4633-4653	AGAAAAGUAUCAUUGAGAGUAGG	174	4631-4653
AD-1615219.1	CUAUCAAAGGAAUUUAAUCCU	109	4652-4672	AGGATUAAAUUCCUUUGAUAGAA	2497	4650-4672
AD-1615220.1	ACUAUGCUGAAAUUGAUUAUU	111	4755-4775	AAUAAUCAAUUTCAGCAUAGUCA	2498	4753-4775
AD-1615221.1	AAACAGAAGAAAUUAUACAU	44	4876-4896	ATGUAATAAUUUCUUCUGUUUCC	2499	4874-4896
AD-1615222.1	AGCACUUUUACCAACGUGAU	45	5021-5041	ATCACGTUUGGTAAAAGUGCUGU	2500	5019-5041
AD-1615223.1	UUUAUCCAAAGUUCGUUUUAAA	114	5109-5129	ATUUA AAAACGAACUUGGAUAACA	2501	5107-5129
AD-1615224.1	AUGCUGUUCAGCCAAAUAAGCU	115	5238-5258	AGCUAUTUGGCTGAACAGCAUUA	2502	5236-5258
AD-1615225.1	UAGCAGUUUAUACCUACGUUU	116	5254-5274	AAUACGTAGUAUAACUGCUAUU	2503	5252-5274
AD-1615226.1	GACAUUUCACGUGGUUCACUUU	47	5657-5677	AAAGTGAACCAACGUGAAUGUCUU	2504	5655-5677
AD-1615227.1	CUGGUUUCAUUUAAAACUCUUU	117	5742-5762	AAAGAGTUUUAAAUGAACCAAGGC	2505	5740-5762
AD-1615228.1	GAGCAGGGAUGCAAACGCCAU	2011	5823-5843	ATGGCGTUUGCAUCCUGCUCUC	2506	5821-5843
AD-1615229.1	AGCAGGGAUGCAAACGCCAU	2012	5824-5844	AAUGCGUUUGCAUCCUGCUCUC	2082	5822-5844
AD-1615230.1	AGGGAUGCAAACGCCAUUUUCU	2013	5827-5847	AGAAAUGGCGTUGCAUCCUGC	2507	5825-5847
AD-1615231.1	GGGAUGCAAACGCCAUUUUCU	2014	5828-5848	AAGAAATGGCGTUUGCAUCCUG	2508	5826-5848
AD-1615232.1	GGAUGCCAAACGCCAUUUUCUU	2015	5829-5849	AAAGAAUUGGCGUUUGCAUCCU	2085	5827-5849
AD-1615233.1	GAUGCAAACGCCAUUUUCUUU	2016	5830-5850	ATAAGAAUUGGCGUUUGCAUCCC	2509	5828-5850
AD-1615234.1	UGCAAACGCCAUUUUCUUUAUCU	17	5832-5852	AGAUAGAAUUGGCGUUUGCAUC	18	5830-5852
AD-1615235.1	CAAACGCCAUUUUCUUUAUCAU	2017	5834-5854	AAUGAUAGAAUUGGCGUUUGCA	2088	5832-5854
AD-1615236.1	AAACGCCAUUUUCUUUAUCAUGU	2018	5835-5855	ACAUGATAAGAAUUGGCGUUUGC	2510	5833-5855
AD-1615237.1	AACGCCAUUUUCUUUAUCAUGGU	2019	5836-5856	ACCATGAUAGAAUUGGCGUUUG	2511	5834-5856
AD-1615238.1	ACGCCAUUUUCUUUAUCAUGGAU	2020	5837-5857	ATCCAUGAUAGAAUUGGCGUUU	2512	5835-5857
AD-1615239.1	CGCCAUUUUCUUUAUCAUGGACU	2021	5838-5858	AGUCCATGAUAGAAUUGGCGUU	2513	5836-5858
AD-1615240.1	AUGGGACUAAGCACUGGUUAUU	2022	5876-5896	AAUACCAUGGCTUAGUCCCAUUG	2514	5874-5896
AD-1615241.1	UGGGACUAAGCACUGGUUAUCU	2023	5877-5897	AGAUACCAUGGCUUAGUCCCAU	2094	5875-5897
AD-1615242.1	GGGACUAAGCACUGGUUAUCAU	2024	5878-5898	ATGATACCAUGGCUUAGUCCCAU	2515	5876-5898

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1615243.1	GGACUAAAGCACUGGUUAUCAUU	2025	5879-5899	AAUGAUACCAGTGCUUAGUCCCA	2516	5877-5899
AD-1615244.1	CUAAGCACUGGUUAUCAUAUCU	2026	5882-5902	AGAUUAUGAUACCAGUGCUUAGUC	2097	5880-5902
AD-1615245.1	AAGCACUGGUUAUCAUAUCUGU	2027	5884-5904	ACAGAUUAUGAUACCAGUGCUUAG	2099	5882-5904
AD-1615246.1	AGCACUGGUUAUCAUAUCUGAU	2028	5885-5905	ATCAGATAUGATACACAGUGCUUA	2517	5883-5905
AD-1615247.1	GCACUGGUUAUCAUAUCUGAUU	2029	5886-5906	AAUCAGAUUAUGAUACCAGUGCUU	2101	5884-5906
AD-1615248.1	CACUGGUUAUCAUAUCUGAUUU	2030	5887-5907	AAUCAGAUUAUGAUACCAGUGCU	2102	5885-5907
AD-1615249.1	UGGUUAUCAUAUCUGAUUACAU	2031	5890-5910	AGUGAATCAGATAUGAUACCAGU	2518	5888-5910
AD-1615250.1	UCAGAGUUUUCUGGGUUACUGU	119	5921-5941	ACAGTAACCCAGAAACUCUGAAG	2519	5919-5941
AD-1615251.1	AGAAUUUGCCUCUAAACCUUU	120	6010-6030	AAAGGUTUAGAGGGCAAUUUCUGC	2520	6008-6030
AD-1615252.1	CUGAAGUCCUGCUAUACCAU	2032	6098-6118	AGUGGUUAUAGCAGGACUUCAGGU	2104	6096-6118
AD-1615253.1	CUGCUAUACCACAGAGUUCUU	19	6106-6126	AAGAACTCUGUGGUUAUAGCAGGA	20	6104-6126
AD-1615253.2	CUGCUAUACCACAGAGUUCUU	19	6106-6126	AAGAACTCUGUGGUUAUAGCAGGA	20	6104-6126
AD-1615254.1	UGCUAUACCACAGAGUUCUAU	2033	6107-6127	ATAGAACUCUGTGGUUAUAGCAGG	2521	6105-6127
AD-1615255.1	GCUAUACCACAGAGUUCUAUU	2034	6108-6128	AAUAGAACUCUGUGGUUAUAGCAG	2107	6106-6128
AD-1615256.1	CUAUACCACAGAGUUCUAUGU	2035	6109-6129	ACAUAGAACUCTGUGGUUAUAGCA	2522	6107-6129
AD-1615257.1	AUACCACAGAGUUCUAUGUAU	2036	6111-6131	ATACAUAGAACTCUGUGGUUAUAG	2523	6109-6131
AD-1615258.1	ACCACAGAGUUCUAUGUAGCU	2037	6113-6133	AGCUACAUAGAACUCUCUGUGUAU	2112	6111-6133
AD-1615259.1	CCACAGAGUUCUAUGUAGCUU	903	6114-6134	AAGCTACAUAGAACUCUCUGUGUA	1159	6112-6134
AD-1615260.1	AGAGUUCUAUGUAGCUUACAU	905	6118-6138	ATGUAAGCUACAUAGAACUCUGU	2524	6116-6138
AD-1615260.2	AGAGUUCUAUGUAGCUUACAU	905	6118-6138	ATGUAAGCUACAUAGAACUCUGU	2524	6116-6138
AD-1615261.1	GAGUUCUAUGUAGCUUACAGU	2038	6119-6139	ACUGTAAGCUACAUAGAACUCUG	2525	6117-6139
AD-1615262.1	UCUAUGUAGCUUACAGUUCU	907	6123-6143	AGGAACTGUAAGCUACAUAGAAC	1163	6121-6143
AD-1615262.2	UCUAUGUAGCUUACAGUUCU	907	6123-6143	AGGAACTGUAAGCUACAUAGAAC	1163	6121-6143
AD-1615263.1	CUAUGUAGCUUACAGUUCU	2039	6124-6144	ATGGAACUGUAAGCUACAUAGAA	2526	6122-6144
AD-1615264.1	UAUGUAGCUUACAGUUCU	2040	6125-6145	ATUGGAACUGUAAGCUACAUAGA	2527	6123-6145
AD-1615265.1	UAGCUUACAGUUCUCCAACCAU	2041	6129-6149	ACUGGUTGGAACUGUAAGCUACA	2528	6127-6149

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1615266.1	GAAUGUGAUGAUUUUAAUGU	122	6184-6204	ACAUTAAAAUACAUCACAUUCCU	2529	6182-6204
AD-1615267.1	ACCUAUUUGUGGCUAGAUAAU	2042	6247-6267	ATAUAUCUAGCCACAAUAGGUGG	2530	6245-6267
AD-1615268.1	CCUAUUUGUGGCUAGAUAAU	2043	6248-6268	AAUATATCUAGCCACAAUAGGUG	2531	6246-6268
AD-1615269.1	UAUUUGUGGCUAGAUAAUAAU	2044	6250-6270	ATAATATAUCUAGCCACAAUAGG	2532	6248-6270
AD-1615270.1	AUUUGUGGCUAGAUAAUAAU	2045	6251-6271	ACUAAUAUAUCTAGCCACAAUAG	2533	6249-6271
AD-1615271.1	UUUGUGGCUAGAUAAUAAUAGGU	2046	6252-6272	ACCUAATAUAUCUAGCCACAAUA	2534	6250-6272
AD-1615272.1	UGUGGCUAGAUAAUAAUAGGAU	2047	6253-6273	ATCCTAAUAUATCUAGCCACAAU	2535	6251-6273
AD-1615273.1	GUGGCUAGAUAAUAAUAGGAU	2048	6254-6274	AAUCCUAAUAUAUCUAGCCACAA	2125	6252-6274
AD-1615274.1	GGCUAGAUAAUAAUAGGAUCUU	915	6256-6276	AAGATCCUAAUAUAUCUAGCCAC	1171	6254-6276
AD-1615275.1	GCUAGAUAAUAAUAGGAUCUCU	2049	6257-6277	AGAGAUCCUAATAUAUCUAGCCA	2536	6255-6277
AD-1615276.1	CCUCUGAAUAAUAAUAGGAU	126	6579-6599	ACUUTACAUACAUUUCAGAGGAC	2537	6577-6599
AD-1615277.1	CUGUGUAAUAAUAAUAGGAU	48	6896-6916	AACUGUTAAACATUUAACACAGCG	2538	6894-6916
AD-1615278.1	ACAGUUUCCACUAAUUCUCU	21	6911-6931	AGAGAAUAAGUGGAAAAACUGUUA	22	6909-6931
AD-1615279.1	AUGCAAACGCCAUUUCUUAU	888	5831-5851	AAUAAAGAAUUGGCGUUUGCAUCC	1144	5829-5851
AD-1615280.1	AUGCAAACGCCAUUUCUUAUA	2388	5831-5851	UAUAAAGAAUUGGCGUUUGCAUCC	2539	5829-5851
AD-1615281.1	AUGCAAACGCCAUUUCUUAUA	2388	5831-5851	UAUAAAGAAUUGGCGUUUGCAUCC	2539	5829-5851
AD-1615282.1	AUGCAAACGCCAUUUCUUAUA	2388	5831-5851	UAUAAAGAAUUGGCGUUUGCAUCC	2540	5829-5851
AD-1615283.1	AUGCAAACGCCAUUUCUUAUA	2389	5831-5851	UAUAAAGAAUUGGCGUUUGCAUCC	2541	5829-5851
AD-1615284.1	AUGCAUACGCCAUUUCUUAUA	2390	5831-5851	UAUAAAGAAUUGGCGUUUGCAUCC	2542	5829-5851
AD-1615285.1	AUGCUAACGCCAUUUCUUAUA	2391	5831-5851	UAUAAAGAAUUGGCGUUUGCAUCC	2543	5829-5851
AD-1615286.1	GCAAACGCCAUUUCUUAUA	2392	5833-5851	UAUAAAGAAUUGGCGUUUGCGU	2544	5831-5851
AD-1615287.1	AUGCAAACGCCAUUUCUUAU	888	5831-5851	AAUAAAGAAUUGGCGUUUGCAUCC	1144	5829-5851
AD-1615288.1	AUGCAAACGCCAUUUCUUAU	888	5831-5851	AAUAAAGAAUUGGCGUUUGCAUCC	1144	5829-5851
AD-1615289.1	GCAAACGCCAUUUCUUAU	2393	5833-5851	AAUAAAGAAUUGGCGUUUGCGU	2545	5831-5851
AD-1615290.1	GCAAACGCCAUUUCUUAU	2393	5833-5851	AAUAAAGAAUUGGCGUUUGCGU	2545	5831-5851
AD-1615291.1	AUGCAAUCGCCAUUUCUUAU	2394	5831-5851	AAUAAAGAAUUGGCGUUUGCAUCC	2546	5829-5851

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1615292.1	AUGCAAUCGCCAUUUCUUAUU	2394	5831-5851	AAUAAAGAAUUGCGAUUGCAUCC	2546	5829-5851
AD-1615293.1	AUGCAUACGCCAUUUCUUAUU	2395	5831-5851	AAUAAAGAAUUGCGAUUGCAUCC	2547	5829-5851
AD-1615294.1	AUGCAUACGCCAUUUCUUAUU	2395	5831-5851	AAUAAAGAAUUGCGAUUGCAUCC	2547	5829-5851
AD-1615295.1	AUGCUAACGCCAUUUCUUAUU	2396	5831-5851	AAUAAAGAAUUGCGUUAAGCAUCC	2548	5829-5851
AD-1615296.1	AUGCUAACGCCAUUUCUUAUU	2396	5831-5851	AAUAAAGAAUUGCGUUAAGCAUCC	2548	5829-5851
AD-1615297.1	AUGCAAACGCCAUUUCUUAUA	2388	5831-5851	UAUAAAGAAUUGCGUUAAGCAUCC	2539	5829-5851
AD-1615298.1	GCAAACGCCAUUUCUUAUA	2392	5833-5851	UAUAAAGAAUUGCGUUAAGCGU	2549	5831-5851
AD-1615299.1	AUGCAUACGCCAUUUCUUAUA	2390	5831-5851	UAUAAAGAAUUGCGUUAAGCAUCC	2550	5829-5851
AD-1615300.1	AUGCCUCACACACAUUUUAUU	2397	643-663	AAAUAAAUGUGTGUGAGGCAUGG	2551	641-663
AD-1615301.1	CUCACACACAUUAUUUCU	2398	647-667	AGAATAAUAGATGUGUGAGGCG	2552	645-667
AD-1615302.1	CUCACACACAUUAUUUCU	2399	647-667	AGAGAAUAGATGUGUGAGGCG	2553	645-667
AD-1615303.1	AAUGUACACAGUCAUUGGAUU	2400	835-855	AAUCCAAUGACTGUGUACAUAUAG	2554	833-855
AD-1615304.1	GCAGGCUUACAUUGACAUAU	745	1105-1125	ATAATGTCAAUGUAAAGCCUGCAU	2555	1103-1125
AD-1615305.1	GCAGGCUUACAUUGAUUAUU	2401	1105-1125	ATAATATCAAUGUAAAGCCUGCAU	2556	1103-1125
AD-1615306.1	GCAGGCUUACAUUGUCAUAU	2402	1105-1125	ATAATGACAAUGUAAAGCCUGCAU	2557	1103-1125
AD-1615307.1	CAGGCUUACAUUGACAUAUAU	71	1106-1126	AUUAAUGUCAAUUGUAAAGCCUGCA	202	1104-1126
AD-1615308.1	CAGGCUUACAUUGACUUAUAU	2403	1106-1126	AUUAAAGUCAAUUGUAAAGCCUGCA	2558	1104-1126
AD-1615309.1	CAGGCUUACAUUGAUUAUAUAU	23	1106-1126	AUUAAUACAAUUGUAAAGCCUGCA	2559	1104-1126
AD-1615310.1	CAGGCUUACAUUGACAUAUAU	71	1106-1126	AUUAAUGUCAAUUGUAAAGCCUGCG	2560	1104-1126
AD-1615311.1	CAGGCUUACAUUGACUUAUAU	2403	1106-1126	AUUAAAGUCAAUUGUAAAGCCUGCG	2561	1104-1126
AD-1615312.1	CAGGCUUACAUUGAUUAUAUAU	23	1106-1126	AUUAAUACAAUUGUAAAGCCUGCG	24	1104-1126
AD-1615313.1	UACAUUGACAUAUAAUACUGU	2404	1112-1132	ACAGTATUUAAATGUCAAUGUAAG	2562	1110-1132
AD-1615314.1	UACAUUGACAUAUAAUAAACUGU	2405	1112-1132	ACAGTUAUUAAATGUCAAUGUAAG	2563	1110-1132
AD-1615315.1	CACCUGUAAUACCAUGGAAUU	2406	1236-1256	AAUUCACUGGUAAUUAACAGGUGCA	2564	1234-1256
AD-1615316.1	CACCUGUAAUACCAUCGAAUU	2407	1236-1256	AAUUCGAUGGUAAUUAACAGGUGCA	2565	1234-1256
AD-1615317.1	CACCUGUAAUACCAUGGAAUU	2406	1236-1256	AAUUCACUGGUAAUUAACAGGUGCG	2566	1234-1256

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-1615318.1	CACCUGUAAUACCAUCGAAUU	2407	1236-1256	AAUUCGAUGGUUUACAGGUGCG	2567	1234-1256
AD-1615319.1	UCGGAAUUCUUGGUCCUAUUU	113	5067-5087	AAAUAGGACCAAGAAUUCGAGAG	244	5065-5087
AD-1615320.1	UCGGAAUUCUUGGUUUUAUUU	2408	5067-5087	AAAUAGACCAAGAAUUCGAGAG	2568	5065-5087
AD-1615321.1	UCGGAAUUCUUGGUUUUAUUU	2409	5067-5087	AAAUAGAACCAAGAAUUCGAGAG	2569	5065-5087
AD-1615322.1	UCGGAAUUCUUGGUUUUAUUU	113	5067-5087	AAAUAGGACCAAGAAUUCGAGAG	2570	5065-5087
AD-1615323.1	UCGGAAUUCUUGGUUUUAUUU	2408	5067-5087	AAAUAGACCAAGAAUUCGAGAG	2571	5065-5087
AD-1615324.1	UCGGAAUUCUUGGUUUUAUUU	2409	5067-5087	AAAUAGAACCAAGAAUUCGAGAG	2572	5065-5087
AD-1615325.1	AAAGAAGAGCUGGUUUUAUGU	2410	5479-5499	ACAUAAATACCAAGCUCUUCUUUC	2573	5477-5499
AD-1615326.1	AAAGAAGAGCUGGUUUUAUGU	2411	5479-5499	ACAUAGAACCAAGCUCUUCUUUC	2574	5477-5499
AD-1615327.1	UAAAGCACUGGUUUCUUAUCUU	2412	5883-5903	AAGATAAGAUACCAAGUGCUUAGU	2575	5881-5903
AD-1615328.1	CUGCUAUACCAACAGAUUUCUU	2413	6106-6126	AAGAAATCUGUGGUUAUAGCAGGA	2576	6104-6126
AD-1615329.1	CUGCUAUACCAACAGUGUUCUU	2414	6106-6126	AAGAACACUGUGGUUAUAGCAGGA	2577	6104-6126
AD-1615330.1	CUGCUAUACCAACAGAGUUCUU	19	6106-6126	AAGAACTCUGUGGUUAUAGCAGGG	2578	6104-6126
AD-1615331.1	CUGCUAUACCAACAGAUUUCUU	2413	6106-6126	AAGAAATCUGUGGUUAUAGCAGGG	2579	6104-6126
AD-1615332.1	CUGCUAUACCAACAGUGUUCUU	2414	6106-6126	AAGAACACUGUGGUUAUAGCAGGG	2580	6104-6126
AD-1615333.1	AGAGUUCUAUGUAGUUUACAU	2415	6118-6138	ATGUAAAACUACAUAGAACUCUGU	2581	6116-6138
AD-1615334.1	UCUAUGUAGCUUACAUUUCUU	2416	6123-6143	AGGAAATGUAAGCUACAUAGAAC	2582	6121-6143
AD-1615335.1	UCUAUGUAGCUUACUGUUCUU	2417	6123-6143	AGGAAACAGUAAGCUACAUAGAAC	2583	6121-6143
AD-1615336.1	CUAUUGUGGCUAGAUUUUAUUU	2418	6249-6269	AAAUAAAUCUAGCCACAAUAGGU	2584	6247-6269
AD-1615337.1	UCCAUGGUGGACAGUUUUUUU	2419	6659-6679	AAAAAACUUUGUCCACCAUGGAGG	2585	6657-6679
AD-1615338.1	UCCAUGGUGGACAAUUAUUUUU	2420	6659-6679	AAAAAUUUUGUCCACCAUGGAGG	2586	6657-6679
AD-1615339.1	AAGAUUUUUUGAAGGAAUACU	936	6671-6691	AGUATUTCCUUUCAAUUAUCUUGU	1192	6669-6691
AD-1615340.1	AAGAUUUUUUGAAGGAUUAUCU	2421	6671-6691	AGUATATCCUUUCAAUUAUCUUGU	2587	6669-6691
AD-1615341.1	AAGAUUUUUUGAAGGAUUAUCU	2422	6671-6691	AGUATUACCUUCAAUUAUCUUGU	2588	6669-6691
AD-1615342.1	AGAUAUUUUUGAAGGAUUAUCU	2423	6672-6692	AAGUAATUCCUTCAAAAAUUCUUG	2589	6670-6692
AD-1615343.1	AGAUAUUUUUGAAGGAUUAUCU	2424	6672-6692	AAGUAUAUCCUTCAAAAAUUCUUG	2590	6670-6692

Duplex Name	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_000130.4
AD-109630.1	CAGGCUUACAUUGACAUUAAA	9	1106-1126	UUUAAUGUCAUUGAAAGCCUGCA	10	1104-1126

Table 11. Modified Sense and Antisense Strand Sequences of Coagulation Factor V dsRNA Agents

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO:	Antisense Strand Sequence 5' to 3'	SEQ ID NO:	mRNA target sequence 5' to 3'	SEQ ID NO:
AD-110532.1	ususaacuUfcCfAfUfgaauucuauguL96	2591	asCfsuagAfaUfUfcaugGfaAfguaaascsa	2792	UGUUAAACUUCCAUAGAAUUCUAGU	1830
AD-110931.1	asgsaacuCfaGfUfUfcauuaucuuL96	2592	asAfsagaUfuGfAfgaacUfgAfguuucusug	2793	CAAGAACUCAGUUCUCAAUUCUU	3000
AD-112393.1	uscsuacUfcUfCfAfaugaucuuuL96	2593	asAfsaguAfuCfAfuugaGfaGfuaggagsga	2794	UCUCCUACUCUCAAUAGAUACUUU	3001
AD-114469.2	ascsaguuUfuCfCfAfcuaauucuuL96	311	asGfsagaAfaUfAfguggAfaAfacugusasa	445	UAAACAGUUUCCACUAUUUCUCU	579
AD-1410823.1	csesucacAfcAfCfAfcuaauucuuL96	2132	asAfsuaAfuAfGfauuGfuGfugaggscsa	2210	UGCCUCACACACAUUAUUACUC	1751
AD-1411340.1	ascsaacUfcAfAfAfaucuguguuL96	2594	asGfsaacAfcGfAfuuuGfaGfuguguscu	2795	AGACACACUCAAAAUCGUGUUA	3002
AD-1411342.2	ascsacucAfaAfAfUfuguguucauL96	340	asUfsugaAfcAfCfcauuUfuGfagugugsu	474	ACACACUCAAAAUCGUGUUA	608
AD-1411797.1	gsusuaacUfuCfCfAfaugaucuuL96	2595	asUfsagaAfuUfCfauugAfaGfuaaacsasu	2796	AUGUUAAACUUCCAUAGAAUUCUAG	3003
AD-1411798.2	usasaauCfcAfUfGfaauucuauguL96	346	asAfsuaAfaUfUfcauGfAfaaguuasasc	480	GUUAAACUUCCAUAGAAUUCUAGUC	614
AD-1412539.2	ususuucAfuUfAfAfagacagaaauL96	359	asUfsuucGfuGfUfcauaAfuGfagaascsu	493	AGUUUCUCAUUAAGACACGAAA	627
AD-1413196.1	csusacucUfcAfAfUfgauucuuuuL96	2596	asAfsaaaGfuAfUfcauuGfaGfaguagsga	2797	UCCUACUCUCAAUAGAUACUUUUC	3004
AD-1414748.1	asascaguUfuUfCfCfcauauucuuL96	2597	asAfsagaAfuAfGfuggAfaAfcuguuasasa	2798	UUAAACAGUUUCCACUAUUUCUC	3005
AD-1452126.1	asusauguCfuUfUfCfaugaucuuuL96	2598	asCfsaagAfuCfAfuugaAfgAfcuausag	2799	GGCAGGAUCUCUCUCUUGAUUCUAGA	3006
AD-1452209.1	ascscaucAfaGfGfUfcauuauguL96	2599	asCfsuaaAfgUfGfaaccUfuGfauugugsu	2800	ACAUCAUAAAAAGUUUCACUUUAAA	3007
AD-1452212.1	asuscaagGfuUfCfAfcuaaagaaauL96	2600	asUfsuucUfaAfAfugaAfcCfuugaugsg	2801	UCAUAAAAAGUUCACUUUAAAAAU	3008
AD-1452985.1	gsusuuncUfaUfUfCfcauuaacuuL96	2601	asCfsuugGfaAfGfugaUfaGfaaacsasa	2802	UUUUCUCCAUUCAUUUUAACACGG	3009
AD-1453516.1	usgsuacAfuCfAfGfuaucuaaguL96	2602	asCfsuugUfaGfAfaucAfuGfugacagsg	2803	AUGAUCAGAGCAGUUAACACAGG	3010
AD-1453784.1	csasucauGfaAfCfAfcuaucuauguL96	2603	asCfsauuGfaUfAfuguuUfcafuugaugsu	2804	AACAUCAGAGCAGCUAUCAAUGG	3011
AD-1454175.1	gsascucaUfaUfGfAfgaauuaucuuL96	2604	asUfsagaAfaAfUfcauUfaUfaguguscu	2805	AAGACUCAUUAUGAGAUUUUUGAA	3012
AD-1454221.1	csuscggaAfaAfUfUfcauuaucuuL96	2605	asAfsagaUfcAfUfcauuUfuUfcauguscu	2806	UACACGGAUUAUGCAUUAUCGUU	3013
AD-1454350.1	uscsuaauCfGfGfcauuaucuuL96	2606	asAfsuugGfaAfAfuccuUfcauuaucuuL96	2807	AAUCUGAUCGAGGAUUUUAACUC	599

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.:	Antisense Strand Sequence 5' to 3'	SEQ ID NO.:	mRNA target sequence 5' to 3'	SEQ ID NO.:
AD-1454529.1	csasaaauCfcUfCfAfagaaacuuuL96	2607	asAfsaggUfuUfCfuaagGfgAfuuuugsag	2808	GAAAGAGGCAUGAGGACACCUUG	3014
AD-1454534.1	uscsucaAfgAfAfccmagaauL96	2608	asUfsuacUfaAfGfguuuUfuUfgaggasuu	2809	CUUCCCCAAGUAUAUUAAGUAAG	3015
AD-1454719.1	ascsccuuCfaAfCfAfgaaucauuL96	2609	asAfsugaUfaUfUfcuugUfgAfgaggusug	2810	GGUACCUUGAGGACAAACAAC	3016
AD-1454720.1	csccuucAfaCfAfGfaaucauuuL96	2610	asAfsaugAfuUfUfcuugUfuGfagggsuu	2811	AAUUCUCCACAGCAGAGCAUUC	3017
AD-1454911.1	asasaucAfaAfGfAfaucuuuuL96	2611	asAfsagaAfgUfAfuuuUfuGfgaauuugsa	2812	AUUGAUCUGGAAAAUACUUGUUU	3018
AD-1455310.1	asasagacUfaCfUfCfaucuuuL96	2612	asUfsgaaUfgAfUfugagUfaGfucuuuusc	2813	CACUUCACUGGGCACUCAUUCAU	3019
AD-1455313.1	asgsacuaCfuCfAfAfucauuuL96	2613	asAfsaugAfaUfGfaungAfgUfagucuuu	2814	CUUCACUGGGCACUCAUUCUUCU	3020
AD-1455314.1	gsasacuacUfcAfAfUfcauuuuL96	2614	asUfsaauGfaAfUfuaauGfaGfuagucuuu	2815	AUGACUAUGCUGAAAAUUGAUUAU	3021
AD-1455522.1	asascacuCfuCfCfAfacaauuuL96	2615	asAfsagaAfaUfGfuungAfgAfguuuusc	2816	GAUGCCAUUCUCCUUCUUCUCCUA	3022
AD-1455659.1	gsasugaaGfuCfAfAfcuacuuuL96	2616	asAfsaagUfaGfAfguugAfcUfcaucuuu	2817	AAGAUGAAGUCAACUCUUCUUC	3023
AD-1455664.1	asgsucaaaCfuCfUfAfcuuuacuuL96	2617	asAfsaguGfaAfAfguagAfgUfugacuuu	2818	GAAAGUCAUCUUCUUCUUCACCCUC	3024
AD-1455701.1	gsascauuAfgUfCfAfacaucuuuL96	2618	asAfsaagAfuGfUfuaagCfuAfaugucuu	2819	AAAAAAACAGCCAAAGCAUCUUC	3025
AD-1455771.1	csccuuccUfcAfGfAfcuuuaauuL96	2619	asAfsaguUfuUfAfAfgucUfgAfgaaggsga	2820	UCCUAGAGUUAGACAUAAAAUCUC	625
AD-1455780.1	uscsagacUfuUfAfAfAfcuuuuuL96	2620	asGfsuaaAfgAfGfauuuAfaGfucugagsg	2821	AGUUAGACAUAAAUUCUCUACAAG	3026
AD-1455807.1	gsasaungGfaUfCfAfacaauuuL96	2621	asAfsuaaUfuGfUfuaagUfcCfaucuuu	2822	GUCUUUCCCAUAUAACAAGAUU	3027
AD-1457108.1	asusuaggUfcAfUfUfcagaaacuuL96	2622	asGfsaguUfuCfUfuaauGfaCfcuaauusc	2823	GAAUCAGGUCAUUCCGAAACUCA	3028
AD-1457130.1	gsasagaaGfaGfUfAfaucuuuL96	2623	asGfsuaaGfaUfUfuaagUfcUfucuuu	2824	AAGAAAGAGAGUUCAUUCUUCU	567
AD-1457237.1	ususcgaacCfaCfAfGfaauuaauuL96	2624	asCfsaauUfaUfAfucugUfgUfucgaagsga	2825	UCUUCAAAACACAGAUUAUUAUUGU	3029
AD-1458307.1	asasgcaaAfuUfAfCfugcancuuL96	2625	asGfsaagAfuGfCfuaagAfuUfugcuuugsu	2826	ACAAGCAAUUCACAGCUUCUUCG	3030
AD-1458619.1	uscsaungUfuGfCfUfucuaaaauL96	2626	asGfsaauUfaUfGfaagCfaCfaugagasuu	2827	AUUCGUUGGUGCUUCUCAAUAAUCC	3031
AD-1458724.1	usasaucaGfaAfUfUfcccgaauuL96	2627	asCfsaauCfGfAfGfaauUfcUfgaauuasug	2828	CAUAAUCAGAAUUCUCAAUUAUGA	3032
AD-1459277.1	uscsugaaUfcUfAfGfucaguuuuL96	2628	asAfsuaaAfcUfGfuaaGfaUfucagagasg	2829	CUUCUGAAUUCUAGUCAGUCAUUG	640
AD-1459922.1	gsasacugAfaUfAfUfucuaaaacuuL96	2629	asGfsuugUfuUfGfaauUfuCfaguuuusa	2830	UAGAAUUGAACAUAUUCAAAAACCC	3033
AD-1465918.3	asusgcucaCfAfCfacaucuuuL96	1224	asdAsandAgdAugudTgUfgaggcausgsg	1484	CCAUGCCUCACACACAUCUAUUA	1748
AD-1465918.4	asusgcucaCfAfCfacaucuuuL96	1224	asdAsandAgdAugudTgUfgaggcausgsg	1484	CCAUGCCUCACACACAUCUAUUA	1748
AD-1465919.2	usgscuacAfCfAfaucuuuuL96	1225	asdTsaadTadGaugudGuGfugaggcausg	1485	CAUGCCUCACACACAUCUAUUAAC	1749

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.:	Antisense Strand Sequence 5' to 3'	SEQ ID NO.:	mRNA target sequence 5' to 3'	SEQ ID NO.:
AD-1465920.2	gscscucacaCfAfCfaucauauacuL96	1226	asdGsuadAudAgaugdTgUfugugaggsasu	1486	AUGCCUCACACACAUCUAUUACU	1750
AD-1465921.2	cscscacacAfCfAfucuauiacuL96	1227	asdAsgudAadTagaudGuGfugugaggsasa	1487	UGCCUCACACACAUCUAUUACUC	1751
AD-1465922.3	csuscacacaCfAfUfuauiacuL96	1228	asdGsaqdTadAuaqadTgUfugugaggsac	1488	GCCUCACACACAUCUAUUACUCC	1752
AD-1465922.4	csuscacacaCfAfUfuauiacuL96	1228	asdGsaqdTadAuaqadTgUfugugaggsac	1488	GCCUCACACACAUCUAUUACUCC	1752
AD-1465927.2	gsascgunuugAfCfAfagcaauacuL96	1233	asdCsgadTudTgcundGuCfaaacgucsuu	1493	AAGACGUUUGACAAAGCAAAUCGU	1757
AD-1465932.3	asasuguaCaCfAfGfuaauggauL96	1238	asdAsudCadTugadTgUfuguauiuasg	1498	CUAAUGUACACACAGUCAAUUGGAUA	1762
AD-1465932.4	asasuguaCaCfAfGfuaauggauL96	1238	asdAsudCadTugadTgUfuguauiuasg	1498	CUAAUGUACACACAGUCAAUUGGAUA	1762
AD-1465953.3	gscsagcUfuAfCfAfugacauiuuL96	1259	asUfsaadTg(Tgn)caanguAfafGfccugcsasu	1519	AUGCAGGCUUACAUAUGACAUAUA	1783
AD-1465954.3	csasggcuUfaCfAfUfugacauiuuL96	335	asUfsaadAu(G2p)ucaaugUfaAfccugcsa	1520	UGCAGGCUUACAUAUGACAUAUA	603
AD-1465960.3	usascuugaCfAfUfuaaaacugL96	1265	asdCsgadTudTmaadTgUfcaauguasag	1526	CUUACAUAUGACAUAUAAAAACUGC	1789
AD-1465968.3	csascuuguaAfUfAfccagcgauiL96	1273	asdAsundCgdCugudAuUfacagugscsa	1534	UGCACCUGUAUAUACCAGCGAAUA	1797
AD-1465968.4	csascuuguaAfUfAfccagcgauiL96	1273	asdAsundCgdCugudAuUfacagugscsa	1534	UGCACCUGUAUAUACCAGCGAAUA	1797
AD-1465969.2	usgsuauacCfAfGfcauauugL96	1274	asdCscadTadTucgdTgGfuauiuasg	1535	CCUGUAAUACCAGCGAAUAUUGGA	1798
AD-1465970.2	gsusauiacAfGfCfcauauugL96	1275	asdTscadAudAumgdCuGfuauiuasg	1536	CUGUAAUACCAGCGAAUAUUGGAC	1799
AD-1466053.3	uscsaggaaUfuCfUfuguccuauL96	377	asAfisadAg(G2p)accaagAfafUfuccaggsa	1618	UCUCGGAUUUCUUGGUCUUAUA	645
AD-1466070.2	gsasgagaauUfuGfucuauiuuL96	1373	asdAsuadGudAagadAaAfuucucsuu	1635	AUGAGAGAAUUUGUCUUAUAUAU	576
AD-1466083.3	asasagaagaGfCfUfuguauiuuL96	1386	asdCsauadAgdTaccadGcUfucuauiusuc	1648	GAAAAAGAAAGAGCUGGUAUAUA	1909
AD-1466100.4	asusgcaaacGfCfCfauiuuuauL96	1403	asdAsuadAgdAaagdTgGfuauiuasg	1665	GGAUGCAAAACGCCAUUUUCUUAUC	1926
AD-1466100.5	asusgcaaacGfCfCfauiuuuauL96	1403	asdAsuadAgdAaagdTgGfuauiuasg	1665	GGAUGCAAAACGCCAUUUUCUUAUC	1926
AD-1466101.2	gscaaacgcCfAfUfuauiuuL96	1404	asdTsgadTadAgaadTgGfuauiuasg	1666	AUGCAAAACGCCAUUUUCUUAUAUA	1927
AD-1466104.3	usasagcacuGfGfUfuauiuuL96	1407	asdAsgadTadTgaudCcAfugcuauiuasg	1669	ACUAAAGCACUGGUAUAUAUAUA	1930
AD-1466104.4	usasagcacuGfGfUfuauiuuL96	1407	asdAsgadTadTgaudCcAfugcuauiuasg	1669	ACUAAAGCACUGGUAUAUAUAUA	1930
AD-1466114.4	csusgcuafCfCfAfagaguiuuL96	1416	asAfsgadAc(Tgn)cuugdTgUfagcaggsa	1679	UCCUGCUUAUACCACAGAGUUAUA	1939
AD-1466115.2	usasuaaccAfGfAfuguauiuuL96	1417	asdAscadTadTgaudCcAfugcuauiuasg	1680	GCUAUACCACAGAGUUAUAUAUA	1940
AD-1466116.2	usasacacagAfGfUfuauiuuL96	1418	asdCsuaadCadTgaudCcAfugcuauiuasg	1681	UAUACCACAGAGUUAUAUAUAUA	1941
AD-1466118.3	csascagagUfuCfUfuauiuuL96	1420	asdAsagdTadTgaudCcAfugcuauiuasg	1683	ACCACAGAGUUAUAUAUAUAUA	1943

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.:	Antisense Strand Sequence 5' to 3'	SEQ ID NO.:	mRNA target sequence 5' to 3'	SEQ ID NO.:
AD-1466119.3	asgsaguuCfuAfUfGfuaagcuuacuL96	1421	asUfsgudAa(G2p)cuacuAfGfAfacucugsu	1684	ACAGAGUUUUAUGUAGCUUACAG	1944
AD-1466120.2	asgsuucuaUfGfUfAfgcuuacugnuL96	1422	asdAascudGudAagcudAcAfuaagacucsu	1685	AGAGUUUUAUGUAGCUUACAGUU	1945
AD-1466121.3	uscsuauUfAfgCfUfuaagcuuL96	1423	asGfsgudAc(Tgn)guuagCfuaagacasc	1686	GUUCUAUGUAGCUUACAGUUCCA	1946
AD-1466128.3	csusaauUfGfUfuaagcuuL96	1430	asdAsauudAudAucudGcCfacaauagsgsu	1693	ACCUAUUGUGGCUAGAUUAUUA	1953
AD-1466128.4	csusaauUfGfUfuaagcuuL96	1430	asdAsauudAudAucudGcCfacaauagsgsu	1693	ACCUAUUGUGGCUAGAUUAUUA	1953
AD-1466139.3	uscsauUfGfUfuaagcuuL96	1440	asdAsauudAudAucudGcCfacaauagsgsu	1704	CCUCCAUGGUGGACAAAGAUUUUU	1963
AD-1466151.3	asasgaUfUfUfGfAfgaagcuuL96	1452	asGfsgudTu(Tgn)ccuacAfuaagcuuL96	1716	ACAAGAUAUUUUGAAGGAAUACU	1975
AD-1466152.3	asgsauUfUfUfGfAfgaagcuuL96	1453	asdAsgudAudTuccudTcAfuaagcuuL96	1717	CAAGAUAUUUUGAAGGAAUACU	1976
AD-1615169.1	csesacaUfUfUfGfAfgaagcuuL96	2630	asdAsuudCadAacudGcGfuaagcuuL96	2831	GCCCACAAACUCACAAAGUUUGAAC	591
AD-1615170.1	asuscuUfUfUfGfAfgaagcuuL96	2631	asdAsauudGgdAagudAcAfuaagcuuL96	2832	GAAUCUUUCUGUAACUUCUUUA	592
AD-1615171.1	asgsuauGaaCfCfAfgaagcuuL96	2632	asdCsnuudAadAauudGcUfuaagcuuL96	2833	AGAGUAUGAACCAUAUUUAAGA	593
AD-1615172.1	csusaauUfUfUfGfAfgaagcuuL96	2633	asdAsagudAadGucudGcAfgaagcuuL96	2834	AUCUACCAUUUCAGGACUUCUUG	594
AD-1615173.1	csasuUfUfUfGfAfgaagcuuL96	2634	asdAsuudGadTgugudGcUfuaagcuuL96	2835	UCCAUGCCUCACACACAUUUUA	2290
AD-1615174.1	usesacaUfUfUfGfAfgaagcuuL96	2635	asdGsgudGudAauudGcUfuaagcuuL96	2836	CCUCACACACAUUUUAUUACUCCC	598
AD-1615175.1	csasuUfUfUfGfAfgaagcuuL96	2636	asdTsuudCadTgggudGcUfuaagcuuL96	2837	CACAUCUAUUACUCCCAUGAAAA	2291
AD-1615176.1	usesuauGaaCfCfAfgaagcuuL96	2637	asdAsgudTgdAauudGcUfuaagcuuL96	2838	AAUCUGAUCGAGGAGUUUUAACUC	599
AD-1615177.1	gsagsacaUfUfUfGfAfgaagcuuL96	2638	asdTscadAadGucudTcUfuaagcuuL96	2839	GUGGACACACAGAGACGUUUUGAC	2292
AD-1615178.1	gsagsacaUfUfUfGfAfgaagcuuL96	2639	asdGsuudAadAagudTcUfuaagcuuL96	2840	UGGGACACACAGAGACGUUUUGACA	2293
AD-1615179.1	gsagsacaUfUfUfGfAfgaagcuuL96	2640	asdTsgudCadAagudGcUfuaagcuuL96	2841	GGGACACACAGAGACGUUUUGACA	2294
AD-1615180.1	gsagsacaUfUfUfGfAfgaagcuuL96	2641	asdTsuudGcdTugudGcUfuaagcuuL96	2842	CAGAAAGACGUUUUGACAAAGCAAU	1755
AD-1615181.1	asesuauGaaCfCfAfgaagcuuL96	2642	asdAsgudAudTgududGcUfuaagcuuL96	2843	AGACGUUUUGACAAAGCAAUUCGUG	2295
AD-1615182.1	csusuauGaaCfCfAfgaagcuuL96	2643	asdCsadGadTugudGcUfuaagcuuL96	2844	GACGUUUUGACAAAGCAAUUCGUGC	2296
AD-1615183.1	gsusuauGaaCfCfAfgaagcuuL96	2644	asdGscudCgdAauudGcUfuaagcuuL96	2845	ACGUUUUGACAAAGCAAUUCGUGCU	2297
AD-1615184.1	ususuauGaaCfCfAfgaagcuuL96	2645	asdAsgudAadGauudGcUfuaagcuuL96	2846	CGUUUUGACAAAGCAAUUCGUGCUA	2298
AD-1615185.1	csusuauGaaCfCfAfgaagcuuL96	2646	asdCsadTgdAagudGcUfuaagcuuL96	2847	UCCCUAAUGUACACAGUCAAUUGG	2299
AD-1615186.1	csusuauGaaCfCfAfgaagcuuL96	2647	asdCsadTudGacudGcUfuaagcuuL96	2848	CCCUAAUGUACACAGUCAAUUGGA	2300

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.:	Antisense Strand Sequence 5' to 3'	SEQ ID NO.:	mRNA target sequence 5' to 3'	SEQ ID NO.:
AD-1615187.1	usasauguaacAfCfAfGuaaauL96	2648	asdTscadAadTgacudGuGfuacuaaasgsg	2849	CCUAAUGUACACAGUCAUUGGAU	2301
AD-1615188.1	asusuaucucCfCfAfuaucuaucL96	2649	asdTsgadAadTgaudGgAfgaauaauusc	2850	GAAUUAUUCUCCAUUCAUUUCA	602
AD-1615189.1	asasaguggaUfCfAfuaucucucL96	2650	asdGsgadAadGauadGaUfccacuuuscsc	2851	GGAAAGUGGAUCAUAUCUUCUCU	561
AD-1615190.1	csasaggaauCfUfUfaagaaauL96	2651	asdTsaudTudTcuadAgAfuaucuggsusu	2852	AACCAGGAUUCUUAAGAAAAUAA	604
AD-1615191.1	gsgsacuaugCfAfCfGuaaauL96	2652	asdGsuadTudAcaggdTgCfuaaguccsca	2853	UGGGACUAUGCACCUUGUAAUACC	2302
AD-1615192.1	gsasuaugcAfCfCfuaaauL96	2653	asdGsgudAadTaccadGuGfuaaagucscsc	2854	GGGACUAUGCACCUUGUAAUACCA	2303
AD-1615193.1	ascsuaugcaCfCfUfuaaauL96	2654	asdTsggdTadTuaadGgUfuaaagucscsc	2855	GGACUAUGCACCUUGUAAUACCA	2304
AD-1615194.1	csusaugacCfUfGfuaaauL96	2655	asdCsuadGudAuaadAgGfuaaagucscsc	2856	GACUAUGCACCUUGUAAUACCA	2305
AD-1615195.1	gsasacuguaAfAfUfaccaggaL96	2656	asdTsuadGcdTgguadTuaAfuaagucgsasu	2857	AUGCACCUUGUAAUACCAAGCGAAU	2306
AD-1615196.1	ascsuguaaUfAfCfagcgaauL96	2657	asdTsaudTcdGcugdTgUfuaagucgsasu	2858	GCACCUUGUAAUACCAAGCGAAU	2307
AD-1615197.1	csasuguaaAfCfCfagcgaauL96	2658	asdAsuadTudCgucdTgUfuaaagucgsasu	2859	CACCUGUAAUACCAAGCGAAU	2308
AD-1615198.1	csusuaaCfCfAfagcgaauL96	2659	asdCsaudAadTgcudGgUfuaaagucgsasu	2860	ACCUGUAAUACCAAGCGAAU	2309
AD-1615199.1	usasaaucaGfCfGfuaaauL96	2660	asdGsuadCudTuaadGcUfuaaagucgsasu	2861	UGUAAUACCAAGCGAAU	2310
AD-1615200.1	usasaauUfGfGfuaaauL96	2661	asdAsgadAadTuaadCaAfuaagucgsasu	2862	UCUCAGCAUUGGAAUAAUUCUC	605
AD-1615201.1	ascsacuaaAfAfUfagcgaauL96	2662	asdTsgudAadCagadTuUfuaagucgsasu	2863	ACACACUCAAUUCGUGUUCAAA	608
AD-1615202.1	usasauggaAfCfAfuaaauL96	2663	asdAscudCudAagadGuUfccacuaasasa	2864	UAUAAUGUGGAACAUCUUAAGAUU	563
AD-1615203.1	usasaagaCfCfAfuaaauL96	2664	asdAscudGudAuaadGgUfuaaagucgsasu	2865	CUUAAACAAGACCAUACUACAGUG	610
AD-1615204.1	csasuaucUfAfUfaggaaggaL96	2665	asdCscudCudTuaadTaGfuaaagucgsasu	2866	CUCAUUCAUUCUUAUGGAAAGAGGC	613
AD-1615205.1	usuggaacuUfGfGfuaaauL96	2666	asdAsgadTadAuaadCaAfuaaagucgsasu	2867	UGUUGGAACUUGGAAUUAACUU	566
AD-1615206.1	usasaucCfUfGfuaaauL96	2667	asdAscudAadAuaadAuGfuaaagucgsasu	2868	GUUAAACUCCAUUGAAUUCUAGUC	614
AD-1615207.1	csasgaacuCfAfUfuaaauL96	2668	asdGsaudTcdAuaadTgAfuaaagucgsasu	2869	UUCGGAACUUAUCAUUGAAUCA	616
AD-1615208.1	usasaacacAfGfAfuaaauL96	2669	asdAscudAadTuaadCuGfuaaagucgsasu	2870	CUUCAAACACAGAUUAUAAUUGUU	568
AD-1615209.1	gsusuguaCfAfAfuaaauL96	2670	asdGsaadGadAuaadTuGfuaaagucgsasu	2871	UUUUGGUUCAAUUAUUCUUC	618
AD-1615210.1	ascsuagunCfUfCfuaaauL96	2671	asdGsgadAadAuaadAgAfuaaagucgsasu	2872	GAACUCAGUUCUCAAUUCUUC	620
AD-1615211.1	usascuacCfUfUfuaaauL96	2672	asdAscudAadGuaadAgUfuaaagucgsasu	2873	GAUACGUCUACUUAUUCUUGGUG	621
AD-1615212.1	asasgaacuCfAfUfuaaauL96	2673	asdAsaadTcdTuaadTgAfuaaagucgsasu	2874	CAAAGUAACUUAUUCUUAUUCU	569

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.:	Antisense Strand Sequence 5' to 3'	SEQ ID NO.:	mRNA target sequence 5' to 3'	SEQ ID NO.:
AD-1615213.1	csusagaguuAfGfAfcauaaauuuL96	2674	asdAsgadTudTaugndCuAfacucuaagsgsa	2875	UCCUAGAGUUAGACAUAAAUCUC	625
AD-1615214.1	ususucauUfAfAfagacagaaauL96	2675	asdTsuudCgdTgucudTaAfugagaaascsu	2876	AGUUUCUCAUUAAAGACACGAAAA	627
AD-1615215.1	usgsaagccuAfCfAfacaauuuuuL96	2676	asdAsaadAudGuguudGuAfggcuucascsu	2877	AGUGAAGCCUACAACACACAUUUUC	628
AD-1615216.1	asasuccaauGfAfAfacaucuuuuL96	2677	asdAsagdAgdAuguudTcAfuuaggauususa	2878	UAAAUCCAAUGAAAAACAUCUCUUC	629
AD-1615217.1	uscsaaugcAfCfUfcuacuuuaguuL96	2678	asdCsuagAadGuagadGuGfcauunugasc	2879	GAUCAAUUGCACUCUACUUCUACAGA	632
AD-1615218.1	usasucuecaAfUfGfauacuuuuuuL96	2679	asdGsaadAadGuauedAuUfagagagaaagsg	2880	CCUACUCUCAUGAUACUUUUUCU	573
AD-1615219.1	csusaucaaaGfGfAfauuuauuccuL96	2680	asdGsgadTudAaauudCcUfuuagauasasa	2881	UUCUAUCAAAAGGAAUUUAAUCCA	641
AD-1615220.1	ascsuauugcuGfAfAfauugauuuuuL96	2681	asdAsuadAudCaauudTcAfgaugauagucsa	2882	UGACUAUGCUGAAAAUUUGAUUAUG	643
AD-1615221.1	asasacagaaGfAfAfauuuuuuuuuL96	2682	asdTsgudAadTaaudTcUfueuunuuusc	2883	GGAAACAGAAAGAAUUUAUUACAU	574
AD-1615222.1	asgscacuuUfAfCfcaacgugauL96	2683	asdTscadCgdTuugadTaAfagugcuugsu	2884	ACAGCACUUUUUACCAAACGUGAU	575
AD-1615223.1	ususauecaaGfUfUfcguuuuuuuuuL96	2684	asdTsuudAadAacgadAcUfuggauaascsa	2885	UGUUAUCCAAGUUCGUUUUUAAA	646
AD-1615224.1	asusgucguuUfAfGfcaaaauagcuL96	2685	asdGscudAudTuggdTgAfacagcaususa	2886	UAAUGCUGUUCAGGCCAAAUAAGCA	647
AD-1615225.1	usasgcaguuAfUfAfccuacguuuuL96	2686	asdAsuadCgdTugndAuAfagucuaususu	2887	AAUAGCAGUUUAUACCUACGUAUG	648
AD-1615226.1	gsasacaucaCfGfUfggucacuuuL96	2687	asdAsagdTgdAaacadCgUfgaauugcususu	2888	AAGACAUUCACGUGGUUUCACUUU	577
AD-1615227.1	csusgguucaUfUfUfaaaacuuuuL96	2688	asdAsagdAgdTuuuadAaUfgaaccagsgsc	2889	GCCUGGUUCAUUUAAAACUCUUG	649
AD-1615228.1	gsasgcagggAfUfGfcaaaagccauL96	2689	asdTsggdCgdTuugcdAuCfcccugcucusc	2890	GAGAGCAGGGAUGCAAAACGCCAU	2311
AD-1615229.1	asgscaggggUfGfCfcaaacgccauL96	2690	asdAsugdGcdGuuugcdCaUfcccugcuscusu	2891	AGAGCAGGGAUGCAAAACGCCAUU	2312
AD-1615230.1	asgsaggagcAfAfAfcccauuuuuL96	2691	asdGsaadAudGcgudTuGfcauuccugsgc	2892	GCAGGGAUGCAAAACGCCAUUUUCU	2313
AD-1615231.1	gsagsaugcaAfAfCfgccauuuuuuL96	2692	asdAsgadAadTggcdTuUfgaucuccusug	2893	CAGGGAUGCAAAACGCCAUUUUCUU	2314
AD-1615232.1	gsagsaugcaaAfCfGfccaauuuuuuL96	2693	asdAsagdAadAuggcdGuUfgaucuccscsu	2894	AGGGAUGCAAAACGCCAUUUUCUUA	2315
AD-1615233.1	gsasugcaaaCfGfCfcauuuuuuuuL96	2694	asdTsaadGadAauggdCgUfuuagaucscsc	2895	GGGAUGCAAAACGCCAUUUUCUUAU	2316
AD-1615234.1	usgscaaaagCfCfAfuuuuuuuuuuL96	2695	asdGsaudAadGaaudGgCfuuuugcasusc	2896	GAUGCAAAACGCCAUUUUCUUAUCA	650
AD-1615235.1	csasaagcccAfUfUfuuuuuuuuuuL96	2696	asdAsugdAudAgaadAuGfcccguuugscsa	2897	UGCAAAACGCCAUUUUCUUAUCAUG	2317
AD-1615236.1	asasacgccaUfUfUfuuuuuuuuuuL96	2697	asdCsaadGadTaaadAaUfggcguuugsgc	2898	GCAAAACGCCAUUUUCUUAUCAUGG	2318
AD-1615237.1	asascgccaUfUfCfuuuuuuuuuuL96	2698	asdCscadTgdAuaadAaAfugcguuugsg	2899	CAAAACGCCAUUUUCUUAUCAUGGA	2319
AD-1615238.1	ascsagccauUfCfUfuuuuuuuuuuL96	2699	asdTscadAudGauaadGaAfauugcgugusuu	2900	AAACGCCAUUUUCUUAUCAUGGAC	2320

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.:	Antisense Strand Sequence 5' to 3'	SEQ ID NO.:	mRNA target sequence 5' to 3'	SEQ ID NO.:
AD-1615239.1	csGCCaunUfUfaucauggacU.96	2700	asdGsuadCadTgaunadAgAfaunggcsusu	2901	AAGCCAUUUUUUAUCAUGGACA	2321
AD-1615240.1	asusgggacuAfAfGfcacugguauU.96	2701	asdAsuadCcdAugcdTuAfucccausug	2902	CAAU'GGGACUAAGCACUGGUUUC	2322
AD-1615241.1	usgggacuaAfGfCfcacugguauU.96	2702	asdGsandAcdCagugdCuUfaguuccasuu	2903	AAUGGGACUAAGCACUGGUUUAUA	2323
AD-1615242.1	gsGgacuaaGfCfAfcugguauU.96	2703	asdTsgadTadCcaugdGcUfaguucccsasu	2904	AUGGGACUAAGCACUGGUUUAUCAU	2324
AD-1615243.1	gsGgacuaaGfCfAfcugguauU.96	2704	asdAsugdAudAccagdTgCfhuaguucccsa	2905	UGGGACUAAGCACUGGUUUAUCAU	2325
AD-1615244.1	csusaagcacUfGfGfuaucuaU.96	2705	asdGsandAudGauacdCaGfugcuuagsuc	2906	GACUAAGCACUGGUUUAUCAUUCU	2326
AD-1615245.1	asasgcacugGfUfAfuaucuaU.96	2706	asdCsagdAudAugaudAcCfagugcuusag	2907	CUAAGCACUGGUUUAUCAUUCUGA	2327
AD-1615246.1	asgsacacugUfAfUfuaucuaU.96	2707	asdTscadGadTaugadTaCfagugcuusasa	2908	UAAGCACUGGUUUAUCAUUCUGAU	2328
AD-1615247.1	gsesacugguAfUfCfuaucuaU.96	2708	asdAsudAgdAuagadAuAfccagugcsusu	2909	AAGCACUGGUUUAUCAUUCUGAUU	2329
AD-1615248.1	csascugguUfCfAfuaucuaU.96	2709	asdAsandCadGauandGaUfaccagugcsu	2910	AGCACUGGUUUAUCAUUCUGAUUC	2330
AD-1615249.1	usgsuaucaUfAfUfuaucuaU.96	2710	asdGsuadAadTcaugadTaUfuaucuaU.96	2911	ACUGGUUUAUCAUUCUGAUUCACA	2331
AD-1615250.1	uscsagguUfCfUfuaucuaU.96	2711	asdCsagdTadAccadGaAfucucugcsag	2912	CUUCAGAGUUUCUGGUUACUGG	652
AD-1615251.1	asgsaunugCfCfUfuaucuaU.96	2712	asdAsagdGudTuaugadGgCfaaunucgsc	2913	GCAGAAUUUGCCUCUAAAACCUUG	653
AD-1615252.1	csusgaagcUfUfGfuaucuaU.96	2713	asdGsuadGudAuagadAgGfucucugcsu	2914	ACCUGAAGUCCUGCUUAUACCACA	2332
AD-1615253.1	csusgcuaaCfCfAfcaugguU.96	2714	asdAsagdAcdTcugndGgUfuaucuggsa	2915	UCCUGCUUAUACCACAGAGUUCUA	1939
AD-1615253.2	csusgcuaaCfCfAfcaugguU.96	2714	asdAsagdAcdTcugndGgUfuaucuggsa	2915	UCCUGCUUAUACCACAGAGUUCUA	1939
AD-1615254.1	usgsuauacCfAfCfagguuU.96	2715	asdTsgadAadCucugdTgGfuaucugcsag	2916	CCUGCUUAUACCACAGAGUUCUAU	2333
AD-1615255.1	gsesuauaccAfCfAfagguuU.96	2716	asdAsuadGadAcucudGuGfuaucugcsag	2917	CUGCUUAUACCACAGAGUUCUAUUG	2334
AD-1615256.1	csusuauaccaAfGfagguuU.96	2717	asdCsandAgdAacudTgUfagguuagcsa	2918	UGCUAUACCACAGAGUUCUAUUGU	2335
AD-1615257.1	asusaccacaGfAfGfuaucuaU.96	2718	asdTsacdAudAgaacdTcUfagguuagcsa	2919	CUAUACCACAGAGUUCUAUUGUAG	2336
AD-1615258.1	ascsacagaGfUfUfuaucuaU.96	2719	asdGscudAcdAuagadAcUfucugugcsusu	2920	AUACCACAGAGUUCUAUUGUAGCU	2337
AD-1615259.1	csesacagagUfUfCfuaucuaU.96	2720	asdAsgcdTadCaugadAaCfucugugcsusu	2921	UACCACAGAGUUCUAUUGUAGCUU	1942
AD-1615260.1	asgsaguuUfUfGfuaucuaU.96	2721	asdTsgudAadGcuacdAuAfgaauucgusu	2922	ACAGAGUUCUAUUGUAGCUUACAG	1944
AD-1615260.2	asgsaguuUfUfGfuaucuaU.96	2721	asdTsgudAadGcuacdAuAfgaauucgusu	2922	ACAGAGUUCUAUUGUAGCUUACAG	1944
AD-1615261.1	gsasguncuaUfGfUfagguuU.96	2722	asdCsugdTadAguacdCaUfagguuucgusu	2923	CAGAGUUCUAUUGUAGCUUACAGU	2338
AD-1615262.1	uscsuauguaGfCfUfuaucuaU.96	2723	asdGsagdAcdTgaunadGcUfuaucuaU.96	2924	GUUCUAUGUAGCUUACAGUUCUA	1946

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.:	Antisense Strand Sequence 5' to 3'	SEQ ID NO.:	mRNA target sequence 5' to 3'	SEQ ID NO.:
AD-1615262.2	uscsuauuguaGfCfUfuacaguuuL96	2723	asdGsgadAcdTguaadGcUfauaiugasasc	2924	GUUCUAUGUAGCUUACAGUUCCA	1946
AD-1615263.1	csusauuguaGfCfUfuacaguuuL96	2724	asdTsgadAadCugnadAgCfuacauagsasa	2925	UUCUAUGUAGCUUACAGUUCCA	2339
AD-1615264.1	usasuguaGfCfUfuacaguuuL96	2725	asdTsgadGadAcugudAaGfcauauagsa	2926	UCUAUGUAGCUUACAGUUCCA	2340
AD-1615265.1	usasuguaGfCfUfuacaguuuL96	2726	asdCsgadGudTggaadCuGfuauagcuasasa	2927	UGUAUGCUUACAGUUCCA	2341
AD-1615266.1	gsasauuguaGfCfUfuacaguuuL96	2727	asdCsaadTadAaauadCaUfcauauagsa	2928	AGGAAUGUGAGUAUUUAAUUGG	655
AD-1615267.1	ascsuauugUfGfGfuaaguuuL96	2728	asdTsaadAadCuagadCaCfauauagsg	2929	CCACCUAUUGUGGCUAGAUUAU	2342
AD-1615268.1	csusauuguaGfCfUfuacaguuuL96	2729	asdAsuadTadTcuagdCcAfcuauagsg	2930	CACCUAUUGUGGCUAGAUUAU	2343
AD-1615269.1	usasuguaGfCfUfuacaguuuL96	2730	asdTsaadTadTcuagdCcAfcuauagsg	2931	CCUAUUGUGGCUAGAUUAU	2344
AD-1615270.1	asusuguaGfCfUfuacaguuuL96	2731	asdCsuadAadAuaadTaGfcauauagsa	2932	CUAUUGUGGCUAGAUUAU	2345
AD-1615271.1	usuguguaGfCfUfuacaguuuL96	2732	asdCsuadAadAuaadTaGfcauauagsa	2933	UAUUGUGGCUAGAUUAU	2346
AD-1615272.1	usuguguaGfCfUfuacaguuuL96	2733	asdTsaadTadAuaadTaGfcauauagsa	2934	AUUGUGGCUAGAUUAU	2347
AD-1615273.1	gsusuguaGfCfUfuacaguuuL96	2734	asdAsuadCudAuaadAuCfuauagcuasasa	2935	UUGUGGCUAGAUUAU	2348
AD-1615274.1	gsusuguaGfCfUfuacaguuuL96	2735	asdAsuadCudAuaadAuCfuauagcuasasa	2936	GUGGCUAGAUUAU	1954
AD-1615275.1	gsusuguaGfCfUfuacaguuuL96	2736	asdGsgadAadCuadTaUfauauagcuasasa	2937	UGGCUAGAUUAU	2349
AD-1615276.1	csusuguaGfCfUfuacaguuuL96	2737	asdCsuadTadCuaadAuUfcauauagsa	2938	GUCCUCUGAAUUGUAU	659
AD-1615277.1	csusuguaGfCfUfuacaguuuL96	2738	asdAsuadGudTaaadTuUfcauauagsa	2939	CGCUGUGUAAAUGUAU	578
AD-1615278.1	ascsuauugUfGfGfuaaguuuL96	2739	asdGsgadAadCuadTaUfcauauagsa	2940	UAACAGUUUCCACUAU	579
AD-1615279.1	asusuguaGfCfUfuacaguuuL96	2165	asAfsuadGfauagcuGfUfcauauagsa	2941	GGAUGCAAAACGCCAUU	1926
AD-1615280.1	asusuguaGfCfUfuacaguuuL96	2740	usdAsuadAadAuaadTaGfcauauagsa	2942	GGAUGCAAAACGCCAUU	1926
AD-1615281.1	asusuguaGfCfUfuacaguuuL96	2740	usdAsuadAadAuaadTaGfcauauagsa	2943	GGAUGCAAAACGCCAUU	1926
AD-1615282.1	asusuguaGfCfUfuacaguuuL96	2740	usdAsuadAadAuaadTaGfcauauagsa	2944	GGAUGCAAAACGCCAUU	1926
AD-1615283.1	asusuguaGfCfUfuacaguuuL96	2741	usdAsuadAadAuaadTaGfcauauagsa	2945	GGAUGCAAAACGCCAUU	1926
AD-1615284.1	asusuguaGfCfUfuacaguuuL96	2742	usdAsuadAadAuaadTaGfcauauagsa	2946	GGAUGCAAAACGCCAUU	1926
AD-1615285.1	asusuguaGfCfUfuacaguuuL96	2743	usdAsuadAadAuaadTaGfcauauagsa	2947	GGAUGCAAAACGCCAUU	1926
AD-1615286.1	asusuguaGfCfUfuacaguuuL96	2744	usdAsuadAadAuaadTaGfcauauagsa	2948	AUGCAAAACGCCAUU	3034
AD-1615287.1	asusuguaGfCfUfuacaguuuL96	2745	asdAsuadAadAuaadTaGfcauauagsa	1665	GGAUGCAAAACGCCAUU	1926

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.:	Antisense Strand Sequence 5' to 3'	SEQ ID NO.:	mRNA target sequence 5' to 3'	SEQ ID NO.:
AD-1615288.1	asusgcaaacgCfCfdAnnucuuauuL96	2746	asdAsuadAgdAaaugdGcGfuuugcauscsc	1665	GGAUGCAAACGCCCAUUUCUUUAUC	1926
AD-1615289.1	gscsaacgCfCfAfuuucuuauuL96	2747	asdAsuadAgdAaaugdGcGfuuugcsgsu	2949	AUGCAAACGCCCAUUUCUUUAUC	3034
AD-1615290.1	gscsaacgCfCfdAnnucuuauuL96	2748	asdAsuadAgdAaaugdGcGfuuugcsgsu	2949	AUGCAAACGCCCAUUUCUUUAUC	3034
AD-1615291.1	asusgcaaacgCfCfAfuuucuuauuL96	2749	asdAsuadAgdAaaugdGcGfuuugcauscsc	2950	GGAUGCAAACGCCCAUUUCUUUAUC	1926
AD-1615292.1	asusgcaaacgCfCfdAnnucuuauuL96	2750	asdAsuadAgdAaaugdGcGfuuugcauscsc	2950	GGAUGCAAACGCCCAUUUCUUUAUC	1926
AD-1615293.1	asusgcaaacgCfCfAfuuucuuauuL96	2751	asdAsuadAgdAaaugdGcGfuuugcauscsc	2951	GGAUGCAAACGCCCAUUUCUUUAUC	1926
AD-1615294.1	asusgcaaacgCfCfdAnnucuuauuL96	2752	asdAsuadAgdAaaugdGcGfuuugcauscsc	2951	GGAUGCAAACGCCCAUUUCUUUAUC	1926
AD-1615295.1	asusgcaaacgCfCfAfuuucuuauuL96	2753	asdAsuadAgdAaaugdGcGfuuugcauscsc	2952	GGAUGCAAACGCCCAUUUCUUUAUC	1926
AD-1615296.1	asusgcaaacgCfCfdAnnucuuauuL96	2754	asdAsuadAgdAaaugdGcGfuuugcauscsc	2952	GGAUGCAAACGCCCAUUUCUUUAUC	1926
AD-1615297.1	asusgcaaacgCfCfAfuuucuuauuL96	2755	usdAsuadAgdAaaugdGcGfuuugcauscsc	2942	GGAUGCAAACGCCCAUUUCUUUAUC	1926
AD-1615298.1	gscsaacgCfCfAfuuucuuauuL96	2756	usdAsuadAgdAaaugdGcGfuuugcsgsu	2953	AUGCAAACGCCCAUUUCUUUAUC	3034
AD-1615299.1	asusgcaaacgCfCfAfuuucuuauuL96	2757	usdAsuadAgdAaaugdGcGfuuugcauscsc	2954	GGAUGCAAACGCCCAUUUCUUUAUC	1926
AD-1615300.1	asusgccaacgCfAfCfacaunuuuuL96	2758	asdAsuadAadAaaugdTgUfagggcauscsg	2955	CCAUGCCUCACACACACAUUUA	1748
AD-1615301.1	csusacacacCfAfUfcauuaauuL96	2759	asdGsaadTadAaaugdTgUfagggcauscsg	2956	GCCUCACACACACAUUUAUACUCC	1752
AD-1615302.1	csusacacacCfAfUfcauuaauuL96	2760	asdGsaadAadAaaugdTgUfagggcauscsg	2957	GCCUCACACACACAUUUAUACUCC	1752
AD-1615303.1	asasuguaacCfAfGfuaauuuuuL96	2761	asdAsuadCadAaaugdTgUfaggaauuasg	2958	CUAAUGUACACAGUCAAUUGGAUA	1762
AD-1615304.1	gscsagggcuuAfCfAfugacuuuuL96	2762	asdTsaadTgdTcaudGuAfagccugcsasu	2959	AUGCAGGCUUACAUAUGACAUUAA	1783
AD-1615305.1	gscsagggcuuAfCfAfugacuuuuL96	2763	asdTsaadTadTcaudGuAfagccugcsasu	2960	AUGCAGGCUUACAUAUGACAUUAA	1783
AD-1615306.1	gscsagggcuuAfCfAfugacuuuuL96	2764	asdTsaadTgdAcaudGuAfagccugcsasu	2961	AUGCAGGCUUACAUAUGACAUUAA	1783
AD-1615307.1	csasggccuuaCfAfUfugacuuuuL96	2765	asUfsuadAudGucaaugUfaAfagccugcsa	2962	UGCAGGCUUACAUAUGACAUUAAA	603
AD-1615308.1	csasggccuuaCfAfUfugacuuuuL96	2766	asUfsuadAudGucaaugUfaAfagccugcsa	2963	UGCAGGCUUACAUAUGACAUUAAA	603
AD-1615309.1	csasggccuuaCfAfUfugacuuuuL96	2767	asUfsuadAudAucaaugUfaAfagccugcsa	2964	UGCAGGCUUACAUAUGACAUUAAA	603
AD-1615310.1	csasggccuuaCfAfUfugacuuuuL96	2765	asUfsuadAudGucaaugUfaAfagccugcsa	2965	UGCAGGCUUACAUAUGACAUUAAA	603
AD-1615311.1	csasggccuuaCfAfUfugacuuuuL96	2766	asUfsuadAudGucaaugUfaAfagccugcsa	2966	UGCAGGCUUACAUAUGACAUUAAA	603
AD-1615312.1	csasggccuuaCfAfUfugacuuuuL96	2767	asUfsuadAudAucaaugUfaAfagccugcsa	2967	UGCAGGCUUACAUAUGACAUUAAA	603
AD-1615313.1	usascuuaaCfAfUfuaauuacuuL96	2768	asdCsagdTadTuaadTgUfcaauuuaasag	2968	CUUACAUAUGACAUUAAAAACUCC	1789

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.:	Antisense Strand Sequence 5' to 3'	SEQ ID NO.:	mRNA target sequence 5' to 3'	SEQ ID NO.:
AD-1615314.1	usascuaguaCfAfUfuauaauacugul.96	2769	asdCsgdTudAnuaadTgUfcaagunuasag	2969	CUUACAUUGACAUUAAAAACUGC	1789
AD-1615315.1	csascuaguaAfUfAfccagugaauL.96	2770	asdAsundCadCuggudAuUfacagugscsa	2970	UGCACCUUGUAUUAUACCAGCGAAUA	1797
AD-1615316.1	csascuaguaAfUfAfccagugaauL.96	2771	asdAsundCgdAugudAuUfacagugscsa	2971	UGCACCUUGUAUUAUACCAGCGAAUA	1797
AD-1615317.1	csascuaguaAfUfAfccagugaauL.96	2770	asdAsundCadCuggudAuUfacagugscsg	2972	UGCACCUUGUAUUAUACCAGCGAAUA	1797
AD-1615318.1	csascuaguaAfUfAfccagugaauL.96	2771	asdAsundCgdAugudAuUfacagugscsg	2973	UGCACCUUGUAUUAUACCAGCGAAUA	1797
AD-1615319.1	uscsaggaaunCfUfUfggucuaauL.96	2772	asdAsandAgdGaccadAgAfauuaccgagsga	2974	UCUCGGAAUUCUUGGUGGUCCUAUUA	645
AD-1615320.1	uscsaggaaunCfUfUfggucuaauL.96	2773	asdAsandAadGaccadAgAfauuaccgagsga	2975	UCUCGGAAUUCUUGGUGGUCCUAUUA	645
AD-1615321.1	uscsaggaaunCfUfUfggucuaauL.96	2774	asdAsandAgdAaccadAgAfauuaccgagsga	2976	UCUCGGAAUUCUUGGUGGUCCUAUUA	645
AD-1615322.1	uscsaggaaunCfUfUfggucuaauL.96	2772	asdAsandAgdGaccadAgAfauuaccgagsgg	2977	UCUCGGAAUUCUUGGUGGUCCUAUUA	645
AD-1615323.1	uscsaggaaunCfUfUfggucuaauL.96	2773	asdAsandAadGaccadAgAfauuaccgagsgg	2978	UCUCGGAAUUCUUGGUGGUCCUAUUA	645
AD-1615324.1	uscsaggaaunCfUfUfggucuaauL.96	2774	asdAsandAgdAaccadAgAfauuaccgagsgg	2979	UCUCGGAAUUCUUGGUGGUCCUAUUA	645
AD-1615325.1	asasagagaaGfCfUfggucuaauL.96	2775	asdCsaundAadTaccadGcUfcuucuuususc	2980	GAAAAAGAGAGCUGGUGGUACUAUGA	1909
AD-1615326.1	asasagagaaGfCfUfggucuaauL.96	2776	asdCsaundAgdAaccadGcUfcuucuuususc	2981	GAAAAAGAGAGCUGGUGGUACUAUGA	1909
AD-1615327.1	usasagacauGfGfUfauuuaucuuL.96	2777	asdAsgadTadAgaadCcAfugucuaasgsu	2982	ACUAAAGCACUGGUAUCAUAUCUG	1930
AD-1615328.1	csusgcuauaCfCfAfcaaguuuuL.96	2778	asdAsgadAadTcugudGgUfauuacagsgsa	2983	UCCUGCUAUACCCACAGAGUUCUA	1939
AD-1615329.1	csusgcuauaCfCfAfcaaguuuuL.96	2779	asdAsgadAadTcugudGgUfauuacagsgsa	2984	UCCUGCUAUACCCACAGAGUUCUA	1939
AD-1615330.1	csusgcuauaCfCfAfcaaguuuuL.96	2714	asdAsgadAadTcugudGgUfauuacagsgsg	2985	UCCUGCUAUACCCACAGAGUUCUA	1939
AD-1615331.1	csusgcuauaCfCfAfcaaguuuuL.96	2778	asdAsgadAadTcugudGgUfauuacagsgsg	2986	UCCUGCUAUACCCACAGAGUUCUA	1939
AD-1615332.1	csusgcuauaCfCfAfcaaguuuuL.96	2779	asdAsgadAadTcugudGgUfauuacagsgsg	2987	UCCUGCUAUACCCACAGAGUUCUA	1939
AD-1615333.1	asgsaguuuAfUfGfuaguuuuacauL.96	2780	asdTsgudAadAduuadAuAfgaacucugsu	2988	ACAGAGUUUCUAUGUAGCUUACAG	1944
AD-1615334.1	uscsuauaguaGfCfUfuacuuuuuuL.96	2781	asdGsgadAadTguuadGcUfauuacagsgsa	2989	GUUCUAUGUAGCUUACAGUUCUA	1946
AD-1615335.1	uscsuauaguaGfCfUfuacuuuuuuL.96	2782	asdGsgadAadTguuadGcUfauuacagsgsa	2990	GUUCUAUGUAGCUUACAGUUCUA	1946
AD-1615336.1	csusauuugugGfCfUfagaauuuuuL.96	2783	asdAsandAadAduuadGcUfauuacagsgsu	2991	ACCUAUUUGUGGCUAGAUUAUUA	1953
AD-1615337.1	uscsauuugugGfCfUfagaauuuuuL.96	2784	asdAsandAadAduuadGcUfauuacagsgsu	2992	CCUCCAUUGGUGGCUAGAUUAUUA	1963
AD-1615338.1	uscsauuugugGfCfUfagaauuuuuL.96	2785	asdAsandAadAduuadGcUfauuacagsgsu	2993	CCUCCAUUGGUGGCUAGAUUAUUA	1963
AD-1615339.1	asasgaauuuUfGfAfaggaauuuL.96	2786	asdGsuadTudTccuudCaAfauuauucugsu	2994	ACAAGAUUUUUGAAGGAAUAUCU	1975

Duplex Name	Sense Strand Sequence 5' to 3'	SEQ ID NO.:	Antisense Strand Sequence 5' to 3'	SEQ ID NO.:	mRNA target sequence 5' to 3'	SEQ ID NO.:
AD-1615340.1	asasgaunuuUfGfAfaggauauacuL96	2787	asdGsuadTadTccuudCaAfaaaucuuusgu	2995	ACAAGA UUUUUUGAAGGAAA UACU	1975
AD-1615341.1	asasgaunuuUfGfAfaggauauacuL96	2788	asdGsuadTudAccuudCaAfaaaucuuusgu	2996	ACAAGA UUUUUUGAAGGAAA UACU	1975
AD-1615342.1	asgsaunuuUfGfAfaggauauacuL96	2789	asdAsgudAadTuccudTcAfaaaucuuusgu	2997	CAAGA UUUUUUGAAGGAAA UACUA	1976
AD-1615343.1	asgsaunuuUfGfAfaggauauacuL96	2790	asdAsgudAudAuccudTcAfaaaucuuusgu	2998	CAAGA UUUUUUGAAGGAAA UACUA	1976
AD-109630.1	csasggcuUfaCfAtUfugacauuaaaL96	2791	usUfsuaaUfGfUfCfaaugUfaAfgccuugscsa	2999	UGCAGGCUUACA UUGACAUUAAA	603

Table 12 Coagulation Factor V Single Dose Screens in Primary Human Hepatocytes

	10 nM		1 nM		0.1 nM	
Duplex	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1615169.1	19.61	2.96	23.03	1.68	34.68	4.64
AD-1615170.1	9.34	2.01	16.84	0.89	20.30	1.29
AD-1615171.1	10.83	1.58	20.81	2.15	25.81	4.01
AD-1615172.1	19.13	1.04	27.51	6.36	34.74	7.69
AD-1452209.1	95.97	18.27	107.65	4.60	72.03	4.84
AD-1452212.1	102.65	12.31	104.27	2.41	102.70	1.05
AD-1615173.1	25.76	4.89	23.92	3.50	25.41	7.03
AD-1465918.3	11.40	1.00	12.43	1.23	17.39	0.70
AD-1615300.1	35.31	4.74	32.85	1.48	40.40	6.59
AD-1465918.4	11.47	1.60	18.33	2.57	23.58	3.65
AD-1465919.2	31.07	2.99	30.06	7.09	33.37	6.50
AD-1465920.2	18.18	0.81	16.54	1.80	20.14	0.68
AD-1410823.1	32.27	4.27	44.57	3.38	42.43	2.31
AD-1465921.2	25.01	1.78	26.16	5.77	39.81	3.94
AD-1465922.3	12.35	1.70	23.84	3.46	26.15	2.18
AD-1615301.1	31.80	6.20	43.09	5.28	45.95	1.40
AD-1615302.1	28.25	2.78	40.70	3.44	48.78	6.29
AD-1465922.4	18.53	1.33	22.95	2.26	37.45	4.81
AD-1615174.1	35.90	3.82	41.27	6.31	57.23	6.15
AD-1615175.1	18.84	1.18	23.13	2.37	39.38	8.04
AD-1454350.1	40.47	2.43	52.78	5.44	71.69	6.74
AD-1615176.1	16.62	2.73	21.61	1.76	29.78	3.47
AD-1615177.1	21.51	2.44	28.43	3.46	39.50	5.36
AD-1615178.1	29.26	3.15	33.32	3.18	40.85	5.41
AD-1615179.1	23.85	6.63	27.73	5.10	30.14	2.64
AD-1615180.1	19.52	0.96	21.40	2.21	34.49	4.13
AD-1465927.2	29.57	0.79	36.70	2.73	53.33	10.25
AD-1615181.1	14.28	2.51	23.41	5.42	31.25	5.06
AD-1615182.1	14.72	0.68	27.60	2.31	38.56	3.66
AD-1615183.1	24.04	1.86	32.04	2.11	45.51	5.73
AD-1615184.1	9.51	1.63	17.98	1.39	21.02	2.22
AD-1615185.1	18.32	2.44	19.25	3.60	24.27	2.16
AD-1615186.1	18.77	1.50	26.91	4.05	34.73	4.35
AD-1615187.1	43.24	3.92	49.91	5.01	72.11	5.44
AD-1465932.3	17.29	1.90	19.49	1.27	22.93	2.01
AD-1615303.1	14.01	0.83	18.08	1.50	22.39	3.12
AD-1465932.4	14.61	1.38	23.28	3.33	30.97	6.50
AD-1615188.1	19.49	1.00	26.99	4.65	35.11	3.79
AD-1452985.1	121.76	5.55	111.64	4.81	112.61	7.14
AD-1615189.1	20.03	4.37	24.21	3.71	35.18	3.89

	10 nM		1 nM		0.1 nM	
Duplex	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1465953.3	9.67	1.88	11.62	0.58	16.18	0.87
AD-1615304.1	9.84	1.25	15.30	0.79	21.26	4.06
AD-1615305.1	32.05	8.21	34.17	4.18	40.12	6.21
AD-1615306.1	21.09	1.41	28.29	2.60	37.13	3.99
AD-1465954.3	12.58	1.34	14.66	2.28	18.98	1.62
AD-1615307.1	9.14	1.17	14.61	1.18	14.89	2.94
AD-1615308.1	26.79	2.43	32.19	3.25	31.56	4.38
AD-1615309.1	11.89	1.28	11.04	2.69	21.23	4.05
AD-1615310.1	6.86	0.92	8.38	0.88	14.17	3.54
AD-1615311.1	21.31	3.23	21.51	7.39	15.11	0.39
AD-1615312.1	12.75	1.73	18.36	3.38	18.37	1.58
AD-1465960.3	12.66	0.67	20.33	2.93	18.79	2.53
AD-1615313.1	34.74	4.85	31.70	4.10	43.14	9.13
AD-1615314.1	37.48	3.77	36.17	2.37	33.18	1.24
AD-1615190.1	18.74	2.43	25.34	2.90	30.29	4.24
AD-1454911.1	89.52	13.17	94.99	6.35	78.03	15.42
AD-1615191.1	20.21	2.24	24.56	1.16	31.37	2.16
AD-1615192.1	62.12	4.56	63.67	2.56	79.15	3.00
AD-1615193.1	24.12	1.20	35.49	0.72	48.64	3.49
AD-1615194.1	28.86	1.81	33.94	3.15	53.82	5.99
AD-1615195.1	22.36	1.86	27.86	1.99	47.97	3.44
AD-1465968.3	17.57	1.97	20.90	2.88	18.46	4.89
AD-1615315.1	26.59	5.01	20.24	3.77	36.07	7.85
AD-1615316.1	16.57	1.72	21.08	2.99	25.85	3.72
AD-1615317.1	23.28	1.44	26.94	0.41	29.62	3.39
AD-1615318.1	21.74	2.50	22.11	5.30	28.82	4.28
AD-1465968.4	17.28	3.68	20.93	2.00	31.07	2.94
AD-1615196.1	14.63	1.81	27.73	4.13	40.39	7.39
AD-1615197.1	20.10	1.86	27.35	2.85	39.64	4.25
AD-1615198.1	18.65	2.05	27.03	2.73	31.24	3.18
AD-1465969.2	26.71	5.31	34.58	5.05	42.00	1.43
AD-1465970.2	63.54	4.90	79.87	8.62	95.91	5.22
AD-1615199.1	20.20	1.85	21.28	4.19	38.03	4.19
AD-1615200.1	21.63	1.66	25.63	0.83	31.41	5.51
AD-1411340.1	33.93	4.55	47.50	4.30	70.04	1.50
AD-1411342.2	27.86	3.91	38.68	4.42	46.88	5.15
AD-1615201.1	22.04	0.93	31.14	2.35	38.35	1.16
AD-1454529.1	101.06	10.58	86.25	9.89	87.87	11.41
AD-1455659.1	34.38	3.40	48.89	8.56	51.81	3.33
AD-1455664.1	75.46	5.40	80.73	8.57	85.24	3.65
AD-1453516.1	108.90	7.04	102.05	5.00	92.88	0.84
AD-1615202.1	18.14	4.02	29.27	3.47	38.76	2.74

	10 nM		1 nM		0.1 nM	
Duplex	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1615203.1	21.56	2.55	32.43	2.01	40.78	3.16
AD-1453784.1	50.97	6.45	52.69	4.50	76.16	11.01
AD-1615204.1	63.12	5.13	68.49	2.99	82.50	14.91
AD-1615205.1	23.72	1.49	24.50	0.78	34.33	1.10
AD-1411797.1	25.11	2.40	35.16	1.50	47.02	2.95
AD-110532.1	57.13	8.33	62.15	6.83	76.90	4.57
AD-1411798.2	93.84	6.26	60.36	5.70	105.26	9.03
AD-1615206.1	35.48	3.11	46.00	3.58	61.24	6.57
AD-1454175.1	85.99	8.93	90.46	7.74	86.83	14.08
AD-1454221.1	107.00	1.57	107.00	19.78	102.63	7.81
AD-1457108.1	84.50	4.44	53.47	11.80	92.79	15.28
AD-1615207.1	16.50	2.52	24.86	3.32	30.68	2.91
AD-1457130.1	34.29	2.37	38.98	5.36	50.42	10.79
AD-1457237.1	27.22	0.60	33.02	5.20	48.06	2.55
AD-1615208.1	20.23	2.36	26.97	3.11	33.74	4.78
AD-1615209.1	20.43	2.57	35.23	6.36	40.22	7.48
AD-1454534.1	117.47	12.05	88.25	13.04	110.32	7.50
AD-110931.1	20.67	1.79	31.19	6.20	40.87	2.64
AD-1615210.1	18.93	1.50	27.31	1.57	38.84	4.69
AD-1454719.1	98.59	8.57	100.98	11.53	88.88	15.84
AD-1454720.1	87.00	8.17	105.09	10.43	76.40	15.13
AD-1615211.1	20.67	1.49	30.27	3.38	34.74	0.96
AD-1615212.1	12.54	1.93	19.34	3.29	24.88	3.41
AD-1455771.1	105.78	16.60	97.10	16.16	106.08	8.33
AD-1615213.1	14.85	1.73	19.39	1.73	25.76	1.21
AD-1412539.2	29.21	1.58	31.71	0.73	46.33	5.89
AD-1615214.1	15.90	0.51	23.27	2.24	34.08	2.99
AD-1615215.1	16.98	2.18	23.59	1.05	21.30	3.85
AD-1455310.1	105.66	14.84	90.80	20.50	114.48	5.58
AD-1455313.1	81.97	14.75	104.10	6.69	87.53	11.75
AD-1455314.1	87.04	10.11	93.84	11.90	84.33	15.90
AD-1458619.1	59.20	4.16	43.56	5.66	70.10	9.37
AD-1455701.1	102.60	8.09	107.23	9.47	98.74	3.38
AD-1615216.1	14.83	1.20	26.19	4.58	26.72	2.07
AD-1458724.1	79.38	8.96	70.03	6.58	99.83	7.51
AD-1455522.1	95.35	14.81	104.05	5.93	84.76	21.56
AD-1615217.1	30.87	1.78	42.71	0.38	52.10	8.67
AD-1455780.1	114.40	14.12	100.40	13.53	93.66	14.64
AD-1455807.1	103.09	18.99	96.11	10.03	112.14	12.72
AD-1459277.1	46.30	3.52	51.01	4.82	72.76	4.56
AD-112393.1	28.34	2.57	36.01	4.50	51.38	5.48
AD-1413196.1	33.79	4.63	40.18	2.16	51.59	2.52

	10 nM		1 nM		0.1 nM	
Duplex	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1615218.1	19.11	4.18	29.19	4.37	32.39	3.79
AD-1615219.1	21.28	5.77	28.26	5.74	32.48	4.86
AD-1615220.1	10.09	1.72	17.40	1.67	24.16	5.20
AD-1615221.1	22.09	1.76	31.25	1.60	43.54	3.14
AD-1615222.1	24.85	2.10	35.35	1.98	46.03	2.06
AD-1466053.3	18.23	1.54	16.77	2.26	20.05	2.32
AD-1615319.1	18.40	2.52	18.90	1.41	23.27	3.34
AD-1615320.1	39.24	4.80	35.53	1.89	37.37	6.49
AD-1615321.1	14.43	1.76	24.52	2.97	31.11	2.65
AD-1615322.1	10.93	1.91	20.89	2.66	33.86	2.82
AD-1615323.1	21.68	2.25	35.49	4.34	41.49	10.95
AD-1615324.1	11.35	0.62	27.46	1.27	36.65	4.81
AD-1615223.1	15.97	2.89	25.23	3.11	38.40	5.05
AD-1615224.1	26.91	5.68	39.50	8.84	47.13	9.82
AD-1615225.1	20.07	0.96	28.27	5.54	35.35	7.55
AD-1466070.2	16.18	2.02	25.04	3.47	26.13	2.62
AD-1466083.3	13.64	1.36	30.43	3.95	28.88	5.15
AD-1615325.1	20.68	4.66	36.33	3.73	36.98	12.07
AD-1615326.1	17.18	3.24	28.39	1.38	29.62	7.92
AD-1615226.1	12.46	0.86	16.32	1.63	21.66	5.56
AD-1615227.1	17.87	1.96	22.78	1.99	28.14	2.11
AD-1615228.1	65.18	14.56	63.16	3.33	72.51	5.75
AD-1615229.1	18.69	0.62	28.57	2.83	33.63	4.53
AD-1615230.1	38.21	8.53	38.82	2.31	47.79	4.34
AD-1615231.1	24.37	4.50	29.32	3.56	45.81	6.31
AD-1615232.1	22.61	1.51	26.56	2.11	30.23	4.05
AD-1615233.1	13.78	2.36	22.63	3.10	25.18	4.01
AD-1466100.4	17.06	4.19	21.22	0.66	30.77	3.56
AD-1615279.1	27.11	2.20	39.02	4.45	50.98	4.41
AD-1615280.1	19.69	3.66	24.00	3.36	29.98	4.96
AD-1615281.1	25.34	2.90	29.89	3.40	33.46	2.85
AD-1615282.1	22.19	3.32	30.27	1.17	37.25	4.78
AD-1615283.1	60.04	3.49	63.42	6.66	62.27	4.65
AD-1615284.1	35.84	3.14	34.25	5.22	46.96	3.78
AD-1615285.1	29.87	3.89	28.62	3.76	33.54	3.74
AD-1615287.1	30.09	4.86	34.67	1.75	41.50	1.72
AD-1615288.1	48.14	6.75	51.41	3.16	49.89	4.89
AD-1615291.1	80.92	7.15	74.34	9.29	73.12	2.43
AD-1615292.1	78.74	2.87	71.96	4.46	71.77	5.24
AD-1615293.1	64.80	6.40	63.00	4.34	57.01	5.52
AD-1615294.1	79.46	9.80	64.65	8.74	67.12	7.59
AD-1615295.1	32.90	3.78	31.10	4.78	37.75	4.21

	10 nM		1 nM		0.1 nM	
Duplex	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1615296.1	54.83	2.43	54.74	3.67	57.69	2.44
AD-1615297.1	47.71	3.24	47.85	6.18	41.30	5.80
AD-1615299.1	72.63	5.56	64.43	5.83	63.38	7.44
AD-1466100.5	12.13	3.73	24.66	8.07	20.91	4.13
AD-1615234.1	16.07	3.29	21.79	3.13	20.46	4.71
AD-1615286.1	19.68	1.30	27.22	3.50	36.20	2.70
AD-1615289.1	28.25	3.55	39.71	8.59	37.39	3.39
AD-1615290.1	22.37	1.35	30.79	1.95	40.82	2.36
AD-1615298.1	22.81	0.97	30.37	1.11	36.70	4.61
AD-1466101.2	26.98	2.47	23.42	4.98	35.30	4.13
AD-1615235.1	19.00	3.18	23.35	2.86	27.73	4.91
AD-1615236.1	24.35	4.69	27.01	3.59	33.01	0.11
AD-1615237.1	28.84	2.32	36.73	5.29	52.08	6.15
AD-1615238.1	34.08	5.24	40.58	5.54	52.89	5.38
AD-1615239.1	15.55	4.08	17.08	1.04	25.33	6.07
AD-1615240.1	17.40	1.16	16.52	2.36	25.24	4.61
AD-1615241.1	24.05	3.61	25.31	6.24	33.44	3.61
AD-1615242.1	27.18	5.81	28.38	6.73	33.29	7.02
AD-1615243.1	17.15	4.90	24.65	1.31	30.22	3.88
AD-1615244.1	26.63	2.64	31.35	4.83	39.94	3.89
AD-1466104.3	17.51	1.71	21.62	3.16	25.75	1.80
AD-1466104.4	9.51	1.22	21.91	2.81	21.97	3.69
AD-1615327.1	27.07	5.33	33.19	4.79	40.32	4.99
AD-1615245.1	16.23	2.49	17.17	6.32	24.15	2.42
AD-1615246.1	18.50	1.44	22.65	3.84	25.38	3.39
AD-1615247.1	18.44	3.56	17.79	3.52	26.69	5.95
AD-1615248.1	9.27	1.48	13.51	2.64	15.36	1.27
AD-1615249.1	14.91	0.83	17.76	3.75	16.04	3.73
AD-1615250.1	41.95	4.99	49.08	4.22	59.19	10.96
AD-1615251.1	18.75	2.29	18.80	2.09	16.50	1.03
AD-1615252.1	17.16	2.57	19.49	2.85	21.88	3.63
AD-1615253.1	12.18	1.97	13.92	1.62	19.52	4.74
AD-1466114.4	22.38	0.98	28.53	2.62	44.86	5.45
AD-1615253.2	11.09	0.39	23.05	2.53	28.97	5.20
AD-1615328.1	25.46	2.10	30.19	5.39	48.55	5.01
AD-1615329.1	18.00	2.07	29.35	3.44	45.88	8.47
AD-1615330.1	12.28	1.04	21.69	2.50	32.09	4.96
AD-1615331.1	26.69	5.11	39.59	7.06	46.73	8.67
AD-1615332.1	15.69	2.64	25.35	2.65	26.26	2.38
AD-1615254.1	18.85	0.62	22.39	2.46	28.03	2.37
AD-1615255.1	17.57	4.67	21.59	3.07	23.17	3.45
AD-1615256.1	13.59	1.54	17.80	3.60	21.95	2.51

	10 nM		1 nM		0.1 nM	
Duplex	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1466115.2	22.34	3.17	31.58	1.68	40.98	5.49
AD-1615257.1	14.42	1.10	19.93	1.27	26.92	5.78
AD-1466116.2	26.58	4.75	33.30	4.95	39.77	5.85
AD-1615258.1	25.03	4.09	27.69	2.84	38.18	5.49
AD-1615259.1	19.53	1.57	24.17	4.73	31.07	3.87
AD-1466118.3	10.82	1.71	15.07	1.30	18.07	1.39
AD-1615260.1	21.14	0.82	28.23	1.76	35.08	3.87
AD-1466119.3	19.29	3.36	20.98	3.70	36.60	6.73
AD-1615260.2	26.16	3.28	27.11	3.36	41.53	3.41
AD-1615333.1	21.43	1.52	30.81	1.69	46.49	7.39
AD-1615261.1	20.18	1.97	27.94	2.98	30.40	1.63
AD-1466120.2	23.67	2.32	31.97	3.22	40.33	4.12
AD-1615262.1	18.19	1.50	26.40	3.71	30.38	3.77
AD-1466121.3	22.16	4.20	36.47	3.98	52.73	3.89
AD-1615262.2	18.29	1.06	28.20	1.61	37.47	2.66
AD-1615334.1	26.20	3.20	40.07	5.51	43.08	3.68
AD-1615335.1	18.49	1.58	31.04	5.05	38.00	5.34
AD-1615263.1	24.20	2.99	30.15	0.49	33.36	4.58
AD-1615264.1	18.44	2.08	27.76	3.99	33.93	4.44
AD-1615265.1	19.44	2.58	27.39	2.63	42.95	4.48
AD-1615266.1	15.52	1.86	18.50	4.38	24.88	1.62
AD-1615267.1	25.59	1.37	29.33	3.43	31.63	2.44
AD-1615268.1	11.99	0.80	15.26	1.55	23.34	2.65
AD-1466128.3	15.21	1.17	20.79	0.93	26.59	2.54
AD-1466128.4	16.20	1.33	27.80	3.07	29.68	1.73
AD-1615336.1	30.06	3.48	33.61	0.42	34.88	4.69
AD-1615269.1	20.60	5.45	27.78	4.39	35.30	5.97
AD-1615270.1	21.28	4.32	24.30	2.85	33.43	4.39
AD-1615271.1	30.04	4.73	39.89	5.10	61.97	3.27
AD-1615272.1	20.91	2.48	30.00	4.76	37.93	3.53
AD-1615273.1	16.57	3.56	24.24	3.42	28.05	5.71
AD-1615274.1	21.86	1.17	30.42	1.92	36.50	2.58
AD-1615275.1	16.20	2.69	25.78	2.05	32.41	1.60
AD-1458307.1	50.25	6.41	93.34	8.38	68.75	21.39
AD-1615276.1	18.70	2.80	23.82	2.47	34.61	4.43
AD-1466139.3	17.76	3.09	23.49	4.19	29.19	2.03
AD-1615337.1	37.55	3.14	41.43	5.33	56.33	4.51
AD-1615338.1	29.12	2.65	40.54	4.48	47.77	8.73
AD-1466151.3	19.08	1.43	26.91	2.70	32.55	6.09
AD-1615339.1	16.72	1.03	23.82	2.85	27.13	4.58
AD-1615340.1	26.06	0.67	32.17	3.25	38.62	5.61
AD-1615341.1	21.65	1.89	24.76	3.96	32.37	3.35

Duplex	10 nM		1 nM		0.1 nM	
	Avg % message remaining	SD	Avg % message remaining	SD	Avg % message remaining	SD
AD-1466152.3	16.42	1.84	18.28	2.33	28.16	3.13
AD-1615342.1	23.27	2.06	28.91	1.56	41.76	3.51
AD-1615343.1	20.33	2.32	26.10	2.30	37.86	2.77
AD-1459922.1	81.25	11.77	67.16	8.31	83.60	11.52
AD-1615277.1	13.01	1.26	18.11	1.55	25.55	2.72
AD-1414748.1	43.51	8.48	48.30	6.56	56.75	4.45
AD-114469.2	21.62	1.90	30.79	7.10	39.28	1.60
AD-1615278.1	13.75	2.22	16.86	1.89	18.68	4.81
AD-1452126.1	109.46	11.45	99.43	16.11	118.34	15.48

Example 5. *In vivo* Assessment of RNAi Agents in Non-Human Primates (NHP)

Based on the *in vitro* analyses described above, duplexes targeting Factor V were selected for pre-clinical pharmacodynamics analysis in non-human primates.

Briefly, on Day 0 male non-human primates (n=3) were subcutaneously administered a single 3 mg/kg dose of AD-1615171; AD-1465920; AD-1615312; AD-109630; AD-1615234; AD-1615253; AD-1615278; AD-109630; or AD-1465922; or a single 20 mg/kg dose of AD-109630; or PBS control (see Table below). At Days 1, 8, 15, 21, and 29, post-dose, plasma samples were obtained and the protein level of Factor V was determined by ELISA. The Factor V ELISA was performed in 96-well format, using affinity-purified antibodies to human Factor V from Affinity Biologicals (Cat. No. FV-EIA) - coating antibody and peroxidase-conjugated capture antibody. An eight point standard curve ranging from 200 ng/ml to 0.685ng/ml was generated using purified human FV protein (Invitrogen Cat. No. RP-43126). Before adding to wells, cynomolgus monkey plasma samples were diluted 1:1000 in VisuLize™ Buffer Pak from affinity Biologicals (Cat. No. EIA-PAK-1), supplemented with bovine serum albumin (BSA) to 6%. The peroxidase activity was measured by incubation with chromogenic substrate 3,3',5,5'-tetramethylbenzidine (TMB).

As depicted in FIG. 2 and FIG. 3, all of the duplexes durably and potently reduced Factor V protein levels in plasma.

Group	Number of Males	Test Article	Target Dose Level (mg/kg)	Target Dose Concentration (mg/mL)	Target Dose Volume (mL/kg)
1	3	AD-1615171	3	3	1
2	3	AD-1465920	3	3	1
3	3	AD-1615312	3	3	1
4	3	AD-109630	3	3	1
5	3	AD-1615234	3	3	1
6	3	AD-1615253	3	3	1
7	3	AD-1615278	3	3	1
8	3	AD-109630	20	20	1
9	3	vehicle	NA	NA	1
10	3	AD-1465922	3	3	1

EQUIVALENTS

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

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We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation Factor V (F5) 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 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5.
2. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation Factor V (F5) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding F5, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2, 3, 5, 6-8, 10 and 11.
3. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation Factor V (F5) 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 three nucleotides from any one of the nucleotide sequences of nucleotides 640-668; 747-771; 755-784; 830-855; 1226-1262; 3351-3380; 5821-5858; 5874-5910; 6104-6149; and 6245-6277 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:5.
4. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of coagulation Factor V (F5) 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 three nucleotides from any one of the nucleotide sequence of nucleotides 643-665; 645-667; 346-368; 5830-5852; 6104-6126; 6909-6931; and 1104-1126 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:5.
5. The dsRNA agent of any one of claims 1-4, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-109630;

AD-1465920; AD-1465922; AD-1615171; AD-1615234; AD-1615253; AD-1615278; and AD-1615312.

6. The dsRNA agent of any one of claims 1-4, wherein the dsRNA agent is selected from the group consisting of

AD-109630 comprising a sense strand comprising the nucleotide sequence 5'-CAGGCUUACAUUGACAUAUAAA-3' (SEQ ID NO: 9) and an antisense strand comprising the nucleotide sequence 5'-UUUAAUGUCAAGUAAGCCUGCA-3' (SEQ ID NO: 10);

AD-1465920 comprising a sense strand comprising the nucleotide sequence 5'-GCCUCACACACAUCUAUUACU-3' (SEQ ID NO: 11) and an antisense strand comprising the nucleotide sequence 5'-AGUAAUAGAUGTGUGUGAGGCAU-3' (SEQ ID NO: 12);

AD-1465922 comprising a sense strand comprising the nucleotide sequence 5'-CUCACACACAUCUAUUACUCU-3' (SEQ ID NO: 13) and an antisense strand comprising the nucleotide sequence 5'-AGAGTAAUAGATGUGUGUGAGGC-3' (SEQ ID NO: 14);

AD-1615171 comprising a sense strand comprising the nucleotide sequence 5'-AGUAUGAACCAUAUUUUAAGU-3' (SEQ ID NO: 15) and an antisense strand comprising the nucleotide sequence 5'-ACUUAUUUAUUGGUUCAUACUCU-3' (SEQ ID NO: 16);

AD-1615234 comprising a sense strand comprising the nucleotide sequence 5'-UGCAAACGCCAUUUCUUAUCU-3' (SEQ ID NO: 17) and an antisense strand comprising the nucleotide sequence 5'-AGAUAAGAAUGGCGUUUGCAUC-3' (SEQ ID NO: 18);

AD-1615253 comprising a sense strand comprising the nucleotide sequence 5'-CUGCUAUACCACAGAGUUCUU-3' (SEQ ID NO: 19) and an antisense strand comprising the nucleotide sequence 5'-AAGAACTCUGUGGUUAUAGCAGGA-3' (SEQ ID NO: 20);

AD-1615278 comprising a sense strand comprising the nucleotide sequence 5'-ACAGUUUCCACUAUUUCUCU-3' (SEQ ID NO: 21) and an antisense strand comprising the nucleotide sequence 5'-AGAGAAAUAGUGGAAAACUGUUA-3' (SEQ ID NO: 22); and

AD-1615312 comprising a sense strand comprising the nucleotide sequence 5'-CAGGCUUACAUUGAUUAUAAU-3' (SEQ ID NO: 23) and an antisense strand comprising the nucleotide sequence 5'-AUUAAUAUCAAGUAAGCCUGCG-3' (SEQ ID NO: 24).

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 comprise a modification; substantially all of the nucleotides of the antisense strand

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

9. The dsRNA agent of any one of claims 1-8, wherein all of the nucleotides of the sense strand
5 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
10 is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythymidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxyl-modified nucleotide, a 2'-
15 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 thermally
20 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
25 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.

12. 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 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA),
30 and, a vinyl-phosphonate nucleotide; and combinations thereof.

13. The dsRNA agent 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 agent of claim 13, wherein the thermally destabilizing nucleotide modification is
35 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 glycerol nucleic acid (GNA)

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

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

10 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.

15 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
20 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.

25 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 1-21, wherein the region of complementarity is
between 19 and 23 nucleotides in length.

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

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

26. The dsRNA agent of any one of claims 1-25, 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.

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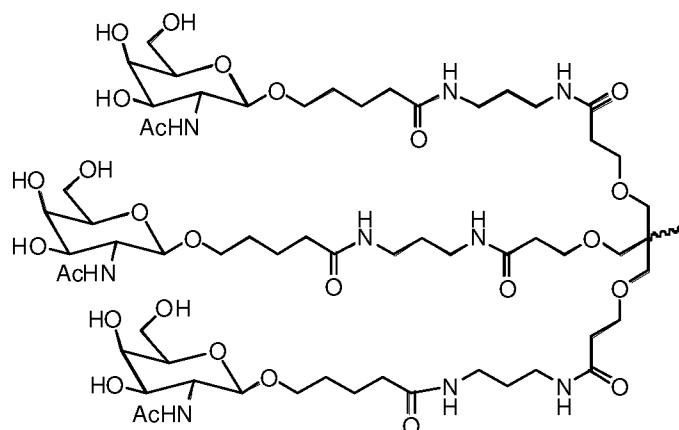
28. The dsRNA agent of claim 27, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

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

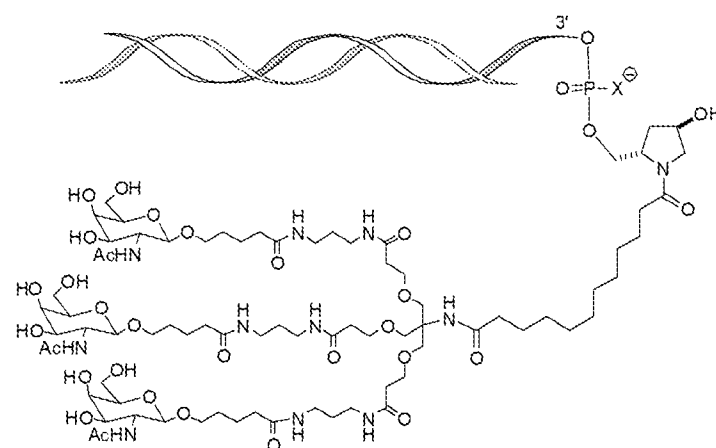
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30. The dsRNA agent of any one of claims 27-29, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

15 31. The dsRNA agent of claim 27 or 28, 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



20

and, wherein X is O or S.

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

5 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.

10

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.

15 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.

20 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 both the 5'- and 3'-terminus of one strand.

25 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.

30 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 coagulation Factor V (F5) comprising the dsRNA agent of any one of claims 1-43.

35 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 45, 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 coagulation Factor V (F5) 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 F5 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 an F5-associated disorder.

55. The method of claim 54, wherein the F5-associated disorder is a disorder associated with thrombosis.

56. The method of claim 55, wherein the disorder associated with thrombosis is selected from the group consisting of venous thrombosis, deep vein thrombosis, genetic thrombophilia, Factor V leiden, prothrombin thrombophilia, purpura fulminans, acquired thrombophilia, antiphospholipid syndrome, systemic lupus erythematosus, drug induced thrombophilia, arterial thrombosis, myocardial infarction, peripheral arterial disease, thromboembolic disease, pulmonary embolus embolic, ischemic stroke, atrial fibrillation, post-surgery deep vein thrombosis, cancer thrombosis and infectious disease thrombosis.

57. The method of any one of claims 51-56, wherein contacting the cell with the dsRNA agent inhibits the expression of F5 by at least 50%, 60%, 70%, 80%, 90%, or 95%.

58. The method of any one of claims 51-57, wherein inhibiting expression of F5 causes a decrease in F5 protein levels in the subject's serum by at least 50%, 60%, 70%, 80%, 90%, or 95%.

59. A method of treating a subject having a disorder that would benefit from reduction in coagulation Factor V (F5) expression, the method comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-44, or the pharmaceutical composition of any one of claims 45-50, thereby treating the subject having the disorder that would benefit from reduction in F5 expression.

60. A method of preventing at least one symptom in a subject having a disorder that would benefit from reduction in coagulation Factor V (F5) expression, the method 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 F5 expression.

61. The method of claim 59 or 60, wherein the disorder is an F5-associated disorder.

62. The method of claim 61, wherein the F5-associated disorder is a disorder associated with thrombosis.

63. The method of claim 62, wherein the disorder associated with thrombosis is selected from a group consisting of venous thrombosis, deep vein thrombosis, genetic thrombophilia, Factor V leiden, prothrombin thrombophilia, purpura fulminans, acquired thrombophilia, antiphospholipid syndrome, systemic lupus erythematosus, drug induced thrombophilia, arterial thrombosis, myocardial infarction, peripheral arterial disease, thromboembolic disease, pulmonary embolus embolic, ischemic stroke, atrial fibrillation, post-surgery deep vein thrombosis, cancer thrombosis and infectious disease thrombosis.

64. The method of claim 59 or 60, wherein the subject is a human.

65. The method of any one of claims 59-64, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

66. The method of any one of claims 59-65, wherein the dsRNA agent is administered to the subject subcutaneously.

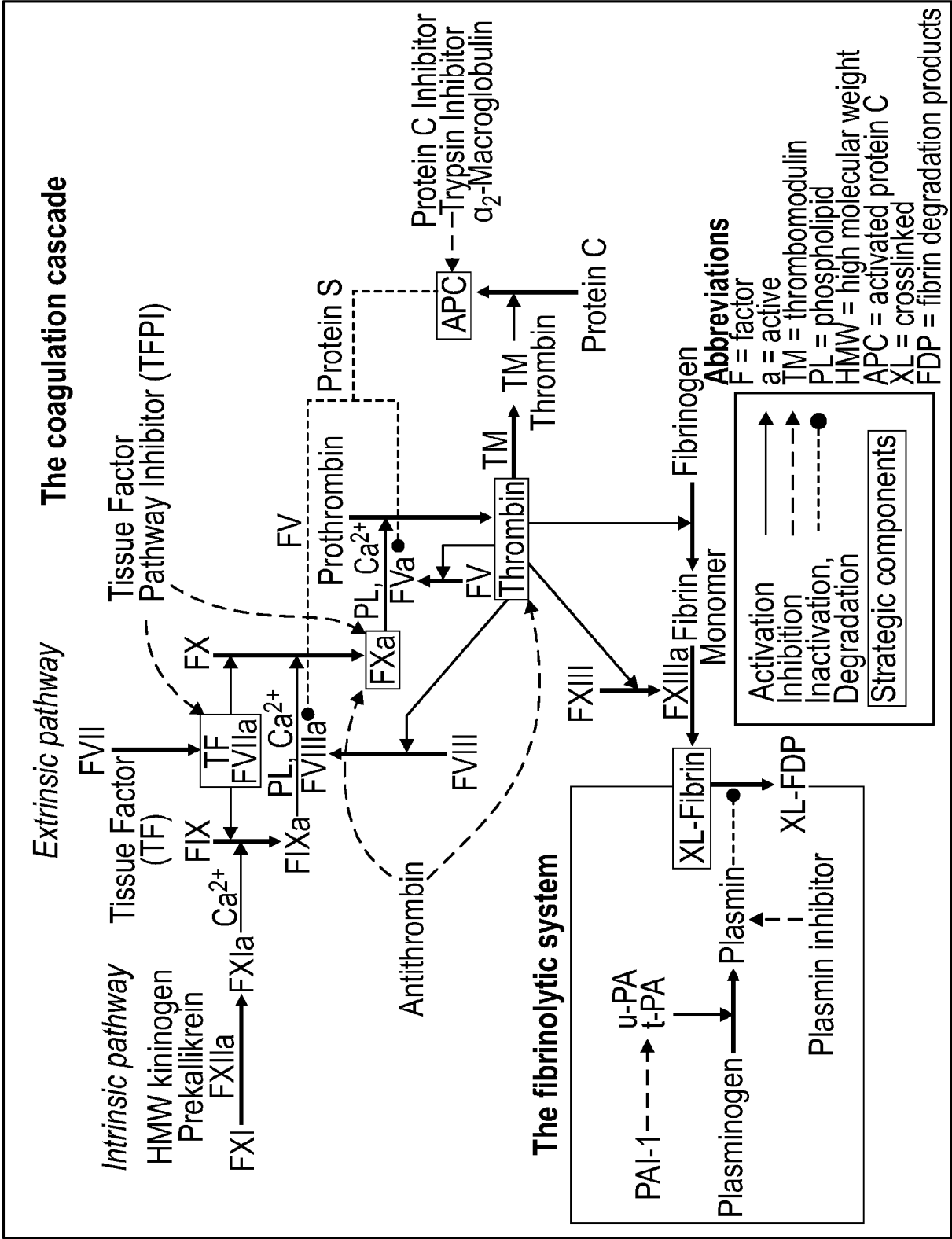
67. The method of any one of claims 59-66, further comprising determining the level of F5 in a sample from the subject.

68. The method of claim 67, wherein the level of F5 in the subject sample is F5 protein level in a blood or serum sample.

69. The method of any one of claims 59-68, further comprising administering to the subject an additional therapeutic agent and/or treatment.

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. An RNA-induced silencing complex (RISC) comprising an antisense strand of any of the dsRNA agents of any one of claims 1-43.



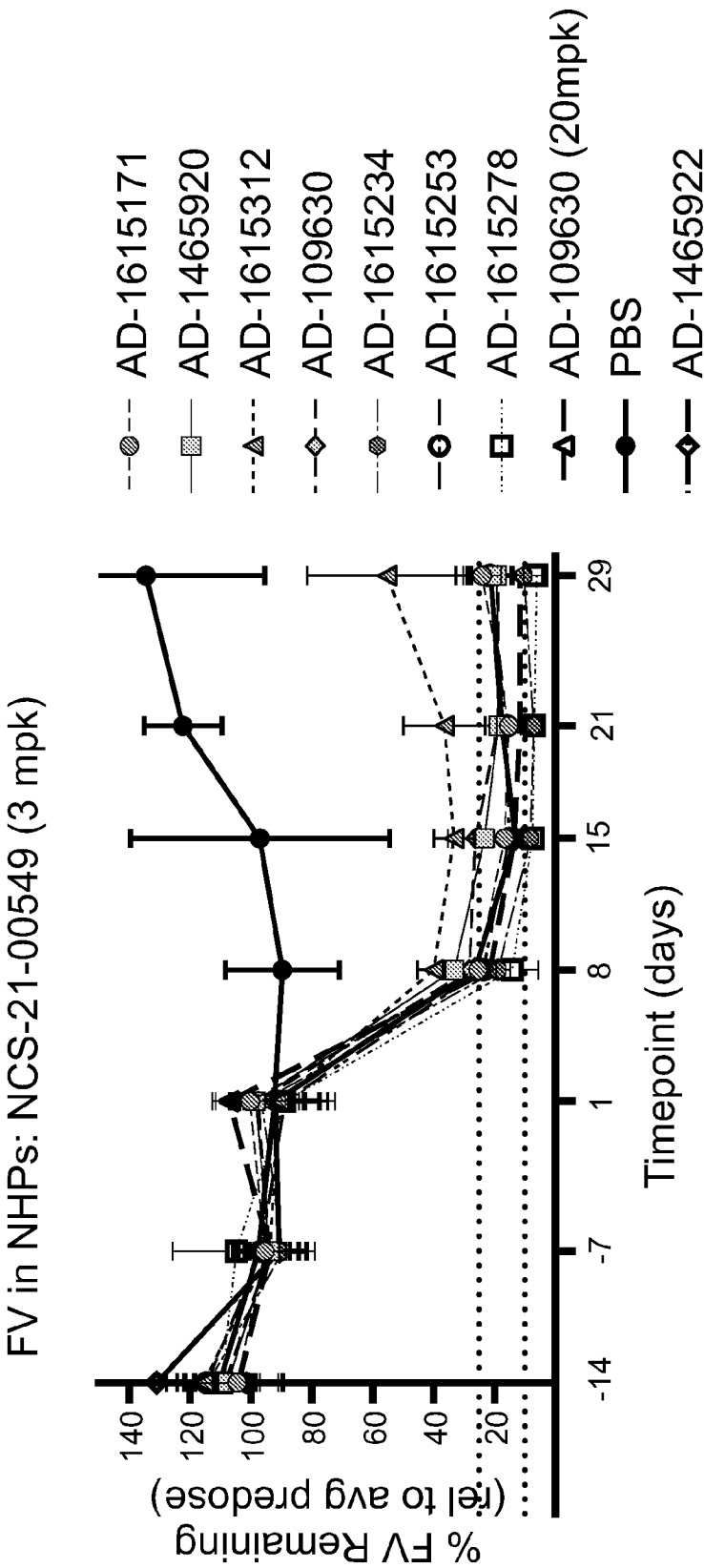
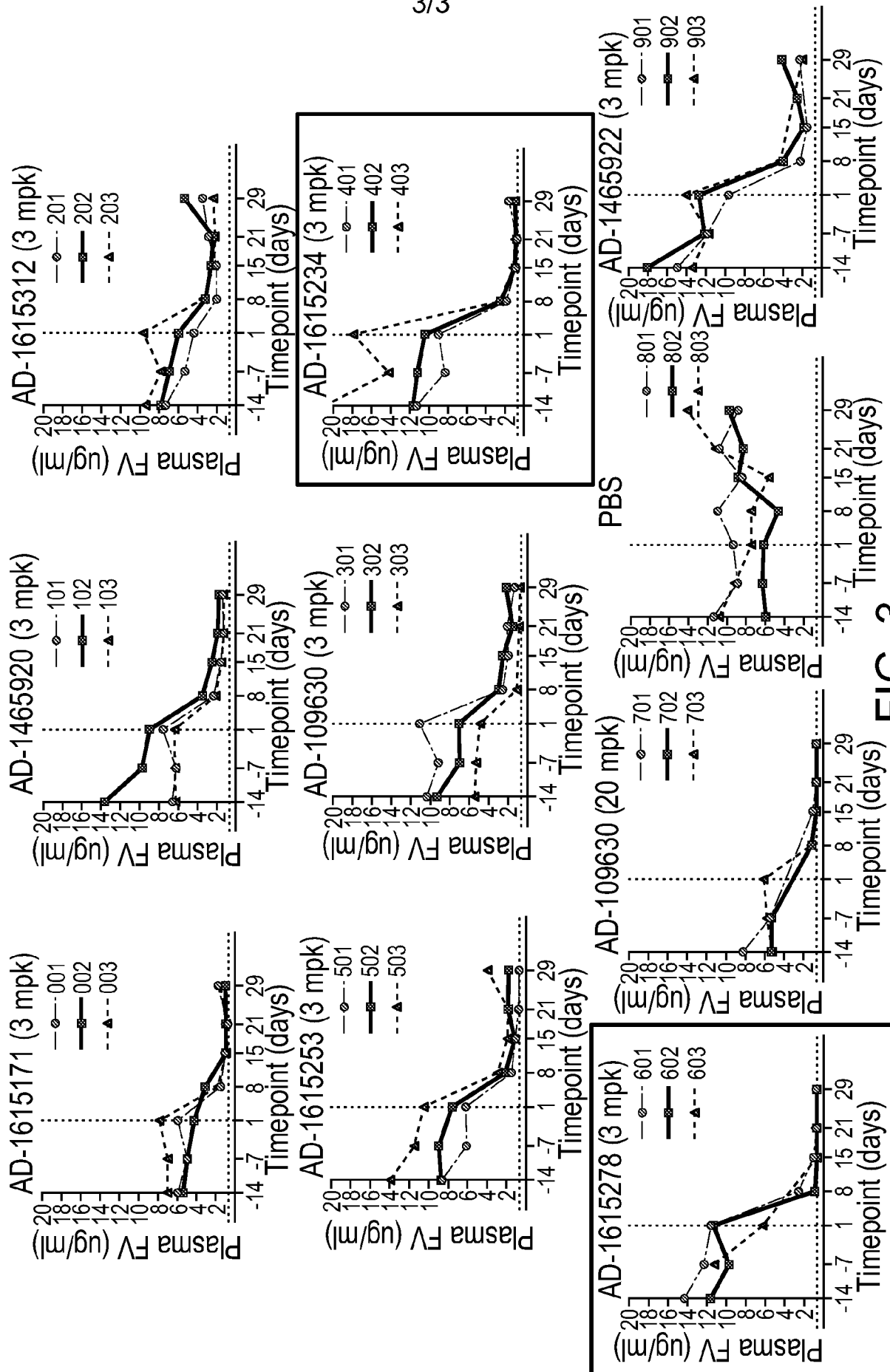


FIG. 2



INTERNATIONAL SEARCH REPORT

International application No

PCT/US2021/059047

A. CLASSIFICATION OF SUBJECT MATTER

INV. C12N15/113

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, Sequence Search, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 752 536 A1 (RNAI CO LTD [JP])	1-5, 7-71
A	14 February 2007 (2007-02-14) claims 1, 7, 8, 10, 15, 18-22, 32; figure 46; sequences 162564-162716 the whole document -& DATABASE EMBL [Online] 18 April 2011 (2011-04-18), Anonymous: "WO 2005116204-A/162592: Double strand polynucleotides generating RNA interference.", XP055892265, retrieved from EBI accession no. EM_PAT:FW756066 Database accession no. FW756066 the whole document -/--	6



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

16 February 2022

Date of mailing of the international search report

24/02/2022

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/059047

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2021/059047

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	-& DATABASE EMBL [Online] 18 April 2011 (2011-04-18), Anonymous: "WO 2005116204-A/162577: Double strand polynucleotides generating RNA interference.", XP055892321, retrieved from EBI accession no. EM_PAT:FW756051 Database accession no. FW756051 the whole document -----	
X	WO 2007/056331 A2 (ALNYLAM PHARMACEUTICALS INC [US]; VORNLOCHER HANS-PETER [DE] ET AL.) 18 May 2007 (2007-05-18) claims 1-14; table 1 the whole document -----	1-5, 7-71
X	WO 2008/043561 A2 (MAX PLANCK GESELLSCHAFT [DE]; MEYER THOMAS F [DE] ET AL.) 17 April 2008 (2008-04-17) claims 10-16, 18, 19, 42; example 4; table 4; sequences 2983, 2984, 2986 the whole document -----	1, 4, 5, 7-54, 57-61, 64-71
A	JAYAPRAKASH K. NAIR ET AL: "Multivalent N-Acetylgalactosamine-Conjugated siRNA Localizes in Hepatocytes and Elicits Robust RNAi-Mediated Gene Silencing", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 136, no. 49, 10 December 2014 (2014-12-10), pages 16958-16961, XP055181463, ISSN: 0002-7863, DOI: 10.1021/ja505986a page 16959 the whole document -----	7-43
A	SHIGEO MATSUDA ET AL: "siRNA Conjugates Carrying Sequentially Assembled Trivalent N-Acetylgalactosamine Linked Through Nucleosides Elicit Robust Gene Silencing In Vivo in Hepatocytes", ACS CHEMICAL BIOLOGY, vol. 10, no. 5, 2 March 2015 (2015-03-02), pages 1181-1187, XP055448305, ISSN: 1554-8929, DOI: 10.1021/cb501028c figure 1; table 1 the whole document -----	7-43

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2021/059047

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