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(71) Applicant(s)
ALNYLAM PHARMACEUTICALS, INC.

(72) Inventor(s)
KEATING, Mark;MCININCH, James, D.;SCHLEGEL, Mark, K.

(74) Agent / Attorney
Griffith Hack, Level 15, 376-390 Collins Street, Melbourne, VIC, 3000, AU

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(71) Applicant: **ALNYLAM PHARMACEUTICALS, INC.** [US/US]; 675 West Kendall Street, Henri A. Termeer Square, Cambridge, MA 02142 (US).

(72) Inventors: **KEATING, Mark**; 675 West Kendall Street, Henri A. Termeer Square, Cambridge, MA 02142 (US). **MCININCH, James, D.**; 675 West Kendall Street, Henri A. Termeer Square, Cambridge, MA 02142 (US). **SCHLEGEL, Mark, K.**; 675 West Kendall Street, Henri A. Termeer Square, Cambridge, MA 02142 (US).

(74) Agent: **ZACHARAKIS, Maria, Laccotripe** et al.; McCarter & English, LLP, 265 Franklin Street, Boston, MA 02110 (US).

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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.

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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.

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 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 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) 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 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 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 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'-CAGGCUUACAUUGACAUUAAA-3' (SEQ ID NO: 9) and an antisense strand comprising the nucleotide sequence 5'-UUUAAUGUCAAUGUAAGCCUGCA-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'-AGUAUGAACCAUAUUUUAAGU -3' (SEQ ID NO: 15) and an antisense strand comprising the nucleotide sequence 5'- ACUUAAAAUAUGGUUCAUACUCU -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);

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'-ACAGUUUUCCACUAUUUCUCU -3' (SEQ ID NO: 21) and an antisense strand comprising the nucleotide sequence 5'- AGAGAAAUAGUGGAAAACUGUUA -3' (SEQ ID NO: 22); and

wherein AD-1615278 comprises a sense strand comprising the nucleotide sequence 5'-ACAGUUUUCCACUAUUUCUCU -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'-CAGGCUUACAUUGAUAUUAAU -3' (SEQ ID NO: 23) and an antisense strand comprising the nucleotide sequence 5'- AUUAAUAUCAAUGUAAGCCUGCG -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'-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'-ACAGUUUUCCACUAUUUCUCU -3' (SEQ ID NO: 21) and an antisense strand comprising the nucleotide sequence 5'- AGAGAAAUAGUGGAAAACUGUUA -3' (SEQ ID NO: 22).

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.

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

In one embodiment, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythimidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a 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.

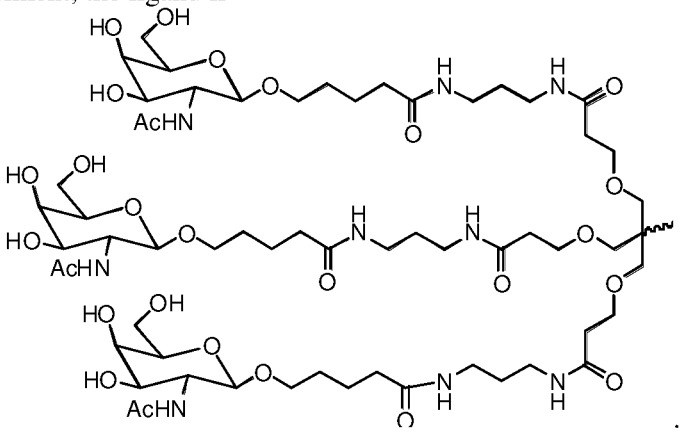
In one embodiment, the dsRNA agent further comprises a ligand.

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

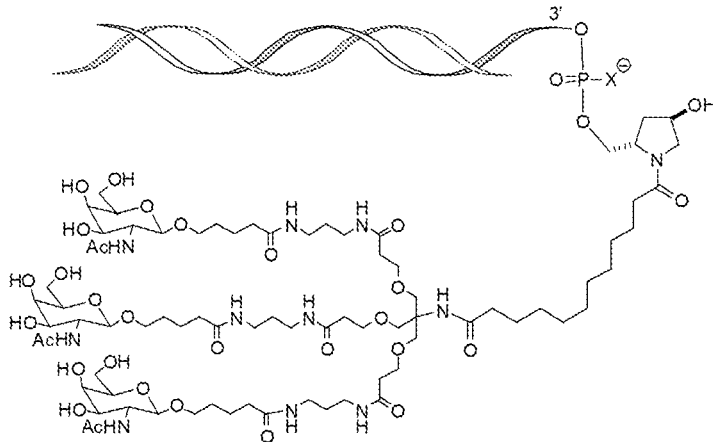
In one embodiment, the ligand is an N-acetylgalactosamine (GalNAc) derivative.

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



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



and, wherein X is O or S.

In one embodiment, the X is O.

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

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

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

In one embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at 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.

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; 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, 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 emdobiment, 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 emboidments, 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 antistreplase (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 immunosuppresant 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 stablizer. 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 μg/ml, The lower limit of quantification (LLOQ) is 0.69 μg /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; 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, using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a coagulation Factor V gene.

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

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.

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 potently 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.

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.

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.

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

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

As used herein, "no more than" or "or less 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 embodiments, the target sequence is about 21 to about 23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

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

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

The terms "iRNA", "RNAi agent," "iRNA agent,", "RNA interference agent" as used interchangeably herein, refer to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript *via* an RNA-induced silencing complex (RISC) pathway. iRNA directs the sequence-specific degradation of mRNA through a process known as RNA interference (RNAi). The iRNA modulates, *e.g.,* inhibits, the expression of a 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 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). 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.

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

In certain embodiments, an "iRNA" for use in the compositions, uses, and methods of the invention is a double stranded RNA and is referred to herein as a "double stranded RNA agent," "double stranded RNA (dsRNA) molecule," "dsRNA agent," or "dsRNA". The term "dsRNA", refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary nucleic acid strands, referred to as having "sense" and "antisense" orientations with respect to a target RNA, *i.e.,* a coagulation Factor V (F5) gene. In some embodiments of the invention, a double stranded RNA (dsRNA) triggers the degradation of a target RNA, *e.g.,* an mRNA, through a post-transcriptional gene-silencing mechanism referred to herein as RNA interference or RNAi.

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

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

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

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

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

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

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

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

In certain embodiments, an iRNA agent of the invention is a dsRNA, each strand of which comprises 19-23 nucleotides, that interacts with a target RNA sequence, *e.g.*, a 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 oC or 70 oC for 12-16 hours followed by washing (see, e.g., "Molecular Cloning: A Laboratory Manual, Sambrook, et al. (1989) Cold Spring Harbor Laboratory Press). Other conditions, such as physiologically relevant conditions as can be encountered inside an organism, can apply. The skilled person will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides.

Complementary sequences within an iRNA, *e.g.*, within a dsRNA as described herein, include base-pairing of the oligonucleotide or polynucleotide comprising a first nucleotide sequence to an oligonucleotide or polynucleotide comprising a second nucleotide sequence over the entire length of one or both nucleotide sequences. Such sequences can be referred to as "fully complementary" with respect to each other herein. However, where a first sequence is referred to as "substantially complementary" with respect to a second sequence herein, the two sequences can be fully complementary, or they can form one or more, but generally not more than 5, 4, 3, or 2 mismatched base pairs upon hybridization for a duplex up to 30 base pairs, while retaining the ability to hybridize under the conditions most relevant to their ultimate application, *e.g.*, inhibition of gene expression *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; 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.

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 lowerng 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 symtoms thereby meeting the diagnostic criteria for that disease. In certain embodiments, prevention includes delayed progression to meeting the diagnostic criteria of the disease by days, weeks, months or years as compared to what would be predicted by natural history studies or the typical progression of the disease.

As used herein, the 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; 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.

"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.

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

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

sometimes referenced in the art, modified RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In some embodiments, a modified iRNA will have a phosphorus atom in its internucleoside backbone.

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

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

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

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

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

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

Modified RNAs can also contain one or more substituted sugar moieties. The iRNAs, *e.g.*, dsRNAs, featured herein can include one of the following at the 2'-position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nOCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an iRNA, or a group for improving the pharmacodynamic properties of an iRNA, and other substituents having similar

properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminooxyethoxy, *i.e.*, a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH_2--O--CH_2--$N(CH_2)_2$. Further exemplary modifications include : 5'-Me-2'-F nucleotides, 5'-Me-2'-OMe nucleotides, 5'-Me-2'-deoxynucleotides, (both R and S isomers in these three families); 2'-alkoxyalkyl; and 2'-NMA (N-methylacetamide).

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

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

featured in the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., dsRNA Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

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

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'-CH_2-O-2' bridge. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193). Examples of bicyclic nucleosides for use in the polynucleotides of the invention include without limitation nucleosides comprising a bridge between the 4′ and the 2′ ribosyl ring atoms. In certain embodiments, the antisense polynucleotide agents of the invention include one or more bicyclic nucleosides comprising a 4′ to 2′ bridge. Examples of such 4′ to 2′ bridged bicyclic nucleosides, include but are not limited to 4′-(CH_2)—O-2′ (LNA); 4′-(CH_2)—S-2′; 4′-(CH_2)$_2$—O-2′ (ENA); 4′-CH(CH_3)—O-2′

(also referred to as "constrained ethyl" or "cEt") and 4′-CH(CH_2OCH_3)—O-2′ (and analogs thereof; see, *e.g.*, U.S. Patent No. 7,399,845); 4′-C(CH_3)(CH_3)—O-2′ (and analogs thereof; see *e.g.*, U.S. Patent No. 8,278,283); 4′-CH_2—N(OCH_3)-2′ (and analogs thereof; see *e.g.*, U.S. Patent No. 8,278,425); 4′-CH_2—O—N(CH_3)-2′ (see, *e.g.*, U.S. Patent Publication No. 2004/0171570); 4′-CH_2—N(R)—O-2′, wherein R is H, C1-C12 alkyl, or a protecting group (see, *e.g.*, U.S. Patent No. 7,427,672); 4′-CH_2—C(H)(CH_3)-2′ (see, *e.g.*, Chattopadhyaya *et al., J. Org. Chem.*, 2009, 74, 118-134); and 4′-CH_2—C(=CH_2)-2′ (and analogs thereof; see, *e.g.*, U.S. Patent No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein by reference.

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

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

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(CH_3)-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-(acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-0-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"- phosphate, inverted base dT(idT) and others. Disclosure of this modification can be found in WO2011/005861.

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

A. Modified iRNAs Comprising Motifs of the Invention

In certain aspects of the invention, the double stranded RNA agents of the invention include agents with chemical modifications as disclosed, for example, in WO2013/075035, the entire contents of each of which are incorporated herein by reference. 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 antisense strand of the dsRNAi agent may otherwise be completely modified. The introduction of these motifs interrupts the modification pattern, if present, of the sense or antisense strand. The dsRNAi agent may be optionally conjugated with a GalNAc derivative ligand, for instance on the sense strand.

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

Accordingly, the invention provides double stranded RNA agents capable of inhibiting the expression of a target gene (*i.e.*, F5 gene) *in vivo*. The RNAi agent comprises a sense strand and an antisense strand. Each strand of the RNAi agent may be, for example, 17-30 nucleotides in length, 25-30 nucleotides in length, 27-30 nucleotides in length, 19-25 nucleotides in length, 19-23 nucleotides in length, 19-21 nucleotides in length, 21-25 nucleotides in length, or 21-23 nucleotides in length.

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

length, or 21-23 nucleotide pairs in length. In another example, the duplex region is selected from 19, 20, 21, 22, 23, 24, 25, 26, and 27 nucleotides in length.

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

In certain embodiments, the nucleotides in the overhang region of the dsRNAi agent can each independently be a modified or unmodified nucleotide including, but no limited to 2'-sugar modified, such as, 2'-F, 2'-O-methyl, thymidine (T), 2`-O-methoxyethyl-5-methyluridine (Teo), 2`-O-methoxyethyladenosine (Aeo), 2`-O-methoxyethyl-5-methylcytidine (m5Ceo), and any combinations thereof.

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

The 5'- or 3'- overhangs at the sense strand, antisense strand, or both strands of the dsRNAi agent may be phosphorylated. In some embodiments, the overhang region(s) contains two nucleotides having a phosphorothioate between the two nucleotides, where the two nucleotides can be the same or different. In some embodiments, the overhang is present at the 3'-end of the sense strand, antisense strand, or both strands. In some embodiments, this 3'-overhang is present in the antisense strand. In some embodiments, this 3'-overhang is present in the sense strand.

The 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. Alternatively, at least two nucleotides may overlap, or all three nucleotides may overlap.

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

Like the sense strand, the antisense strand of the dsRNAi agent may contain more than one motifs of three identical modifications on three consecutive nucleotides, with at least one of the motifs occurring at or near the cleavage site of the strand. This antisense strand may also contain one or more wing modifications in an alignment similar to the wing modifications that may be present on the sense strand.

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

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

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

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

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

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

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

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

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

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

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

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

The type of modifications contained in the alternating motif may be the same or different. For example, if A, B, C, D each represent one type of modification on the nucleotide, the alternating pattern, *i.e.*, modifications on every other nucleotide, may be the same, but each of the sense strand or antisense strand can be selected from several possibilities of modifications within the alternating motif such as "ABABAB…", "ACACAC…" "BDBDBD…" or "CDCDCD…," *etc.*

In some embodiments, the dsRNAi agent of the invention comprises the modification pattern for the alternating motif on the sense strand relative to the modification pattern for the alternating motif on the antisense strand is shifted. The shift may be such that the modified group of nucleotides of the sense strand corresponds to a differently modified group of nucleotides of the antisense strand and *vice versa*. For example, the sense strand when paired with the antisense strand in the dsRNA duplex, the alternating motif in the sense strand may start with "ABABAB" from 5'to 3' of the strand and the alternating motif in the antisense strand may start with "BABABA" from 5' to 3' of the strand within the duplex region. As another example, the alternating motif in the sense strand may start with "AABBAABB" from 5' to 3' of the strand and the alternating motif in the antisense strand may start with "BBAABBAA" from 5' to 3' of the strand within the duplex region, so that there is a complete or partial shift of the modification patterns between the sense strand and the antisense strand.

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

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

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

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

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

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

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

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

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

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

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

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

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

wherein:

i and j are each independently 0 or 1;

p and q are each independently 0-6;

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

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

each n_p and n_q independently represent an overhang nucleotide;

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

XXX, YYY, and ZZZ each independently represent one motif of three identical modifications on three consecutive nucleotides. In 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);

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

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

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

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

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

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

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

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

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

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

wherein:

k and l are each independently 0 or 1;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

When the antisense strand is represented as formula (IIa), each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

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

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

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

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

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

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

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

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

antisense: 3' n_p'-N_a'-(X'X'X')$_k$-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')$_l$-N_a'-n_q' 5'

(III)

wherein:

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

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

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

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

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

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

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

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

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

3' n_p'-N_a'-Y′Y′Y′ -N_a'n_q' 5'

(IIIa)

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

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

(IIIb)

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

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

(IIIc)

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

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

(IIId)

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

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

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

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

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

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

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

nucleotides form base pairs with the corresponding Z′ nucleotides; or all three of the Z nucleotides all form base pairs with the corresponding Z′ nucleotides.

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

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

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

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

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

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

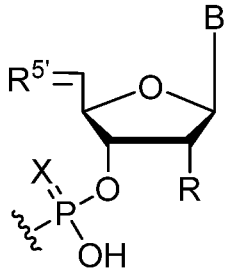
In one embodiment, two dsRNAi agents represented by at least one of formulas (III), (IIIa), (IIIb), (IIIc), and (IIId) are linked to each other at the 5' end, and one or both of the 3' ends, and are optionally conjugated to a ligand. Each of the agents can target the same gene or two different genes;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

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

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

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

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



wherein X is O or S;

R is hydrogen, hydroxy, fluoro, or 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.

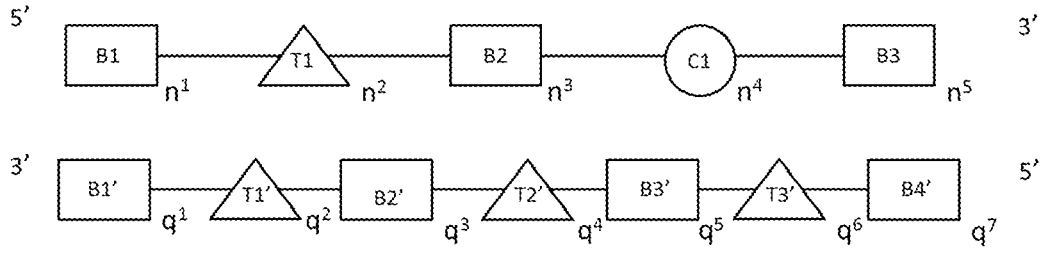
i. Thermally Destabilizing Modifications

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

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

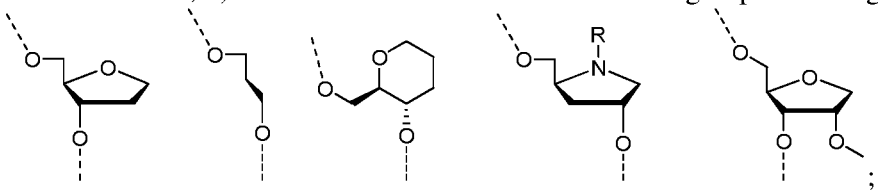
An iRNA agent comprises a sense strand and an antisense strand, each strand having 14 to 40 nucleotides. The RNAi agent may be represented by formula (L):



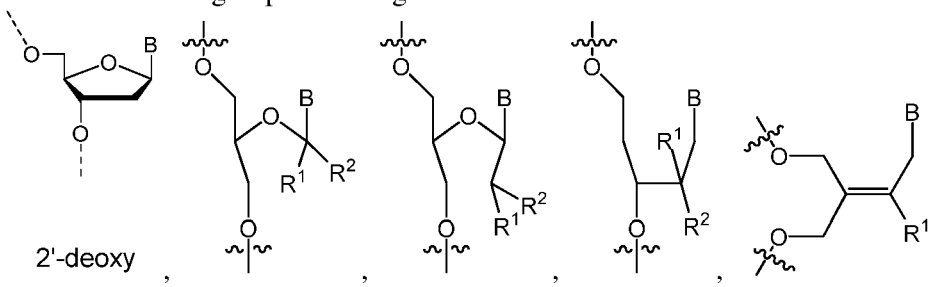
(L),

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

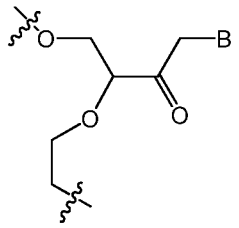
C1 is a thermally destabilizing nucleotide placed at a site opposite to the seed region of the antisense strand (*i.e.*, at positions 2-8 of the 5'-end of the antisense strand or at positions 2-9 of the 5'-end of the antisense strand). For example, C1 is at a position of the sense strand that pairs with 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:



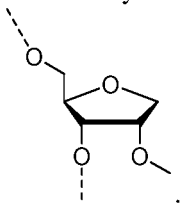
; and iii) sugar modification selected from the group consisting of:



2'-deoxy , , , , , and



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



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T1, T1', T2', and T3' each independently represent a nucleotide comprising a modification providing the nucleotide a steric bulk that is less or equal to the steric bulk of a 2'-OMe modification. A steric bulk refers to the sum of steric effects of a modification. Methods for determining steric effects of a modification of a nucleotide are known to one skilled in the art. The modification can be at the 2'

position of a ribose sugar of the nucleotide, or a modification to a non-ribose nucleotide, acyclic nucleotide, or the backbone of the nucleotide that is similar or equivalent to the 2' position of the ribose sugar, and provides the nucleotide a steric bulk that is less than or equal to the steric bulk of a 2'-OMe modification. For example, T1, T1', T2', and T3' are each independently selected from DNA, RNA, LNA, 2'-F, and 2'-F-5'-methyl. In one embodiment, T1 is DNA. In one embodiment, T1' is DNA, RNA or LNA. In one embodiment, T2' is DNA or RNA. In one embodiment, T3' is DNA or RNA.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In an exemplary embodiment, T1 is at the cleavage site of the sense strand, for instance, at position 11 from the 5' end of the sense strand, when the sense strand is 19-22 nucleotides in length, and n^2 is 1; T1' is at position 14 from the 5' end of the antisense strand, and q^2 is equal to 1, and the modification to T1' is at the 2' position of a ribose sugar or at positions in a non-ribose, acyclic or backbone that provide less steric bulk than a 2'-OMe ribose; T2' is at positions 6-10 from the 5' end of the antisense strand, and q^4 is 1; and T3' is at position 2 from the 5' end of the antisense strand, and q^6 is equal to 1, and the modification to T3' is at the 2' position or at positions in a non-ribose, acyclic or backbone that provide less than or equal to steric bulk than a 2'-OMe ribose.

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

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

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

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

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

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

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

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

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

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

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

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

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

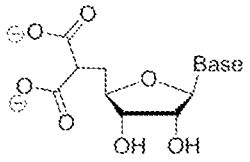
optionally with at least 2 additional TT at the 3'-end of the antisense strand; with two phosphorothioate internucleotide linkage modifications within positions 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions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

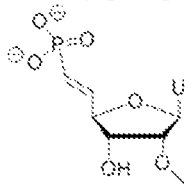
In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'-OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, q^4 is 0, B3' is 2'-OMe or 2'-F, q^5 is 7, T3' is 2'-F, q^6 is 1, B4' is 2'-OMe, and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

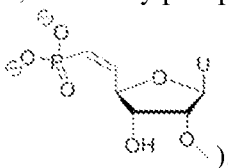
In one embodiment, B1 is 2'-OMe or 2'-F, n^1 is 8, T1 is 2'F, n^2 is 3, B2 is 2'-OMe, n^3 is 7, n^4 is 0, B3 is 2'OMe, n^5 is 3, B1' is 2'-OMe or 2'-F, q^1 is 9, T1' is 2'-F, q^2 is 1, B2' is 2'-OMe or 2'-F, q^3 is 4, T2' is 2'-F, q^4 is 2, B3' is 2'-OMe or 2'-F, q^5 is 5, T3' is 2'-F, q^6 is 1, B4'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

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

The RNAi agent can comprise a phosphorus-containing group at the 5'-end of the sense strand or antisense strand. The 5'-end phosphorus-containing group can be 5'-end phosphate (5'-P), 5'-end phosphorothioate (5'-PS), 5'-end phosphorodithioate (5'-PS_2), 5'-end vinylphosphonate (5'-

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

). When the 5'-end phosphorus-containing group is 5'-end vinylphosphonate (5'-VP), the 5'-VP can be either 5'-*E*-VP isomer (*i.e.*, *trans*-vinylphosphonate, 

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

), or mixtures thereof.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

two phosphorothioate internucleotide linkage modifications within position 1-5 of the sense strand (counting from the 5'-end of the sense strand), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end of the antisense strand). The RNAi agent also comprises a 5'- PS_2.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

strand). The RNAi agent also comprises a 5'- PS_2 and a targeting ligand. In one embodiment, the 5'-PS_2 is at the 5'-end of the antisense strand, and the targeting ligand is at the 3'-end of the sense strand.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

and

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 25 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 21 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

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

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

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

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

(a) a sense strand having:

(i) a length of 19 nucleotides;

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

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

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

and

(b) an antisense strand having:

(i) a length of 21 nucleotides;

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

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

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

In certain embodiments, the iRNA for use in the methods of the invention is an agent selected from agents listed in any one of Tables 2, 3, 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. Acid. Sci. USA*, 1989, 86: 6553-6556). In other embodiments, the ligand is cholic acid (Manoharan *et al.*, *Biorg. Med. Chem. Let.*, 1994, 4:1053-1060), a thioether, *e.g.*, beryl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660:306-309; Manoharan *et al.*, *Biorg. Med. Chem. Let.*, 1993, 3:2765-2770), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, 20:533-538), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J*, 1991, 10:1111-1118; Kabanov *et al.*, *FEBS Lett.*, 1990, 259:327-330; Svinarchuk *et al.*, *Biochimie*, 1993, 75:49-54), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651-3654; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18:3777-3783), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995, 14:969-973), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651-3654), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, 1264:229-237), or an octadecylamine or hexylamino-carbonyloxycholesterol moiety (Crooke *et al.*, J. *Pharmacol. Exp. Ther.*, 1996, 277:923-937).

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

Ligands can include a naturally occurring substance, such as a protein (*e.g.*, human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (*e.g.*, a dextran, pullulan,

chitin, chitosan, inulin, cyclodextrin, N-acetylglucosamine, N-acetylgalactosamine, or hyaluronic acid); or a lipid. The ligand can also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.*, a synthetic polyamino acid. Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

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

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

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

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

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

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

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

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

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

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

A. Lipid Conjugates

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

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

In certain embodiments, the lipid based ligand binds HSA. In 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 reversed.

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

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

B. Cell Permeation Agents

In another aspect, the ligand is a cell-permeation agent, such as a helical cell-permeation agent. In some embodiments, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopedia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. In some embodiments, the helical agent is an alpha-helical agent, which 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 peptidiomimemtics may include D-amino acids, as well as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the integrin ligand, such as PECAM-1 or VEGF.

A "cell permeation peptide" is capable of permeating a cell, *e.g.,* a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, an α-helical linear peptide (*e.g.*, LL-37 or Ceropin P1), a disulfide bond-containing peptide (*e.g.*, α -defensin, β-defensin or bactenecin), or a peptide containing only one or two dominating amino acids (*e.g.*, PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni *et al.*, Nucl. Acids Res. 31:2717-2724, 2003).

C. Carbohydrate Conjugates

In some embodiments of the compositions and methods of the invention, an iRNA further comprises a carbohydrate. The carbohydrate conjugated iRNA is advantageous for the *in vivo* delivery of nucleic acids, as well as compositions suitable for *in vivo* therapeutic use, as described herein. As used herein, "carbohydrate" refers to a compound which is either a carbohydrate *per se* made up of one or more monosaccharide units having at least 6 carbon atoms (which can be linear, branched or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom; or a compound having as a part thereof a carbohydrate moiety made up of one or more monosaccharide units each having at least six carbon atoms (which can be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Representative carbohydrates include the sugars (mono-, di-, tri-, and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9 monosaccharide units), and polysaccharides such as starches, glycogen, cellulose and polysaccharide gums. Specific monosaccharides include C5 and above (*e.g.,* C5, C6, C7, or C8) sugars; di- and trisaccharides include sugars having two or three monosaccharide units (*e.g.,* C5, C6, C7, or C8).

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

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

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

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

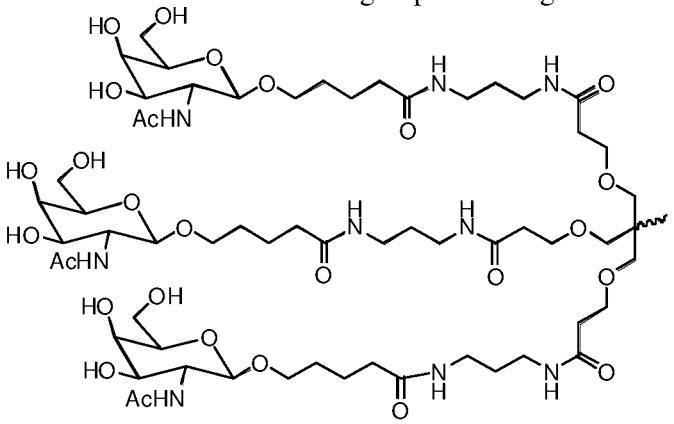
In certain embodiments, the double stranded RNAi agents of the invention comprise one GalNAc or GalNAc derivative attached to the iRNA agent. In certain embodiments, the double

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

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

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

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



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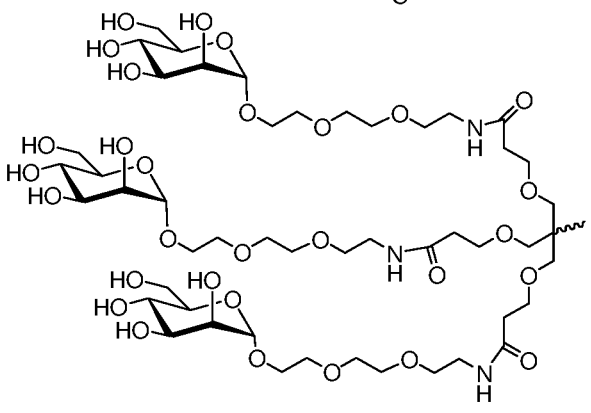

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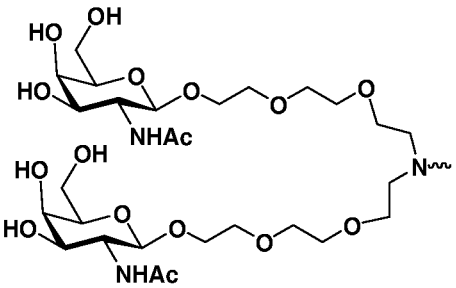

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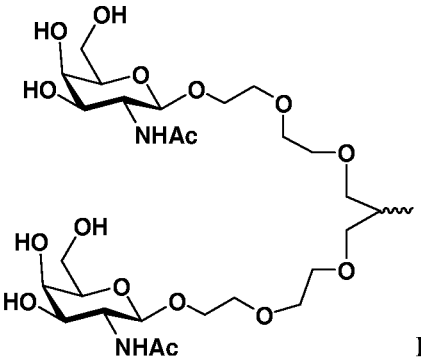

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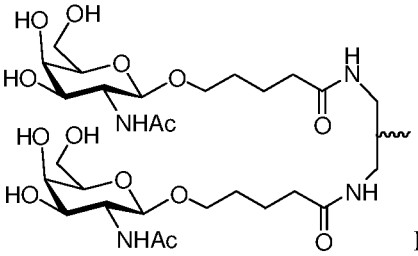

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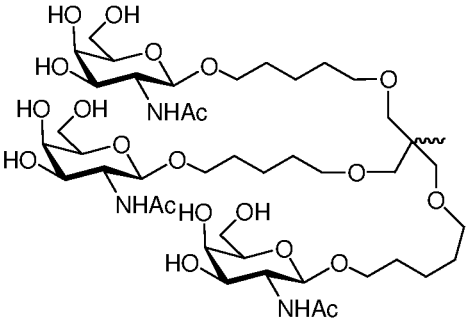

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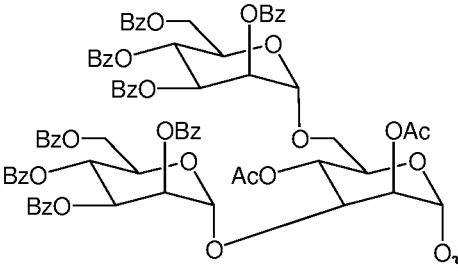

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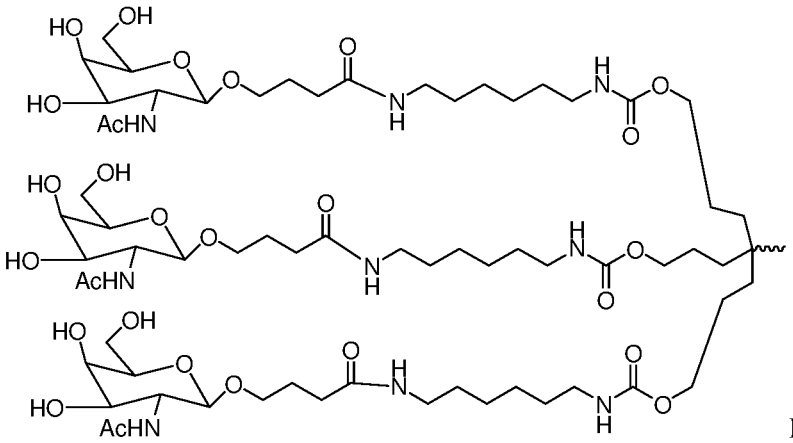

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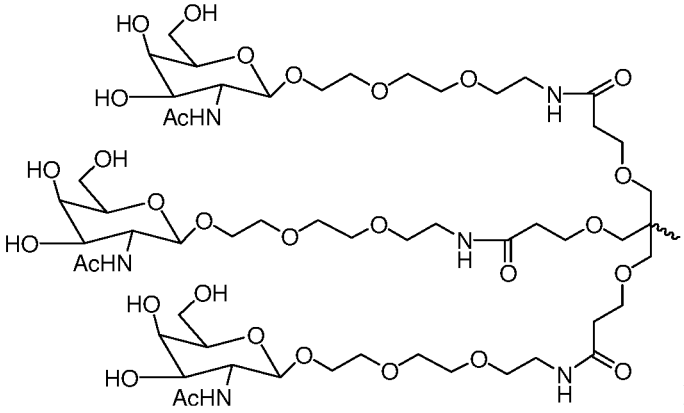

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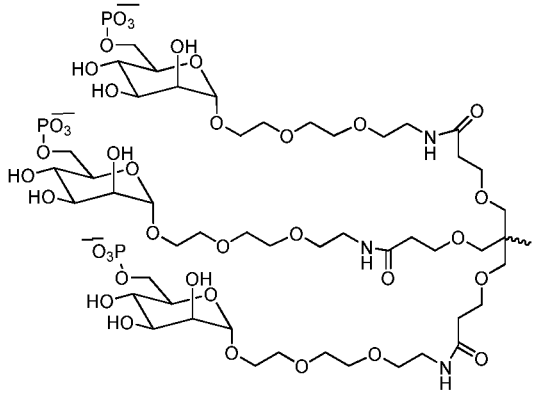

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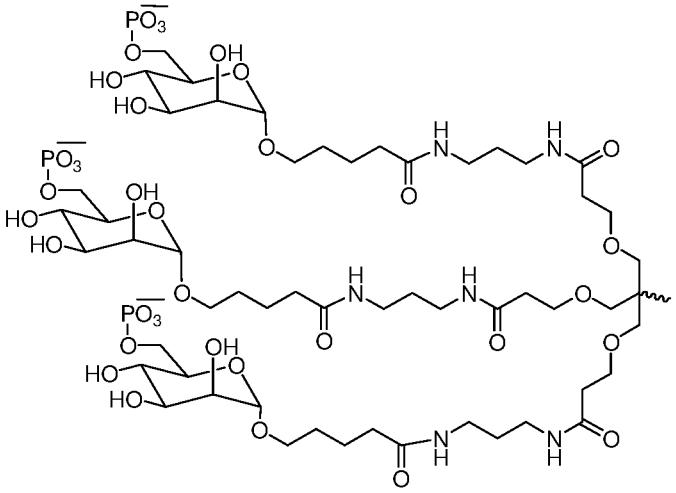

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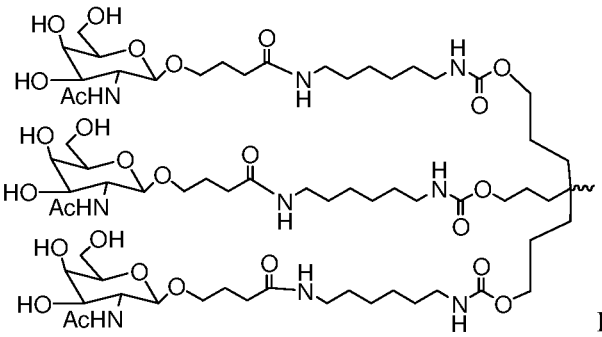

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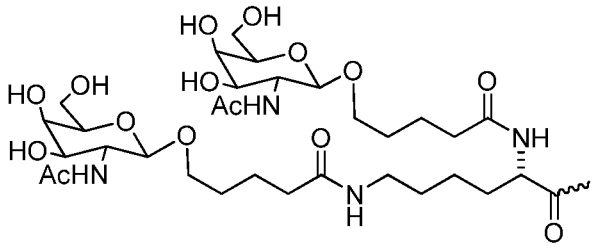

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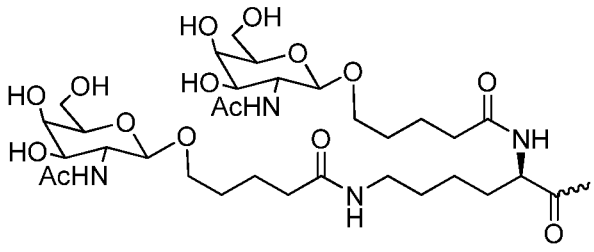

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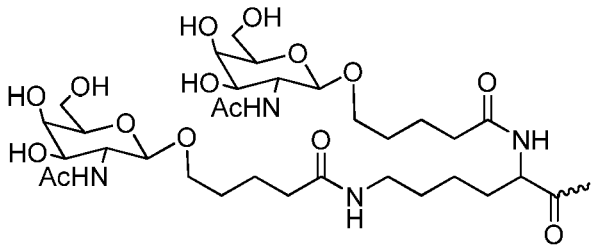

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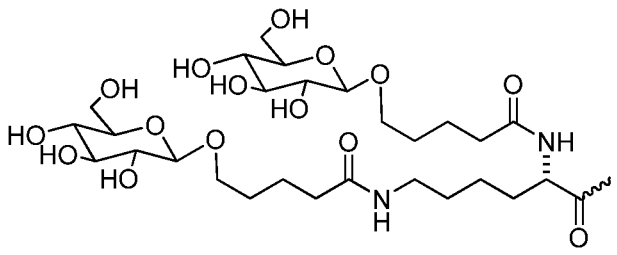

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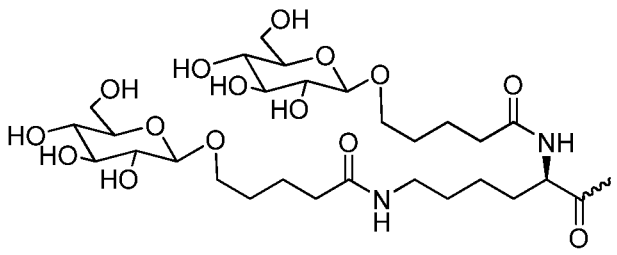

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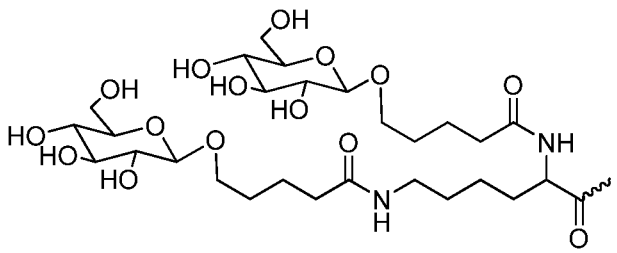

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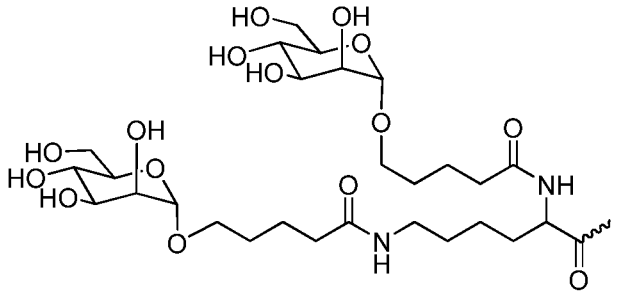
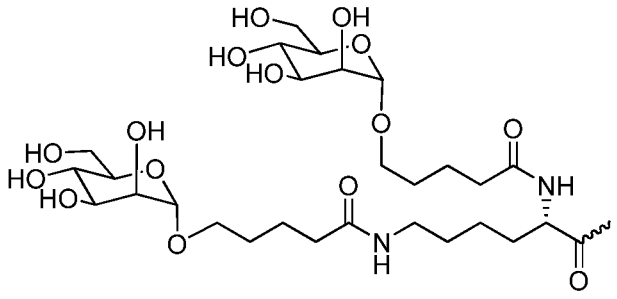
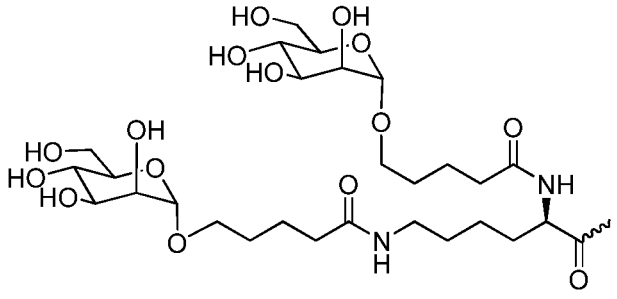


Formula XX,



Formula XXI,



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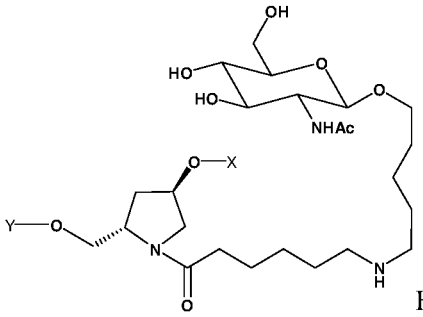

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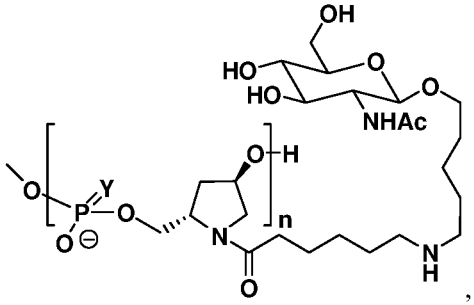
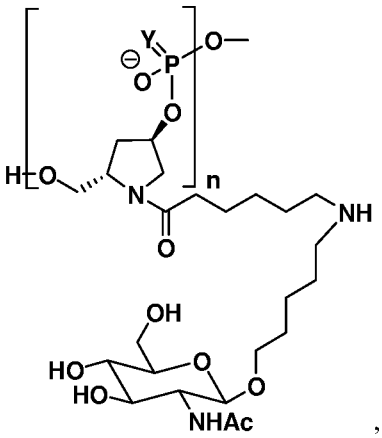
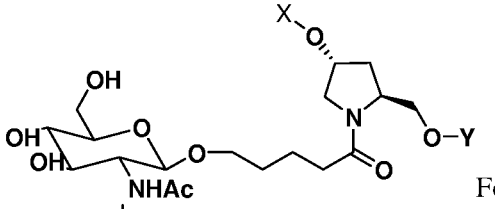


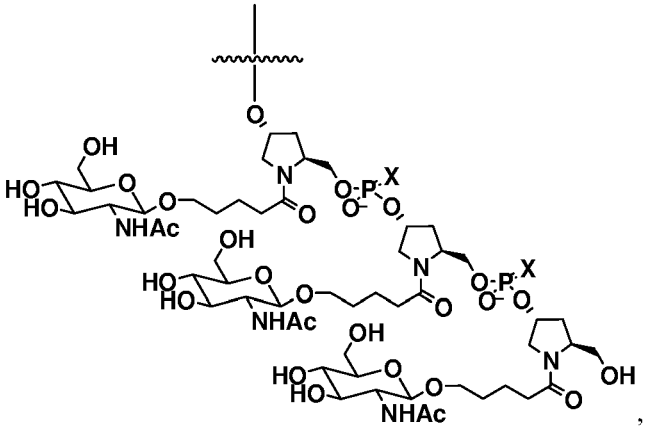
, wherein Y is O or S and n is 3 -6 (Formula XXIV);



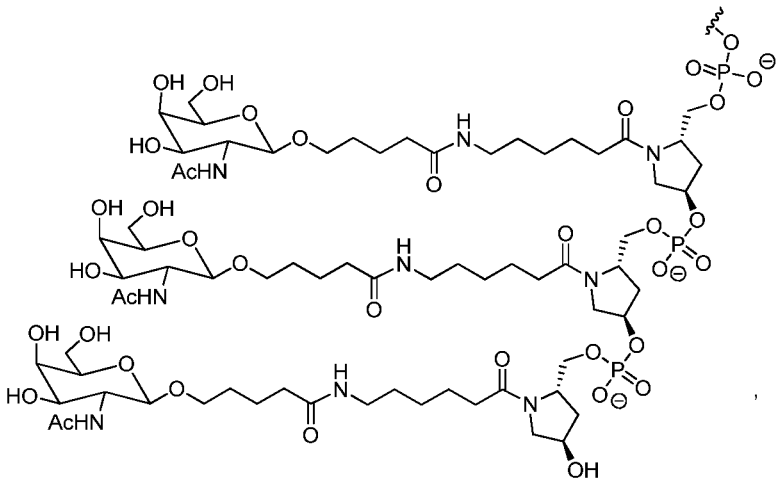
, wherein Y is O or S and n is 3-6 (Formula XXV);



Formula XXVI;



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



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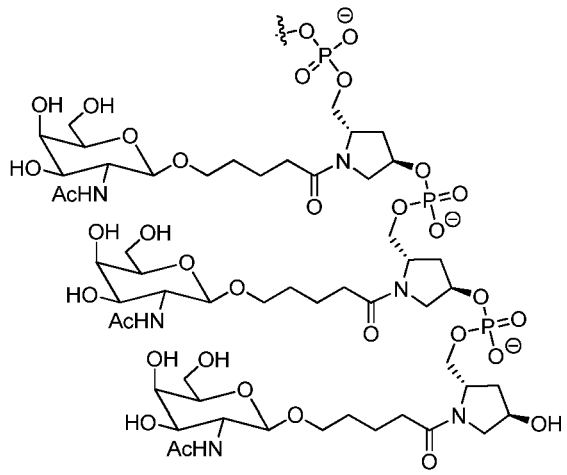
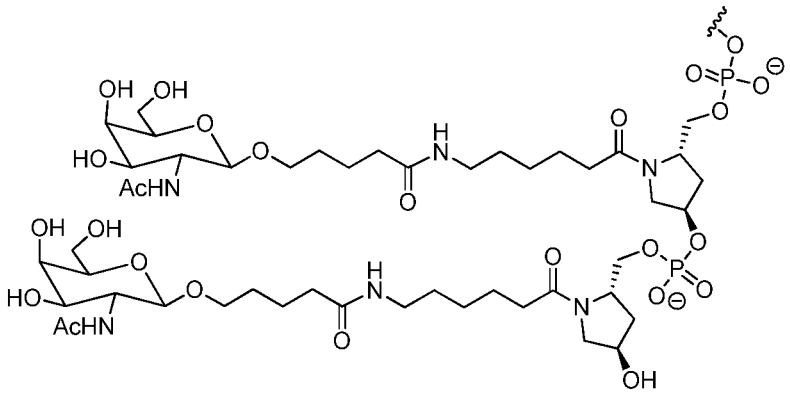


,

Formula XXVII; Formula XXIX;



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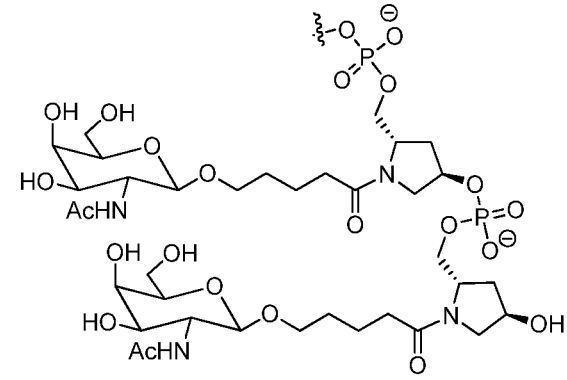
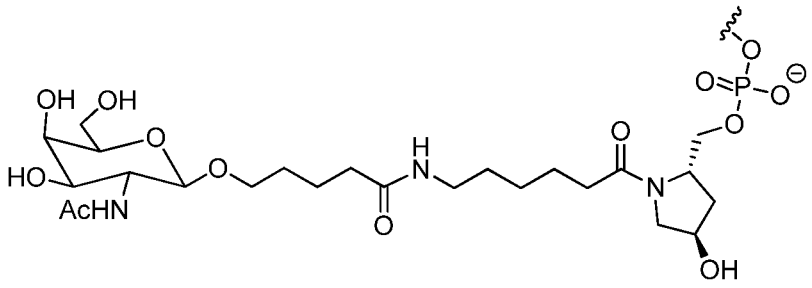


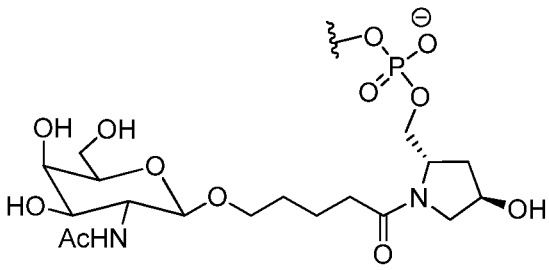
,

Formula XXX;

Formula XXXI;

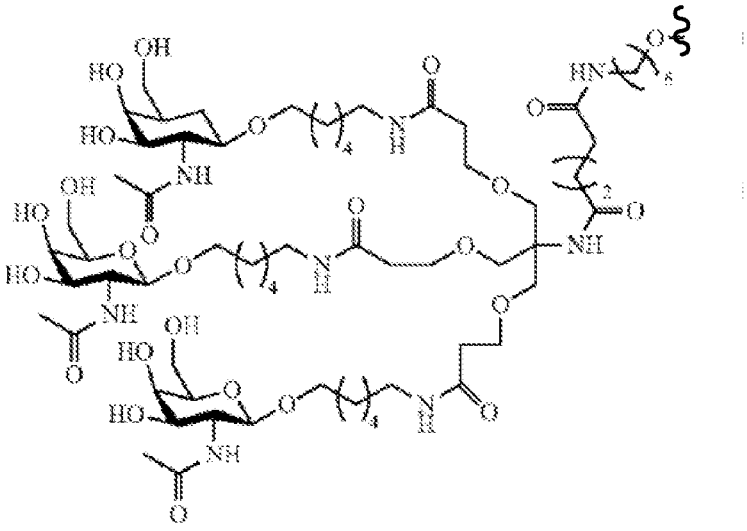


, and



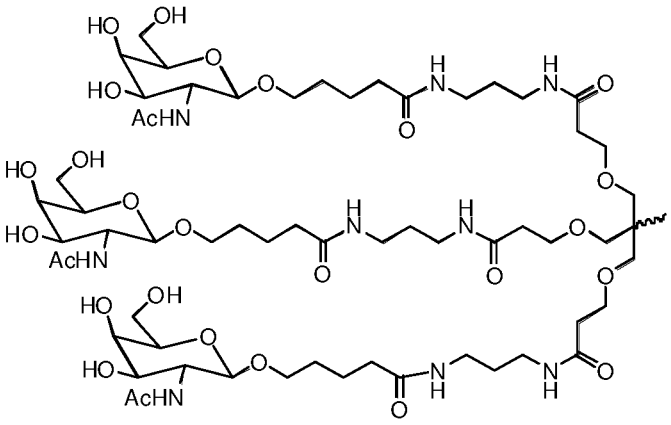
Formula XXXII;

Formula XXXIII.



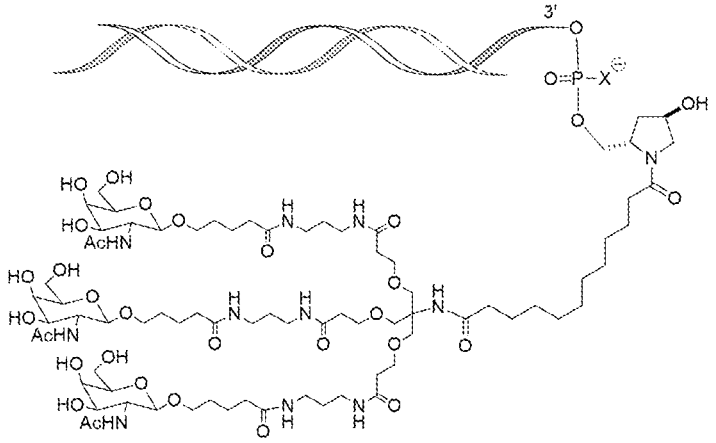
Formula XXXIV.

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

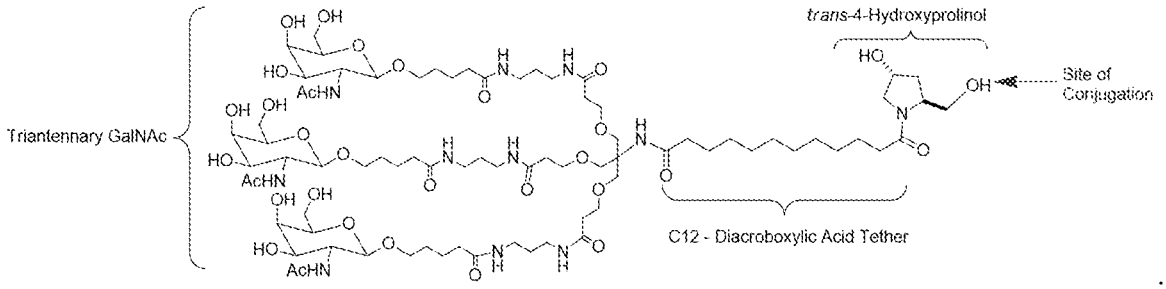


Formula II.

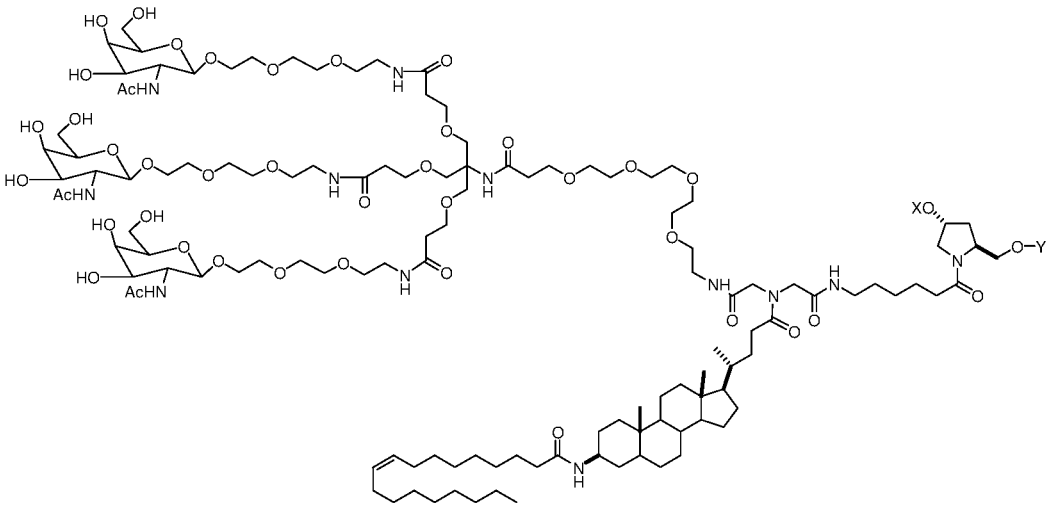
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate *via* a linker as shown in the following schematic, wherein X is O or S



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

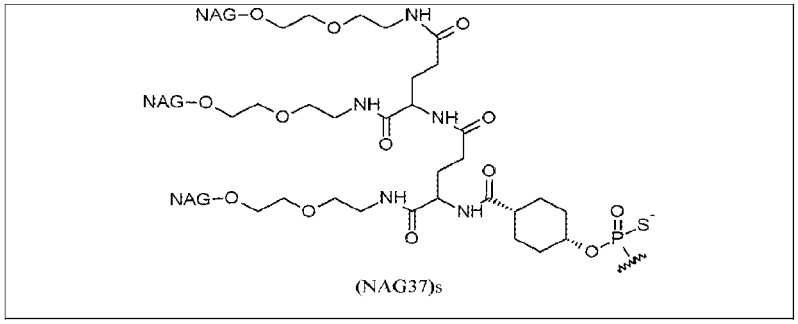


Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,



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

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



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

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

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

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

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

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

D. Linkers

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

The term "linker" or "linking group" means an organic moiety that connects two parts of a compound, *e.g.,* covalently attaches two parts of a compound. Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR8, C(O), C(O)NH, SO, SO_2, SO_2NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclylalkyl, alkylheterocyclylalkenyl, alkylhererocyclylalkynyl, alkenylheterocyclylalkyl, alkenylheterocyclylalkenyl, alkenylheterocyclylalkynyl, alkynylheterocyclylalkyl, alkynylheterocyclylalkenyl, alkynylheterocyclylalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylhereroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO_2, N(R8), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclic; where R8 is hydrogen, acyl, aliphatic, or substituted aliphatic. In one embodiment, the linker is about 1-24 atoms, 2-24, 3-24, 4-24, 5-24, 6-24, 6-18, 7-18, 8-18, 7-17, 8-17, 6-16, 7-17, or 8-16 atoms.

A cleavable linking group is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In one

embodiment, the cleavable linking group is cleaved at least about 10 times, 20, times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, or more, or at least 100 times faster in a target cell or under a first reference condition (which can, *e.g.*, be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, *e.g.*, be selected to mimic or represent conditions found in the blood or serum).

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

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

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

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

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

10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

i. Redox cleavable linking groups

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

ii. Phosphate-based cleavable linking groups

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

iii. Acid cleavable linking groups

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

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

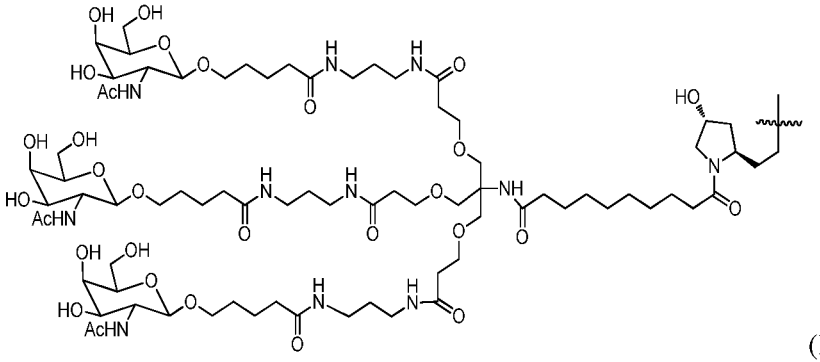
iv. Ester-based linking groups

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

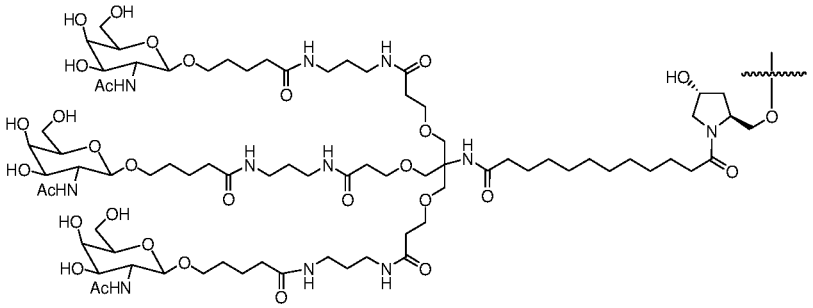
v. Peptide-based cleaving groups

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

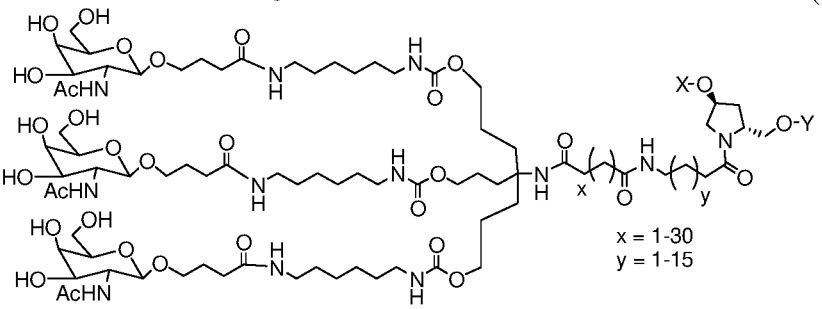
In some embodiments, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



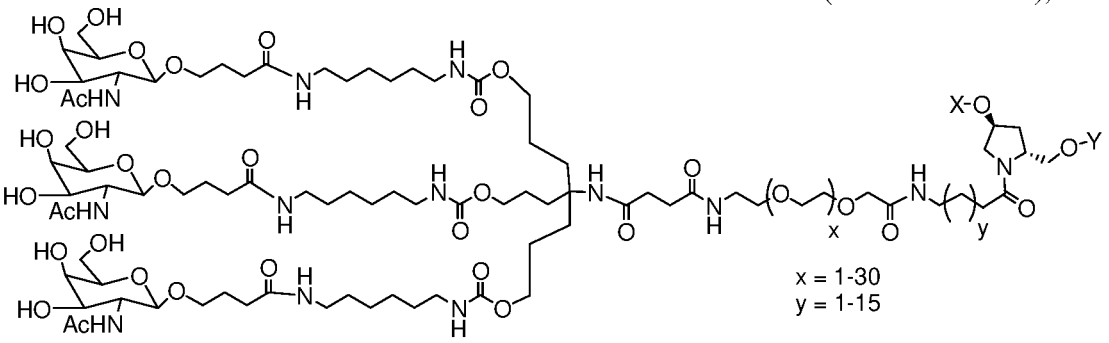
(Formula XXXVII),



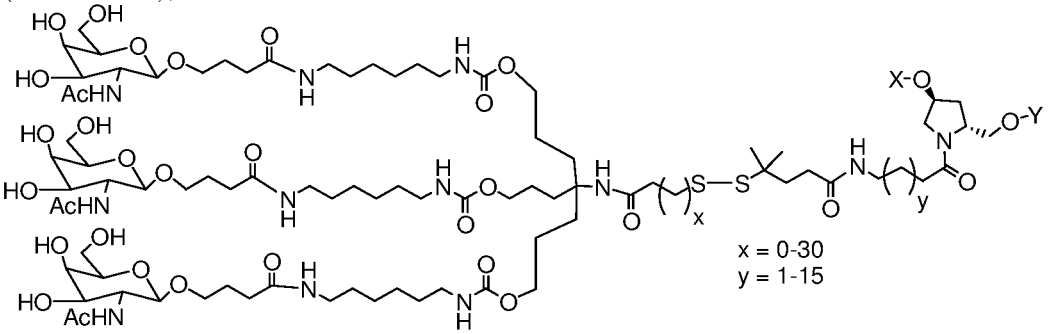
(Formula XXXVIII),



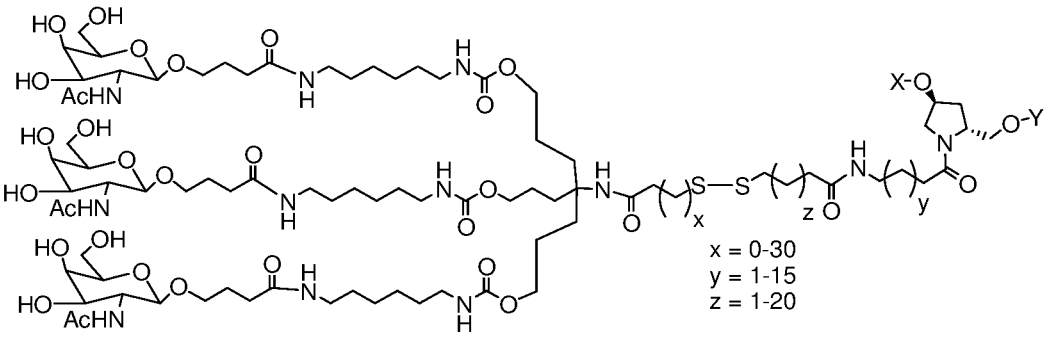
(Formula XXXIX),



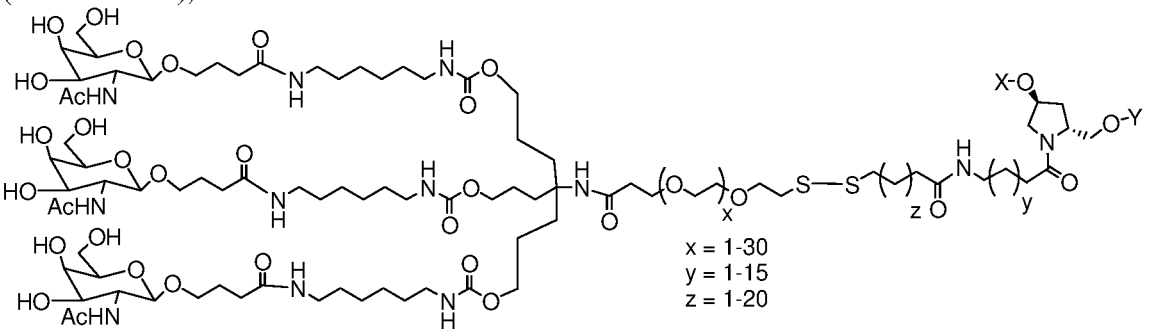
(Formula XL),



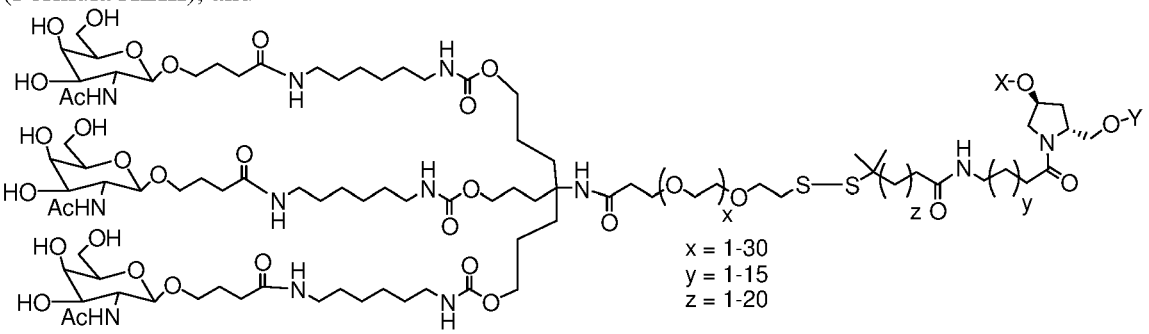
(Formula XLI),



(Formula XLII),



(Formula XLIII), and

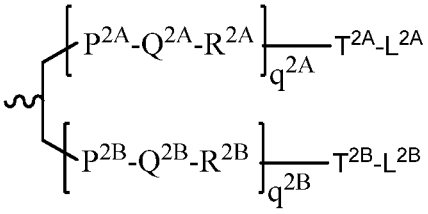


(Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

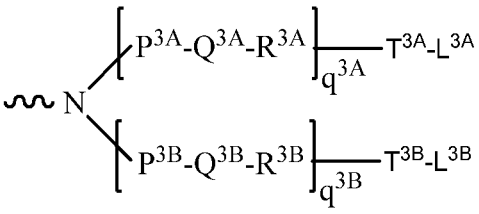
In certain embodiments of the compositions and methods of the invention, a ligand is one or more "GalNAc" (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

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

Formula XXXXV



Formula XLVI



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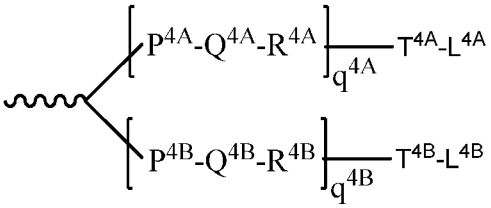
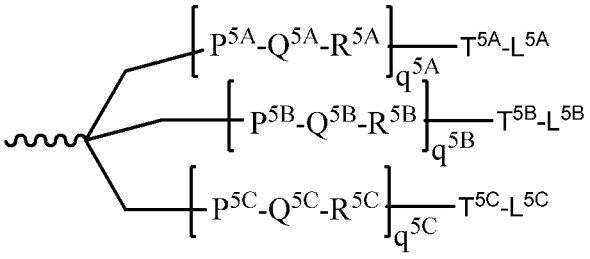


, or



;

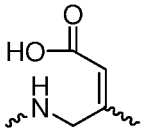
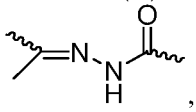
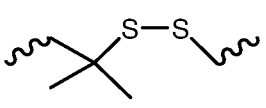
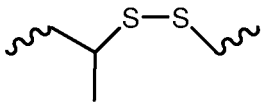
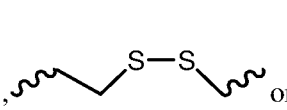
Formula XLVII Formula XLVIII

wherein:

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

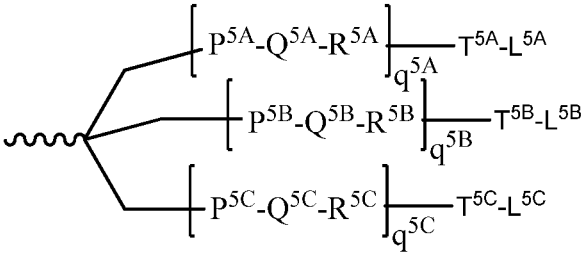
P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{4A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2, CH_2NH or CH_2O;

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

R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{5C} are each independently for each occurrence absent, NH, O, S, CH_2, C(O)O, C(O)NH, NHCH(R^a)C(O), -C(O)-CH(R^a)-NH-, CO, CH=N-O,  ,  ,  ,  ,  or heterocyclyl;

L^{2A}, L^{2B}, L^{3A}, L^{3B}, L^{4A}, L^{4B}, L^{5A}, L^{5B} and L^{5C} represent the ligand; *i.e.* each independently for each occurrence a monosaccharide (such as GalNAc), disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, or polysaccharide; and R^a is H or amino acid side chain. Trivalent conjugating GalNAc derivatives are particularly useful for use with RNAi agents for inhibiting the expression of a target gene, such as those of formula (XLIX):

Formula XLIX



,

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

Examples of suitable bivalent and trivalent branched linker groups conjugating GalNAc derivatives include, but are not limited to, the structures recited above as formulas II, VII, XI, X, and XIII.

Representative U.S. Patents that teach the preparation of RNA conjugates include, but are not limited to, U.S. Patent Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928;5,688,941; 6,294,664; 6,320,017; 6,576,752; 6,783,931; 6,900,297; 7,037,646; and 8,106,022, the entire contents of each of which are hereby incorporated herein by reference.

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

"Chimeric" iRNA compounds or "chimeras," in the context of this invention, are iRNA compounds, such as dsRNAi agents, that contain two or more chemically distinct regions, each made up of at least one monomer unit, *i.e.*, a nucleotide in the case of a dsRNA compound. These iRNAs typically contain at least one region wherein the RNA is modified so as to confer upon the iRNA increased resistance to nuclease degradation, increased cellular uptake, or increased binding affinity for the target nucleic acid. An additional region of the iRNA can serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of iRNA inhibition of gene expression. Consequently, comparable results can often be obtained with shorter iRNAs when chimeric dsRNAs are used, compared to phosphorothioate deoxy dsRNAs hybridizing to

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

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

IV. Delivery of an iRNA of the Invention

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

A. Vector encoded iRNAs of the Invention

iRNA targeting the 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

In one embodiment, the present invention employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly iRNAs, to the skin of animals. Most drugs are present in solution in both ionized and nonionized forms. However, usually only lipid soluble or lipophilic drugs readily cross cell membranes. It has been discovered that even non-lipophilic drugs can cross cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs.

Penetration enhancers can be classified as belonging to one of five broad categories, *i.e.*, surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92). Each of the above mentioned classes of penetration enhancers and their use in manufacture of pharmaceutical compositions and delivery of pharmaceutical agents are well known in the art.

v. Excipients

In contrast to a carrier compound, a "pharmaceutical carrier" or "excipient" is a pharmaceutically acceptable solvent, suspending agent, or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient can be liquid or solid and is selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, etc., when combined with a nucleic acid and the other components of a given pharmaceutical composition. Such agent are well known in the art.

vi. Other Components

The compositions of the present invention can additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions can contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or can contain additional materials useful in physically formulating various dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present invention. The formulations can be sterilized and, if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings,

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

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

In some embodiments, pharmaceutical compositions featured in the invention include (a) one or more iRNA and (b) one or more agents which function by a non-iRNA mechanism and which are useful in treating a 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. Furthermore, contacting a cell may be accomplished *via* a targeting ligand, including any ligand described herein or known in the art. In certain embodiments, the targeting ligand is a carbohydrate moiety, *e.g.*, a GalNAc ligand, or any other ligand that directs the RNAi agent to a site of interest.

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

The phrase "inhibiting expression of a 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 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 supression. The expression of the coagulation Factor V 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 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 (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 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), RNeasy™ RNA preparation kits (Qiagen®) or PAXgene™ (PreAnalytix™, Switzerland). Typical assay formats utilizing ribonucleic acid hybridization include nuclear run-on assays, RT-PCR, RNase protection assays, northern blotting, *in situ* hybridization, and microarray analysis.

In some embodiments, the level of expression of 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 it the art, *e.g.* ELISA. In certain embodiments, a puncture liver biopsy sample serves as the tissue material for monitoring the reduction in the 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 wtih 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 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; 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.

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 emboidments, 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 antistreplase (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 immunosuppresant 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 stablizer. 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 comprise means for determining the therapeutically effective or prophylactically effective amount.

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

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

EXAMPLES

Example 1. iRNA Synthesis

Source of reagents

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

siRNA Design

siRNAs targeting the 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 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.

siRNA Synthesis

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

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

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

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

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

Example 2. *In vitro* screening methods

Cell culture and 384-well transfections

Hep3b cells (ATCC, Manassas, VA) were grown to near confluence at 37°C in an atmosphere of 5% CO_2 in Eagle's Minimum Essential Medium (Gibco) supplemented with 10% FBS (ATCC) before being released from the plate by trypsinization. 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 $x10^4$ 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 H_2O 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

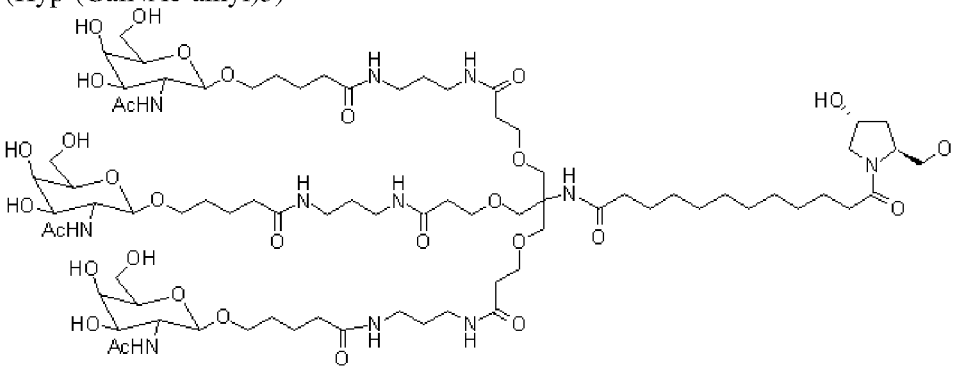
Two microlitre (µl) of cDNA were added to a master mix containing 0.5µl of human GAPDH TaqMan Probe (4326317E), 0.5µl human F5 probe, 2µl nuclease-free water and 5µl Lightcycler 480 probe master mix (Roche Cat # 04887301001) per well in a 384 well plates (Roche cat # 04887301001). Real time PCR was done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

To calculate relative fold change, data were analyzed using the ΔΔCt method and normalized to assays performed with cells transfected with 10nM AD-1955, or mock transfected cells. IC_{50}s 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: 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.

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

Abbre*via*tion	**Nucleotide(s)**
A	Adenosine-3'-phosphate
Ab	beta-L-adenosine-3`-phosphate
Abs	beta-L-adenosine-3`-phosphorothioate
Af	2'-fluoroadenosine-3'-phosphate
Afs	2'-fluoroadenosine-3'-phosphorothioate
As	adenosine-3'-phosphorothioate
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

Abbre*via*tion	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-tetrahydrofurane-4-methoxy-3-phosphate (abasic 2'-OMe furanose)
Y44	inverted abasic DNA (2-hydroxymethyl-tetrahydrofurane-5-phosphate)
(Agn)	Adenosine-glycol nucleic acid (GNA)
(Cgn)	Cytidine-glycol nucleic acid (GNA)
(Ggn)	Guanosine-glycol nucleic acid (GNA)
(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`- deoxythimidine -3`-phosphate
dTs	2`- deoxythimidine -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

Abbre*via*tion	**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 ange in NM_000130.4
AD-109601	AAAGUGGAUCAUAUCUUCUCU	31	1057-1077	AGAGAAGAUAUGAUCCACUUUCC	162	1055-1077
AD-109799	UCAAACCAAAUUGGAAAACAU	32	1295-1315	AUGUUUUCCAAUUUGGUUUGAGA	163	1293-1315
AD-110052	UAAGUGGAACAUCUUAGAGUU	33	1594-1614	AACUCUAAGAUGUUCCACUUAUA	164	1592-1614
AD-110281	GAGGACAACAUCAACAAGUUU	34	1823-1843	AAACUUGUUGAUGUUGUCCUCAA	165	1821-1843
AD-110370	GCAUAACUACUCUUGGAUUCU	35	1932-1952	AGAAUCCAAGAGUAGUUAUGCUC	166	1930-1952
AD-110518	UUGGAACUUGGAUGUUAACUU	36	2118-2138	AAGUUAACAUCCAAGUUCCAACA	167	2116-2138
AD-110787	GAAGAAGAGUUCAAUCUUACU	37	2387-2407	AGUAAGAUUGAACUCUUCUUCUU	168	2385-2407
AD-110844	UCAAACACAGAUAUAAUUGUU	38	2444-2464	AACAAUUAUAUCUGUGUUUGAAG	169	2442-2464
AD-111287	AAGUAACUCAUCUAAGAUUUU	39	2953-2973	AAAAUCUUAGAUGAGUUACUUUG	170	2951-2973
AD-111345	UAUGAAAUAAUCCAAGAUACU	40	3011-3031	AGUAUCUUGGAUUAUUUCAUAGC	171	3009-3031
AD-111483	ACUGAAGAAAAGCCAGUUUCU	41	3202-3222	AGAAACUGGCUUUUCUUCAGUCU	172	3200-3222
AD-112322	UCAUUGCUUCUUCAAGAAUUU	42	4559-4579	AAAUUCUUGAAGAAGCAAUGACU	173	4557-4579
AD-112396	UACUCUCAAUGAUACUUUUCU	43	4633-4653	AGAAAAGUAUCAUUGAGAGUAGG	174	4631-4653
AD-112618	AAACAGAAGAAAUUAUUACAU	44	4876-4896	AUGUAAUAAUUUCUUCUGUUUCC	175	4874-4896
AD-112760	AGCACUUUUACCAAACGUGAU	45	5021-5041	AUCACGUUUGGUAAAAGUGCUGU	176	5019-5041
AD-113137	GAGAGAAUUUGUCUUACUAUU	46	5443-5463	AAUAGUAAGACAAAUUCUCUCAU	177	5441-5463
AD-113331	GACAUUCACGUGGUUCACUUU	47	5657-5677	AAAGUGAACCACGUGAAUGUCUU	178	5655-5677
AD-114455	CUGUGUUAAAUGUUAACAGUU	48	6896-6916	AACUGUUAACAUUUAACACAGCG	179	6894-6916
AD-114469	ACAGUUUUCCACUAUUUCUCU	21	6911-6931	AGAGAAAUAGUGGAAAACUGUUA	22	6909-6931
AD-114478	CUUUCUUUUCUAUUAGUGAAU	49	6930-6950	AUUCACUAAUAGAAAAGAAAGAG	180	6928-6950
AD-114698	UUUCACAAACACAUGAUUUUU	50	7211-7231	AAAAAUCAUGUGUUUGUGAAAGU	181	7209-7231
AD-114728	UACUUAAAAUAUCCUGUCUUU	51	7283-7303	AAAGACAGGAUAUUUUAAGUACU	182	7281-7303
AD-114746	UUUCCCAUAUAACAAUGAUUU	52	7301-7321	AAAUCAUUGUUAUAUGGGAAAGA	183	7299-7321
AD-115217	GUGUACAUAUAUCAAAAUGUU	53	7936-7956	AACAUUUUGAUAUAUGUACACGU	184	7934-7956
AD-115235	CAACGAAAUUCAUAACAAUCU	54	7986-8006	AGAUUGUUAUGAAUUUCGUUGAU	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:	R ange in NM_000130.4
AD-115563	GAAACUACCAGAGUUACCUGU	55	8322-8342	ACAGGUAACUCUGGUAGUUUCUA	186	8320-8342
AD-115659	CUUUCUUUUCAUGAUUCAUGU	56	8437-8457	ACAUGAAUCAUGAAAAGAAAGGA	187	8435-8457
AD-115814	CGCAUGCUAAAUUUAAUGCUU	57	8612-8632	AAGCAUUAAAUUUAGCAUGCGGU	188	8610-8632
AD-115844	CCUCUUGAAAUCCUUUAUUUU	58	8642-8662	AAAAUAAAGGAUUUCAAGAGGGU	189	8640-8662
AD-115919	UCUCUUGAUCUAGAAUUUACU	59	8755-8775	AGUAAAUUCUAGAUCAAGAGAGA	190	8753-8775
AD-1410569	CCACAAACUCAAGUUUGAAUU	60	291-311	AAUUCAAACUUGAGUUUGUGGGC	191	289-311
AD-1410577	AUCUUUCUGUAACUUCCUUUU	61	309-329	AAAAGGAAGUUACAGAAAGAUUC	192	307-329
AD-1410605	AGUAUGAACCAUAUUUUAAGU	15	348-368	ACUUAAAAUAUGGUUCAUACUCU	16	346-368
AD-1410628	CUACCAUUUCAGGACUUCUUU	62	384-404	AAAGAAGUCCUGAAAUGGUAGAU	193	382-404
AD-1410662	CAUCAUAAAAGUUCACUUUAU	63	433-453	AUAAAGUGAACUUUUAUGAUGUC	194	431-453
AD-1410700	UCAAGGAAUUAGGUACAGUAU	64	487-507	AUACUGUACCUAAUUCCUUGAGG	195	485-507
AD-1410725	UCUUACCUUGACCACACAUUU	65	524-544	AAAUGUGUGGUCAAGGUAAGAAG	196	522-544
AD-1410825	UCACACACAUCUAUUACUCCU	66	648-668	AGGAGUAAUAGAUGUGUGUGAGG	197	646-668
AD-1410845	UCUGAUCGAGGAUUUUCAACUU	67	676-696	AAGUUGAAAUCCUCGAUCAGAUU	198	674-696
AD-1410880	GACAAGCAAAUCGUGCUACUU	68	767-787	AAGUAGCACGAUUUGCUUGUCAA	199	765-787
AD-1410926	CCCUAAUGUACACAGUCAAUU	69	831-851	AAUUGACUGUGUACAUUAGGGAU	200	829-851
AD-1410994	AUUAUUCUCCCAUUCAUUUCAU	70	940-960	AUGAAAUGAAUGGAGAAUAAUUC	201	938-960
AD-1411107	CAGGCUUACAUUGACAUUAAU	71	1106-1126	AUUAAUGUCAAUGUAAGCCUGCA	202	1104-1126
AD-1411138	CCAGGAAUCUUAAGAAAAUAU	72	1143-1163	AUAUUUUCUUAAGAUUCCUGGUU	203	1141-1163
AD-1411226	UCAGCAUUUGGAUAAUUUCUU	73	1276-1296	AAGAAAUUAUCCAAAUGCUGAGA	204	1274-1296
AD-1411270	UACGAAGAUGAGUCCUUCACU	74	1340-1360	AGUGAAGGACUCAUCUUCGUACU	205	1338-1360
AD-1411284	CACCAAACAUACAGUGAAUCU	75	1357-1377	AGAUUCACUGUAUGUUUGGUGAA	206	1355-1377
AD-1411342	ACACUCAAAAUCGUGUUCAAU	76	1433-1453	AUUGAACACGAUUUUGAGUGUGU	207	1431-1453
AD-1411387	AUGAAGUCAACUCUUCUUUCU	77	1515-1535	AGAAAGAAGAGUUGACUUCAUCU	208	1513-1535
AD-1411480	UAACAAGACCAUACUACAGUU	78	1647-1667	AACUGUAGUAUGGUCUUGUUAAG	209	1645-1667
AD-1411521	AAUAGGACUACUUCUAAUCUU	79	1702-1722	AAGAUUAGAAGUAGUCCUAUUAG	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:	R ange in NM_000130.4
AD-1411657	AAACAUCAUGAGCACUAUCAU	80	1894-1914	AUGAUAGUGCUCAUGAUGUUUGA	211	1892-1914
AD-1411743	CAUUCAUCUAUGGAAAGAGGU	81	2034-2054	ACCUCUUUCCAUAGAUGAAUGAG	212	2032-2054
AD-1411798	UAACUUCCAUGAAUUCUAGUU	82	2133-2153	AACUAGAAUUCAUGGAAGUUAAC	213	2131-2153
AD-1411935	GACUAUGAUUACCAGAACAGU	83	2312-2332	ACUGUUCUGGUAAUCAUAGUCAG	214	2310-2332
AD-1411972	CCGAAACUCAUCAUUGAAUCU	84	2362-2382	AGAUUCAAUGAUGAGUUUCGGAA	215	2360-2382
AD-1412021	ACUGAAUUCGUUUCUUCAAAU	85	2429-2449	AUUUGAAGAAACGAAUUCAGUGC	216	2427-2449
AD-1412040	GUUGGUUCAAAUUAUUCUUCU	86	2462-2482	AGAAGAAUAAUUUGAACCAACAA	217	2460-2482
AD-1412052	AGUUCACUGUCAAUAACCUUU	87	2499-2519	AAAGGUUAUUGACAGUGAACUUA	218	2497-2519
AD-1412095	ACUCAGUUCUCAAUUCUUCCU	88	2595-2615	AGGAAGAAUUGAGAACUGAGUUC	219	2593-2615
AD-1412163	UACGUCUACUUUCACUUGGUU	89	2685-2705	AACCAAGUGAAAGUAGACGUAUC	220	2683-2705
AD-1412250	GGAUGAAAUUACUAGCACAUU	90	2790-2810	AAUGUGCUAGUAAUUUCAUCCAG	221	2788-2810
AD-1412364	GUUACUCUUAAAACAAAGUAU	91	2938-2958	AUACUUUGUUUUAAGAGUAACAG	222	2936-2958
AD-1412429	CUGAUGAAGACACAGCUGUUU	92	3030-3050	AAACAGCUGUGUCUUCAUCAGUA	223	3028-3050
AD-1412482	CUAGAGUUAGACAUAAAUCUU	93	3150-3170	AAGAUUUAUGUCUAACUCUAGGA	224	3148-3170
AD-1412497	CUCUACAAGUAAGACAGGAUU	94	3168-3188	AAUCCUGUCUUACUUGUAGAGAU	225	3166-3188
AD-1412539	UUUCUCAUUAAGACACGAAAU	95	3218-3238	AUUUCGUGUCUUAAUGAGAAACU	226	3216-3238
AD-1412582	UGAAGCCUACAACACAUUUUU	96	3304-3324	AAAAAUGUGUUGUAGGCUUCACU	227	3302-3324
AD-1412622	AAUCCAAUGAAACAUCUCUUU	97	3360-3380	AAAGAGAUGUUUCAUUGGAUUUA	228	3358-3380
AD-1412683	AUAAUCAGAAUUCCCUCAAAUU	98	3444-3464	AAUUUGAGGAAUUCUGAUUAUGG	229	3442-3464
AD-1412721	AGGAACACUAUCAAACAUUCU	99	3516-3536	AGAAUGUUUGAUAGUGUUCCUCU	230	3514-3536
AD-1412733	UCAAAUGCACUCUACUUCAGU	100	3553-3573	ACUGAAGUAGAGUGCAUUUGAUC	231	3551-3573
AD-1412756	UCAGUGAAAUGCUUGAGUAUU	101	3603-3623	AAUACUCAAGCAUUUCACUGAGC	232	3601-3623
AD-1412779	UCCUCAGAACAUGAAGUCUGU	102	3671-3691	ACAGACUUCAUGUUCUGAGGAAG	233	3669-3691
AD-1412870	CUCAUUCAGAGAAACCUUUCU	103	3794-3814	AGAAAGGUUUCUCUGAAUGAGUU	234	3792-3814
AD-1412963	ACAACCCUUUCUCUAGACUUU	104	3992-4012	AAAGUCUAGAGAAAGGGUUGUAU	235	3990-4012
AD-1412982	CUCCAGAACUCAGUCAAACAU	105	4164-4184	AUGUUUGACUGAGUUCUGGAGAG	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:	R ange in NM_000130.4
AD-1413036	UUGCAGAUCUCAGUCAAAUUU	106	4326-4346	AAAUUUGACUGAGAUCUGCAAAG	237	4324-4346
AD-1413128	GACCUUGAUCAGAUAUUCUAU	107	4520-4540	AUAGAAUAUCUGAUCAAGGUCUG	238	4518-4540
AD-1413143	UCUGAAUCUAGUCAGUCAUUU	108	4544-4564	AAAUGACUGACUAGAUUCAGAAG	239	4542-4564
AD-1413210	CUAUCAAAGGAAUUUAAUCCU	109	4652-4672	AGGAUUAAAAUUCCUUUGAUAGAA	240	4650-4672
AD-1413251	UACAUUGAGAUCAUUCCAAAU	110	4709-4729	AUUUGGAAUGAUCUCAAUGUAAU	241	4707-4729
AD-1413286	ACUAUGCUGAAAUUGAUUAUU	111	4755-4775	AAUAAUCAAUUUCAGCAUAGUCA	242	4753-4775
AD-1413311	UAGGACAAACAUCAACUCCUU	112	4807-4827	AAGGAGUUGAUGUUUGUCCUAAC	243	4805-4827
AD-1413488	UCGGAAUUCUUGGUCCUAUUU	113	5067-5087	AAAUAGGACCAAGAAUUCCGAGA	244	5065-5087
AD-1413517	UUAUCCAAGUUCGUUUUAAAU	114	5109-5129	AUUUAAAACGAACUUGGAUAACA	245	5107-5129
AD-1413605	AUGCUGUUCAGCCAAAUAGCU	115	5238-5258	AGCUAUUUGGCUGAACAGCAUUA	246	5236-5258
AD-1413615	UAGCAGUUAUACCUACGUAUU	116	5254-5274	AAUACGUAGGUAUAACUGCUAUU	247	5252-5274
AD-1413936	CUGGUUCAUUUAAAACUCUUU	117	5742-5762	AAAGAGUUUUAAAUGAACCAGGC	248	5740-5762
AD-1414009	UGCAAACGCCAUUUCUUAUCU	17	5832-5852	AGAUAAGAAAUGGCGUUUGCAUC	18	5830-5852
AD-1414059	AUAUCUGAUUCACAGAUCAAU	118	5897-5917	AUUGAUCUGUGAAUCAGAUAUGA	249	5895-5917
AD-1414074	UCAGAGUUUCUGGGUUACUGU	119	5921-5941	ACAGUAACCCAGAAACUCUGAAG	250	5919-5941
AD-1414139	AGAAUUUGCCUCUAAACCUUU	120	6010-6030	AAAGGUUUAGAGGCAAAUUCUGC	251	6008-6030
AD-1414232	AUGUAGCUUACAGUUCCAACU	121	6126-6146	AGUUGGAACUGUAAGCUACAUAG	252	6124-6146
AD-1414275	GAAUGUGAUGUAUUUUAAUGU	122	6184-6204	ACAUUAAAAUACAUCACAUUCCU	253	6182-6204
AD-1414328	UAGAUAUAUUAGGAUCUCUCU	123	6259-6279	AGAGAGAUCCUAAUAUAUCUAGC	254	6257-6279
AD-1414410	UCACAGCUUCUUCGUUUAAGU	124	6390-6410	ACUUAAACGAAGAAGCUGUGAUU	255	6388-6410
AD-1414498	AUUGAUCUACUCAAGAUCAAU	125	6518-6538	AUUGAUCUUGAGUAGAUCAAUUU	256	6516-6538
AD-1414544	CCUCUGAAAUGUAUGUAAAGU	126	6579-6599	ACUUUACAUACAUUUCAGAGGAC	257	6577-6599
AD-1414625	AAGGAAAUACUAAUACCAAAU	127	6681-6701	AUUUGGUAUUAGUAUUUCCUUCA	258	6679-6701
AD-1414662	CAUUCCUAAAAACAUGGAAUCU	128	6754-6774	AGAUUCCAUGUUUUAGGAAUGAC	259	6752-6774
AD-1414713	AGACUCUUUAAGACCUCAAAU	129	6848-6868	AUUUGAGGUCUUAAAGAGUCUCU	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:	R ange in NM_000130.4
AD-1414796	UUCUGCAUUAAUUUGAAUACU	131	7019-7039	AGUAUUCAAAUUAAUGCAGAAGU	262	7017-7039
AD-1414831	AAGGGCUUAUCUUUCUUAAUU	132	7069-7089	AAUUAAGAAAGAUAAGCCCUUUU	263	7067-7089
AD-1414857	CUCUUUUAAAUCCUUUACACU	133	7141-7161	AGUGUAAAGGAUUUAAAAGAGUU	264	7139-7161
AD-1414871	CACUAGUAAAACAGAUAUUAU	134	7160-7180	AUAAUAUCUGUUUUACUAGUGUG	265	7158-7180
AD-1414931	UUUCUGACUUUCCAUGAGUAU	135	7321-7341	AUACUCAUGGAAAGUCAGAAAAA	266	7319-7341
AD-1415052	AAAACAUAAUUUCACCUACUU	136	7532-7552	AAGUAGGUGAAAUUAUGUUUUGA	267	7530-7552
AD-1415096	CUGGUCUAAAUGCAGUUGUUU	137	7589-7609	AAACAACUGCAUUUAGACCAGCA	268	7587-7609
AD-1415166	UCUCUUCUUCCAGCAACUUCU	138	7696-7716	AGAAGUUGCUGGAAGAAGAGAGA	269	7694-7716
AD-1415169	UUUCAUCAUUCCUUUCCCUGU	139	7719-7739	ACAGGGAAAGGAAUGAUGAAAGG	270	7717-7739
AD-1415194	UUUAGACAUCCUUAAAAUCAU	140	7787-7807	AUGAUUUUAAGGAUGUCUAAAGG	271	7785-7807
AD-1415243	UGAUUUAAUCAUCCUGUAACU	141	7916-7936	AGUUACAGGAUGAUUAAAUCAAG	272	7914-7936
AD-1415314	GACUAAGAAACUCACUCGAAU	142	8040-8060	AUUCGAGUGAGUUUCUUAGUCCU	273	8038-8060
AD-1415327	UCGAAACCACACAACUACAUU	143	8055-8075	AAUGUAGUUGUGUGGUUUCGAGU	274	8053-8075
AD-1415412	ACAACAUACCAGAAUCUCUAU	144	8170-8190	AUAGAGAUUCUGGUAUGUUGUCU	275	8168-8190
AD-1415439	GCAUUCUAUUCGUUGUGAACU	145	8213-8233	AGUUCACAACGAAUAGAAUGCAG	276	8211-8233
AD-1415466	GUCUCGAUUCAGUGUAGAAGU	146	8248-8268	ACUUCUACACUGAAUCGAGACUG	277	8246-8268
AD-1415563	AUCCACAAAACAUUGGCUUUU	147	8393-8413	AAAAGCCAAUGUUUUGUGGAUGU	278	8391-8413
AD-1415578	CGUAUUCCCACUAUUCCUUUU	148	8421-8441	AAAAGGAAUAGUGGGAAUACGAA	279	8419-8441
AD-1415602	CAUCAACAUUUUCUAAGAUUUU	149	8466-8486	AAAAUCUUAGAAAUGUUGAUGGG	280	8464-8486
AD-1415633	AAAACAUUUCUUUGUUUUUCUU	150	8527-8547	AAGAAAACACAAGAAAUGUUUUCC	281	8525-8547
AD-1415663	GUGAUCUGUUCAGUUGCAAAU	151	8571-8591	AUUUGCAACUGAACAGAUCACAC	282	8569-8591
AD-1415714	AUUCGACAUUUCCAUUUUUCU	152	8673-8693	AGAAAAAUGGAAAUGUCGAAUUC	283	8671-8693
AD-1415738	CUUCUCUACUCUGAAAUUGGU	153	8727-8747	ACCAAUUUCAGAGUAGAGAAGCC	284	8725-8747
AD-1415798	GUUAUUCUCUACUUGAGAAAU	154	8857-8877	AUUUCUCAAGUAGAGAAUAACGA	285	8855-8877
AD-1415830	UGUUAGUGUCAGAACUGAAAU	155	8920-8940	AUUUCAGUUCUGACACUAACAAG	286	8918-8940
AD-1415857	UAUCCCUAGACUUUUAGUCUU	156	8958-8978	AAGACUAAAAAGUCUAGGGAUAUG	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 ange in NM_000130.4
AD-1415873	UCUUCCAUAAAAUGAAACUUU	157	8984-9004	AAAGUUUCAUUUUAUGGAAGAGA	288	8982-9004
AD-1415881	AUGUUUCUAAUCCAUUGCUCU	158	9007-9027	AGAGCAAUGGAUUAGAAACAUUA	289	9005-9027
AD-1415899	GUAGACAUGAAUAUUAAUUGU	159	9033-9053	ACAAUUAAUAUUCAUGUCUACCU	290	9031-9053
AD-1415910	GAUCUGGAAAAUACUUGUUUU	160	9069-9089	AAAACAAGUAUUUUCCAGAUCAA	291	9067-9089
AD-1415934	CUGUGUAGAAAUAUUAAAACU	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	asasagugGfaUfCfAfuaucuucucuL96	293	asGfsagaAfgAfUfaugaUfcCfacuuuscsc	427	GGAAAGUGGAUCAUAUCUUCUCU	561
AD-109799	uscsaaacCfaAfAfUfuggaaaacauL96	294	asUfsguuUfuCfCfaauuUfgGfuuugasgsa	428	UCUCAAACCAAAUUGGAAAACAU	562
AD-110052	usasagugGfaAfCfAfucuuagaguuL96	295	asAfscucUfaAfGfauguUfcCfacuuasusa	429	UAUAAGUGGAACAUCUUAGAGUU	563
AD-110281	gsasggacAfaCfAfUfcaacaaguuuL96	296	asAfsacuUfgUfUfgaugUfuGfuccucsasa	430	UUGAGGACAACAUCAACAAGUUU	564
AD-110370	gscsauaaCfuAfCfUfcuuggauucuL96	297	asGfsaauCfcAfAfgaguAfgUfuaugcsusc	431	GAGCAUAACUACUCUUGGAUUCU	565
AD-110518	ususggaaCfuUfGfGfauguuaacuuL96	298	asAfsguuAfaCfAfuccaAfgUfuccaascsa	432	UGUUGGAACUUGGAUGUUAACUU	566
AD-110787	gsasagaaGfaGfUfUfcaaucuuacuL96	299	asGfsuaaGfaUfUfgaacUfcUfucuucsusu	433	AAGAAGAAGAGUUCAAUCUUACU	567
AD-110844	uscsaaacAfcAfGfAfuauaauuguuL96	300	asAfscaaUfuAfUfaucuGfuGfuuugasasg	434	CUUCAAACACAGAUAUAAUUGUU	568
AD-111287	asasguaaCfuCfAfUfcuaagauuuuL96	301	asAfsaauCfuUfAfgaugAfgUfuacuususg	435	CAAAGUAACUCAUCUAAGAUUUU	569
AD-111345	usasugaaAfuAfAfUfccaagauacuL96	302	asGfsuauCfuUfGfgauuAfuUfucauasgsc	436	GCUAUGAAAUAAUCCAAGAUACU	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	ascsugaaGfaAfAfAfgccaguuucuL96	303	asGfsaaaCfuGfGfcuuuUfcUfucaguscsu	437	AGACUGAAGAAAAGCCAGUUUCU	571
AD-112322	uscsauugCfuUfCfUfucaagaauuuL96	304	asAfsauuCfuUfGfaagaAfgCfaaugascsu	438	AGUCAUUGCUUCUUCAAGAAUUU	572
AD-112396	usascucuCfaAfUfGfauacuuuucuL96	305	asGfsaaaAfgUfAfucauUfgAfgaguasgsg	439	CCUACUCUCAAUGAUACUUUUCU	573
AD-112618	asasacagAfaGfAfAfauuauuacauL96	306	asUfsguaAfuAfAfuuucUfuCfuguuuscsc	440	GGAAACAGAAGAAAUUAUUACAU	574
AD-112760	asgscacuUfuUfAfCfcaaacgugauL96	307	asUfscacGfuUfUfgguaAfaAfgugcusgsu	441	ACAGCACUUUUACCAAACGUGAU	575
AD-113137	gsasgagaAfuUfUfGfucuuacuauuL96	308	asAfsuagUfaAfGfacaaAfuUfcucucsasu	442	AUGAGAGAAUUUGUCUUACUAUU	576
AD-113331	gsascauuCfaCfGfUfgguucacuuuL96	309	asAfsaguGfaAfCfcacgUfgAfaugucsusu	443	AAGACAUUCACGUGGUUCACUUU	577
AD-114455	csusguguUfaAfAfUfguuaacaguuL96	310	asAfscugUfuAfAfcauuUfaAfcacagscsg	444	CGCUGUGUUAAAUGUUAACAGUU	578
AD-114469	ascsaguuUfuCfCfAfcuauuucucuL96	311	asGfsagaAfaUfAfguggAfaAfacugususa	445	UAACAGUUUUCCACUAUUUCUCU	579
AD-114478	csusuucuUfuUfCfUfauuagugaauL96	312	asUfsucaCfuAfAfuagaAfaAfgaaagsasg	446	CUCUUUCUUUUCUAUUAGUGAAU	580
AD-114698	ususucacAfaAfCfAfcaugauuuuuL96	313	asAfsaaaUfcAfUfguguUfuGfugaaasgsu	447	ACUUUCACAAACACAUGAUUUUU	581
AD-114728	usascuuaAfaAfUfAfuccugucuuuL96	314	asAfsagaCfaGfGfauauUfuUfaaguascsu	448	AGUACUUAAAAUAUCCUGUCUUU	582
AD-114746	ususucccAfuAfUfAfacaaugauuuL96	315	asAfsaucAfuUfGfuuauAfuGfggaaasgsa	449	UCUUUCCCAUAUAACAAUGAUUU	583
AD-115217	gsusguacAfuAfUfAfucaaaauguuL96	316	asAfscauUfuUfGfauauAfuGfuacacsgsu	450	ACGUGUACAUAUAUCAAAAUGUU	584
AD-115235	csasacgaAfaUfUfCfauaacaaucuL96	317	asGfsauuGfuUfAfugaaUfuUfcguugsasu	451	AUCAACGAAAUUCAUAACAAUCU	585
AD-115563	gsasaacuAfcCfAfGfaguuaccuguL96	318	asCfsaggUfaAfCfucugGfuAfguuucsusa	452	UAGAAACUACCAGAGUUACCUGU	586
AD-115659	csusuucuUfuUfCfAfugauucauguL96	319	asCfsaugAfaUfCfaugaAfaAfgaaagsgsa	453	UCCUUUCUUUUCAUGAUUCAUGU	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	csgscaugCfuAfAfAfuuuaaugcuuL96	320	asAfsgcaUfuAfAfauuuAfgCfaugcgsgsu	454	ACCGCAUGCUAAAUUUAAUGCUU	588
AD-115844	cscsucuuGfaAfAfUfccuuuauuuuL96	321	asAfsaauAfaAfGfgauuUfcAfagaggsgsu	455	ACCCUCUUGAAAUCCUUUAUUUU	589
AD-115919	uscsucuuGfaUfCfUfagaauuuacuL96	322	asGfsuaaAfuUfCfuagaUfcAfagagasgsa	456	UCUCUCUUGAUCUAGAAUUUACU	590
AD-1410569	cscsacaaAfcUfCfAfaguuugaauuL96	323	asAfsuucAfaAfCfuugaGfuUfuguggsgsc	457	GCCCACAAACUCAAGUUUGAAUC	591
AD-1410577	asuscuuuCfuGfUfAfacuuccuuuuL96	324	asAfsaagGfaAfGfuuacAfgAfaagaususc	458	GAAUCUUUCUGUAACUUCCUUUA	592
AD-1410605	asgsuaugAfaCfCfAfuauuuuaaguL96	325	asCfsuuaAfaAfUfauggUfuCfauacuscsu	459	AGAGUAUGAACCAUAUUUUAAGA	593
AD-1410628	csusaccaUfuUfCfAfggacuucuuuL96	326	asAfsagaAfgUfCfcugaAfaUfgguagsasu	460	AUCUACCAUUUCAGGACUUCUUG	594
AD-1410662	csasucauAfaAfAfGfuucacuuuauL96	327	asUfsaaaGfuGfAfacuuUfuAfugaugsusc	461	GACAUCAUAAAAGUUCACUUUAA	595
AD-1410700	uscsaaggAfaUfUfAfgguacaguauL96	328	asUfsacuGfuAfCfcuaaUfuCfcuugasgsg	462	CCUCAAGGAAUUAGGUACAGUAA	596
AD-1410725	uscsuuacCfuUfGfAfccacacauuuL96	329	asAfsaugUfgUfGfgucaAfgGfuaagasasg	463	CUUCUUACCUUGACCACACAUUC	597
AD-1410825	uscsacacAfcAfUfCfuauuacuccuL96	330	asGfsgagUfaAfUfagauGfuGfugugasgsg	464	CCUCACACACAUCUAUUACUCCC	598
AD-1410845	uscsugauCfgAfGfGfauuucaacuuL96	331	asAfsguuGfaAfAfuccuCfgAfucagasusu	465	AAUCUGAUCGAGGAUUUCAACUC	599
AD-1410880	gsascaagCfaAfAfUfcgugcuacuuL96	332	asAfsguaGfcAfCfgauuUfgCfuugucsasa	466	UUGACAAGCAAAUCGUGCUACUA	600
AD-1410926	cscscuaaUfgUfAfCfacagucaauuL96	333	asAfsuugAfcUfGfuguaCfaUfuagggsasu	467	AUCCCUAAUGUACACAGUCAAUG	601
AD-1410994	asusuauuCfuCfCfAfuucauuucauL96	334	asUfsgaaAfuGfAfauggAfgAfauaaususc	468	GAAUUAUUCUCCAUUCAUUUCAA	602
AD-1411107	csasggcuUfaCfAfUfugacauuaauL96	335	asUfsuaaUfgUfCfaaugUfaAfgccugscsa	469	UGCAGGCUUACAUUGACAUUAAA	603
AD-1411138	cscsaggaAfuCfUfUfaagaaaauauL96	336	asUfsauuUfuCfUfuaagAfuUfccuggsusu	470	AACCAGGAAUCUUAAGAAAAUAA	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	uscsagcaUfuUfGfGfauaauuucuuL96	337	asAfsgaaAfuUfAfuccaAfaUfgcugasgsa	471	UCUCAGCAUUUGGAUAAUUUCUC	605
AD-1411270	usascgaaGfaUfGfAfguccuucacuL96	338	asGfsugaAfgGfAfcucaUfcUfucguascsu	472	AGUACGAAGAUGAGUCCUUCACC	606
AD-1411284	csasccaaAfcAfUfAfcagugaaucuL96	339	asGfsauuCfaCfUfguauGfuUfuggugsasa	473	UUCACCAAACAUACAGUGAAUCC	607
AD-1411342	ascsacucAfaAfAfUfcguguucaauL96	340	asUfsugaAfcAfCfgauuUfuGfagugusgsu	474	ACACACUCAAAAUCGUGUUCAAA	608
AD-1411387	asusgaagUfcAfAfCfucuucuuucuL96	341	asGfsaaaGfaAfGfaguuGfaCfuucauscsu	475	AGAUGAAGUCAACUCUUCUUUCA	609
AD-1411480	usasacaaGfaCfCfAfuacuacaguuL96	342	asAfscugUfaGfUfauggUfcUfuguuasasg	476	CUUAACAAGACCAUACUACAGUG	610
AD-1411521	asasuaggAfcUfAfCfuucuaaucuuL96	343	asAfsgauUfaGfAfaguaGfuCfcuauusasg	477	CUAAUAGGACUACUUCUAAUCUG	611
AD-1411657	asasacauCfaUfGfAfgcacuaucauL96	344	asUfsgauAfgUfGfcucaUfgAfuguuusgsa	478	UCAAACAUCAUGAGCACUAUCAA	612
AD-1411743	csasuucaUfcUfAfUfggaaagagguL96	345	asCfscucUfuUfCfcauaGfaUfgaaugsasg	479	CUCAUUCAUCUAUGGAAAGAGGC	613
AD-1411798	usasacuuCfcAfUfGfaauucuaguuL96	346	asAfscuaGfaAfUfucauGfgAfaguuasasc	480	GUUAACUUCCAUGAAUUCUAGUC	614
AD-1411935	gsascuauGfaUfUfAfccagaacaguL96	347	asCfsuguUfcUfGfguaaUfcAfuagucsasg	481	CUGACUAUGAUUACCAGAACAGA	615
AD-1411972	cscsgaaaCfuCfAfUfcauugaaucuL96	348	asGfsauuCfaAfUfgaugAfgUfuucggsasa	482	UUCCGAAACUCAUCAUUGAAUCA	616
AD-1412021	ascsugaaUfuCfGfUfuucuucaaauL96	349	asUfsuugAfaGfAfaacgAfaUfucagusgsc	483	GCACUGAAUUCGUUUCUUCAAAC	617
AD-1412040	gsusugguUfcAfAfAfuuauucuucuL96	350	asGfsaagAfaUfAfauuuGfaAfccaacsasa	484	UUGUUGGUUCAAAUUAUUCUUCC	618
AD-1412052	asgsuucaCfuGfUfCfaauaaccuuuL96	351	asAfsaggUfuAfUfugacAfgUfgaacususa	485	UAAGUUCACUGUCAAUAACCUUG	619
AD-1412095	ascsucagUfuCfUfCfaauucuuccuL96	352	asGfsgaaGfaAfUfugagAfaCfugagususc	486	GAACUCAGUUCUCAAUUCUUCCA	620
AD-1412163	usascgucUfaCfUfUfucacuugguuL96	353	asAfsccaAfgUfGfaaagUfaGfacguasusc	487	GAUACGUCUACUUUCACUUGGUG	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	gsgsaugaAfaUfUfAfcuagcacauuL96	354	asAfsuguGfcUfAfguaaUfuUfcauccsasg	488	CUGGAUGAAAUUACUAGCACAUA	622
AD-1412364	gsusuacuCfuUfAfAfaacaaaguauL96	355	asUfsacuUfuGfUfuuuaAfgAfguaacsasg	489	CUGUUACUCUUAAAACAAAGUAA	623
AD-1412429	csusgaugAfaGfAfCfacagcuguuuL96	356	asAfsacaGfcUfGfugucUfuCfaucagsusa	490	UACUGAUGAAGACACAGCUGUUA	624
AD-1412482	csusagagUfuAfGfAfcauaaaucuuL96	357	asAfsgauUfuAfUfgucuAfaCfucuagsgsa	491	UCCUAGAGUUAGACAUAAAUCUC	625
AD-1412497	csuscuacAfaGfUfAfagacaggauuL96	358	asAfsuccUfgUfCfuuacUfuGfuagagsasu	492	AUCUCUACAAGUAAGACAGGAUG	626
AD-1412539	ususucucAfuUfAfAfgacacgaaauL96	359	asUfsuucGfuGfUfcuuaAfuGfagaaascsu	493	AGUUUCUCAUUAAGACACGAAAA	627
AD-1412582	usgsaagcCfuAfCfAfacacauuuuuL96	360	asAfsaaaUfgUfGfuuguAfgGfcuucascsu	494	AGUGAAGCCUACAACACAUUUUC	628
AD-1412622	asasuccaAfuGfAfAfacaucucuuuL96	361	asAfsagaGfaUfGfuuucAfuUfggauususa	495	UAAAUCCAAUGAAACAUCUCUUC	629
AD-1412683	asusaaucAfgAfAfUfuccucaaauuL96	362	asAfsuuuGfaGfGfaauuCfuGfauuausgsg	496	CCAUAAUCAGAAUUCCUCAAAUG	630
AD-1412721	asgsgaacAfcUfAfUfcaaacauucuL96	363	asGfsaauGfuUfUfgauaGfuGfuuccuscsu	497	AGAGGAACACUAUCAAACAUUCC	631
AD-1412733	uscsaaauGfcAfCfUfcuacuucaguL96	364	asCfsugaAfgUfAfgaguGfcAfuuugasusc	498	GAUCAAAUGCACUCUACUUCAGA	632
AD-1412756	uscsagugAfaAfUfGfcuugaguauuL96	365	asAfsuacUfcAfAfgcauUfuCfacugasgsc	499	GCUCAGUGAAAUGCUUGAGUAUG	633
AD-1412779	uscscucaGfaAfCfAfugaagucuguL96	366	asCfsagaCfuUfCfauguUfcUfgaggasasg	500	CUUCCUCAGAACAUGAAGUCUGG	634
AD-1412870	csuscauuCfaGfAfGfaaaccuuucuL96	367	asGfsaaaGfgUfUfucucUfgAfaugagsusu	501	AACUCAUUCAGAGAAACCUUUCC	635
AD-1412963	ascsaaccCfuUfUfCfucuagacuuuL96	368	asAfsaguCfuAfGfagaaAfgGfguugusasu	502	AUACAACCCUUUCUCUAGACUUC	636
AD-1412982	csusccagAfaCfUfCfagucaaacauL96	369	asUfsguuUfgAfCfugagUfuCfuggagsasg	503	CUCUCCAGAACUCAGUCAAACAA	637
AD-1413036	ususgcagAfuCfUfCfagucaaauuuL96	370	asAfsauuUfgAfCfugagAfuCfugcaasasg	504	CUUUGCAGAUCUCAGUCAAAUUC	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	gsasccuuGfaUfCfAfgauauucuauL96	371	asUfsagaAfuAfUfcugaUfcAfaggucsusg	505	CAGACCUUGAUCAGAUAUUCUAC	639
AD-1413143	uscsugaaUfcUfAfGfucagucauuuL96	372	asAfsaugAfcUfGfacuaGfaUfucagasasg	506	CUUCUGAAUCUAGUCAGUCAUUG	640
AD-1413210	csusaucaAfaGfGfAfauuuaauccuL96	373	asGfsgauUfaAfAfuuccUfuUfgauagsasa	507	UUCUAUCAAAGGAAUUUAAUCCA	641
AD-1413251	usascauuGfaGfAfUfcauuccaaauL96	374	asUfsuugGfaAfUfgaucUfcAfauguasasu	508	AUUACAUUGAGAUCAUUCCAAAG	642
AD-1413286	ascsuaugCfuGfAfAfauugauuauuL96	375	asAfsuaaUfcAfAfuuucAfgCfauaguscsa	509	UGACUAUGCUGAAAUUGAUUAUG	643
AD-1413311	usasggacAfaAfCfAfucaacuccuuL96	376	asAfsggaGfuUfGfauguUfuGfuccuasasc	510	GUUAGGACAAACAUCAACUCCUC	644
AD-1413488	uscsggaaUfuCfUfUfgguccuauuuL96	377	asAfsauaGfgAfCfcaagAfaUfuccgasgsa	511	UCUCGGAAUUCUUGGUCCUAUUA	645
AD-1413517	ususauccAfaGfUfUfcguuuuaaauL96	378	asUfsuuaAfaAfCfgaacUfuGfgauaascsa	512	UGUUAUCCAAGUUCGUUUUAAAA	646
AD-1413605	asusgcugUfuCfAfGfccaaauagcuL96	379	asGfscuaUfuUfGfgcugAfaCfagcaususa	513	UAAUGCUGUUCAGCCAAAUAGCA	647
AD-1413615	usasgcagUfuAfUfAfccuacguauuL96	380	asAfsuacGfuAfGfguauAfaCfugcuasusu	514	AAUAGCAGUUAUACCUACGUAUG	648
AD-1413936	csusgguuCfaUfUfUfaaaacucuuuL96	381	asAfsagaGfuUfUfuaaaUfgAfaccagsgsc	515	GCCUGGUUCAUUUAAAACUCUUG	649
AD-1414009	usgscaaaCfgCfCfAfuuucuuaucuL96	382	asGfsauaAfgAfAfauggCfgUfuugcasusc	516	GAUGCAAACGCCAUUUCUUAUCA	650
AD-1414059	asusaucuGfaUfUfCfacagaucaauL96	383	asUfsugaUfcUfGfugaaUfcAfgauausgsa	517	UCAUAUCUGAUUCACAGAUCAAG	651
AD-1414074	uscsagagUfuUfCfUfggguuacuguL96	384	asCfsaguAfaCfCfcagaAfaCfucugasasg	518	CUUCAGAGUUUCUGGGUUACUGG	652
AD-1414139	asgsaauuUfgCfCfUfcuaaaccuuuL96	385	asAfsaggUfuUfAfgaggCfaAfauucusgsc	519	GCAGAAUUUGCCUCUAAACCUUG	653
AD-1414232	asusguagCfuUfAfCfaguuccaacuL96	386	asGfsuugGfaAfCfuguaAfgCfuacausasg	520	CUAUGUAGCUUACAGUUCCAACC	654
AD-1414275	gsasauguGfaUfGfUfauuuuaauguL96	387	asCfsauuAfaAfAfuacaUfcAfcauucscsu	521	AGGAAUGUGAUGUAUUUUAAUGG	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	usasgauaUfaUfUfAfggaucucucuL96	388	asGfsagaGfaUfCfcuaaUfaUfaucuasgsc	522	GCUAGAUAUAUUAGGAUCUCUCC	656
AD-1414410	uscsacagCfuUfCfUfucguuuaaguL96	389	asCfsuuaAfaCfGfaagaAfgCfugugasusu	523	AAUCACAGCUUCUUCGUUUAAGA	657
AD-1414498	asusugauCfuAfCfUfcaagaucaauL96	390	asUfsugaUfcUfUfgaguAfgAfucaaususu	524	AAAUUGAUCUACUCAAGAUCAAG	658
AD-1414544	cscsucugAfaAfUfGfuauguaaaguL96	391	asCfsuuuAfcAfUfacauUfuCfagaggsasc	525	GUCCUCUGAAAUGUAUGUAAAGA	659
AD-1414625	asasggaaAfuAfCfUfaauaccaaauL96	392	asUfsuugGfuAfUfuaguAfuUfuccuuscsa	526	UGAAGGAAAUACUAAUACCAAAG	660
AD-1414662	csasuuccUfaAfAfAfcauggaaucuL96	393	asGfsauuCfcAfUfguuuUfaGfgaaugsasc	527	GUCAUUCCUAAAACAUGGAAUCA	661
AD-1414713	asgsacucUfuUfAfAfgaccucaaauL96	394	asUfsuugAfgGfUfcuuaAfaGfagucuscsu	528	AGAGACUCUUUAAGACCUCAAAC	662
AD-1414786	asgsauaaUfgGfCfUfauuacuucuuL96	395	asAfsgaaGfuAfAfuagcCfaUfuaucususa	529	UAAGAUAAUGGCUAUUACUUCUG	663
AD-1414796	ususcugcAfuUfAfAfuuugaauacuL96	396	asGfsuauUfcAfAfauuaAfuGfcagaasgsu	530	ACUUCUGCAUUAAUUUGAAUACA	664
AD-1414831	asasgggcUfuAfUfCfuuucuuaauuL96	397	asAfsuuaAfgAfAfagauAfaGfcccuususu	531	AAAAGGGCUUAUCUUUCUUAAUG	665
AD-1414857	csuscuuuUfaAfAfUfccuuuacacuL96	398	asGfsuguAfaAfGfgauuUfaAfaagagsusu	532	AACUCUUUUAAAUCCUUUACACA	666
AD-1414871	csascuagUfaAfAfAfcagauauuauL96	399	asUfsaauAfuCfUfguuuUfaCfuagugsusg	533	CACACUAGUAAAACAGAUAUUAC	667
AD-1414931	ususucugAfcUfUfUfccaugaguauL96	400	asUfsacuCfaUfGfgaaaGfuCfagaaasasa	534	UUUUUCUGACUUUCCAUGAGUAA	668
AD-1415052	asasaacaUfaAfUfUfucaccuacuuL96	401	asAfsguaGfgUfGfaaauUfaUfguuuusgsa	535	UCAAAACAUAAUUUCACCUACUG	669
AD-1415096	csusggucUfaAfAfUfgcaguuguuuL96	402	asAfsacaAfcUfGfcauuUfaGfaccagscsa	536	UGCUGGUCUAAAUGCAGUUGUUC	670
AD-1415166	uscsucuuCfuUfCfCfagcaacuucuL96	403	asGfsaagUfuGfCfuggaAfgAfagagasgsa	537	UCUCUCUUCUUCCAGCAACUUCC	671
AD-1415169	ususucauCfaUfUfCfcuuucccuguL96	404	asCfsaggGfaAfAfggaaUfgAfugaaasgsg	538	CCUUUCAUCAUUCCUUUCCCUGG	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	ususuagaCfaUfCfCfuuaaaaucauL96	405	asUfsgauUfuUfAfaggaUfgUfcuaaasgsg	539	CCUUUAGACAUCCUUAAAAUCAC	673
AD-1415243	usgsauuuAfaUfCfAfuccuguaacuL96	406	asGfsuuaCfaGfGfaugaUfuAfaaucasasg	540	CUUGAUUUAAUCAUCCUGUAACG	674
AD-1415314	gsascuaaGfaAfAfCfucacucgaauL96	407	asUfsucgAfgUfGfaguuUfcUfuagucscsu	541	AGGACUAAGAAACUCACUCGAAA	675
AD-1415327	uscsgaaaCfcAfCfAfcaacuacauuL96	408	asAfsuguAfgUfUfguguGfgUfuucgasgsu	542	ACUCGAAACCACACAACUACAUG	676
AD-1415412	ascsaacaUfaCfCfAfgaaucucuauL96	409	asUfsagaGfaUfUfcuggUfaUfguugucsu	543	AGACAACAUACCAGAAUCUCUAG	677
AD-1415439	gscsauucUfaUfUfCfguugugaacuL96	410	asGfsuucAfcAfAfcgaaUfaGfaaugcsasg	544	CUGCAUUCUAUUCGUUGUGAACA	678
AD-1415466	gsuscucgAfuUfCfAfguguagaaguL96	411	asCfsuucUfaCfAfcugaAfuCfgagacsusg	545	CAGUCUCGAUUCAGUGUAGAAGG	679
AD-1415563	asusccacAfaAfAfCfauuggcuuuuL96	412	asAfsaagCfcAfAfuguuUfuGfuggausgsu	546	ACAUCCACAAAACAUUGGCUUUC	680
AD-1415578	csgsuauuCfcCfAfCfuauuccuuuuL96	413	asAfsaagGfaAfUfagugGfgAfauacgsasa	547	UUCGUAUUCCCACUAUUCCUUUC	681
AD-1415602	csasucaaCfaUfUfUfcuaagauuuuL96	414	asAfsaauCfuUfAfgaaaUfgUfugaugsgsg	548	CCCAUCAACAUUUCUAAGAUUUC	682
AD-1415633	asasaacaUfuUfCfUfuuguuuucuuL96	415	asAfsgaaAfaCfAfaagaAfaUfguuuuscsc	549	GGAAAACAUUUCUUUGUUUUCUA	683
AD-1415663	gsusgaucUfgUfUfCfaguugcaaauL96	416	asUfsuugCfaAfCfugaaCfaGfaucacsasc	550	GUGUGAUCUGUUCAGUUGCAAAG	684
AD-1415714	asusucgaCfaUfUfUfccauuuuucuL96	417	asGfsaaaAfaUfGfgaaaUfgUfcgaaususc	551	GAAUUCGACAUUUCCAUUUUUCA	685
AD-1415738	csusucucUfaCfUfCfugaaauugguL96	418	asCfscaaUfuUfCfagagUfaGfagaagscsc	552	GGCUUCUCUACUCUGAAAUUGGG	686
AD-1415798	gsusuauuCfuCfUfAfcuugagaaauL96	419	asUfsuucUfcAfAfguagAfgAfauaacsgsa	553	UCGUUAUUCUCUACUUGAGAAAA	687
AD-1415830	usgsuuagUfgUfCfAfgaacugaaauL96	420	asUfsuucAfgUfUfcugaCfaCfuaacasasg	554	CUUGUUAGUGUCAGAACUGAAAC	688
AD-1415857	usasucccUfaGfAfCfuuuuagucuuL96	421	asAfsgacUfaAfAfagucUfaGfggauasusg	555	CAUAUCCCUAGACUUUUAGUCUG	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	uscsuuccAfuAfAfAfaugaaacuuuL96	422	asAfsaguUfuCfAfuuuuAfuGfgaagasgsa	556	UCUCUUCCAUAAAAUGAAACUUA	690
AD-1415881	asusguuuCfuAfAfUfccauugcucuL96	423	asGfsagcAfaUfGfgauuAfgAfaacaususa	557	UAAUGUUUCUAAUCCAUUGCUCA	691
AD-1415899	gsusagacAfuGfAfAfuauuaauuguL96	424	asCfsaauUfaAfUfauucAfuGfucuacscsu	558	AGGUAGACAUGAAUAUUAAUUGA	692
AD-1415910	gsasucugGfaAfAfAfuacuuguuuuL96	425	asAfsaacAfaGfUfauuuUfcCfagaucsasa	559	UUGAUCUGGAAAAUACUUGUUUG	693
AD-1415934	csusguguAfgAfAfAfuauuaaaacuL96	426	asGfsuuuUfaAfUfauuuCfuAfcacagscsa	560	UGCUGUGUAGAAAUAUUAAAACC	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.

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.

For free uptake, experiments were performed by adding 2.5 µl of siRNA duplexes in PBS per well into a 96 well plate. Complete growth media (47.5 µl) containing about 1.5 x 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.

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 H_2O 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 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	AGGGCAUCAGUUGGAGCUACU	696	261-281	AGUAGCTCCAACUGAUGCCCUGA	952	259-281
AD-1465903.1	UCUACAGAGAGUAUGAACCAU	697	339-359	AUGGTUCAUACUCUCUGUAGACA	953	337-359
AD-1465904.1	UACAGAGAGUAUGAACCAUAU	698	341-361	AUAUGGTUCAUACUCUCUGUAGA	954	339-361
AD-1465905.1	ACAGAGAGUAUGAACCAUAUU	699	342-362	AAUATGGUUCAUACUCUCUGUAG	955	340-362
AD-1465906.1	UUCUUGGGCCUACUUUAUAUU	700	399-419	AAUATAAAGUAGGCCCAAGAAGU	956	397-419
AD-1465907.1	UACUUUAUAUGCUGAAGUCGU	701	409-429	ACGACUTCAGCAUAUAAAGUAGG	957	407-429
AD-1465908.1	ACUUUAUAUGCUGAAGUCGGU	702	410-430	ACCGACTUCAGCAUAUAAAGUAG	958	408-430
AD-1465909.1	AGUAAAUUAUCAGAAGGUGCU	703	503-523	AGCACCTUCUGAUAAUUUACUGU	959	501-523
AD-1465910.1	AAAUUAUCAGAAGGUGCUUCU	704	506-526	AGAAGCACCUUCUGAUAAUUUAC	960	504-526
AD-1465911.1	AUCAGAAGGUGCUUCUUACCU	705	511-531	AGGUAAGAAGCACCUUCUGAUAA	961	509-531
AD-1465912.1	UCAGAAGGUGCUUCUUACCUU	706	512-532	AAGGTAAGAAGCACCUUCUGAUA	962	510-532
AD-1465913.1	CAGAAGGUGCUUCUUACCUUU	707	513-533	AAAGGUAAGAAGCACCUUCUGAU	963	511-533
AD-1465914.1	AUACACCUAUGAAUGGAGUAU	708	586-606	AUACTCCAUUCAUAGGUGUAUUC	964	584-606
AD-1465915.1	ACCUAUGAAUGGAGUAUCAGU	709	590-610	ACUGAUACUCCAUUCAUAGGUGU	965	588-610
AD-1465916.1	CCUAUGAAUGGAGUAUCAGUU	710	591-611	AACUGATACUCCAUUCAUAGGUG	966	589-611
AD-1465917.1	AUGAAUGGAGUAUCAGUGAGU	711	594-614	ACUCACTGAUACUCCAUUCAUAG	967	592-614
AD-1465918.1	AUGCCUCACACACAUCUAUUU	712	643-663	AAAUAGAUGUGTGUGAGGCAUGG	968	641-663
AD-1465919.1	UGCCUCACACACAUCUAUUAU	713	644-664	ATAATAGAUGUGUGUGAGGCAUG	969	642-664
AD-1465920.1	GCCUCACACACAUCUAUUACU	11	645-665	AGUAAUAGAUGTGUGUGAGGCAU	12	643-665
AD-1465921.1	CCUCACACACAUCUAUUACUU	714	646-666	AAGUAATAGAUGUGUGUGAGGCA	970	644-666
AD-1465922.1	CUCACACACAUCUAUUACUCU	13	647-667	AGAGTAAUAGATGUGUGUGAGGC	14	645-667
AD-1465923.1	CACACACAUCUAUUACUCCCU	715	649-669	AGGGAGTAAUAGAUGUGUGUGAG	971	647-669
AD-1465924.1	ACAUCUAUUACUCCCAUGAAU	716	654-674	AUUCAUGGGAGUAAUAGAUGUG	972	652-674
AD-1465925.1	GAAGACGUUUGACAAGCAAAU	717	757-777	AUUUGCTUGUCAAACGUCUUCUG	973	755-777
AD-1465926.1	AGACGUUUGACAAGCAAAUCU	718	759-779	AGAUTUGCUUGUCAAACGUCUUC	974	757-779
AD-1465927.1	GACGUUUGACAAGCAAAUCGU	719	760-780	ACGATUTGCUUGUCAAACGUCUU	975	758-780
AD-1465928.1	GCCAGUCAUCAUCCCUAAUGU	720	819-839	ACAUTAGGGAUGAUGACUGGCUC	976	817-839
AD-1465929.1	GUCAUCAUCCCUAAUGUACAU	721	823-843	AUGUACAUUAGGGAUGAUGACU	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
				G		
AD-1465930.1	CAUCAUCCCUAAUGUACACAU	722	825-845	AUGUGUACAUUAGGGAUGAUGA C	978	823-845
AD-1465931.1	AUCAUCCCUAAUGUACACAGU	723	826-846	ACUGUGTACAUUAGGGAUGAUGA	979	824-846
AD-1465932.1	AAUGUACACAGUCAAUGGAUU	724	835-855	AAUCCATUGACTGUGUACAUUAG	980	833-855
AD-1465933.1	AUGUACACAGUCAAUGGAUAU	725	836-856	AUAUCCAUUGACUGUGUACAUUA	981	834-856
AD-1465934.1	AUGUGAAUGGGACAAUGCCAU	726	855-875	AUGGCATUGUCCCAUUCACAUAU	982	853-875
AD-1465935.1	GCCAGAUAUAACAGUUUGUGU	727	871-891	ACACAAACUGUTAUAUCUGGCAU	983	869-891
AD-1465936.1	CCAGAUAUAACAGUUUGUGCU	728	872-892	AGCACAAACUGTUAUAUCUGGCA	984	870-892
AD-1465937.1	GAGCAGAACCAUCAUAAGGUU	729	974-994	AACCTUAUGAUGGUUCUGCUCCA	985	972-994
AD-1465938.1	CAGAACCAUCAUAAGGUCUCU	730	977-997	AGAGACCUUAUGAUGGUUCUGCU	986	975-997
AD-1465939.1	AGAACCAUCAUAAGGUCUCAU	731	978-998	AUGAGACCUUAUGAUGGUUCUGC	987	976-998
AD-1465940.1	AUCACCCUUGUCAGUGCUACU	732	1001-1021	AGUAGCACUGACAAGGGUGAUGG	988	999-1021
AD-1465941.1	UUGUCAGUGCUACAUCCACUU	733	1008-1028	AAGUGGAUGUAGCACUGACAAGG	989	1006-1028
AD-1465942.1	CAUCCACUACCGCAAAUAUGU	734	1020-1040	ACAUAUTUGCGGUAGUGGAUGUA	990	1018-1040
AD-1465943.1	AAGCUGGGAUGCAGGCUUACU	735	1095-1115	AGUAAGCCUGCAUCCCAGCUUGC	991	1093-1115
AD-1465944.1	AGCUGGGAUGCAGGCUUACAU	736	1096-1116	AUGUAAGCCUGCAUCCCAGCUUG	992	1094-1116
AD-1465945.1	GCUGGGAUGCAGGCUUACAUU	737	1097-1117	AAUGTAAGCCUGCAUCCCAGCUU	993	1095-1117
AD-1465946.1	CUGGGAUGCAGGCUUACAUUU	738	1098-1118	AAAUGUAAGCCTGCAUCCCAGCU	994	1096-1118
AD-1465947.1	UGGGAUGCAGGCUUACAUUGU	739	1099-1119	ACAATGTAAGCCUGCAUCCCAGC	995	1097-1119
AD-1465948.1	GGGAUGCAGGCUUACAUUGAU	740	1100-1120	AUCAAUGUAAGCCUGCAUCCCAG	996	1098-1120
AD-1465949.1	GGAUGCAGGCUUACAUUGACU	741	1101-1121	AGUCAATGUAAGCCUGCAUCCCA	997	1099-1121
AD-1465950.1	GAUGCAGGCUUACAUUGACAU	742	1102-1122	AUGUCAAUGUAAGCCUGCAUCCC	998	1100-1122
AD-1465951.1	AUGCAGGCUUACAUUGACAUU	743	1103-1123	AAUGTCAAUGUAAGCCUGCAUCC	999	1101-1123
AD-1465952.1	UGCAGGCUUACAUUGACAUUU	744	1104-1124	AAAUGUCAAUGUAAGCCUGCAUC	1000	1102-1124
AD-1465953.1	GCAGGCUUACAUUGACAUUAU	745	1105-1125	AUAATGTCAAUGUAAGCCUGCAU	1001	1103-1125
AD-1465954.1	CAGGCUUACAUUGACAUUAAU	71	1106-1126	AUUAAUGUCAAUGUAAGCCUGCA	202	1104-1126
AD-1465955.1	AGGCUUACAUUGACAUUAAAU	746	1107-1127	ATUUAATGUCAAUGUAAGCCUGC	1002	1105-1127
AD-1465956.1	GGCUUACAUUGACAUUAAAAU	747	1108-1128	ATUUTAAUGUCAAUGUAAGCCUG	1003	1106-1128
AD-1465957.1	GCUUACAUUGACAUUAAAAAU	748	1109-1129	ATUUTUAAUGUCAAUGUAAGCCU	1004	1107-1129
AD-1465958.1	CUUACAUUGACAUUAAAAACU	749	1110-1130	AGUUTUTAAUGTCAAUGUAAGCC	1005	1108-1130
AD-1465959.1	UUACAUUGACAUUAAAAACUU	750	1111-1131	AAGUTUTUAAUGUCAAUGUAAGC	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	UACAUUGACAUUAAAAAACUGU	751	1112-1132	ACAGTUTUUAATGUCAAUGUAAG	1007	1110-1132
AD-1465961.1	ACAUUGACAUUAAAAAACUGCU	752	1113-1133	AGCAGUTUUUAAUGUCAAUGUAA	1008	1111-1133
AD-1465962.1	CAUUGACAUUAAAAAACUGCCU	753	1114-1134	AGGCAGTUTUUUAAUGUCAAUGUA	1009	1112-1134
AD-1465963.1	AUUGACAUUAAAAAACUGCCCU	754	1115-1135	AGGGCAGUUUUUAAUGUCAAUG U	1010	1113-1135
AD-1465964.1	UUGACAUUAAAAAACUGCCCAU	755	1116-1136	AUGGGCAGUUUUUAAUGUCAAU G	1011	1114-1136
AD-1465965.1	GGGAAUACUUCAUUGCUGCAU	756	1194-1214	AUGCAGCAAUGAAGUAUUCCCAC	1012	1192-1214
AD-1465966.1	AGUCAUUUGGGACUAUGCACU	757	1219-1239	AGUGCATAGUCCCAAAUGACUUC	1013	1217-1239
AD-1465967.1	GGGACUAUGCACCUGUAAUAU	758	1227-1247	AUAUTACAGGUGCAUAGUCCCAA	1014	1225-1247
AD-1465968.1	CACCUGUAAUACCAGCGAAUU	759	1236-1256	AAUUCGCUGGUAUUACAGGUGCA	1015	1234-1256
AD-1465969.1	UGUAAUACCAGCGAAUAUGGU	760	1240-1260	ACCATATUCGCTGGUAUUACAGG	1016	1238-1260
AD-1465970.1	GUAAUACCAGCGAAUAUGGAU	761	1241-1261	ATCCAUAUUCGCUGGUAUUACAG	1017	1239-1261
AD-1465971.1	AGGUCUCAGCAUUUGGAUAAU	762	1271-1291	AUUATCCAAAUGCUGAGACCUGU	1018	1269-1291
AD-1465972.1	GUUAUGUACACACAGUACGAU	763	1325-1345	ATCGTACUGUGTGUACAUAACUU	1019	1323-1345
AD-1465973.1	UUAUGUACACACAGUACGAAU	764	1326-1346	ATUCGUACUGUGUGUACAUAACU	1020	1324-1346
AD-1465974.1	AUGUACACACAGUACGAAGAU	765	1328-1348	AUCUTCGUACUGUGUGUACAUAA	1021	1326-1348
AD-1465975.1	UGUACACACAGUACGAAGAUU	766	1329-1349	AAUCTUCGUACUGUGUGUACAUA	1022	1327-1349
AD-1465976.1	GUACACACAGUACGAAGAUGU	767	1330-1350	ACAUCUTCGUACUGUGUGUACAU	1023	1328-1350
AD-1465977.1	AGUACGAAGAUGAGUCCUUCU	768	1338-1358	AGAAGGACUCAUCUUCGUACUGU	1024	1336-1358
AD-1465978.1	GUACGAAGAUGAGUCCUUCAU	769	1339-1359	AUGAAGGACUCAUCUUCGUACUG	1025	1337-1359
AD-1465979.1	GUGAAUCCCAAUAUGAAAGAU	770	1370-1390	AUCUTUCAUAUUGGGAUUCACUG	1026	1368-1390
AD-1465980.1	ACCCUCAUGGAGUGACCUUCU	771	1482-1502	AGAAGGTCACUCCAUGAGGGUAA	1027	1480-1502
AD-1465981.1	GAACAACACCAUGAUCAGAGU	772	1546-1566	ACUCTGAUCAUGGUGUUGUUCCU	1028	1544-1566
AD-1465982.1	CAACACCAUGAUCAGAGCAGU	773	1549-1569	ACUGCUCUGAUCAUGGUGUUGUU	1029	1547-1569
AD-1465983.1	CACCAUGAUCAGAGCAGUUCU	774	1552-1572	AGAACUGCUCUGAUCAUGGUGUU	1030	1550-1572
AD-1465984.1	CAUGAUCAGAGCAGUUCAACU	775	1555-1575	AGUUGAACUGCUCUGAUCAUGGU	1031	1553-1575
AD-1465985.1	UGAUCAGAGCAGUUCAACCAU	776	1557-1577	AUGGTUGAACUGCUCUGAUCAUG	1032	1555-1577
AD-1465986.1	AAACCUAUACUUAUAAGUGGU	777	1581-1601	ACCACUTAUAAGUAUAGGUUUCC	1033	1579-1601
AD-1465987.1	AACCUAUACUUAUAAGUGGAU	778	1582-1602	AUCCACTUAUAAGUAUAGGUUUC	1034	1580-1602
AD-1465988.1	CUUAUAAGUGGAACAUCUUAU	779	1590-1610	AUAAGATGUUCCACUUAUAAGUA	1035	1588-1610
AD-1465989.1	UCUAAUCUGUAAGAGCAGAUU	780	1714-1734	AAUCTGCUCUUACAGAUUAGAAG	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	ACCUUGAGGACAACAUCAACU	782	1818-1838	AGUUGATGUUGUCCUCAAGGUAC	1038	1816-1838
AD-1465992.1	AUGAAUCAAACAUCAUGAGCU	783	1887-1907	AGCUCATGAUGTUUGAUUCAUAA	1039	1885-1907
AD-1465993.1	GAAUCAAACAUCAUGAGCACU	784	1889-1909	AGUGCUCAUGAUGUUUGAUUCAU	1040	1887-1909
AD-1465994.1	UGAGCACUAUCAAUGGCUAUU	785	1902-1922	AAUAGCCAUUGAUAGUGCUCAUG	1041	1900-1922
AD-1465996.1	GAUUCUGCUUUGAUGACACUU	786	1947-1967	AAGUGUCAUCAAAGCAGAAUCCA	1042	1945-1967
AD-1465997.1	CCAGUGGCACUUCUGUAGUGU	787	1969-1989	ACACTACAGAAGUGCCACUGGAC	1043	1967-1989
AD-1465998.1	AGUGGCACUUCUGUAGUGUGU	788	1971-1991	ACACACTACAGAAGUGCCACUGG	1044	1969-1991
AD-1465999.1	CUGGGCACUCAUUCAUCUAUU	789	2025-2045	AAUAGATGAAUGAGUGCCCAGUG	1045	2023-2045
AD-1466000.1	GUGACGGUCACAAUGGAUAAU	790	2096-2116	AUUATCCAUUGUGACCGUCACAG	1046	2094-2116
AD-1466001.1	GGAACUUGGAUGUUAACUUCU	791	2120-2140	AGAAGUTAACAUCCAAGUUCCAA	1047	2118-2140
AD-1466002.1	UUAACUUCCAUGAAUUCUAGU	792	2132-2152	ACUAGAAUUCATGGAAGUUAACA	1048	2130-2152
AD-1466003.1	AUGAUGAUGAAGACUCAUAUU	793	2205-2225	AAUATGAGUCUUCAUCAUCAUCU	1049	2203-2225
AD-1466004.1	UGAUGAAGACUCAUAUGAGAU	794	2209-2229	ATCUCATAUGAGUCUUCAUCAUC	1050	2207-2229
AD-1466005.1	AAACUCAUCAUUGAAUCAGGU	795	2365-2385	ACCUGATUCAATGAUGAGUUUCG	1051	2363-2385
AD-1466006.1	AAACACAGAUAUAAUUGUUGU	796	2446-2466	ACAACAAUUAUAUCUGUGUUUGA	1052	2444-2466
AD-1466007.1	CACAGAUAUAAUUGUUGGUUU	797	2449-2469	AAACCAACAAUTAUAUCUGUGUU	1053	2447-2469
AD-1466008.1	CAUAUUCUGAAGACCCUAUAU	798	2634-2654	AUAUAGGGUCUUCAGAAUAUGGG	1054	2632-2654
AD-1466009.1	AUUCUGAAGACCCUAUAGAGU	799	2637-2657	ACUCTATAGGGTCUUCAGAAUAU	1055	2635-2657
AD-1466010.1	CGUCUACUUUCACUUGGUGCU	800	2687-2707	AGCACCAAGUGAAAGUAGACGUA	1056	2685-2707
AD-1466011.1	AUGAAAUUACUAGCACAUAAU	801	2792-2812	AUUATGTGCUAGUAAUUUCAUCC	1057	2790-2812
AD-1466012.1	AAUUACUAGCACAUAAAGUUU	802	2796-2816	AAACTUTAUGUGCUAGUAAUUUC	1058	2794-2816
AD-1466013.1	UACUAGCACAUAAAGUUGGGU	803	2799-2819	ACCCAACUUUATGUGCUAGUAAU	1059	2797-2819
AD-1466014.1	GAGAUGGCAUUUGGCUUCUGU	804	2980-3000	ACAGAAGCCAAAUGCCAUCUCCC	1060	2978-3000
AD-1466015.1	GUAGCUAUGAAAUAAUCCAAU	805	3006-3026	AUUGGATUAUUUCAUAGCUACCU	1061	3004-3026
AD-1466016.1	CAAGAUACUGAUGAAGACACU	806	3023-3043	AGUGTCTUCAUCAGUAUCUUGGA	1062	3021-3043
AD-1466017.1	GAUACUGAUGAAGACACAGCU	807	3026-3046	AGCUGUGUCUUCAUCAGUAUCUU	1063	3024-3046
AD-1466018.1	AAGACACAGCUGUUAACAAUU	808	3036-3056	AAUUGUTAACAGCUGUGUCUUCA	1064	3034-3056
AD-1466019.1	AAGUUUCCUAGAGUUAGACAU	809	3143-3163	ATGUCUAACUCTAGGAAACUUUG	1065	3141-3163
AD-1466020.1	CCUAGAGUUAGACAUAAAUCU	810	3149-3169	AGAUTUAUGUCTAACUCUAGGAA	1066	3147-3169
AD-1466021.1	UACAAGUAAGACAGGAUGGAU	811	3171-3191	ATCCAUCCUGUCUUACUUGUAGA	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	AUUCGUGUCUUAAUGAGAAACUG	1068	3215-3237
AD-1466023.1	CACCAUGCUCCUUUAUCUCCU	813	3260-3280	AGGAGATAAAGGAGCAUGGUGUG	1069	3258-3280
AD-1466024.1	AGGACCUUUUCACCCUCUAAGU	814	3281-3301	ACUUAGAGGGUGAAAGGUCCUCG	1070	3279-3301
AD-1466025.1	GUGCUUCAUAAAUCCAAUGAU	815	3350-3370	AUCATUGGAUUUAUGAAGCACCA	1071	3348-3370
AD-1466026.1	UGCUUCAUAAAUCCAAUGAAU	816	3351-3371	ATUCAUTGGAUTUAUGAAGCACC	1072	3349-3371
AD-1466027.1	CCAAUGAAACAUCUCUUCCCU	817	3363-3383	AGGGAAGAGAUGUUUCAUUGGA U	1073	3361-3383
AD-1466028.1	ACUUCCUGACCAUAAUCAGAU	818	3433-3453	AUCUGATUAUGGUCAGGAAGUGA	1074	3431-3453
AD-1466029.1	AAAUGCUUGAGUAUGACCGAU	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	AUUGTGACUUCGGUCAUACUCAA	1077	3615-3637
AD-1466032.1	UAUGACCGAAGUCACAAGUCU	822	3620-3640	AGACTUGUGACUUCGGUCAUACU	1078	3618-3640
AD-1466033.1	UGACCGAAGUCACAAGUCCUU	823	3622-3642	AAGGACTUGUGACUUCGGUCAUA	1079	3620-3642
AD-1466034.1	GACCGAAGUCACAAGUCCUUU	824	3623-3643	AAAGGACUUGUGACUUCGGUCAU	1080	3621-3643
AD-1466035.1	ACCGAAGUCACAAGUCCUUCU	825	3624-3644	AGAAGGACUUGUGACUUCGGUCA	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	AGAGAGAGGUUUGUCUGGCUGA A	1084	3740-3762
AD-1466038.2	CAGCCAGACAAACCUCUCUCU	828	3742-3762	AGAGAGAGGUUUGUCUGGCUGA A	1084	3740-3762
AD-1466039.1	UUCUACCCUUCUGAAUCUAGU	829	4535-4555	ACUAGATUCAGAAGGGUAGAAUA	1085	4533-4555
AD-1466040.1	CAUCUCCUACUCUCAAUGAUU	830	4626-4646	AAUCAUTGAGAGUAGGAGAUGAA	1086	4624-4646
AD-1466041.1	AUCAAAGGAAUUUAAUCCACU	831	4654-4674	AGUGGATUAAAUUCCUUUGAUAG	1087	4652-4674
AD-1466042.1	AAGGAAUUUAAUCCACUGGUU	832	4658-4678	AACCAGTGGAUUAAAUUCCUUUG	1088	4656-4678
AD-1466043.1	UUUAAUCCACUGGUUAUAGUU	833	4664-4684	AACUAUAACCAGUGGAUUAAAUU	1089	4662-4684
AD-1466044.1	UUAAUCCACUGGUUAUAGUGU	834	4665-4685	ACACTATAACCAGUGGAUUAAAU	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	AUGGUACAGAUUACAUUGAGU	836	4698-4718	ACUCAATGUAATCUGUACCAUCU	1092	4696-4718
AD-1466047.1	ACUGAUGUUAGGACAAACAUU	837	4799-4819	AAUGUUTGUCCTAACAUCAGUUU	1093	4797-4819
AD-1466048.1	CUGAUGUUAGGACAAACAUCU	838	4800-4820	AGAUGUUTGUCCUAACAUCAGUU	1094	4798-4820
AD-1466049.1	GAAGAAAUAUCCUGGGAUUAU	839	4904-4924	AUAATCCCAGGAUAUUUCUUCAG	1095	4902-4924
AD-1466050.1	UGAAGACUCUGAUGAUAUUCU	840	4954-4974	AGAATATCAUCAGAGUCUUCAAU	1096	4952-4974
AD-1466051.1	GUAUGAAGAGCAUCUCGGAAU	841	5053-5073	ATUCCGAGAUGCUCUUCAUACUC	1097	5051-5073
AD-1466052.1	AGAGCAUCUCGGAAUUCUUGU	842	5059-5079	ACAAGAAUUCCGAGAUGCUCUUC	1098	5057-5079
AD-1466053.1	UCGGAAUUCUUGGUCCUAUUU	113	5067-5087	AAAUAGGACCAAGAAUUCCGAGA	244	5065-5087
AD-1466054.1	CGGAAUUCUUGGUCCUAUUAU	843	5068-5088	AUAATAGGACCAAGAAUUCCGAG	1099	5066-5088
AD-1466055.1	AAUUCUUGGUCCUAUUAUCAU	844	5071-5091	ATGATAAUAGGACCAAGAAUUCC	1100	5069-5091
AD-1466056.1	UCUUGGUCCUAUUAUCAGAGU	845	5074-5094	ACUCTGAUAAUAGGACCAAGAAU	1101	5072-5094
AD-1466057.1	GUCCUAUUAUCAGAGCUGAAU	846	5079-5099	AUUCAGCUCUGAUAAUAGGACCA	1102	5077-5099
AD-1466058.1	UGAAGUGGAUGAUGUUAUCCU	847	5095-5115	AGGATAACAUCAUCCACUUCAGC	1103	5093-5115
AD-1466059.1	GAAGUGGAUGAUGUUAUCCAU	848	5096-5116	ATGGAUAACAUCAUCCACUUCAG	1104	5094-5116
AD-1466060.1	AUCAGAGGGAAAGACUUAUGU	849	5185-5205	ACAUAAGUCUUTCCCUCUGAUGA	1105	5183-5205
AD-1466061.1	AGGGAAAGACUUAUGAAGAUU	850	5190-5210	AAUCTUCAUAAGUCUUUCCCUCU	1106	5188-5210
AD-1466062.1	AGCCAAAUAGCAGUUAUACCU	851	5247-5267	AGGUAUAACUGCUAUUUGGCUGA	1107	5245-5267
AD-1466063.1	AGCAGUUAUACCUACGUAUGU	852	5255-5275	ACAUACGUAGGTAUAACUGCUAU	1108	5253-5275
AD-1466064.1	GAUAUUCACUCAGGCUUGAUU	853	5360-5380	AAUCAAGCCUGAGUGAAUAUCUU	1109	5358-5380
AD-1466065.1	GGAAUACUACACAUAAGGACAGU	854	5405-5425	ACUGTCCUUAUGUAGUAUUCCUU	1110	5403-5425
AD-1466066.1	CUACAUAAGGACAGCAACAUU	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	AUAAGACAAAUUCUCUCAUGUCC	1113	5437-5459
AD-1466069.1	CAUGAGAGAAUUUGUCUUACU	858	5440-5460	AGUAAGACAAAUUCUCUCAUGUC	1114	5438-5460
AD-1466070.1	GAGAGAAUUUGUCUUACUAUU	46	5443-5463	AAUAGUAAGACAAAUUCUCUCAU	177	5441-5463
AD-1466071.1	GACCUUUGAUGAAAAGAAGAU	859	5467-5487	AUCUTCTUUUCAUCAAAGGUCAU	1115	5465-5487
AD-1466072.1	ACCUUUGAUGAAAAGAAGAGU	860	5468-5488	ACUCTUCUUUUCAUCAAAGGUCA	1116	5466-5488
AD-1466073.1	CCUUUGAUGAAAAGAAGAGCU	861	5469-5489	AGCUCUTCUUUUCAUCAAAGGUC	1117	5467-5489
AD-1466074.1	CUUUGAUGAAAAGAAGAGCUU	862	5470-5490	AAGCTCTUCUUUUCAUCAAAGGU	1118	5468-5490
AD-1466075.1	UUUGAUGAAAAGAAGAGCUGU	863	5471-5491	ACAGCUCUUCUUUUCAUCAAAGG	1119	5469-5491
AD-1466076.1	UUGAUGAAAAGAAGAGCUGGU	864	5472-5492	ACCAGCTCUUCUUUUCAUCAAAG	1120	5470-5492
AD-1466077.1	UGAUGAAAAGAAGAGCUGGUU	865	5473-5493	AACCAGCUCUUCUUUUCAUCAAA	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	GAUGAAAAGAAGAGCUGGUAU	866	5474-5494	AUACCAGCUCUUCUUUUCAUCAA	1122	5472-5494
AD-1466079.1	AUGAAAAGAAGAGCUGGUACU	867	5475-5495	AGUACCAGCUCUUCUUUUCAUCA	1123	5473-5495
AD-1466080.1	UGAAAAGAAGAGCUGGUACUU	868	5476-5496	AAGUACCAGCUCUUCUUUUCAUC	1124	5474-5496
AD-1466081.1	GAAAAGAAGAGCUGGUACUAU	869	5477-5497	ATAGTACCAGCTCUUCUUUUCAU	1125	5475-5497
AD-1466082.1	AAAAGAAGAGCUGGUACUAUU	870	5478-5498	AAUAGUACCAGCUCUUCUUUUCA	1126	5476-5498
AD-1466083.1	AAAGAAGAGCUGGUACUAUGU	871	5479-5499	ACAUAGTACCAGCUCUUCUUUUC	1127	5477-5499
AD-1466084.1	AAGAAGAGCUGGUACUAUGAU	872	5480-5500	AUCATAGUACCAGCUCUUCUUUU	1128	5478-5500
AD-1466085.1	AGAAGAGCUGGUACUAUGAAU	873	5481-5501	ATUCAUAGUACCAGCUCUUCUUU	1129	5479-5501
AD-1466086.1	GAAGAGCUGGUACUAUGAAAU	874	5482-5502	AUUUCATAGUACCAGCUCUUCUU	1130	5480-5502
AD-1466087.1	AAGAGCUGGUACUAUGAAAAU	875	5483-5503	AUUUTCAUAGUACCAGCUCUUCU	1131	5481-5503
AD-1466088.1	AGAGCUGGUACUAUGAAAAGU	876	5484-5504	ACUUTUCAUAGUACCAGCUCUUC	1132	5482-5504
AD-1466089.1	GAGCUGGUACUAUGAAAAGAU	877	5485-5505	ATCUTUTCAUAGUACCAGCUCUU	1133	5483-5505
AD-1466090.1	AGCUGGUACUAUGAAAAGAAU	878	5486-5506	AUUCTUTUCAUAGUACCAGCUCU	1134	5484-5506
AD-1466091.1	GCUGGUACUAUGAAAAGAAGU	879	5487-5507	ACUUCUTUUCATAGUACCAGCUC	1135	5485-5507
AD-1466092.1	CUGGUACUAUGAAAAGAAGUU	880	5488-5508	AACUTCTUUUCAUAGUACCAGCU	1136	5486-5508
AD-1466093.1	CCGAAGUUCUUGGAGACUCAU	881	5509-5529	AUGAGUCUCCAAGAACUUCGGGA	1137	5507-5529
AD-1466094.1	GAAGUUCUUGGAGACUCACAU	882	5511-5531	AUGUGAGUCUCCAAGAACUUCGG	1138	5509-5531
AD-1466095.1	UUUCACGCCAUUAAUGGGAUU	883	5558-5578	AAUCCCAUUAATGGCGUGAAACU	1139	5556-5578
AD-1466096.1	AUUAAUGGGAUGAUCUACAGU	884	5567-5587	ACUGTAGAUCATCCCAUUAAUGG	1140	5565-5587
AD-1466097.1	GCUCCCAAGACAUUCACGUGU	885	5649-5669	ACACGUGAAUGTCUUGGGAGCCG	1141	5647-5669
AD-1466098.1	CCAAGACAUUCACGUGGUUCU	886	5653-5673	AGAACCACGUGAAUGUCUUGGGA	1142	5651-5673
AD-1466099.1	AUUCACGUGGUUCACUUUCAU	887	5660-5680	AUGAAAGUGAACCACGUGAAUGU	1143	5658-5680
AD-1466100.1	AUGCAAACGCCAUUUCUUAUU	888	5831-5851	AAUAAGAAAUGGCGUUUGCAUCC	1144	5829-5851
AD-1466101.1	GCAAACGCCAUUUCUUAUCAU	889	5833-5853	ATGATAAGAAATGGCGUUUGCAU	1145	5831-5853
AD-1466102.1	UCUUAUCAUGGACAGAGACUU	890	5845-5865	AAGUCUCUGUCCAUGAUAAGAAA	1146	5843-5865
AD-1466103.1	UUAUCAUGGACAGAGACUGUU	891	5847-5867	AACAGUCUCUGUCCAUGAUAAGA	1147	5845-5867
AD-1466104.1	UAAGCACUGGUAUCAUAUCUU	892	5883-5903	AAGATATGAUACCAGUGCUUAGU	1148	5881-5903
AD-1466105.1	UCAUAUCUGAUUCACAGAUCU	893	5895-5915	AGAUCUGUGAAUCAGAUAUGAU A	1149	5893-5915
AD-1466106.1	AUAUCUGAUUCACAGAUCAAU	118	5897-5917	AUUGAUCUGUGAAUCAGAUAUG A	249	5895-5917
AD-1466107.1	UAAACAAUGGUGGAUCUUAUU	894	5961-5981	AAUAAGAUCCACCAUUGUUUAAU	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	ATAUAAGAUCCACCAUUGUUUAA	1151	5960-5982
AD-1466109.1	CAAUGGUGGAUCUUAUAAUGU	896	5965-5985	ACAUTATAAGATCCACCAUUGUU	1152	5963-5985
AD-1466110.1	GGUGGAUCUUAUAAUGCUUGU	897	5969-5989	ACAAGCAUUAUAAGAUCCACCAU	1153	5967-5989
AD-1466111.1	AUCUUAUAAUGCUUGGAGUGU	898	5974-5994	ACACTCCAAGCAUUAUAAGAUCC	1154	5972-5994
AD-1466112.1	CAAGGUGCCAAACACUACCUU	899	6080-6100	AAGGTAGUGUUUGGCACCUUGGG	1155	6078-6100
AD-1466113.1	CCUGCUAUACCACAGAGUUCU	900	6105-6125	AGAACUCUGUGGUAUAGCAGGAC	1156	6103-6125
AD-1466114.1	CUGCUAUACCACAGAGUUCUU	19	6106-6126	AAGAACTCUGUGGUAUAGCAGGA	20	6104-6126
AD-1466115.1	UAUACCACAGAGUUCUAUGUU	901	6110-6130	AACATAGAACUCUGUGGUAUAGC	1157	6108-6130
AD-1466116.1	UACCACAGAGUUCUAUGUAGU	902	6112-6132	ACUACATAGAACUCUGUGGUAUA	1158	6110-6132
AD-1466117.1	CCACAGAGUUCUAUGUAGCUU	903	6114-6134	AAGCTACAUAGAACUCUGUGGUA	1159	6112-6134
AD-1466118.1	CACAGAGUUCUAUGUAGCUUU	904	6115-6135	AAAGCUACAUAGAACUCUGUGGU	1160	6113-6135
AD-1466119.1	AGAGUUCUAUGUAGCUUACAU	905	6118-6138	AUGUAAGCUACAUAGAACUCUGU	1161	6116-6138
AD-1466120.1	AGUUCUAUGUAGCUUACAGUU	906	6120-6140	AACUGUAAGCUACAUAGAACUCU	1162	6118-6140
AD-1466121.1	UCUAUGUAGCUUACAGUUCCU	907	6123-6143	AGGAACTGTAAGCUACAUAGAAC	1163	6121-6143
AD-1466122.1	CAAUUCAGAUGCCUCUACAAU	908	6205-6225	AUUGTAGAGGCAUCUGAAUUGCC	1164	6203-6225
AD-1466123.1	AAUUCAGAUGCCUCUACAAUU	909	6206-6226	AAUUGUAGAGGCAUCUGAAUUGC	1165	6204-6226
AD-1466124.1	UUCAGAUGCCUCUACAAUAAU	910	6208-6228	AUUATUGUAGAGGCAUCUGAAUU	1166	6206-6228
AD-1466125.1	AUCAGUUUGACCCACCUAUUU	911	6234-6254	AAAUAGGUGGGGUCAAACUGAUUC	1167	6232-6254
AD-1466126.1	UCAGUUUGACCCACCUAUUGU	912	6235-6255	ACAATAGGUGGGGUCAAACUGAUU	1168	6233-6255
AD-1466127.1	CAGUUUGACCCACCUAUUGUU	913	6236-6256	AACAAUAGGUGGGGUCAAACUGAU	1169	6234-6256
AD-1466128.1	CUAUUGUGGGCUAGAUAUAUUU	914	6249-6269	AAAUAUAUCUAGCCCACAAUAGGU	1170	6247-6269
AD-1466129.1	GGCUAGAUAUAUUAGGAUCUU	915	6256-6276	AAGATCCUAAUAUAUCUAGCCAC	1171	6254-6276
AD-1466130.1	GAUAUAUUAGGAUCUCUCCAU	916	6261-6281	AUGGAGAGAUCCUAAUAUAUCUA	1172	6259-6281
AD-1466131.1	AGCAAAUCACAGCUUCUUCGU	917	6384-6404	ACGAAGAAGCUGUGAUUUGCUUG	1173	6382-6404
AD-1466132.1	AGUGGCUAGAAAUUGAUCUAU	918	6507-6527	AUAGAUCAAUUUCUAGCCACUGC	1174	6505-6527
AD-1466133.1	AAAUUGAUCUACUCAAGAUCU	919	6516-6536	AGAUCUTGAGUAGAUCAAUUUCU	1175	6514-6536
AD-1466134.1	AUUGAUCUACUCAAGAUCAAU	125	6518-6538	AUUGAUCUUGAGUAGAUCAAUU U	256	6516-6538
AD-1466135.1	AAAUGUAUGUAAAGAGCUAUU	920	6585-6605	AAUAGCTCUUUACAUACAUUUCA	1176	6583-6605
AD-1466136.1	AUGUAAAGAGCUAUACCAUCU	921	6591-6611	AGAUGGTAUAGCUCUUUACAUAC	1177	6589-6611
AD-1466137.1	AAGAGCUAUACCAUCCACUAU	922	6596-6616	AUAGTGGAUGGUAUAGCUCUUUA	1178	6594-6616
AD-1466138.1	CUCCAUGGUGGACAAGAUUUU	923	6658-6678	AAAATCTUGUCCACCAUGGAGGA	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	UCCAUGGUGGACAAGAUUUUU	924	6659-6679	AAAAAUCUUGUCCACCAUGGAGG	1180	6657-6679
AD-1466140.1	CCAUGGUGGACAAGAUUUUUU	925	6660-6680	AAAAAATCUUGTCCACCAUGGAG	1181	6658-6680
AD-1466141.1	CAUGGUGGACAAGAUUUUUGU	926	6661-6681	ACAAAAAAUCUUGUCCACCAUGGA	1182	6659-6681
AD-1466142.1	AUGGUGGACAAGAUUUUUGAU	927	6662-6682	ATCAAAAAAUCUTGUCCACCAUGG	1183	6660-6682
AD-1466143.1	UGGUGGACAAGAUUUUUGAAU	928	6663-6683	ATUCAAAAAAUCTUGUCCACCAUG	1184	6661-6683
AD-1466144.1	GGUGGACAAGAUUUUUGAAGU	929	6664-6684	ACUUCAAAAAAUCUUGUCCACCAU	1185	6662-6684
AD-1466145.1	GUGGACAAGAUUUUUGAAGGU	930	6665-6685	ACCUTCAAAAAATCUUGUCCACCA	1186	6663-6685
AD-1466146.1	UGGACAAGAUUUUUGAAGGAU	931	6666-6686	AUCCTUCAAAAAAUCUUGUCCACC	1187	6664-6686
AD-1466147.1	GGACAAGAUUUUUGAAGGAAU	932	6667-6687	AUUCCUTCAAAAAAUCUUGUCCAC	1188	6665-6687
AD-1466148.1	GACAAGAUUUUUGAAGGAAAU	933	6668-6688	AUUUCCTUCAAAAAAUCUUGUCCA	1189	6666-6688
AD-1466149.1	ACAAGAUUUUUGAAGGAAAUU	934	6669-6689	AAUUTCCUUCAAAAAAUCUUGUCC	1190	6667-6689
AD-1466150.1	CAAGAUUUUUGAAGGAAAUAU	935	6670-6690	AUAUTUCCUUCAAAAAAUCUUGUC	1191	6668-6690
AD-1466151.1	AAGAUUUUUGAAGGAAAUACU	936	6671-6691	AGUATUTCCUUCAAAAAAUCUUGU	1192	6669-6691
AD-1466152.1	AGAUUUUUGAAGGAAAUACUU	937	6672-6692	AAGUAUTUCCUTCAAAAAAUCUUG	1193	6670-6692
AD-1466153.1	GAUUUUUGAAGGAAAUACUAU	938	6673-6693	ATAGTATUTUCCTUCAAAAAAUCUU	1194	6671-6693
AD-1466154.1	AUUUUUGAAGGAAAUACUAAU	939	6674-6694	AUUAGUAUUUUCCUUCAAAAAAUCU	1195	6672-6694
AD-1466155.1	UUUUUGAAGGAAAUACUAAUU	940	6675-6695	AAUUAGTAUUUUCCUUCAAAAAAUC	1196	6673-6695
AD-1466156.1	UUUUGAAGGAAAUACUAAUAU	941	6676-6696	AUAUTAGUAUUUUCCUUCAAAAAAU	1197	6674-6696
AD-1466157.1	UUUGAAGGAAAUACUAAUACU	942	6677-6697	AGUATUAGUAUTUCCUUCAAAAAA	1198	6675-6697
AD-1466158.1	UUGAAGGAAAUACUAAUACCU	943	6678-6698	AGGUAUTAGUATUUCCUUCAAAAA	1199	6676-6698
AD-1466159.1	ACUAAUACCAAAGGACAUGUU	944	6689-6709	AACATGTCCUUUGGUAUUAGUAU	1200	6687-6709
AD-1466160.1	CUAAUACCAAAGGACAUGUGU	945	6690-6710	ACACAUGUCCUTUGGUAUUAGUA	1201	6688-6710
AD-1466161.1	UAAUACCAAAGGACAUGUGAU	946	6691-6711	ATCACATGUCCTUUGGUAUUAGU	1202	6689-6711
AD-1466162.1	CAAUCAUUUCCAGGUUUAUCU	947	6729-6749	AGAUAAACCUGGGAAAUGAUUGG G	1203	6727-6749
AD-1466163.1	AUCAUUUCCAGGUUUAUCCGU	948	6731-6751	ACGGAUAAACCTGGAAAUGAUUG	1204	6729-6751
AD-1466164.1	AUGGAAUCAAAGUAUUGCACU	949	6766-6786	AGUGCAAUACUUUGAUUCCAUGU	1205	6764-6786
AD-1466165.1	GCCUGGAACUCUUUGGCUGUU	950	6789-6809	AACAGCCAAAGAGUUCCAGGCGA	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	csasgcuaagGfCfAfguucuacguuL96	1207	asdAscgdTadGaacudGcCfuuagcugsusg	1467	CACAGCUAAGGCAGUUCUACGUG	1731
AD-1465902.1	asgsggcaUfcAfGfUfuggagcuacuL96	1208	asGfsuadGc(Tgn)ccaacuGfaUfgcccusgsa	1468	UCAGGGCAUCAGUUGGAGCUACC	1732
AD-1465903.1	uscsuacaGfaGfAfGfuaugaaccauL96	1209	asUfsggdTu(C2p)auacucUfcUfguagascsa	1469	UGUCUACAGAGAGUAUGAACCAU	1733
AD-1465904.1	usascagaGfaGfUfAfugaaccauauL96	1210	asUfsaudGg(Tgn)ucauacUfcUfcuguasgsa	1470	UCUACAGAGAGUAUGAACCAUAU	1734
AD-1465905.1	ascsagagAfgUfAfUfgaaccauauuL96	1211	asAfsuadTg(G2p)uucauaCfuCfucugusasg	1471	CUACAGAGAGUAUGAACCAUAUU	1735
AD-1465906.1	ususcuugggCfCfUfacuuuauauuL96	1212	asdAsuadTadAaguadGgCfccaagaasgsu	1472	ACUUCUUGGGCCUACUUUAUAUG	1736
AD-1465907.1	usascuuuauAfUfGfcugaagucguL96	1213	asdCsgadCudTcagcdAuAfuaaaguasgsg	1473	CCUACUUUAUAUGCUGAAGUCGG	1737
AD-1465908.1	ascsuuuauaUfGfCfugaagucgguL96	1214	asdCscgdAcdTucagdCaUfauaaagusasg	1474	CUACUUUAUAUGCUGAAGUCGGA	1738
AD-1465909.1	asgsuaaauuAfUfCfagaaggugcuL96	1215	asdGscadCcdTucugdAuAfauuuacusgsu	1475	ACAGUAAAUUAUCAGAAGGUGCU	1739
AD-1465910.1	asasauuaUfcAfGfAfaggugcuucuL96	1216	asGfsaadGc(Agn)ccuucuGfaUfaauuusasc	1476	GUAAAUUAUCAGAAGGUGCUUCU	1740
AD-1465911.1	asuscagaagGfUfGfcuucuuaccuL96	1217	asdGsgudAadGaagcdAcCfuucugausasa	1477	UUAUCAGAAGGUGCUUCUUACCU	1741
AD-1465912.1	uscsagaaggUfGfCfuucuuaccuuL96	1218	asdAsggdTadAgaagdCaCfcuucugasusa	1478	UAUCAGAAGGUGCUUCUUACCUU	1742
AD-1465913.1	csasgaagguGfCfUfucuuaccuuuL96	1219	asdAsagdGudAagaadGcAfccuucugsasu	1479	AUCAGAAGGUGCUUCUUACCUUG	1743
AD-1465914.1	asusacacCfuAfUfGfaauggaguauL96	1220	asUfsacdTc(C2p)auucauAfgGfuguaususc	1480	GAAUACACCUAUGAAUGGAGUAU	1744
AD-1465915.1	ascscuaugaAfUfGfgaguaucaguL96	1221	asdCsugdAudAcuccdAuUfcauaggusgsu	1481	ACACCUAUGAAUGGAGUAUCAGU	1745
AD-1465916.1	cscsuaugaaUfGfGfaguaucaguuL96	1222	asdAscudGadTacucdCaUfucauaggsusg	1482	CACCUAUGAAUGGAGUAUCAGUG	1746
AD-	asusgaauggAfGfUfaucagugaguL96	1223	asdCsucdAcdTgauadCuCfcauucausasg	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	asusgccucaCfAfCfacaucuauuuL96	1224	asdAsaudAgdAugugdTgUfgaggcausgsg	1484	CCAUGCCUCACACACAUCUAUUA	1748
AD-1465919.1	usgsccucacAfCfAfcaucuauuauL96	1225	asdTsaadTadGaugudGuGfugaggcasusg	1485	CAUGCCUCACACACAUCUAUUAC	1749
AD-1465920.1	gscscucacaCfAfCfaucuauuacuL96	1226	asdGsuadAudAgaugdTgUfgugaggcsasu	1486	AUGCCUCACACACAUCUAUUACU	1750
AD-1465921.1	cscsucacacAfCfAfucuauuacuuL96	1227	asdAsgudAadTagaudGuGfugugaggscsa	1487	UGCCUCACACACAUCUAUUACUC	1751
AD-1465922.1	csuscacacaCfAfUfcuauuacucuL96	1228	asdGsagdTadAuagadTgUfgugugagsgsc	1488	GCCUCACACACAUCUAUUACUCC	1752
AD-1465923.1	csascacaCfaUfCfUfauuacucccuL96	1229	asGfsggdAg(Tgn)aauagaUfgUfgugugsasg	1489	CUCACACACAUCUAUUACUCCCA	1753
AD-1465924.1	ascsaucuAfuUfAfCfucccaugaauL96	1230	asUfsucdAu(G2p)ggaguaAfuAfgaugusgsu	1490	ACACAUCUAUUACUCCCAUGAAA	1754
AD-1465925.1	gsasagacGfuUfUfGfacaagcaaauL96	1231	asUfsuudGc(Tgn)ugucaaAfcGfucuucsusg	1491	CAGAAGACGUUUGACAAGCAAAU	1755
AD-1465926.1	asgsacguUfuGfAfCfaagcaaaucuL96	1232	asGfsaudTu(G2p)cuugucAfaAfcgucususc	1492	GAAGACGUUUGACAAGCAAAUCG	1756
AD-1465927.1	gsascguuugAfCfAfagcaaaucguL96	1233	asdCsgadTudTgcuudGuCfaaacgucsusu	1493	AAGACGUUUGACAAGCAAAUCGU	1757
AD-1465928.1	gscscagucaUfCfAfucccuaauguL96	1234	asdCsaudTadGggaudGaUfgacuggcsusc	1494	GAGCCAGUCAUCAUCCCUAAUGU	1758
AD-1465929.1	gsuscaucAfuCfCfCfuaauguacauL96	1235	asUfsgudAc(Agn)uuagggAfuGfaugacsusg	1495	CAGUCAUCAUCCCUAAUGUACAC	1759
AD-1465930.1	csasucauCfcCfUfAfauguacacauL96	1236	asUfsgudGu(Agn)cauuagGfgAfugaugsasc	1496	GUCAUCAUCCCUAAUGUACACAG	1760
AD-1465931.1	asuscaucCfcUfAfAfuguacacaguL96	1237	asCfsugdTg(Tgn)acauuaGfgGfaugausgsa	1497	UCAUCAUCCCUAAUGUACACAGU	1761
AD-1465932.1	asasuguacaCfAfGfucaauggauuL96	1238	asdAsucdCadTugacdTgUfguacauusasg	1498	CUAAUGUACACAGUCAAUGGAUA	1762
AD-1465933.1	asusguacAfcAfGfUfcaauggauauL96	1239	asUfsaudCc(Agn)uugacuGfuGfuacaususa	1499	UAAUGUACACAGUCAAUGGAUAU	1763
AD-	asusgugaAfuGfGfGfacaaugccauL96	1240	asUfsggdCa(Tgn)ugucccAfuUfcacausasu	1500	AUAUGUGAAUGGGACAAUGCCAG	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	gscscagauaUfAfAfcaguuuguguL96	1241	asdCsacdAadAcugudTaUfaucuggcsasu	1501	AUGCCAGAUAUAACAGUUUGUGC	1765
AD-1465936.1	cscsagauauAfAfCfaguuugugcuL96	1242	asdGscadCadAacugdTuAfuaucuggscsa	1502	UGCCAGAUAUAACAGUUUGUGCC	1766
AD-1465937.1	gsasgcagaaCfCfAfucauaagguuL96	1243	asdAsccdTudAugaudGgUfucugcucscsa	1503	UGGAGCAGAACCAUCAUAAGGUC	1767
AD-1465938.1	csasgaacCfaUfCfAfuaaggucucuL96	1244	asGfsagdAc(C2p)uuaugaUfgGfuucugscsu	1504	AGCAGAACCAUCAUAAGGUCUCA	1768
AD-1465939.1	asgsaaccAfuCfAfUfaaggucucauL96	1245	asUfsgadGa(C2p)cuuaugAfuGfguucusgsc	1505	GCAGAACCAUCAUAAGGUCUCAG	1769
AD-1465940.1	asuscaccCfuUfGfUfcagugcuacuL96	1246	asGfsuadGc(Agn)cugacaAfgGfgugausgsg	1506	CCAUCACCCUUGUCAGUGCUACA	1770
AD-1465941.1	ususgucaGfuGfCfUfacauccacuuL96	1247	asAfsgudGg(Agn)uguagcAfcUfgacaasgsg	1507	CCUUGUCAGUGCUACAUCCACUA	1771
AD-1465942.1	csasuccacuAfCfCfgcaaauauguL96	1248	asdCsaudAudTugcgdGuAfguggaugsusa	1508	UACAUCCACUACCGCAAAUAUGA	1772
AD-1465943.1	asasgcugGfgAfUfGfcaggcuuacuL96	1249	asGfsuadAg(C2p)cugcauCfcCfagcuusgsc	1509	GCAAGCUGGGAUGCAGGCUUACA	1773
AD-1465944.1	asgscuggGfaUfGfCfaggcuuacauL96	1250	asUfsgudAa(G2p)ccugcaUfcCfcagcususg	1510	CAAGCUGGGAUGCAGGCUUACAU	1774
AD-1465945.1	gscsugggauGfCfAfggcuuacauuL96	1251	asdAsugdTadAgccudGcAfucccagcsusu	1511	AAGCUGGGAUGCAGGCUUACAUU	1775
AD-1465946.1	csusgggaugCfAfGfgcuuacauuuL96	1252	asdAsaudGudAagccdTgCfaucccagscsu	1512	AGCUGGGAUGCAGGCUUACAUUG	1776
AD-1465947.1	usgsggaugcAfGfGfcuuacauuguL96	1253	asdCsaadTgdTaagcdCuGfcaucccasgsc	1513	GCUGGGAUGCAGGCUUACAUUGA	1777
AD-1465948.1	gsgsgaugCfaGfGfCfuuacauugauL96	1254	asUfscadAu(G2p)uaagccUfgCfaucccsasg	1514	CUGGGAUGCAGGCUUACAUUGAC	1778
AD-1465949.1	gsgsaugcagGfCfUfuacauugacuL96	1255	asdGsucdAadTguaadGcCfugcauccscsa	1515	UGGGAUGCAGGCUUACAUUGACA	1779
AD-1465950.1	gsasugcaGfgCfUfUfacauugacauL96	1256	asUfsgudCa(Agn)uguaagCfcUfgcaucscsc	1516	GGGAUGCAGGCUUACAUUGACAU	1780
AD-	asusgcaggcUfUfAfcauugacauuL96	1257	asdAsugdTcdAaugudAaGfccugcauscsc	1517	GGAUGCAGGCUUACAUUGACAUU	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	usgscaggCfuUfAfCfauugacauuuL96	1258	asAfsaudGu(C2p)aauguaAfgCfcugcasusc	1518	GAUGCAGGCUUACAUUGACAUUA	1782
AD-1465953.1	gscsaggcUfuAfCfAfuugacauuauL96	1259	asUfsaadTg(Tgn)caauguAfaGfccugcsasu	1519	AUGCAGGCUUACAUUGACAUUAA	1783
AD-1465954.1	csasggcuUfaCfAfUfugacauuaauL96	335	asUfsuadAu(G2p)ucaaugUfaAfgccugscsa	1520	UGCAGGCUUACAUUGACAUUAAA	603
AD-1465955.1	asgsgcuuacAfUfUfgacauuaaauL96	1260	asdTsuudAadTgucadAuGfuaagccusgsc	1521	GCAGGCUUACAUUGACAUUAAAA	1784
AD-1465956.1	gsgscuuacaUfUfUfGfacauuaaaauL96	1261	asdTsuudTadAugucdAaUfguaagccsusg	1522	CAGGCUUACAUUGACAUUAAAAA	1785
AD-1465957.1	gscsuuacauUfGfAfcauuaaaaauL96	1262	asdTsuudTudAaugudCaAfuguaagcscsu	1523	AGGCUUACAUUGACAUUAAAAAC	1786
AD-1465958.1	csusuacauuGfAfCfauuaaaaacuL96	1263	asdGsuudTudTaaugdTcAfauguaagscsc	1524	GGCUUACAUUGACAUUAAAAACU	1787
AD-1465959.1	ususacauugAfCfAfuuaaaaacuuL96	1264	asdAsgudTudTuaaudGuCfaauguaasgsc	1525	GCUUACAUUGACAUUAAAAACUG	1788
AD-1465960.1	usascauugaCfAfUfuaaaaacuguL96	1265	asdCsagdTudTuuaadTgUfcaauguasasg	1526	CUUACAUUGACAUUAAAAACUGC	1789
AD-1465961.1	ascsauugacAfUfUfaaaaacugcuL96	1266	asdGscadGudTuuuadAuGfucaaugusasa	1527	UUACAUUGACAUUAAAAACUGCC	1790
AD-1465962.1	csasuugaCfaUfUfAfaaaacugccuL96	1267	asGfsgcdAg(Tgn)uuuuaaUfgUfcaaugsusa	1528	UACAUUGACAUUAAAAACUGCCC	1791
AD-1465963.1	asusugacAfuUfAfAfaaacugcccuL96	1268	asGfsggdCa(G2p)uuuuuaAfuGfucaaugsgsu	1529	ACAUUGACAUUAAAAACUGCCCA	1792
AD-1465964.1	ususgacaUfuAfAfAfaacugcccauL96	1269	asUfsggdGc(Agn)guuuuuAfaUfgucaasusg	1530	CAUUGACAUUAAAAACUGCCCAA	1793
AD-1465965.1	gsgsgaauAfcUfUfCfauugcugcauL96	1270	asUfsgcdAg(C2p)aaugaaGfuAfuucccsasc	1531	GUGGGAAUACUUCAUUGCUGCAG	1794
AD-1465966.1	asgsucauUfuGfGfGfacuaugcacuL96	1271	asGfsugdCa(Tgn)agucccAfaAfugacususc	1532	GAAGUCAUUUGGGACUAUGCACC	1795
AD-1465967.1	gsgsgacuAfuGfCfAfccuguaauauL96	1272	asUfsaudTa(C2p)aggugcAfuAfgucccsasa	1533	UUGGGACUAUGCACCUGUAAUAC	1796
AD-1465968.1	csasccuguaAfUfAfccagcgaauuL96	1273	asdAsuudCgdCuggudAuUfacaggugscsa	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	usgsuaauacCfAfGfcgaauaugguL96	1274	asdCscadTadTucgcdTgGfuauuacasgsg	1535	CCUGUAAUACCAGCGAAUAUGGA	1798
AD-1465970.1	gsusaauaccAfGfCfgaauauggauL96	1275	asdTsccdAudAuucgdCuGfguauuacsasg	1536	CUGUAAUACCAGCGAAUAUGGAC	1799
AD-1465971.1	asgsgucuCfaGfCfAfuuuggauaauL96	1276	asUfsuadTc(C2p)aaaugcUfgAfgaccusgsu	1537	ACAGGUCUCAGCAUUUGGAUAAU	1800
AD-1465972.1	gsusuauguaCfAfCfacaguacgauL96	1277	asdTscgdTadCugugdTgUfacauaacsusu	1538	AAGUUAUGUACACACAGUACGAA	1801
AD-1465973.1	ususauguacAfCfAfcaguacgaauL96	1278	asdTsucdGudAcugudGuGfuacauaascsu	1539	AGUUAUGUACACACAGUACGAAG	1802
AD-1465974.1	asusguacAfcAfCfAfguacgaagauL96	1279	asUfscudTc(G2p)uacuguGfuGfuacausasa	1540	UUAUGUACACACAGUACGAAGAU	1803
AD-1465975.1	usgsuacaCfaCfAfGfuacgaagauuL96	1280	asAfsucdTu(C2p)guacugUfgUfguacasusa	1541	UAUGUACACACAGUACGAAGAUG	1804
AD-1465976.1	gsusacacacAfGfUfacgaagauguL96	1281	asdCsaudCudTcguadCuGfuguguacsasu	1542	AUGUACACACAGUACGAAGAUGA	1805
AD-1465977.1	asgsuacgAfaGfAfUfgaguccuucuL96	1282	asGfsaadGg(Agn)cucaucUfuCfguacusgsu	1543	ACAGUACGAAGAUGAGUCCUUCA	1806
AD-1465978.1	gsusacgaAfgAfUfGfaguccuucauL96	1283	asUfsgadAg(G2p)acucauCfuUfcguacsusg	1544	CAGUACGAAGAUGAGUCCUUCAC	1807
AD-1465979.1	gsusgaauCfcCfAfAfuaugaaagauL96	1284	asUfscudTu(C2p)auauugGfgAfuucacsusg	1545	CAGUGAAUCCCAAUAUGAAAGAA	1808
AD-1465980.1	ascsccucAfuGfGfAfgugaccuucuL96	1285	asGfsaadGg(Tgn)cacuccAfuGfagggusasa	1546	UUACCCUCAUGGAGUGACCUUCU	1809
AD-1465981.1	gsasacaaCfaCfCfAfugaucagaguL96	1286	asCfsucdTg(Agn)ucauggUfgUfuguucscsu	1547	AGGAACAACACCAUGAUCAGAGC	1810
AD-1465982.1	csasacacCfaUfGfAfucagagcaguL96	1287	asCfsugdCu(C2p)ugaucaUfgGfuguugsusu	1548	AACAACACCAUGAUCAGAGCAGU	1811
AD-1465983.1	csasccauGfaUfCfAfgagcaguucuL96	1288	asGfsaadCu(G2p)cucugaUfcAfuggugsusu	1549	AACACCAUGAUCAGAGCAGUUCA	1812
AD-1465984.1	csasugauCfaGfAfGfcaguucaacuL96	1289	asGfsuudGa(Agn)cugcucUfgAfucaugsgsu	1550	ACCAUGAUCAGAGCAGUUCAACC	1813
AD-	usgsaucaGfaGfCfAfguucaaccauL96	1290	asUfsggdTu(G2p)aacugcUfcUfgaucasusg	1551	CAUGAUCAGAGCAGUUCAACCAG	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	asasaccuauAfCfUfuauaaguggguL96	1291	asdCscadCudTauaadGuAfuaggguuuscsc	1552	GGAAACCUAUACUUAUAAGUGGA	1815
AD-1465987.1	asasccuaUfaCfUfUfauaaguggauL96	1292	asUfsccdAc(Tgn)uauaagUfaUfagguususc	1553	GAAACCUAUACUUAUAAGUGGAA	1816
AD-1465988.1	csusuauaAfgUfGfGfaacaucuuauL96	1293	asUfsaadGa(Tgn)guuccaCfuUfauaagsusa	1554	UACUUAUAAGUGGAACAUCUUAG	1817
AD-1465989.1	uscsuaauCfuGfUfAfagagcagauuL96	1294	asAfsucdTg(C2p)ucuuacAfgAfuuagasasg	1555	CUUCUAAUCUGUAAGAGCAGAUC	1818
AD-1465990.1	asasucugUfaAfGfAfgcagaucccuL96	1295	asGfsggdAu(C2p)ugcucuUfaCfagauusasg	1556	CUAAUCUGUAAGAGCAGAUCCCU	1819
AD-1465991.1	ascscuugAfgGfAfCfaacaucaacuL96	1296	asGfsuudGa(Tgn)guugucCfuCfaaggusasc	1557	GUACCUUGAGGACAACAUCAACA	1820
AD-1465992.1	asusgaaucaAfAfCfaucaugagcuL96	1297	asdGscudCadTgaugdTuUfgauucausasa	1558	UUAUGAAUCAAACAUCAUGAGCA	1821
AD-1465993.1	gsasaucaAfaCfAfUfcaugagcacuL96	1298	asGfsugdCu(C2p)augaugUfuUfgauucsasu	1559	AUGAAUCAAACAUCAUGAGCACU	1822
AD-1465994.1	usgsagcaCfuAfUfCfaauggcuauuL96	1299	asAfsuadGc(C2p)auugauAfgUfgcucasusg	1560	CAUGAGCACUAUCAAUGGCUAUG	1823
AD-1465996.1	gsasuucuGfcUfUfUfgaugacacuuL96	1300	asAfsgudGu(C2p)aucaaaGfcAfgaaucscsa	1561	UGGAUUCUGCUUUGAUGACACUG	1824
AD-1465997.1	cscsaguggcAfCfUfucuguaguguL96	1301	asdCsacdTadCagaadGuGfccacuggsasc	1562	GUCCAGUGGCACUUCUGUAGUGU	1825
AD-1465998.1	asgsuggcacUfUfCfuguaguguguL96	1302	asdCsacdAcdTacagdAaGfugccacusgsg	1563	CCAGUGGCACUUCUGUAGUGUGG	1826
AD-1465999.1	csusgggcacUfCfAfuucaucuauuL96	1303	asdAsuadGadTgaaudGaGfugcccagsusg	1564	CACUGGGCACUCAUUCAUCUAUG	1827
AD-1466000.1	gsusgacgGfuCfAfCfaauggauaauL96	1304	asUfsuadTc(C2p)auugugAfcCfgucacsasg	1565	CUGUGACGGUCACAAUGGAUAAU	1828
AD-1466001.1	gsgsaacuUfgGfAfUfguuaacuucuL96	1305	asGfsaadGu(Tgn)aacaucCfaAfguuccsasa	1566	UUGGAACUUGGAUGUUAACUUCC	1829
AD-1466002.1	ususaacuucCfAfUfgaauucuaguL96	1306	asdCsuadGadAuucadTgGfaaguuaascsa	1567	UGUUAACUUCCAUGAAUUCUAGU	1830
AD-	asusgaugAfuGfAfAfgacucauauuL96	1307	asAfsuadTg(Agn)gucuucAfuCfaucauscsu	1568	AGAUGAUGAUGAAGACUCAUAU	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	usgsaugaagAfCfUfcauaugagauL96	1308	asdTscudCadTaugadGuCfuucaucasusc	1569	GAUGAUGAAGACUCAUAUGAGAU	1832
AD-1466005.1	asasacucauCfAfUfugaaucagguL96	1309	asdCscudGadTucaadTgAfugaguuuscsg	1570	CGAAACUCAUCAUUGAAUCAGGA	1833
AD-1466006.1	asasacacagAfUfAfuaauuguuguL96	1310	asdCsaadCadAuuaudAuCfuguguuusgsa	1571	UCAAACACAGAUAUAAUUGUUGG	1834
AD-1466007.1	csascagauaUfAfAfuuguugguuuL96	1311	asdAsacdCadAcaaudTaUfaucugugsusu	1572	AACACAGAUAUAAUUGUUGGUUC	1835
AD-1466008.1	csasuauuCfuGfAfAfgacccuauauL96	1312	asUfsaudAg(G2p)gucuucAfgAfauaugsgsg	1573	CCCAUAUUCUGAAGACCCUAUAG	1836
AD-1466009.1	asusucugaaGfAfCfccuauagaguL96	1313	asdCsucdTadTagggdTcUfucagaausasu	1574	AUAUUCUGAAGACCCUAUAGAGG	1837
AD-1466010.1	csgsucuacuUfUfCfacuuggugcuL96	1314	asdGscadCcdAagugdAaAfguagacgsusa	1575	UACGUCUACUUUCACUUGGUGCU	1838
AD-1466011.1	asusgaaaUfuAfCfUfagcacauaauL96	1315	asUfsuadTg(Tgn)gcuaguAfaUfuucauscsc	1576	GGAUGAAAUUACUAGCACAUAAA	1839
AD-1466012.1	asasuuacuaGfCfAfcauaaaguuuL96	1316	asdAsacdTudTaugudGcUfaguaauususc	1577	GAAAUUACUAGCACAUAAAGUUG	1840
AD-1466013.1	usascuagcaCfAfUfaaaguuggguL96	1317	asdCsccdAadCuuuadTgUfgcuaguasasu	1578	AUUACUAGCACAUAAAGUUGGGA	1841
AD-1466014.1	gsasgauggcAfUfUfuggcuucuguL96	1318	asdCsagdAadGccaadAuGfccaucucscsc	1579	GGGAGAUGGCAUUUGGCUUCUGA	1842
AD-1466015.1	gsusagcuAfuGfAfAfauaauccaauL96	1319	asUfsugdGa(Tgn)uauuucAfuAfgcuacscsu	1580	AGGUAGCUAUGAAAUAAUCCAAG	1843
AD-1466016.1	csasagauAfcUfGfAfugaagacacuL96	1320	asGfsugdTc(Tgn)ucaucaGfuAfucuugsgsa	1581	UCCAAGAUACUGAUGAAGACACA	1844
AD-1466017.1	gsasuacuGfaUfGfAfagacacagcuL96	1321	asGfscudGu(G2p)ucuucaUfcAfguaucsusu	1582	AAGAUACUGAUGAAGACACAGCU	1845
AD-1466018.1	asasgacaCfaGfCfUfguuaacaauuL96	1322	asAfsuudGu(Tgn)aacagcUfgUfgucuuscsa	1583	UGAAGACACAGCUGUUAACAAUU	1846
AD-1466019.1	asasguuuccUfAfGfaguuagacauL96	1323	asdTsgudCudAacucdTaGfgaaacuususg	1584	CAAAGUUUCCUAGAGUUAGACAU	1847
AD-	cscsuagaguUfAfGfacauaaaucuL96	1324	asdGsaudTudAugucdTaAfcucuaggsasa	1585	UUCCUAGAGUUAGACAUAAAUCU	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	usascaaguaAfGfAfcaggauggauL96	1325	asdTsccdAudCcugudCuUfacuuguasgsa	1586	UCUACAAGUAAGACAGGAUGGAG	1849
AD-1466022.1	gsusuucuCfaUfUfAfagacacgaauL96	1326	asUfsucdGu(G2p)ucuuaaUfgAfgaaacsusg	1587	CAGUUUCUCAUUAAGACACGAAA	1850
AD-1466023.1	csasccauGfcUfCfCfuuuaucuccuL96	1327	asGfsgadGa(Tgn)aaaggaGfcAfuggugsusg	1588	CACACCAUGCUCCUUUAUCUCCG	1851
AD-1466024.1	asgsgaccuuUfCfAfcccucuaaguL96	1328	asdCsuudAgdAgggudGaAfagguccuscsg	1589	CGAGGACCUUUCACCCUCUAAGA	1852
AD-1466025.1	gsusgcuuCfaUfAfAfauccaaugauL96	1329	asUfscadTu(G2p)gauuuaUfgAfagcacscsa	1590	UGGUGCUUCAUAAAUCCAAUGAA	1853
AD-1466026.1	usgscuucauAfAfAfuccaaugaauL96	1330	asdTsucdAudTggaudTuAfugaagcascsc	1591	GGUGCUUCAUAAAUCCAAUGAAA	1854
AD-1466027.1	cscsaaugaaAfCfAfucucuucccuL96	1331	asdGsggdAadGagaudGuUfucauuggsasu	1592	AUCCAAUGAAACAUCUCUUCCCA	1855
AD-1466028.1	ascsuuccUfgAfCfCfauaaucagauL96	1332	asUfscudGa(Tgn)uaugguCfaGfgaagusgsa	1593	UCACUUCCUGACCAUAAUCAGAA	1856
AD-1466029.1	asasaugcUfuGfAfGfuaugaccgauL96	1333	asUfscgdGu(C2p)auacucAfaGfcauuuscsa	1594	UGAAAUGCUUGAGUAUGACCGAA	1857
AD-1466030.1	gscsuugaGfuAfUfGfaccgaagucuL96	1334	asGfsacdTu(C2p)ggucauAfcUfcaagcsasu	1595	AUGCUUGAGUAUGACCGAAGUCA	1858
AD-1466031.1	gsasguauGfaCfCfGfaagucacaauL96	1335	asUfsugdTg(Agn)cuucggUfcAfuacucsasa	1596	UUGAGUAUGACCGAAGUCACAAG	1859
AD-1466032.1	usasugacCfgAfAfGfucacaagucuL96	1336	asGfsacdTu(G2p)ugacuuCfgGfucauascsu	1597	AGUAUGACCGAAGUCACAAGUCC	1860
AD-1466033.1	usgsaccgAfaGfUfCfacaaguccuuL96	1337	asAfsggdAc(Tgn)ugugacUfuCfggucasusa	1598	UAUGACCGAAGUCACAAGUCCUU	1861
AD-1466034.1	gsasccgaagUfCfAfcaaguccuuuL96	1338	asdAsagdGadCuugudGaCfuucggucsasu	1599	AUGACCGAAGUCACAAGUCCUUC	1862
AD-1466035.1	ascscgaaGfuCfAfCfaaguccuucuL96	1339	asGfsaadGg(Agn)cuugugAfcUfucggucsca	1600	UGACCGAAGUCACAAGUCCUUCC	1863
AD-1466036.1	uscsuccaGfaAfCfUfcagucagacuL96	1340	asGfsucdTg(Agn)cugaguUfcUfggagasgsa	1601	UCUCUCCAGAACUCAGUCAGACA	1864
AD-	uscsuccaGfaAfCfUfcagucagacuL96	1340	asGfsucdTg(Agn)cugaguUfcUfggagasgsa	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	uscsuccaGfaAfCfUfcagucagacuL96	1340	asGfsucdTg(Agn)cugaguUfcUfggagasgsa	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	csasgccaGfaCfAfAfaccucucuL96	1342	asGfsagdAg(Agn)gguuugUfcUfggcugsas a	1603	CUCAGCCAGACAAACCUCUCUCC	1866
AD-1466038.2	csasgccaGfaCfAfAfaccucucuL96	1342	asGfsagdAg(Agn)gguuugUfcUfggcugsas a	1603	CUCAGCCAGACAAACCUCUCUCC	1866
AD-1466039.1	ususcuacccUfUfCfugaaucuaguL96	1343	asdCsuadGadTucagdAaGfgguagaasusa	1604	UAUUCUACCCUUCUGAAUCUAGU	1867
AD-1466040.1	csasucuccuAfCfUfcucaaugauuL96	1344	asdAsucdAudTgagadGuAfggagaugsasa	1605	UUCAUCUCCUACUCUCAAUGAUA	1868
AD-1466041.1	asuscaaaGfgAfAfUfuuaauccacuL96	1345	asGfsugdGa(Tgn)uaaauuCfcUfuugausasg	1606	CUAUCAAAGGAAUUUAAUCCACU	1869
AD-1466042.1	asasggaaUfuUfAfAfuccacugguuL96	1346	asAfsccdAg(Tgn)ggauuaAfaUfuccuususg	1607	CAAAGGAAUUUAAUCCACUGGUU	1870
AD-1466043.1	ususuaauccAfCfUfgguuauaguuL96	1347	asdAscudAudAaccadGuGfgauuaaasusu	1608	AAUUUAAUCCACUGGUUAUAGUG	1871
AD-1466044.1	ususaauccaCfUfGfguuauaguguL96	1348	asdCsacdTadTaaccdAgUfggauuaasasu	1609	AUUUAAUCCACUGGUUAUAGUGG	1872
AD-1466045.1	asgsauggUfaCfAfGfauuacauuguL96	1349	asCfsaadTg(Tgn)aaucugUfaCfcaucususu	1610	AAAGAUGGUACAGAUUACAUUG A	1873
AD-1466046.1	asusgguacaGfAfUfuacauugaguL96	1350	asdCsucdAadTguaadTcUfguaccausesu	1611	AGAUGGUACAGAUUACAUUGAG A	1874
AD-1466047.1	ascsugauguUfAfGfgacaaacauuL96	1351	asdAsugdTudTgucdTaAfcaucagususu	1612	AAACUGAUGUUAGGACAAACAUC	1875
AD-1466048.1	csusgaugUfuAfGfGfacaaacaucuL96	1352	asGfsaudGu(Tgn)uguccuAfaCfaucagsusu	1613	AACUGAUGUUAGGACAAACAUCA	1876
AD-	gsasagaaAfuAfUfCfcuggguauuL96	1353	asUfsaadTc(C2p)caggauAfuUfucuucsasg	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	usgsaagacuCfUfGfaugauauucuL96	1354	asdGsaadTadTcaucdAgAfgucuucasasu	1615	AUUGAAGACUCUGAUGAUAUUCC	1878
AD-1466051.1	gsusaugaagAfGfCfaucucggaauL96	1355	asdTsucdCgdAgaugdCuCfuucauacsusc	1616	GAGUAUGAAGAGCAUCUCGGAAU	1879
AD-1466052.1	asgsagcaucUfCfGfgaauucuuguL96	1356	asdCsaadGadAuuccdGaGfaugcucususc	1617	GAAGAGCAUCUCGGAAUUCUUGG	1880
AD-1466053.1	uscsggaaUfuCfUfUfgguccuauuuL96	377	asAfsaudAg(G2p)accaagAfaUfuccgasgsa	1618	UCUCGGAAUUCUUGGUCCUAUUA	645
AD-1466054.1	csgsgaauUfcUfUfGfguccuauuauL96	1357	asUfsaadTa(G2p)gaccaaGfaAfuuccgsasg	1619	CUCGGAAUUCUUGGUCCUAUUAU	1881
AD-1466055.1	asasuucuugGfUfCfcuauuaucauL96	1358	asdTsgadTadAuaggdAcCfaagaauuscsc	1620	GGAAUUCUUGGUCCUAUUAUCAG	1882
AD-1466056.1	uscsuuggUfcCfUfAfuuaucagaguL96	1359	asCfsucdTg(Agn)uaauagGfaCfcaagasasu	1621	AUUCUUGGUCCUAUUAUCAGAGC	1883
AD-1466057.1	gsusccuaUfuAfUfCfagagcugaauL96	1360	asUfsucdAg(C2p)ucugauAfaUfaggacscsa	1622	UGGUCCUAUUAUCAGAGCUGAAG	1884
AD-1466058.1	usgsaaguggAfUfGfauguuauccuL96	1361	asdGsgadTadAcaucdAuCfcacuucasgsc	1623	GCUGAAGUGGAUGAUGUUAUCCA	1885
AD-1466059.1	gsasaguggaUfGfAfuguuauccauL96	1362	asdTsggdAudAacaudCaUfccacuucsasg	1624	CUGAAGUGGAUGAUGUUAUCCAA	1886
AD-1466060.1	asuscagaggGfAfAfagacuuauguL96	1363	asdCsaudAadGucuudTcCfcucugausgsa	1625	UCAUCAGAGGGAAAGACUUAUGA	1887
AD-1466061.1	asgsggaaAfgAfCfUfuaugaagauuL96	1364	asAfsucdTu(C2p)auaaguCfuUfucccuscsu	1626	AGAGGGAAAGACUUAUGAAGAUG	1888
AD-1466062.1	asgsccaaauAfGfCfaguuauaccuL96	1365	asdGsgudAudAacugdCuAfuuuggcusgsa	1627	UCAGCCAAAUAGCAGUUAUACCU	1889
AD-1466063.1	asgscaguuaUfAfCfcuacguauguL96	1366	asdCsaudAcdGuaggdTaUfaacugcusasu	1628	AUAGCAGUUAUACCUACGUAUGG	1890
AD-1466064.1	gsasuauuCfaCfUfCfaggcuugauuL96	1367	asAfsucdAa(G2p)ccugagUfgAfauaucsusu	1629	AAGAUAUUCACUCAGGCUUGAUA	1891
AD-1466065.1	gsgsaauaCfuAfCfAfuaaggacaguL96	1368	asCfsugdTc(C2p)uuauguAfgUfauuccsusu	1630	AAGGAAUACUACAUAAGGACAGC	1892
AD-	csusacauAfaGfGfAfcagcaacauuL96	1369	asAfsugdTu(G2p)cuguccUfuAfuguagsusa	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	ascsauaaGfgAfCfAfgcaacaugcuL96	1370	asGfscadTg(Tgn)ugcuguCfcUfuaugusasg	1632	CUACAUAAGGACAGCAACAUGCC	1894
AD-1466068.1	ascsaugaGfaGfAfAfuuugucuuauL96	1371	asUfsaadGa(C2p)aaauucUfcUfcauguscsc	1633	GGACAUGAGAGAAUUUGUCUUAC	1895
AD-1466069.1	csasugagAfgAfAfUfuugucuuacuL96	1372	asGfsuadAg(Agn)caaauuCfuCfucaugsusc	1634	GACAUGAGAGAAUUUGUCUUACU	1896
AD-1466070.1	gsasgagaauUfUfGfucuuacuauuL96	1373	asdAsuadGudAagacdAaAfuucucucsasu	1635	AUGAGAGAAUUUGUCUUACUAU U	576
AD-1466071.1	gsasccuuUfgAfUfGfaaaagaagauL96	1374	asUfscudTc(Tgn)uuucauCfaAfaggucsasu	1636	AUGACCUUUGAUGAAAAGAAGA G	1897
AD-1466072.1	ascscuuuGfaUfGfAfaaagaagaguL96	1375	asCfsucdTu(C2p)uuuucaUfcAfaaggucsa	1637	UGACCUUUGAUGAAAAGAAGAGC	1898
AD-1466073.1	cscsuuugAfuGfAfAfaagaagagcuL96	1376	asGfscudCu(Tgn)cuuuucAfuCfaaaggsusc	1638	GACCUUUGAUGAAAAGAAGAGCU	1899
AD-1466074.1	csusuugaUfgAfAfAfagaagagcuuL96	1377	asAfsgcdTc(Tgn)ucuuuuCfaUfcaaagsgsu	1639	ACCUUUGAUGAAAAGAAGAGCUG	1900
AD-1466075.1	ususugauGfaAfAfAfgaagagcuguL96	1378	asCfsagdCu(C2p)uucuuuUfcAfucaaasgsg	1640	CCUUUGAUGAAAAGAAGAGCUGG	1901
AD-1466076.1	ususgaugAfaAfAfGfaagagcugguL96	1379	asCfscadGc(Tgn)cuucuuUfuCfaucaasasg	1641	CUUUGAUGAAAAGAAGAGCUGG U	1902
AD-1466077.1	usgsaugaAfaAfGfAfagagcugguuL96	1380	asAfsccdAg(C2p)ucuucuUfuUfcaucasasa	1642	UUUGAUGAAAAGAAGAGCUGGU A	1903
AD-1466078.1	gsasugaaAfaGfAfAfgagcugguauL96	1381	asUfsacdCa(G2p)cucuucUfuUfucaucsasa	1643	UUGAUGAAAAGAAGAGCUGGUA C	1904
AD-1466079.1	asusgaaaAfgAfAfGfagcugguacuL96	1382	asGfsuadCc(Agn)gcucuuCfuUfuucauscsa	1644	UGAUGAAAAGAAGAGCUGGUAC U	1905
AD-1466080.1	usgsaaaaGfaAfGfAfgcugguacuuL96	1383	asAfsgudAc(C2p)agcucuUfcUfuuucasusc	1645	GAUGAAAAGAAGAGCUGGUACU A	1906
AD-1466081.1	gsasaaagaaGfAfGfcugguacuauL96	1384	asdTsagdTadCcagcdTcUfucuuuucsasu	1646	AUGAAAAGAAGAGCUGGUACUA U	1907
AD-1466082.1	asasaagaAfgAfGfCfugguacuauuL96	1385	asAfsuadGu(Agn)ccagcuCfuUfcuuuuscsa	1647	UGAAAAGAAGAGCUGGUACUAU G	1908
AD-	asasagaagaGfCfUfgguacuauguL96	1386	asdCsaudAgdTaccadGcUfcuucuuususc	1648	GAAAAGAAGAGCUGGUACUAUG	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	asasgaagAfgCfUfGfguacuaugauL96	1387	asUfscadTa(G2p)uaccagCfuCfuucuususu	1649	AAAAGAAGAGCUGGUACUAUGAA	1910
AD-1466085.1	asgsaagagcUfGfGfuacuaugaauL96	1388	asdTsucdAudAguacdCaGfcucuucususu	1650	AAAGAAGAGCUGGUACUAUGAAA	1911
AD-1466086.1	gsasagagCfuGfGfUfacuaugaaauL96	1389	asUfsuudCa(Tgn)aguaccAfgCfucuucsusu	1651	AAGAAGAGCUGGUACUAUGAAAA	1912
AD-1466087.1	asasgagcUfgGfUfAfcuaugaaaauL96	1390	asUfsuudTc(Agn)uaguacCfaGfcucuuscsu	1652	AGAAGAGCUGGUACUAUGAAAAG	1913
AD-1466088.1	asgsagcuGfgUfAfCfuaugaaaaguL96	1391	asCfsuudTu(C2p)auaguaCfcAfgcucususc	1653	GAAGAGCUGGUACUAUGAAAAGA	1914
AD-1466089.1	gsasgcugguAfCfUfaugaaaagauL96	1392	asdTscudTudTcauadGuAfccagcucsusu	1654	AAGAGCUGGUACUAUGAAAAGAA	1915
AD-1466090.1	asgscuggUfaCfUfAfugaaaagaauL96	1393	asUfsucdTu(Tgn)ucauagUfaCfcagcuscsu	1655	AGAGCUGGUACUAUGAAAAGAAG	1916
AD-1466091.1	gscsugguacUfAfUfgaaaagaaguL96	1394	asdCsuudCudTuucadTaGfuaccagcsusc	1656	GAGCUGGUACUAUGAAAAGAAGU	1917
AD-1466092.1	csusgguaCfuAfUfGfaaaagaaguuL96	1395	asAfscudTc(Tgn)uuucauAfgUfaccagscsu	1657	AGCUGGUACUAUGAAAAGAAGUC	1918
AD-1466093.1	cscsgaagUfuCfUfUfggagacucauL96	1396	asUfsgadGu(C2p)uccaagAfaCfuucggsgsa	1658	UCCCGAAGUUCUUGGAGACUCAC	1919
AD-1466094.1	gsasaguuCfuUfGfGfagacucacauL96	1397	asUfsgudGa(G2p)ucuccaAfgAfacuucsgsg	1659	CCGAAGUUCUUGGAGACUCACAU	1920
AD-1466095.1	ususucacgcCfAfUfuaaugggauuL96	1398	asdAsucdCcdAuuaadTgGfcgugaaascsu	1660	AGUUUCACGCCAUUAAUGGGAUG	1921
AD-1466096.1	asusuaauggGfAfUfgaucuacaguL96	1399	asdCsugdTadGaucadTcCfcauuaausgsg	1661	CCAUUAAUGGGAUGAUCUACAGC	1922
AD-1466097.1	gscsucccaaGfAfCfauucacguguL96	1400	asdCsacdGudGaaugdTcUfugggagcscsg	1662	CGGCUCCCAAGACAUUCACGUGG	1923
AD-1466098.1	cscsaagaCfaUfUfCfacgugguucuL96	1401	asGfsaadCc(Agn)cgugaaUfgUfcuuggsgsa	1663	UCCCAAGACAUUCACGUGGUUCA	1924
AD-1466099.1	asusucacGfuGfGfUfucacuuucauL96	1402	asUfsgadAa(G2p)ugaaccAfcGfugaausgsu	1664	ACAUUCACGUGGUUCACUUUCAC	1925
AD-	asusgcaaacGfCfCfauuucuuauuL96	1403	asdAsuadAgdAaaugdGcGfuuugcauscsc	1665	GGAUGCAAACGCCAUUUCUUAUC	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	gscsaaacgcCfAfUfuucuuaucauL96	1404	asdTsgadTadAgaaadTgGfcguuugcsasu	1666	AUGCAAACGCCAUUUCUUAUCAU	1927
AD-1466102.1	uscsuuauCfaUfGfGfacagagacuuL96	1405	asAfsgudCu(C2p)uguccaUfgAfuaagasasa	1667	UUUCUUAUCAUGGACAGAGACUG	1928
AD-1466103.1	ususaucaUfgGfAfCfagagacuguuL96	1406	asAfscadGu(C2p)ucugucCfaUfgauaasgsa	1668	UCUUAUCAUGGACAGAGACUGUA	1929
AD-1466104.1	usasagcacuGfGfUfaucauaucuuL96	1407	asdAsgadTadTgauadCcAfgugcuuasgsu	1669	ACUAAGCACUGGUAUCAUAUCUG	1930
AD-1466105.1	uscsauauCfuGfAfUfucacagaucuL96	1408	asGfsaudCu(G2p)ugaaucAfgAfuaugasusa	1670	UAUCAUAUCUGAUUCACAGAUCA	1931
AD-1466106.1	asusaucuGfaUfUfCfacagaucaauL96	383	asUfsugdAu(C2p)ugugaaUfcAfgauausgsa	1671	UCAUAUCUGAUUCACAGAUCAAG	651
AD-1466107.1	usasaacaAfuGfGfUfggaucuuauuL96	1409	asAfsuadAg(Agn)uccaccAfuUfguuuasasu	1672	AUUAAACAAUGGUGGAUCUUAUA	1932
AD-1466108.1	asasacaaugGfUfGfgaucuuauauL96	1410	asdTsaudAadGauccdAcCfauuguuusasa	1673	UUAAACAAUGGUGGAUCUUAUAA	1933
AD-1466109.1	csasauggugGfAfUfcuuauaauguL96	1411	asdCsaudTadTaagadTcCfaccauugsusu	1674	AACAAUGGUGGAUCUUAUAAUGC	1934
AD-1466110.1	gsgsuggaucUfUfAfuaaugcuuguL96	1412	asdCsaadGcdAuuaudAaGfauccaccsasu	1675	AUGGUGGAUCUUAUAAUGCUUGG	1935
AD-1466111.1	asuscuuauaAfUfGfcuuggaguguL96	1413	asdCsacdTcdCaagcdAuUfauaagauscsc	1676	GGAUCUUAUAAUGCUUGGAGUGU	1936
AD-1466112.1	csasagguGfcCfAfAfacacuaccuuL96	1414	asAfsggdTa(G2p)uguuugGfcAfccuugsgsg	1677	CCCAAGGUGCCAAACACUACCUG	1937
AD-1466113.1	cscsugcuAfuAfCfCfacagaguucuL96	1415	asGfsaadCu(C2p)ugugguAfuAfgcaggsasc	1678	GUCCUGCUAUACCACAGAGUUCU	1938
AD-1466114.1	csusgcuaUfaCfCfAfcagaguucuuL96	1416	asAfsgadAc(Tgn)cuguggUfaUfagcagsgsa	1679	UCCUGCUAUACCACAGAGUUCUA	1939
AD-1466115.1	usasuaccacAfGfAfguucuauguuL96	1417	asdAscadTadGaacudCuGfugguauasgsc	1680	GCUAUACCACAGAGUUCUAUGUA	1940
AD-1466116.1	usasccacagAfGfUfucuauguaguL96	1418	asdCsuadCadTagaadCuCfugugguasusa	1681	UAUACCACAGAGUUCUAUGUAGC	1941
AD-	cscsacagAfgUfUfCfuauguagcuuL96	1419	asAfsgcdTa(C2p)auagaaCfuCfuguggsusa	1682	UACCACAGAGUUCUAUGUAGCUU	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	csascagaguUfCfUfauguagcuuuL96	1420	asdAsagdCudAcauadGaAfcucugugsgsu	1683	ACCACAGAGUUCUAUGUAGCUUA	1943
AD-1466119.1	asgsaguuCfuAfUfGfuagcuuacauL96	1421	asUfsgudAa(G2p)cuacauAfgAfacucusgsu	1684	ACAGAGUUCUAUGUAGCUUACAG	1944
AD-1466120.1	asgsuucuauGfUfAfgcuuacaguuL96	1422	asdAscudGudAagcudAcAfuagaacuscsu	1685	AGAGUUCUAUGUAGCUUACAGUU	1945
AD-1466121.1	uscsuaugUfaGfCfUfuacaguuccuL96	1423	asGfsgadAc(Tgn)guaagcUfaCfauagasasc	1686	GUUCUAUGUAGCUUACAGUUCCA	1946
AD-1466122.1	csasauucAfgAfUfGfccucuacaauL96	1424	asUfsugdTa(G2p)aggcauCfuGfaauugscsc	1687	GGCAAUUCAGAUGCCUCUACAAU	1947
AD-1466123.1	asasuucaGfaUfGfCfcucuacaauuL96	1425	asAfsuudGu(Agn)gaggcaUfcUfgaauusgsc	1688	GCAAUUCAGAUGCCUCUACAAUA	1948
AD-1466124.1	ususcagaUfgCfCfUfcuacaauaauL96	1426	asUfsuadTu(G2p)uagaggCfaUfcugaasusu	1689	AAUUCAGAUGCCUCUACAAUAAA	1949
AD-1466125.1	asuscaguUfuGfAfCfccaccuauuuL96	1427	asAfsaudAg(G2p)ugggucAfaAfcugaususc	1690	GAAUCAGUUUGACCCACCUAUUG	1950
AD-1466126.1	uscsaguuugAfCfCfcaccuauuguL96	1428	asdCsaadTadGguggdGuCfaaacugasusu	1691	AAUCAGUUUGACCCACCUAUUGU	1951
AD-1466127.1	csasguuugaCfCfCfaccuauuguuL96	1429	asdAscadAudAggugdGgUfcaaacugsasu	1692	AUCAGUUUGACCCACCUAUUGUG	1952
AD-1466128.1	csusauugugGfCfUfagauauauuuL96	1430	asdAsaudAudAucuadGcCfacaauagsgsu	1693	ACCUAUUGUGGCUAGAUAUAUUA	1953
AD-1466129.1	gsgscuagAfuAfUfAfuuaggaucuuL96	1431	asAfsgadTc(C2p)uaauauAfuCfuagccsasc	1694	GUGGCUAGAUAUAUUAGGAUCUC	1954
AD-1466130.1	gsasuauaUfuAfGfGfaucucuccauL96	1432	asUfsggdAg(Agn)gauccuAfaUfauaucsusa	1695	UAGAUAUAUUAGGAUCUCUCCAA	1955
AD-1466131.1	asgscaaaucAfCfAfgcuucuucguL96	1433	asdCsgadAgdAagcudGuGfauuugcususg	1696	CAAGCAAAUCACAGCUUCUUCGU	1956
AD-1466132.1	asgsuggcUfaGfAfAfauugaucuauL96	1434	asUfsagdAu(C2p)aauuucUfaGfccacusgsc	1697	GCAGUGGCUAGAAAUUGAUCUAC	1957
AD-1466133.1	asasauugauCfUfAfcucaagaucuL96	1435	asdGsaudCudTgagudAgAfucaauuuscsu	1698	AGAAAUUGAUCUACUCAAGAUCA	1958
AD-	asusugauCfuAfCfUfcaagaucaauL96	390	asUfsugdAu(C2p)uugaguAfgAfucaausus	1699	AAAUUGAUCUACUCAAGAUCAAG	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	asasauguAfuGfUfAfaagagcuauuL96	1436	asAfsuadGc(Tgn)cuuuacAfuAfcauuuscsa	1700	UGAAAUGUAUGUAAAGAGCUAUA	1959
AD-1466136.1	asusguaaAfgAfGfCfuauaccaucuL96	1437	asGfsaudGg(Tgn)auagcuCfuUfuacausasc	1701	GUAUGUAAAGAGCUAUACCAUCC	1960
AD-1466137.1	asasgagcUfaUfAfCfcauccacuauL96	1438	asUfsagdTg(G2p)augguaUfaGfcucuususa	1702	UAAAGAGCUAUACCAUCCACUAC	1961
AD-1466138.1	csusccauGfgUfGfGfacaagauuuuL96	1439	asAfsaadTc(Tgn)uguccaCfcAfuggagsgsa	1703	UCCUCCAUGGUGGACAAGAUUUU	1962
AD-1466139.1	uscscaugguGfGfAfcaagauuuuuL96	1440	asdAsaadAudCuugudCcAfccauggasgsg	1704	CCUCCAUGGUGGACAAGAUUUUU	1963
AD-1466140.1	cscsauggugGfAfCfaagauuuuuuL96	1441	asdAsaadAadTcuugdTcCfaccauggsasg	1705	CUCCAUGGUGGACAAGAUUUUUG	1964
AD-1466141.1	csasugguggAfCfAfagauuuuuguL96	1442	asdCsaadAadAucuudGuCfcaccaugsgsa	1706	UCCAUGGUGGACAAGAUUUUUGA	1965
AD-1466142.1	asusgguggaCfAfAfgauuuuugauL96	1443	asdTscadAadAaucudTgUfccaccausgsg	1707	CCAUGGUGGACAAGAUUUUUGAA	1966
AD-1466143.1	usgsguggacAfAfGfauuuuugaauL96	1444	asdTsucdAadAaaucdTuGfuccaccasusg	1708	CAUGGUGGACAAGAUUUUUGAAG	1967
AD-1466144.1	gsgsuggacaAfGfAfuuuuugaaguL96	1445	asdCsuudCadAaaaudCuUfguccaccsasu	1709	AUGGUGGACAAGAUUUUUGAAGG	1968
AD-1466145.1	gsusggacaaGfAfUfuuuugaagguL96	1446	asdCscudTcdAaaaadTcUfuguccacscsa	1710	UGGUGGACAAGAUUUUUGAAGGA	1969
AD-1466146.1	usgsgacaAfgAfUfUfuuugaaggauL96	1447	asUfsccdTu(C2p)aaaaauCfuUfguccascsc	1711	GGUGGACAAGAUUUUUGAAGGAA	1970
AD-1466147.1	gsgsacaaGfaUfUfUfuugaaggaauL96	1448	asUfsucdCu(Tgn)caaaaaUfcUfuguccsasc	1712	GUGGACAAGAUUUUUGAAGGAAA	1971
AD-1466148.1	gsascaagAfuUfUfUfugaaggaaauL96	1449	asUfsuudCc(Tgn)ucaaaaAfuCfuugucscsa	1713	UGGACAAGAUUUUUGAAGGAAAU	1972
AD-1466149.1	ascsaagaUfuUfUfUfgaaggaaauuL96	1450	asAfsuudTc(C2p)uucaaaAfaUfcuugucscsc	1714	GGACAAGAUUUUUGAAGGAAAUA	1973
AD-1466150.1	csasagauUfuUfUfGfaaggaaauauL96	1451	asUfsaudTu(C2p)cuucaaAfaAfucuugsusc	1715	GACAAGAUUUUUGAAGGAAAUAC	1974
AD-	asasgauuUfuUfGfAfaggaaauacuL96	1452	asGfsuadTu(Tgn)ccuucaAfaAfaucuusgsu	1716	ACAAGAUUUUUGAAGGAAAUAC	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	asgsauuuuuuGfAfAfAfggaaauacuuL96	1453	asdAsgudAudTuccudTcAfaaaaucususg	1717	CAAGAUUUUUUGAAGGAAAUACUA	1976
AD-1466153.1	gsasuuuuuuGAfAfGfgaaauacuauL96	1454	asdTsagdTadTuuccdTuCfaaaaaucsusu	1718	AAGAUUUUUUGAAGGAAAUACUA	1977
AD-1466154.1	asusuuuuuGfaAfGfGfaaauacuaauL96	1455	asUfsuadGu(Agn)uuuccuUfcAfaaaauscsu	1719	AGAUUUUUUGAAGGAAAUACUAA U	1978
AD-1466155.1	ususuuuuGAfaGfGfAfaauacuaauuL96	1456	asAfsuudAg(Tgn)auuuccUfuCfaaaaasusc	1720	GAUUUUUUGAAGGAAAUACUAAU A	1979
AD-1466156.1	ususuugaAfgGfAfAfauacuaauauL96	1457	asUfsaudTa(G2p)uauuucCfuUfcaaaasasu	1721	AUUUUUGAAGGAAAUACUAAUA C	1980
AD-1466157.1	ususugaaggAfAfAfuacuaauacuL96	1458	asdGsuadTudAguaudTuCfcuucaaasasa	1722	UUUUUGAAGGAAAUACUAAUACC	1981
AD-1466158.1	ususgaaggaAfAfUfacuaauaccuL96	1459	asdGsgudAudTaguadTuUfccuucaasasa	1723	UUUUGAAGGAAAUACUAAUACCA	1982
AD-1466159.1	ascsuaauAfcCfAfAfaggacauguuL96	1460	asAfscadTg(Tgn)ccuuugGfuAfuuagusasu	1724	AUACUAAUACCAAAGGACAUGUG	1983
AD-1466160.1	csusaauaccAfAfAfggacaugugL96	1461	asdCsacdAudGuccudTuGfguauuagsusa	1725	UACUAAUACCAAAGGACAUGUGA	1984
AD-1466161.1	usasauaccaAfAfGfgacaugugauL96	1462	asdTscadCadTguccdTuUfgguauuasgsu	1726	ACUAAUACCAAAGGACAUGUGAA	1985
AD-1466162.1	csasaucauuUfCfCfagguuuauccuL96	1463	asdGsaudAadAccugdGaAfaugauugsgsg	1727	CCCAAUCAUUUCCAGGUUUAUCC	1986
AD-1466163.1	asuscauuucCfAfGfguuuauccguL96	1464	asdCsggdAudAaaccdTgGfaaaugaususg	1728	CAAUCAUUUCCAGGUUUAUCCGU	1987
AD-1466164.1	asusggaaUfcAfAfAfguauugcacuL96	1465	asGfsugdCa(Agn)uacuuuGfaUfuccausgsu	1729	ACAUGGAAUCAAAGUAUUGCACU	1988
AD-1466165.1	gscscuggAfaCfUfCfuuuggcuguuL96	1466	asAfscadGc(C2p)aaagagUfuCfcaggcsgsa	1730	UCGCCUGGAACUCUUUGGCUGUG	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	CCACAAACUCAAGUUUGAAUU	60	291-311	AAUUCAAACUUGAGUUUGUGGGC	191	289-311
AD-1410577	AUCUUUCUGUAACUUCCUUUU	61	309-329	AAAAGGAAGUUACAGAAAGAUUC	192	307-329
AD-1410605	AGUAUGAACCAUAUUUUAAGU	15	348-368	ACUUAAAAUAUGGUUCAUACUCU	16	346-368
AD-1410628	CUACCAUUUCAGGACUUCUUU	62	384-404	AAAGAAGUCCUGAAAUGGUAGAU	193	382-404
AD-109252	CAUGCCUCACACACAUCUAUU	1990	642-662	AAUAGAUGUGUGUGAGGCAUGGA	2050	640-662
AD-1410821	AUGCCUCACACACAUCUAUUU	712	643-663	AAAUAGAUGUGUGUGAGGCAUGG	2051	641-663
AD-1410822	UGCCUCACACACAUCUAUUAU	713	644-664	AUAAUAGAUGUGUGUGAGGCAUG	2052	642-664
AD-109255	GCCUCACACACAUCUAUUACU	11	645-665	AGUAAUAGAUGUGUGUGAGGCAU	2053	643-665
AD-1410823	CCUCACACACAUCUAUUACUU	714	646-666	AAGUAAUAGAUGUGUGUGAGGCA	2054	644-666
AD-1410824	CUCACACACAUCUAUUACUCU	13	647-667	AGAGUAAUAGAUGUGUGUGAGGC	2055	645-667
AD-1410825	UCACACACAUCUAUUACUCCU	66	648-668	AGGAGUAAUAGAUGUGUGUGAGG	197	646-668
AD-1410831	CAUCUAUUACUCCCAUGAAAU	1991	655-675	AUUUCAUGGGAGUAAUAGAUGUG	2056	653-675
AD-1410845	UCUGAUCGAGGAUUUCAACUU	67	676-696	AAGUUGAAAUCCUCGAUCAGAUU	198	674-696
AD-1410866	GGGACACAGAAGACGUUUGAU	1992	749-769	AUCAAACGUCUUCUGUGUCCCAC	2057	747-769
AD-1410867	GGACACAGAAGACGUUUGACU	1993	750-770	AGUCAAACGUCUUCUGUGUCCCA	2058	748-770
AD-1410868	GACACAGAAGACGUUUGACAU	1994	751-771	AUGUCAAACGUCUUCUGUGUCCC	2059	749-771
AD-109319	GAAGACGUUUGACAAGCAAAU	717	757-777	AUUUGCUUGUCAAACGUCUUCUG	2060	755-777
AD-109322	GACGUUUGACAAGCAAAUCGU	719	760-780	ACGAUUUGCUUGUCAAACGUCUU	2061	758-780
AD-1410876	ACGUUUGACAAGCAAAUCGUU	1995	761-781	AACGAUUUGCUUGUCAAACGUCU	2062	759-781
AD-1410877	CGUUUGACAAGCAAAUCGUGU	1996	762-782	ACACGAUUUGCUUGUCAAACGUC	2063	760-782
AD-109325	GUUUGACAAGCAAAUCGUGCU	1997	763-783	AGCACGAUUUGCUUGUCAAACGU	2064	761-783
AD-1410878	UUUGACAAGCAAAUCGUGCUU	1998	764-784	AAGCACGAUUUGCUUGUCAAACG	2065	762-784
AD-1410927	CCUAAUGUACACAGUCAAUGU	1999	832-852	ACAUUGACUGUGUACAUUAGGGA	2066	830-852
AD-1410928	CUAAUGUACACAGUCAAUGGU	2000	833-853	ACCAUUGACUGUGUACAUUAGGG	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	UAAUGUACACAGUCAAUGGAU	2001	834-854	AUCCAUUGACUGUGUACAUUAGG	2068	832-854
AD-1410929	AAUGUACACAGUCAAUGGAUU	724	835-855	AAUCCAUUGACUGUGUACAUUAG	2069	833-855
AD-1410994	AUUAUUCUCCAUUCAUUUCAU	70	940-960	AUGAAAUGAAUGGAGAAUAAUUC	201	938-960
AD-109601	AAAGUGGAUCAUAUCUUCUCU	31	1057-1077	AGAGAAGAUAUGAUCCACUUUCC	162	1055-1077
AD-1411138	CCAGGAAUCUUAAGAAAAUAU	72	1143-1163	AUAUUUUCUUAAGAUUCCUGGUU	203	1141-1163
AD-1411203	GGACUAUGCACCUGUAAUACU	2002	1228-1248	AGUAUUACAGGUGCAUAGUCCCA	2070	1226-1248
AD-1411204	GACUAUGCACCUGUAAUACCU	2003	1229-1249	AGGUAUUACAGGUGCAUAGUCCC	2071	1227-1249
AD-1411205	ACUAUGCACCUGUAAUACCAU	2004	1230-1250	AUGGUAUUACAGGUGCAUAGUCC	2072	1228-1250
AD-1411206	CUAUGCACCUGUAAUACCAGU	2005	1231-1251	ACUGGUAUUACAGGUGCAUAGUC	2073	1229-1251
AD-109757	GCACCUGUAAUACCAGCGAAU	2006	1235-1255	AUUCGCUGGUAUUACAGGUGCAU	2074	1233-1255
AD-1411210	CACCUGUAAUACCAGCGAAUU	759	1236-1256	AAUUCGCUGGUAUUACAGGUGCA	1015	1234-1256
AD-109759	ACCUGUAAUACCAGCGAAUAU	2007	1237-1257	AUAUUCGCUGGUAUUACAGGUGC	2075	1235-1257
AD-1411211	CCUGUAAUACCAGCGAAUAUU	2008	1238-1258	AAUAUUCGCUGGUAUUACAGGUG	2076	1236-1258
AD-1411212	CUGUAAUACCAGCGAAUAUGU	2009	1239-1259	ACAUAUUCGCUGGUAUUACAGGU	2077	1237-1259
AD-1411213	UGUAAUACCAGCGAAUAUGGU	760	1240-1260	ACCAUAUUCGCUGGUAUUACAGG	2078	1238-1260
AD-1411214	GUAAUACCAGCGAAUAUGGAU	761	1241-1261	AUCCAUAUUCGCUGGUAUUACAG	2079	1239-1261
AD-1411215	UAAUACCAGCGAAUAUGGACU	2010	1242-1262	AGUCCAUAUUCGCUGGUAUUACA	2080	1240-1262
AD-1411226	UCAGCAUUUGGAUAAUUUCUU	73	1276-1296	AAGAAAUUAUCCAAAUGCUGAGA	204	1274-1296
AD-1411342	ACACUCAAAAAUCGUGUUCAAU	76	1433-1453	AUUGAACACGAUUUUGAGUGUGU	207	1431-1453
AD-110052	UAAGUGGAACAUCUUAGAGUU	33	1594-1614	AACUCUAAGAUGUUCCACUUAUA	164	1592-1614
AD-1411480	UAACAAGACCAUACUACAGUU	78	1647-1667	AACUGUAGUAUGGUCUUGUUAAG	209	1645-1667
AD-1411743	CAUUCAUCUAUGGAAAGAGGU	81	2034-2054	ACCUCUUUCCAUAGAUGAAUGAG	212	2032-2054
AD-110518	UUGGAACUUGGAUGUUAACUU	36	2118-2138	AAGUUAACAUCCAAGUUCCAACA	167	2116-2138
AD-1411798	UAACUUCCAUGAAUUCUAGUU	82	2133-2153	AACUAGAAUUCAUGGAAGUUAAC	213	2131-2153
AD-1411972	CCGAAACUCAUCAUUGAAUCU	84	2362-2382	AGAUUCAAUGAUGAGUUUCGGAA	215	2360-2382
AD-110844	UCAAACACAGAUAUAAUUGUU	38	2444-2464	AACAAUUAUAUCUGUGUUUGAAG	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	GUUGGUUCAAAUUAUUCUUCU	86	2462-2482	AGAAGAAUAAUUUGAACCAACAA	217	2460-2482
AD-1412095	ACUCAGUUCUCAAUUCUUCCU	88	2595-2615	AGGAAGAAUUGAGAACUGAGUUC	219	2593-2615
AD-1412163	UACGUCUACUUUCACUUGGUU	89	2685-2705	AACCAAGUGAAAGUAGACGUAUC	220	2683-2705
AD-111287	AAGUAACUCAUCUAAGAUUUU	39	2953-2973	AAAAUCUUAGAUGAGUUACUUUG	170	2951-2973
AD-1412482	CUAGAGUUAGACAUAAAUCUU	93	3150-3170	AAGAUUUAUGUCUAACUCUAGGA	224	3148-3170
AD-1412539	UUUCUCAUUAAGACACGAAAU	95	3218-3238	AUUUCGUGUCUUAAUGAGAAACU	226	3216-3238
AD-1412582	UGAAGCCUACAACACAUUUUU	96	3304-3324	AAAAAUGUGUUGUAGGCUUCACU	227	3302-3324
AD-1412622	AAUCCAAUGAAACAUCUCUUU	97	3360-3380	AAAGAGAUGUUUCAUUGGAUUUA	228	3358-3380
AD-1412733	UCAAAUGCACUCUACUUCAGU	100	3553-3573	ACUGAAGUAGAGUGCAUUUGAUC	231	3551-3573
AD-112396	UACUCUCAAUGAUACUUUUCU	43	4633-4653	AGAAAAGUAUCAUUGAGAGUAGG	174	4631-4653
AD-1413210	CUAUCAAAGGAAUUUAAUCCU	109	4652-4672	AGGAUUAAAUUCCUUUGAUAGAA	240	4650-4672
AD-1413286	ACUAUGCUGAAAUUGAUUAUU	111	4755-4775	AAUAAUCAAUUUCAGCAUAGUCA	242	4753-4775
AD-112618	AAACAGAAGAAAUUAUUACAU	44	4876-4896	AUGUAAUAAUUUCUUCUGUUUCC	175	4874-4896
AD-112760	AGCACUUUUACCAAACGUGAU	45	5021-5041	AUCACGUUUGGUAAAAGUGCUGU	176	5019-5041
AD-1413517	UUAUCCAAGUUCGUUUUAAAU	114	5109-5129	AUUUAAAACGAACUUGGAUAACA	245	5107-5129
AD-1413605	AUGCUGUUCAGCCAAAUAGCU	115	5238-5258	AGCUAUUUGGCUGAACAGCAUUA	246	5236-5258
AD-1413615	UAGCAGUUAUACCUACGUAUU	116	5254-5274	AAUACGUAGGUAUAACUGCUAUU	247	5252-5274
AD-113137	GAGAGAAUUUGUCUUACUAUU	46	5443-5463	AAUAGUAAGACAAAUUCUCUCAU	177	5441-5463
AD-113331	GACAUUCACGUGGUUCACUUU	47	5657-5677	AAAGUGAACCACGUGAAUGUCUU	178	5655-5677
AD-1413936	CUGGUUCAUUUAAAACUCUUU	117	5742-5762	AAAGAGUUUUAAAUGAACCAGGC	248	5740-5762
AD-113467	GAGCAGGGAUGCAAACGCCAU	2011	5823-5843	AUGGCGUUUGCAUCCCUGCUCUC	2081	5821-5843
AD-113468	AGCAGGGAUGCAAACGCCAUU	2012	5824-5844	AAUGGCGUUUGCAUCCCUGCUCU	2082	5822-5844
AD-113471	AGGGAUGCAAACGCCAUUUCU	2013	5827-5847	AGAAAUGGCGUUUGCAUCCCUGC	2083	5825-5847
AD-113472	GGGAUGCAAACGCCAUUUCUU	2014	5828-5848	AAGAAAUGGCGUUUGCAUCCCUG	2084	5826-5848
AD-1414007	GGAUGCAAACGCCAUUUCUUU	2015	5829-5849	AAAGAAAUGGCGUUUGCAUCCCU	2085	5827-5849
AD-113474	GAUGCAAACGCCAUUUCUUAU	2016	5830-5850	AUAAGAAAUGGCGUUUGCAUCCC	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	AAUAAGAAAUGGCGUUUGCAUCC	1144	5829-5851
AD-1414009	UGCAAACGCCAUUUCUUAUCU	17	5832-5852	AGAUAAGAAAUGGCGUUUGCAUC	18	5830-5852
AD-113477	GCAAACGCCAUUUCUUAUCAU	889	5833-5853	AUGAUAAGAAAUGGCGUUUGCAU	2087	5831-5853
AD-1414010	CAAACGCCAUUUCUUAUCAUU	2017	5834-5854	AAUGAUAAGAAAUGGCGUUUGCA	2088	5832-5854
AD-1414011	AAACGCCAUUUCUUAUCAUGU	2018	5835-5855	ACAUGAUAAGAAAUGGCGUUUGC	2089	5833-5855
AD-1414012	AACGCCAUUUCUUAUCAUGGU	2019	5836-5856	ACCAUGAUAAGAAAUGGCGUUUG	2090	5834-5856
AD-1414013	ACGCCAUUUCUUAUCAUGGAU	2020	5837-5857	AUCCAUGAUAAGAAAUGGCGUUU	2091	5835-5857
AD-1414014	CGCCAUUUCUUAUCAUGGACU	2021	5838-5858	AGUCCAUGAUAAGAAAUGGCGUU	2092	5836-5858
AD-1414044	AUGGGACUAAGCACUGGUAUU	2022	5876-5896	AAUACCAGUGCUUAGUCCCAUUG	2093	5874-5896
AD-1414045	UGGGACUAAGCACUGGUAUCU	2023	5877-5897	AGAUACCAGUGCUUAGUCCCAUU	2094	5875-5897
AD-113522	GGGACUAAGCACUGGUAUCAU	2024	5878-5898	AUGAUACCAGUGCUUAGUCCCAU	2095	5876-5898
AD-1414046	GGACUAAGCACUGGUAUCAUU	2025	5879-5899	AAUGAUACCAGUGCUUAGUCCCA	2096	5877-5899
AD-113526	CUAAGCACUGGUAUCAUAUCU	2026	5882-5902	AGAUAUGAUACCAGUGCUUAGUC	2097	5880-5902
AD-1414048	UAAGCACUGGUAUCAUAUCUU	892	5883-5903	AAGAUAUGAUACCAGUGCUUAGU	2098	5881-5903
AD-1414049	AAGCACUGGUAUCAUAUCUGU	2027	5884-5904	ACAGAUAUGAUACCAGUGCUUAG	2099	5882-5904
AD-113529	AGCACUGGUAUCAUAUCUGAU	2028	5885-5905	AUCAGAUAUGAUACCAGUGCUUA	2100	5883-5905
AD-113530	GCACUGGUAUCAUAUCUGAUU	2029	5886-5906	AAUCAGAUAUGAUACCAGUGCUU	2101	5884-5906
AD-1414050	CACUGGUAUCAUAUCUGAUUU	2030	5887-5907	AAAUCAGAUAUGAUACCAGUGCU	2102	5885-5907
AD-1414053	UGGUAUCAUAUCUGAUUCACU	2031	5890-5910	AGUGAAUCAGAUAUGAUACCAGU	2103	5888-5910
AD-1414074	UCAGAGUUUCUGGGUUACUGU	119	5921-5941	ACAGUAACCCAGAAACUCUGAAG	250	5919-5941
AD-1414139	AGAAUUUGCCUCUAAACCUUU	120	6010-6030	AAAGGUUUAGAGGGCAAAUUCUGC	251	6008-6030
AD-1414213	CUGAAGUCCUGCUAUACCACU	2032	6098-6118	AGUGGUAUAGCAGGACUUCAGGU	2104	6096-6118
AD-1414218	CUGCUAUACCACAGAGUUCUU	19	6106-6126	AAGAACUCUGUGGUAUAGCAGGA	2105	6104-6126
AD-113751	UGCUAUACCACAGAGUUCUAU	2033	6107-6127	AUAGAACUCUGUGGUAUAGCAGG	2106	6105-6127
AD-1414219	GCUAUACCACAGAGUUCUAUU	2034	6108-6128	AAUAGAACUCUGUGGUAUAGCAG	2107	6106-6128
AD-113753	CUAUACCACAGAGUUCUAUGU	2035	6109-6129	ACAUAGAACUCUGUGGUAUAGCA	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	UAUACCACACAGAGUUCUAUGUU	901	6110-6130	AACAUAGAACUCUGUGGUAUAGC	2109	6108-6130
AD-1414221	AUACCACACAGAGUUCUAUGUAU	2036	6111-6131	AUACAUAGAACUCUGUGGUAUAG	2110	6109-6131
AD-1414222	UACCACACAGAGUUCUAUGUAGU	902	6112-6132	ACUACAUAGAACUCUGUGGUAUA	2111	6110-6132
AD-113757	ACCACACAGAGUUCUAUGUAGCU	2037	6113-6133	AGCUACAUAGAACUCUGUGGUAU	2112	6111-6133
AD-113758	CCACACAGAGUUCUAUGUAGCUU	903	6114-6134	AAGCUACAUAGAACUCUGUGGUA	2113	6112-6134
AD-1414223	CACAGAGUUCUAUGUAGCUUU	904	6115-6135	AAAGCUACAUAGAACUCUGUGGU	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	UCUAUGUAGCUUACAGUUCCU	907	6123-6143	AGGAACUGUAAGCUACAUAGAAC	2115	6121-6143
AD-1414230	CUAUGUAGCUUACAGUUCCAU	2039	6124-6144	AUGGAACUGUAAGCUACAUAGAA	2116	6122-6144
AD-1414231	UAUGUAGCUUACAGUUCCAAU	2040	6125-6145	AUUGGAACUGUAAGCUACAUAGA	2117	6123-6145
AD-1414235	UAGCUUACAGUUCCAACCAGU	2041	6129-6149	ACUGGUUGGAACUGUAAGCUACA	2118	6127-6149
AD-1414275	GAAUGUGAUGUAUUUUAAUGU	122	6184-6204	ACAUUAAAAUACAUCACACAUUCCU	253	6182-6204
AD-113890	ACCUAUUGUGGCUAGAUAUAU	2042	6247-6267	AUAUAUCUAGCCACAAUAGGUGG	2119	6245-6267
AD-113891	CCUAUUGUGGCUAGAUAUAUU	2043	6248-6268	AAUAUAUCUAGCCACAAUAGGUG	2120	6246-6268
AD-1414321	CUAUUGUGGCUAGAUAUAUUU	914	6249-6269	AAAUAUAUCUAGCCACAAUAGGU	1170	6247-6269
AD-1414322	UAUUGUGGCUAGAUAUAUUAU	2044	6250-6270	AUAAUAUAUCUAGCCACAAUAGG	2121	6248-6270
AD-1414323	AUUGUGGCUAGAUAUAUUAGU	2045	6251-6271	ACUAAUAUAUCUAGCCACAAUAG	2122	6249-6271
AD-1414324	UUGUGGCUAGAUAUAUUAGGU	2046	6252-6272	ACCUAAUAUAUCUAGCCACAAUA	2123	6250-6272
AD-113896	UGUGGCUAGAUAUAUUAGGAU	2047	6253-6273	AUCCUAAUAUAUCUAGCCACAAU	2124	6251-6273
AD-1414325	GUGGCUAGAUAUAUUAGGAUU	2048	6254-6274	AAUCCUAAUAUAUCUAGCCACAA	2125	6252-6274
AD-1414326	GGCUAGAUAUAUUAGGAUCUU	915	6256-6276	AAGAUCCUAAUAUAUCUAGCCAC	2126	6254-6276
AD-113900	GCUAGAUAUAUUAGGAUCUCU	2049	6257-6277	AGAGAUCCUAAUAUAUCUAGCCA	2127	6255-6277
AD-1414544	CCUCUGAAAUGUAUGUAAAGU	126	6579-6599	ACUUUACAUACAUUUCAGAGGAC	257	6577-6599
AD-114455	CUGUGUUAAAUGUUAACAGUU	48	6896-6916	AACUGUUAACAUUUAACACAGCG	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	ACAGUUUUCCACUAUUUCUCU	21	6911-6931	AGAGAAAUAGUGGAAAACUGUUA	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	cscsacaaAfcUfCfAfaguuugaauuL96	323	asAfsuucAfaAfCfuugaGfuUfuguggsgsc	457	GCCCACAAACUCAAGUUUGAAUC	591
AD-1410577	asuscuuuCfuGfUfAfacuuccuuuuL96	324	asAfsaagGfaAfGfuuacAfgAfaagaususc	458	GAAUCUUUCUGUAACUUCCUUUA	592
AD-1410605	asgsuaugAfaCfCfAfuauuuuaaguL96	325	asCfsuuaAfaAfUfauggUfuCfauacuscsu	459	AGAGUAUGAACCAUAUUUUAAGA	593
AD-1410628	csusaccaUfuUfCfAfggacuucuuuL96	326	asAfsagaAfgUfCfcugaAfaUfgguagsasu	460	AUCUACCAUUUCAGGACUUCUUG	594
AD-109252	csasugccUfcAfCfAfcacaucuauuL96	2128	asAfsuagAfuGfUfguguGfaGfgcaugsgsa	2206	UCCAUGCCUCACACACAUCUAUU	2290
AD-1410821	asusgccuCfaCfAfCfacaucuauuuL96	2129	asAfsauaGfaUfGfugugUfgAfggcausgsg	2207	CCAUGCCUCACACACAUCUAUUA	1748
AD-1410822	usgsccucAfcAfCfAfcaucuauuauL96	2130	asUfsaauAfgAfUfguguGfuGfaggcasusg	2208	CAUGCCUCACACACAUCUAUUAC	1749
AD-109255	gscscucaCfaCfAfCfaucuauuacuL96	2131	asGfsuaaUfaGfAfugugUfgUfgaggcsasu	2209	AUGCCUCACACACAUCUAUUACU	1750
AD-1410823	cscsucacAfcAfCfAfucuauuacuuL96	2132	asAfsguaAfuAfGfauguGfuGfugaggscsa	2210	UGCCUCACACACAUCUAUUACUC	1751
AD-1410824	csuscacaCfaCfAfUfcuauuacucuL96	2133	asGfsaguAfaUfAfgaugUfgUfgugagsgsc	2211	GCCUCACACACAUCUAUUACUCC	1752
AD-1410825	uscsacacAfcAfUfCfuauuacuccuL96	330	asGfsgagUfaAfUfagauGfuGfugugasgsg	464	CCUCACACACAUCUAUUACUCCC	598
AD-1410831	csasucuaUfuAfCfUfcccaugaaauL96	2134	asUfsuucAfuGfGfgaguAfaUfagaugsusg	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	uscsugauCfgAfGfGfGfauuucaacuuL96	331	asAfsguuGfaAfAfuccuCfgAfucagasusu	465	AAUCUGAUCGAGGAUUUCAACUC	599
AD-1410866	gsgsgacaCfaGfAfAfAfgacguuugauL96	2135	asUfscaaAfcGfUfcuucUfgUfgucccsasc	2213	GUGGGACACAGAAGACGUUUGAC	2292
AD-1410867	gsgsacacAfgAfAfAfGfacguuugacuL96	2136	asGfsucaAfaCfGfucuuCfuGfugucccsca	2214	UGGGACACAGAAGACGUUUGACA	2293
AD-1410868	gsascacaGfaAfGfAfAfcguuugacauL96	2137	asUfsgucAfaAfCfgucuUfcUfgugucscsc	2215	GGGACACAGAAGACGUUUGACAA	2294
AD-109319	gsasagacGfuUfUfUfGfacaagcaaauL96	1231	asUfsuugCfuUfGfucaaAfcGfucuucsusg	2216	CAGAAGACGUUUGACAAGCAAAU	1755
AD-109322	gsascguuUfgAfCfAfagcaaaucguL96	2138	asCfsgauUfuGfCfuuguCfaAfacgucsusu	2217	AAGACGUUUGACAAGCAAAUCGU	1757
AD-1410876	ascsguuuGfaCfAfAfgcaaaucguuL96	2139	asAfscgaUfuUfGfcuugUfcAfaacguscsu	2218	AGACGUUUGACAAGCAAAUCGUG	2295
AD-1410877	csgsuuugAfcAfAfGfcaaaucgugL96	2140	asCfsacgAfuUfUfgcuuGfuCfaaacgsusc	2219	GACGUUUGACAAGCAAAUCGUGC	2296
AD-109325	gsusuugaCfaAfGfCfaaaucgugcuL96	2141	asGfscacGfaUfUfugcuUfgUfcaaacsgsu	2220	ACGUUUGACAAGCAAAUCGUGCU	2297
AD-1410878	ususugacAfaGfCfAfaaucgugcuuL96	2142	asAfsgcaCfgAfUfuugcUfuGfucaaascsg	2221	CGUUUGACAAGCAAAUCGUGCUA	2298
AD-1410927	cscsuaauGfuAfCfAfcagucaauguL96	2143	asCfsauuGfaCfUfguguAfcAfuuaggsgsa	2222	UCCCUAAUGUACACAGUCAAUGG	2299
AD-1410928	csusaaugUfaCfAfCfagucaaugguL96	2144	asCfscauUfgAfCfugugUfaCfauuagsgsg	2223	CCCUAAUGUACACAGUCAAUGGA	2300
AD-109396	usasauguAfcAfCfAfgucaauggauL96	2145	asUfsccaUfuGfAfcuguGfuAfcauuasgsg	2224	CCUAAUGUACACAGUCAAUGGAU	2301
AD-1410929	asasuguaCfaCfAfGfucaauggauuL96	2146	asAfsuccAfuUfGfacugUfgUfacauusasg	2225	CUAAUGUACACAGUCAAUGGAUA	1762
AD-1410994	asusuauuCfuCfCfAfuucauuucauL96	334	asUfsgaaAfuGfAfauggAfgAfauaaususc	468	GAAUUAUUCUCCAUUCAUUUCAA	602
AD-109601	asasagugGfaUfCfAfuaucuucucuL96	293	asGfsagaAfgAfUfaugaUfcCfacuuuscsc	427	GGAAAGUGGAUCAUAUCUUCUCU	561
AD-1411138	cscsaggaAfuCfUfUfaagaaaauauL96	336	asUfsauuUfuCfUfuaagAfuUfccuggsusu	470	AACCAGGAAUCUUAAGAAAAUAA	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	asGfsuauUfaCfAfggugCfaUfaguccscsa	2226	UGGGACUAUGCACCUGUAAUACC	2302
AD-1411204	gsascuauGfcAfCfCfuguaauaccuL96	2148	asGfsguaUfuAfCfagguGfcAfuagucscsc	2227	GGGACUAUGCACCUGUAAUACCA	2303
AD-1411205	ascsuaugCfaCfCfUfguaauaccauL96	2149	asUfsgguAfuUfAfcaggUfgCfauaguscsc	2228	GGACUAUGCACCUGUAAUACCAG	2304
AD-1411206	csusaugcAfcCfUfGfuaauaccaguL96	2150	asCfsuggUfaUfUfacagGfuGfcauagsusc	2229	GACUAUGCACCUGUAAUACCAGC	2305
AD-109757	gscsaccuGfuAfAfUfaccagcgaauL96	2151	asUfsucgCfuGfGfuauuAfcAfggugcsasu	2230	AUGCACCUGUAAUACCAGCGAAU	2306
AD-1411210	csasccugUfaAfUfAfccagcgaauuL96	2152	asAfsuucGfcUfGfguauUfaCfaggugscsa	2231	UGCACCUGUAAUACCAGCGAAUA	1797
AD-109759	ascscuguAfaUfAfCfcagcgaauauL96	2153	asUfsauuCfgCfUfgguaUfuAfcaggusgsc	2232	GCACCUGUAAUACCAGCGAAUAU	2307
AD-1411211	cscsuguaAfuAfCfCfagcgaauauuL96	2154	asAfsuauUfcGfCfugguAfuUfacaggsusg	2233	CACCUGUAAUACCAGCGAAUAUG	2308
AD-1411212	csusguaaUfaCfCfAfgcgaauauguL96	2155	asCfsauaUfuCfGfcuggUfaUfuacagsgsu	2234	ACCUGUAAUACCAGCGAAUAUGG	2309
AD-1411213	usgsuaauAfcCfAfGfcgaauaugguL96	2156	asCfscauAfuUfCfgcugGfuAfuuacasgsg	2235	CCUGUAAUACCAGCGAAUAUGGA	1798
AD-1411214	gsusaauaCfcAfGfCfgaauauggauL96	2157	asUfsccaUfaUfUfcgcuGfgUfauuacsasg	2236	CUGUAAUACCAGCGAAUAUGGAC	1799
AD-1411215	usasauacCfaGfCfGfaauauggacuL96	2158	asGfsuccAfuAfUfucgcUfgGfuauuascsa	2237	UGUAAUACCAGCGAAUAUGGACA	2310
AD-1411226	uscsagcaUfuUfGfGfauaauuucuuL96	337	asAfsgaaAfuUfAfuccaAfaUfgcugasgsa	471	UCUCAGCAUUUGGAUAAUUUCUC	605
AD-1411342	ascsacucAfaAfAfUfcguguucaauL96	340	asUfsugaAfcAfCfgauuUfuGfagugusgsu	474	ACACACUCAAAAUCGUGUUCAAA	608
AD-110052	usasagugGfaAfCfAfucuuagaguuL96	295	asAfscucUfaAfGfauguUfcCfacuuasusa	429	UAUAAGUGGAACAUCUUAGAGUU	563
AD-1411480	usasacaaGfaCfCfAfuacuacaguuL96	342	asAfscugUfaGfUfauggUfcUfuguuasasg	476	CUUAACAAGACCAUACUACAGUG	610
AD-1411743	csasuucaUfcUfAfUfggaaagagguL96	345	asCfscucUfuUfCfcauaGfaUfgaaugsasg	479	CUCAUUCAUCUAUGGAAAGAGGC	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	ususggaaCfuUfGfGfauguuaacuuL96	298	asAfsguuAfaCfAfuccaAfgUfuccaascsa	432	UGUUGGAACUUGGAUGUUAACUU	566
AD-1411798	usasacuuCfcAfUfGfaauucuaguuL96	346	asAfscuaGfaAfUfucauGfgAfaguuasasc	480	GUUAACUUCCAUGAAUUCUAGUC	614
AD-1411972	cscsgaaaCfuCfAfUfcauugaaucuL96	348	asGfsauuCfaAfUfgaugAfgUfuucggsasa	482	UUCCGAAACUCAUCAUUGAAUCA	616
AD-110844	uscsaaacAfcAfGfAfuauaauuguuL96	300	asAfscaaUfuAfUfaucuGfuGfuuugasasg	434	CUUCAAACACAGAUAUAAUUGUU	568
AD-1412040	gsusugguUfcAfAfAfuuauucuucuL96	350	asGfsaagAfaUfAfauuuGfaAfccaacsasa	484	UUGUUGGUUCAAAUUAUUCUUCC	618
AD-1412095	ascsucagUfuCfUfCfaauucuuccuL96	352	asGfsgaaGfaAfUfugagAfaCfugagususc	486	GAACUCAGUUCUCAAUUCUUCCA	620
AD-1412163	usascgucUfaCfUfUfucacuugguuL96	353	asAfsccaAfgUfGfaaagUfaGfacguasusc	487	GAUACGUCUACUUUCACUUGGUG	621
AD-111287	asasguaaCfuCfAfUfcuaagauuuuL96	301	asAfsaauCfuUfAfgaugAfgUfuacuususg	435	CAAAGUAACUCAUCUAAGAUUUU	569
AD-1412482	csusagagUfuAfGfAfcauaaaucuuL96	357	asAfsgauUfuAfUfgucuAfaCfucuagsgsa	491	UCCUAGAGUUAGACAUAAAUCUC	625
AD-1412539	ususucucAfuUfAfAfgacacgaaauL96	359	asUfsuucGfuGfUfcuuaAfuGfagaaascsu	493	AGUUUCUCAUUAAGACACGAAAA	627
AD-1412582	usgsaagcCfuAfCfAfacacauuuuuL96	360	asAfsaaaUfgUfGfuuguAfgGfcuucascsu	494	AGUGAAGCCUACAACACAUUUUC	628
AD-1412622	asasuccaAfuGfAfAfacaucucuuuL96	361	asAfsagaGfaUfGfuuucAfuUfggauususa	495	UAAAUCCAAUGAAACAUCUCUUC	629
AD-1412733	uscsaaauGfcAfCfUfcuacuucaguL96	364	asCfsugaAfgUfAfgaguGfcAfuuugasusc	498	GAUCAAAUGCACUCUACUUCAGA	632
AD-112396	usascucuCfaAfUfGfauacuuuucuL96	305	asGfsaaaAfgUfAfucauUfgAfgaguasgsg	439	CCUACUCUCAAUGAUACUUUUCU	573
AD-1413210	csusaucaAfaGfGfAfauuuaauccuL96	373	asGfsgauUfaAfAfuuccUfuUfgauagsasa	507	UUCUAUCAAAGGAAUUUAAUCCA	641
AD-1413286	ascsuaugCfuGfAfAfauugauuauuL96	375	asAfsuaaUfcAfAfuuucAfgCfauaguscsa	509	UGACUAUGCUGAAAUUGAUUAUG	643
AD-112618	asasacagAfaGfAfAfauauuacauL96	306	asUfsguaAfuAfAfuuucUfuCfuguuuscsc	440	GGAAACAGAAGAAAUUAUUACAU	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	asgscacuUfuUfAfCfcaaacgugauL96	307	asUfscacGfuUfUfgguaAfaAfgugcusgsu	441	ACAGCACUUUUACCAAACGUGAU	575
AD-1413517	ususauccAfaGfUfUfcguuuuaaauL96	378	asUfsuuaAfaAfCfgaacUfuGfgauaascsa	512	UGUUAUCCAAGUUCGUUUUAAAA	646
AD-1413605	asusgcugUfuCfAfGfccaaauagcuL96	379	asGfscuaUfuUfGfgcugAfaCfagcaususa	513	UAAUGCUGUUCAGCCAAAUAGCA	647
AD-1413615	usasgcagUfuAfUfAfccuacguauuL96	380	asAfsuacGfuAfGfguauAfaCfugcuasusu	514	AAUAGCAGUUAUACCUACGUAUG	648
AD-113137	gsasgagaAfuUfUfGfucuuacuauuL96	308	asAfsuagUfaAfGfacaaAfuUfcucucsasu	442	AUGAGAGAAUUUGUCUUACUAUU	576
AD-113331	gsascauuCfaCfGfUfgguucacuuuL96	309	asAfsaguGfaAfCfcacgUfgAfaugucsusu	443	AAGACAUUCACGUGGUUCACUUU	577
AD-1413936	csusgguuCfaUfUfUfaaaacucuuuL96	381	asAfsagaGfuUfUfuaaaUfgAfaccagsgsc	515	GCCUGGUUCAUUUAAAACUCUUG	649
AD-113467	gsasgcagGfgAfUfGfcaaacgccauL96	2159	asUfsggcGfuUfUfgcauCfcCfugcucsusc	2238	GAGAGCAGGGAUGCAAACGCCAU	2311
AD-113468	asgscaggGfaUfGfCfcaaacgccauuL96	2160	asAfsuggCfgUfUfugcaUfcCfcugcuscsu	2239	AGAGCAGGGAUGCAAACGCCAUU	2312
AD-113471	asgsggauGfcAfAfAfcgccauuucuL96	2161	asGfsaaaUfgGfCfguuuGfcAfucccusgsc	2240	GCAGGGAUGCAAACGCCAUUUCU	2313
AD-113472	gsgsgaugCfaAfAfCfgccauuucuuL96	2162	asAfsgaaAfuGfGfcguuUfgCfaucccsusg	2241	CAGGGAUGCAAACGCCAUUUCUU	2314
AD-1414007	gsgsaugcAfaAfCfGfccauuucuuuL96	2163	asAfsagaAfaUfGfgcguUfuGfcauccscsu	2242	AGGGAUGCAAACGCCAUUUCUUA	2315
AD-113474	gsasugcaAfaCfGfCfcauuucuuauL96	2164	asUfsaagAfaAfUfggcgUfuUfgcaucscsc	2243	GGGAUGCAAACGCCAUUUCUUAU	2316
AD-1414008	asusgcaaAfcGfCfCfauuucuuauuL96	2165	asAfsuaaGfaAfAfuggcGfuUfugcauscsc	2244	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1414009	usgscaaaCfgCfCfAfuuucuuaucuL96	382	asGfsauaAfgAfAfauggCfgUfuugcasusc	516	GAUGCAAACGCCAUUUCUUAUCA	650
AD-113477	gscsaaacGfcCfAfUfuucuuaucauL96	2166	asUfsgauAfaGfAfaaugGfcGfuuugcsasu	2245	AUGCAAACGCCAUUUCUUAUCAU	1927
AD-1414010	csasaacgCfcAfUfUfucuuaucauuL96	2167	asAfsugaUfaAfGfaaauGfgCfguuugscsa	2246	UGCAAACGCCAUUUCUUAUCAUG	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	asasacgcCfaUfUfUfcuuaucauguL96	2168	asCfsaugAfuAfAfgaaaUfgGfcguuusgsc	2247	GCAAACGCCAUUUCUUAUCAUGG	2318
AD-1414012	asascgccAfuUfUfCfuuaucaugguL96	2169	asCfscauGfaUfAfagaaAfuGfgcguususg	2248	CAAACGCCAUUUCUUAUCAUGGA	2319
AD-1414013	ascsgccaUfuUfCfUfuaucauggauL96	2170	asUfsccaUfgAfUfaagaAfaUfggcgususu	2249	AAACGCCAUUUCUUAUCAUGGAC	2320
AD-1414014	csgsccauUfuCfUfUfaucauggacuL96	2171	asGfsuccAfuGfAfuaagAfaAfuggcgsusu	2250	AACGCCAUUUCUUAUCAUGGACA	2321
AD-1414044	asusgggaCfuAfAfGfcacugguauuL96	2172	asAfsuacCfaGfUfgcuuAfgUfcccaususg	2251	CAAUGGGACUAAGCACUGGUAUC	2322
AD-1414045	usgsggacUfaAfGfCfacugguaucuL96	2173	asGfsauaCfcAfGfugcuUfaGfucccasusu	2252	AAUGGGACUAAGCACUGGUAUCA	2323
AD-113522	gsgsgacuAfaGfCfAfcugguaucauL96	2174	asUfsgauAfcCfAfgugcUfuAfgucccsasu	2253	AUGGGACUAAGCACUGGUAUCAU	2324
AD-1414046	gsgsacuaAfgCfAfCfugguaucauuL96	2175	asAfsugaUfaCfCfagugCfuUfagucccsa	2254	UGGGACUAAGCACUGGUAUCAUA	2325
AD-113526	csusaagcAfcUfGfGfuaucauaucuL96	2176	asGfsauaUfgAfUfaccaGfuGfcuuagsusc	2255	GACUAAGCACUGGUAUCAUAUCU	2326
AD-1414048	usasagcaCfuGfGfUfaucauaucuuL96	2177	asAfsgauAfuGfAfuaccAfgUfgcuuasgsu	2256	ACUAAGCACUGGUAUCAUAUCUG	1930
AD-1414049	asasgcacUfgGfUfAfucauaucuguL96	2178	asCfsagaUfaUfUfGfauacCfaGfugcuusasg	2257	CUAAGCACUGGUAUCAUAUCUGA	2327
AD-113529	asgscacuGfgUfAfUfcauaucugauL96	2179	asUfscagAfuAfUfgauaCfcAfgugcususa	2258	UAAGCACUGGUAUCAUAUCUGAU	2328
AD-113530	gscsacugGfuAfUfCfauaucugauuL96	2180	asAfsucaGfaUfAfugauAfcCfagugcsusu	2259	AAGCACUGGUAUCAUAUCUGAUU	2329
AD-1414050	csascuggUfaUfCfAfuaucugauuuL96	2181	asAfsaucAfgAfUfaugaUfaCfcagugcsu	2260	AGCACUGGUAUCAUAUCUGAUUC	2330
AD-1414053	usgsguauCfaUfAfUfcugauucacuL96	2182	asGfsugaAfuCfAfgauaUfgAfuaccasgsu	2261	ACUGGUAUCAUAUCUGAUUCACA	2331
AD-1414074	uscsagagUfuUfCfUfggguuacuguL96	384	asCfsaguAfaCfCfcagaAfaCfucugasasg	518	CUUCAGAGUUUCUGGGUUACUGG	652
AD-1414139	asgsaauuUfgCfCfUfcuaaaccuuuL96	385	asAfsaggUfuUfAfgaggCfaAfauucusgsc	519	GCAGAAUUUGCCUCUAAACCUUG	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	csusgaagUfcCfUfGfcuauaccacuL96	2183	asGfsuggUfaUfAfgcagGfaCfuucagsgsu	2262	ACCUGAAGUCCUGCUAUACCACA	2332
AD-1414218	csusgcuaUfaCfCfAfcagaguucuuL96	1416	asAfsgaaCfuCfUfguggUfaUfagcagsgsa	2263	UCCUGCUAUACCACAGAGUUCUA	1939
AD-113751	usgscuauAfcCfAfCfagaguucuauL96	2184	asUfsagaAfcUfCfugugGfuAfuagcasgsg	2264	CCUGCUAUACCACAGAGUUCUAU	2333
AD-1414219	gscsuauaCfcAfCfAfgaguucuauuL96	2185	asAfsuagAfaCfUfcuguGfgUfauagcsasg	2265	CUGCUAUACCACAGAGUUCUAUG	2334
AD-113753	csusauacCfaCfAfGfaguucuauguL96	2186	asCfsauaGfaAfCfucugUfgGfuauagscsa	2266	UGCUAUACCACAGAGUUCUAUGU	2335
AD-1414220	usasuaccAfcAfGfAfguucuauguuL96	2187	asAfscauAfgAfAfcucuGfuGfguauasgsc	2267	GCUAUACCACAGAGUUCUAUGUA	1940
AD-1414221	asusaccaCfaGfAfGfuucuauguauL96	2188	asUfsacaUfaGfAfacucUfgUfgguausasg	2268	CUAUACCACAGAGUUCUAUGUAG	2336
AD-1414222	usasccacAfgAfGfUfucuauguaguL96	2189	asCfsuacAfuAfGfaacuCfuGfugguasusa	2269	UAUACCACAGAGUUCUAUGUAGC	1941
AD-113757	ascscacaGfaGfUfUfcuauguagcuL96	2190	asGfscuaCfaUfAfgaacUfcUfguggusasu	2270	AUACCACAGAGUUCUAUGUAGCU	2337
AD-113758	cscsacagAfgUfUfCfuauguagcuuL96	1419	asAfsgcuAfcAfUfagaaCfuCfuguggsusa	2271	UACCACAGAGUUCUAUGUAGCUU	1942
AD-1414223	csascagaGfuUfCfUfauguagcuuuL96	2191	asAfsagcUfaCfAfuagaAfcUfcugugsgsu	2272	ACCACAGAGUUCUAUGUAGCUUA	1943
AD-1414226	asgsaguuCfuAfUfGfuagcuuacauL96	1421	asUfsguaAfgCfUfacauAfgAfacucusgsu	2273	ACAGAGUUCUAUGUAGCUUACAG	1944
AD-113763	gsasguucUfaUfGfUfagcuuacaguL96	2192	asCfsuguAfaGfCfuacaUfaGfaacucsusg	2274	CAGAGUUCUAUGUAGCUUACAGU	2338
AD-113764	asgsuucuAfuGfUfAfgcuuacaguuL96	2193	asAfscugUfaAfGfcuacAfuAfgaacuscsu	2275	AGAGUUCUAUGUAGCUUACAGUU	1945
AD-1414229	uscsuaugUfaGfCfUfuacaguuccuL96	1423	asGfsgaaCfuGfUfaagcUfaCfauagasasc	2276	GUUCUAUGUAGCUUACAGUUCCA	1946
AD-1414230	csusauguAfgCfUfUfacaguuccauL96	2194	asUfsggaAfcUfGfuaagCfuAfcauagsasa	2277	UUCUAUGUAGCUUACAGUUCCAA	2339
AD-1414231	usasuguaGfcUfUfAfcaguuccaauL96	2195	asUfsuggAfaCfUfguaaGfcUfacauasgsa	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	usasgcuuAfcAfGfUfuccaaccaguL96	2196	asCfsuggUfuGfGfaacuGfuAfagcuascsa	2279	UGUAGCUUACAGUUCCAACCAGA	2341
AD-1414275	gsasauguGfaUfGfUfauuuuaauguL96	387	asCfsauuAfaAfAfuacaUfcAfcauucscsu	521	AGGAAUGUGAUGUAUUUUAAUGG	655
AD-113890	ascscuauUfgUfGfGfcuagauauauL96	2197	asUfsauaUfcUfAfgccaCfaAfuaggusgsg	2280	CCACCUAUUGUGGCUAGAUAUAU	2342
AD-113891	cscsuauuGfuGfGfCfuagauauauuL96	2198	asAfsuauAfuCfUfagccAfcAfauaggsusg	2281	CACCUAUUGUGGCUAGAUAUAUU	2343
AD-1414321	csusauugUfgGfCfUfagauauauuuL96	2199	asAfsauaUfaUfCfuagcCfaCfaauagsgsu	2282	ACCUAUUGUGGCUAGAUAUAUUA	1953
AD-1414322	usasuuguGfgCfUfAfgauauauuauL96	2200	asUfsaauAfuAfUfcuagCfcAfcaauasgsg	2283	CCUAUUGUGGCUAGAUAUAUUAG	2344
AD-1414323	asusugugGfcUfAfGfauauauuaguL96	2201	asCfsuaaUfaUfAfucuaGfcCfacaausasg	2284	CUAUUGUGGCUAGAUAUAUUAGG	2345
AD-1414324	ususguggCfuAfGfAfuauauuagguL96	2202	asCfscuaAfuAfUfaucuAfgCfcacaasusa	2285	UAUUGUGGCUAGAUAUAUUAGGA	2346
AD-113896	usgsuggcUfaGfAfUfauauuaggauL96	2203	asUfsccuAfaUfAfuaucUfaGfccacasasu	2286	AUUGUGGCUAGAUAUAUUAGGAU	2347
AD-1414325	gsusggcuAfgAfUfAfauauuaggauuL96	2204	asAfsuccUfaAfUfauauCfuAfgccacsasa	2287	UUGUGGCUAGAUAUAUUAGGAUC	2348
AD-1414326	gsgscuagAfuAfUfAfuuaggaucuuL96	1431	asAfsgauCfcUfAfauauAfuCfuagccsasc	2288	GUGGCUAGAUAUAUUAGGAUCUC	1954
AD-113900	gscsuagaUfaUfAfUfuaggaucucuL96	2205	asGfsagaUfcCfUfaauaUfaUfcuagcscsa	2289	UGGCUAGAUAUAUUAGGAUCUCU	2349
AD-1414544	cscsucugAfaAfUfGfuauguaaaguL96	391	asCfsuuuAfcAfUfacauUfuCfagaggsasc	525	GUCCUCUGAAAUGUAUGUAAAGA	659
AD-114455	csusguguUfaAfAfUfguuaacaguuL96	310	asAfscugUfuAfAfcauuUfaAfcacagscsg	444	CGCUGUGUUAAAUGUUAACAGUU	578
AD-114469	ascsaguuUfuCfCfAfcuauuucucuL96	311	asGfsagaAfaUfAfguggAfaAfacugususa	445	UAACAGUUUUCCACUAUUUCUCU	579

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

	100 nM		10 nM		1 nM	
Duplex	**Avg % messange remaining**	**SD**	**Avg % messange remaining**	**SD**	**Avg % messange 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 % messange remaining	SD	Avg % messange remaining	SD	Avg % messange 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 % messange remaining	SD	Avg % messange remaining	SD	Avg % messange 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 % messange remaining	SD	Avg % messange remaining	SD	Avg % messange 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 % messange remaining	SD	Avg % messange remaining	SD	Avg % messange 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 % messange remaining	SD	Avg % messange remaining	SD	Avg % messange 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 % messange remaining	SD	Avg % messange remaining	SD	Avg % messange 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 µl of Opti-MEM plus 0.1 µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) was added to 2.5 µl of each siRNA duplex to an individual well in a 384-well plate. The mixture was then incubated at room temperature for 15 minutes. Forty µl of complete growth media without antibiotic containing ~1.5 x10^4 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 H_2O 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	UUAACUUCCAUGAAUUCUAGU	792	2132-2152	ACUAGAAUUCAUGGAAGUUAACA	2425	2130-2152
AD-110931.1	AGAACUCAGUUCUCAAUUCUU	2350	2592-2612	AAGAAUUGAGAACUGAGUUCUUG	2426	2590-2612
AD-112393.1	UCCUACUCUCAAUGAUACUUU	2351	4630-4650	AAAGUAUCAUUGAGAGUAGGAGA	2427	4628-4650
AD-114469.2	ACAGUUUUCCACUAUUUCUCU	21	6911-6931	AGAGAAAUAGUGGAAAACUGUUA	22	6909-6931
AD-1410823.1	CCUCACACACAUCUAUUACUU	714	646-666	AAGUAAUAGAUGUGUGUGAGGCA	2054	644-666
AD-1411340.1	ACACACUCAAAAUCGUGUUCU	2352	1431-1451	AGAACACGAUUUUUGAGUGUGUCU	2428	1429-1451
AD-1411342.2	ACACUCAAAAUCGUGUUCAAU	76	1433-1453	AUUGAACACGAUUUUUGAGUGUGU	207	1431-1453
AD-1411797.1	GUUAACUUCCAUGAAUUCUAU	2353	2131-2151	AUAGAAUUCAUGGAAGUUAACAU	2429	2129-2151
AD-1411798.2	UAACUUCCAUGAAUUCUAGUU	82	2133-2153	AACUAGAAUUCAUGGAAGUUAAC	213	2131-2153
AD-1412539.2	UUUCUCAUUAAGACACGAAAU	95	3218-3238	AUUUCGUGUCUUAAUGAGAAACU	226	3216-3238
AD-1413196.1	CUACUCUCAAUGAUACUUUUU	2354	4632-4652	AAAAAGUAUCAUUGAGAGUAGGA	2430	4630-4652
AD-1414748.1	AACAGUUUUCCACUAUUUCUU	2355	6910-6930	AAGAAAUAGUGGAAAACUGUUAA	2431	6908-6930
AD-1452126.1	AUAUGUCUUUCAUGAUCUUGU	2356	8748-8768	ACAAGAUCAUGAAAGACAUAUAG	2432	8746-8768
AD-1452209.1	ACCAUCAAGGUUCACUUUAGU	2357	434-454	ACUAAAGUGAACCUUGAUGGUGU	2433	432-454
AD-1452212.1	AUCAAGGUUCACUUUAGAAAU	2358	437-457	AUUUCUAAAGUGAACCUUGAUGG	2434	435-457
AD-1452985.1	GUUUUCUAUUCACUUCAACGU	2359	943-963	ACGUUGAAGUGAAUAGAAAACAA	2435	941-963
AD-1453516.1	UGUCACAUCAGUUCUACAAGU	2360	1558-1578	ACUUGUAGAACUGAUGUGACAGC	2436	1556-1578
AD-1453784.1	CAUCAUGAACACUAUCAAUGU	2361	1897-1917	ACAUUGAUAGUGUUCAUGAUGUU	2437	1895-1917
AD-1454175.1	GACUCAUAUGAGAUUUAUCAU	2362	2216-2236	AUGAUAAAUCUCAUAUGAGUCUU	2438	2214-2236
AD-1454221.1	CUCGGAAAAUUUCAUGAUUCUU	2363	2262-2282	AAGAAUCAUGAAUUUUUCCGAGUU	2439	2260-2282
AD-1454350.1	UCUAAUCGAGGAUUUUCAACUU	2364	676-696	AAGUUGAAAAUCCUCGAUUAGAUU	2440	674-696
AD-1454529.1	CAAAAUCCUCAAGAAACCUUU	2365	2048-2068	AAAGGUUUCUUGAGGAUUUUGAG	2441	2046-2068
AD-1454534.1	UCCUCAAGAAACCUUAGUAAU	2366	2480-2500	AUUACUAAGGUUUCUUGAGGAUU	2442	2478-2500
AD-1454719.1	ACCCUUCAACAGAAUAUCAUU	2367	1817-1837	AAUGAUAUUCUGUUGAAGGGUUG	2443	1815-1837
AD-1454720.1	CCCUUCAACAGAAUAUCAUUU	2368	2608-2628	AAAUGAUAUUCUGUUGAAGGGUU	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-1454911.1	AAAUCCAAAGAAUACUUCUUU	2369	9068-9088	AAAGAAGUAUUCUUUGGAUUUGA	2445	9066-9088
AD-1455310.1	AAAGACUACUCAAUCAUUCAU	2370	2020-2040	AUGAAUGAUUGAGUAGUCUUUUC	2446	2018-2040
AD-1455313.1	AGACUACUCAAUCAUUCAUUU	2371	2022-2042	AAAUGAAUGAUUGAGUAGUCUUU	2447	2020-2042
AD-1455314.1	GACUACUCAAUCAUUCAUUAU	2372	4754-4774	AUAAUGAAUGAUUGAGUAGUCUU	2448	4752-4774
AD-1455522.1	AACACUCUCCAACAUUUCCUU	2373	4614-4634	AAGGAAAUGUUGGAGAGUGUUCC	2449	4612-4634
AD-1455659.1	GAUGAAGUCAACUCUACUUUU	2374	1514-1534	AAAAGUAGAGUUGACUUCAUCUU	2450	1512-1534
AD-1455664.1	AGUCAACUCUACUUUCACCUU	2375	1519-1539	AAGGUGAAAGUAGAGUUGACUUC	2451	1517-1539
AD-1455701.1	GACAUUAGUCAAACAUCUUUU	2376	7342-7362	AAAAGAUGUUUGACUAAUGUCAU	2452	7340-7362
AD-1455771.1	CCUUCCUCAGACUUAAAUCUU	2377	3150-3170	AAGAUUUAAGUCUGAGGAAGGGA	2453	3148-3170
AD-1455780.1	UCAGACUUAAAUCUCUUUACU	2378	3156-3176	AGUAAAGAGAUUUAAGUCUGAGG	2454	3154-3176
AD-1455807.1	GAAUUGGAUCAAACAAUAUU	2379	7300-7320	AAUAAUUGUUUGAUCCAAUUCUG	2455	7298-7320
AD-1457108.1	AUUAGGUCAUUCAGAAACUCU	2380	2351-2371	AGAGUUUCUGAAUGACCUAAUUC	2456	2349-2371
AD-1457130.1	GAAGAAGAGUACAAUCUUACU	2381	2387-2407	AGUAAGAUUGUACUCUUCUUCUU	2457	2385-2407
AD-1457237.1	UUCGAACACAGAUAUAAUUGU	2382	2443-2463	ACAAUUAUAUCUGUGUUCGAAGA	2458	2441-2463
AD-1458307.1	AAGCAAAUUACUGCAUCUUCU	2383	6383-6403	AGAAGAUGCAGUAAUUUGCUUGU	2459	6381-6403
AD-1458619.1	UCAUUGUUGCUUCAUAAAUCU	2384	3344-3364	AGAUUUAUGAAGCAACAAUGAAU	2460	3342-3364
AD-1458724.1	UAAUCAGAAUUCCUCGAAUGU	2385	3445-3465	ACAUUCGAGGAAUUCUGAUUAUG	2461	3443-3465
AD-1459277.1	UCUGAAUCUAGUCAGUUAUUU	2386	4544-4564	AAAUAACUGACUAGAUUCAGAAG	2462	4542-4564
AD-1459922.1	GAACUGAAUAUUCAAAAACCU	2387	6820-6840	AGGUUUUUGAAUAUUCAGUUCUA	2463	6818-6840
AD-1465918.3	AUGCCUCACACACAUCUAUUU	712	643-663	AAAUAGAUGUGTGUGAGGCAUGG	968	641-663
AD-1465918.4	AUGCCUCACACACAUCUAUUU	712	643-663	AAAUAGAUGUGTGUGAGGCAUGG	968	641-663
AD-1465919.2	UGCCUCACACACAUCUAUUAU	713	644-664	ATAATAGAUGUGUGUGAGGCAUG	969	642-664
AD-1465920.2	GCCUCACACACAUCUAUUACU	11	645-665	AGUAAUAGAUGTGUGUGAGGCAU	12	643-665
AD-1465921.2	CCUCACACACAUCUAUUACUU	714	646-666	AAGUAATAGAUGUGUGUGAGGCA	970	644-666
AD-1465922.3	CUCACACACAUCUAUUACUCU	13	647-667	AGAGTAAUAGATGUGUGUGAGGC	14	645-667
AD-1465922.4	CUCACACACAUCUAUUACUCU	13	647-667	AGAGTAAUAGATGUGUGUGAGGC	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	GACGUUUGACAAGCAAAUCGU	719	760-780	ACGATUTGCUUGUCAAACGUCUU	975	758-780
AD-1465932.3	AAUGUACACAGUCAAUGGAUU	724	835-855	AAUCCATUGACTGUGUACAUUAG	980	833-855
AD-1465932.4	AAUGUACACAGUCAAUGGAUU	724	835-855	AAUCCATUGACTGUGUACAUUAG	980	833-855
AD-1465953.3	GCAGGCUUACAUUGACAUUAU	745	1105-1125	AUAATGTCAAUGUAAGCCUGCAU	1001	1103-1125
AD-1465954.3	CAGGCUUACAUUGACAUUAAU	71	1106-1126	AUUAAUGUCAAUGUAAGCCUGCA	202	1104-1126
AD-1465960.3	UACAUUGACAUUAAAAACUGU	751	1112-1132	ACAGTUTUUAATGUCAAUGUAAG	1007	1110-1132
AD-1465968.3	CACCUGUAAUACCAGCGAAUU	759	1236-1256	AAUUCGCUGGUAUUACAGGUGCA	1015	1234-1256
AD-1465968.4	CACCUGUAAUACCAGCGAAUU	759	1236-1256	AAUUCGCUGGUAUUACAGGUGCA	1015	1234-1256
AD-1465969.2	UGUAAUACCAGCGAAUAUGGU	760	1240-1260	ACCATATUCGCTGGUAUUACAGG	1016	1238-1260
AD-1465970.2	GUAAUACCAGCGAAUAUGGAU	761	1241-1261	ATCCAUAUUCGCUGGUAUUACAG	1017	1239-1261
AD-1466053.3	UCGGAAUUCUUGGUCCUAUUU	113	5067-5087	AAAUAGGACCAAGAAUUCCGAGA	244	5065-5087
AD-1466070.2	GAGAGAAUUUGUCUUACUAUU	46	5443-5463	AAUAGUAAGACAAAUUCUCUCAU	177	5441-5463
AD-1466083.3	AAAGAAGAGCUGGUACUAUGU	871	5479-5499	ACAUAGTACCAGCUCUUCUUUUC	1127	5477-5499
AD-1466100.4	AUGCAAACGCCAUUUCUUAUU	888	5831-5851	AAUAAGAAAUGGCGUUUGCAUCC	1144	5829-5851
AD-1466100.5	AUGCAAACGCCAUUUCUUAUU	888	5831-5851	AAUAAGAAAUGGCGUUUGCAUCC	1144	5829-5851
AD-1466101.2	GCAAACGCCAUUUCUUAUCAU	889	5833-5853	ATGATAAGAAATGGCGUUUGCAU	1145	5831-5853
AD-1466104.3	UAAGCACUGGUAUCAUAUCUU	892	5883-5903	AAGATATGAUACCAGUGCUUAGU	1148	5881-5903
AD-1466104.4	UAAGCACUGGUAUCAUAUCUU	892	5883-5903	AAGATATGAUACCAGUGCUUAGU	1148	5881-5903
AD-1466114.4	CUGCUAUACCACACAGAGUUCUU	19	6106-6126	AAGAACTCUGUGGUAUAGCAGGA	20	6104-6126
AD-1466115.2	UAUACCACACAGAGUUCUAUGUU	901	6110-6130	AACATAGAACUCUGUGGUAUAGC	1157	6108-6130
AD-1466116.2	UACCACACAGAGUUCUAUGUAGU	902	6112-6132	ACUACATAGAACUCUGUGGUAUA	1158	6110-6132
AD-1466118.3	CACAGAGUUCUAUGUAGCUUU	904	6115-6135	AAAGCUACATAGAACUCUGUGGU	1160	6113-6135
AD-1466119.3	AGAGUUCUAUGUAGCUUACAU	905	6118-6138	AUGUAAGCUACATAGAACUCUGU	1161	6116-6138
AD-1466120.2	AGUUCUAUGUAGCUUACAGUU	906	6120-6140	AACUGUAAGCUACATAGAACUCU	1162	6118-6140
AD-1466121.3	UCUAUGUAGCUUACAGUUCCU	907	6123-6143	AGGAACTGUAAGCUACATAGAAC	1163	6121-6143
AD-1466128.3	CUAUUGUGGCUAGAUAUAUUU	914	6249-6269	AAAUAUAUCUAGCCACAATAGGU	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	CUAUUGUGGCUAGAUAUAUUU	914	6249-6269	AAAUAUAUCUAGCCACAAUAGGU	1170	6247-6269
AD-1466139.3	UCCAUGGUGGACAAGAUUUUU	924	6659-6679	AAAAAUCUUGUCCACCAUGGAGG	1180	6657-6679
AD-1466151.3	AAGAUUUUUGAAGGAAAUACU	936	6671-6691	AGUAUTUTCCUUCAAAAAUCUUGU	1192	6669-6691
AD-1466152.3	AGAUUUUUGAAGGAAAUACUU	937	6672-6692	AAGUAUTUCCUTCAAAAAUCUUG	1193	6670-6692
AD-1615169.1	CCACAAACUCAAGUUUGAAUU	60	291-311	AAUUCAAACUUGAGUUUGUGGGC	191	289-311
AD-1615170.1	AUCUUUCUGUAACUUCCUUUU	61	309-329	AAAAGGAAGUUACAGAAAGAUUC	192	307-329
AD-1615171.1	AGUAUGAACCAUAUUUUAAGU	15	348-368	ACUUAAAAAUAUGGUUCAUACUCU	16	346-368
AD-1615172.1	CUACCAUUUCAGGACUUCUUU	62	384-404	AAAGAAGUCCUGAAAUGGUAGAU	193	382-404
AD-1615173.1	CAUGCCUCACACACAUCUAUU	1990	642-662	AAUAGATGUGUGUGAGGCAUGGA	2464	640-662
AD-1615174.1	UCACACACAUCUAUUUACUCCU	66	648-668	AGGAGUAAUAGAUGUGUGUGAGG	197	646-668
AD-1615175.1	CAUCUAUUACUCCCAUGAAAU	1991	655-675	ATUUCATGGGAGUAAUAGAUGUG	2465	653-675
AD-1615176.1	UCUGAUCGAGGAUUUCAACUU	67	676-696	AAGUTGAAAUCCUCGAUCAGAUU	2466	674-696
AD-1615177.1	GGGACACAGAAGACGUUUGAU	1992	749-769	ATCAAACGUCUTCUGUGUCCCAC	2467	747-769
AD-1615178.1	GGACACAGAAGACGUUUGACU	1993	750-770	AGUCAAACGUCTUCUGUGUCCCA	2468	748-770
AD-1615179.1	GACACAGAAGACGUUUGACAU	1994	751-771	ATGUCAAACGUCUUCUGUGUCCC	2469	749-771
AD-1615180.1	GAAGACGUUUGACAAGCAAAU	717	757-777	ATUUGCTUGUCAAACGUCUUCUG	2470	755-777
AD-1615181.1	ACGUUUGACAAGCAAAUCGUU	1995	761-781	AACGAUTUGCUTGUCAAACGUCU	2471	759-781
AD-1615182.1	CGUUUGACAAGCAAAUCGUGU	1996	762-782	ACACGATUUGCTUGUCAAACGUC	2472	760-782
AD-1615183.1	GUUUGACAAGCAAAUCGUGCU	1997	763-783	AGCACGAUUUGCUUGUCAAACGU	2064	761-783
AD-1615184.1	UUUGACAAGCAAAUCGUGCUU	1998	764-784	AAGCACGAUUUGCUUGUCAAACG	2065	762-784
AD-1615185.1	CCUAAUGUACACAGUCAAUGU	1999	832-852	ACAUTGACUGUGUACAUUAGGGA	2473	830-852
AD-1615186.1	CUAAUGUACACAGUCAAUGGU	2000	833-853	ACCATUGACUGTGUACAUUAGGG	2474	831-853
AD-1615187.1	UAAUGUACACAGUCAAUGGAU	2001	834-854	ATCCAUTGACUGUGUACAUUAGG	2475	832-854
AD-1615188.1	AUUAUUCUCCAUUCAUUUCAU	70	940-960	ATGAAATGAAUGGAGAAUAAUUC	2476	938-960
AD-1615189.1	AAAGUGGAUCAUAUCUUCUCU	31	1057-1077	AGAGAAGAUAUGAUCCACUUUCC	162	1055-1077
AD-1615190.1	CCAGGAAUCUUAAGAAAAUAU	72	1143-1163	ATAUTUTCUUAAGAUUCCUGGUU	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	AGUAUUACAGGUGCAUAGUCCCA	2478	1226-1248
AD-1615192.1	GACUAUGCACCUGUAAUACCU	2003	1229-1249	AGGUAUUACAGGUGCAUAGUCCC	2479	1227-1249
AD-1615193.1	ACUAUGCACCUGUAAUACCAU	2004	1230-1250	ATGGTATUACAGGUGCAUAGUCC	2480	1228-1250
AD-1615194.1	CUAUGCACCUGUAAUACCAGU	2005	1231-1251	ACUGGUAUUACAGGUGCAUAGUC	2073	1229-1251
AD-1615195.1	GCACCUGUAAUACCAGCGAAU	2006	1235-1255	ATUCGCTGGUATUACAGGUGCAU	2481	1233-1255
AD-1615196.1	ACCUGUAAUACCAGCGAAUAU	2007	1237-1257	ATAUTCGCUGGTAUUACAGGUGC	2482	1235-1257
AD-1615197.1	CCUGUAAUACCAGCGAAUAUU	2008	1238-1258	AAUATUCGCUGGUAUUACAGGUG	2483	1236-1258
AD-1615198.1	CUGUAAUACCAGCGAAUAUGU	2009	1239-1259	ACAUAUTCGCUGGUAUUACAGGU	2484	1237-1259
AD-1615199.1	UAAUACCAGCGAAUAUGGACU	2010	1242-1262	AGUCCATAUUCGCUGGUAUUACA	2485	1240-1262
AD-1615200.1	UCAGCAUUUGGAUAAUUUCUU	73	1276-1296	AAGAAATUAUCCAAAUGCUGAGA	2486	1274-1296
AD-1615201.1	ACACUCAAAAAUCGUGUUCAAU	76	1433-1453	ATUGAACACGATUUUGAGUGUGU	2487	1431-1453
AD-1615202.1	UAAGUGGAACAUCUUAGAGUU	33	1594-1614	AACUCUAAGAUGUUCCACUUAUA	164	1592-1614
AD-1615203.1	UAACAAGACCAUACUACAGUU	78	1647-1667	AACUGUAGUAUGGUCUUGUUAAG	209	1645-1667
AD-1615204.1	CAUUCAUCUAUGGAAAGAGGU	81	2034-2054	ACCUCUTUCCATAGAUGAAUGAG	2488	2032-2054
AD-1615205.1	UUGGAACUUGGAUGUUAACUU	36	2118-2138	AAGUTAACAUCCAAGUUCCAACA	2489	2116-2138
AD-1615206.1	UAACUUCCAUGAAUUCUAGUU	82	2133-2153	AACUAGAAUUCAUGGAAGUUAAC	213	2131-2153
AD-1615207.1	CCGAAACUCAUCAUUGAAUCU	84	2362-2382	AGAUTCAAUGATGAGUUUCGGAA	2490	2360-2382
AD-1615208.1	UCAAACACAGAUAUAAUUGUU	38	2444-2464	AACAAUTAUAUCUGUGUUUGAAG	2491	2442-2464
AD-1615209.1	GUUGGUUCAAAUUAUUCUUCU	86	2462-2482	AGAAGAAUAAUTUGAACCAACAA	2492	2460-2482
AD-1615210.1	ACUCAGUUCUCAAUUCUUCCU	88	2595-2615	AGGAAGAAUUGAGAACUGAGUUC	219	2593-2615
AD-1615211.1	UACGUCUACUUUCACUUGGUU	89	2685-2705	AACCAAGUGAAAGUAGACGUAUC	220	2683-2705
AD-1615212.1	AAGUAACUCAUCUAAGAUUUU	39	2953-2973	AAAATCTUAGATGAGUUACUUUG	2493	2951-2973
AD-1615213.1	CUAGAGUUAGACAUAAAAUCUU	93	3150-3170	AAGATUTAUGUCUAACUCUAGGA	2494	3148-3170
AD-1615214.1	UUUCUCAUUAAGACACGAAAU	95	3218-3238	ATUUCGTGUCUTAAUGAGAAACU	2495	3216-3238
AD-1615215.1	UGAAGCCUACAACACAUUUUU	96	3304-3324	AAAAAUGUGUUGUAGGCUUCACU	227	3302-3324
AD-1615216.1	AAUCCAAUGAAACAUCUCUUU	97	3360-3380	AAAGAGAUGUUTCAUUGGAUUUA	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	UCAAAUGCACUCUACUUCAGU	100	3553-3573	ACUGAAGUAGAGUGCAUUUGAUC	231	3551-3573
AD-1615218.1	UACUCUCAAUGAUACUUUUCU	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	AAACAGAAGAAAUUAUUACAU	44	4876-4896	ATGUAATAAUUTCUUCUGUUUCC	2499	4874-4896
AD-1615222.1	AGCACUUUUACCAAACGUGAU	45	5021-5041	ATCACGTUUGGTAAAAGUGCUGU	2500	5019-5041
AD-1615223.1	UUAUCCAAGUUCGUUUUAAAU	114	5109-5129	ATUUAAAACGAACUUGGAUAACA	2501	5107-5129
AD-1615224.1	AUGCUGUUCAGCCAAAUAGCU	115	5238-5258	AGCUAUTUGGCTGAACAGCAUUA	2502	5236-5258
AD-1615225.1	UAGCAGUUAUACCUACGUAUU	116	5254-5274	AAUACGTAGGUAUAACUGCUAUU	2503	5252-5274
AD-1615226.1	GACAUUCACGUGGUUCACUUU	47	5657-5677	AAAGTGAACCACGUGAAUGUCUU	2504	5655-5677
AD-1615227.1	CUGGUUCAUUUAAAACUCUUU	117	5742-5762	AAAGAGTUUUAAAUGAACCAGGC	2505	5740-5762
AD-1615228.1	GAGCAGGGAUGCAAACGCCAU	2011	5823-5843	ATGGCGTUUGCAUCCCUGCUCUC	2506	5821-5843
AD-1615229.1	AGCAGGGAUGCAAACGCCAUU	2012	5824-5844	AAUGGCGUUUGCAUCCCUGCUCU	2082	5822-5844
AD-1615230.1	AGGGAUGCAAACGCCAUUUCU	2013	5827-5847	AGAAAUGGCGUTUGCAUCCCUGC	2507	5825-5847
AD-1615231.1	GGGAUGCAAACGCCAUUUCUU	2014	5828-5848	AAGAAATGGCGTUUGCAUCCCUG	2508	5826-5848
AD-1615232.1	GGAUGCAAACGCCAUUUCUUU	2015	5829-5849	AAAGAAAUGGCGUUUGCAUCCCU	2085	5827-5849
AD-1615233.1	GAUGCAAACGCCAUUUCUUAU	2016	5830-5850	ATAAGAAAUGGCGUUUGCAUCCC	2509	5828-5850
AD-1615234.1	UGCAAACGCCAUUUCUUAUCU	17	5832-5852	AGAUAAGAAAUGGCGUUUGCAUC	18	5830-5852
AD-1615235.1	CAAACGCCAUUUCUUAUCAUU	2017	5834-5854	AAUGAUAAGAAAUGGCGUUUGCA	2088	5832-5854
AD-1615236.1	AAACGCCAUUUCUUAUCAUGU	2018	5835-5855	ACAUGATAAGAAAUGGCGUUUGC	2510	5833-5855
AD-1615237.1	AACGCCAUUUCUUAUCAUGGU	2019	5836-5856	ACCATGAUAAGAAAUGGCGUUUG	2511	5834-5856
AD-1615238.1	ACGCCAUUUCUUAUCAUGGAU	2020	5837-5857	ATCCAUGAUAAGAAAUGGCGUUU	2512	5835-5857
AD-1615239.1	CGCCAUUUCUUAUCAUGGACU	2021	5838-5858	AGUCCATGAUAAGAAAUGGCGUU	2513	5836-5858
AD-1615240.1	AUGGGACUAAGCACUGGUAUU	2022	5876-5896	AAUACCAGUGCTUAGUCCCAUUG	2514	5874-5896
AD-1615241.1	UGGGACUAAGCACUGGUAUCU	2023	5877-5897	AGAUACCAGUGCUUAGUCCCAUU	2094	5875-5897
AD-1615242.1	GGGACUAAGCACUGGUAUCAU	2024	5878-5898	ATGATACCAGUGCUUAGUCCCAU	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	GGACUAAGCACUGGUAUCAUU	2025	5879-5899	AAUGAUACCAGUGCUUAGUCCCA	2516	5877-5899
AD-1615244.1	CUAAGCACUGGUAUCAUAUCU	2026	5882-5902	AGAUAUGAUACCAGUGCUUAGUC	2097	5880-5902
AD-1615245.1	AAGCACUGGUAUCAUAUCUGU	2027	5884-5904	ACAGAUAUGAUACCAGUGCUUAG	2099	5882-5904
AD-1615246.1	AGCACUGGUAUCAUAUCUGAU	2028	5885-5905	ATCAGATAUGATACCAGUGCUUA	2517	5883-5905
AD-1615247.1	GCACUGGUAUCAUAUCUGAUU	2029	5886-5906	AAUCAGAUAUGAUACCAGUGCUU	2101	5884-5906
AD-1615248.1	CACUGGUAUCAUAUCUGAUUU	2030	5887-5907	AAAUCAGAUAUGAUACCAGUGCU	2102	5885-5907
AD-1615249.1	UGGUAUCAUAUCUGAUUCACU	2031	5890-5910	AGUGAATCAGATAUGAUACCAGU	2518	5888-5910
AD-1615250.1	UCAGAGUUUCUGGGUUACUGU	119	5921-5941	ACAGTAACCCAGAAACUCUGAAG	2519	5919-5941
AD-1615251.1	AGAAUUUGCCUCUAAACCUUU	120	6010-6030	AAAGGUTUAGAGGCAAAUUCUGC	2520	6008-6030
AD-1615252.1	CUGAAGUCCUGCUAUACCACU	2032	6098-6118	AGUGGUAUAGCAGGACUUCAGGU	2104	6096-6118
AD-1615253.1	CUGCUAUACCACAGAGUUCUU	19	6106-6126	AAGAACTCUGUGGUAUAGCAGGA	20	6104-6126
AD-1615253.2	CUGCUAUACCACAGAGUUCUU	19	6106-6126	AAGAACTCUGUGGUAUAGCAGGA	20	6104-6126
AD-1615254.1	UGCUAUACCACAGAGUUCUAU	2033	6107-6127	ATAGAACUCUGTGGUAUAGCAGG	2521	6105-6127
AD-1615255.1	GCUAUACCACAGAGUUCUAUU	2034	6108-6128	AAUAGAACUCUGUGGUAUAGCAG	2107	6106-6128
AD-1615256.1	CUAUACCACAGAGUUCUAUGU	2035	6109-6129	ACAUAGAACUCTGUGGUAUAGCA	2522	6107-6129
AD-1615257.1	AUACCACAGAGUUCUAUGUAU	2036	6111-6131	ATACAUAGAACTCUGUGGUAUAG	2523	6109-6131
AD-1615258.1	ACCACAGAGUUCUAUGUAGCU	2037	6113-6133	AGCUACAUAGAACUCUGUGGUAU	2112	6111-6133
AD-1615259.1	CCACAGAGUUCUAUGUAGCUU	903	6114-6134	AAGCTACAUAGAACUCUGUGGUA	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	UCUAUGUAGCUUACAGUUCCU	907	6123-6143	AGGAACTGUAAGCUACAUAGAAC	1163	6121-6143
AD-1615262.2	UCUAUGUAGCUUACAGUUCCU	907	6123-6143	AGGAACTGUAAGCUACAUAGAAC	1163	6121-6143
AD-1615263.1	CUAUGUAGCUUACAGUUCCAU	2039	6124-6144	ATGGAACUGUAAGCUACAUAGAA	2526	6122-6144
AD-1615264.1	UAUGUAGCUUACAGUUCCAAU	2040	6125-6145	ATUGGAACUGUAAGCUACAUAGA	2527	6123-6145
AD-1615265.1	UAGCUUACAGUUCCAACCAGU	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	GAAUGUGAUGUAUUUUAAUGU	122	6184-6204	ACAUUAAAAUACAUCACAUUCCU	2529	6182-6204
AD-1615267.1	ACCUAUUGUGGCUAGAUAUAU	2042	6247-6267	ATAUAUCUAGCCACAAUAGGUGG	2530	6245-6267
AD-1615268.1	CCUAUUGUGGCUAGAUAUAUU	2043	6248-6268	AAUAUATCUAGCCACAAUAGGUG	2531	6246-6268
AD-1615269.1	UAUUGUGGCUAGAUAUAUUAU	2044	6250-6270	ATAATATAUCUAGCCACAAUAGG	2532	6248-6270
AD-1615270.1	AUUGUGGCUAGAUAUAUUAGU	2045	6251-6271	ACUAAUAUAUCTAGCCACAAUAG	2533	6249-6271
AD-1615271.1	UUGUGGCUAGAUAUAUUAGGU	2046	6252-6272	ACCUAATAUAUCUAGCCACAAUA	2534	6250-6272
AD-1615272.1	UGUGGCUAGAUAUAUUAGGAU	2047	6253-6273	ATCCTAAUAUATCUAGCCACAAU	2535	6251-6273
AD-1615273.1	GUGGCUAGAUAUAUUAGGAUU	2048	6254-6274	AAUCCUAAUAUAUCUAGCCACAA	2125	6252-6274
AD-1615274.1	GGCUAGAUAUAUUAGGAUCUU	915	6256-6276	AAGATCCUAAUAUAUCUAGCCAC	1171	6254-6276
AD-1615275.1	GCUAGAUAUAUUAGGAUCUCU	2049	6257-6277	AGAGAUCCUAATAUAUCUAGCCA	2536	6255-6277
AD-1615276.1	CCUCUGAAAUGUAUGUAAAGU	126	6579-6599	ACUUTACAUACAUUUCAGAGGAC	2537	6577-6599
AD-1615277.1	CUGUGUUAAAUGUUAACAGUU	48	6896-6916	AACUGUTAACATUUAACACAGCG	2538	6894-6916
AD-1615278.1	ACAGUUUUCCACUAUUUCUCU	21	6911-6931	AGAGAAAUAGUGGAAAACUGUUA	22	6909-6931
AD-1615279.1	AUGCAAACGCCAUUUCUUAUU	888	5831-5851	AAUAAGAAAUGGCGUUUGCAUCC	1144	5829-5851
AD-1615280.1	AUGCAAACGCCAUUUCUUAUA	2388	5831-5851	UAUAAGAAAUGGCGUUUGCAUCC	2539	5829-5851
AD-1615281.1	AUGCAAACGCCAUUUCUUAUA	2388	5831-5851	UAUAAGAAAUGGCGUUUGCAUCC	2539	5829-5851
AD-1615282.1	AUGCAAACGCCAUUUCUUAUA	2388	5831-5851	UAUAAGAAATGGCGUUUGCAUCC	2540	5829-5851
AD-1615283.1	AUGCAAUCGCCAUUUCUUAUA	2389	5831-5851	UAUAAGAAATGGCGAUUGCAUCC	2541	5829-5851
AD-1615284.1	AUGCAUACGCCAUUUCUUAUA	2390	5831-5851	UAUAAGAAATGGCGUAUGCAUCC	2542	5829-5851
AD-1615285.1	AUGCUAACGCCAUUUCUUAUA	2391	5831-5851	UAUAAGAAATGGCGUUAGCAUCC	2543	5829-5851
AD-1615286.1	GCAAACGCCAUUUCUUAUA	2392	5833-5851	UAUAAGAAATGGCGUUUGCGU	2544	5831-5851
AD-1615287.1	AUGCAAACGCCAUUUCUUAUU	888	5831-5851	AAUAAGAAAUGGCGUUUGCAUCC	1144	5829-5851
AD-1615288.1	AUGCAAACGCCAUUUCUUAUU	888	5831-5851	AAUAAGAAAUGGCGUUUGCAUCC	1144	5829-5851
AD-1615289.1	GCAAACGCCAUUUCUUAUU	2393	5833-5851	AAUAAGAAAUGGCGUUUGCGU	2545	5831-5851
AD-1615290.1	GCAAACGCCAUUUCUUAUU	2393	5833-5851	AAUAAGAAAUGGCGUUUGCGU	2545	5831-5851
AD-1615291.1	AUGCAAUCGCCAUUUCUUAUU	2394	5831-5851	AAUAAGAAAUGGCGAUUGCAUCC	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	AAUAAGAAAUGGCGAUUGCAUCC	2546	5829-5851
AD-1615293.1	AUGCAUACGCCAUUUCUUAUU	2395	5831-5851	AAUAAGAAAUGGCGUAUGCAUCC	2547	5829-5851
AD-1615294.1	AUGCAUACGCCAUUUCUUAUU	2395	5831-5851	AAUAAGAAAUGGCGUAUGCAUCC	2547	5829-5851
AD-1615295.1	AUGCUAACGCCAUUUCUUAUU	2396	5831-5851	AAUAAGAAAUGGCGUUAGCAUCC	2548	5829-5851
AD-1615296.1	AUGCUAACGCCAUUUCUUAUU	2396	5831-5851	AAUAAGAAAUGGCGUUAGCAUCC	2548	5829-5851
AD-1615297.1	AUGCAAACGCCAUUUCUUAUA	2388	5831-5851	UAUAAGAAAUGGCGUUUGCAUCC	2539	5829-5851
AD-1615298.1	GCAAACGCCAUUUCUUAUA	2392	5833-5851	UAUAAGAAAUGGCGUUUGCGU	2549	5831-5851
AD-1615299.1	AUGCAUACGCCAUUUCUUAUA	2390	5831-5851	UAUAAGAAAUGGCGUAUGCAUCC	2550	5829-5851
AD-1615300.1	AUGCCUCACACACAUUUAUUU	2397	643-663	AAAUAAAUGUGTGUGAGGCAUGG	2551	641-663
AD-1615301.1	CUCACACACAUCUAUUAUUCU	2398	647-667	AGAATAAUAGATGUGUGUGAGGC	2552	645-667
AD-1615302.1	CUCACACACAUCUAUUUCUCU	2399	647-667	AGAGAAAUAGATGUGUGUGAGGC	2553	645-667
AD-1615303.1	AAUGUACACAGUCAUUGGAUU	2400	835-855	AAUCCAAUGACTGUGUACAUUAG	2554	833-855
AD-1615304.1	GCAGGCUUACAUUGACAUUAU	745	1105-1125	ATAATGTCAAUGUAAGCCUGCAU	2555	1103-1125
AD-1615305.1	GCAGGCUUACAUUGAUAUUAU	2401	1105-1125	ATAATATCAAUGUAAGCCUGCAU	2556	1103-1125
AD-1615306.1	GCAGGCUUACAUUGUCAUUAU	2402	1105-1125	ATAATGACAAUGUAAGCCUGCAU	2557	1103-1125
AD-1615307.1	CAGGCUUACAUUGACAUUAAU	71	1106-1126	AUUAAUGUCAAUGUAAGCCUGCA	202	1104-1126
AD-1615308.1	CAGGCUUACAUUGACUUUAAU	2403	1106-1126	AUUAAAGUCAAUGUAAGCCUGCA	2558	1104-1126
AD-1615309.1	CAGGCUUACAUUGAUAUUAAU	23	1106-1126	AUUAAUAUCAAUGUAAGCCUGCA	2559	1104-1126
AD-1615310.1	CAGGCUUACAUUGACAUUAAU	71	1106-1126	AUUAAUGUCAAUGUAAGCCUGCG	2560	1104-1126
AD-1615311.1	CAGGCUUACAUUGACUUUAAU	2403	1106-1126	AUUAAAGUCAAUGUAAGCCUGCG	2561	1104-1126
AD-1615312.1	CAGGCUUACAUUGAUAUUAAU	23	1106-1126	AUUAAUAUCAAUGUAAGCCUGCG	24	1104-1126
AD-1615313.1	UACAUUGACAUUAAAAUACUGU	2404	1112-1132	ACAGTATUUAATGUCAAUGUAAG	2562	1110-1132
AD-1615314.1	UACAUUGACAUUAAUAACUGU	2405	1112-1132	ACAGTUAUUAATGUCAAUGUAAG	2563	1110-1132
AD-1615315.1	CACCUGUAAUACCAGUGAAUU	2406	1236-1256	AAUUCACUGGUAUUACAGGUGCA	2564	1234-1256
AD-1615316.1	CACCUGUAAUACCAUCGAAUU	2407	1236-1256	AAUUCGAUGGUAUUACAGGUGCA	2565	1234-1256
AD-1615317.1	CACCUGUAAUACCAGUGAAUU	2406	1236-1256	AAUUCACUGGUAUUACAGGUGCG	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	AAUUCGAUGGUAUUACAGGUGCG	2567	1234-1256
AD-1615319.1	UCGGAAUUCUUGGUCCUAUUU	113	5067-5087	AAAUAGGACCAAGAAUUCCGAGA	244	5065-5087
AD-1615320.1	UCGGAAUUCUUGGUCUUAUUU	2408	5067-5087	AAAUAAGACCAAGAAUUCCGAGA	2568	5065-5087
AD-1615321.1	UCGGAAUUCUUGGUUCUAUUU	2409	5067-5087	AAAUAGAACCAAGAAUUCCGAGA	2569	5065-5087
AD-1615322.1	UCGGAAUUCUUGGUCCUAUUU	113	5067-5087	AAAUAGGACCAAGAAUUCCGAGG	2570	5065-5087
AD-1615323.1	UCGGAAUUCUUGGUCUUAUUU	2408	5067-5087	AAAUAAGACCAAGAAUUCCGAGG	2571	5065-5087
AD-1615324.1	UCGGAAUUCUUGGUUCUAUUU	2409	5067-5087	AAAUAGAACCAAGAAUUCCGAGG	2572	5065-5087
AD-1615325.1	AAAGAAGAGCUGGUAUUAUGU	2410	5479-5499	ACAUAATACCAGCUCUUCUUUUC	2573	5477-5499
AD-1615326.1	AAAGAAGAGCUGGUUCUAUGU	2411	5479-5499	ACAUAGAACCAGCUCUUCUUUUC	2574	5477-5499
AD-1615327.1	UAAGCACUGGUAUCUUAUCUU	2412	5883-5903	AAGATAAGAUACCAGUGCUUAGU	2575	5881-5903
AD-1615328.1	CUGCUAUACCACACAGAUUUCUU	2413	6106-6126	AAGAAATCUGUGGUAUAGCAGGA	2576	6104-6126
AD-1615329.1	CUGCUAUACCACACAGUGUUCUU	2414	6106-6126	AAGAACACUGUGGUAUAGCAGGA	2577	6104-6126
AD-1615330.1	CUGCUAUACCACACAGAGUUCUU	19	6106-6126	AAGAACTCUGUGGUAUAGCAGGG	2578	6104-6126
AD-1615331.1	CUGCUAUACCACACAGAUUUCUU	2413	6106-6126	AAGAAATCUGUGGUAUAGCAGGG	2579	6104-6126
AD-1615332.1	CUGCUAUACCACACAGUGUUCUU	2414	6106-6126	AAGAACACUGUGGUAUAGCAGGG	2580	6104-6126
AD-1615333.1	AGAGUUCUAUGUAGUUUACAU	2415	6118-6138	ATGUAAACUACAUAGAACUCUGU	2581	6116-6138
AD-1615334.1	UCUAUGUAGCUUACAUUUCCU	2416	6123-6143	AGGAAATGUAAGCUACAUAGAAC	2582	6121-6143
AD-1615335.1	UCUAUGUAGCUUACUGUUCCU	2417	6123-6143	AGGAACAGUAAGCUACAUAGAAC	2583	6121-6143
AD-1615336.1	CUAUUGUGGCUAGAUUUAUUU	2418	6249-6269	AAAUAAAUCUAGCCACAAUAGGU	2584	6247-6269
AD-1615337.1	UCCAUGGUGGACAAGUUUUUU	2419	6659-6679	AAAAAACUUGUCCACCAUGGAGG	2585	6657-6679
AD-1615338.1	UCCAUGGUGGACAAUAUUUUU	2420	6659-6679	AAAAAUAUUGUCCACCAUGGAGG	2586	6657-6679
AD-1615339.1	AAGAUUUUUGAAGGAAAUACU	936	6671-6691	AGUATUTCCUUCAAAAAUCUUGU	1192	6669-6691
AD-1615340.1	AAGAUUUUUGAAGGAUAUACU	2421	6671-6691	AGUATATCCUUCAAAAAUCUUGU	2587	6669-6691
AD-1615341.1	AAGAUUUUUGAAGGUAAUACU	2422	6671-6691	AGUATUACCUUCAAAAAUCUUGU	2588	6669-6691
AD-1615342.1	AGAUUUUUGAAGGAAUUACUU	2423	6672-6692	AAGUAATUCCUTCAAAAAUCUUG	2589	6670-6692
AD-1615343.1	AGAUUUUUGAAGGAUAUACUU	2424	6672-6692	AAGUAUAUCCUTCAAAAAUCUUG	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	UUUAAUGUCAAUGUAAGCCUGCA	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	ususaacuUfcCfAfUfgaauucuaguL96	2591	asCfsuagAfaUfUfcaugGfaAfguuaascsa	2792	UGUUAACUUCCAUGAAUUCUAGU	1830
AD-110931.1	asgsaacuCfaGfUfUfcucaauucuuL96	2592	asAfsgaaUfuGfAfgaacUfgAfguucususg	2793	CAAGAACUCAGUUCUCAAUUCUU	3000
AD-112393.1	uscscuacUfcUfCfAfaugauacuuuL96	2593	asAfsaguAfuCfAfuugaGfaGfuaggasgsa	2794	UCUCCUACUCUCAAUGAUACUUU	3001
AD-114469.2	ascsaguuUfuCfCfAfcuauuucucuL96	311	asGfsagaAfaUfAfguggAfaAfacugususa	445	UAACAGUUUUCCACUAUUUCUCU	579
AD-1410823.1	cscsucacAfcAfCfAfucuauuacuuL96	2132	asAfsguaAfuAfGfauguGfuGfugaggscsa	2210	UGCCUCACACACAUCUAUUACUC	1751
AD-1411340.1	ascsacacUfcAfAfAfaucguguucuL96	2594	asGfsaacAfcGfAfuuuuGfaGfuguguscsu	2795	AGACACACUCAAAAUCGUGUUCA	3002
AD-1411342.2	ascsacucAfaAfAfUfcguguucaauL96	340	asUfsugaAfcAfCfgauuUfuGfagugusgsu	474	ACACACUCAAAAUCGUGUUCAAA	608
AD-1411797.1	gsusuaacUfuCfCfAfugaauucuauL96	2595	asUfsagaAfuUfCfauggAfaGfuuaacsasu	2796	AUGUUAACUUCCAUGAAUUCUAG	3003
AD-1411798.2	usasacuuCfcAfUfGfaauucuaguuL96	346	asAfscuaGfaAfUfucauGfgAfaguuasasc	480	GUUAACUUCCAUGAAUUCUAGUC	614
AD-1412539.2	ususucucAfuUfAfAfgacacgaaauL96	359	asUfsuucGfuGfUfcuuaAfuGfagaaascsu	493	AGUUUCUCAUUAAGACACGAAAA	627
AD-1413196.1	csusacucUfcAfAfUfgauacuuuuuL96	2596	asAfsaaaGfuAfUfcauuGfaGfaguagsgsa	2797	UCCUACUCUCAAUGAUACUUUUC	3004
AD-1414748.1	asascaguUfuUfCfCfacuauuucuuL96	2597	asAfsgaaAfuAfGfuggaAfaAfcuguusasa	2798	UUAACAGUUUUCCACUAUUUCUC	3005
AD-1452126.1	asusauguCfuUfUfCfaugaucuuguL96	2598	asCfsaagAfuCfAfugaaAfgAfcauausasg	2799	GGCAGGAUCUCUCUUGAUCUAGA	3006
AD-1452209.1	ascscaucAfaGfGfUfucacuuuaguL96	2599	asCfsuaaAfgUfGfaaccUfuGfauggusgsu	2800	ACAUCAUAAAAGUUCACUUUAAA	3007
AD-1452212.1	asuscaagGfuUfCfAfcuuuagaaauL96	2600	asUfsuucUfaAfAfgugaAfcCfuugausgsg	2801	UCAUAAAAGUUCACUUUAAAAAU	3008
AD-1452985.1	gsusuuucUfaUfUfCfacuucaacguL96	2601	asCfsguuGfaAfGfugaaUfaGfaaaacsasa	2802	UUAUUCUCCAUUCAUUUCAACGG	3009
AD-1453516.1	usgsucacAfuCfAfGfuucuacaaguL96	2602	asCfsuugUfaGfAfacugAfuGfugacasgsc	2803	AUGAUCAGAGCAGUUCAACCAGG	3010
AD-1453784.1	csasucauGfaAfCfAfcuaucaauguL96	2603	asCfsauuGfaUfAfguguUfcAfugaugsusu	2804	AACAUCAUGAGCACUAUCAAUGG	3011
AD-1454175.1	gsascucaUfaUfGfAfgauuuaucauL96	2604	asUfsgauAfaAfUfcucaUfaUfgagucsusu	2805	AAGACUCAUAUGAGAUUUUUGAA	3012
AD-1454221.1	csuscggaAfaAfUfUfcaugauucuuL96	2605	asAfsgaaUfcAfUfgaauUfuUfccgagsusu	2806	UACACGGAAAAUGCAUGAUCGUU	3013
AD-1454350.1	uscsuaauCfgAfGfGfauuucaacuuL96	2606	asAfsguuGfaAfAfuccuCfgAfuuagasusu	2807	AAUCUGAUCGAGGAUUUCAACUC	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	csasaaauCfcUfCfAfagaaaccuuuL96	2607	asAfsaggUfuUfCfuugaGfgAfuuuugsasg	2808	GAAAGAGGCAUGAGGACACCUUG	3014
AD-1454534.1	uscscucaAfgAfAfAfccuuaguaauL96	2608	asUfsuacUfaAfGfguuuCfuUfgaggasusu	2809	CUUCCCCAAGUAAUAUUAGUAAG	3015
AD-1454719.1	ascsccuuCfaAfCfAfgaauaucauuL96	2609	asAfsugaUfaUfUfcuguUfgAfagggususg	2810	GGUACCUUGAGGACAACAUCAAC	3016
AD-1454720.1	cscscuucAfaCfAfGfaauaucauuuL96	2610	asAfsaugAfuAfUfucugUfuGfaagggsusu	2811	AAUUCUUCCACAGCAGAGCAUUC	3017
AD-1454911.1	asasauccAfaAfGfAfauacuucuuuL96	2611	asAfsagaAfgUfAfuucuUfuGfgauuusgsa	2812	AUUGAUCUGGAAAAUACUUGUUU	3018
AD-1455310.1	asasagacUfaCfUfCfaaucauucauL96	2612	asUfsgaaUfgAfUfugagUfaGfucuuususc	2813	CACUUCACUGGGCACUCAUUCAU	3019
AD-1455313.1	asgsacuaCfuCfAfAfucauucauuuL96	2613	asAfsaugAfaUfGfauugAfgUfagucususu	2814	CUUCACUGGGCACUCAUUCAUCU	3020
AD-1455314.1	gsascuacUfcAfAfUfcauucauuauL96	2614	asUfsaauGfaAfUfgauuGfaGfuagucsusu	2815	AUGACUAUGCUGAAAUUGAUUAU	3021
AD-1455522.1	asascacuCfuCfCfAfacauuuccuuL96	2615	asAfsggaAfaUfGfuuggAfgAfguguuscsc	2816	GAUGCCAUCUCCUUCAUCUCCUA	3022
AD-1455659.1	gsasugaaGfuCfAfAfcucuacuuuuL96	2616	asAfsaagUfaGfAfguugAfcUfucaucsusu	2817	AAGAUGAAGUCAACUCUUCUUUC	3023
AD-1455664.1	asgsucaaCfuCfUfAfcuuucaccuuL96	2617	asAfsgguGfaAfAfguagAfgUfugacususc	2818	GAAGUCAACUCUUCUUUCACCUC	3024
AD-1455701.1	gsascauuAfgUfCfAfaacaucuuuuL96	2618	asAfsaagAfuGfUfuugaCfuAfaugucsasu	2819	AAAAAAACAGCCAAGCAUCUUUC	3025
AD-1455771.1	cscsuuccUfcAfGfAfcuuaaaucuuL96	2619	asAfsgauUfuAfAfgucuGfaGfgaaggsgsa	2820	UCCUAGAGUUAGACAUAAAUCUC	625
AD-1455780.1	uscsagacUfuAfAfAfucucuuuacuL96	2620	asGfsuaaAfgAfGfauuuAfaGfucugasgsg	2821	AGUUAGACAUAAAUCUCUACAAG	3026
AD-1455807.1	gsasauugGfaUfCfAfaacaauuauuL96	2621	asAfsuaaUfuGfUfuugaUfcCfaauucsusg	2822	GUCUUUCCCAUAUAACAAUGAUU	3027
AD-1457108.1	asusuaggUfcAfUfUfcagaaacucuL96	2622	asGfsaguUfuCfUfgaauGfaCfcuaaususc	2823	GAAUCAGGUCAUUCCGAAACUCA	3028
AD-1457130.1	gsasagaaGfaGfUfAfcaaucuuacuL96	2623	asGfsuaaGfaUfUfguacUfcUfucuucsusu	2824	AAGAAGAAGAGUUCAAUCUUACU	567
AD-1457237.1	ususcgaaCfaCfAfGfauauaauuguL96	2624	asCfsaauUfaUfAfucugUfgUfucgaasgsa	2825	UCUUCAAACACAGAUAUAAUUGU	3029
AD-1458307.1	asasgcaaAfuUfAfCfugcaucuucuL96	2625	asGfsaagAfuGfCfaguaAfuUfugcuusgsu	2826	ACAAGCAAAUCACAGCUUCUUCG	3030
AD-1458619.1	uscsauugUfuGfCfUfucauaaaucuL96	2626	asGfsauuUfaUfGfaagcAfaCfaaugasasu	2827	AUUCGUUGGUGCUUCAUAAAUCC	3031
AD-1458724.1	usasaucaGfaAfUfUfccucgaauguL96	2627	asCfsauuCfgAfGfgaauUfcUfgauuasusg	2828	CAUAAUCAGAAUUCCUCAAAUGA	3032
AD-1459277.1	uscsugaaUfcUfAfGfucaguuauuuL96	2628	asAfsauaAfcUfGfacuaGfaUfucagasasg	2829	CUUCUGAAUCUAGUCAGUCAUUG	640
AD-1459922.1	gsasacugAfaUfAfUfucaaaaaccuL96	2629	asGfsguuUfuUfGfaauaUfuCfaguucsusa	2830	UAGAAUUGAACAUUCAAAAACCC	3033
AD-1465918.3	asusgccucaCfAfCfacaucuauuuL96	1224	asdAsaudAgdAugugdTgUfgaggcausgsg	1484	CCAUGCCUCACACACAUCUAUUA	1748
AD-1465918.4	asusgccucaCfAfCfacaucuauuuL96	1224	asdAsaudAgdAugugdTgUfgaggcausgsg	1484	CCAUGCCUCACACACAUCUAUUA	1748
AD-1465919.2	usgsccucacAfCfAfcaucuauuauL96	1225	asdTsaadTadGaugudGuGfugaggcasusg	1485	CAUGCCUCACACACAUCUAUUAC	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	gscscucacaCfAfCfaucuauuacuL96	1226	asdGsuadAudAgaugdTgUfgugaggcsasu	1486	AUGCCUCACACACAUCUAUUACU	1750
AD-1465921.2	cscsucacacAfCfAfucuauuacuuL96	1227	asdAsgudAadTagaudGuGfugugaggscsa	1487	UGCCUCACACACAUCUAUUACUC	1751
AD-1465922.3	csuscacacaCfAfUfcuauuacucuL96	1228	asdGsagdTadAuagadTgUfgugugagsgsc	1488	GCCUCACACACAUCUAUUACUCC	1752
AD-1465922.4	csuscacacaCfAfUfcuauuacucuL96	1228	asdGsagdTadAuagadTgUfgugugagsgsc	1488	GCCUCACACACAUCUAUUACUCC	1752
AD-1465927.2	gsascguuugAfCfAfagcaaaucguL96	1233	asdCsgadTudTgcuudGuCfaaacgucsusu	1493	AAGACGUUUGACAAGCAAAUCGU	1757
AD-1465932.3	asasuguacaCfAfGfucaauggauuL96	1238	asdAsucdCadTugacdTgUfguacauusasg	1498	CUAAUGUACACAGUCAAUGGAUA	1762
AD-1465932.4	asasuguacaCfAfGfucaauggauuL96	1238	asdAsucdCadTugacdTgUfguacauusasg	1498	CUAAUGUACACAGUCAAUGGAUA	1762
AD-1465953.3	gscsaggcUfuAfCfAfuugacauuauL96	1259	asUfsaadTg(Tgn)caauguAfaGfccugcsasu	1519	AUGCAGGCUUACAUUGACAUUAA	1783
AD-1465954.3	csasggcuUfaCfAfUfugacauuaauL96	335	asUfsuadAu(G2p)ucaaugUfaAfgccugscsa	1520	UGCAGGCUUACAUUGACAUUAAA	603
AD-1465960.3	usascauugaCfAfUfuaaaaacuguL96	1265	asdCsagdTudTuuaadTgUfcaauguasasg	1526	CUUACAUUGACAUUAAAAACUGC	1789
AD-1465968.3	csasccuguaAfUfAfccagcgaauuL96	1273	asdAsuudCgdCuggudAuUfacaggugscsa	1534	UGCACCUGUAAUACCAGCGAAUA	1797
AD-1465968.4	csasccuguaAfUfAfccagcgaauuL96	1273	asdAsuudCgdCuggudAuUfacaggugscsa	1534	UGCACCUGUAAUACCAGCGAAUA	1797
AD-1465969.2	usgsuaauacCfAfGfcgaauaugguL96	1274	asdCscadTadTucgcdTgGfuauuacasgsg	1535	CCUGUAAUACCAGCGAAUAUGGA	1798
AD-1465970.2	gsusaauaccAfGfCfgaauauggauL96	1275	asdTsccdAudAuucgdCuGfguauuacsasg	1536	CUGUAAUACCAGCGAAUAUGGAC	1799
AD-1466053.3	uscsggaaUfuCfUfUfgguccuauuuL96	377	asAfsaudAg(G2p)accaagAfaUfuccgasgsa	1618	UCUCGGAAUUCUUGGUCCUAUUA	645
AD-1466070.2	gsasgagaauUfUfGfucuuacuauuL96	1373	asdAsuadGudAagacdAaAfuucucucsasu	1635	AUGAGAGAAUUUGUCUUACUAUU	576
AD-1466083.3	asasagaagaGfCfUfgguacuauguL96	1386	asdCsaudAgdTaccadGcUfcuucuuususc	1648	GAAAAGAAGAGCUGGUACUAUGA	1909
AD-1466100.4	asusgcaaacGfCfCfauuucuuauuL96	1403	asdAsuadAgdAaaugdGcGfuuugcauscsc	1665	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1466100.5	asusgcaaacGfCfCfauuucuuauuL96	1403	asdAsuadAgdAaaugdGcGfuuugcauscsc	1665	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1466101.2	gscsaaacgcCfAfUfuucuuaucauL96	1404	asdTsgadTadAgaaadTgGfcguuugcsasu	1666	AUGCAAACGCCAUUUCUUAUCAU	1927
AD-1466104.3	usasagcacuGfGfUfaucauaucuuL96	1407	asdAsgadTadTgauadCcAfgugcuuasgsu	1669	ACUAAGCACUGGUAUCAUAUCUG	1930
AD-1466104.4	usasagcacuGfGfUfaucauaucuuL96	1407	asdAsgadTadTgauadCcAfgugcuuasgsu	1669	ACUAAGCACUGGUAUCAUAUCUG	1930
AD-1466114.4	csusgcuaUfaCfCfAfcagaguucuuL96	1416	asAfsgadAc(Tgn)cuguggUfaUfagcagsgsa	1679	UCCUGCUAUACCACAGAGUUCUA	1939
AD-1466115.2	usasuaccacAfGfAfguucuauguuL96	1417	asdAscadTadGaacudCuGfugguauasgsc	1680	GCUAUACCACAGAGUUCUAUGUA	1940
AD-1466116.2	usasccacagAfGfUfucuauguaguL96	1418	asdCsuadCadTagaadCuCfugugguasusa	1681	UAUACCACAGAGUUCUAUGUAGC	1941
AD-1466118.3	csascagaguUfCfUfauguagcuuuL96	1420	asdAsagdCudAcauadGaAfcucugugsgsu	1683	ACCACAGAGUUCUAUGUAGCUUA	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	asgsaguuCfuAfUfGfuagcuuacauL96	1421	asUfsgudAa(G2p)cuacauAfgAfacucusgsu	1684	ACAGAGUUCUAUGUAGCUUACAG	1944
AD-1466120.2	asgsuucuauGfUfAfgcuuacaguuL96	1422	asdAscudGudAagcudAcAfuagaacuscsu	1685	AGAGUUCUAUGUAGCUUACAGUU	1945
AD-1466121.3	uscsuaugUfaGfCfUfuacaguuccuL96	1423	asGfsgadAc(Tgn)guaageUfaCfauagasasc	1686	GUUCUAUGUAGCUUACAGUUCCA	1946
AD-1466128.3	csusauugugGfCfUfagauauauuuL96	1430	asdAsaudAudAucuadGcCfacaauagsgsu	1693	ACCUAUUGUGGCUAGAUAUAUUA	1953
AD-1466128.4	csusauugugGfCfUfagauauauuuL96	1430	asdAsaudAudAucuadGcCfacaauagsgsu	1693	ACCUAUUGUGGCUAGAUAUAUUA	1953
AD-1466139.3	uscscauggguGfGfAfcaagauuuuuL96	1440	asdAsaadAudCuugudCcAfccauggasgsg	1704	CCUCCAUGGUGGACAAGAUUUUU	1963
AD-1466151.3	asasgauuUfuUfGfAfaggaaauacuL96	1452	asGfsuadTu(Tgn)ccuucaAfaAfaucuusgsu	1716	ACAAGAUUUUUGAAGGAAAUACU	1975
AD-1466152.3	asgsauuuuuGfAfAfggaaauacuuL96	1453	asdAsgudAudTuccudTcAfaaaaucususg	1717	CAAGAUUUUUGAAGGAAAUACUA	1976
AD-1615169.1	cscsacaaacUfCfAfaguuugaauuL96	2630	asdAsuudCadAacuudGaGfuuuguggsgsc	2831	GCCCACAAACUCAAGUUUGAAUC	591
AD-1615170.1	asuscuuucuGfUfAfacuuccuuuuL96	2631	asdAsaadGgdAaguudAcAfgaaagaususc	2832	GAAUCUUUCUGUAACUUCCUUUA	592
AD-1615171.1	asgsuaugaaCfCfAfuauuuuaaguL96	2632	asdCsuudAadAauaudGgUfucauacuscsu	2833	AGAGUAUGAACCAUAUUUUAAGA	593
AD-1615172.1	csusaccauuUfCfAfggacuucuuuL96	2633	asdAsagdAadGuccudGaAfaugguagsasu	2834	AUCUACCAUUUCAGGACUUCUUG	594
AD-1615173.1	csasugccucAfCfAfcacaucuauuL96	2634	asdAsuadGadTgugudGuGfaggcaugsgsa	2835	UCCAUGCCUCACACACAUCUAUU	2290
AD-1615174.1	uscsacacacAfUfCfuauuacuccuL96	2635	asdGsgadGudAauagdAuGfugugugasgsg	2836	CCUCACACACAUCUAUUACUCCC	598
AD-1615175.1	csasucuauuAfCfUfcccaugaaauL96	2636	asdTsuudCadTgggadGuAfauagaugsusg	2837	CACAUCUAUUACUCCCAUGAAAA	2291
AD-1615176.1	uscsugaucgAfGfGfauuucaacuuL96	2637	asdAsgudTgdAaaucdCuCfgaucagasusu	2838	AAUCUGAUCGAGGAUUUCAACUC	599
AD-1615177.1	gsgsgacacaGfAfAfgacguuugauL96	2638	asdTscadAadCgucudTcUfguguccsasc	2839	GUGGGACACAGAAGACGUUUGAC	2292
AD-1615178.1	gsgsacacagAfAfGfacguuugacuL96	2639	asdGsucdAadAcgucdTuCfuguguccscsa	2840	UGGGACACAGAAGACGUUUGACA	2293
AD-1615179.1	gsascacagaAfGfAfcguuugacauL96	2640	asdTsgudCadAacgudCuUfcuguguccsc	2841	GGGACACAGAAGACGUUUGACAA	2294
AD-1615180.1	gsasagacguUfUfGfacaagcaaauL96	2641	asdTsuudGcdTugucdAaAfcgucuucsusg	2842	CAGAAGACGUUUGACAAGCAAAU	1755
AD-1615181.1	ascsguuugaCfAfAfgcaaaucguuL96	2642	asdAscgdAudTugcudTgUfcaaacguscsu	2843	AGACGUUUGACAAGCAAAUCGUG	2295
AD-1615182.1	csgsuuugacAfAfGfcaaaucguguL96	2643	asdCsacdGadTuugcdTuGfucaaacgsusc	2844	GACGUUUGACAAGCAAAUCGUGC	2296
AD-1615183.1	gsusuugacaAfGfCfaaaucgugcuL96	2644	asdGscadCgdAuuugdCuUfgucaaacsgsu	2845	ACGUUUGACAAGCAAAUCGUGCU	2297
AD-1615184.1	ususugacaaGfCfAfaaucgugcuuL96	2645	asdAsgcdAcdGauuudGcUfugucaaascsg	2846	CGUUUGACAAGCAAAUCGUGCUA	2298
AD-1615185.1	cscsuaauguAfCfAfcagucaauguL96	2646	asdCsaudTgdAcugudGuAfcauuagsgsa	2847	UCCCUAAUGUACACAGUCAAUGG	2299
AD-1615186.1	csusaauguaCfAfCfagucaaugguL96	2647	asdCscadTudGacugdTgUfacauuagsgsg	2848	CCCUAAUGUACACAGUCAAUGGA	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	usasauguacAfCfAfgucaauggauL96	2648	asdTscccdAudTgacudGuGfuacauuasgsg	2849	CCUAAUGUACACAGUCAAUGGAU	2301
AD-1615188.1	asusuauucuCfCfAfuucauuucauL96	2649	asdTsgadAadTgaaudGgAfgaauaaususc	2850	GAAUUAUUCUCCAUUCAUUUCAA	602
AD-1615189.1	asasaguggaUfCfAfuaucuucucuL96	2650	asdGsagdAadGauauudGaUfccacuuuscsc	2851	GGAAAGUGGAUCAUAUCUUCUCU	561
AD-1615190.1	cscsaggaauCfUfUfaagaaaauauL96	2651	asdTsaudTudTcuuadAgAfuuccuggsusu	2852	AACCAGGAAUCUUAAGAAAAUAA	604
AD-1615191.1	gsgsacuaugCfAfCfcuguauaacuL96	2652	asdGsuadTudAcaggdTgCfauagucccsca	2853	UGGGACUAUGCACCUGUAAUACC	2302
AD-1615192.1	gsascuaugcAfCfCfuguaauaccuL96	2653	asdGsgudAudTacagdGuGfcauagucscsc	2854	GGGACUAUGCACCUGUAAUACCA	2303
AD-1615193.1	ascsuaugcaCfCfUfguaauaccauL96	2654	asdTsggdTadTuacadGgUfgcauaguscsc	2855	GGACUAUGCACCUGUAAUACCAG	2304
AD-1615194.1	csusaugcacCfUfGfuaauaccaguL96	2655	asdCsugdGudAuuacdAgGfugcauagsusc	2856	GACUAUGCACCUGUAAUACCAGC	2305
AD-1615195.1	gscsaccuguAfAfUfaccagcgaauL96	2656	asdTsucdGcdTgguadTuAfcaggugcsasu	2857	AUGCACCUGUAAUACCAGCGAAU	2306
AD-1615196.1	ascscuguaaUfAfCfcagcgaauauL96	2657	asdTsaudTcdGcuggdTaUfuacaggusgsc	2858	GCACCUGUAAUACCAGCGAAUAU	2307
AD-1615197.1	cscsuguaauAfCfCfagcgaauauuL96	2658	asdAsuadTudCgcugdGuAfuuacaggsusg	2859	CACCUGUAAUACCAGCGAAUAUG	2308
AD-1615198.1	csusguaauaCfCfAfgcgaauauguL96	2659	asdCsaudAudTcgcudGgUfauuacagsgsu	2860	ACCUGUAAUACCAGCGAAUAUGG	2309
AD-1615199.1	usasauaccaGfCfGfaauauggacuL96	2660	asdGsucdCadTauucdGcUfgguauuascsa	2861	UGUAAUACCAGCGAAUAUGGACA	2310
AD-1615200.1	uscsagcauuUfGfGfauaauucuuuL96	2661	asdAsgadAadTuaucdCaAfaugcugagsga	2862	UCUCAGCAUUUGGAUAAUUUCUC	605
AD-1615201.1	ascsacucaaAfAfUfcguguucaauL96	2662	asdTsugdAadCacgadTuUfugagugusgsu	2863	ACACACUCAAAAUCGUGUUCAAA	608
AD-1615202.1	usasaguggaAfCfAfucuuagaguuL96	2663	asdAscudCudAagaudGuUfccacuuasusa	2864	UAUAAGUGGAACAUCUUAGAGUU	563
AD-1615203.1	usasacaagaCfCfAfuacuacaguuL96	2664	asdAscudGudAguaudGgUfcuuguuasasg	2865	CUUAACAAGACCAUACUACAGUG	610
AD-1615204.1	csasuucauuUfAfUfggaaaggguL96	2665	asdCscudCudTuccadTaGfaugaauusasg	2866	CUCAUUCAUCUAUGGAAAGAGGC	613
AD-1615205.1	ususggaacuUfGfGfauguuaacuuL96	2666	asdAsgudTadAcaucdCaAfguuccaascsa	2867	UGUUGGAACUUGGAUGUUAACUU	566
AD-1615206.1	usasacuuccAfUfGfaauucuaguuL96	2667	asdAscudAgdAauucdAuGfgaaguuasasc	2868	GUUAACUUCCAUGAAUUCUAGUC	614
AD-1615207.1	cscsgaaacuCfAfUfcauugaaucuL96	2668	asdGsaudTcdAaugadTgAfguuucggsasa	2869	UUCCGAAACUCAUCAUUGAAUCA	616
AD-1615208.1	uscsaaacacAfGfAfuauaauuguuL96	2669	asdAscadAudTauaudCuGfuguuugasasg	2870	CUUCAAACACAGAUAUAAUUGUU	568
AD-1615209.1	gsusugguucAfAfAfuuauucuucuL96	2670	asdGsaadGadAuaaudTuGfaaccaacsasa	2871	UUGUUGGUUCAAAUUAUUCUUCC	618
AD-1615210.1	ascsucaguuCfUfCfaauucuuccuL96	2671	asdGsgadAgdAauugdAgAfacugagususc	2872	GAACUCAGUUCUCAAUUCUUCCA	620
AD-1615211.1	usascgucuaCfUfUfucacuuggguL96	2672	asdAsccdAadGugaadAgUfagacguasusc	2873	GAUACGUCUACUUUCACUUGGUG	621
AD-1615212.1	asasguaacuCfAfUfcuaagauuuuL96	2673	asdAsaadTcdTuagadTgAfguuacuususg	2874	CAAAGUAACUCAUCUAAGAUUUU	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	csusagaguuAfGfAfcauaaaucuuL96	2674	asdAsgadTudTaugudCuAfacucuagsgsa	2875	UCCUAGAGUUAGACAUAAAUCUC	625
AD-1615214.1	ususucucauUfAfAfgacacgaaauL96	2675	asdTsuudCgdTgucudTaAfugagaaascsu	2876	AGUUUCUCAUUAAGACACGAAAA	627
AD-1615215.1	usgsaagccuAfCfAfacacauuuuuL96	2676	asdAsaadAudGuguudGuAfggcuucascsu	2877	AGUGAAGCCUACAACACAUUUUC	628
AD-1615216.1	asasuccaauGfAfAfacaucucuuuL96	2677	asdAsagdAgdAuguudTcAfuuggauususa	2878	UAAAUCCAAUGAAACAUCUCUUC	629
AD-1615217.1	uscsaaaugcAfCfUfcuacuucaguL96	2678	asdCsugdAadGuagadGuGfcauuugasusc	2879	GAUCAAAUGCACUCUACUUCAGA	632
AD-1615218.1	usascucucaAfUfGfauacuuuucuL96	2679	asdGsaadAadGuaucdAuUfgagaguasgsg	2880	CCUACUCUCAAUGAUACUUUUCU	573
AD-1615219.1	csusaucaaaGfGfAfauuuaauccuL96	2680	asdGsgadTudAaauudCcUfuugauagsasa	2881	UUCUAUCAAAGGAAUUUAAUCCA	641
AD-1615220.1	ascsuaugcuGfAfAfauugauuauuL96	2681	asdAsuadAudCaauudTcAfgcauaguscsa	2882	UGACUAUGCUGAAAUUGAUUAUG	643
AD-1615221.1	asasacagaaGfAfAfauauuacacuL96	2682	asdTsgudAadTaauudTcUfucuguuuscsc	2883	GGAAACAGAAGAAAUUAUUACAU	574
AD-1615222.1	asgscacuuuUfAfCfcaaacgugauL96	2683	asdTscadCgdTuuggdTaAfaagugcusgsu	2884	ACAGCACUUUUACCAAACGUGAU	575
AD-1615223.1	ususauccaaGfUfUfcguuuuaaauL96	2684	asdTsuudAadAacgadAcUfuggauaascsa	2885	UGUUAUCCAAGUUCGUUUUAAAA	646
AD-1615224.1	asusgcuguuCfAfGfccaaauagcuL96	2685	asdGscudAudTuggcdTgAfacagcaususa	2886	UAAUGCUGUUCAGCCAAAUAGCA	647
AD-1615225.1	usasgcaguuAfUfAfccuacguauuL96	2686	asdAsuadCgdTaggudAuAfacugcuasusu	2887	AAUAGCAGUUAUACCUACGUAUG	648
AD-1615226.1	gsascauucaCfGfUfgguucacuuuL96	2687	asdAsagdTgdAaccadCgUfgaaugucsusu	2888	AAGACAUUCACGUGGUUCACUUU	577
AD-1615227.1	csusgguucaUfUfUfaaaacucuuuL96	2688	asdAsagdAgdTuuuadAaUfgaaccagsgsc	2889	GCCUGGUUCAUUUAAAACUCUUG	649
AD-1615228.1	gsasgcagggAfUfGfcaaacgccauL96	2689	asdTsggdCgdTuugcdAuCfccugcucsusc	2890	GAGAGCAGGGAUGCAAACGCCAU	2311
AD-1615229.1	asgscagggaUfGfCfaaacgccauuL96	2690	asdAsugdGcdGuuugdCaUfcccugcuscsu	2891	AGAGCAGGGAUGCAAACGCCAUU	2312
AD-1615230.1	asgsggaugcAfAfAfcgccauuucuL96	2691	asdGsaadAudGgcgudTuGfcaucccusgsc	2892	GCAGGGAUGCAAACGCCAUUUCU	2313
AD-1615231.1	gsgsgaugcaAfAfCfgccauuucuuL96	2692	asdAsgadAadTggcgdTuUfgcaucccsusg	2893	CAGGGAUGCAAACGCCAUUUCUU	2314
AD-1615232.1	gsgsaugcaaAfCfGfccauuucuuuL96	2693	asdAsagdAadAuggcdGuUfugcauccscsu	2894	AGGGAUGCAAACGCCAUUUCUUA	2315
AD-1615233.1	gsasugcaaaCfGfCfcauuucuuauL96	2694	asdTsaadGadAauggdCgUfuugcaucscsc	2895	GGGAUGCAAACGCCAUUUCUUAU	2316
AD-1615234.1	usgscaaacgCfCfAfuuucuuaucuL96	2695	asdGsaudAadGaaaudGgCfguuugcasusc	2896	GAUGCAAACGCCAUUUCUUAUCA	650
AD-1615235.1	csasaacgccAfUfUfucuuaucauuL96	2696	asdAsugdAudAagaadAuGfgcguuugscsa	2897	UGCAAACGCCAUUUCUUAUCAUG	2317
AD-1615236.1	asasacgccaUfUfUfcuuaucauguL96	2697	asdCsaudGadTaagadAaUfggcguuusgsc	2898	GCAAACGCCAUUUCUUAUCAUGG	2318
AD-1615237.1	asascgccauUfUfCfuuaucaugguL96	2698	asdCscadTgdAuaagdAaAfuggcguususg	2899	CAAACGCCAUUUCUUAUCAUGGA	2319
AD-1615238.1	ascsgccauuUfCfUfuaucauggauL96	2699	asdTsccdAudGauaadGaAfauggcgususu	2900	AAACGCCAUUUCUUAUCAUGGAC	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	csgsccauuuCfUfUfaucauggacuL96	2700	asdGsucdCadTgauadAgAfaauggcgsusu	2901	AACGCCAUUUCUUAUCAUGGACA	2321
AD-1615240.1	asusgggacuAfAfGfcacugguauuL96	2701	asdAsuadCcdAgugcdTuAfgucccaususg	2902	CAAUGGGACUAAGCACUGGUAUC	2322
AD-1615241.1	usgsggacuaAfGfCfacugguaucuL96	2702	asdGsaudAcdCagugdCuUfagucccasusu	2903	AAUGGGACUAAGCACUGGUAUCA	2323
AD-1615242.1	gsgsgacuaaGfCfAfcugguaucauL96	2703	asdTsgadTadCcagudGcUfuagucccsasu	2904	AUGGGACUAAGCACUGGUAUCAU	2324
AD-1615243.1	gsgsacuaagCfAfCfugguaucauuL96	2704	asdAsugdAudAccagdTgCfuuagucccsca	2905	UGGGACUAAGCACUGGUAUCAUA	2325
AD-1615244.1	csusaagcacUfGfGfuaucauaucuL96	2705	asdGsaudAudGauacdCaGfugcuuagsusc	2906	GACUAAGCACUGGUAUCAUAUCU	2326
AD-1615245.1	asasgcacugGfUfAfucauaucuguL96	2706	asdCsagdAudAugaudAcCfagugcuusasg	2907	CUAAGCACUGGUAUCAUAUCUGA	2327
AD-1615246.1	asgscacuggUfAfUfcauaucugauL96	2707	asdTscadGadTaugadTaCfcagugcususa	2908	UAAGCACUGGUAUCAUAUCUGAU	2328
AD-1615247.1	gscsacugguAfUfCfauaucugauuL96	2708	asdAsucdAgdAuaugdAuAfccagugcsusu	2909	AAGCACUGGUAUCAUAUCUGAUU	2329
AD-1615248.1	csascugguaUfCfAfuaucugauuuL96	2709	asdAsaudCadGauaudGaUfaccagugscsu	2910	AGCACUGGUAUCAUAUCUGAUUC	2330
AD-1615249.1	usgsguaucaUfAfUfcugauucacuL96	2710	asdGsugdAadTcagadTaUfgauaccasgsu	2911	ACUGGUAUCAUAUCUGAUUCACA	2331
AD-1615250.1	uscsagaguuUfCfUfggguuacuguL96	2711	asdCsagdTadAcccadGaAfacucugasasg	2912	CUUCAGAGUUUCUGGGUUACUGG	652
AD-1615251.1	asgsaauuugCfCfUfcuaaaccuuuL96	2712	asdAsagdGudTuagadGgCfaaauucusgsc	2913	GCAGAAUUUGCCUCUAAACCUUG	653
AD-1615252.1	csusgaagucCfUfGfcuauaccacuL96	2713	asdGsugdGudAuagcdAgGfacuucagsgsu	2914	ACCUGAAGUCCUGCUAUACCACA	2332
AD-1615253.1	csusgcuauaCfCfAfcagaguucuuL96	2714	asdAsgadAcdTcugudGgUfauagcagsgsa	2915	UCCUGCUAUACCACAGAGUUCUA	1939
AD-1615253.2	csusgcuauaCfCfAfcagaguucuuL96	2714	asdAsgadAcdTcugudGgUfauagcagsgsa	2915	UCCUGCUAUACCACAGAGUUCUA	1939
AD-1615254.1	usgscuauacCfAfCfagaguucuauL96	2715	asdTsagdAadCucugdTgGfuauagcasgsg	2916	CCUGCUAUACCACAGAGUUCUAU	2333
AD-1615255.1	gscsuauaccAfCfAfgaguucuauuL96	2716	asdAsuadGadAcucudGuGfguauagcsasg	2917	CUGCUAUACCACAGAGUUCUAUG	2334
AD-1615256.1	csusauaccaCfAfGfaguucuauguL96	2717	asdCsaudAgdAacucdTgUfgguauagscsa	2918	UGCUAUACCACAGAGUUCUAUGU	2335
AD-1615257.1	asusaccacaGfAfGfuucuauguauL96	2718	asdTsacdAudAgaacdTcUfgugguausasg	2919	CUAUACCACAGAGUUCUAUGUAG	2336
AD-1615258.1	ascscacagaGfUfUfcuauguagcuL96	2719	asdGscudAcdAuagadAcUfcuguggusasu	2920	AUACCACAGAGUUCUAUGUAGCU	2337
AD-1615259.1	cscsacagagUfUfCfuauguagcuuL96	2720	asdAsgcdTadCauagdAaCfucuguggsusa	2921	UACCACAGAGUUCUAUGUAGCUU	1942
AD-1615260.1	asgsaguucuAfUfGfuagcuuacauL96	2721	asdTsgudAadGcuacdAuAfgaacucusgsu	2922	ACAGAGUUCUAUGUAGCUUACAG	1944
AD-1615260.2	asgsaguucuAfUfGfuagcuuacauL96	2721	asdTsgudAadGcuacdAuAfgaacucusgsu	2922	ACAGAGUUCUAUGUAGCUUACAG	1944
AD-1615261.1	gsasguucuaUfGfUfagcuuacaguL96	2722	asdCsugdTadAgcuadCaUfagaacucsusg	2923	CAGAGUUCUAUGUAGCUUACAGU	2338
AD-1615262.1	uscsuauguaGfCfUfuacaguuccuL96	2723	asdGsgadAcdTguaadGcUfacauagasasc	2924	GUUCUAUGUAGCUUACAGUUCCA	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	uscsuauguaGfCfUfuacaguuccuL96	2723	asdGsgadAcdTguaadGcUfacauagasasc	2924	GUUCUAUGUAGCUUACAGUUCCA	1946
AD-1615263.1	csusauguagCfUfUfacaguuccauL96	2724	asdTsggdAadCuguadAgCfuacauagsasa	2925	UUCUAUGUAGCUUACAGUUCCAA	2339
AD-1615264.1	usasuguagcUfUfAfcaguuccaauL96	2725	asdTsugdGadAcugudAaGfcuacauasgsa	2926	UCUAUGUAGCUUACAGUUCCAAC	2340
AD-1615265.1	usasgcuuacAfGfUfuccaaccaguL96	2726	asdCsugdGudTggaadCuGfuaagcuascsa	2927	UGUAGCUUACAGUUCCAACCAGA	2341
AD-1615266.1	gsasaugugaUfGfUfauuuuaauguL96	2727	asdCsaudTadAaauadCaUfcacauucscsu	2928	AGGAAUGUGAUGUAUUUUAAUGG	655
AD-1615267.1	ascscuauugUfGfGfcuagauauauL96	2728	asdTsaudAudCuagcdCaCfaauaggusgsg	2929	CCACCUAUUGUGGCUAGAUAUAU	2342
AD-1615268.1	cscsuauuguGfGfCfuagauauauuL96	2729	asdAsuadTadTcuagdCcAfcaauaggsusg	2930	CACCUAUUGUGGCUAGAUAUAUU	2343
AD-1615269.1	usasuuguggCfUfAfgauauauuauL96	2730	asdTsaadTadTaucudAgCfcacaauasgsg	2931	CCUAUUGUGGCUAGAUAUAUUAG	2344
AD-1615270.1	asusuguggcUfAfGfauauauuaguL96	2731	asdCsuadAudAuaucdTaGfccacaausasg	2932	CUAUUGUGGCUAGAUAUAUUAGG	2345
AD-1615271.1	ususguggcuAfGfAfuauauuagguL96	2732	asdCscudAadTauaudCuAfgccacaasusa	2933	UAUUGUGGCUAGAUAUAUUAGGA	2346
AD-1615272.1	usgsuggcuaGfAfUfauauuaggauL96	2733	asdTsccdTadAuauadTcUfagccacasasu	2934	AUUGUGGCUAGAUAUAUUAGGAU	2347
AD-1615273.1	gsusggcuagAfUfAfuauuaggauuL96	2734	asdAsucdCudAauaudAuCfuagccacsasa	2935	UUGUGGCUAGAUAUAUUAGGAUC	2348
AD-1615274.1	gsgscuagauAfUfAfuuaggaucuuL96	2735	asdAsgadTcdCuaaudAuAfucuagccsasc	2936	GUGGCUAGAUAUAUUAGGAUCUC	1954
AD-1615275.1	gscsuagauaUfAfUfuaggaucucuL96	2736	asdGsagdAudCcuaadTaUfaucuagcscsa	2937	UGGCUAGAUAUAUUAGGAUCUCU	2349
AD-1615276.1	cscsucugaaAfUfGfuauguaaaguL96	2737	asdCsuudTadCauacdAuUfucagaggsasc	2938	GUCCUCUGAAAUGUAUGUAAAGA	659
AD-1615277.1	csusguguuaAfAfUfguuaacaguuL96	2738	asdAscudGudTaacadTuUfaacacagscsg	2939	CGCUGUGUUAAAUGUUAACAGUU	578
AD-1615278.1	ascsaguuuuCfCfAfcuauuucucuL96	2739	asdGsagdAadAuagudGgAfaaacugususa	2940	UAACAGUUUUCCACUAUUUCUCU	579
AD-1615279.1	asusgcaaAfcGfCfCfauuucuuauuL96	2165	asAfsuaaGfaaauggcGfuUfugcauscsc	2941	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615280.1	asusgcaaacGfCfCfauuucuuauaL96	2740	usdAsuadAgdAaaugdGcGfuuugcauscsc	2942	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615281.1	asusgcaaacGfCfCfauuucuuauaL96	2740	usdAsuadAgdAaauggcGfuuugcauscsc	2943	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615282.1	asusgcaaacGfCfCfauuucuuauaL96	2740	usdAsuadAgdAaadTggcGfuuugcauscsc	2944	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615283.1	asusgcaaucGfCfCfauuucuuauaL96	2741	usdAsuadAgdAaadTggcGfauugcauscsc	2945	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615284.1	asusgcauacGfCfCfauuucuuauaL96	2742	usdAsuadAgdAaadTggcGfuaugcauscsc	2946	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615285.1	asusgcuaacGfCfCfauuucuuauaL96	2743	usdAsuadAgdAaadTggcGfuuagcauscsc	2947	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615286.1	gscsaaacGfCfCfauuucuuauaL96	2744	usdAsuadAgdAaadTggcGfuuugcsgsu	2948	AUGCAAACGCCAUUUCUUAUC	3034
AD-1615287.1	asusgcaaacgCfCfAfuuucuuauuL96	2745	asdAsuadAgdAaaugdGcGfuuugcauscsc	1665	GGAUGCAAACGCCAUUUCUUAUC	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	asusgcaaacgCfCfdAuuucuuauuL96	2746	asdAsuadAgdAaaugdGcGfuuugcauscsc	1665	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615289.1	gscsaaacgCfCfAfuuucuuauuL96	2747	asdAsuadAgdAaaugdGcGfuuugcsgsu	2949	AUGCAAACGCCAUUUCUUAUC	3034
AD-1615290.1	gscsaaacgCfCfdAuuucuuauuL96	2748	asdAsuadAgdAaaugdGcGfuuugcsgsu	2949	AUGCAAACGCCAUUUCUUAUC	3034
AD-1615291.1	asusgcaaucgCfCfAfuuucuuauuL96	2749	asdAsuadAgdAaaugdGcGfauugcauscsc	2950	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615292.1	asusgcaaucgCfCfdAuuucuuauuL96	2750	asdAsuadAgdAaaugdGcGfauugcauscsc	2950	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615293.1	asusgcauacgCfCfAfuuucuuauuL96	2751	asdAsuadAgdAaaugdGcGfuaugcauscsc	2951	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615294.1	asusgcauacgCfCfdAuuucuuauuL96	2752	asdAsuadAgdAaaugdGcGfuaugcauscsc	2951	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615295.1	asusgcuaacgCfCfAfuuucuuauuL96	2753	asdAsuadAgdAaaugdGcGfuuagcauscsc	2952	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615296.1	asusgcuaacgCfCfdAuuucuuauuL96	2754	asdAsuadAgdAaaugdGcGfuuagcauscsc	2952	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615297.1	asusgcaaacgCfCfAfuuucuuauaL96	2755	usdAsuadAgdAaaugdGcGfuuugcauscsc	2942	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615298.1	gscsaaacgCfCfAfuuucuuauaL96	2756	usdAsuadAgdAaaugdGcGfuuugcsgsu	2953	AUGCAAACGCCAUUUCUUAUC	3034
AD-1615299.1	asusgcauacgCfCfAfuuucuuauaL96	2757	usdAsuadAgdAaaugdGcGfuaugcauscsc	2954	GGAUGCAAACGCCAUUUCUUAUC	1926
AD-1615300.1	asusgccucaCfAfCfacauuuauuuL96	2758	asdAsaudAadAugugdTgUfgaggcausgsg	2955	CCAUGCCUCACACACAUCUAUUA	1748
AD-1615301.1	csuscacacaCfAfUfcuauuauucuL96	2759	asdGsaadTadAuagadTgUfgugugagsgsc	2956	GCCUCACACACAUCUAUUACUCC	1752
AD-1615302.1	csuscacacaCfAfUfcuauuucucuL96	2760	asdGsagdAadAuagadTgUfgugugagsgsc	2957	GCCUCACACACAUCUAUUACUCC	1752
AD-1615303.1	asasuguacaCfAfGfucauuggauuL96	2761	asdAsucdCadAugacdTgUfguacauusasg	2958	CUAAUGUACACAGUCAAUGGAUA	1762
AD-1615304.1	gscsaggcuuAfCfAfuugacauuauL96	2762	asdTsaadTgdTcaaudGuAfagccugcsasu	2959	AUGCAGGCUUACAUUGACAUUAA	1783
AD-1615305.1	gscsaggcuuAfCfAfuugauauuauL96	2763	asdTsaadTadTcaaudGuAfagccugcsasu	2960	AUGCAGGCUUACAUUGACAUUAA	1783
AD-1615306.1	gscsaggcuuAfCfAfuugucauuauL96	2764	asdTsaadTgdAcaaudGuAfagccugcsasu	2961	AUGCAGGCUUACAUUGACAUUAA	1783
AD-1615307.1	csasggcuuaCfAfUfugacauuaauL96	2765	asUfsuadAudGucaaugUfaAfgccugscsa	2962	UGCAGGCUUACAUUGACAUUAAA	603
AD-1615308.1	csasggcuuaCfAfUfugacuuuaauL96	2766	asUfsuadAadGucaaugUfaAfgccugscsa	2963	UGCAGGCUUACAUUGACAUUAAA	603
AD-1615309.1	csasggcuuaCfAfUfugauauuaauL96	2767	asUfsuadAudAucaaugUfaAfgccugscsa	2964	UGCAGGCUUACAUUGACAUUAAA	603
AD-1615310.1	csasggcuuaCfAfUfugacauuaauL96	2765	asUfsuadAudGucaaugUfaAfgccugscsg	2965	UGCAGGCUUACAUUGACAUUAAA	603
AD-1615311.1	csasggcuuaCfAfUfugacuuuaauL96	2766	asUfsuadAadGucaaugUfaAfgccugscsg	2966	UGCAGGCUUACAUUGACAUUAAA	603
AD-1615312.1	csasggcuuaCfAfUfugauauuaauL96	2767	asUfsuadAudAucaaugUfaAfgccugscsg	2967	UGCAGGCUUACAUUGACAUUAAA	603
AD-1615313.1	usascauugaCfAfUfuaaauacuguL96	2768	asdCsagdTadTuuaadTgUfcaauguasasg	2968	CUUACAUUGACAUUAAAAACUGC	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	usascauugaCfAfUfuaauaacuguL96	2769	asdCsagdTudAuuaadTgUfcaauguasasg	2969	CUUACAUUGACAUUAAAAACUGC	1789
AD-1615315.1	csasccuguaAfUfAfccagugaauuL96	2770	asdAsuudCadCuggudAuUfacaggugscsa	2970	UGCACCUGUAAUACCAGCGAAUA	1797
AD-1615316.1	csasccuguaAfUfAfccaucgaauuL96	2771	asdAsuudCgdAuggudAuUfacaggugscsa	2971	UGCACCUGUAAUACCAGCGAAUA	1797
AD-1615317.1	csasccuguaAfUfAfccagugaauuL96	2770	asdAsuudCadCuggudAuUfacaggugscsg	2972	UGCACCUGUAAUACCAGCGAAUA	1797
AD-1615318.1	csasccuguaAfUfAfccaucgaauuL96	2771	asdAsuudCgdAuggudAuUfacaggugscsg	2973	UGCACCUGUAAUACCAGCGAAUA	1797
AD-1615319.1	uscsggaauuCfUfUfgguccuauuuL96	2772	asdAsaudAgdGaccadAgAfauuccgasgsa	2974	UCUCGGAAUUCUUGGUCCUAUUA	645
AD-1615320.1	uscsggaauuCfUfUfggucuuauuuL96	2773	asdAsaudAadGaccadAgAfauuccgasgsa	2975	UCUCGGAAUUCUUGGUCCUAUUA	645
AD-1615321.1	uscsggaauuCfUfUfgguucuauuuL96	2774	asdAsaudAgdAaccadAgAfauuccgasgsa	2976	UCUCGGAAUUCUUGGUCCUAUUA	645
AD-1615322.1	uscsggaauuCfUfUfgguccuauuuL96	2772	asdAsaudAgdGaccadAgAfauuccgasgsg	2977	UCUCGGAAUUCUUGGUCCUAUUA	645
AD-1615323.1	uscsggaauuCfUfUfggucuuauuuL96	2773	asdAsaudAadGaccadAgAfauuccgasgsg	2978	UCUCGGAAUUCUUGGUCCUAUUA	645
AD-1615324.1	uscsggaauuCfUfUfgguucuauuuL96	2774	asdAsaudAgdAaccadAgAfauuccgasgsg	2979	UCUCGGAAUUCUUGGUCCUAUUA	645
AD-1615325.1	asasagaagaGfCfUfgguauuauguL96	2775	asdCsaudAadTaccadGcUfcuucuuususc	2980	GAAAAGAAGAGCUGGUACUAUGA	1909
AD-1615326.1	asasagaagaGfCfUfgguucuauguL96	2776	asdCsaudAgdAaccadGcUfcuucuuususc	2981	GAAAAGAAGAGCUGGUACUAUGA	1909
AD-1615327.1	usasagcacuGfGfUfaucuuaucuuL96	2777	asdAsgadTadAgauadCcAfgugcuuasgsu	2982	ACUAAGCACUGGUAUCAUAUCUG	1930
AD-1615328.1	csusgcuauaCfCfAfcagauuucuuL96	2778	asdAsgadAadTcugudGgUfauagcagsgsa	2983	UCCUGCUAUACCACAGAGUUCUA	1939
AD-1615329.1	csusgcuauaCfCfAfcaguguucuuL96	2779	asdAsgadAcdAcugudGgUfauagcagsgsa	2984	UCCUGCUAUACCACAGAGUUCUA	1939
AD-1615330.1	csusgcuauaCfCfAfcagaguucuuL96	2714	asdAsgadAcdTcugudGgUfauagcagsgsg	2985	UCCUGCUAUACCACAGAGUUCUA	1939
AD-1615331.1	csusgcuauaCfCfAfcagauuucuuL96	2778	asdAsgadAadTcugudGgUfauagcagsgsg	2986	UCCUGCUAUACCACAGAGUUCUA	1939
AD-1615332.1	csusgcuauaCfCfAfcaguguucuuL96	2779	asdAsgadAcdAcugudGgUfauagcagsgsg	2987	UCCUGCUAUACCACAGAGUUCUA	1939
AD-1615333.1	asgsaguucuAfUfGfuaguuuacauL96	2780	asdTsgudAadAcuacdAuAfgaacucusgsu	2988	ACAGAGUUCUAUGUAGCUUACAG	1944
AD-1615334.1	uscsuauguaGfCfUfuacauuuccuL96	2781	asdGsgadAadTguaadGcUfacauagasasc	2989	GUUCUAUGUAGCUUACAGUUCCA	1946
AD-1615335.1	uscsuauguaGfCfUfuacuguuccuL96	2782	asdGsgadAcdAguaadGcUfacauagasasc	2990	GUUCUAUGUAGCUUACAGUUCCA	1946
AD-1615336.1	csusauugugGfCfUfagauuuauuuL96	2783	asdAsaudAadAucuadGcCfacaauagsgsu	2991	ACCUAUUGUGGCUAGAUAUAUUA	1953
AD-1615337.1	uscscaugguGfGfAfcaaguuuuuuL96	2784	asdAsaadAadCuugudCcAfccauggasgsg	2992	CCUCCAUGGUGGACAAGAUUUUU	1963
AD-1615338.1	uscscaugguGfGfAfcaauauuuuuL96	2785	asdAsaadAudAuugudCcAfccauggasgsg	2993	CCUCCAUGGUGGACAAGAUUUUU	1963
AD-1615339.1	asasgauuuuUfGfAfaggaaauacuL96	2786	asdGsuadTudTccuudCaAfaaaucuusgsu	2994	ACAAGAUUUUUGAAGGAAAUACU	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	asasgauuuuUfGfAfaggauauacuL96	2787	asdGsuadTadTccuudCaAfaaaucuusgsu	2995	ACAAGAUUUUUGAAGGAAAUACU	1975
AD-1615341.1	asasgauuuuUfGfAfagguaauacuL96	2788	asdGsuadTudAccuudCaAfaaaucuusgsu	2996	ACAAGAUUUUUGAAGGAAAUACU	1975
AD-1615342.1	asgsauuuuuGfAfAfggaauuacuuL96	2789	asdAsgudAadTuccudTcAfaaaaucususg	2997	CAAGAUUUUUUGAAGGAAAUACUA	1976
AD-1615343.1	asgsauuuuuGfAfAfggauauacuuL96	2790	asdAsgudAudAuccudTcAfaaaaucususg	2998	CAAGAUUUUUUGAAGGAAAUACUA	1976
AD-1109630.1	csasggcuUfaCfAfUfugacauuaaaL96	2791	usUfsuaaUfgUfCfaaugUfaAfgccugscsa	2999	UGCAGGCUUACAUUGACAUUAAA	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

	10 nM		1 nM		0.1 nM	
Duplex	**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 form 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 Biologics (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.

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'-CAGGCUUACAUUGACAUUAAA-3' (SEQ ID NO: 9) and an antisense strand comprising the nucleotide sequence 5'-UUUAAUGUCAAUGUAAGCCUGCA-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'- ACUUAAAAUAUGGUUCAUACUCU -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'- AGAUAAGAAAUGGCGUUUGCAUC -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'- AAGAACTCUGUGGUAUAGCAGGA -3' (SEQ ID NO: 20);

AD-1615278 comprising a sense strand comprising the nucleotide sequence 5'-ACAGUUUUCCACUAUUUCUCU -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'-CAGGCUUACAUUGAUAUUAAU -3' (SEQ ID NO: 23) and an antisense strand comprising the nucleotide sequence 5'- AUUAAUAUCAAUGUAAGCCUGCG -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 comprise a modification; all of the nucleotides of the antisense strand comprise a modification; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

10. The dsRNA agent of any one of claims 7-9, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythimidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

11. The dsRNA agent of any one of claims 7-9, wherein the modifications on the nucleotides are selected from the group consisting of LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C- allyl, 2'-fluoro, 2'-deoxy, 2'-hydroxyl, and 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), 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 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 nucleotide pairs in length.

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

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

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

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

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

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

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

23. The dsRNA agent of any one of claims 1-21, wherein the region of complementarity is between 19 and 23 nucleotides in length.

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' 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.

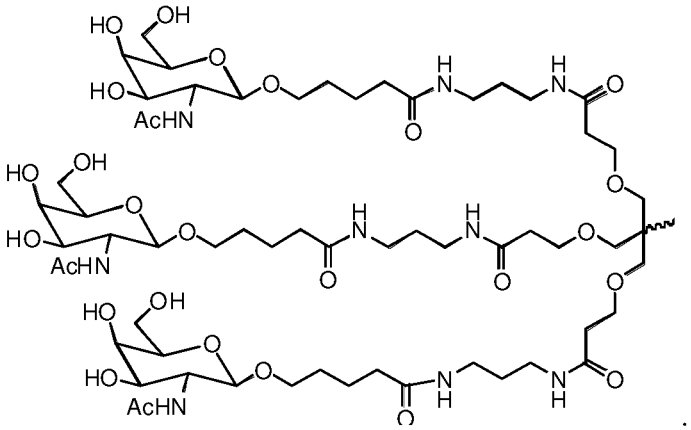
27. The dsRNA agent of any one of claims 1-26, further comprising a ligand.

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

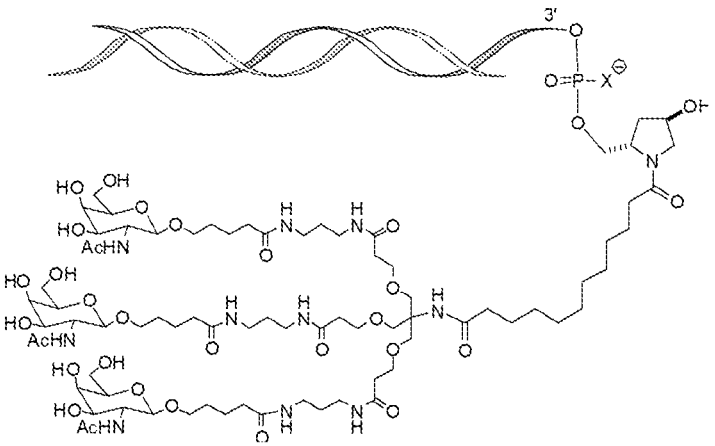
29. The dsRNA agent of claim 27 or 28, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

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

31. The dsRNA agent of claim 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



and, wherein X is O or S.

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

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

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

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

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

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

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

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

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

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

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

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

45. A pharmaceutical composition for inhibiting expression of a gene encoding coagulation Factor V (F5) comprising the dsRNA agent of any one of claims 1-43.

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

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

48. The pharmaceutical composition of claim 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, plurpura 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 roup consisting of venous thrombosis, deep vein thrombosis, genetic thrombophilia, Factor V leiden, prothrombin thrombophilia, plurpura 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.

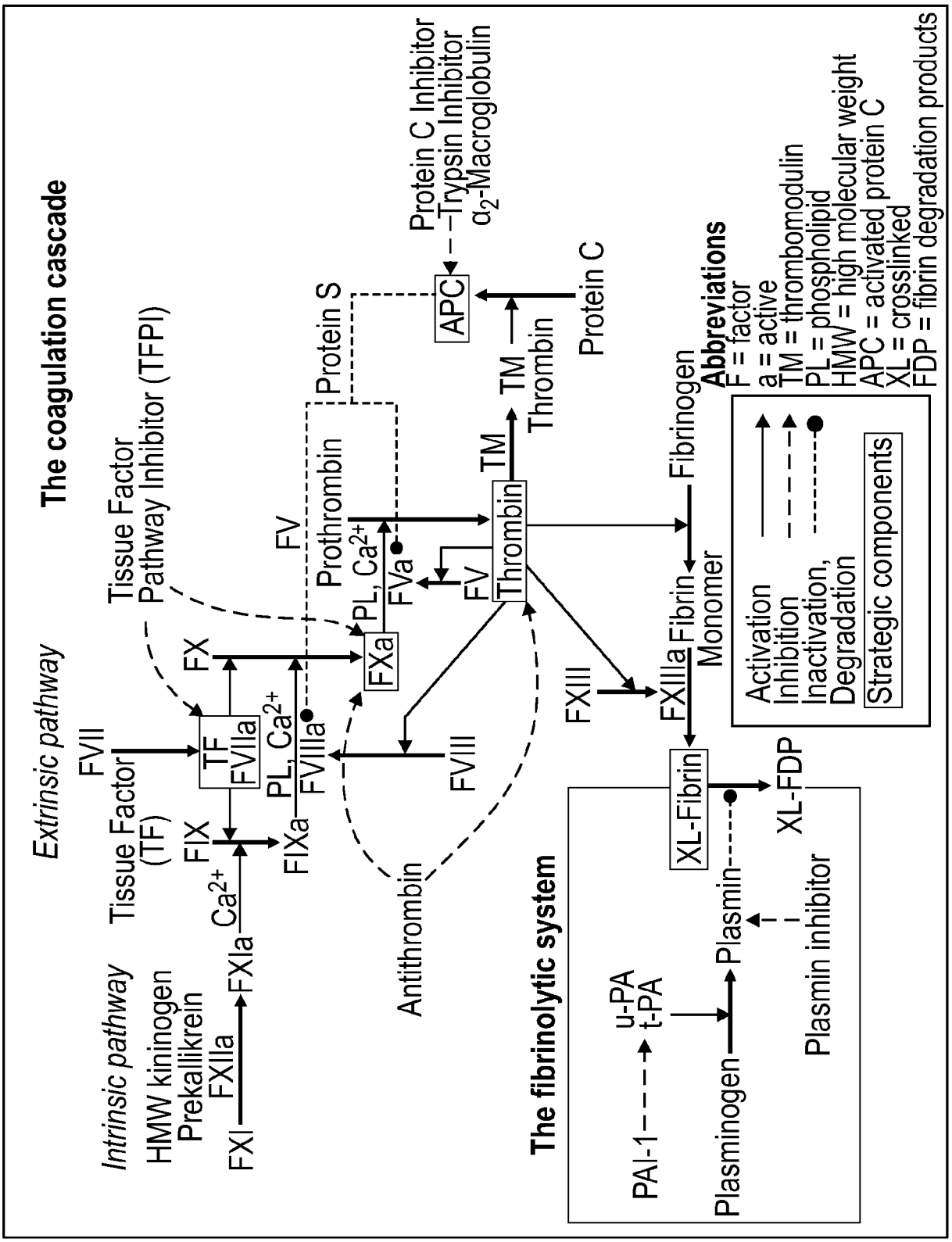
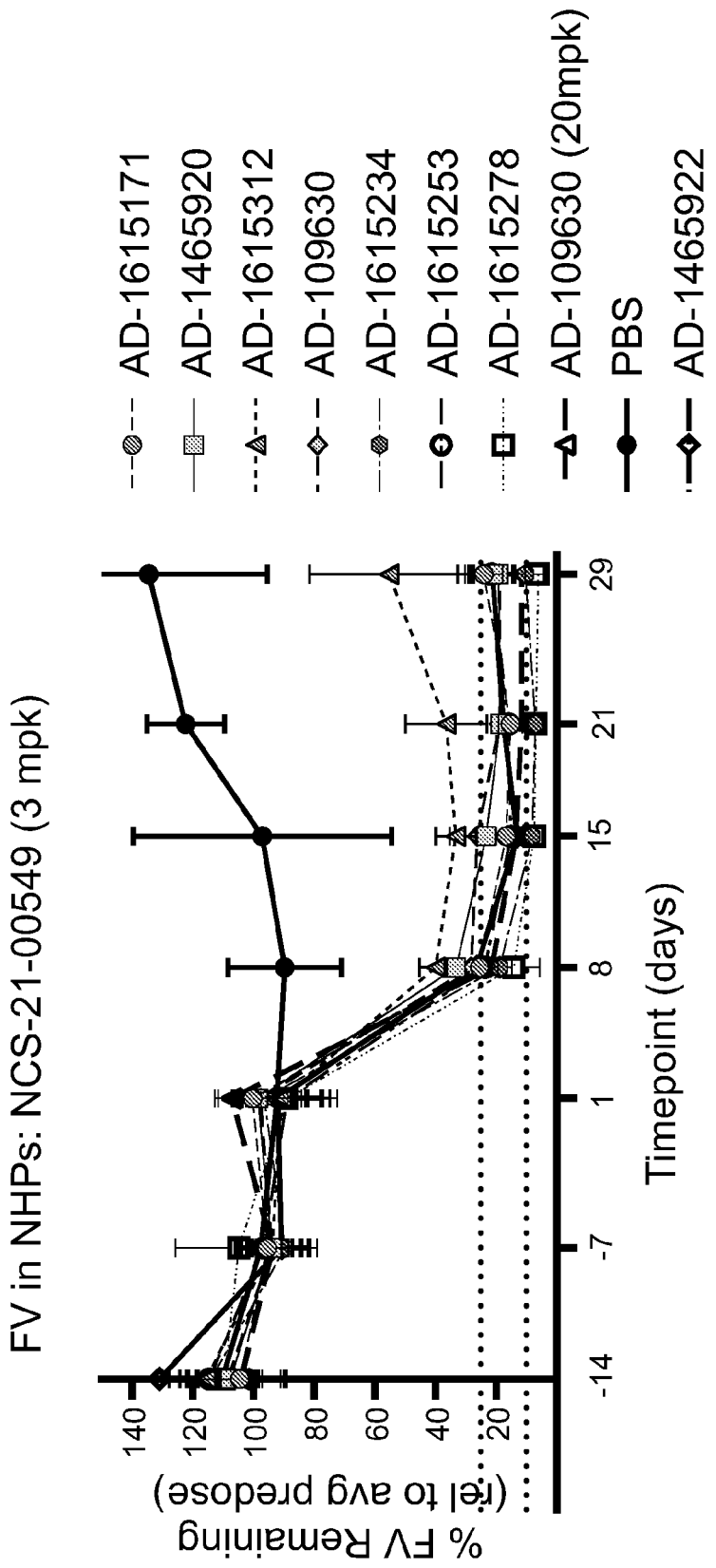

The coagulation cascade
Extrinsic pathway
Intrinsic pathway
FVII
Tissue Factor (TF)
TF FVIIa
FIX
FIXa
FX
FXa
PL, Ca2+
FVIIIa
FVIII
FXI
FXIa
HMW kininogen
Prekallikrein
FXIIa
Ca2+
Tissue Factor Pathway Inhibitor (TFPI)
FV
Prothrombin
Thrombin
FVa
Protein S
APC
Protein C Inhibitor
Trypsin Inhibitor
α2-Macroglobulin
TM
Protein C
Antithrombin
FXIII
FXIIIa
Fibrin Monomer
Fibrinogen
XL-Fibrin
XL-FDP
The fibrinolytic system
u-PA
t-PA
PAI-1
Plasminogen
Plasmin
Plasmin inhibitor
Abbreviations
F = factor
a = active
TM = thrombomodulin
PL = phospholipid
HMW = high molecular weight
APC = activated protein C
XL = crosslinked
FDP = fibrin degradation products
Activation
Inhibition
Inactivation, Degradation
Strategic components

FIG. 1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(rel to avg predose)
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120
100
80
60
40
20
-14
-7
1
8
15
21
29
Timepoint (days)
AD-1615171
AD-1465920
AD-1615312
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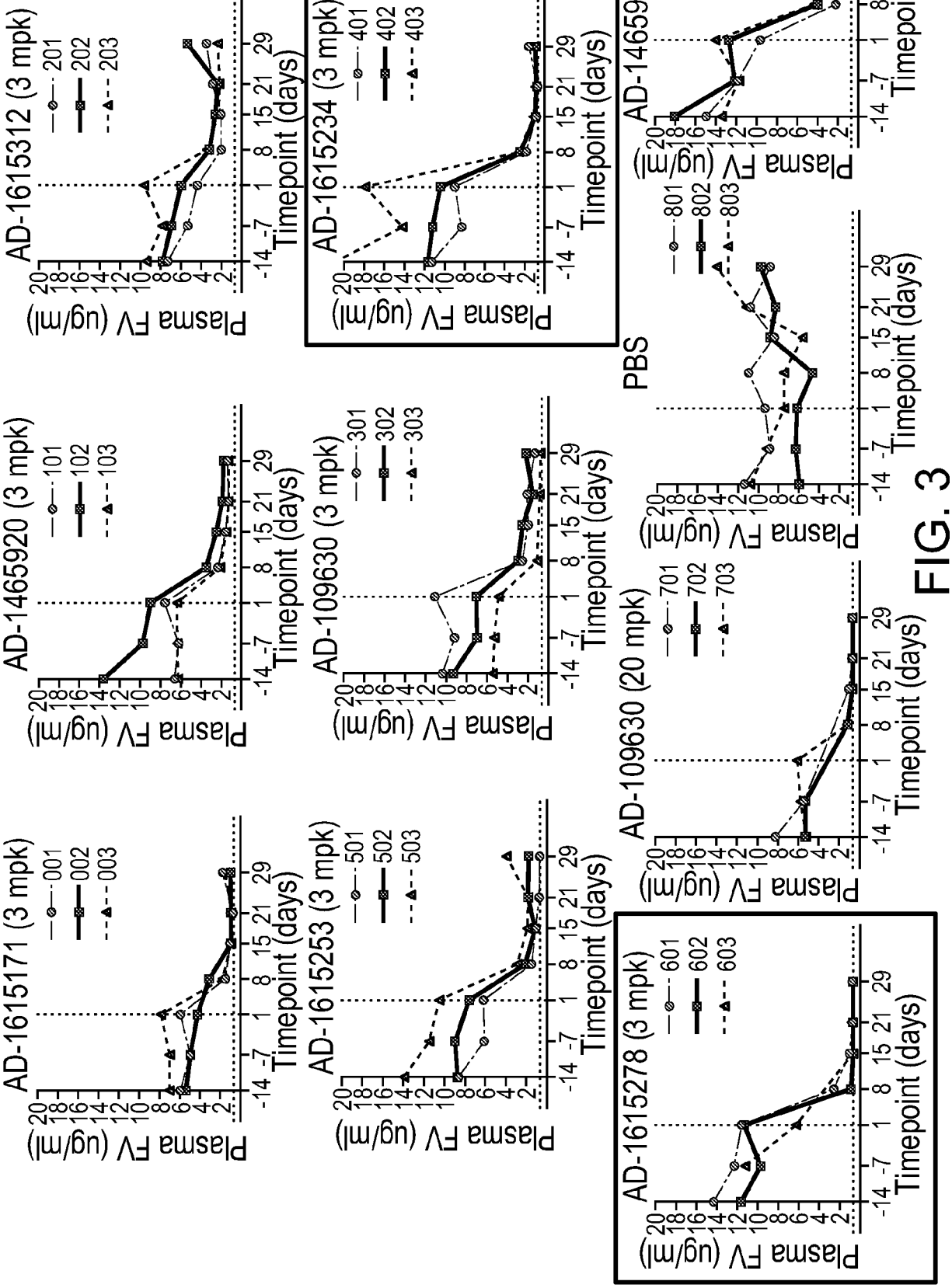
AD-109630 (20mpk)
PBS
AD-1465922

FIG. 2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001
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701
702
703
AD-1615312 (3 mpk)
201
202
203
AD-1615234 (3 mpk)
401
402
403
PBS
801
802
803
AD-1465922 (3 mpk)
901
902
903
Plasma FV (ug/ml)
Timepoint (days)
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2 4 6 8 10 12 14 16 18 20

FIG. 3

SEQUENCE LISTING

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oligonucleotide"

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oligonucleotide"

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<210> 19
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oligonucleotide"

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1 5 10 15

<210> 26
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<212> PRT
<213> Unknown

<220>
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RFGF analogue peptide sequence"

<400> 26
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1 5 10

<210> 27
<211> 13
<212> PRT
<213> Human immunodeficiency virus

<400> 27
Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln
1 5 10

<210> 28
<211> 16
<212> PRT
<213> Drosophila sp.

<400> 28
Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
1 5 10 15

<210> 29
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oligonucleotide"

<400> 29
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<210> 30
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<220>
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<210> 37
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<220>
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<210> 69
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