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(54) Title: RNAI AGENTS AND COMPOSITIONS FOR INHIBITING EXPRESSION OF ASIALOGLYCOPROTEIN RECEPTOR 1

(57) Abstract: Described herein are compositions and methods for inhibition of Asialoglycoprotein receptor 1 (*ASGR1*) gene expression. RNA interference (RNAi) agents, e.g., double stranded RNAi agents, and RNAi agent-targeting ligand conjugates for inhibiting the expression of an *ASGR1* gene are described. Pharmaceutical compositions comprising one or more *ASGR1* RNAi agents, optionally with one or more additional therapeutics, are also described. The *ASGR1* RNAi agents can be used in methods of treatment of various diseases and conditions, such as cardiometabolic diseases related to elevated non-HDL cholesterol (non-HDL-C) levels, elevated LDL cholesterol (LDL-C) levels, elevated total cholesterol levels, and/or elevated triglyceride (TG) levels.

WO 2019/079294 A1

RNAi Agents and Compositions for Inhibiting Expression of Asialoglycoprotein Receptor 1

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from United States Provisional Patent Application Serial No. 62/635,277, filed on February 26, 2018, United States Provisional Patent Application Serial No. 62/608,606, filed on December 21, 2017, and United States Provisional Patent Application Serial No. 62/573,206, filed on October 17, 2017, the contents of each of which are incorporated herein by reference in their entirety.

SEQUENCE LISTING

This application contains a Sequence Listing which has been submitted in ASCII format and is hereby incorporated by reference in its entirety. The ASCII copy is named 30653-WO1_SEQLIST.txt and is 226 kb in size.

FIELD OF THE INVENTION

The present disclosure relates to RNA interference (RNAi) agents, *e.g.*, double stranded RNAi agents, for inhibition of asialoglycoprotein receptor 1 (*ASGR1*) gene expression, compositions that include *ASGR1* RNAi agents, and methods of use thereof.

BACKGROUND

Asialoglycoprotein receptor 1 (ASGR1, also known as ASGPR, ASGPR1, HL-1, and CLEC4H1), was previously known as the Ashwell-Morell receptor. ASGR1 is a transmembrane protein that plays a primary physiological role of binding, internalization, and clearance from the circulation of desialylated glycoproteins. ASGR1 is predominantly expressed in the liver by the Asialoglycoprotein receptor 1 gene (*ASGR1* gene).

Genome-wide association studies for variants that affect non-HDL cholesterol levels and risk of coronary artery disease and myocardial infarction have identified a sequence variant in *ASGR1*. The del12 *ASGR1* sequence variant, which results in haploinsufficiency of ASGR1, has been reported to be associated with reduced non-HDL cholesterol, and reduced risk for coronary artery disease and myocardial infarction (Nioi, Sigurdsson et al., *N. Engl. J. Med.*

2016, *374*, 2131-41). As predicted by ~50% reduction of ASGR1 levels in del12 carriers, there was an increase of alkaline phosphatase (ALP or ALKP) and vitamin B_{12} levels, as both these proteins are substrates for the asialoglycoprotein receptor. Reducing ASGR1 protein has thus emerged as a promising target for the treatment of cardiovascular diseases. Therapeutics that are able to target the *ASGR1* gene and reduce ASGR1 protein levels represent a novel way of treating cardiovascular disease, including coronary artery disease.

SUMMARY

There exists a need for novel *ASGR1*-specific RNA interference (RNAi) agents (also herein termed RNAi agent, RNAi trigger, or trigger), *e.g.*, double stranded RNAi agents, that are able to selectively and efficiently inhibit the expression of an *ASGR1* gene. Further, there exists a need for compositions of novel *ASGR1*-specific RNAi agents for the treatment (including preventative treatment) of diseases associated with, among other things, elevated non-HDL cholesterol (non-HDL-C) levels, elevated LDL cholesterol (LDL-C) levels, elevated total cholesterol levels, and/or elevated triglyceride (TG) levels.

In general, the present disclosure features novel *ASGR1* gene-specific RNAi agents, compositions that include the *ASGR1* gene-specific RNAi agents, and methods for inhibiting expression of an *ASGR1* gene *in vivo* and/or *in vitro* using the *ASGR1* gene-specific RNAi agents and compositions that include *ASGR1* gene-specific RNAi agents described herein. Further described herein are methods of treatment of diseases or disorders that are mediated at least in part by *ASGR1* gene expression, the methods including administration to a subject one or more of the *ASGR1* RNAi agents disclosed herein.

The *ASGR1* gene-specific RNAi agents described herein are able to selectively and efficiently decrease expression of an *ASGR1* gene. The described herein *ASGR1* RNAi agents are thereby capable of reducing non-HDL cholesterol levels, and/or LDL cholesterol levels, and/or total cholesterol levels, and/or triglyceride levels, in a subject, *e.g.*, a human or animal subject. The *ASGR1* RNAi agents described herein can also impact other endogenous factors associated with atherosclerosis and/or vascular disease. For example, the described *ASGR1* RNAi agents can be used in methods for therapeutic treatment and/or prevention of symptoms and diseases associated with abnormal serum lipoprotein levels, including but not limited to obesity, metabolic syndrome, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, abnormal

lipid and/or cholesterol metabolism, atherosclerosis, diabetes, cardiovascular disease, coronary artery disease, myocardial infarction, peripheral vascular disease, cerebrovascular disease, and other metabolic-related disorders and diseases. In some embodiments, the methods disclosed herein include the administration of one or more *ASGR1* RNAi agents to a subject. The one or more *ASGR1* RNAi agents described herein may be administered to a subject by any suitable methods known in the art, such as subcutaneous injection or intravenous administration.

In one aspect, the disclosure features compositions comprising one or more *ASGR1* RNAi agents that are able to selectively and efficiently decrease or inhibit expression of an *ASGR1* gene. In some embodiments, the disclosed herein compositions comprising one or more *ASGR1* RNAi agents are able to reduce the level of ASGR1 protein in the subject. In some embodiments, the disclosed herein compositions comprising one or more *ASGR1* RNAi agents are able to reduce the level of *ASGR1* mRNA in the subject. The compositions comprising one or more *ASGR1* RNAi agents can be administered to a subject, such as a human or animal subject, for the treatment and/or prevention of symptoms and diseases associated with elevated non-HDL-C levels, and/or elevated LDL-C levels, and/or elevated total cholesterol levels, and/or elevated TG levels.

An *ASGR1* RNAi agent described herein includes a sense strand (also referred to as a passenger strand), and an antisense strand (also referred to as a guide strand). The sense strand and the antisense strand can be partially, substantially, or fully complementary to each other. The length of the RNAi agent sense and antisense strands described herein each can be 16 to 30 nucleotides in length. In some embodiments, the sense and antisense strands are independently 17 to 26 nucleotides in length. In some embodiments, the sense and antisense strands are independently 21 to 26 nucleotides in length. In some embodiments, the sense and antisense strands are independently 21 to 24 nucleotides in length. In some embodiments, the sense and antisense strands are both 21 nucleotides in length. In some embodiments, the sense and/or antisense strands are independently 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. The sense and antisense strands can be either the same length or different lengths. The RNAi agents described herein, upon delivery to a cell expressing *ASGR1*, inhibit the expression of one or more *ASGR1* genes *in vivo* or *in vitro*.

A sense strand of the *ASGR1* RNAi agents described herein includes at least 16 consecutive nucleotides that have at least 85% identity to a core stretch sequence (also referred to herein as

a "core stretch" or "core sequence") of the same number of nucleotides in an *ASGR1* mRNA. In some embodiments, the sense strand core stretch having at least 85% identity to a sequence in an *ASGR1* mRNA is 16, 17, 18, 19, 20, 21, 22, or 23 nucleotides in length. In some embodiments, this sense strand core stretch is 16, 17, 18, 19, 20, 21, 22, or 23 nucleotides in length. In some embodiments, this sense strand core stretch is 17 nucleotides in length. In some embodiments, this sense strand core stretch is 19 nucleotides in length.

An antisense strand of an *ASGR1* RNAi agent includes at least 16 consecutive nucleotides that have at least 85% complementarity to a core stretch of the same number of nucleotides in an *ASGR1* mRNA and to a core stretch of the same number of nucleotides in the corresponding sense strand. In some embodiments, the antisense strand core nucleotide stretch having at least 85% complementarity to a sequence in an *ASGR1* mRNA or the corresponding sense strand is 16, 17, 18, 19, 20, 21, 22, or 23 nucleotides in length. In some embodiments, this antisense strand core stretch is 17 nucleotides in length. In some embodiments, this antisense strand core stretch is 19 nucleotides in length.

In some embodiments, the *ASGR1* RNAi agents disclosed herein are designed to target the portion of an *ASGR1* gene having the sequence of any of the sequences disclosed in Table 1.

Examples of *ASGR1* RNAi agent sense strands and antisense strands that can be included in the *ASGR1* RNAi agents disclosed herein are provided in Tables 2, 3, and 4. Examples of *ASGR1* RNAi agent duplexes are provided in Table 5. Examples of 19-nucleotide core stretch sequences that consist of or are included in the sense strands and antisense strands of *ASGR1* RNAi agents disclosed herein, are provided in Table 2.

In another aspect, the disclosure features methods for delivering *ASGR1* RNAi agents to liver cells in a subject, such as a mammal, *in vivo*. Also described herein are compositions for use in such methods. The one or more *ASGR1* RNAi agents can be delivered to target cells or tissues using any oligonucleotide delivery technology known in the art. Nucleic acid delivery methods include, but are not limited to, by encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres, proteinaceous vectors, or Dynamic Polyconjugates™ (DPCs) (see, for example WO 2000/053722, WO 2008/0022309, WO 2011/104169, and WO 2012/083185, each of which is incorporated herein by reference).

In some embodiments, an *ASGR1* RNAi agent is delivered to target cells or tissues by covalently linking or conjugating the RNAi agent to a targeting group. In some embodiments, the targeting group includes, consists of, or consists essentially of an antibody, such as a monoclonal antibody. (*See, e.g.*, International Patent Application Publication No. WO 2018/039647, which is incorporated by reference herein in its entirety). In some embodiments, the targeting group consists of, consists essentially of, or comprises as an asialoglycoprotein receptor ligand (*i.e.*, a ligand that includes a compound having affinity for the asialoglycoprotein receptor). In some embodiments, an asialoglycoprotein receptor ligand includes, consists of, or consists essentially of a galactose or galactose derivative cluster. In some embodiments, an *ASGR1* RNAi agent is linked to a targeting ligand comprising the galactose derivative N-acetyl-galactosamine. In some embodiments, a galactose derivative cluster includes an N-acetyl-galactosamine trimer or an N-acetyl-galactosamine tetramer. In some embodiments, a galactose derivative cluster is an N-acetyl-galactosamine trimer or an N-acetyl-galactosamine tetramer. In some embodiments, the *ASGR1* RNAi agents that are conjugated to targeting ligands that include N-acetyl-galactosamine are selectively internalized by liver cells, and hepatocytes in particular, either through receptor-mediated endocytosis or by other means. Examples of targeting groups useful for delivering RNAi agents are disclosed, for example, in International Patent Application Publication Nos. WO 2018/044350 and WO 2017/156012 to Arrowhead Pharmaceuticals, Inc., which are incorporated by reference herein in their entirety.

A targeting group can be linked to the 3′ or 5′ end of a sense strand or an antisense strand of an *ASGR1* RNAi agent. In some embodiments, a targeting group is linked to the 3′ or 5′ end of the sense strand. In some embodiments, a targeting group is linked internally to a nucleotide on the sense strand and/or the antisense strand of the RNAi agent. In some embodiments, a targeting group is linked to the 5′ end of the sense strand. In some embodiments, a targeting group is linked to the RNAi agent via a linker.

A targeting group, with or without a linker, can be linked to the 5′ or 3′ end of any of the sense and/or antisense strands disclosed in Tables 2, 3, and 4. A linker, with or without a targeting group, can be attached to the 5′ or 3′ end of any of the sense and/or antisense strands disclosed in Tables 2, 3, and 4.

In some embodiments, described herein are compositions that include one or more *ASGR1* RNAi agents having the duplex structures disclosed in Table 5.

In a further aspect, described herein are pharmaceutical compositions that include one or more described *ASGR1* RNAi agent(s), optionally combined with one or more additional (i.e., second, third, etc.) therapeutics. An additional therapeutic can be another *ASGR1* RNAi agent (*e.g.*, an *ASGR1* RNAi agent which targets a different sequence within an *ASGR1* gene). An additional therapeutic can also be a small molecule drug, antibody, antibody fragment, peptide, and/or aptamer. The *ASGR1* RNAi agents, with or without the one or more additional therapeutics, can be combined with one or more excipients to form pharmaceutical compositions. The described *ASGR1* RNAi agent(s) can be optionally combined with one or more additional therapeutics in a single dosage form (*i.e.*, a cocktail included in a single injection). In some embodiments, the pharmaceutical compositions that include one or more described *ASGR1* RNAi agent(s), optionally combined with one or more additional (*i.e.*, second, third, etc.) therapeutics, can be formulated in a pharmaceutically acceptable carrier or diluent. In some embodiments, these compositions can be administered to a subject, such as a mammal. In some embodiments, the mammal is a human.

In some embodiments, the described *ASGR1* RNAi agent(s) may be administered separately from one or more optional additional therapeutics. In some embodiments, the described *ASGR1* RNAi agent(s) are administered to a subject in need thereof via subcutaneous injection, and the one or more optional additional therapeutics are administered orally, which together provide for a treatment regimen for diseases and conditions associated with elevated non-HDL-C levels, and/or elevated LDL-C levels, and/or elevated total cholesterol levels, and/or elevated TG levels. In some embodiments, the described *ASGR1* RNAi agent(s) are administered to a subject in need thereof via subcutaneous injection, and the one or more optional additional therapeutics are administered via a separate subcutaneous injection.

In some embodiments, described herein are compositions that include a combination or cocktail of at least two *ASGR1* RNAi agents having different nucleotide sequences. In some embodiments, the two or more different *ASGR1* RNAi agents are each separately and independently linked to targeting groups. In some embodiments, the two or more different *ASGR1* RNAi agents are each separately and independently linked to targeting groups that include or consist of targeting ligands that include one or more moieties that target an

asialoglycoprotein receptor. In some embodiments, the two or more different *ASGR1* RNAi agents are each linked to targeting groups that include or consist of targeting ligands that include one or more galactose derivatives. In some embodiments, the two or more different *ASGR1* RNAi agents are each linked to targeting groups that include or consist of targeting ligands that include one or more N-acetyl-galactosamines. In some embodiments, when two or more RNAi agents are included in a composition, each of the RNAi agents is independently linked to the same targeting group. In some embodiments, when two or more RNAi agents are included in a composition, each of the RNAi agents is independently linked to a different targeting group, such as targeting groups having different chemical structures.

In some embodiments, targeting groups are linked to the *ASGR1* RNAi agents without the use of an additional linker. In some embodiments, the targeting group is designed having a linker readily present to facilitate the linkage to an *ASGR1* RNAi agent. In some embodiments, when two or more RNAi agents are included in a composition, the two or more RNAi agents may be linked to their respective targeting groups using the same linkers. In some embodiments, when two or more RNAi agents are included in a composition, the two or more RNAi agents are linked to their respective targeting groups using different linkers.

In another aspect, the disclosure features methods of treatment (including prevention or preventative treatment) of diseases or symptoms caused by or attributable to elevated non-HDL-C levels, and/or elevated LDL-C levels, and/or elevated total cholesterol levels, and/or elevated TG levels, wherein the methods include administering an *ASGR1* RNAi agent having an antisense strand comprising the sequence of any of the sequences in Tables 2 or 3.

In some embodiments, disclosed herein are methods of inhibiting expression of an *ASGR1* gene, wherein the methods include administering to a cell an *ASGR1* RNAi agent that includes an antisense strand comprising the sequence of any of the sequences in Tables 2 or 3.

In some embodiments, disclosed herein are methods of treatment or prevention of diseases or symptoms caused by elevated non-HDL-C levels, and/or elevated LDL-C levels, and/or elevated total cholesterol levels, and/or elevated TG levels, wherein the methods include administering an *ASGR1* RNAi agent having a sense strand comprising the sequence of any of the sequences in Tables 2 or 4.

In some embodiments, disclosed herein are methods of inhibiting expression of an *ASGR1* gene, wherein the methods include administering an *ASGR1* RNAi agent having a sense strand comprising the sequence of any of the sequences in Tables 2 or 4.

In some embodiments, disclosed herein are methods of inhibiting expression of an *ASGR1* gene, wherein the methods include administering to a subject a therapeutically effective amount of an *ASGR1* RNAi agent that includes a sense strand comprising the sequence of any of the sequences in Table 4, and an antisense strand comprising the sequence of any of the sequences in Table 3.

In some embodiments, disclosed herein are methods of inhibiting expression of an *ASGR1* gene, wherein the methods include administering an *ASGR1* RNAi agent that includes a sense strand consisting of the nucleobase sequence of any of the sequences in Table 4, and the antisense strand consisting of the nucleobase sequence of any of the sequences in Table 3. In other embodiments, disclosed herein are methods of inhibiting expression of an *ASGR1* gene, wherein the methods include administering an *ASGR1* RNAi agent that includes a sense strand consisting of the modified sequence of any of the modified sequences in Table 4, and an antisense strand consisting of the modified sequence of any of the modified sequences in Table 3.

In some embodiments, disclosed herein are methods for inhibiting expression of an *ASGR1* gene in a cell, wherein the methods include administering one or more *ASGR1* RNAi agents having the duplex structure of any of the duplexes in Table 5.

In a further aspect, the disclosure features methods of treatment (including preventative or prophylactic treatment) of diseases or symptoms caused by elevated non-HDL-C levels, and/or elevated LDL-C levels, and/or elevated total cholesterol levels, and/or elevated TG levels, wherein the methods include administering an *ASGR1* RNAi agent that has an antisense strand that is at least partially complementary to the portion of an *ASGR1* mRNA having any one of the sequences listed in Table 1.

In some embodiments, disclosed herein are methods for inhibiting expression of an *ASGR1* gene in a cell, wherein the methods include administering an *ASGR1* RNAi agent that has an

antisense strand that is at least partially complementary to the portion of an *ASGR1* mRNA having any one of the sequences listed in Table 1.

In some embodiments, disclosed herein are methods of treatment or prevention of diseases or symptoms caused by elevated non-HDL-C levels, and/or elevated LDL-C levels, and/or elevated total cholesterol levels, and/or elevated TG levels, wherein the methods include administering an *ASGR1* RNAi agent having an antisense strand that includes the sequence of any of the sequences in Tables 2 or 3, and a sense strand that includes any of the sequences in Tables 2 or 4 that is at least partially complementary to the antisense strand.

In some embodiments, disclosed herein are methods of treatment or prevention of diseases or symptoms caused by elevated non-HDL-C levels, and/or elevated LDL-C levels, and/or elevated total cholesterol levels, and/or elevated TG levels, wherein the methods include administering an *ASGR1* RNAi agent having a sense strand that includes any of the sequences in Tables 2 or 4, and an antisense strand that includes the sequence of any of the sequences in Tables 2 or 3 that is at least partially complementary to the sense strand.

In some embodiments, disclosed herein are methods of inhibiting expression of an *ASGR1* gene, wherein the methods include administering an *ASGR1* RNAi agent that includes an antisense strand comprising the sequence of any of the sequences in Tables 2 or 3, and a sense strand that includes any of the sequences in Tables 2 or 4 that is at least partially complementary to the antisense strand.

In some embodiments, disclosed herein are methods of inhibiting expression of an *ASGR1* gene, wherein the methods include administering an *ASGR1* RNAi agent that includes a sense strand that comprises any of the sequences in Tables 2 or 4, and an antisense strand that includes the sequence of any of the sequences in Tables 2 or 3 that is at least partially complementary to the sense strand.

In some embodiments, disclosed herein are compositions for inhibiting expression of an *ASGR1* gene in a cell, the composition comprising any of the *ASGR1* RNAi agents described herein.

In some embodiments, disclosed herein are compositions for delivering an *ASGR1* RNAi agent to a liver cell *in vivo*, wherein the composition includes an *ASGR1* RNAi agent conjugated or linked to a targeting group. In some embodiments, the targeting group is an asialoglycoprotein receptor ligand. In some embodiments, compositions for delivering an *ASGR1* RNAi agent to a liver cell *in vivo* are described, wherein the compositions include an *ASGR1* RNAi agent linked to a targeting ligand that comprises N-acetyl-galactosamine.

In some embodiments, one or more of the described *ASGR1* RNAi agents are administered to a subject, such as a mammal, in a pharmaceutically acceptable carrier or diluent. In some embodiments, the mammal is a human.

The use of *ASGR1* RNAi agents provide methods for therapeutic and/or prophylactic treatment of diseases/disorders which are associated with elevated non-HDL-C levels, and/or elevated LDL-C levels, and/or elevated total cholesterol levels, and/or elevated TG levels, and/or enhanced or elevated *ASGR1* expression. The described *ASGR1* RNAi agents can mediate RNA interference to inhibit the expression of one or more genes necessary for production of ASGR1 protein. *ASGR1* RNAi agents can also be used to treat or prevent various diseases or disorders associated with abnormal serum lipoprotein levels, including but not limited to obesity, metabolic syndrome, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, diabetes, cardiovascular disease, coronary artery disease, myocardial infarction, peripheral vascular disease, cerebrovascular disease and other metabolic-related disorders and diseases. The described herein *ASGR1* RNAi agents may also impact other endogenous factors associated with atherosclerosis and/or vascular disease. Further, compositions for delivery of *ASGR1* RNAi agents to liver cells *in vivo* are described.

The pharmaceutical compositions comprising one or more *ASGR1* RNAi agents can be administered in a number of ways depending upon whether local or systemic treatment is desired. Administration can be, but is not limited to, intravenous, intraarterial, subcutaneous, intraperitoneal, subdermal (e.g., via an implanted device), and intraparenchymal administration. In some embodiments, the pharmaceutical compositions described herein are administered by subcutaneous injection.

The described *ASGR1* RNAi agents and/or compositions that include *ASGR1* RNAi agents can be used in methods for therapeutic treatment of diseases or conditions caused by elevated non-

HDL-C levels, and/or elevated LDL-C levels, and/or elevated total cholesterol levels, and/or elevated TG levels. Such methods include administration of an *ASGR1* RNAi agent as described herein to a subject, e.g., a human or animal subject.

In some embodiments, the *ASGR1* RNAi agents described herein can include one or more targeting groups having the structure of (NAG25), (NAG25)s, (NAG26), (NAG26)s, (NAG27), (NAG27)s, (NAG28), (NAG28)s, (NAG29), (NAG29)s, (NAG30), (NAG30)s, (NAG31), (NAG31)s, (NAG32), (NAG32)s, (NAG33), (NAG33)s, (NAG34), (NAG34)s, (NAG35), (NAG35)s, (NAG36), (NAG36)s, (NAG37), (NAG37)s, (NAG38), (NAG38)s, (NAG39), (NAG39)s, each as defined herein in Table 6.

In some embodiments, the *ASGR1* RNAi agents described herein include one targeting group at the 5' end of the sense strand having the structure of (NAG25), (NAG25)s, (NAG26), (NAG26)s, (NAG27), (NAG27)s, (NAG28), (NAG28)s, (NAG29), (NAG29)s, (NAG30), (NAG30)s, (NAG31), (NAG31)s, (NAG32), (NAG32)s, (NAG33), (NAG33)s, (NAG34), (NAG34)s, (NAG35), (NAG35)s, (NAG36), (NAG36)s, (NAG37), (NAG37)s, (NAG38), (NAG38)s, (NAG39), (NAG39)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3), wherein all or substantially all of the nucleotides are modified nucleotides. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3), wherein SEQ ID NO:3 is located at positions 1-21 (5′ → 3′) of the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′)

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. As the person of ordinary skill in the art would clearly understand, the inclusion of a phosphorothioate linkage as shown in the modified nucleotide sequences disclosed herein replaces the phosphodiester linkage typically present in oligonucleotides (*see, e.g.*, Figs. 1A through 1M showing all internucleoside linkages). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5′ → 3′) usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) usAfscUfcCfU_{UNA}UfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:4), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; U_{UNA} represents a 2′,3′-seco-uridine (*see, e.g.*, Table 6); and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. As the person of ordinary skill in the art would clearly understand, the inclusion of a phosphorothioate linkage as shown in the modified nucleotide sequences disclosed herein replaces the phosphodiester linkage typically present in oligonucleotides (*see, e.g.*, Figs. 1A through 1M showing all internucleoside linkages). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5′ → 3′) usAfscUfcCfU_{UNA}UfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:4), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; U_{UNA} represents a 2′,3′-seco-uridine (*see, e.g.*, Table 6); and s represents a

phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6), wherein all or substantially all of the nucleotides are modified nucleotides. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6), wherein SEQ ID NO:6 is located at positions 1-21 (5′ → 3′) of the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. As the person of ordinary skill in the art would clearly understand, the inclusion of a phosphorothioate linkage as shown in the modified nucleotide sequences disclosed herein replaces the phosphodiester linkage typically present in oligonucleotides (*see, e.g.*, Figs. 1A through 1M showing all internucleoside linkages). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5′ → 3′) asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8), wherein all or substantially all of the nucleotides are modified nucleotides. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8), wherein SEQ ID NO:8 is located at positions 1-21 (5′ → 3′) of the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) asGfscGfaCfuucauCfuUfuCfuUfcsGfsu (SEQ ID NO:7), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5′ → 3′) asGfscGfaCfuucauCfuUfuCfuUfcsGfsu (SEQ ID NO:7), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) asGfscsgacuucauCfuUfuCfuUfcGfsu (SEQ ID NO:9), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent

2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5′ → 3′) asGfscsgacuucauCfuUfuCfuUfcGfsu (SEQ ID NO:9), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) ACUUCAUCUUUCUUCCCACGC (SEQ ID NO:11). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) ACUUCAUCUUUCUUCCCACGC (SEQ ID NO:11), wherein all or substantially all of the nucleotides are modified nucleotides. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) ACUUCAUCUUUCUUCCCACGC (SEQ ID NO:11), wherein SEQ ID NO:11 is located at positions 1-21 (5′ → 3′) of the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5′ → 3′) asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf,

Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) UGAAAUAAAUUAAAGGAGAGG (SEQ ID NO:27). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) UGAAAUAAAUUAAAGGAGAGG (SEQ ID NO:27), wherein all or substantially all of the nucleotides are modified nucleotides. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) UGAAAUAAAUUAAAGGAGAGG (SEQ ID NO:27), wherein SEQ ID NO:27 is located at positions 1-21 (5′ → 3′) of the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) usGfsaAfaUfaAfaUfuAfaAfgGfaGfasGfsg (SEQ ID NO:28), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the nucleotide sequence (5′ → 3′) usGfsaAfaUfaAfaUfuAfaAfgGfaGfasGfsg (SEQ ID NO:28), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage, and wherein the sense strand is at least substantially complementary to the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1

nucleobases from the nucleotide sequence (5′ → 3′) UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3) and a sense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) ACCUAUCAUGACCAAGGAIUA (SEQ ID NO:12). (I represents an inosine nucleotide.) In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3), wherein all or substantially all of the nucleotides are modified nucleotides, and a sense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) ACCUAUCAUGACCAAGGAIUA (SEQ ID NO:12), wherein all or substantially all of the nucleotides are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3) and a sense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) ACCUAUCAUGACCAAGGAGUA (SEQ ID NO:13). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3), wherein all or substantially all of the nucleotides are modified nucleotides, and a sense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) ACCUAUCAUGACCAAGGAGUA (SEQ ID NO:13), wherein all or substantially all of the nucleotides are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3) and a sense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) ACCUAUCAUGACCAAIGAIUA (SEQ ID NO:14). (I represents an inosine nucleotide.) In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that

consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3), wherein all or substantially all of the nucleotides are modified nucleotides, and a sense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) ACCUAUCAUGACCAAIGAIUA (SEQ ID NO:14), wherein all or substantially all of the nucleotides are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6) and a sense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) CGGAAGAAAGAUGAAGUCICU (SEQ ID NO:15). (I represents an inosine nucleotide.) In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6), wherein all or substantially all of the nucleotides are modified nucleotides, and a sense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) CGGAAGAAAGAUGAAGUCICU (SEQ ID NO:15), wherein all or substantially all of the nucleotides are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8) and a sense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) ACGAAGAAAGAUGAAGUCICU (SEQ ID NO:16). (I represents an inosine nucleotide.) In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8), wherein all or substantially all of the nucleotides are modified nucleotides, and a sense strand that consists of, consists essentially of, or comprises a nucleotide sequence

differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) ACGAAGAAAGAUGAAGUCICU (SEQ ID NO:16), wherein all or substantially all of the nucleotides are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8) and a sense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) ACGAAGAAAGAUGAAGUCGCU (SEQ ID NO:17). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8), wherein all or substantially all of the nucleotides are modified nucleotides, and a sense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) ACGAAGAAAGAUGAAGUCGCU (SEQ ID NO:17), wherein all or substantially all of the nucleotides are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) ACUUCAUCUUUCUUCCCACGC (SEQ ID NO:11) and a sense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) GCGUGGGAAGAAAGAUGAAGU (SEQ ID NO:18). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) ACUUCAUCUUUCUUCCCACGC (SEQ ID NO:11), wherein all or substantially all of the nucleotides are modified nucleotides, and a sense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) GCGUGGGAAGAAAGAUGAAGU (SEQ ID NO:18), wherein all or substantially all of the nucleotides are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1

nucleobases from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6) and a sense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) CGGAAGAAAGAUGAAIUCICU (SEQ ID NO:31). (I represents an inosine nucleotide.) In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6), wherein all or substantially all of the nucleotides are modified nucleotides, and a sense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) CGGAAGAAAGAUGAAIUCICU (SEQ ID NO:31), wherein all or substantially all of the nucleotides are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6) and a sense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) CGGAAGAAAGAUGAAGUCGCU (SEQ ID NO:33). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6), wherein all or substantially all of the nucleotides are modified nucleotides, and a sense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) CGGAAGAAAGAUGAAGUCGCU (SEQ ID NO:33), wherein all or substantially all of the nucleotides are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) UGAAAUAAAUUAAAGGAGAGG (SEQ ID NO:27) and a sense strand that consists of, consists essentially of, or comprises a nucleobase sequence differing by 0 or 1 nucleobases from the nucleotide sequence (5′ → 3′) CCUCUCCUUUAAUUUAUUUCA (SEQ ID NO:35). In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially

of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) UGAAAUAAAUUAAAGGAGAGG (SEQ ID NO:27), wherein all or substantially all of the nucleotides are modified nucleotides, and a sense strand that consists of, consists essentially of, or comprises a nucleotide sequence differing by no more than 1 nucleotide from the nucleotide sequence (5′ → 3′) CCUCUCCUUUAAUUUAUUUCA (SEQ ID NO:35), wherein all or substantially all of the nucleotides are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) accuaucaUfGfAfccaaggaiua (SEQ ID NO:19), wherein a, c, g, i, and u represent 2′-O-methyl adenosine, cytidine, guanosine, inosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) accuaucaUfGfAfccaaggaiua (SEQ ID NO:19), and wherein the sense strand further includes inverted abasic residues at the 3’ terminal end and at the 5’ end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3’ and/or 5’ terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usAfscUfcCfU$_{UNA}$UfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:4), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) accuaucaUfGfAfccaaggagua (SEQ ID NO:20), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; U$_{UNA}$ represents a 2′,3′-seco-uridine (*see, e.g.*, Table 6); Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′)

usAfscUfcCfU$_{UNA}$UfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:4), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) accuaucaUfGfAfccaaggagua (SEQ ID NO:20), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) accuaucaUfGfAfcCaaggagua (SEQ ID NO:21), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) accuaucaUfGfAfcCaaggagua (SEQ ID NO:21), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) accuaucaUfGfAfcCaaigaiua (SEQ ID NO:22), wherein a, c, g, i, and u represent 2′-O-methyl adenosine, cytidine, guanosine, inosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified

nucleotide sequence (5′ → 3′) usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) accuaucaUfGfAfcCaaigaiua (SEQ ID NO:22), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cggaagaaAfGfAfugaagucicu (SEQ ID NO:23), wherein a, c, g, i, and u represent 2′-O-methyl adenosine, cytidine, guanosine, inosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cggaagaaAfGfAfugaagucicu (SEQ ID NO:23), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asGfscGfaCfuucauCfuUfuCfuUfcsGfsu (SEQ ID NO:7), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) acgaagaaAfGfAfugaagucicu (SEQ ID NO:24), wherein a, c, g, i, and u represent 2′-O-methyl adenosine, cytidine, guanosine, inosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified

nucleotide sequence (5′ → 3′) asGfscGfaCfuucauCfuUfuCfuUfcsGfsu (SEQ ID NO:7), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) acgaagaaAfGfAfugaagucicu (SEQ ID NO:24), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asGfscsgacuucauCfuUfuCfuUfcGfsu (SEQ ID NO:9), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) acgaagaaAfGfAfugaagucgcu (SEQ ID NO:25), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asGfscsgacuucauCfuUfuCfuUfcGfsu (SEQ ID NO:9), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) acgaagaaAfGfAfugaagucgcu (SEQ ID NO:25), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) gcgugggaAfGfAfaagaugaagu (SEQ ID NO:26), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence

(5′ → 3′) asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) gcgugggaAfGfAfaagaugaagu (SEQ ID NO:26), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) gscgugggaAfGfAfaagaugaagu (SEQ ID NO:29), wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) gscgugggaAfGfAfaagaugaagu (SEQ ID NO:29), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) accuaucaUfGfAfccaaigaiua (SEQ ID NO:30), wherein a, c, g, i, and u represent 2′-O-methyl adenosine, cytidine, guanosine, inosine or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified

nucleotide sequence (5′ → 3′) usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) accuaucaUfGfAfccaaigaiua (SEQ ID NO:30), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cggaagaaAfGfAfugaaiucicu (SEQ ID NO:32), wherein a, c, g, i, and u represent 2′-O-methyl adenosine, cytidine, guanosine, inosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cggaagaaAfGfAfugaaiucicu (SEQ ID NO:32), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cggaagaaAfGfAfugaagucgcu (SEQ ID NO:34), wherein a, c, g, i, and u represent 2′-O-methyl adenosine, cytidine, guanosine, inosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified

nucleotide sequence (5′ → 3′) asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cggaagaaAfGfAfugaagucgcu (SEQ ID NO:34), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usGfsaAfaUfaAfaUfuAfaAfgGfaGfasGfsg (SEQ ID NO:28), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) ccucuccuUfUfAfauuuauuuca (SEQ ID NO:36), wherein a, c, g, i, and u represent 2′-O-methyl adenosine, cytidine, guanosine, inosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; and s represents a phosphorothioate linkage. In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usGfsaAfaUfaAfaUfuAfaAfgGfaGfasGfsg (SEQ ID NO:28), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) ccucuccuUfUfAfauuuauuuca (SEQ ID NO:36), and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3);
AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6);
AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8);
ACUUCAUCUUUCUUCCCACGC (SEQ ID NO:11); or
UGAAAUAAAUUAAAGGAGAGG (SEQ ID NO:27);

wherein the *ASGR1* RNAi agent further includes a sense strand that is at least partially complementary to the antisense strand; and wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3);
AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6);
AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8);
ACUUCAUCUUUCUUCCCACGC (SEQ ID NO:11); or
UGAAAUAAAUUAAAGGAGAGG (SEQ ID NO:27);

wherein the *ASGR1* RNAi agent further includes a sense strand that is at least partially complementary to the antisense strand; wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides; and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3);
AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6);
AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8);
ACUUCAUCUUUCUUCCCACGC (SEQ ID NO:11); or
UGAAAUAAAUUAAAGGAGAGG (SEQ ID NO:27);

wherein the *ASGR1* RNAi agent further includes a sense strand that is at least partially complementary to the antisense strand; wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides; and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end; and wherein the respective antisense strand sequence is located at positions 1-21 of the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand and a sense strand, wherein the antisense strand and the sense strand consist of, consist essentially of, or comprise nucleotide sequences that differ by 0 or 1 nucleotides from one of the following nucleotide sequence (5′ → 3′) pairs:

UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3) and ACCUAUCAUGACCAAGGAIUA (SEQ ID NO:12), wherein I represents an inosine nucleotide;

UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3) and ACCUAUCAUGACCAAGGAGUA (SEQ ID NO:13);

UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3) and ACCUAUCAUGACCAAIGAIUA (SEQ ID NO:14), wherein I represents an inosine nucleotide;

AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6) and CGGAAGAAAGAUGAAGUCICU (SEQ ID NO:15), wherein I represents an inosine nucleotide;

AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8) and ACGAAGAAAGAUGAAGUCICU (SEQ ID NO:16), wherein I represents an inosine nucleotide;

AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8) and ACGAAGAAAGAUGAAGUCGCU (SEQ ID NO:17);

ACUUCAUCUUUCUUCCCACGC (SEQ ID NO:11) and GCGUGGGAAGAAAGAUGAAGU (SEQ ID NO:18);

AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6) and CGGAAGAAAGAUGAAIUCICU (SEQ ID NO:31), wherein I represents an inosine nucleotide;

AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6) and CGGAAGAAAGAUGAAGUCGCU (SEQ ID NO:33); or

UGAAAUAAAUUAAAGGAGAGG (SEQ ID NO:27) and CCUCUCCUUUAAUUUAUUUCA (SEQ ID NO:35);

wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand and a sense strand, wherein the antisense strand and the sense strand consist of, consist essentially of, or comprise nucleotide sequences that differ by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′) pairs:

UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3) and ACCUAUCAUGACCAAGGAIUA (SEQ ID NO:12), wherein I represents an inosine nucleotide;

UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3) and ACCUAUCAUGACCAAGGAGUA (SEQ ID NO:13);

UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3) and ACCUAUCAUGACCAAIGAIUA (SEQ ID NO:14), wherein I represents an inosine nucleotide;

AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6) and CGGAAGAAAGAUGAAGUCICU (SEQ ID NO:15), wherein I represents an inosine nucleotide;

AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8) and ACGAAGAAAGAUGAAGUCICU (SEQ ID NO:16), wherein I represents an inosine nucleotide;

AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8) and ACGAAGAAAGAUGAAGUCGCU (SEQ ID NO:17);

ACUUCAUCUUUCUUCCCACGC (SEQ ID NO:11) and GCGUGGGAAGAAAGAUGAAGU (SEQ ID NO:18);

AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6) and CGGAAGAAAGAUGAAIUCICU (SEQ ID NO:31), wherein I represents an inosine nucleotide;

AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6) and CGGAAGAAAGAUGAAGUCGCU (SEQ ID NO:33); or

UGAAAUAAAUUAAAGGAGAGG (SEQ ID NO:27) and CCUCUCCUUUAAUUUAUUUCA (SEQ ID NO:35);

wherein all or substantially all of the nucleotides on both the antisense strand and the sense strand are modified nucleotides; and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2);

usAfscUfcCfU$_{UNA}$UfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:4);

asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5);

asGfscGfaCfuucauCfuUfuCfuUfcsGfsu (SEQ ID NO:7);

asGfscsgacuucauCfuUfuCfuUfcGfsu (SEQ ID NO:9);

asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10); or

usGfsaAfaUfaAfaUfuAfaAfgGfaGfasGfsg (SEQ ID NO:28)

wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; U$_{UNA}$ represents a 2′,3′-seco-uridine (*see, e.g.*, Table 6); s represents a phosphorothioate linkage; and wherein the *ASGR1* RNAi agent further includes the sense strand that is at least partially complementary to the antisense strand; and wherein all or substantially all of the nucleotides on the sense strand are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that consists of, consists essentially of, or comprises a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2);

usAfscUfcCfU$_{UNA}$UfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:4);

asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5);

asGfscGfaCfuucauCfuUfuCfuUfcsGfsu (SEQ ID NO:7);

asGfscsgacuucauCfuUfuCfuUfcGfsu (SEQ ID NO:9);

asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10); or

usGfsaAfaUfaAfaUfuAfaAfgGfaGfasGfsg (SEQ ID NO:28)

wherein the *ASGR1* RNAi agent further includes the sense strand that is at least partially complementary to the antisense strand; wherein all or substantially all of the nucleotides on the sense strand are modified nucleotides; and wherein the sense strand further includes inverted abasic residues at the 3’ terminal end and at the 5’ end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3’ and/or 5’ terminal

end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand and a sense strand that consists of, consists essentially of, or comprises modified nucleotide sequences that differs by 0 or 1 nucleotides from one of the following nucleotide sequence pairs (5′ → 3′):

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2) and accuaucaUfGfAfccaaggaiua (SEQ ID NO:19);

usAfscUfcCfU$_{UNA}$UfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:4) and accuaucaUfGfAfccaaggagua (SEQ ID NO:20);

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2) and accuaucaUfGfAfcCaaggagua (SEQ ID NO:21);

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2) and accuaucaUfGfAfcCaaigaiua (SEQ ID NO:22);

asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5) and cggaagaaAfGfAfugaagucicu (SEQ ID NO:23);

asGfscGfaCfuucauCfuUfuCfuUfcsGfsu (SEQ ID NO:7) and acgaagaaAfGfAfugaagucicu (SEQ ID NO:24);

asGfscsgacuucauCfuUfuCfuUfcGfsu (SEQ ID NO:9) and acgaagaaAfGfAfugaagucgcu (SEQ ID NO:25);

asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10) and gcgugggaAfGfAfaagaugaagu (SEQ ID NO:26);

asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10) and gscgugggaAfGfAfaagaugaagu (SEQ ID NO:29);

asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10) and accuaucaUfGfAfccaaigaiua (SEQ ID NO:30);

asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5) and cggaagaaAfGfAfugaaiucicu (SEQ ID NO:32);

asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5) and cggaagaaAfGfAfugaagucgcu (SEQ ID NO:34); or

usGfsaAfaUfaAfaUfuAfaAfgGfaGfasGfsg (SEQ ID NO:28) and ccucuccuUfUfAfauuuauuuca (SEQ ID NO:36);

wherein a, c, g, i, and u represent 2′-O-methyl adenosine, cytidine, guanosine, inosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; U_{UNA} represents a 2′,3′-seco-uridine (*see, e.g.*, Table 6); and s represents a phosphorothioate linkage.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand and a sense strand that consists of, consists essentially of, or comprises one of the following nucleotide sequence pairs (5′ → 3′):

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2) and accuaucaUfGfAfccaaggaiua (SEQ ID NO:19);

usAfscUfcCfU_{UNA}UfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:4) and accuaucaUfGfAfccaaggagua (SEQ ID NO:20);

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2) and accuaucaUfGfAfcCaaggagua (SEQ ID NO:21);

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2) and accuaucaUfGfAfcCaaigaiua (SEQ ID NO:22);

asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5) and cggaagaaAfGfAfugaagucicu (SEQ ID NO:23);

asGfscGfaCfuucauCfuUfuCfuUfcsGfsu (SEQ ID NO:7) and acgaagaaAfGfAfugaagucicu (SEQ ID NO:24);

asGfscsgacuucauCfuUfuCfuUfcGfsu (SEQ ID NO:9) and acgaagaaAfGfAfugaagucgcu (SEQ ID NO:25);

asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10) and gcgugggaAfGfAfaagaugaagu (SEQ ID NO:26);

asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10) and gscgugggaAfGfAfaagaugaagu (SEQ ID NO:29);

asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10) and accuaucaUfGfAfccaaigaiua (SEQ ID NO:30);

asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5) and cggaagaaAfGfAfugaaiucicu (SEQ ID NO:32);

asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5) and cggaagaaAfGfAfugaagucgcu (SEQ ID NO:34); or

usGfsaAfaUfaAfaUfuAfaAfgGfaGfasGfsg (SEQ ID NO:28) and ccucuccuUfUfAfauuuauuuca (SEQ ID NO:36);

wherein a, c, g, i, and u represent 2′-O-methyl adenosine, cytidine, guanosine, inosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; U_{UNA} represents a 2′,3′-seco-uridine (*see, e.g.*, Table 6); s represents a phosphorothioate linkage; and wherein the sense strand further includes inverted abasic residues at the 3' terminal end and at the 5' end of the nucleotide sequence, and the sense strand also includes a targeting ligand that is covalently linked to the 3' and/or 5' terminal end. In certain embodiments, the targeting ligand is selected from (NAG25), (NAG25)s, (NAG37), and (NAG37)s, each as defined herein in Table 6.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that includes a nucleobase sequence that differs by 0 or 1 nucleobases from the nucleotide sequences selected from the group consisting of (5′ → 3′):

UACUCCUUGGUCAUGAUAG (SEQ ID NO:87);
AGCGACUUCAUCUUUCUUC (SEQ ID NO:141);
ACUUCAUCUUUCUUCCCAC (SEQ ID NO:133); or
UGAAAUAAAUUAAAGGAGA (SEQ ID NO:239).

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that includes a nucleobase sequence that differs by 0 or 1 nucleobases from the nucleotide sequences selected from the group consisting of (5′ → 3′):

UACUCCUUGGUCAUGAUAG (SEQ ID NO:87);
AGCGACUUCAUCUUUCUUC (SEQ ID NO:141);
ACUUCAUCUUUCUUCCCAC (SEQ ID NO:133); or
UGAAAUAAAUUAAAGGAGA (SEQ ID NO:239); and

wherein all or substantially all of the nucleotides are modified nucleotides.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand that includes a nucleobase sequence that differs by 0 or 1 nucleobases from the nucleotide sequences selected from the group consisting of (5′ → 3′):

UACUCCUUGGUCAUGAUAG (SEQ ID NO:87);
AGCGACUUCAUCUUUCUUC (SEQ ID NO:141);
ACUUCAUCUUUCUUCCCAC (SEQ ID NO:133); or
UGAAAUAAAUUAAAGGAGA (SEQ ID NO:239); and

wherein all or substantially all of the nucleotides are modified nucleotides, and wherein SEQ ID NO:87, SEQ ID NO:141, SEQ ID NO:133, or SEQ ID NO:239, respectively, is located at nucleotide positions 1-19 (5′ → 3′) of the antisense strand.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand and a sense strand that each include a nucleobase sequences that differs by 0 or 1 nucleobases from the nucleotide sequence pairs selected from the group consisting of (5′ → 3′):

UACUCCUUGGUCAUGAUAG (SEQ ID NO:87) and CUAUCAUGACCAAGGAIUA (SEQ ID NO: 253);

UACUCCUUGGUCAUGAUAG (SEQ ID NO:87) and CUAUCAUGACCAAGGAGUA (SEQ ID NO: 250);

UACUCCUUGGUCAUGAUAG (SEQ ID NO:87) and CUAUCAUGACCAAIGAIUA (SEQ ID NO: 257);

AGCGACUUCAUCUUUCUUC (SEQ ID NO:141) and GAAGAAAGAUGAAGUCICU (SEQ ID NO:316);

AGCGACUUCAUCUUUCUUC (SEQ ID NO:141) and GAAGAAAGAUGAAGUCGCU (SEQ ID NO:312);

ACUUCAUCUUUCUUCCCAC (SEQ ID NO:133) and GUGGGAAGAAAGAUGAAGU (SEQ ID NO:304);

AGCGACUUCAUCUUUCUUC (SEQ ID NO:141) and GAAGAAAGAUGAAIUCICU (SEQ ID NO:852);

AGCGACUUCAUCUUUCUUC (SEQ ID NO:141) and GAAGAAAGAUGAAGUCGCU (SEQ ID NO:312);

UGAAAUAAAUUAAAGGAGA (SEQ ID NO:239) and UCUCCUUUAAUUUAUUUCA (SEQ ID NO:414); wherein I represents an inosine nucleotide.

In some embodiments, an *ASGR1* RNAi agent disclosed herein includes an antisense strand and a sense strand that each include a nucleobase sequences that differs by 0 or 1 nucleobases from the nucleotide sequence pairs selected from the group consisting of (5′ → 3′):

UACUCCUUGGUCAUGAUAG (SEQ ID NO:87) and CUAUCAUGACCAAGGAIUA (SEQ ID NO: 253);

UACUCCUUGGUCAUGAUAG (SEQ ID NO:87) and CUAUCAUGACCAAGGAGUA (SEQ ID NO: 250);

UACUCCUUGGUCAUGAUAG (SEQ ID NO:87) and CUAUCAUGACCAAIGAIUA (SEQ ID NO: 257);

AGCGACUUCAUCUUUCUUC (SEQ ID NO:141) and GAAGAAAGAUGAAGUCICU (SEQ ID NO:316);

AGCGACUUCAUCUUUCUUC (SEQ ID NO:141) and GAAGAAAGAUGAAGUCGCU (SEQ ID NO:312);

ACUUCAUCUUUCUUCCCAC (SEQ ID NO:133) and GUGGGAAGAAAGAUGAAGU (SEQ ID NO:304);

AGCGACUUCAUCUUUCUUC (SEQ ID NO:141) and GAAGAAAGAUGAAIUCICU (SEQ ID NO:852);

AGCGACUUCAUCUUUCUUC (SEQ ID NO:141) and GAAGAAAGAUGAAGUCGCU (SEQ ID NO:312);

UGAAAUAAAUUAAAGGAGA (SEQ ID NO:239) and UCUCCUUUAAUUUAUUUCA (SEQ ID NO:414); wherein I represents an inosine nucleotide, and wherein all or substantially all of the nucleotides are modified nucleotides.

In some embodiments, the compositions described herein comprising one or more *ASGR1* RNAi agents are packaged in a kit, container, pack, dispenser, pre-filled syringes, or vials. In some embodiments, the compositions described herein are administered parenterally.

Other objects, features, aspects, and advantages of the invention will be apparent from the following detailed description, accompanying figures, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A. Schematic diagram of the modified sense and antisense strands of *ASGR1* RNAi agent AD05126 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6). Fig. 1A discloses SEQ ID NOs: 10 and 631.

The following abbreviations are used in Figures 1A to 1M: a, c, g, i, and u are 2′-O-methyl modified nucleotides; Af, Cf, Gf, and Uf are 2′-fluoro modified nucleotides; p is a phosphodiester linkage; s is a phosphorothioate linkage; invAb is an inverted abasic residue (*see, e.g.*, Table 6); C is a cytidine ribonucleotide; $U_{UNA\ IS}$ a 2′,3′-seco-uridine

(*see, e.g.*, Table 6); and (NAG37)s and (NAG37)p are the respective tridentate N-acetyl-galactosamine targeting ligands having the structure depicted in Table 6.

FIG. 1B. Schematic diagram of the modified sense and antisense strands of *ASGR1* RNAi agent AD05150 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6). Fig. 1B discloses SEQ ID NOs: 10 and 632.

FIG. 1C. Schematic diagram of the modified sense and antisense strands of *ASGR1* RNAi agent AD05183 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6). Fig. 1C discloses SEQ ID NOs: 2 and 636.

FIG. 1D. Schematic diagram of the modified sense and antisense strands of *ASGR1*RNAi agent AD05186 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6). Fig. 1D discloses SEQ ID NOs: 2 and 639.

FIG. 1E. Schematic diagram of the modified sense and antisense strands of *ASGR1* RNAi agent AD05193 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6). Fig. 1E discloses SEQ ID NOs: 5 and 645.

FIG. 1F. Schematic diagram of the modified sense and antisense strands of *ASGR1* RNAi agent AD05195 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6). Fig. 1F discloses SEQ ID NOs: 5 and 647.

FIG. 1G. Schematic diagram of the modified sense and antisense strands of *ASGR1* RNAi agent AD05196 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6). Fig. 1G discloses SEQ ID NOs: 5 and 648.

FIG. 1H. Schematic diagram of the modified sense and antisense strands of *ASGR1* RNAi agent AD05206 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6). Fig. 1H discloses SEQ ID NOs: 28 and 658.

FIG. 1I. Schematic diagram of the modified sense and antisense strands of *ASGR1* RNAi agent AD05209 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand

having the structure of (NAG37)s (*see* Table 6). Fig. 1I discloses SEQ ID NOs: 4 and 602.

FIG. 1J. Schematic diagram of the modified sense and antisense strands of *ASGR1* RNAi agent AD05256 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6). Fig. 1J discloses SEQ ID NOs: 2 and 674.

FIG. 1K. Schematic diagram of the modified sense and antisense strands of *ASGR1* RNAi agent AD05374 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6). Fig. 1K discloses SEQ ID NOs: 2 and 700.

FIG. 1L. Schematic diagram of the modified sense and antisense strands of *ASGR1* RNAi agent AD05609 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6). Fig. 1L discloses SEQ ID NOs: 7 and 708.

FIG. 1M. Schematic diagram of the modified sense and antisense strands of *ASGR1* RNAi agent AD05692 (*see* Tables 3-5), conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6). Fig. 1M discloses SEQ ID NOs: 9 and 721.

FIG. 2A to 2D. Chemical structure representation of *ASGR1* RNAi agent AD05193, conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6) at the 5' terminal end of the sense strand, shown in a sodium salt form.

FIG. 3A to 3D. Chemical structure representation of *ASGR1* RNAi agent AD05193, conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6) at the 5' terminal end of the sense strand, shown in a free acid form.

FIG. 4A to 4D. Chemical structure representation of *ASGR1* RNAi agent AD05209, conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of (NAG37)s (*see* Table 6) at the 5' terminal end of the sense strand, shown in a sodium salt form.

FIG. 5A to 5D. Chemical structure representation of *ASGR1* RNAi agent AD05209, conjugated to an N-acetyl-galactosamine tridentate ligand having the structure of

(NAG37)s (*see* Table 6) at the 5' terminal end of the sense strand, shown in a free acid form.

DETAILED DESCRIPTION

Definitions

As used herein, the terms "oligonucleotide" and "polynucleotide" mean a polymer of linked nucleosides each of which can be independently modified or unmodified.

As used herein, an "RNAi agent" (also referred to as an "RNAi trigger") means a composition that contains an RNA or RNA-like (e.g., chemically modified RNA) oligonucleotide molecule that is capable of degrading or inhibiting (e.g., degrades or inhibits under appropriate conditions) translation of messenger RNA (mRNA) transcripts of a target mRNA in a sequence specific manner. As used herein, RNAi agents may operate through the RNA interference mechanism (i.e., inducing RNA interference through interaction with the RNA interference pathway machinery (RNA-induced silencing complex or RISC) of mammalian cells), or by any alternative mechanism(s) or pathway(s). While it is believed that RNAi agents, as that term is used herein, operate primarily through the RNA interference mechanism, the disclosed RNAi agents are not bound by or limited to any particular pathway or mechanism of action. RNAi agents disclosed herein are comprised of a sense strand and an antisense strand, and include, but are not limited to: short (or small) interfering RNAs (siRNAs), double stranded RNAs (dsRNA), micro RNAs (miRNAs), short hairpin RNAs (shRNA), and dicer substrates. The antisense strand of the RNAi agents described herein is at least partially complementary to the mRNA being targeted (i.e. *ASGR1* mRNA). RNAi agents can include one or more modified nucleotides and/or one or more non-phosphodiester linkages.

As used herein, the terms "silence," "reduce," "inhibit," "down-regulate," or "knockdown" when referring to expression of a given gene, mean that the expression of the gene, as measured by the level of RNA transcribed from the gene or the level of polypeptide, protein, or protein subunit translated from the mRNA in a cell, group of cells, tissue, organ, or subject in which the gene is transcribed, is reduced when the cell, group of cells, tissue, organ, or subject is treated with the RNAi agents described herein as compared to a second cell, group of cells, tissue, organ, or subject that has not or have not been so treated.

As used herein, the terms "sequence" and "nucleotide sequence" mean a succession or order of nucleobases or nucleotides, described with a succession of letters using standard nomenclature.

As used herein, a "base," "nucleotide base," or "nucleobase," is a heterocyclic pyrimidine or purine compound that is a component of a nucleotide, and includes the primary purine bases adenine and guanine, and the primary pyrimidine bases cytosine, thymine, and uracil. A nucleobase may further be modified to include, without limitation, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. (*See, e.g.*, Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P. ed. Wiley-VCH, 2008). The synthesis of such modified nucleobases (including phosphoramidite compounds that include modified nucleobases) is known in the art.

As used herein, and unless otherwise indicated, the term "complementary," when used to describe a first nucleobase or nucleotide sequence (e.g., RNAi agent sense strand or targeted mRNA) in relation to a second nucleobase or nucleotide sequence (e.g., RNAi agent antisense strand or a single-stranded antisense oligonucleotide), means the ability of an oligonucleotide or polynucleotide including the first nucleotide sequence to hybridize (form base pair hydrogen bonds under mammalian physiological conditions (or similar conditions in vitro)) and form a duplex or double helical structure under certain standard conditions with an oligonucleotide or polynucleotide including the second nucleotide sequence. Complementary sequences include Watson-Crick base pairs or non-Watson-Crick base pairs and include natural or modified nucleotides or nucleotide mimics, at least to the extent that the above hybridization requirements are fulfilled. Sequence identity or complementarity is independent of modification. For example, a and Af, as defined herein, are complementary to U (or T) and identical to A for the purposes of determining identity or complementarity.

As used herein, "perfectly complementary" or "fully complementary" means that in a hybridized pair of nucleobase or nucleotide sequence molecules, all (100%) of the bases in a contiguous sequence of a first oligonucleotide will hybridize with the same number of bases in a contiguous sequence of a second oligonucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

As used herein, "partially complementary" means that in a hybridized pair of nucleobase or nucleotide sequence molecules, at least 70%, but not all, of the bases in a contiguous sequence of a first oligonucleotide will hybridize with the same number of bases in a contiguous sequence of a second oligonucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

As used herein, "substantially complementary" means that in a hybridized pair of nucleobase or nucleotide sequence molecules, at least 85%, but not all, of the bases in a contiguous sequence of a first oligonucleotide will hybridize with the same number of bases in a contiguous sequence of a second oligonucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

As used herein, the terms "complementary," "fully complementary," "partially complementary," and "substantially complementary" are used with respect to the nucleobase or nucleotide matching between the sense strand and the antisense strand of an RNAi agent, or between the antisense strand of an RNAi agent and a sequence of an *ASGR1* mRNA.

As used herein, the term "substantially identical" or "substantial identity," as applied to a nucleic acid sequence means the nucleotide sequence (or a portion of a nucleotide sequence) has at least about 85% sequence identity or more, e.g., at least 90%, at least 95%, or at least 99% identity, compared to a reference sequence. Percentage of sequence identity is determined by comparing two optimally aligned sequences over a comparison window. The percentage is calculated by determining the number of positions at which the same type of nucleic acid base occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity. The inventions disclosed herein encompass nucleotide sequences substantially identical to those disclosed herein.

As used herein, the terms "treat," "treatment," and the like, mean the methods or steps taken to provide relief from or alleviation of the number, severity, and/or frequency of one or more symptoms of a disease in a subject. As used herein, "treat" and "treatment" may include the preventative treatment, management, prophylactic treatment, and/or inhibition or reduction of the number, severity, and/or frequency of one or more symptoms of a disease in a subject.

As used herein, the phrase "introducing into a cell," when referring to an RNAi agent, means functionally delivering the RNAi agent into a cell. The phrase "functional delivery," means delivering the RNAi agent to the cell in a manner that enables the RNAi agent to have the expected biological activity, e.g., sequence-specific inhibition of gene expression.

Unless stated otherwise, use of the symbol  as used herein means that any group or groups may be linked thereto that is in accordance with the scope of the inventions described herein.

As used herein, the term "isomers" refers to compounds that have identical molecular formulae, but that differ in the nature or the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed "diastereoisomers," and stereoisomers that are non-superimposable mirror images are termed "enantiomers," or sometimes optical isomers. A carbon atom bonded to four non-identical substituents is termed a "chiral center."

As used herein, unless specifically identified in a structure as having a particular conformation, for each structure in which asymmetric centers are present and thus give rise to enantiomers, diastereomers, or other stereoisomeric configurations, each structure disclosed herein is intended to represent all such possible isomers, including their optically pure and racemic forms. For example, the structures disclosed herein are intended to cover mixtures of diastereomers as well as single stereoisomers.

As used in a claim herein, the phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. When used in a claim herein, the phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention.

The person of ordinary skill in the art would readily understand and appreciate that the compounds and compositions disclosed herein may have certain atoms (e.g., N, O, or S atoms) in a protonated or deprotonated state, depending upon the environment in which the compound or composition is placed. Accordingly, as used herein, the structures disclosed herein envisage

that certain functional groups, such as, for example, OH, SH, or NH, may be protonated or deprotonated. The disclosure herein is intended to cover the disclosed compounds and compositions regardless of their state of protonation based on the environment (such as pH), as would be readily understood by the person of ordinary skill in the art.

As used herein, the term "linked" or "conjugated" when referring to the connection between two compounds or molecules means that two compounds or molecules are joined by a covalent bond. Unless stated, the terms "linked" and "conjugated" as used herein may refer to the connection between a first compound and a second compound either with or without any intervening atoms or groups of atoms.

As used herein, the term "including" is used to herein 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 the context clearly indicates otherwise.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

RNAi Agents

Described herein are RNAi agents for inhibiting expression of an *ASGR1* gene (referred to herein as *ASGR1* RNAi agents or *ASGR1* RNAi triggers). Each *ASGR1* RNAi agent comprises a sense strand and an antisense strand. The sense strand and the antisense strand each can be 16 to 30 nucleotides in length. In some embodiments, the sense and antisense strands each can be 17 to 26 nucleotides in length. The sense and antisense strands can be either the same length or they can be different lengths. In some embodiments, the sense and antisense strands are each independently 17-21 nucleotides in length. In some embodiments, the sense and antisense strands are each 21-26 nucleotides in length. In some embodiments, the sense strand is about 19 nucleotides in length while the antisense strand is about 21 nucleotides in length. In some

embodiments, the sense strand is about 21 nucleotides in length while the antisense strand is about 23 nucleotides in length. In some embodiments, a sense strand is 23 nucleotides in length and an antisense strand is 21 nucleotides in length. In some embodiments, both the sense and antisense strands are each 21 nucleotides in length. In some embodiments, both the sense and antisense strands are each 26 nucleotides in length. In some embodiments, a sense strand is 22 nucleotides in length and an antisense strand is 21 nucleotides in length. In some embodiments, a sense strand is 19 nucleotides in length and an antisense strand is 21 nucleotides in length. In some embodiments, the RNAi agent sense and antisense strands are each independently 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26 nucleotides in length.

In some embodiments, a double-stranded RNAi agent has a duplex length of about 16, 17, 18, 19, 20, 21, 22, 23 or 24 nucleotides. This region of perfect or substantial complementarity between the sense strand and the antisense strand is typically 15-26 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26) nucleotides in length and occurs at or near the 5′ end of the antisense strand (e.g., this region may be separated from the 5’ end of the antisense strand by 0, 1, 2, 3, or 4 nucleotides that are not perfectly or substantially complementary).

The sense strand and antisense strand each contain a core stretch sequence that is 16 to 23 nucleobases in length. An antisense strand core stretch sequence is 100% (perfectly) complementary or at least about 85% (substantially) complementary to a nucleotide sequence (sometimes referred to, e.g., as a target sequence) present in the *ASGR1* mRNA target. A sense strand core stretch sequence is 100% (perfectly) complementary or at least about 85% (substantially) complementary to a core stretch sequence in the antisense strand, and thus the sense strand core stretch sequence is perfectly identical or at least about 85% identical to a nucleotide sequence (target sequence) present in the *ASGR1* mRNA target. A sense strand core stretch sequence can be the same length as a corresponding antisense core sequence or it can be a different length. In some embodiments, the antisense strand core stretch sequence is 16, 17, 18, 19, 20, 21, 22, or 23 nucleotides in length. In some embodiments, the sense strand core stretch sequence is 16, 17, 18, 19, 20, 21, 22, or 23 nucleotides in length.

Examples of sense and antisense strand nucleotide sequences used in forming *ASGR1* RNAi agents are provided in Tables 2, 3 and 4. Examples of RNAi agent duplexes, that include the sense strand and antisense strand sequences in Tables 3 and 4, are shown in Table 5.

The *ASGR1* RNAi agent sense and antisense strands anneal to form a duplex. A sense strand and an antisense strand of an *ASGR1* RNAi agent may be partially, substantially, or fully complementary to each other. Within the complementary duplex region, the sense strand core stretch sequence is at least 85% complementary or 100% complementary to the antisense core stretch sequence. In some embodiments, the sense strand core stretch sequence contains a sequence of at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 nucleotides that is at least 85% or 100% complementary to a corresponding 16, 17, 18, 19, 20, 21, 22, or 23 nucleotide sequence of the antisense strand core stretch sequence (i.e., the sense and antisense core stretch sequences of an *ASGR1* RNAi agent have a region of at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23 nucleotides that is at least 85% base paired or 100% base paired.)

In some embodiments, the antisense strand of an *ASGR1* RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the antisense strand sequences in Table 2 or Table 3. In some embodiments, the sense strand of an *ASGR1* RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the sense strand sequences in Table 2 or Table 4.

The sense strand and/or the antisense strand may optionally and independently contain an additional 1, 2, 3, 4, 5, or 6 nucleotides (extension) at the 3′ end, the 5′ end, or both the 3′ and 5′ ends of the core stretch sequences. The antisense strand additional nucleotides, if present, may or may not be complementary to the corresponding sequence in an *ASGR1* mRNA. The sense strand additional nucleotides, if present, may or may not be identical to the corresponding sequence in an *ASGR1* mRNA. The antisense strand additional nucleotides, if present, may or may not be complementary to the corresponding sense strand's additional nucleotides, if present.

As used herein, an extension comprises 1, 2, 3, 4, 5, or 6 nucleotides at the 5' and/or 3' end of the sense strand core stretch sequence and/or antisense strand core stretch sequence. The extension nucleotides on a sense strand may or may not be complementary to nucleotides, either core stretch sequence nucleotides or extension nucleotides, in the corresponding antisense strand. Conversely, the extension nucleotides on an antisense strand may or may not be complementary to nucleotides, either core stretch nucleotides or extension nucleotides, in the corresponding sense strand. In some embodiments, both the sense strand and the antisense strand of an RNAi agent contain 3′ and 5′ extensions. In some embodiments, one or more of

the 3′ extension nucleotides of one strand base pairs with one or more 5′ extension nucleotides of the other strand. In other embodiments, one or more of 3′ extension nucleotides of one strand do not base pair with one or more 5′ extension nucleotides of the other strand. In some embodiments, an *ASGR1* RNAi agent has an antisense strand having a 3′ extension and a sense strand having a 5′ extension.

In some embodiments, an *ASGR1* RNAi agent comprises an antisense strand having a 3′ extension of 1, 2, 3, 4, 5, or 6 nucleotides in length. In other embodiments, an *ASGR1* RNAi agent comprises an antisense strand having a 3′ extension of 1, 2, or 3 nucleotides in length. In some embodiments, one or more of the antisense strand extension nucleotides comprise uracil or thymidine nucleotides or nucleotides which are complementary to the corresponding *ASGR1* mRNA sequence. In some embodiments, a 3′ antisense strand extension includes or consists of one of the following sequences, but is not limited to: AUA, UGCUU, CUG, UG, UGCC, CUGCC, CGU, CUU, UGCCUA, CUGCCU, UGCCU, UGAUU, GCCUAU, T, TT, U, UU (each listed 5′ to 3′).

In some embodiments, the 3′ end of the antisense strand may include additional abasic residues or sites (Ab). An “abasic residue” or “abasic site” is a nucleotide or nucleoside that lacks a nucleobase at the 1′ position of the sugar. In some embodiments, Ab or AbAb may be added to the 3′ end of the antisense strand. In some embodiments, the abasic residue(s) may be added as inverted abasic residue(s) (see Table 6). (*See, e.g.*, F. Czauderna, Nucleic Acids Res., 2003, 31(11), 2705-16).

In some embodiments, an *ASGR1* RNAi agent comprises an antisense strand having a 5′ extension of 1, 2, 3, 4, or 5 nucleotides in length. In other embodiments, an *ASGR1* RNAi agent comprises an antisense strand having a 5′ extension of 1 or 2 nucleotides in length. In some embodiments, one or more of the antisense strand extension nucleotides comprises uracil or thymidine nucleotides or nucleotides which are complementary to the corresponding *ASGR1* mRNA sequence. In some embodiments, the 5′ antisense strand extension includes or consists of one of the following sequences, but is not limited to, UA, TU, U, T, UU, TT, CUC (each listed 5′ to 3′). An antisense strand may have any of the 3' extensions described above in combination with any of the 5′ antisense strand extensions described, if present.

In some embodiments, an *ASGR1* RNAi agent comprises a sense strand having a 3′ extension of 1, 2, 3, 4, or 5 nucleotides in length. In some embodiments, one or more of the sense strand extension nucleotides comprises adenosine, uracil, or thymidine nucleotides, AT dinucleotide, or nucleotides which correspond to nucleotides in the *ASGR1* mRNA sequence. In some embodiments, the 3′ sense strand extension includes or consists of one of the following sequences, but is not limited to: T, UT, TT, UU, UUT, TTT, or TTTT (each listed 5′ to 3′).

In some embodiments, the 3′ end of the sense strand may include additional abasic residues. In some embodiments, UUAb, UAb, or Ab may be added to the 3′ end of the sense strand. In some embodiments, the one or more abasic residues added to the 3′ end of the sense strand may be inverted (invAb). In some embodiments, one or more inverted abasic residues may be inserted between the targeting ligand and the nucleobase sequence of the sense strand of the RNAi agent. In some embodiments, the inclusion of one or more inverted abasic residues at or near the terminal end or terminal ends of the sense strand of an RNAi agent may allow for enhanced activity or other desired properties of an RNAi agent.

In some embodiments, an *ASGR1* RNAi agent comprises a sense strand having a 5′ extension of 1, 2, 3, 4, 5, or 6 nucleotides in length. In some embodiments, one or more of the sense strand extension nucleotides comprise uracil or adenosine nucleotides or nucleotides which correspond to nucleotides in the *ASGR1* mRNA sequence. In some embodiments, the sense strand 5′ extension can be one of the following sequences, but is not limited to: CA, AUAGGC, AUAGG, AUAG, AUA, A, AA, AC, GCA, GGCA, GGC, UAUCA, UAUC, UCA, UAU, U, UU (each listed 5′ to 3′). A sense strand may have a 3′ extension and/or a 5' extension.

In some embodiments, the 5′ end of the sense strand may include one or more additional abasic residues (e.g., (Ab) or (AbAb)). In some embodiments, the one or more abasic residues added to the 5′ end of the sense strand may be inverted (e.g., invAb). In some embodiments, one or more inverted abasic residues may be inserted between the targeting ligand and the nucleobase sequence of the sense strand of the RNAi agent. In some embodiments, the inclusion of one or more inverted abasic residues at or near the terminal end or terminal ends of the sense strand of an RNAi agent may allow for enhanced activity or other desired properties of an RNAi agent.

In some embodiments, the 3′ end of the sense strand core stretch sequence, or the 3′ end of the sense strand sequence, may include an inverted abasic residue (invAb (*see* Table 6)). In some embodiments, the 5′ end of the sense core stretch, or the 5′ end of the sense strand sequence, may include an inverted abasic site or residue. In some embodiments, both the 3′ and 5′ ends of the sense strand core stretch sequence may include an inverted abasic residue. In some embodiments, both the 3′ and 5′ ends of the sense strand sequence may include an inverted abasic residue.

In some embodiments, the 3′ end of the antisense strand core stretch sequence, or the 3′ end of the antisense strand sequence, may include an inverted abasic residue (invAb (*see* Table 6)). In some embodiments, the 5′ end of the antisense core stretch, or the 5′ end of the antisense strand sequence, may include an inverted abasic site or residue. In some embodiments, both the 3′ and 5′ ends of the antisense strand core stretch sequence may include an inverted abasic residue. In some embodiments, both the 3′ and 5′ ends of the antisense strand sequence may include an inverted abasic residue.

Examples of sequences used in forming *ASGR1* RNAi agents are provided in Tables 2, 3, and 4. In some embodiments, an *ASGR1* RNAi agent antisense strand includes a sequence of any of the sequences in Tables 2 or 3. In some embodiments, an *ASGR1* RNAi agent antisense strand includes the sequence of nucleotides 1-17, 2-15, 2-17, 1-18, 2-18, 1-19, 2-19, 1-20, 2-20, 1-21, 2-21, 1-22, 2-22, 1-23, 2-23, 1-24, 2-24, 1-25, 2-25, 1-26, or 2-26 of any of the sequences in Tables 2 or 3. In certain embodiments, an *ASGR1* RNAi agent antisense strand comprises or consists of a modified sequence of any one of the modified sequences in Table 3. In some embodiments, an *ASGR1* RNAi agent sense strand includes the sequence of any of the sequences in Tables 2 or 4. In some embodiments, an *ASGR1* RNAi agent sense strand includes the sequence of nucleotides 1-18, 1-19, 1-20, 1-21, 1-22, 1-23, 1-24, 1-25, 1-26, 2-19, 2-20, 2-21, 2-22, 2-23, 2-24, 2-25, 2-26, 3-20, 3-21, 3-22, 3-23, 3-24, 3-25, 3-26, 4-21, 4-22, 4-23, 4-24, 4-25, 4-26, 5-22, 5-23, 5-24, 5-25, 5-26, 6-23, 6-24, 6-25, 6-26, 7-24, 7-25, 7-25, 8-25, 8-26 of any of the sequences in Tables 2 or 4. In certain embodiments, an *ASGR1* RNAi agent sense strand comprises or consists of a modified sequence of any one of the modified sequences in Table 4.

In some embodiments, the sense and antisense strands of the RNAi agents described herein contain the same number of nucleotides. In some embodiments, the sense and antisense strands

of the RNAi agents described herein contain different numbers of nucleotides. In some embodiments, the sense strand 5′ end and the antisense strand 3′ end of an RNAi agent form a blunt end. In some embodiments, the sense strand 3′ end and the antisense strand 5′ end of an RNAi agent form a blunt end. In some embodiments, both ends of an RNAi agent form blunt ends. In some embodiments, neither end of an RNAi agent is blunt-ended. As used herein a blunt end refers to an end of a double stranded RNAi agent in which the terminal nucleotides of the two annealed strands are complementary (form a complementary base-pair).

In some embodiments, the sense strand 5′ end and the antisense strand 3′ end of an RNAi agent form a frayed end. In some embodiments, the sense strand 3′ end and the antisense strand 5′ end of an RNAi agent form a frayed end. In some embodiments, both ends of an RNAi agent form a frayed end. In some embodiments, neither end of an RNAi agent is a frayed end. As used herein a frayed end refers to an end of a double stranded RNAi agent in which the terminal nucleotides of the two annealed strands form a pair (i.e. do not form an overhang) but are not complementary (i.e. form a non-complementary pair). As used herein, an overhang is a stretch of one or more unpaired nucleotides at the end of one strand of a double stranded RNAi agent. The unpaired nucleotides may be on the sense strand or the antisense strand, creating either 3' or 5' overhangs. In some embodiments, the RNAi agent contains: a blunt end and a frayed end, a blunt end and 5′ overhang end, a blunt end and a 3′ overhang end, a frayed end and a 5′ overhang end, a frayed end and a 3′ overhang end, two 5′ overhang ends, two 3′ overhang ends, a 5′ overhang end and a 3′ overhang end, two frayed ends, or two blunt ends.

A nucleotide base (or nucleobase) is a heterocyclic pyrimidine or purine compound which is a constituent of all nucleic acids and includes adenine (A), guanine (G), cytosine (C), thymine (T), and uracil (U). As used herein, the term “nucleotide” can include a modified nucleotide (such as, for example, a nucleotide mimic, abasic site or residue (Ab), or a surrogate replacement moiety). Modified nucleotides, when used in various polynucleotide or oligonucleotide constructs, may preserve activity of the compound in cells while at the same time increasing the serum stability of these compounds, and can also minimize the possibility of activating interferon activity in humans upon administering of the polynucleotide or oligonucleotide construct.

In some embodiments, an *ASGR1* RNAi agent is prepared or provided as a salt, mixed salt, or a free-acid. In some embodiments, an *ASGR1* RNAi agent is prepared as a sodium salt. Such forms are within the scope of the inventions disclosed herein.

Modified Nucleotides

In some embodiments, an *ASGR1* RNAi agent contains one or more modified nucleotides. As used herein, a "modified nucleotide" is a nucleotide other than a ribonucleotide (2′-hydroxyl nucleotide). In some embodiments, at least 50% (e.g., at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100%) of the nucleotides are modified nucleotides. As used herein, modified nucleotides include, but are not limited to, deoxyribonucleotides, nucleotide mimics, abasic nucleotides (represented herein as Ab), 2′-modified nucleotides, 3′ to 3′ linkages (inverted) nucleotides (represented herein as invdN, invN, invn, invAb), modified nucleobase-comprising nucleotides, bridged nucleotides, peptide nucleic acids (PNAs), 2′,3′-seco nucleotide mimics (unlocked nucleobase analogues, represented herein as N_{UNA} or NUNA), locked nucleotides (represented herein as N_{LNA} or NLNA), 3′-O-methoxy (2′ internucleoside linked) nucleotides (represented herein as 3′-OMen), 2'-F-Arabino nucleotides (represented herein as NfANA or Nf_{ANA}), 5'-Me, 2'-fluoro nucleotide (represented herein as 5Me-Nf), morpholino nucleotides, vinyl phosphonate deoxyribonucleotides (represented herein as vpdN), vinyl phosphonate containing nucleotides, and cyclopropyl phosphonate containing nucleotides (cPrpN). 2′-modified nucleotides (i.e. a nucleotide with a group other than a hydroxyl group at the 2′ position of the five-membered sugar ring) include, but are not limited to, 2′-O-methyl nucleotides (represented herein as a lower case letter 'n' in a nucleotide sequence), 2′-deoxy-2′-fluoro nucleotides (represented herein as Nf, also represented herein as 2′-fluoro nucleotide), 2′-deoxy nucleotides (represented herein as dN), 2′-methoxyethyl (2′-O-2-methoxylethyl) nucleotides (represented herein as NM or 2′-MOE), 2′-amino nucleotides, and 2′-alkyl nucleotides. It is not necessary for all positions in a given compound to be uniformly modified. Conversely, more than one modification may be incorporated in a single *ASGR1* RNAi agent or even in a single nucleotide thereof. The *ASGR1* RNAi agent sense strands and antisense strands may be synthesized and/or modified by methods known in the art. Modification at one nucleotide is independent of modification at another nucleotide.

Modified nucleobases include synthetic and natural nucleobases, such as 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, (e.g.,

2-aminopropyladenine, 5-propynyluracil, or 5-propynylcytosine), 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, inosine, xanthine, hypoxanthine, 2-aminoadenine, 6-alkyl (e.g., 6-methyl, 6-ethyl, 6-isopropyl, or 6-n-butyl) derivatives of adenine and guanine, 2-alkyl (e.g., 2-methyl, 2-ethyl, 2-isopropyl, or 2-n-butyl) and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine, 2-thiocytosine, 5-halouracil, cytosine, 5-propynyl uracil, 5-propynyl cytosine, 6-azo uracil, 6-azo cytosine, 6-azo thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-sulfhydryl, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo (e.g., 5-bromo), 5-trifluoromethyl, and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, and 3-deazaadenine.

In some embodiments, all or substantially all of the nucleotides of an RNAi agent are modified nucleotides. As used herein, an RNAi agent wherein substantially all of the nucleotides present are modified nucleotides is an RNAi agent having four or fewer (i.e., 0, 1, 2, 3, or 4) nucleotides in both the sense strand and the antisense strand being ribonucleotides. As used herein, a sense strand wherein substantially all of the nucleotides present are modified nucleotides is a sense strand having two or fewer (i.e., 0, 1, or 2) nucleotides in the sense strand being ribonucleotides. As used herein, an antisense sense strand wherein substantially all of the nucleotides present are modified nucleotides is an antisense strand having two or fewer (i.e., 0, 1, or 2) nucleotides in the sense strand being ribonucleotides. In some embodiments, one or more nucleotides of an RNAi agent is a ribonucleotide.

Modified Internucleoside Linkages

In some embodiments, one or more nucleotides of an *ASGR1* RNAi agent are linked by non-standard linkages or backbones (i.e., modified internucleoside linkages or modified backbones). Modified internucleoside linkages or backbones include, but are not limited to, phosphorothioate groups (represented herein as a lower case "s"), chiral phosphorothioates, thiophosphates, phosphorodithioates, phosphotriesters, aminoalkyl-phosphotriesters, alkyl phosphonates (e.g., methyl phosphonates or 3′-alkylene phosphonates), chiral phosphonates, phosphinates, phosphoramidates (e.g., 3′-amino phosphoramidate, aminoalkylphosphoramidates, or thionophosphoramidates), thionoalkyl-phosphonates, thionoalkylphosphotriesters, morpholino linkages, boranophosphates having normal 3′-5′ linkages, 2′-5′ linked analogs of boranophosphates, or boranophosphates having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3′-5′ to 5′-3′ or 2′-5′ to 5′-2′.

In some embodiments, a modified internucleoside linkage or backbone lacks a phosphorus atom. Modified internucleoside linkages lacking a phosphorus atom include, but are not limited to, short chain alkyl or cycloalkyl inter-sugar linkages, mixed heteroatom and alkyl or cycloalkyl inter-sugar linkages, or one or more short chain heteroatomic or heterocyclic inter-sugar linkages. In some embodiments, modified internucleoside backbones include, but are not limited to, siloxane backbones, sulfide backbones, sulfoxide backbones, 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 other backbones having mixed N, O, S, and CH_2 components.

In some embodiments, a sense strand of an *ASGR1* RNAi agent can contain 1, 2, 3, 4, 5, or 6 phosphorothioate linkages, an antisense strand of an *ASGR1* RNAi agent can contain 1, 2, 3, 4, 5, or 6 phosphorothioate linkages, or both the sense strand and the antisense strand independently can contain 1, 2, 3, 4, 5, or 6 phosphorothioate linkages. In some embodiments, a sense strand of an *ASGR1* RNAi agent can contain 1, 2, 3, or 4 phosphorothioate linkages, an antisense strand of an *ASGR1* RNAi agent can contain 1, 2, 3, or 4 phosphorothioate linkages, or both the sense strand and the antisense strand independently can contain 1, 2, 3, or 4 phosphorothioate linkages.

In some embodiments, an *ASGR1* RNAi agent sense strand contains at least two phosphorothioate internucleoside linkages. In some embodiments, the at least two phosphorothioate internucleoside linkages are between the nucleotides at positions 1-3 from the 3′ end of the sense strand. In some embodiments, the at least two phosphorothioate internucleoside linkages are between the nucleotides at positions 1-3, 2-4, 3-5, 4-6, 4-5, or 6-8 from the 5' end of the sense strand. In some embodiments, one phosphorothioate internucleoside linkage is at the 5’ end of the sense strand, and another phosphorothioate linkage is at the 3’ end of the sense strand. In some embodiments, two phosphorothioate internucleoside linkage are located at the 5’ end of the sense strand, and another phosphorothioate linkage is at the 3’ end of the sense strand. In some embodiments, the sense strand does not include any phosphorothioate internucleoside linkages between the nucleotides, but contains one, two, or three phosphorothioate linkages between the terminal nucleotides on both the 5’ and 3’ ends and the optionally present inverted abasic residue terminal caps. In some embodiments, the targeting ligand is linked to the sense strand via a phosphorothioate

linkage. In some embodiments, an *ASGR1* RNAi agent antisense strand contains four phosphorothioate internucleoside linkages. In some embodiments, the four phosphorothioate internucleoside linkages are between the nucleotides at positions 1-3 from the 5′ end of the antisense strand and between the nucleotides at positions 19-21, 20-22, 21-23, 22-24, 23-25, or 24-26 from the 5′ end. In some embodiments, an *ASGR1* RNAi agent contains at least two phosphorothioate internucleoside linkages in the sense strand and three or four phosphorothioate internucleoside linkages in the antisense strand.

In some embodiments, an *ASGR1* RNAi agent antisense strand contains four phosphorothioate internucleoside linkages. In some embodiments, the four phosphorothioate internucleoside linkages are between the nucleotides at positions 1-3 from the 5' end of the antisense strand and between the nucleotides at positions 19-21, 20-22, 21-23, 22-24, 23-25, or 24-26 from the 5' end. In some embodiments, three phosphorothioate internucleoside linkages are located between positions 1-4 from the 5’ end of the antisense strand, and a fourth phosphorothioate internucleoside linkage is located between positions 20-21 from the 5’ end of the antisense strand. In some embodiments, an *ASGR1* RNAi agent contains at least three or four phosphorothioate internucleoside linkages in the antisense strand.

In some embodiments, an *ASGR1* RNAi agent contains one or more modified nucleotides and one or more modified internucleoside linkages. In some embodiments, a 2′-modified nucleoside is combined with modified internucleoside linkage.

***ASGR1* RNAi Agents**

In some embodiments, the *ASGR1* RNAi agents disclosed herein target an *ASGR1* gene at or near the positions of the *ASGR1* gene shown in Table 1. In some embodiments, the antisense strand of an *ASGR1* RNAi agent disclosed herein includes a core stretch sequence that is fully, substantially, or at least partially complementary to a target *ASGR1* 19-mer sequence disclosed in Table 1.

Table 1. *ASGR1* 19-mer mRNA Target Sequences (taken from human *ASGR1* (transcript variant 1) cDNA, GenBank NM_001671.4 (SEQ ID NO:1)).

SEQ ID No.	*ASGR1* 19-mer Target Sequences (5' → 3')	Corresponding Gene Positions (taken from SEQ ID NO: 1)
37	AGCCCUAUCAUGACCAAGG	392-410
38	CCUAUCAUGACCAAGGAGU	395-413
39	CUAUCAUGACCAAGGAGUA	396-414
40	UAUCAUGACCAAGGAGUAU	397-415
41	AUCAUGACCAAGGAGUAUC	398-416
42	CAUGACCAAGGAGUAUCAA	400-418
43	GGAGAGUGACCACCAUCAG	442-460
44	GAGUGACCACCAUCAGCUC	445-463
45	CAACUUCACAGCGAGCACG	634-652
46	AGGGAGGCAAUGUGGGAAG	681-699
47	GGAGGCAAUGUGGGAAGAA	683-701
48	GGCAAUGUGGGAAGAAAGA	686-704
49	CAAUGUGGGAAGAAAGAUG	688-706
50	AAUGUGGGAAGAAAGAUGA	689-707
51	GUGGGAAGAAAGAUGAAGU	692-710
52	GGAAGAAAGAUGAAGUCGC	695-713
53	GAAGAAAGAUGAAGUCGCU	696-714
54	UGCUGCUCCACGUGAAGCA	768-786
55	CUGCUCCACGUGAAGCAGU	770-788
56	UGCUCCACGUGAAGCAGUU	771-789
57	GCUCCACGUGAAGCAGUUC	772-790
58	UCCACGUGAAGCAGUUCGU	774-792
59	GCUCCAGGGCAAUGGCUCA	829-847
60	CACGAGCGCAGCUGCUACU	881-899
61	AGCGCAGCUGCUACUGGUU	885-903
62	GCGCAGCUGCUACUGGUUC	886-904
63	GACGCCGACAACUACUGCC	929-947
64	ACCUGGUGGUGGUCACGUC	963-981
65	UGGUGGUGGUCACGUCCUG	966-984
66	AGGAGCAGAAAUUUGUCCA	987-1005
67	GCAGAAAUUUGUCCAGCAC	991-1009
68	GCCUCCACGACCAAAACGG	1038-1056
69	GGACGGGACGGACUACGAG	1072-1090
70	GACGGGACGGACUACGAGA	1073-1091
71	ACGGGACGGACUACGAGAC	1074-1092
72	CAGCCGGACGACUGGUACG	1118-1136
73	CGCUGGAACGACGACGUCU	1187-1205

SEQ ID No.	*ASGR1* 19-mer Target Sequences (5' → 3')	Corresponding Gene Positions (taken from SEQ ID NO: 1)
74	GGUCUGCGAGACAGAGCUG	1225-1243
75	GGAGCCACCUCUCCUUUAA	1258-1276
76	GAGCCACCUCUCCUUUAAU	1259-1277
77	AGCCACCUCUCCUUUAAUU	1260-1278
78	UCUCCUUUAAUUUAUUUCU	1267-1285

In some embodiments, an *ASGR1* RNAi agent includes an antisense strand wherein position 19 of the antisense strand (5′→3′) is capable of forming a base pair with position 1 of a 19-mer target sequence disclosed in Table 1. In some embodiments, an *ASGR1* RNAi agent includes an antisense strand wherein position 1 of the antisense strand (5′ → 3′) is capable of forming a base pair with position 19 of the 19-mer target sequence disclosed in Table 1.

In some embodiments, an *ASGR1* RNAi agent includes an antisense strand wherein position 2 of the antisense strand (5′ → 3′) is capable of forming a base pair with position 18 of the 19-mer target sequence disclosed in Table 1. In some embodiments, an *ASGR1* RNAi agent includes an antisense strand wherein positions 2 through 18 of the antisense strand (5′ → 3′) are capable of forming base pairs with each of the respective complementary bases located at positions 18 through 2 of the 19-mer target sequence disclosed in Table 1.

For the RNAi agents disclosed herein, the nucleotide at position 1 of the antisense strand (from 5′ end → 3′ end) can be perfectly complementary to the *ASGR1* gene, or can be non-complementary to the *ASGR1* gene. In some embodiments, the nucleotide at position 1 of the antisense strand (from 5′ end → 3′ end) is a U, A, or dT (or a modified version thereof). In some embodiments, the nucleotide at position 1 of the antisense strand (from 5′ end → 3′ end) forms an A:U or U:A base pair with the sense strand.

In some embodiments, an *ASGR1* RNAi agent antisense strand comprises the sequence of nucleotides (from 5′ end → 3′ end) 2-18 or 2-19 of any of the antisense strand sequences in Table 2 or Table 3. In some embodiments, an *ASGR1* RNAi sense strand comprises the sequence of nucleotides (from 5′ end → 3′ end) 1-17, 1-18, or 2-18 of any of the sense strand sequences in Table 2 or Table 4.

In some embodiments, an *ASGR1* RNAi agent is comprised of (i) an antisense strand comprising the sequence of nucleotides (from 5′ end → 3′ end) 2-18 or 2-19 of any of the antisense strand sequences in Table 2 or Table 3, and (ii) a sense strand comprising the sequence of nucleotides (from 5′ end → 3′ end) 1-17, 1-18, or 2-18 of any of the sense strand sequences in Table 2 or Table 4.

In some embodiments, the *ASGR1* RNAi agents include core 19-mer nucleotide sequences in the sense strand, antisense strand, or both the sense and antisense strands, shown in the following Table 2.

Table 2. Example *ASGR1* RNAi Agent Antisense Strand and Sense Strand Core Stretch Base Sequences (N=any nucleobase; I=inosine (hypoxanthine) nucleotide).

SEQ ID No.	Antisense Sequence (5′ → 3′) (19-mer)	SEQ ID No.	Sense Sequence (5′ → 3′) (19-mer)	Gene Position (taken from SEQ ID NO: 1)
79	CCUUGGUCAUGAUAGGGCU	242	AGCCCUAUCAUGACCAAGG	392-410
80	UCUUGGUCAUGAUAGGGCU	243	AGCCCUAUCAUGACCAAGA	392-410
81	NCUUGGUCAUGAUAGGGCU	244	AGCCCUAUCAUGACCAAGN	392-410
82	NCUUGGUCAUGAUAGGGCN	245	NGCCCUAUCAUGACCAAGN	392-410
83	ACUCCUUGGUCAUGAUAGG	246	CCUAUCAUGACCAAGGAGU	395-413
84	UCUCCUUGGUCAUGAUAGG	247	CCUAUCAUGACCAAGGAGA	395-413
85	NCUCCUUGGUCAUGAUAGG	248	CCUAUCAUGACCAAGGAGN	395-413
86	NCUCCUUGGUCAUGAUAGN	249	NCUAUCAUGACCAAGGAGN	395-413
87	UACUCCUUGGUCAUGAUAG	250	CUAUCAUGACCAAGGAGUA	396-414
88	NACUCCUUGGUCAUGAUAG	251	CUAUCAUGACCAAGGAGUN	396-414
89	NACUCCUUGGUCAUGAUAN	252	NUAUCAUGACCAAGGAGUN	396-414
87	UACUCCUUGGUCAUGAUAG	253	CUAUCAUGACCAAGGAIUA	396-414
88	NACUCCUUGGUCAUGAUAG	254	CUAUCAUGACCAAGGAIUN	396-414
89	NACUCCUUGGUCAUGAUAN	255	NUAUCAUGACCAAGGAIUN	396-414
89	NACUCCUUGGUCAUGAUAN	256	NUAUCAUGACCAAGGANUN	396-414
87	UACUCCUUGGUCAUGAUAG	257	CUAUCAUGACCAAIGAIUA	396-414
88	NACUCCUUGGUCAUGAUAG	258	CUAUCAUGACCAAIGAIUN	396-414
89	NACUCCUUGGUCAUGAUAN	259	NUAUCAUGACCAAIGAIUN	396-414
89	NACUCCUUGGUCAUGAUAN	260	NUAUCAUGACCAANGANUN	396-414
90	AUACUCCUUGGUCAUGAUA	261	UAUCAUGACCAAGGAGUAU	397-415
91	UUACUCCUUGGUCAUGAUA	262	UAUCAUGACCAAGGAGUAA	397-415
92	NUACUCCUUGGUCAUGAUA	263	UAUCAUGACCAAGGAGUAN	397-415

SEQ ID No.	Antisense Sequence (5′ → 3′) (19-mer)	SEQ ID No.	Sense Sequence (5′ → 3′) (19-mer)	Gene Position (taken from SEQ ID NO: 1)
93	NUACUCCUUGGUCAUGAUN	264	NAUCAUGACCAAGGAGUAN	397-415
94	GAUACUCCUUGGUCAUGAU	265	AUCAUGACCAAGGAGUAUC	398-416
95	UAUACUCCUUGGUCAUGAU	266	AUCAUGACCAAGGAGUAUA	398-416
96	NAUACUCCUUGGUCAUGAU	267	AUCAUGACCAAGGAGUAUN	398-416
97	NAUACUCCUUGGUCAUGAN	268	NUCAUGACCAAGGAGUAUN	398-416
98	UUGAUACUCCUUGGUCAUG	269	CAUGACCAAGGAGUAUCAA	400-418
99	NUGAUACUCCUUGGUCAUG	270	CAUGACCAAGGAGUAUCAN	400-418
100	NUGAUACUCCUUGGUCAUN	271	NAUGACCAAGGAGUAUCAN	400-418
101	CUGAUGGUGGUCACUCUCC	272	GGAGAGUGACCACCAUCAG	442-460
102	UUGAUGGUGGUCACUCUCC	273	GGAGAGUGACCACCAUCAA	442-460
103	NUGAUGGUGGUCACUCUCC	274	GGAGAGUGACCACCAUCAN	442-460
104	NUGAUGGUGGUCACUCUCN	275	NGAGAGUGACCACCAUCAN	442-460
105	GAGCUGAUGGUGGUCACUC	276	GAGUGACCACCAUCAGCUC	445-463
106	UAGCUGAUGGUGGUCACUC	277	GAGUGACCACCAUCAGCUA	445-463
107	NAGCUGAUGGUGGUCACUC	278	GAGUGACCACCAUCAGCUN	445-463
108	NAGCUGAUGGUGGUCACUN	279	NAGUGACCACCAUCAGCUN	445-463
109	CGUGCUCGCUGUGAAGUUG	280	CAACUUCACAGCGAGCACG	634-652
110	UGUGCUCGCUGUGAAGUUG	281	CAACUUCACAGCGAGCACA	634-652
111	NGUGCUCGCUGUGAAGUUG	282	CAACUUCACAGCGAGCACN	634-652
112	NGUGCUCGCUGUGAAGUUN	283	NAACUUCACAGCGAGCACN	634-652
113	CUUCCCACAUUGCCUCCCA	284	AGGGAGGCAAUGUGGGAAG	681-699
114	UUUCCCACAUUGCCUCCCA	285	AGGGAGGCAAUGUGGGAAA	681-699
115	NUUCCCACAUUGCCUCCCA	286	AGGGAGGCAAUGUGGGAAN	681-699
116	NUUCCCACAUUGCCUCCCN	287	NGGGAGGCAAUGUGGGAAN	681-699
117	UUCUUCCCACAUUGCCUCC	288	GGAGGCAAUGUGGGAAGAA	683-701
118	NUCUUCCCACAUUGCCUCC	289	GGAGGCAAUGUGGGAAGAN	683-701
119	NUCUUCCCACAUUGCCUCN	290	NGAGGCAAUGUGGGAAGAN	683-701

SEQ ID No.	Antisense Sequence (5′ → 3′) (19-mer)	SEQ ID No.	Sense Sequence (5′ → 3′) (19-mer)	Gene Position (taken from SEQ ID NO: 1)
120	UCUUUCUUCCCACAUUGCC	291	GGCAAUGUGGGAAGAAAGA	686-704
121	NCUUUCUUCCCACAUUGCC	292	GGCAAUGUGGGAAGAAAGN	686-704
122	NCUUUCUUCCCACAUUGCN	293	NGCAAUGUGGGAAGAAAGN	686-704
123	CAUCUUUCUUCCCACAUUG	294	CAAUGUGGGAAGAAAGAUG	688-706
124	UAUCUUUCUUCCCACAUUG	295	CAAUGUGGGAAGAAAGAUA	688-706
125	NAUCUUUCUUCCCACAUUG	296	CAAUGUGGGAAGAAAGAUN	688-706
126	NAUCUUUCUUCCCACAUUN	297	NAAUGUGGGAAGAAAGAUN	688-706
127	NAUCUUUCUUCCCACAUUN	298	NAAUGUNGGAAGAAAGAUN	688-706
128	NAUCUUUCUUCCCACAUUN	299	NAAUGUGNGAAGAAAGAUN	688-706
129	UCAUCUUUCUUCCCACAUU	300	AAUGUGGGAAGAAAGAUGA	689-707
130	NCAUCUUUCUUCCCACAUU	301	AAUGUGGGAAGAAAGAUGN	689-707
131	NCAUCUUUCUUCCCACAUN	302	NAUGUGGGAAGAAAGAUGN	689-707
132	NCAUCUUUCUUCCCACAUN	303	NAUGUNGGAAGAAAGAUGN	689-707
133	ACUUCAUCUUUCUUCCCAC	304	GUGGGAAGAAAGAUGAAGU	692-710
134	UCUUCAUCUUUCUUCCCAC	305	GUGGGAAGAAAGAUGAAGA	692-710
135	NCUUCAUCUUUCUUCCCAC	306	GUGGGAAGAAAGAUGAAGN	692-710
136	NCUUCAUCUUUCUUCCCAN	307	NUGGGAAGAAAGAUGAAGN	692-710
137	GCGACUUCAUCUUUCUUCC	308	GGAAGAAAGAUGAAGUCGC	695-713
138	UCGACUUCAUCUUUCUUCC	309	GGAAGAAAGAUGAAGUCGA	695-713
139	NCGACUUCAUCUUUCUUCC	310	GGAAGAAAGAUGAAGUCGN	695-713
140	NCGACUUCAUCUUUCUUCN	311	NGAAGAAAGAUGAAGUCGN	695-713
141	AGCGACUUCAUCUUUCUUC	312	GAAGAAAGAUGAAGUCGCU	696-714
142	UGCGACUUCAUCUUUCUUC	313	GAAGAAAGAUGAAGUCGCA	696-714
143	NGCGACUUCAUCUUUCUUC	314	GAAGAAAGAUGAAGUCGCN	696-714
144	NGCGACUUCAUCUUUCUUN	315	NAAGAAAGAUGAAGUCGCN	696-714
141	AGCGACUUCAUCUUUCUUC	316	GAAGAAAGAUGAAGUCICU	696-714
142	UGCGACUUCAUCUUUCUUC	317	GAAGAAAGAUGAAGUCICA	696-714

SEQ ID No.	Antisense Sequence (5′ → 3′) (19-mer)	SEQ ID No.	Sense Sequence (5′ → 3′) (19-mer)	Gene Position (taken from SEQ ID NO: 1)
143	NGCGACUUCAUCUUUCUUC	318	GAAGAAAGAUGAAGUCICN	696-714
144	NGCGACUUCAUCUUUCUUN	319	NAAGAAAGAUGAAGUCICN	696-714
145	NGCGACUUCAUCUUUCUUN	320	NAAGAAAGAUGAAGUCNCN	696-714
141	AGCGACUUCAUCUUUCUUC	852	GAAGAAAGAUGAAIUCICU	696-714
142	UGCGACUUCAUCUUUCUUC	879	GAAGAAAGAUGAAIUCICA	696-714
143	NGCGACUUCAUCUUUCUUC	883	GAAGAAAGAUGAAIUCICN	696-714
144	NGCGACUUCAUCUUUCUUN	886	NAAGAAAGAUGAAIUCICN	696-714
145	NGCGACUUCAUCUUUCUUN	892	NAAGAAAGAUGAANUCNCN	696-714
146	UGCUUCACGUGGAGCAGCA	321	UGCUGCUCCACGUGAAGCA	768-786
147	NGCUUCACGUGGAGCAGCA	322	UGCUGCUCCACGUGAAGCN	768-786
148	NGCUUCACGUGGAGCAGCN	323	NGCUGCUCCACGUGAAGCN	768-786
149	ACUGCUUCACGUGGAGCAG	324	CUGCUCCACGUGAAGCAGU	770-788
150	UCUGCUUCACGUGGAGCAG	325	CUGCUCCACGUGAAGCAGA	770-788
151	NCUGCUUCACGUGGAGCAG	326	CUGCUCCACGUGAAGCAGN	770-788
152	NCUGCUUCACGUGGAGCAN	327	NUGCUCCACGUGAAGCAGN	770-788
153	AACUGCUUCACGUGGAGCA	328	UGCUCCACGUGAAGCAGUU	771-789
154	UACUGCUUCACGUGGAGCA	329	UGCUCCACGUGAAGCAGUA	771-789
155	NACUGCUUCACGUGGAGCA	330	UGCUCCACGUGAAGCAGUN	771-789
156	NACUGCUUCACGUGGAGCN	331	NGCUCCACGUGAAGCAGUN	771-789
157	GAACUGCUUCACGUGGAGC	332	GCUCCACGUGAAGCAGUUC	772-790
158	UAACUGCUUCACGUGGAGC	333	GCUCCACGUGAAGCAGUUA	772-790
159	NAACUGCUUCACGUGGAGC	334	GCUCCACGUGAAGCAGUUN	772-790
160	NAACUGCUUCACGUGGAGN	335	NCUCCACGUGAAGCAGUUN	772-790
161	ACGAACUGCUUCACGUGGA	336	UCCACGUGAAGCAGUUCGU	774-792
162	UCGAACUGCUUCACGUGGA	337	UCCACGUGAAGCAGUUCGA	774-792
163	NCGAACUGCUUCACGUGGA	338	UCCACGUGAAGCAGUUCGN	774-792
164	NCGAACUGCUUCACGUGGN	339	NCCACGUGAAGCAGUUCGN	774-792

SEQ ID No.	Antisense Sequence (5′ → 3′) (19-mer)	SEQ ID No.	Sense Sequence (5′ → 3′) (19-mer)	Gene Position (taken from SEQ ID NO: 1)
165	UGAGCCAUUGCCCUGGAGC	340	GCUCCAGGGCAAUGGCUCA	829-847
166	NGAGCCAUUGCCCUGGAGC	341	GCUCCAGGGCAAUGGCUCN	829-847
167	NGAGCCAUUGCCCUGGAGN	342	NCUCCAGGGCAAUGGCUCN	829-847
168	AGUAGCAGCUGCGCUCGUG	343	CACGAGCGCAGCUGCUACU	881-899
169	UGUAGCAGCUGCGCUCGUG	344	CACGAGCGCAGCUGCUACA	881-899
170	NGUAGCAGCUGCGCUCGUG	345	CACGAGCGCAGCUGCUACN	881-899
171	NGUAGCAGCUGCGCUCGUN	346	NACGAGCGCAGCUGCUACN	881-899
172	AACCAGUAGCAGCUGCGCU	347	AGCGCAGCUGCUACUGGUU	885-903
173	UACCAGUAGCAGCUGCGCU	348	AGCGCAGCUGCUACUGGUA	885-903
174	NACCAGUAGCAGCUGCGCU	349	AGCGCAGCUGCUACUGGUN	885-903
175	NACCAGUAGCAGCUGCGCN	350	NGCGCAGCUGCUACUGGUN	885-903
176	GAACCAGUAGCAGCUGCGC	351	GCGCAGCUGCUACUGGUUC	886-904
177	UAACCAGUAGCAGCUGCGC	352	GCGCAGCUGCUACUGGUUA	886-904
178	NAACCAGUAGCAGCUGCGC	353	GCGCAGCUGCUACUGGUUN	886-904
179	NAACCAGUAGCAGCUGCGN	354	NCGCAGCUGCUACUGGUUN	886-904
180	GGCAGUAGUUGUCGGCGUC	355	GACGCCGACAACUACUGCC	929-947
181	UGCAGUAGUUGUCGGCGUC	356	GACGCCGACAACUACUGCA	929-947
182	NGCAGUAGUUGUCGGCGUC	357	GACGCCGACAACUACUGCN	929-947
183	NGCAGUAGUUGUCGGCGUN	358	NACGCCGACAACUACUGCN	929-947
184	GACGUGACCACCACCAGGU	359	ACCUGGUGGUGGUCACGUC	963-981
185	UACGUGACCACCACCAGGU	360	ACCUGGUGGUGGUCACGUA	963-981
186	NACGUGACCACCACCAGGU	361	ACCUGGUGGUGGUCACGUN	963-981
187	NACGUGACCACCACCAGGN	362	NCCUGGUGGUGGUCACGUN	963-981
188	CAGGACGUGACCACCACCA	363	UGGUGGUGGUCACGUCCUG	966-984
189	UAGGACGUGACCACCACCA	364	UGGUGGUGGUCACGUCCUA	966-984
190	NAGGACGUGACCACCACCA	365	UGGUGGUGGUCACGUCCUN	966-984
191	NAGGACGUGACCACCACCN	366	NGGUGGUGGUCACGUCCUN	966-984

SEQ ID No.	Antisense Sequence (5′ → 3′) (19-mer)	SEQ ID No.	Sense Sequence (5′ → 3′) (19-mer)	Gene Position (taken from SEQ ID NO: 1)
192	UGGACAAAUUUCUGCUCCU	367	AGGAGCAGAAAUUUGUCCA	987-1005
193	NGGACAAAUUUCUGCUCCU	368	AGGAGCAGAAAUUUGUCCN	987-1005
194	NGGACAAAUUUCUGCUCCN	369	NGGAGCAGAAAUUUGUCCN	987-1005
195	GUGCUGGACAAAUUUCUGC	370	GCAGAAAUUUGUCCAGCAC	991-1009
196	UUGCUGGACAAAUUUCUGC	371	GCAGAAAUUUGUCCAGCAA	991-1009
197	NUGCUGGACAAAUUUCUGC	372	GCAGAAAUUUGUCCAGCAN	991-1009
198	NUGCUGGACAAAUUUCUGN	373	NCAGAAAUUUGUCCAGCAN	991-1009
199	CCGUUUUGGUCGUGGAGGC	374	GCCUCCACGACCAAAACGG	1038-1056
200	UCGUUUUGGUCGUGGAGGC	375	GCCUCCACGACCAAAACGA	1038-1056
201	NCGUUUUGGUCGUGGAGGC	376	GCCUCCACGACCAAAACGN	1038-1056
202	NCGUUUUGGUCGUGGAGGN	377	NCCUCCACGACCAAAACGN	1038-1056
203	CUCGUAGUCCGUCCCGUCC	378	GGACGGGACGGACUACGAG	1072-1090
204	UUCGUAGUCCGUCCCGUCC	379	GGACGGGACGGACUACGAA	1072-1090
205	NUCGUAGUCCGUCCCGUCC	380	GGACGGGACGGACUACGAN	1072-1090
206	NUCGUAGUCCGUCCCGUCN	381	NGACGGGACGGACUACGAN	1072-1090
207	UCUCGUAGUCCGUCCCGUC	382	GACGGGACGGACUACGAGA	1073-1091
208	NCUCGUAGUCCGUCCCGUC	383	GACGGGACGGACUACGAGN	1073-1091
209	NCUCGUAGUCCGUCCCGUN	384	NACGGGACGGACUACGAGN	1073-1091
210	GUCUCGUAGUCCGUCCCGU	385	ACGGGACGGACUACGAGAC	1074-1092
211	UUCUCGUAGUCCGUCCCGU	386	ACGGGACGGACUACGAGAA	1074-1092
212	NUCUCGUAGUCCGUCCCGU	387	ACGGGACGGACUACGAGAN	1074-1092
213	NUCUCGUAGUCCGUCCCGN	388	NCGGGACGGACUACGAGAN	1074-1092
214	CGUACCAGUCGUCCGGCUG	389	CAGCCGGACGACUGGUACG	1118-1136
215	UGUACCAGUCGUCCGGCUG	390	CAGCCGGACGACUGGUACA	1118-1136
216	NGUACCAGUCGUCCGGCUG	391	CAGCCGGACGACUGGUACN	1118-1136
217	NGUACCAGUCGUCCGGCUN	392	NAGCCGGACGACUGGUACN	1118-1136
218	AGACGUCCGUCGUUCCAGCG	393	CGCUGGAACGACGACGUCU	1187-1205

SEQ ID No.	Antisense Sequence (5′ → 3′) (19-mer)	SEQ ID No.	Sense Sequence (5′ → 3′) (19-mer)	Gene Position (taken from SEQ ID NO: 1)
219	UGACGUCCGUCGUUCCAGCG	394	CGCUGGAACGACGACGUCA	1187-1205
220	NGACGUCCGUCGUUCCAGCG	395	CGCUGGAACGACGACGUCN	1187-1205
221	NGACGUCCGUCGUUCCAGCN	396	NGCUGGAACGACGACGUCN	1187-1205
222	NGACGUCCGUCGUUCCAGCN	397	NGCUGGAACGACGANGUCN	1187-1205
223	CAGCUCUGUCUCGCAGACC	398	GGUCUGCGAGACAGAGCUG	1225-1243
224	UAGCUCUGUCUCGCAGACC	399	GGUCUGCGAGACAGAGCUA	1225-1243
225	NAGCUCUGUCUCGCAGACC	400	GGUCUGCGAGACAGAGCUN	1225-1243
226	NAGCUCUGUCUCGCAGACN	401	NGUCUGCGAGACAGAGCUN	1225-1243
227	UUAAAGGAGAGGUGGGCUCC	402	GGAGCCACCUCUCCUUUAA	1258-1276
228	NUAAAGGAGAGGUGGGCUCC	403	GGAGCCACCUCUCCUUUAN	1258-1276
229	NUAAAGGAGAGGUGGGCUCN	404	NGAGCCACCUCUCCUUUAN	1258-1276
230	AUUAAAGGAGAGGUGGGCUC	405	GAGCCACCUCUCCUUUAAU	1259-1277
231	UUUAAAGGAGAGGUGGGCUC	406	GAGCCACCUCUCCUUUAAA	1259-1277
232	NUUAAAGGAGAGGUGGGCUC	407	GAGCCACCUCUCCUUUAAN	1259-1277
233	NUUAAAGGAGAGGUGGGCUN	408	NAGCCACCUCUCCUUUAAN	1259-1277
234	AAUUAAAGGAGAGGUGGGCU	409	AGCCACCUCUCCUUUAAUU	1260-1278
235	UAUUAAAGGAGAGGUGGGCU	410	AGCCACCUCUCCUUUAAUA	1260-1278
236	NAUUAAAGGAGAGGUGGGCU	411	AGCCACCUCUCCUUUAAUN	1260-1278
237	NAUUAAAGGAGAGGUGGGCN	412	NGCCACCUCUCCUUUAAUN	1260-1278
238	AGAAAUAAAUUAAAGGAGA	413	UCUCCUUUAAUUUAUUUCU	1267-1285
239	UGAAAUAAAUUAAAGGAGA	414	UCUCCUUUAAUUUAUUUCA	1267-1285
240	NGAAAUAAAUUAAAGGAGA	415	UCUCCUUUAAUUUAUUUCN	1267-1285
241	NGAAAUAAAUUAAAGGAGN	416	NCUCCUUUAAUUUAUUUCN	1267-1285

The *ASGR1* RNAi agent sense strands and antisense strands that comprise or consist of the nucleotide sequences in Table 2 can be modified nucleotides or unmodified nucleotides. In some embodiments, the *ASGR1* RNAi agents having the sense and antisense strand sequences that comprise or consist of the nucleotide sequences in Table 2 are all or substantially all modified nucleotides.

In some embodiments, the antisense strand of an *ASGR1* RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the antisense strand sequences in Table 2. In some embodiments, the sense strand of an *ASGR1* RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the sense strand sequences in Table 2.

As used herein, each N listed in a sequence disclosed in Table 2 may be independently selected from any and all nucleobases (including those found on both modified and unmodified nucleotides). In some embodiments, an N nucleotide listed in a sequence disclosed in Table 2 has a nucleobase that is complementary to the N nucleotide at the corresponding position on the other strand. In some embodiments, an N nucleotide listed in a sequence disclosed in Table 2 has a nucleobase that is not complementary to the N nucleotide at the corresponding position on the other strand. In some embodiments, an N nucleotide listed in a sequence disclosed in Table 2 has a nucleobase that is the same as the N nucleotide at the corresponding position on the other strand. In some embodiments, an N nucleotide listed in a sequence disclosed in Table 2 has a nucleobase that is different from the N nucleotide at the corresponding position on the other strand.

Certain modified *ASGR1* RNAi agent sense and antisense strands are provided in Table 3 and Table 4. Certain modified *ASGR1* RNAi agent antisense strands, as well as their underlying unmodified nucleobase sequences, are provided in Table 3. Certain modified *ASGR1* RNAi agent sense strands, as well as their underlying unmodified sequences, are provided in Table 4. In forming *ASGR1* RNAi agents, each of the nucleotides in each of the unmodified sequences listed in Tables 3 and 4, as well as in Table 2, above, can be a modified nucleotide.

The *ASGR1* RNAi agents described herein are formed by annealing an antisense strand with a sense strand. A sense strand containing a sequence listed in Table 2 or Table 4, can be

hybridized to any antisense strand containing a sequence listed in Table 2 or Table 3, provided the two sequences have a region of at least 85% complementarity over a contiguous 16, 17, 18, 19, 20, or 21 nucleotide sequence.

In some embodiments, an *ASGR1* RNAi agent antisense strand comprises a nucleotide sequence of any of the sequences in Table 2 or Table 3.

In some embodiments, an *ASGR1* RNAi agent comprises or consists of a duplex having the nucleobase sequences of the sense strand and the antisense strand of any of the sequences in Table 2, Table 3, or Table 4.

Examples of antisense strands containing modified nucleotides are provided in Table 3. Examples of sense strands containing modified nucleotides are provided in Table 4.

As used in Tables 3 and 4, the following notations are used to indicate modified nucleotides, targeting groups, and linking groups. As the person of ordinary skill in the art would readily understand, unless otherwise indicated by the sequence, that when present in an oligonucleotide, the monomers are mutually linked by 5'-3'-phosphodiester bonds:

A	=	adenosine-3′-phosphate;
C	=	cytidine-3′-phosphate;
G	=	guanosine-3′-phosphate;
U	=	uridine-3′-phosphate
I	=	inosine-3′-phosphate
n	=	any 2′-O-methyl modified nucleotide
a	=	2′-O-methyladenosine-3′-phosphate
as	=	2′-O-methyladenosine-3′-phosphorothioate
c	=	2′-O-methylcytidine-3′-phosphate
cs	=	2′-O-methylcytidine-3′-phosphorothioate
g	=	2′-O-methylguanosine-3′-phosphate
gs	=	2′-O-methylguanosine-3′-phosphorothioate
t	=	2′-O-methyl-5-methyluridine-3′-phosphate
ts	=	2′-O-methyl-5-methyluridine-3′-phosphorothioate
u	=	2′-O-methyluridine-3′-phosphate
us	=	2′-O-methyluridine-3′-phosphorothioate
i	=	2′-O-methylinosine-3′-phosphate
is	=	2′-O-methylinosine-3′-phosphorothioate

	Nf	=	any 2′-fluoro modified nucleotide
	Af	=	2′-fluoroadenosine-3′-phosphate
	Afs	=	2′-fluoroadenosine-3′-phosporothioate
	Cf	=	2′-fluorocytidine-3′-phosphate
5	Cfs	=	2′-fluorocytidine-3′-phosphorothioate
	Gf	=	2′-fluoroguanosine-3′-phosphate
	Gfs	=	2′-fluoroguanosine-3′-phosphorothioate
	Tf	=	2′-fluoro-5′-methyluridine-3′-phosphate
	Tfs	=	2′-fluoro-5′-methyluridine-3′-phosphorothioate
10	Uf	=	2′-fluorouridine-3′-phosphate
	Ufs	=	2′-fluorouridine-3′-phosphorothioate
	dN	=	any 2′-deoxyribonucleotide
	dA	=	2′-deoxyadenosine-3′-phosphate
	dAs	=	2′-deoxyadenosine-3′-phosphorothioate
15	dC	=	2′-deoxycytidine-3′-phosphate
	dCs	=	2′-deoxycytidine-3′-phosphorothioate
	dG	=	2′-deoxyguanosine-3′-phosphate
	dGs	=	2′-deoxyguanosine-3′-phosphorothioate
	dT	=	2′-deoxythymidine-3′-phosphate
20	dTs	=	2′-deoxythymidine-3′-phosphorothioate
	dU	=	2′-deoxyuridine-3′-phosphate
	dUs	=	2′-deoxyuridine-3′-phosphorothioate
	N_{UNA}	=	2′,3′-seco nucleotide mimics (unlocked nucleobase analogs)-3′-Phosphate
25	N_{UNAS}	=	2′,3′-seco nucleotide mimics (unlocked nucleobase analogs)-3′-phosphorothioate
	A_{UNA}	=	2′,3′-seco-adenosine-3′-phosphate
	A_{UNAS}	=	2′,3′-seco-adenosine-3′-phosphorothioate
	C_{UNA}	=	2′,3′-seco-cytidine-3′-phosphate
30	C_{UNAS}	=	2′,3′-seco-cytidine-3′-phosphorothioate
	G_{UNA}	=	2′,3′-seco-guanosine-3′-phosphate
	G_{UNAS}	=	2′,3′-seco-guanosine-3′-phosphorothioate
	U_{UNA}	=	2′,3′-seco-uridine-3′-phosphate
	U_{UNAS}	=	2′,3′-seco-uridine-3′-phosphorothioate
35	a_2N	=	see Table 6
	a_2Ns	=	see Table 6
	pu_2N	=	see Table 6
	pu_2Ns	=	see Table 6
	N_{LNA}	=	locked nucleotide
40	Nf_{ANA}	=	2'-F-Arabino nucleotide

	NM	=	2′-O-methoxyethyl nucleotide
	AM	=	2′-O-methoxyethyladenosine-3′-phosphate
	AMs	=	2′-O-methoxyethyladenosine-3′-phosphorothioate
	TM	=	2′-O-methoxyethylthymidine-3′-phosphate
5	TMs	=	2′-O-methoxyethylthymidine-3′-phosphorothioate
	R	=	ribitol
	(invdN)	=	any inverted deoxyribonucleotide (3′-3′ linked nucleotide)
	(invAb)	=	inverted (3′-3′ linked) abasic deoxyribonucleotide, see Table 6
	(invAb)s	=	inverted (3′-3′ linked) abasic deoxyribonucleotide-5′-
10			phosphorothioate, see Table 6
	(invn)	=	any inverted 2′-OMe nucleotide (3′-3′ linked nucleotide)
	s	=	phosphorothioate linkage
	sp	=	see Table 6
	vpdN	=	vinyl phosphonate deoxyribonucleotide
15	(5Me-Nf)	=	5'-Me, 2'-fluoro nucleotide
	cPrp	=	cyclopropyl phosphonate, see Table 6
	epTcPr	=	see Table 6
	epTM	=	see Table 6

20

As the person of ordinary skill in the art would readily understand, unless otherwise indicated by the sequence (such as, for example, by a phosphorothioate linkage "s"), when present in an oligonucleotide, the nucleotide monomers are mutually linked by 5'-3'-phosphodiester bonds. As the person of ordinary skill in the art would clearly understand, 25 the inclusion of a phosphorothioate linkage as shown in the modified nucleotide sequences disclosed herein replaces the phosphodiester linkage typically present in oligonucleotides (*see, e.g.*, Figs. 1A through 1M showing all internucleoside linkages). Further, the person of ordinary skill in the art would readily understand that the terminal nucleotide at the 3' end of a given oligonucleotide sequence would typically have a hydroxyl (-OH) group at 30 the respective 3' position of the given monomer instead of a phosphate moiety *ex vivo*. Moreover, as the person of ordinary skill would readily understand and appreciate, while the phosphorothioate chemical structures depicted herein typically show the anion on the sulfur atom, the inventions disclosed herein encompass all phosphorothioate tautomers and/or diastereomers (*e.g.*, where the sulfur atom has a double-bond and the anion is on an 35 oxygen atom). Unless expressly indicated otherwise herein, such understandings of the

person of ordinary skill in the art are used when describing the *ASGR1* RNAi agents and compositions of *ASGR1* RNAi agents disclosed herein.

Certain examples of targeting groups and linking groups used with the *ASGR1* RNAi agents disclosed herein are provided below in Table 6. More specifically, targeting groups and linking groups include the following, for which their chemical structures are provided below in Table 6: (NAG13), (NAG13)s, (NAG18), (NAG18)s, (NAG24), (NAG24)s, (NAG25), (NAG25)s, (NAG26), (NAG26)s, (NAG27), (NAG27)s, (NAG28), (NAG28)s, (NAG29), (NAG29)s, (NAG30), (NAG30)s, (NAG31), (NAG31)s, (NAG32), (NAG32)s, (NAG33), (NAG33)s, (NAG34), (NAG34)s, (NAG35), (NAG35)s, (NAG36), (NAG36)s, (NAG37), (NAG37)s, (NAG38), (NAG38)s, (NAG39), (NAG39)s . Each sense strand and/or antisense strand can have any targeting groups or linking groups listed herein, as well as other targeting or linking groups, conjugated to the 5′ and/or 3′ end of the sequence.

Table 3. *ASGR1* RNAi Agent Antisense Strand Sequences.

Antisense Strand ID:	SEQ ID NO.	Antisense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM05757-AS	417	asCfsusUfcAfuCfuUfuCfuUfcCfcAfcusu	722	ACUUCAUCUUUCUUCCCACUU
AM05761-AS	418	usAfsgsAfaCfcAfgUfaGfcAfgCfuGfcusu	723	UAGAACCAGUAGCAGCUGCUU
AM05919-AS	419	asCfsusUfcAfuCfUfUfuCfuUfcCfcAfcAfsu	724	ACUUCAUCUUUCUUCCCACAU
AM05920-AS	420	asCfsusUfcAfucuuuCfuUfcCfcAfcAfsu	724	ACUUCAUCUUUCUUCCCACAU
AM05921-AS	421	asCfsusUfcAfuCfuUfuCfuUfcCfcAfcAfsu	724	ACUUCAUCUUUCUUCCCACAU
AM05922-AS	422	asCfsusUfcAfuCfuUfuCfuUfcCfcAfcAfuUfsg	725	ACUUCAUCUUUCUUCCCACAUUG
AM05927-AS	423	usCfsusUfcAfuCfuUfuCfuUfcCfcAfcAfsu	726	UCUUCAUCUUUCUUCCCACAU
AM06016-AS	424	usAfscUfcCfuUfgGfuCfaUfgAfuAfgsgsg	727	UACUCCUUGGUCAUGAUAGGG
AM06017-AS	425	usAfscUfcCfuUfgGfuCfaUfgAfuAfgsgsu	3	UACUCCUUGGUCAUGAUAGGU
AM06020-AS	426	usCfsuCfgUfaGfuCfcGfuCfcCfgUfcscsa	729	UCUCGUAGUCCGUCCCGUCCA
AM06021-AS	427	usCfsuCfgUfaGfuCfcGfuCfcCfgUfcsusu	730	UCUCGUAGUCCGUCCCGUCUU
AM06023-AS	428	usUfsaAfaGfgAfgAfgGfuGfgCfuCfcsusg	731	UUAAAGGAGAGGUGGCUCCUG
AM06026-AS	429	usGfsuAfgCfaGfcUfgCfgCfuCfgUfgscsu	732	UGUAGCAGCUGCGCUCGUGCU
AM06027-AS	430	usGfsuAfgCfaGfcUfgCfgCfuCfgUfgsusu	733	UGUAGCAGCUGCGCUCGUGUU
AM06029-AS	431	usGfsuGfcUfcGfcUfgUfgAfaGfuUfgscsu	734	UGUGCUCGCUGUGAAGUUGCU
AM06030-AS	432	usGfsuGfcUfcGfcUfgUfgAfaGfuUfgcsusg	735	UGUGCUCGCUGUGAAGUUGCUG
AM06033-AS	433	usUfsgAfuGfgUfgGfuCfaCfuCfuCfcsusc	736	UUGAUGGUGGUCACUCUCCUC
AM06172-AS	434	usUfsgAfuGfgUfgGfuCfaCfuCfuCfcsusu	737	UUGAUGGUGGUCACUCUCCUU
AM06175-AS	435	usGfsaCfgUfcGfuCfgUfuCfcAfgCfgusu	738	UGACGUCGUCGUUCCAGCGUU
AM06176-AS	436	asGfsaCfgUfcGfuCfgUfuCfcAfgCfgusu	739	AGACGUCGUCGUUCCAGCGUU
AM06179-AS	437	usAfsgCfuGfaUfgGfuGfgUfcAfcUfcsusc	740	UAGCUGAUGGUGGUCACUCUC
AM06180-AS	438	usAfsgCfuGfaUfgGfuGfgUfcAfcUfcusu	741	UAGCUGAUGGUGGUCACUCUU
AM06183-AS	439	usGfsasGfcCfaUfuGfcCfcUfgGfaGfcusu	742	UGAGCCAUUGCCCUGGAGCUU
AM06185-AS	440	usAfscGfuGfaCfcAfcCfaCfcAfgGfuusu	743	UACGUGACCACCACCAGGUUU

Antisense Strand ID:	SEQ ID NO.	Antisense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM06186-AS	441	usAfscGfuGfaCfcAfcCfaCfcAfgGfusgsc	744	UACGUGACCACCACCAGGUGC
AM06189-AS	442	usCfsuGfcUfuCfaCfgUfgGfaGfcAfgsusu	745	UCUGCUUCACGUGGAGCAGUU
AM06192-AS	443	spasCfsusUfcAfuCfuUfuCfuUfcCfcAfcusu	722	ACUUCAUCUUUCUUCCCACUU
AM06193-AS	444	cPrpusCfsusUfcAfuCfuUfuCfuUfcCfcAfcusu	746	UCUUCAUCUUUCUUCCCACUU
AM06200-AS	445	cPrpdUsCfsusUfcAfuCfuUfuCfuUfcCfcAfcusu	746	UCUUCAUCUUUCUUCCCACUU
AM06201-AS	446	usCfsusUfcAfuCfuUfuCfuUfcCfcAfcusu	746	UCUUCAUCUUUCUUCCCACUU
AM06248-AS	447	usAfscUfcCfuUfgGfuCfaUfgAfuAfggsusu	747	UACUCCUUGGUCAUGAUAGGUU
AM06249-AS	448	usAfscUfcCfuUfgGfuCfaUfgAfuAfsgsg	748	UACUCCUUGGUCAUGAUAGG
AM06250-AS	449	usAfscUfcCfuUfgGfuCfaUfgAfusasg	749	UACUCCUUGGUCAUGAUAG
AM06251-AS	450	usAfscUfcCfuUfgGfuCfaUfgAfuAfgsusu	750	UACUCCUUGGUCAUGAUAGUU
AM06252-AS	451	usAfscUfcCfuUfgGfuCfaUfgAfuAfgsgsgsc	751	UACUCCUUGGUCAUGAUAGGGC
AM06253-AS	452	cPrpdUAfcUfcCfuUfgGfuCfaUfgAfuAfgg(invAb)	748	UACUCCUUGGUCAUGAUAGG
AM06254-AS	453	cPrpdUsAfscUfcCfuUfgGfuCfaUfgAfuAfgsgsu	3	UACUCCUUGGUCAUGAUAGGU
AM06442-AS	454	usUfsaAfaGfgAfgAfgGfuGfgCfuCfcsusu	752	UUAAAGGAGAGGUGGCUCCUU
AM06443-AS	455	cPrpdUsUfsaAfaGfgAfgAfgGfuGfgCfuCfcsusu	752	UUAAAGGAGAGGUGGCUCCUU
AM06444-AS	456	cPrpusUfsaAfaGfgAfgAfgGfuGfgCfuCfcsusu	752	UUAAAGGAGAGGUGGCUCCUU
AM06445-AS	457	usUfsaAfaGfgagagGfuGfgCfuCfcsusu	752	UUAAAGGAGAGGUGGCUCCUU
AM06446-AS	458	usUfsaaaggAfgAfgGfuGfgcuccsusu	752	UUAAAGGAGAGGUGGCUCCUU
AM06447-AS	459	usUfsaAfaGfgAfgAfgGfuGfgCfuscsc	753	UUAAAGGAGAGGUGGCUCC
AM06448-AS	460	usUfsaAfaGfgAfgAfgGfuGfgCfuCfcusgsg	754	UUAAAGGAGAGGUGGCUCCUGG
AM06575-AS	461	asGfsaCfgUfcGfuCfgUfuCfcAfgCfgsusu	739	AGACGUCGUCGUUCCAGCGUU
AM06578-AS	462	usGfsaCfgUfcGfuCfgUfuCfcAfgCfgsusu	738	UGACGUCGUCGUUCCAGCGUU
AM06579-AS	463	cPrpusGfsaCfgUfcGfuCfgUfuCfcAfgCfgsusu	738	UGACGUCGUCGUUCCAGCGUU
AM06581-AS	464	usCfsuCfgUfaguccGfuCfcCfgUfcsusu	730	UCUCGUAGUCCGUCCCGUCUU
AM06582-AS	465	cPrpusCfsuCfgUfaguccGfuCfcCfgUfcsusu	730	UCUCGUAGUCCGUCCCGUCUU

Antisense Strand ID:	SEQ ID NO.	Antisense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM06584-AS	466	asCfsuCfgUfaguccGfuCfcCfgUfcsusu	755	ACUCGUAGUCCGUCCCGUCUU
AM06586-AS	467	asCfsuCfgUfaguccGfuCfcCfgsUfsc	756	ACUCGUAGUCCGUCCCGUC
AM06598-AS	468	usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsg	727	UACUCCUUGGUCAUGAUAGGG
AM06599-AS	469	usAfscUfcCfuugguCfaUfgAfuAfgsGfsg	727	UACUCCUUGGUCAUGAUAGGG
AM06601-AS	2	usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu	3	UACUCCUUGGUCAUGAUAGGU
AM06639-AS	470	usAfscsUfcCfuugguCfaUfgAfuAfgsGfsg	727	UACUCCUUGGUCAUGAUAGGG
AM06641-AS	471	usAfscsUfcCfuUfgGfuCfaUfgAfuAfgsusu	750	UACUCCUUGGUCAUGAUAGUU
AM06643-AS	472	usAfscsUfcCfuugguCfaUfgAfuAfgGfsgs(invAb)	727	UACUCCUUGGUCAUGAUAGGG
AM06645-AS	473	usGfscsUfuCfacgugGfaGfcAfgCfaGfsg	757	UGCUUCACGUGGAGCAGCAGG
AM06647-AS	474	usCfsgsUfuUfuggucGfuGfgAfgGfcCfsu	758	UCGUUUUGGUCGUGGAGGCCU
AM06649-AS	475	usUfsusCfcCfacauuGfcCfuCfcCfuGfsg	759	UUUCCCACAUUGCCUCCCUGG
AM06651-AS	476	asAfscsCfaGfuagcaGfcUfgCfgCfuCfsg	760	AACCAGUAGCAGCUGCGCUCG
AM06653-AS	477	asAfscsCfaGfuagcaGfcUfgCfgCfuusu	761	AACCAGUAGCAGCUGCGCUUU
AM06655-AS	478	usGfscAfgUfaguugUfcGfgCfgUfcsAfsg	762	UGCAGUAGUUGUCGGCGUCAG
AM06657-AS	479	usAfsgsGfaCfgugacCfaCfcAfcCfaGfsg	763	UAGGACGUGACCACCACCAGG
AM06659-AS	480	usUfsgsCfuGfgAfcAfaAfuUfuCfuGfcUfsc	764	UUGCUGGACAAAUUUCUGCUC
AM06661-AS	481	usUfscsGfuAfguccgUfcCfcGfuCfcAfsc	765	UUCGUAGUCCGUCCCGUCCAC
AM06663-AS	482	usUfscsUfcGfuagucCfgUfcCfcGfuCfsu	766	UUCUCGUAGUCCGUCCCGUCU
AM06665-AS	483	usGfsusAfcCfagucgUfcCfgGfcUfgusu	767	UGUACCAGUCCGUCCGGCUGUU
AM06667-AS	484	asGfsasCfgUfcgucgUfuCfcAfgCfgusu	739	AGACGUCCGUCGUUCCAGCGUU
AM06669-AS	485	usAfsasCfuGfcuucaCfgUfgGfaGfcAfsg	768	UAACUGCUUCACGUGGAGCAG
AM06671-AS	486	usUfscsUfuCfccacaUfuGfcCfuCfcCfsu	769	UUCUUCCCACAUUGCCUCCCU
AM06673-AS	487	usUfscsUfuCfccacaUfuGfcCfuCfcusu	770	UUCUUCCCACAUUGCCUCCUU
AM06675-AS	488	usGfscGfaCfuucauCfuUfuCfuUfcsCfsc	771	UGCGACUUCAUCUUUCUUCCC
AM06677-AS	489	asGfscGfaCfuucauCfuUfuCfuUfcsCfsc	772	AGCGACUUCAUCUUUCUUCCC

Antisense Strand ID:	SEQ ID NO.	Antisense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM06679-AS	490	usUfsuAfaAfgGfaGfaGfgUfgGfcUfcsCfsu	773	UUUAAAGGAGAGGUGGCUCCU
AM06681-AS	491	asUfsuAfaAfgGfaGfaGfgUfgGfcUfcsCfsu	774	AUUAAAGGAGAGGUGGCUCCU
AM06683-AS	492	asAfsusUfaAfaGfgAfgAfgGfuGfgCfuCfsc	775	AAUUAAAGGAGAGGUGGCUCC
AM06685-AS	493	asAfsusUfaAfaGfGfAfgAfgGfuGfgCfuCfsc	775	AAUUAAAGGAGAGGUGGCUCC
AM06687-AS	494	usAfsaCfcAfguagcAfgCfuGfcGfcsUfsc	776	UAACCAGUAGCAGCUGCGCUC
AM06689-AS	495	usAfsgCfuCfugucuCfgCfaGfaCfcsCfsa	777	UAGCUCUGUCUCCGCAGACCCA
AM06703-AS	496	cPrpusCfsusUfcAfuCfaAfaCfuUfcCfcAfcusu	778	UCUUCAUCAAACUUCCCACUU
AM06705-AS	497	usAfscUfcCfuUfcCfaCfaUfgAfuAfgsgsu	779	UACUCCUUCCACAUGAUAGGU
AM06708-AS	498	asCfsusUfcAfuCfuUfuCfuUfcCfcAfcAfsc	780	ACUUCAUCUUUCUUCCCACAC
AM06710-AS	10	asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc	11	ACUUCAUCUUUCUUCCCACGC
AM06756-AS	499	asCfsusUfcAfuCfuUfuCfuUfcCfcAfgGfsc	781	ACUUCAUCUUUCUUCCCAGGC
AM06796-AS	500	usAfscsUfcCfuugguCfaUfgAfuAfgGfsc	782	UACUCCUUGGUCAUGAUAGGC
AM06798-AS	501	usAfscsUfcCfuugguCfaUfgAfuAfgCfsc	783	UACUCCUUGGUCAUGAUAGCC
AM06799-AS	502	usAfscsUfcCfuugguCfaUfgAfuAfgGfsu	3	UACUCCUUGGUCAUGAUAGGU
AM06806-AS	503	usAfscUfcCfuugguCfaUfgAfuAfgsGfsu	3	UACUCCUUGGUCAUGAUAGGU
AM06808-AS	504	asAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu	784	AACUCCUUGGUCAUGAUAGGU
AM06810-AS	505	usGfscsUfuCfacgugGfaGfcAfgCfausu	785	UGCUUCACGUGGAGCAGCAUU
AM06815-AS	5	asGfscGfaCfuucauCfuUfuCfuUfcsCfsg	6	AGCGACUUCAUCUUUCUUCCG
AM06820-AS	506	asCfsusCfcUfuGfgUfcAfuGfaUfaGfgGfsc	786	ACUCCUUGGUCAUGAUAGGGC
AM06822-AS	507	usAfsusCfuUfuCfuUfcCfcAfcAfuUfgCfsc	787	UAUCUUUCUUCCCACAUUGCC
AM06824-AS	508	usCfsgsAfcUfuCfaUfcUfuUfcUfuCfcCfsa	788	UCGACUUCAUCUUUCUUCCCA
AM06826-AS	509	asAfscsUfgCfuUfcAfcGfuGfgAfgCfausu	789	AACUGCUUCACGUGGAGCAUU
AM06828-AS	510	asCfsgsAfaCfuGfcUfuCfaCfgUfgGfausu	790	ACGAACUGCUUCACGUGGAUU
AM06830-AS	511	usGfsgsAfcAfaAfuUfuCfuGfcUfcCfuCfsc	791	UGGACAAAUUUCUGCUCCUCC
AM06832-AS	512	usUfsgAfuAfcUfcCfuUfgGfuCfaUfgsAfsu	792	UUGAUACUCCUUGGUCAUGAU

Antisense Strand ID:	SEQ ID NO.	Antisense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM06834-AS	513	usCfsuUfuCfuUfcCfcAfcAfuUfgCfcsUfsc	793	UCUUUCUUCCCCACAUUGCCUC
AM06836-AS	514	usCfsaUfcUfuUfcUfuCfcCfaCfaUfusGfsc	794	UCAUCUUUCUUCCCACAUUGC
AM06838-AS	28	usGfsaAfaUfaAfaUfuAfaAfgGfaGfasGfsg	27	UGAAAUAAAUUAAAGGAGAGG
AM06840-AS	515	usGfsaAfaUfaAfaUfuAfaAfgGfaGfcsGfsg	795	UGAAAUAAAUUAAAGGAGCGG
AM06842-AS	516	asGfsaAfaUfaAfaUfuAfaAfgGfaGfcsGfsg	796	AGAAAUAAAUUAAAGGAGCGG
AM06851-AS	4	usAfscUfcCfU$_{UNA}$UfgGfuCfaUfgAfuAfgsGfsu	3	UACUCCUUGGUCAUGAUAGGU
AM06853-AS	517	usCfsusUfgGfucaugAfuAfgGfgCfuGfsu	797	UCUUGGUCAUGAUAGGGCUGU
AM06855-AS	518	asCfsusCfcUfuggucAfuGfaUfaGfgGfsu	798	ACUCCUUGGUCAUGAUAGGGU
AM06857-AS	519	asUfsasCfuCfcuugUfcAfuGfaUfaGfsc	799	AUACUCCUUGGUCAUGAUAGC
AM06859-AS	520	usAfsusAfcUfccuugGfuCfaUfgAfuCfsc	800	UAUACUCCUUGGUCAUGAUCC
AM06861-AS	521	usAfsusAfcUfccuugGfuCfaUfgAfuAfsc	801	UAUACUCCUUGGUCAUGAUAC
AM06911-AS	522	usAfscsUfcCfuugguCfaUfgAfuAfgGfsg	727	UACUCCUUGGUCAUGAUAGGG
AM06796-AS	523	usAfscsUfcCfuugguCfaUfgAfuAfgGfsc	782	UACUCCUUGGUCAUGAUAGGC
AM06914-AS	524	asGfscsGfaCfuucauCfuUfuCfuUfcCfsc	772	AGCGACUUCAUCUUUCUUCCC
AM06916-AS	525	asGfscsGfaCfuucauCfuUfuCfuUfcCfsg	6	AGCGACUUCAUCUUUCUUCCG
AM06918-AS	526	usUfsusAfaAfGfGfaGfaGfgUfgGfcUfcusu	803	UUUAAAGGAGAGGUGGCUCUU
AM06920-AS	527	usUfsusAfaAfGfGfaGfaGfgUfgGfcUfgusu	804	UUUAAAGGAGAGGUGGCUGUU
AM07073-AS	528	usUfsgAfuAfcUfcCfuUfgGfuCfaUfgsGfsu	805	UUGAUACUCCUUGGUCAUGGU
AM07075-AS	529	usUfsgAfuAfcUfcCfuUfgGfuCfaUfgsAfsg	806	UUGAUACUCCUUGGUCAUGAG
AM07077-AS	530	usUfsgAfuAfcuccuUfgGfuCfaUfgsGfsc	807	UUGAUACUCCUUGGUCAUGGC
AM07079-AS	531	usAfsusCfuUfucuucCfcAfcAfuUfgCfsg	808	UAUCUUUCUUCCCACACAUUGCG
AM07083-AS	532	usAfsusCfuUfucuucCfcAfcAfuUfgGfsg	809	UAUCUUUCUUCCCACACAUUGGG
AM07085-AS	533	usCfsaUfcUfuUfcUfuCfcCfaCfaUfusGfsg	810	UCAUCUUUCUUCCCACACAUUGG
AM07088-AS	534	usCfsaUfcUfuUfcUfuCfcCfaCfaUfusCfsg	811	UCAUCUUUCUUCCCACACAUUCG
AM07090-AS	535	usCfsaUfcUfuUfcUfuCfcCfaCfaUfcsGfsg	812	UCAUCUUUCUUCCCACACAUCGG

Antisense Strand ID:	SEQ ID NO.	Antisense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM07092-AS	536	usGfsaAfaUfaAfaUfuAfaAfgGfaGfasGfsc	813	UGAAAUAAAAUUAAAGGAGAGC
AM07096-AS	537	usGfsaAfaUfaAfaUfuAfaAfgGfaGfgsGfsg	814	UGAAAUAAAAUUAAAGGAGGGG
AM07098-AS	538	usGfsaAfaUfaAfaUfuAfaAfgGfaGfgsGfsc	815	UGAAAUAAAAUUAAAGGAGGGC
AM07209-AS	539	asGfscGfaCfU$_{UNA}$ucauCfuUfuCfuUfcsCfsc	772	AGCGACUUCAUCUUUCUUCCC
AM07210-AS	540	asGfscGfaCfU$_{UNA}$ucauCfuUfuCfuUfcsCfsg	6	AGCGACUUCAUCUUUCUUCCG
AM07213-AS	541	asGfsC$_{UNA}$GfaCfuucauCfuUfuCfuUfcsCfsg	6	AGCGACUUCAUCUUUCUUCCG
AM07214-AS	542	asGfscG$_{UNA}$aCfuucauCfuUfuCfuUfcsCfsg	6	AGCGACUUCAUCUUUCUUCCG
AM07216-AS	543	asGfscGfaCfuucauCfuUfuCfuUfcsCfsu	816	AGCGACUUCAUCUUUCUUCCU
AM07390-AS	544	asGfscGfaCfuucauCfuUfuCfuUfcsusu	817	AGCGACUUCAUCUUUCUUCUU
AM07392-AS	545	asGfscGfaCfuucauCfuUfuCfuUfcsCfsa	818	AGCGACUUCAUCUUUCUUCCA
AM07394-AS	546	asGfscGfaCfuucauCfuUfuCfuUfcsGfsg	819	AGCGACUUCAUCUUUCUUCGG
AM07396-AS	7	asGfscGfaCfuucauCfuUfuCfuUfcsGfsu	8	AGCGACUUCAUCUUUCUUCGU
AM07398-AS	547	asGfscGfaCfuucauCfuUfuCfuUfcsGfsc	820	AGCGACUUCAUCUUUCUUCGC
AM07449-AS	548	asGfscGfA$_{UNA}$CfuucauCfuUfuCfuUfcsCfsg	6	AGCGACUUCAUCUUUCUUCCG
AM07487-AS	549	usAfscsuccuugguCfaUfgAfuAfgGfsu	3	UACUCCUUGGUCAUGAUAGGU
AM07488-AS	550	usAfscsuccU$_{UNA}$ugguCfaUfgAfuAfgGfsu	3	UACUCCUUGGUCAUGAUAGGU
AM07489-AS	551	asGfscsgacuucauCfuUfuCfuUfcCfsg	6	AGCGACUUCAUCUUUCUUCCG
AM07490-AS	552	asGfscsgacU$_{UNA}$ucauCfuUfuCfuUfcCfsg	6	AGCGACUUCAUCUUUCUUCCG
AM07492-AS	553	asGfscGfaCfU$_{UNA}$uguaCfuUfuCfuUfcsCfsg	821	AGCGACUUGUACUUUCUUCCG
AM07501-AS	9	asGfscsgacuucauCfuUfuCfuUfcGfsu	8	AGCGACUUCAUCUUUCUUCGU
AM07576-AS	554	usAfscuccuugguCfaUfgAfuAfgsGfsu	3	UACUCCUUGGUCAUGAUAGGU
AM07577-AS	555	usAfscuccU$_{UNA}$ugguCfaUfgAfuAfgsGfsu	3	UACUCCUUGGUCAUGAUAGGU

Table 4. *ASGR1* RNAi Agent Sense Strand Sequences.

Sense Strand ID:	SEQ ID NO.	Sense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM05756-SS	556	(NAG31)(invAb)GfuGfgGfaAfGfAfaAfgaugaaguuus(invAb)	822	GUGGGAAGAAAGAUGAAGUUU
AM05760-SS	557	(NAG31)(invAb)gcagcuGfCfUfacugguucuauus(invAb)	823	GCAGCUGCUACUGGUUCUAUU
AM05923-SS	558	(NAG25)s(invAb)sauGfuGfgGfaAfGfAfaAfgAfuGfaAfgus(invAb)	824	AUGUGGGAAGAAAGAUGAAGU
AM05924-SS	559	(NAG25)s(invAb)saugugggaAfGfAfaagaugaagus(invAb)	824	AUGUGGGAAGAAAGAUGAAGU
AM05925-SS	560	(NAG25)s(invAb)sgugggaAfGfAfaagaugaagus(invAb)	825	GUGGGAAGAAAGAUGAAGU
AM05926-SS	561	(NAG25)s(invAb)sgugggaAfGfAfaagaugaaguuus(invAb)	822	GUGGGAAGAAAGAUGAAGUUU
AM05928-SS	562	(NAG25)s(invAb)saugugggaAfGfAfaagaugaagas(invAb)	826	AUGUGGGAAGAAAGAUGAAGA
AM06018-SS	563	(NAG25)s(invAb)scccuaucaUfGfAfccaaggagus(invdA)	827	CCCUAUCAUGACCAAGGAGUA
AM06019-SS	564	(NAG25)s(invAb)sccuaucaUfGfAfccaaggagus(invdA)	828	CCUAUCAUGACCAAGGAGUA
AM06022-SS	565	(NAG25)s(invAb)sgacgggAfCfGfgacuacgags(invdA)	829	GACGGGACGGACUACGAGA
AM06024-SS	566	(NAG25)s(invAb)sggagccAfCfCfucuccuuuas(invdA)	830	GGAGCCACCUCUCCUUUAA
AM06025-SS	567	(NAG25)s(invAb)scaggagccAfCfCfucuccuuuas(invdA)	831	CAGGAGCCACCUCUCCUUUAA
AM06028-SS	568	(NAG25)s(invAb)scacgagCfGfCfagcugcuacs(invdA)	832	CACGAGCGCAGCUGCUACA
AM06031-SS	569	(NAG25)s(invAb)sagcaacuuCfAfCfagcgagcacs(invdA)	833	AGCAACUUCACAGCGAGCACA
AM06032-SS	570	(NAG25)s(invAb)scagcaacuuCfAfCfagcgagcacs(invdA)	834	CAGCAACUUCACAGCGAGCACA
AM06034-SS	571	(NAG25)s(invAb)sgaggagagUfGfAfccaccaucas(invdA)	835	GAGGAGAGUGACCACCAUCAA
AM06173-SS	572	(NAG25)s(invAb)sggagagUfGfAfccaccaucas(invdA)	836	GGAGAGUGACCACCAUCAA
AM06174-SS	573	(NAG25)sgsaggagagUfGfAfccaccaucas(invdA)	835	GAGGAGAGUGACCACCAUCAA
AM06177-SS	574	(NAG25)s(invAb)scgcuggAfAfCfgacgacgucs(invdA)	837	CGCUGGAACGACGACGUCA
AM06178-SS	575	(NAG25)s(invAb)scgcuggAfAfCfgacgacgucus(invAb)	838	CGCUGGAACGACGACGUCU
AM06181-SS	576	(NAG25)sgsagagugaCfCfAfccaucagcus(invdA)	839	GAGAGUGACCACCAUCAGCUA
AM06182-SS	577	(NAG25)s(invAb)sgagugaCfCfAfccaucagcus(invdA)	840	GAGUGACCACCAUCAGCUA
AM06184-SS	578	(NAG25)s(invAb)sgcuccaGfGfGfcaauggcucs(invdA)	841	GCUCCAGGGCAAUGGCUCA
AM06187-SS	579	(NAG25)s(invAb)saccuggUfGfGfuggucacgus(invdA)	842	ACCUGGUGGUGGUCACGUA

Sense Strand ID:	SEQ ID NO.	Sense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM06188-SS	580	(NAG25)sgscaccuggUfGfGfuggucacgus(invdA)	843	GCACCUGGUGGUGGUCACGUA
AM06190-SS	581	(NAG25)s(invAb)scugcucCfAfCfgugaagcags(invdA)	844	CUGCUCCACGUGAAGCAGA
AM06194-SS	582	(NAG25)s(invAb)sgugggaAfGfAfaagaugaagas(invAb)	845	GUGGGAAGAAAGAUGAAGA
AM06255-SS	583	(NAG37)s(invAb)sccuaucaUfGfGfAfccaaggagus(invdA)	828	CCUAUCAUGACCAAGGAGUA
AM06256-SS	584	(NAG37)s(invAb)scuaucaUfGfGfAfccaaggagus(invdA)	846	CUAUCAUGACCAAGGAGUA
AM06257-SS	585	(NAG37)s(invAb)scccuaucaUfGfGfAfccaaggagus(invdA)	827	CCCUAUCAUGACCAAGGAGUA
AM06258-SS	586	(NAG37)sgscccuaucaUfGfGfAfccaaggagus(invdA)	847	GCCCUAUCAUGACCAAGGAGUA
AM06259-SS	587	(NAG37)s(invAb)sgcccuaucaUfGfGfAfccaaggagus(invdA)	847	GCCCUAUCAUGACCAAGGAGUA
AM06260-SS	588	(NAG37)(invAb)ccuaucaUfGfGfAfccaaggagu(invdA)	828	CCUAUCAUGACCAAGGAGUA
AM06440-SS	589	(NAG37)s(invAb)sgugggaAfGfAfaagaugaagus(invAb)	825	GUGGGAAGAAAGAUGAAGU
AM06441-SS	590	(NAG37)s(invAb)sggagccAfCfCfucuccuuuas(invdA)	830	GGAGCCACCUCCUCCUUUAA
AM06449-SS	591	(NAG37)sgsgagccAfCfCfucuccuuuas(invdA)	830	GGAGCCACCUCCUCCUUUAA
AM06450-SS	592	(NAG37)scsaggagccAfCfCfucuccuuuas(invdA)	831	CAGGAGCCACCUCCUCCUUUAA
AM06451-SS	593	(NAG37)scscaggagccAfCfCfucuccuuuas(invdA)	848	CCAGGAGCCACCUCCUCCUUUAA
AM06458-SS	594	(NAG37)s(invAb)sgugggaAfGfAfaagaugaagas(invAb)	845	GUGGGAAGAAAGAUGAAGA
AM06574-SS	595	(NAG37)s(invAb)scgcuggAfAfCfgacgacgucus(invAb)	838	CGCUGGAACGACGACGUCU
AM06576-SS	596	(NAG37)s(invAb)scgcuggAfAfCfgacgaugucus(invAb)	849	CGCUGGAACGACGAUGUCU
AM06577-SS	597	(NAG37)s(invAb)scgcuggAfAfCfgacgacgucas(invAb)	837	CGCUGGAACGACGACGUCA
AM06580-SS	598	(NAG37)s(invAb)sgacgggAfCfGfgacuacgagas(invAb)	829	GACGGGACGGACUACGAGA
AM06583-SS	599	(NAG37)s(invAb)sgacgggAfCfGfgacuacgagus(invAb)	850	GACGGGACGGACUACGAGU
AM06585-SS	600	(NAG37)s(invAb)sgacgggAfCfGfgacuacgagauus(invAb)	851	GACGGGACGGACUACGAGAUU
AM06597-SS	601	(NAG37)s(invAb)sccuaucaUfGfAfccaaggaguas(invAb)	827	CCCUAUCAUGACCAAGGAGUA
AM06600-SS	602	(NAG37)s(invAb)saccuaucaUfGfAfccaaggaguas(invAb)	13	ACCUAUCAUGACCAAGGAGUA
AM06640-SS	603	(NAG37)s(invAb)scuaucaUfGfAfccaaggaguauus(invAb)	853	CUAUCAUGACCAAGGAGUAUU
AM06644-SS	604	(NAG37)s(invAb)sccugcugUfCfCfacgugaagcas(invAb)	854	CCUGCUGCUCCACGUGAAGCA

Sense Strand ID:	SEQ ID NO.	Sense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM06646-SS	605	(NAG37)s(invAb)saggccuccAfCfGfaccaaaacgas(invAb)	855	AGGCCUCCACGACCAAAACGA
AM06648-SS	606	(NAG37)s(invAb)sccagggagGfCfAfaugugggaaas(invAb)	856	CCAGGGAGGCAAUGUGGGAAA
AM06650-SS	607	(NAG37)s(invAb)scgagcgcaGfCfUfgcuacugguus(invAb)	857	CGAGCGCAGCUGCUACUGGUU
AM06652-SS	608	(NAG37)s(invAb)sagcgcaGfCfUfgcuacugguuuus(invAb)	858	AGCGCAGCUGCUACUGGUUUU
AM06654-SS	609	(NAG37)s(invAb)scugacgccGfAfCfaacuacugcas(invAb)	859	CUGACGCCGACAACUACUGCA
AM06656-SS	610	(NAG37)s(invAb)sccuggugGUfGfGfucacguccuas(invAb)	860	CCUGGUGGGUGGUCACGUCCUA
AM06658-SS	611	(NAG37)s(invAb)sgagcagaaAfUfUfuguccagcaas(invAb)	861	GAGCAGAAAUUUGUCCAGCAA
AM06660-SS	612	(NAG37)s(invAb)sguggacggGfAfCfggacuacgaas(invAb)	862	GUGGACGGGACGGACUACGAA
AM06662-SS	613	(NAG37)s(invAb)sagacgggaCfGfGfacuacgagaas(invAb)	863	AGACGGGACGGACUACGAGAA
AM06664-SS	614	(NAG37)s(invAb)saacagccgGfAfCfgacugguacas(invAb)	864	AACAGCCGGACGACUGGUACA
AM06666-SS	615	(NAG37)s(invAb)scgcuggAfAfCfgacgacgucuuus(invAb)	865	CGCUGGAACGACGACGUCUUU
AM06668-SS	616	(NAG37)s(invAb)scugcuccaCfGfUfgaagcaguuas(invAb)	866	CUGCUCCACGUGAAGCAGUUA
AM06670-SS	617	(NAG37)s(invAb)sagggaggcAfAfUfgugggaagaas(invAb)	867	AGGGAGGCAAUGUGGGAAGAA
AM06672-SS	618	(NAG37)s(invAb)sggaggcAfAfUfgugggaagaauus(invAb)	868	GGAGGCAAUGUGGGAAGAAUU
AM06674-SS	619	(NAG37)s(invAb)sgggaagaaAfGfAfugaagucgcas(invAb)	869	GGGAAGAAAGAUGAAGUCGCA
AM06676-SS	620	(NAG37)s(invAb)sgggaagaaAfGfAfugaagucgcus(invAb)	870	GGGAAGAAAGAUGAAGUCGCU
AM06678-SS	621	(NAG37)s(invAb)saggagccaCfCfUfcuccuuuaaas(invAb)	871	AGGAGCCACCUCUCCUUUAAA
AM06680-SS	622	(NAG37)s(invAb)saggagccaCfCfUfcuccuuuaaus(invAb)	872	AGGAGCCACCUCUCCUUUAAU
AM06682-SS	623	(NAG37)s(invAb)sggagccacCfUfCfuccuuuaaauus(invAb)	873	GGAGCCACCUCUCCUUUAAUU
AM06684-SS	624	(NAG37)s(invAb)sGfgAfgCfcAfcCfUfCfuCfcUfuUfaAfuus(invAb)	873	GGAGCCACCUCUCCUUUAAUU
AM06686-SS	625	(NAG37)s(invAb)sgagcgcagCfUfGfcuacugguuas(invAb)	874	GAGCGCAGCUGCUACUGGUUA
AM06688-SS	626	(NAG37)s(invAb)sugggucugCfGfAfgacagagcuas(invAb)	875	UGGGUCUGCGAGACAGAGCUA
AM06702-SS	627	(NAG37)s(invAb)sguggggaAfGfUfuugaugaaagas(invAb)	876	GUGGGAAGUUUGAUGAAAGA
AM06704-SS	628	(NAG37)s(invAb)sccuaucaUfGfUfggaaggagus(invdA)	877	CCUAUCAUGUGGGAAGGAGUA
AM06706-SS	629	(NAG37)s(invAb)sauguggggaAfGfAfaagaugaagus(invAb)	824	AUGUGGGAAGAAAGAUGAAGU

Sense Strand ID:	SEQ ID NO.	Sense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM06707-SS	630	(NAG37)s(invAb)sgugugggaAfGfAfaagaugaaagus(invAb)	878	GUGUGGGAAGAAAGAUGAAGU
AM06709-SS	631	(NAG37)s(invAb)sgcgugggaAfGfAfaagaugaaagus(invAb)	18	GCGUGGGAAGAAAGAUGAAGU
AM06754-SS	632	(NAG37)gscgugggaAfGfAfaagaugaaagus(invAb)	18	GCGUGGGAAGAAAGAUGAAGU
AM06755-SS	633	(NAG37)gsccugggaAfGfAfaagaugaaagus(invAb)	880	GCCUGGGAAGAAAGAUGAAGU
AM06795-SS	634	(NAG37)s(invAb)sgccuaucaUfGfAfccaaggaguas(invAb)	881	GCCUAUCAUGACCAAGGAGUA
AM06797-SS	635	(NAG37)s(invAb)sggcuaucaUfGfAfccaaggaguas(invAb)	882	GGCUAUCAUGACCAAGGAGUA
AM06802-SS	636	(NAG37)s(invAb)saccuaucaUfGfAfccaaggaiuas(invAb)	12	ACCUAUCAUGACCAAGGAIUA
AM06803-SS	637	(NAG37)s(invAb)saccuaucaUfGfAfccaagiaguas(invAb)	884	ACCUAUCAUGACCAAGIAGUA
AM06804-SS	638	(NAG37)s(invAb)saccuaucaUfGfAfccaaigaguas(invAb)	885	ACCUAUCAUGACCAAIGAGUA
AM06805-SS	639	(NAG37)s(invAb)saccuaucaUfGfAfccaaigaiuas(invAb)	14	ACCUAUCAUGACCAAIGAIUA
AM06807-SS	640	(NAG37)s(invAb)saccuaucaUfGfAfccaaggaguus(invAb)	887	ACCUAUCAUGACCAAGGAGUU
AM06809-SS	641	(NAG37)s(invAb)sugcugcUfCfCfacgugaagcauus(invAb)	888	UGCUGCUCCACGUGAAGCAUU
AM06811-SS	642	(NAG37)s(invAb)sugcugcUfCfCfacgugaaicauus(invAb)	889	UGCUGCUCCACGUGAAICAUU
AM06812-SS	643	(NAG37)s(invAb)sugcugcUfCfCfacguiaagcauus(invAb)	890	UGCUGCUCCACGUIAAGCAUU
AM06813-SS	644	(NAG37)s(invAb)sugcugcUfCfCfacguiaaicauus(invAb)	891	UGCUGCUCCACGUIAAICAUU
AM06814-SS	645	(NAG37)s(invAb)scggaagaaAfGfAfugaagucicus(invAb)	15	CGGAAGAAAGAUGAAGUCICU
AM06816-SS	646	(NAG37)s(invAb)scggaagaaAfGfAfugaaiucgcus(invAb)	893	CGGAAGAAAGAUGAAIUCGCU
AM06817-SS	647	(NAG37)s(invAb)scggaagaaAfGfAfugaaiucicus(invAb)	31	CGGAAGAAAGAUGAAIUCICU
AM06818-SS	648	(NAG37)s(invAb)scggaagaaAfGfAfugaagucgcus(invAb)	33	CGGAAGAAAGAUGAAGUCGCU
AM06819-SS	649	(NAG37)s(invAb)sgcccuaucAfUfGfaccaaggagus(invAb)	896	GCCCUAUCAUGACCAAGGAGU
AM06821-SS	650	(NAG37)s(invAb)sggcaauguGfGfGfaagaaagauas(invAb)	897	GGCAAUGUGGGAAGAAAGAUA
AM06823-SS	651	(NAG37)s(invAb)sugggaagaAfAfGfaugaagucgas(invAb)	898	UGGGAAGAAAGAUGAAGUCGA
AM06825-SS	652	(NAG37)s(invAb)sugcuccAfCfGfugaagcaguuuus(invAb)	899	UGCUCCACGUGAAGCAGUUUU
AM06827-SS	653	(NAG37)s(invAb)succacgUfGfAfagcaguucguuus(invAb)	900	UCCACGUGAAGCAGUUCGUUU
AM06829-SS	654	(NAG37)s(invAb)sggaggagcAfGfAfaauuuguccas(invAb)	901	GGAGGAGCAGAAAUUUGUCCA

Sense Strand ID:	SEQ ID NO.	Sense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM06831-SS	655	(NAG37)s(invAb)saucaugacCfAfAfggaguaucaas(invAb)	902	AUCAUGACCAAGGAGUAUCAA
AM06833-SS	656	(NAG37)s(invAb)sgaggcaauGfUfGfggaagaaagas(invAb)	903	GAGGCAAUGUGGGAAGAAAGA
AM06835-SS	657	(NAG37)s(invAb)sgcaaugugGfGfAfagaaagaugas(invAb)	904	GCAAUGUGGGAAGAAAGAUGA
AM06837-SS	658	(NAG37)s(invAb)sccucuccuUfUfAfauuuauuucas(invAb)	35	CCUCUCCUUUAAUUUAUUUCA
AM06839-SS	659	(NAG37)s(invAb)sccgcuccuUfUfAfauuuauuucas(invAb)	906	CCGCUCCUUUAAUUUAUUUCA
AM06841-SS	660	(NAG37)s(invAb)sccgcuccuUfUfAfauuuauuucus(invAb)	907	CCGCUCCUUUAAUUUAUUUCU
AM06852-SS	661	(NAG37)s(invAb)sacagcccuAfUfCfaugaccaagas(invAb)	908	ACAGCCCUAUCAUGACCAAGA
AM06854-SS	662	(NAG37)s(invAb)saccuauucAfUfUfGfaccaaggagus(invAb)	909	ACCCUAUCAUGACCAAGGAGU
AM06856-SS	663	(NAG37)s(invAb)sgcuaucauGfAfCfcaaggaguaus(invAb)	910	GCUAUCAUGACCAAGGAGUAU
AM06858-SS	664	(NAG37)s(invAb)sggaucaugAfCfCfaaggaguauas(invAb)	911	GGAUCAUGACCAAGGAGUAUA
AM06860-SS	665	(NAG37)s(invAb)sguaucaugAfCfCfaaggaguauas(invAb)	912	GUAUCAUGACCAAGGAGUAUA
AM06909-SS	666	(NAG37)asccuaucaUfGfAfccaaggaguas(invAb)	13	ACCUAUCAUGACCAAGGAGUA
AM06910-SS	667	(NAG37)csccuaucaUfGfAfccaaggaguas(invAb)	827	CCCUAUCAUGACCAAGGAGUA
AM06912-SS	668	(NAG37)gsccuaucaUfGfAfccaaggaguas(invAb)	881	GCCUAUCAUGACCAAGGAGUA
AM06913-SS	669	(NAG37)gsggaagaaAfGfAfugaagucgcus(invAb)	870	GGGAAGAAAGAUGAAGUCGCU
AM06915-SS	670	(NAG37)csggaagaaAfGfAfugaagucgcus(invAb)	33	CGGAAGAAAGAUGAAGUCGCU
AM06917-SS	671	(NAG37)s(invAb)sgagccaCfCfUfucuccuuuaaauus(invAb)	913	GAGCCACCUCUCCUUUAAAUU
AM06919-SS	672	(NAG37)s(invAb)scagccaCfCfUfucuccuuuaaauus(invAb)	914	CAGCCACCUCUCCUUUAAAUU
AM06921-SS	673	(NAG37)gsagccaCfCfUfucuccuuuaaauus(invAb)	913	GAGCCACCUCUCCUUUAAAUU
AM06930-SS	674	(NAG37)s(invAb)saccuaucaUfGfAfcCaaggaguas(invAb)	13	ACCUAUCAUGACCAAGGAGUA
AM06931-SS	675	(NAG37)asccuaucaUfGfAfcCaaggaguas(invAb)	13	ACCUAUCAUGACCAAGGAGUA
AM06935-SS	676	(NAG37)s(invAb)scggaagaaAfGfAfugaagucpu_2Ncus(invAb)	915	CGGAAGAAAGAUGAAGUC(pu^{2N})CU
AM06936-SS	677	(NAG37)s(invAb)scggaagaaAfGfAfugaagucacus(invAb)	916	CGGAAGAAAGAUGAAGUCACU
AM06937-SS	678	(NAG37)s(invAb)scggaagaaAfGfAfugaagucucus(invAb)	917	CGGAAGAAAGAUGAAGUCUCU
AM06938-SS	679	(NAG37)s(invAb)scggaagaaAfGfAfugaagucccus(invAb)	918	CGGAAGAAAGAUGAAGUCCCU

Sense Strand ID:	SEQ ID NO.	Sense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM06939-SS	680	(NAG37)s(invAb)scggaagaaAfGfAfuGaagucicus(invAb)	15	CGGAAGAAAGAUGAAGUCICU
AM06940-SS	681	(NAG37)s(invAb)scggaagaaAfGfAfUgaagucicus(invAb)	15	CGGAAGAAAGAUGAAGUCICU
AM06941-SS	682	(NAG37)s(invAb)scggaagaaAfGfAfudGaagucicus(invAb)	15	CGGAAGAAAGAUGAAGUCICU
AM07072-SS	683	(NAG37)s(invAb)saccaugacCfAfAfggaguaucaas(invAb)	919	ACCAUGACCAAGGAGUAUCAA
AM07074-SS	684	(NAG37)s(invAb)scucaugacCfAfAfggaguaucaas(invAb)	920	CUCAUGACCAAGGAGUAUCAA
AM07076-SS	685	(NAG37)s(invAb)sgccaugacCfAfAfggaguaucaas(invAb)	921	GCCAUGACCAAGGAGUAUCAA
AM07078-SS	686	(NAG37)s(invAb)scgcaauguGfGfGfaagaaagauas(invAb)	922	CGCAAUGUGGGGAAGAAAGAUA
AM07080-SS	687	(NAG37)s(invAb)scgcaauguGfiGfaagaaagauas(invAb)	923	CGCAAUGUGIGAAGAAAGAUA
AM07081-SS	688	(NAG37)s(invAb)scgcaauguiGfGfaagaaagauas(invAb)	924	CGCAAUGUIGGAAGAAAGAUA
AM07082-SS	689	(NAG37)s(invAb)scccaauguGfGfGfaagaaagauas(invAb)	925	CCCAAUGUGGGAAGAAAGAUA
AM07084-SS	690	(NAG37)s(invAb)sccaaugugGfGfAfagaaagaugas(invAb)	926	CCAAUGUGGGAAGAAAGAUGA
AM07086-SS	691	(NAG37)s(invAb)sccaauguiGfGfAfagaaagaugas(invAb)	927	CCAAUGUIGGAAGAAAGAUGA
AM07087-SS	692	(NAG37)s(invAb)scgaaugugGfGfAfagaaagaugas(invAb)	928	CGAAUGUGGGAAGAAAGAUGA
AM07089-SS	693	(NAG37)s(invAb)sccgaugugGfGfAfagaaagaugas(invAb)	929	CCGAUGUGGGAAGAAAGAUGA
AM07091-SS	694	(NAG37)s(invAb)sgcucuccuUfUfAfauuuauuucas(invAb)	930	GCUCUCCUUUAAUUUAUUUCA
AM07093-SS	695	(NAG37)s(invAb)sgcucuccuUfUfAfauuua_2Nuuucas(invAb)	931	GCUCUCCUUUAAUUU(A^{2N})UUUCA
AM07094-SS	696	(NAG37)s(invAb)sgcucuccuUfUfAfa_2Nuuuauuucas(invAb)	932	GCUCUCCUUUA(A^{2N})UUUAUUUCA
AM07095-SS	697	(NAG37)s(invAb)sccccuccuUfUfAfauuuauuucas(invAb)	933	CCCCUCCUUUAAUUUAUUUCA
AM07097-SS	698	(NAG37)s(invAb)sgcccuccuUfUfAfauuuauuucas(invAb)	934	GCCCUCCUUUAAUUUAUUUCA
AM07109-SS	699	(NAG37)s(invAb)saccuaucaUfGfAfcCaaggaiuas(invAb)	12	ACCUAUCAUGACCAAGGAIUA
AM07110-SS	700	(NAG37)s(invAb)saccuaucaUfGfAfcCaaigaiuas(invAb)	14	ACCUAUCAUGACCAAIGAIUA
AM07211-SS	701	(NAG37)s(invAb)scggaagaaAfGfAfudGaagucgcus(invAb)	33	CGGAAGAAAGAUGAAGUCGCU
AM07212-SS	702	(NAG37)s(invAb)scggaagaaAfGfAfuGaagucgcus(invAb)	33	CGGAAGAAAGAUGAAGUCGCU
AM07215-SS	703	(NAG37)s(invAb)saggaagaaAfGfAfugaagucicus(invAb)	935	AGGAAGAAAGAUGAAGUCICU
AM07388-SS	704	(NAG37)csggaagaaAfGfAfudGaagucgcus(invAb)	33	CGGAAGAAAGAUGAAGUCGCU

Sense Strand ID:	SEQ ID NO.	Sense Sequence (Modified) (5' → 3')	SEQ ID NO.	Underlying Base Sequence (5' → 3')
AM07389-SS	705	(NAG37)s(invAb)sgaagaaAfGfAfugaagucicuuus(invAb)	936	GAAGAAAGAUGAAGUCICUUU
AM07391-SS	706	(NAG37)s(invAb)suggaagaaAfGfAfugaagucicus(invAb)	937	UGGAAGAAAGAUGAAGUCICU
AM07393-SS	707	(NAG37)s(invAb)sccgaagaaAfGfAfugaagucicus(invAb)	938	CCGAAGAAAGAUGAAGUCICU
AM07395-SS	708	(NAG37)s(invAb)sacgaagaaAfGfAfugaagucicus(invAb)	16	ACGAAGAAAGAUGAAGUCICU
AM07397-SS	709	(NAG37)s(invAb)sgcgaagaaAfGfAfugaagucicus(invAb)	940	GCGAAGAAAGAUGAAGUCICU
AM07414-SS	710	(NAG37)s(invAb)scggaagaaAfGfAfudGaA$_{UNA}$gucgcus(invAb)	33	CGGAAGAAAGAUGAAGUCGCU
AM07444-SS	711	(NAG37)s(invAb)scggaagaaAfGfAfugaA$_{UNA}$gucgcus(invAb)	33	CGGAAGAAAGAUGAAGUCGCU
AM07445-SS	712	(NAG37)s(invAb)scggaagaaAfGfAfugaA$_{UNA}$gucicus(invAb)	15	CGGAAGAAAGAUGAAGUCICU
AM07446-SS	713	(NAG37)s(invAb)scggaagaaAfGfAfuGaA$_{UNA}$gucgcus(invAb)	33	CGGAAGAAAGAUGAAGUCGCU
AM07447-SS	714	(NAG37)s(invAb)scggaagaaAfGfAfudGaA$_{UNA}$gucicus(invAb)	15	CGGAAGAAAGAUGAAGUCICU
AM07448-SS	715	(NAG37)s(invAb)scggaagaaAfGfAfugaagU$_{UNA}$cgcus(invAb)	33	CGGAAGAAAGAUGAAGUCGCU
AM07450-SS	716	(NAG37)s(invAb)scggaagaaAfGfAfdTgaagucgcus(invAb)	941	CGGAAGAAAGATGAAGUCGCU
AM07451-SS	717	(NAG37)s(invAb)saccuaucaUfGfAfcdCaaggaguas(invAb)	13	ACCUAUCAUGACCAAGGAGUA
AM07452-SS	718	(NAG37)s(invAb)saccuaucaUfGfAfcdCaaggaiuas(invAb)	12	ACCUAUCAUGACCAAGGAIUA
AM07491-SS	719	(NAG33)s(invAb)scggaagaaAfGfUfadCaagucgcus(invAb)	943	CGGAAGAAAGUACAAGUCGCU
AM07494-SS	720	(NAG33)s(invAb)scggaagaaAfGfAfudGaagucgcus(invAb)	33	CGGAAGAAAGAUGAAGUCGCU
AM07500-SS	721	(NAG37)s(invAb)sacgaagaaAfGfAfugaagucgcus(invAb)	17	ACGAAGAAAGAUGAAGUCGCU

(A^{2N}) = 2-aminoadenine nucleotide
(pu^{2N}) = 2-aminopurine nucleotide

The *ASGR1* RNAi agents described herein are formed by annealing an antisense strand with a sense strand. A sense strand containing a sequence listed in Table 2 or Table 4 can be hybridized to any antisense strand containing a sequence listed in Table 2 or Table 3, provided the two sequences have a region of at least 85% complementarity over a contiguous 16, 17, 18, 19, 20, or 21 nucleotide sequence.

In some embodiments, the antisense strand of an *ASGR1* RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the antisense strand sequences in Table 3. In some embodiments, the sense strand of an *ASGR1* RNAi agent disclosed herein differs by 0, 1, 2, or 3 nucleotides from any of the sense strand sequences in Table 4.

In some embodiments, an *ASGR1* RNAi agent antisense strand comprises a nucleotide sequence of any of the sequences in Table 2 or Table 3. In some embodiments, an *ASGR1* RNAi agent antisense strand comprises the sequence of nucleotides (from 5′ end → 3′ end) 1-17, 2-17, 1-18, 2-18, 1-19, 2-19, 1-20, 2-20, 1-21, 2-21, 1-22, 2-22, 1-23, 2-23, 1-24, 2-24, 1-25, 2-25, 1-26, or 2-26 of any of the sequences in Table 2 or Table 3. In certain embodiments, an *ASGR1* RNAi agent antisense strand comprises or consists of a modified sequence of any one of the modified sequences in Table 3.

In some embodiments, an *ASGR1* RNAi agent sense strand comprises the nucleotide sequence of any of the sequences in Table 2 or Table 4. In some embodiments, an *ASGR1* RNAi agent sense strand comprises the sequence of nucleotides (from 5′ end → 3′ end) 1-17, 2-17, 3-17, 4-17, 1-18, 2-18, 3-18, 4-18, 1-19, 2-19, 3-19, 4-19, 1-20, 2-20, 3-20, 4-20, 1-21, 2-21, 3-21, 4-21, 1-22, 2-22, 3-22, 4-22, 1-23, 2-23, 3-23, 4-23, 1-24, 2-24, 3-24, 4-24, 1-25, 2-25, 3-25, 4-25, 1-26, 2-26, 3-26, or 4-26 of any of the sequences in Table 2 or Table 4. In certain embodiments, an *ASGR1* RNAi agent sense strand comprises or consists of a modified sequence of any one of the modified sequences in Table 4.

For the *ASGR1* RNAi agents disclosed herein, the nucleotide at position 1 of the antisense strand (from 5′ end → 3′ end) can be perfectly complementary to an *ASGR1* gene, or can be non-complementary to an *ASGR1* gene. In some embodiments, the nucleotide at position 1 of the antisense strand (from 5′ end → 3′ end) is a U, A, or dT (or a modified version thereof).

In some embodiments, the nucleotide at position 1 of the antisense strand (from 5′ end → 3′ end) forms an A:U or U:A base pair with the sense strand.

In some embodiments, an *ASGR1* RNAi agent antisense strand comprises the sequence of nucleotides (from 5′ end → 3′ end) 2-18 or 2-19 of any of the antisense strand sequences in Table 2 or Table 3. In some embodiments, an *ASGR1* RNAi sense strand comprises the sequence of nucleotides (from 5′ end → 3′ end) 1-17 or 1-18 of any of the sense strand sequences in Table 2 or Table 4.

In some embodiments, an *ASGR1* RNAi agent includes (i) an antisense strand comprising the sequence of nucleotides (from 5′ end → 3′ end) 2-18 or 2-19 of any of the antisense strand sequences in Table 2 or Table 3, and (ii) a sense strand comprising the sequence of nucleotides (from 5′ end → 3′ end) 1-17 or 1-18 of any of the sense strand sequences in Table 2 or Table 4.

A sense strand containing a sequence listed in Table 2 or Table 4 can be hybridized to any antisense strand containing a sequence listed in Table 2 or Table 3, provided the two sequences have a region of at least 85% complementarity over a contiguous 16, 17, 18, 19, 20, or 21 nucleotide sequence. In some embodiments, the *ASGR1* RNAi agent has a sense strand consisting of the modified sequence of any of the modified sequences in Table 4, and an antisense strand consisting of the modified sequence of any of the modified sequences in Table 3. Representative sequence pairings are exemplified by the Duplex ID Nos. shown in Table 5.

In some embodiments, an *ASGR1* RNAi agent comprises any of the duplexes represented by any of the Duplex ID Nos. presented herein. In some embodiments, an *ASGR1* RNAi agent consists of any of the duplexes represented by any of the Duplex ID Nos. presented herein. In some embodiments, an *ASGR1* RNAi agent comprises the sense strand and antisense strand nucleotide sequences of any of the duplexes represented by any of the Duplex ID Nos. presented herein. In some embodiments, an *ASGR1* RNAi agent comprises the sense strand and antisense strand nucleotide sequences of any of the duplexes represented by any of the Duplex ID Nos. presented herein and a targeting group and/or linking group, wherein the targeting group and/or linking group is covalently linked (i.e.

conjugated) to the sense strand or the antisense strand. In some embodiments, an *ASGR1* RNAi agent comprises a sense strand and an antisense strand having the modified nucleotide sequences of any of the duplexes represented by any of the Duplex ID Nos. presented herein. In some embodiments, an *ASGR1* RNAi agent comprises a sense strand and an antisense strand having the modified nucleotide sequences of any of the duplexes represented by any of the Duplex ID Nos. presented herein and a targeting group and/or linking group, wherein the targeting group and/or linking group is covalently linked to the sense strand or the antisense strand.

In some embodiments, an *ASGR1* RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Table 2 or Table 5, and further comprises a targeting group. In some embodiments, an *ASGR1* RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Table 2 or Table 5, and further comprises an asialoglycoprotein receptor ligand targeting group.

In some embodiments, an *ASGR1* RNAi agent comprises an antisense strand and a sense strand having the nucleotide sequences of any of the antisense strand/sense strand duplexes of Table 2 or Table 5, and further comprises a targeting group selected from the group consisting of (PAZ), (NAG13), (NAG13)s, (NAG18), (NAG18)s, (NAG24), (NAG24)s, (NAG25), (NAG25)s, (NAG26), (NAG26)s, (NAG27), (NAG27)s, (NAG28), (NAG28)s, (NAG29), (NAG29)s, (NAG30), (NAG30)s, (NAG31), (NAG31)s, (NAG32), (NAG32)s, (NAG33), (NAG33)s, (NAG34), (NAG34)s, (NAG35), (NAG35)s, (NAG36), (NAG36)s, (NAG37), (NAG37)s, (NAG38), (NAG38)s, (NAG39), (NAG39)s, each as defined in Table 6. In some embodiments, the targeting group is (NAG25) or (NAG25)s as defined in Table 6. In other embodiments, the targeting group is (NAG37) or (NAG37)s as defined in Table 6.

In some embodiments, an *ASGR1* RNAi agent comprises an antisense strand and a sense strand having the modified nucleotide sequence of any of the antisense strand and/or sense strand nucleotide sequences of any of the duplexes of Table 5.

In some embodiments, an *ASGR1* RNAi agent comprises an antisense strand and a sense strand having a modified nucleotide sequence of any of the antisense strand and/or sense strand nucleotide sequences of any of the duplexes of Table 5, and comprises an asialoglycoprotein receptor ligand targeting group.

In some embodiments, an *ASGR1* RNAi agent comprises any of the duplexes of Table 2 or Table 5. In certain embodiments, an *ASGR1* RNAi agent comprises a duplex selected from the group consisting of AD05126, AD05150, AD05183, AD05186, AD05193, AD05195, AD05196, AD05206, AD05209, AD05256, AD05374, AD05609, and AD05692 or a salt thereof.

In some embodiments, an *ASGR1* RNAi agent consists of any of the duplexes of Table 2 or Table 5. In certain embodiments, an ASGR1 RNAi agent consists of a duplex selected from the group consisting of AD05126, AD05150, AD05183, AD05186, AD05193, AD05195, AD05196, AD05206, AD05209, AD05256, AD05374, AD05609, and AD05692 or a salt thereof.

Table 5. *ASGR1* RNAi Agent Duplexes Identified by Duplex ID No. with Corresponding Sense and Antisense Strands.

Duplex ID	Antisense Strand ID	Sense Strand ID
AD04518	AM05757-AS	AM05756-SS
AD04519	AM05761-AS	AM05760-SS
AD04629	AM05919-AS	AM05923-SS
AD04630	AM05920-AS	AM05924-SS
AD04631	AM05921-AS	AM05924-SS
AD04632	AM05921-AS	AM05925-SS
AD04633	AM05921-AS	AM05926-SS
AD04634	AM05757-AS	AM05925-SS
AD04635	AM05922-AS	AM05924-SS
AD04636	AM05927-AS	AM05928-SS
AD04697	AM06016-AS	AM06018-SS
AD04698	AM06017-AS	AM06019-SS
AD04699	AM06020-AS	AM06022-SS
AD04700	AM06021-AS	AM06022-SS
AD04701	AM06023-AS	AM06024-SS
AD04702	AM06023-AS	AM06025-SS
AD04703	AM06026-AS	AM06028-SS
AD04704	AM06027-AS	AM06028-SS
AD04705	AM06029-AS	AM06031-SS
AD04706	AM06030-AS	AM06032-SS
AD04707	AM06033-AS	AM06034-SS
AD04791	AM06172-AS	AM06173-SS
AD04792	AM06033-AS	AM06174-SS
AD04793	AM06175-AS	AM06177-SS
AD04794	AM06176-AS	AM06178-SS
AD04795	AM06179-AS	AM06181-SS
AD04796	AM06180-AS	AM06182-SS
AD04797	AM06183-AS	AM06184-SS
AD04798	AM06185-AS	AM06187-SS
AD04799	AM06186-AS	AM06188-SS
AD04800	AM06189-AS	AM06190-SS
AD04801	AM06192-AS	AM05925-SS
AD04802	AM06193-AS	AM06194-SS
AD04810	AM06200-AS	AM06194-SS
AD04811	AM06201-AS	AM06194-SS
AD04847	AM06017-AS	AM06255-SS
AD04848	AM06248-AS	AM06255-SS
AD04849	AM06249-AS	AM06255-SS
AD04850	AM06250-AS	AM06256-SS
AD04851	AM06251-AS	AM06256-SS
AD04852	AM06016-AS	AM06257-SS
AD04853	AM06252-AS	AM06258-SS
AD04854	AM06252-AS	AM06259-SS
AD04855	AM06253-AS	AM06260-SS
AD04856	AM06254-AS	AM06255-SS
AD04964	AM05757-AS	AM06440-SS
AD04965	AM06023-AS	AM06441-SS
AD04966	AM06442-AS	AM06441-SS
AD04967	AM06443-AS	AM06441-SS
AD04968	AM06444-AS	AM06441-SS
AD04969	AM06445-AS	AM06441-SS
AD04970	AM06446-AS	AM06441-SS
AD04971	AM06447-AS	AM06441-SS
AD04972	AM06447-AS	AM06449-SS
AD04973	AM06023-AS	AM06450-SS
AD04974	AM06448-AS	AM06451-SS
AD04975	AM06193-AS	AM06458-SS
AD05046	AM06575-AS	AM06574-SS
AD05047	AM06575-AS	AM06576-SS
AD05048	AM06578-AS	AM06577-SS
AD05049	AM06579-AS	AM06577-SS
AD05050	AM06581-AS	AM06580-SS
AD05051	AM06582-AS	AM06580-SS
AD05052	AM06584-AS	AM06583-SS
AD05053	AM06581-AS	AM06585-SS
AD05054	AM06586-AS	AM06583-SS
AD05065	AM06598-AS	AM06597-SS
AD05066	AM06599-AS	AM06597-SS
AD05067	AM06601-AS	AM06600-SS
AD05089	AM06639-AS	AM06597-SS
AD05090	AM06641-AS	AM06640-SS
AD05092	AM06643-AS	AM06597-SS
AD05093	AM06645-AS	AM06644-SS
AD05094	AM06647-AS	AM06646-SS
AD05095	AM06649-AS	AM06648-SS
AD05096	AM06651-AS	AM06650-SS
AD05097	AM06653-AS	AM06652-SS
AD05098	AM06655-AS	AM06654-SS
AD05099	AM06657-AS	AM06656-SS
AD05100	AM06659-AS	AM06658-SS
AD05101	AM06661-AS	AM06660-SS
AD05102	AM06663-AS	AM06662-SS
AD05103	AM06665-AS	AM06664-SS
AD05104	AM06667-AS	AM06666-SS

Duplex ID	Antisense Strand ID	Sense Strand ID
AD05105	AM06669-AS	AM06668-SS
AD05106	AM06671-AS	AM06670-SS
AD05107	AM06673-AS	AM06672-SS
AD05108	AM06675-AS	AM06674-SS
AD05109	AM06677-AS	AM06676-SS
AD05110	AM06679-AS	AM06678-SS
AD05111	AM06681-AS	AM06680-SS
AD05112	AM06683-AS	AM06682-SS
AD05113	AM06685-AS	AM06684-SS
AD05114	AM06687-AS	AM06686-SS
AD05115	AM06689-AS	AM06688-SS
AD05122	AM06703-AS	AM06702-SS
AD05123	AM06705-AS	AM06704-SS
AD05124	AM05921-AS	AM06706-SS
AD05125	AM06708-AS	AM06707-SS
AD05126	AM06710-AS	AM06709-SS
AD05150	AM06710-AS	AM06754-SS
AD05151	AM06756-AS	AM06755-SS
AD05180	AM06796-AS	AM06795-SS
AD05181	AM06798-AS	AM06797-SS
AD05182	AM06799-AS	AM06600-SS
AD05183	AM06601-AS	AM06802-SS
AD05184	AM06601-AS	AM06803-SS
AD05185	AM06601-AS	AM06804-SS
AD05186	AM06601-AS	AM06805-SS
AD05187	AM06806-AS	AM06804-SS
AD05188	AM06808-AS	AM06807-SS
AD05189	AM06810-AS	AM06809-SS
AD05190	AM06810-AS	AM06811-SS
AD05191	AM06810-AS	AM06812-SS
AD05192	AM06810-AS	AM06813-SS
AD05193	AM06815-AS	AM06814-SS
AD05194	AM06815-AS	AM06816-SS
AD05195	AM06815-AS	AM06817-SS
AD05196	AM06815-AS	AM06818-SS
AD05197	AM06820-AS	AM06819-SS
AD05198	AM06822-AS	AM06821-SS
AD05199	AM06824-AS	AM06823-SS
AD05200	AM06826-AS	AM06825-SS
AD05201	AM06828-AS	AM06827-SS
AD05202	AM06830-AS	AM06829-SS
AD05203	AM06832-AS	AM06831-SS
AD05204	AM06834-AS	AM06833-SS
AD05205	AM06836-AS	AM06835-SS
AD05206	AM06838-AS	AM06837-SS

Duplex ID	Antisense Strand ID	Sense Strand ID
AD05207	AM06840-AS	AM06839-SS
AD05208	AM06842-AS	AM06841-SS
AD05209	AM06851-AS	AM06600-SS
AD05210	AM06853-AS	AM06852-SS
AD05211	AM06855-AS	AM06854-SS
AD05212	AM06857-AS	AM06856-SS
AD05213	AM06859-AS	AM06858-SS
AD05214	AM06861-AS	AM06860-SS
AD05240	AM06601-AS	AM06909-SS
AD05241	AM06799-AS	AM06909-SS
AD05242	AM06911-AS	AM06910-SS
AD05243	AM06796-AS	AM06912-SS
AD05244	AM06914-AS	AM06913-SS
AD05245	AM06916-AS	AM06915-SS
AD05246	AM06918-AS	AM06917-SS
AD05247	AM06920-AS	AM06919-SS
AD05248	AM06918-AS	AM06921-SS
AD05256	AM06601-AS	AM06930-SS
AD05257	AM06601-AS	AM06931-SS
AD05261	AM06916-AS	AM06818-SS
AD05262	AM06916-AS	AM06935-SS
AD05263	AM06916-AS	AM06936-SS
AD05264	AM06916-AS	AM06937-SS
AD05265	AM06916-AS	AM06938-SS
AD05266	AM06916-AS	AM06939-SS
AD05267	AM06916-AS	AM06940-SS
AD05268	AM06916-AS	AM06941-SS
AD05352	AM07073-AS	AM07072-SS
AD05353	AM07075-AS	AM07074-SS
AD05354	AM07077-AS	AM07076-SS
AD05355	AM07079-AS	AM07078-SS
AD05356	AM07079-AS	AM07080-SS
AD05357	AM07079-AS	AM07081-SS
AD05358	AM07083-AS	AM07082-SS
AD05359	AM07085-AS	AM07084-SS
AD05360	AM07085-AS	AM07086-SS
AD05361	AM07088-AS	AM07087-SS
AD05362	AM07090-AS	AM07089-SS
AD05363	AM07092-AS	AM07091-SS
AD05364	AM07092-AS	AM07093-SS
AD05365	AM07092-AS	AM07094-SS
AD05366	AM07096-AS	AM07095-SS
AD05367	AM07098-AS	AM07097-SS
AD05373	AM06601-AS	AM07109-SS
AD05374	AM06601-AS	AM07110-SS

Duplex ID	Antisense Strand ID	Sense Strand ID
AD05375	AM06851-AS	AM06930-SS
AD05376	AM06851-AS	AM06802-SS
AD05377	AM06851-AS	AM07109-SS
AD05378	AM06851-AS	AM06805-SS
AD05379	AM06851-AS	AM07110-SS
AD05380	AM06806-AS	AM06802-SS
AD05460	AM07209-AS	AM06676-SS
AD05461	AM07210-AS	AM06818-SS
AD05462	AM07210-AS	AM07211-SS
AD05463	AM07210-AS	AM07212-SS
AD05464	AM07213-AS	AM06818-SS
AD05465	AM07214-AS	AM06818-SS
AD05466	AM07210-AS	AM06814-SS
AD05467	AM07210-AS	AM06941-SS
AD05468	AM07213-AS	AM06814-SS
AD05469	AM07214-AS	AM06814-SS
AD05470	AM07216-AS	AM07215-SS
AD05603	AM06815-AS	AM07212-SS
AD05604	AM06815-AS	AM07211-SS
AD05605	AM07210-AS	AM07388-SS
AD05606	AM07390-AS	AM07389-SS
AD05607	AM07392-AS	AM07391-SS
AD05608	AM07394-AS	AM07393-SS
AD05609	AM07396-AS	AM07395-SS
AD05610	AM07398-AS	AM07397-SS
AD05624	AM06815-AS	AM07414-SS

Duplex ID	Antisense Strand ID	Sense Strand ID
AD05640	AM06815-AS	AM07444-SS
AD05641	AM06815-AS	AM07445-SS
AD05642	AM06815-AS	AM07446-SS
AD05643	AM06815-AS	AM07447-SS
AD05644	AM06815-AS	AM07448-SS
AD05645	AM07449-AS	AM07211-SS
AD05646	AM06815-AS	AM07450-SS
AD05647	AM07210-AS	AM07450-SS
AD05648	AM06601-AS	AM07451-SS
AD05649	AM06851-AS	AM07451-SS
AD05650	AM06601-AS	AM07452-SS
AD05651	AM06851-AS	AM07452-SS
AD05674	AM07487-AS	AM06802-SS
AD05675	AM07488-AS	AM06600-SS
AD05676	AM07487-AS	AM07110-SS
AD05677	AM07489-AS	AM06818-SS
AD05678	AM07489-AS	AM06814-SS
AD05679	AM07490-AS	AM07211-SS
AD05680	AM07492-AS	AM07491-SS
AD05682	AM07210-AS	AM07494-SS
AD05692	AM07501-AS	AM07500-SS
AD05740	AM07576-AS	AM06600-SS
AD05741	AM07577-AS	AM06600-SS
AD05742	AM07576-AS	AM06802-SS

In some embodiments, an *ASGR1* RNAi agent is prepared or provided as a salt, mixed salt, or a free-acid. The RNAi agents described herein, upon delivery to a cell expressing an *ASGR1* gene, inhibit or knockdown expression of one or more *ASGR1* genes *in vivo*.

Targeting Groups, Linking Groups, and Delivery Vehicles

In some embodiments, an *ASGR1* RNAi agent is conjugated to one or more non-nucleotide groups including, but not limited to a targeting group, linking group, delivery polymer, or a delivery vehicle. The non-nucleotide group can enhance targeting, delivery or attachment of the RNAi agent. Examples of targeting groups and linking groups are provided in Table 6. The non-nucleotide group can be covalently linked to the 3′ and/or 5′ end of either the sense strand and/or the antisense strand. In some embodiments, an *ASGR1* RNAi agent contains a non-nucleotide group linked to the 3′ and/or 5′ end of the sense strand. In some embodiments, a non-nucleotide group is linked to the 5′ end of an *ASGR1* RNAi agent sense strand. A non-nucleotide group may be linked directly or indirectly to the RNAi agent via a linker/linking group. In some embodiments, a non-nucleotide group is linked to the RNAi agent via a labile, cleavable, or reversible bond or linker.

In some embodiments, a non-nucleotide group enhances the pharmacokinetic or biodistribution properties of an RNAi agent or conjugate to which it is attached to improve cell- or tissue-specific distribution and cell-specific uptake of the RNAi agent or conjugate. In some embodiments, a non-nucleotide group enhances endocytosis of the RNAi agent.

Targeting groups or targeting moieties enhance the pharmacokinetic or biodistribution properties of a conjugate or RNAi agent to which they are attached to improve cell-specific (including, in some cases, organ specific) distribution and cell-specific (or organ specific) uptake of the conjugate or RNAi agent. A targeting group can be monovalent, divalent, trivalent, tetravalent, or have higher valency for the target to which it is directed. Representative targeting groups include, without limitation, compounds with affinity to cell surface molecules, cell receptor ligands, haptens, antibodies, monoclonal antibodies, antibody fragments, and antibody mimics with affinity to cell surface molecules. In some embodiments, a targeting group is linked to an RNAi agent using a linker, such as a PEG linker or one, two, or three abasic and/or ribitol (abasic ribose) residues, which can in some

instances serve as linkers. In some embodiments, a targeting group comprises a galactose-derivative cluster.

The *ASGR1* RNAi agents described herein may be synthesized having a reactive group, such as an amino group (also referred to herein as an amine), at the 5′-terminus and/or the 3’-terminus. The reactive group may be used to subsequently attach a targeting group using methods typical in the art.

In some embodiments, a targeting group comprises an asialoglycoprotein receptor ligand. As used herein, an asialoglycoprotein receptor ligand is a ligand that contains a compound having affinity for the asialoglycoprotein receptor. As noted herein, the asialoglycoprotein receptor is highly expressed on hepatocytes. In some embodiments, an asialoglycoprotein receptor ligand includes or consists of one or more galactose derivatives. As used herein, the term galactose derivative includes both galactose and derivatives of galactose having affinity for the asialoglycoprotein receptor that is equal to or greater than that of galactose. Galactose derivatives include, but are not limited to: galactose, galactosamine, N-formylgalactosamine, N-acetyl-galactosamine, N-propionyl-galactosamine, N-n-butanoyl-galactosamine, and N-iso-butanoylgalactos-amine (see for example: S.T. Iobst and K. Drickamer, J.B.C., 1996, 271, 6686). Galactose derivatives, and clusters of galactose derivatives, that are useful for *in vivo* targeting of oligonucleotides and other molecules to the liver are known in the art (see, for example, Baenziger and Fiete, 1980, Cell, 22, 611-620; Connolly et al., 1982, J. Biol. Chem., 257, 939-945).

Galactose derivatives have been used to target molecules to hepatocytes *in vivo* through their binding to the asialoglycoprotein receptor expressed on the surface of hepatocytes. Binding of asialoglycoprotein receptor ligands to the asialoglycoprotein receptor(s) facilitates cell-specific targeting to hepatocytes and endocytosis of the molecule into hepatocytes. Asialoglycoprotein receptor ligands can be monomeric (e.g., having a single galactose derivative) or multimeric (e.g., having multiple galactose derivatives). The galactose derivative or galactose derivative cluster may be attached to the 3′ or 5′ end of the sense or antisense strand of the RNAi agent using methods known in the art. The preparation of targeting groups, such as galactose derivative clusters, is described in, for example, International Patent Application Publication No. WO 2018/044350 to Arrowhead

Pharmaceuticals, Inc., and International Patent Application Publication No. WO 2017/156012 to Arrowhead Pharmaceuticals, Inc., the contents of both of which are incorporated by reference herein in their entirety.

As used herein, a galactose derivative cluster comprises a molecule having two to four terminal galactose derivatives. A terminal galactose derivative is attached to a molecule through its C-1 carbon. In some embodiments, the galactose derivative cluster is a galactose derivative trimer (also referred to as tri-antennary galactose derivative or tri-valent galactose derivative). In some embodiments, the galactose derivative cluster comprises N-acetyl-galactosamines. In some embodiments, the galactose derivative cluster comprises three N-acetyl-galactosamines. In some embodiments, the galactose derivative cluster is a galactose derivative tetramer (also referred to as tetra-antennary galactose derivative or tetra-valent galactose derivative). In some embodiments, the galactose derivative cluster comprises four N-acetyl-galactosamines.

As used herein, a galactose derivative trimer contains three galactose derivatives, each linked to a central branch point. As used herein, a galactose derivative tetramer contains four galactose derivatives, each linked to a central branch point. The galactose derivatives can be attached to the central branch point through the C-1 carbons of the saccharides. In some embodiments, the galactose derivatives are linked to the branch point via linkers or spacers. In some embodiments, the linker or spacer is a flexible hydrophilic spacer, such as a PEG group (see, for example, U.S. Patent No. 5,885,968; Biessen et al. J. Med. Chem. 1995 Vol. 39 p. 1538-1546). In some embodiments, the PEG spacer is a PEG_3 spacer. The branch point can be any small molecule which permits attachment of three galactose derivatives and further permits attachment of the branch point to the RNAi agent. An example of branch point group is a di-lysine or di-glutamate. Attachment of the branch point to the RNAi agent can occur through a linker or spacer. In some embodiments, the linker or spacer comprises a flexible hydrophilic spacer, such as, but not limited to, a PEG spacer. In some embodiments, the linker comprises a rigid linker, such as a cyclic group. In some embodiments, a galactose derivative comprises or consists of N-acetyl-galactosamine. In some embodiments, the galactose derivative cluster is comprised of a galactose derivative tetramer, which can be, for example, an N-acetyl-galactosamine tetramer.

Embodiments of the present disclosure include pharmaceutical compositions for delivering an *ASGR1* RNAi agent to a liver cell *in vivo*. Such pharmaceutical compositions can include, for example, an *ASGR1* RNAi agent conjugated to a galactose derivative cluster. In some embodiments, the galactose derivative cluster is comprised of a galactose derivative trimer, which can be, for example, an N-acetyl-galactosamine trimer, or galactose derivative tetramer, which can be, for example, an N-acetyl-galactosamine tetramer.

Targeting groups include, but are not limited to, (PAZ), (NAG13), (NAG13)s, (NAG18), (NAG18)s, (NAG24), (NAG24)s, (NAG25), (NAG25)s, (NAG26), (NAG26)s, (NAG27), (NAG27)s, (NAG28), (NAG28)s, (NAG29), (NAG29)s, (NAG30), (NAG30)s, (NAG31), (NAG31)s, (NAG32), (NAG32)s, (NAG33), (NAG33)s, (NAG34), (NAG34)s, (NAG35), (NAG35)s, (NAG36), (NAG36)s, (NAG37), (NAG37)s, (NAG38), (NAG38)s, (NAG39), and (NAG39)s, as defined in Table 6. Other targeting groups, including galactose cluster targeting ligands, are known in the art.

In some embodiments, a linking group is conjugated to the RNAi agent. The linking group facilitates covalent linkage of the agent to a targeting group or delivery polymer or delivery vehicle. The linking group can be linked to the 3′ or the 5′ end of the RNAi agent sense strand or antisense strand. In some embodiments, the linking group is linked to the RNAi agent sense strand. In some embodiments, the linking group is conjugated to the 5′ or 3′ end of an RNAi agent sense strand. In some embodiments, a linking group is conjugated to the 5′ end of an RNAi agent sense strand. Examples of linking groups, include, but are not limited to: reactive groups such a primary amines and alkynes, alkyl groups, abasic nucleotides, ribitol (abasic ribose), and/or PEG groups.

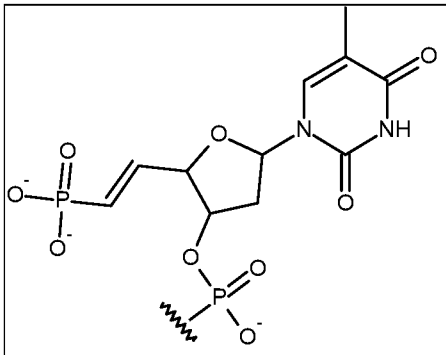
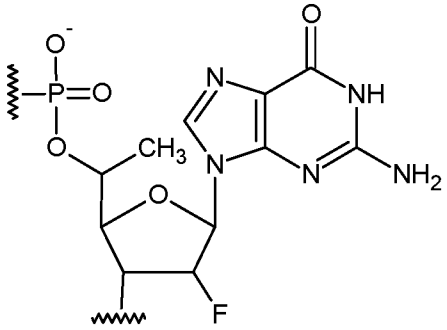
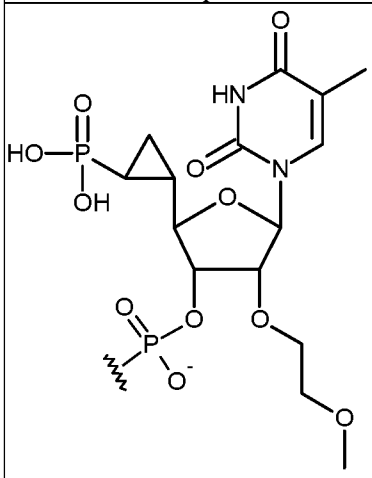
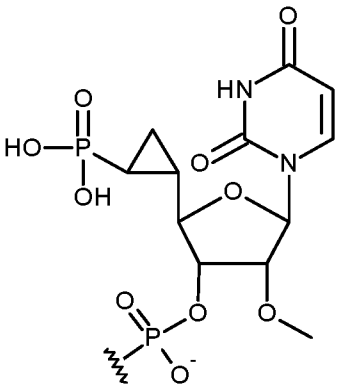
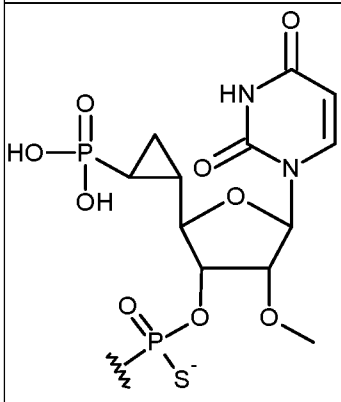
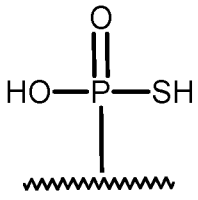
A linker or linking group is a connection between two atoms that links one chemical group (such as an RNAi agent) or segment of interest to another chemical group (such as a targeting group or delivery polymer) or segment of interest via one or more covalent bonds. A labile linkage contains a labile bond. A linkage may optionally include a spacer that increases the distance between the two joined atoms. A spacer may further add flexibility and/or length to the linkage. Spacers may include, but are not be limited to, alkyl groups, alkenyl groups, alkynyl groups, aryl groups, aralkyl groups, aralkenyl groups, and aralkynyl groups; each of which can contain one or more heteroatoms, heterocycles, amino acids,

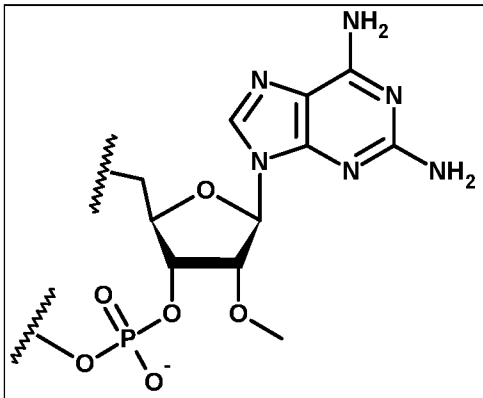
nucleotides, and saccharides. Spacer groups are well known in the art and the preceding list is not meant to limit the scope of the description.

Any of the *ASGR1* RNAi agent nucleotide sequences listed in Tables 2, 3 or 4, whether modified or unmodified, may contain 3′ or 5′ targeting groups or linking groups. Any of the *ASGR1* RNAi agent sequences listed in Tables 3 or 4 which contain a 3′ or 5′ targeting group or linking group, may alternatively contain no 3′ or 5′ targeting group or linking group, or may contain a different 3′ or 5′ targeting group or linking group including, but not limited to, those depicted in Table 6. Any of the *ASGR1* RNAi agent duplexes listed in Table 2 or Table 5, whether modified or unmodified, may further comprise a targeting group or linking group, including, but not limited to, those depicted in Table 6, and the targeting group or linking group may be attached to the 3′ or 5′ terminus of either the sense strand or the antisense strand of the *ASGR1* RNAi agent duplex.

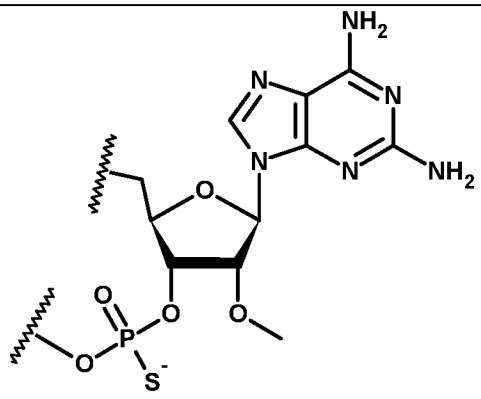
Examples of targeting groups and linking groups are provided in Table 6. Table 4 provides several embodiments of *ASGR1* RNAi agent sense strands having a targeting group or linking group linked to the 5′ or 3′ end.

Table 6. Structures Representing Various Modified Nucleotides, Targeting Groups, and Linking Groups.

 vpdT	 5Me-Gf
 cPrpTM	 cPrpu
 cPrpus	 sp



a_2N



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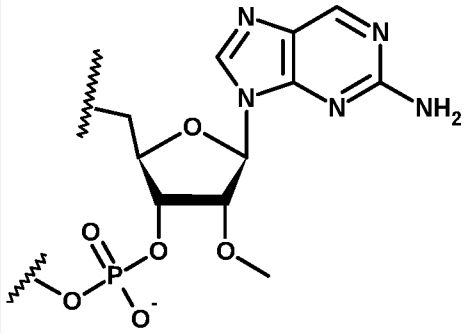
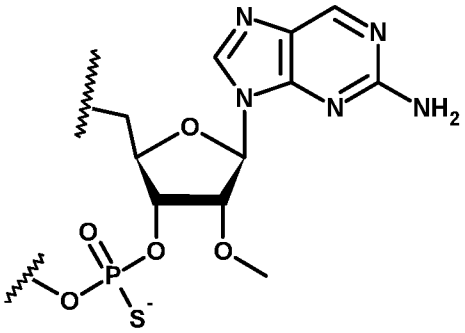


pu_2N



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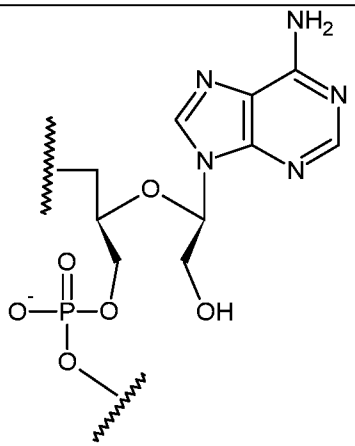
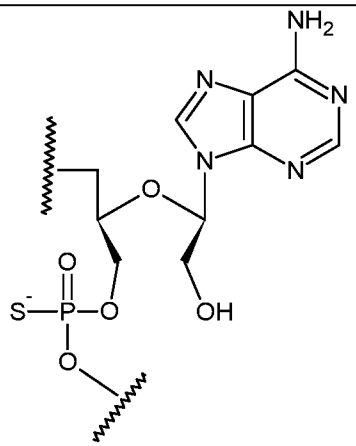


AUNA



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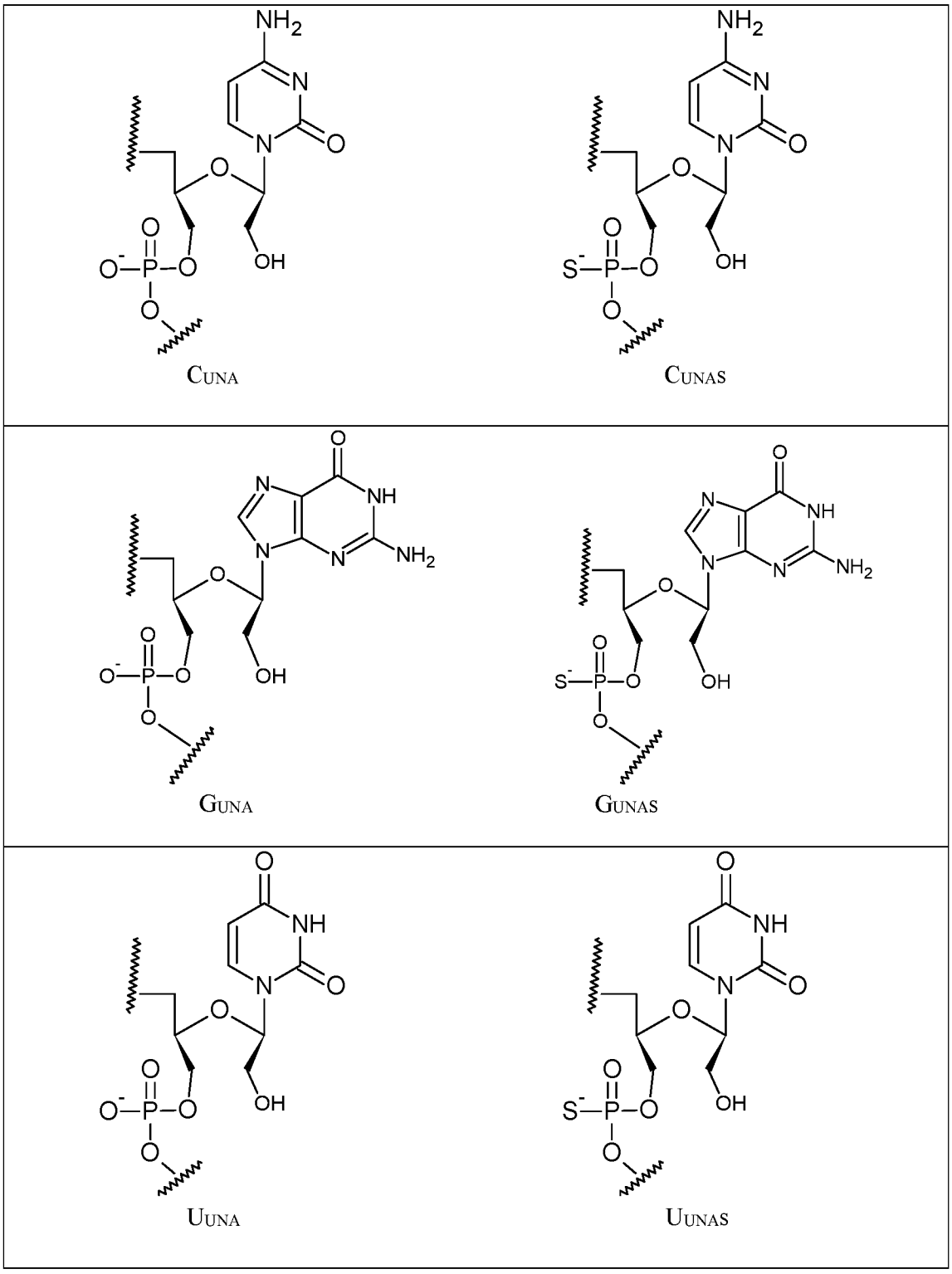
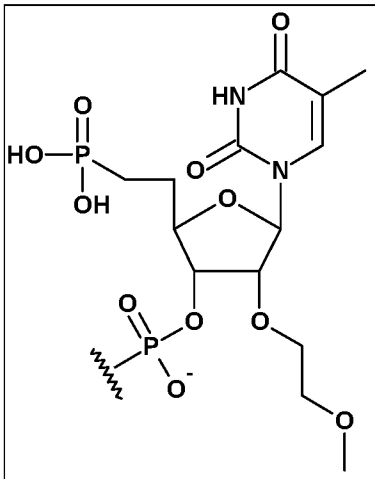
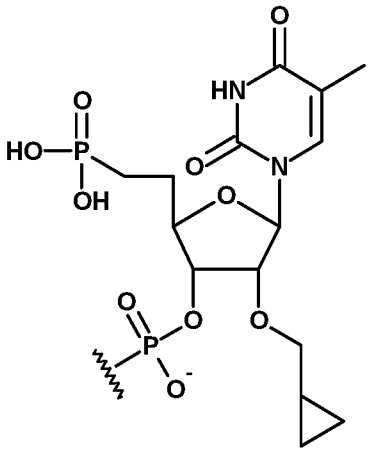

CUNA
CUNAS
GUNA
GUNAS
UUNA
UUNAS



epTM



epTcPr

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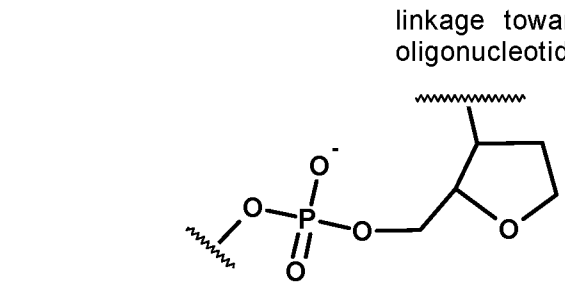
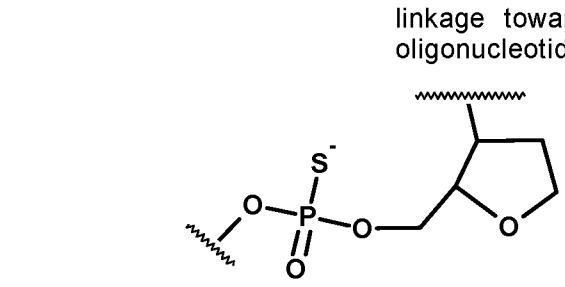


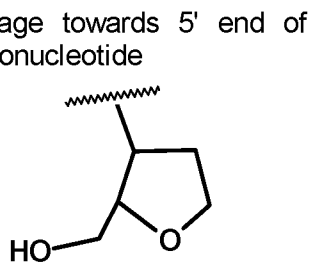
(invAb)

When positioned internally in oligonucleotide:

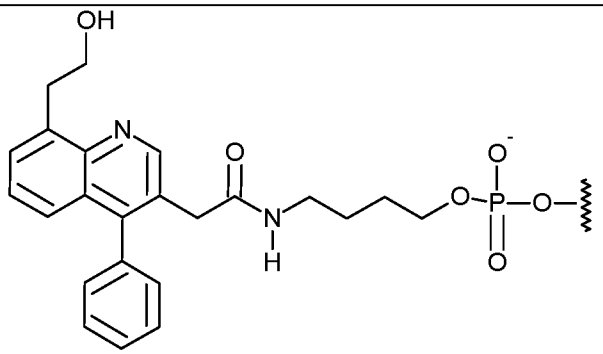


(invAb)s

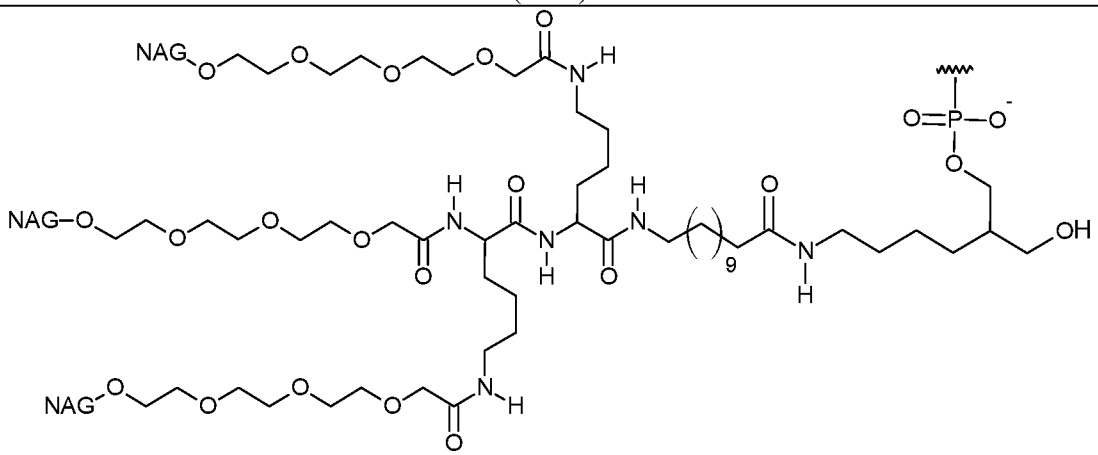
When positioned at the 3′ terminal end of oligonucleotide:



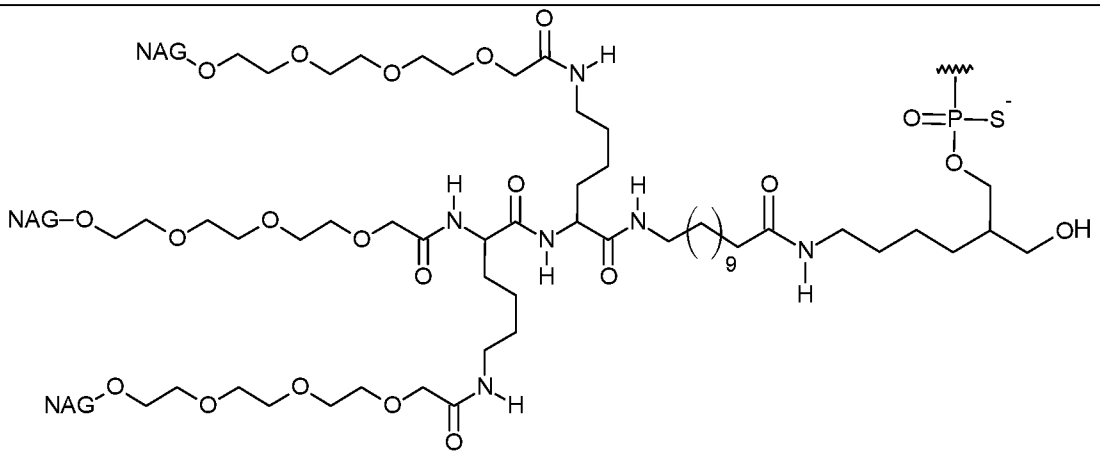
(invAb)



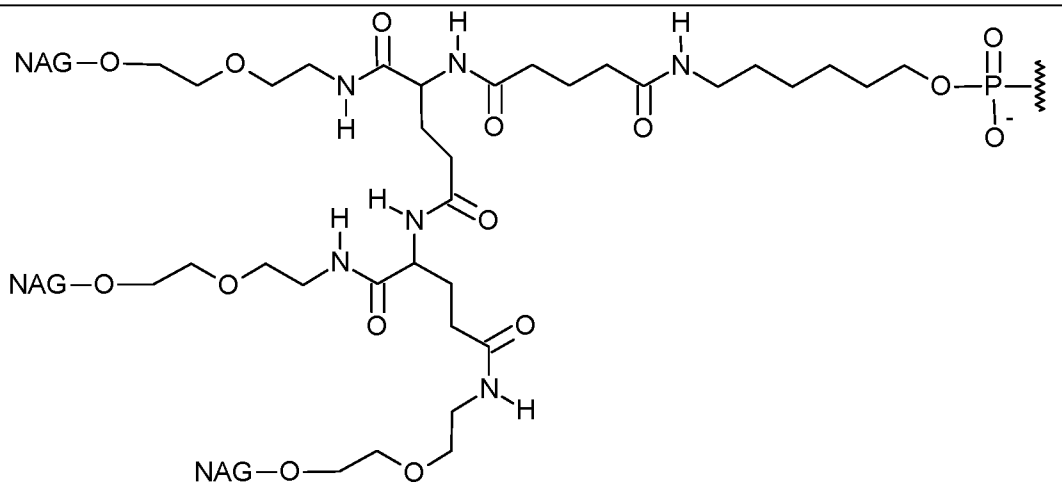
(PAZ)



(NAG13)



(NAG13)s



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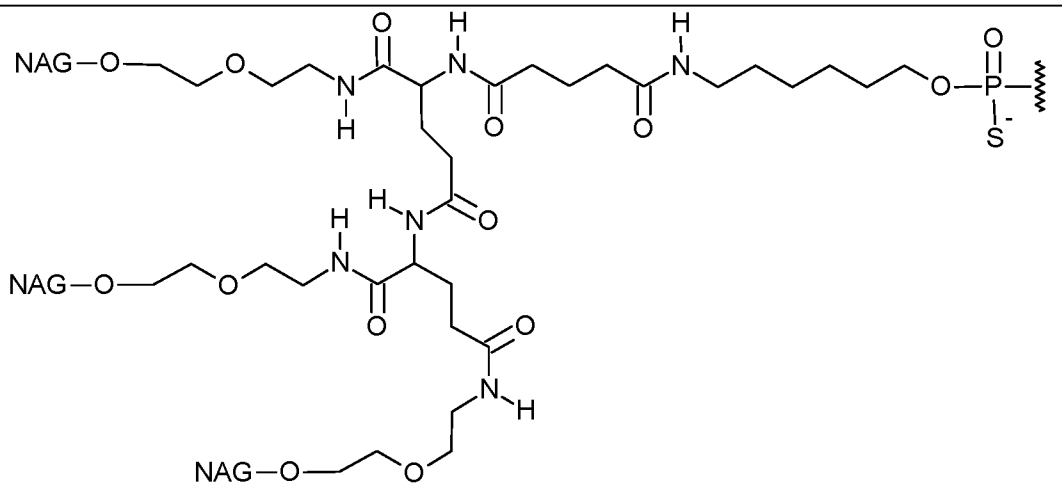

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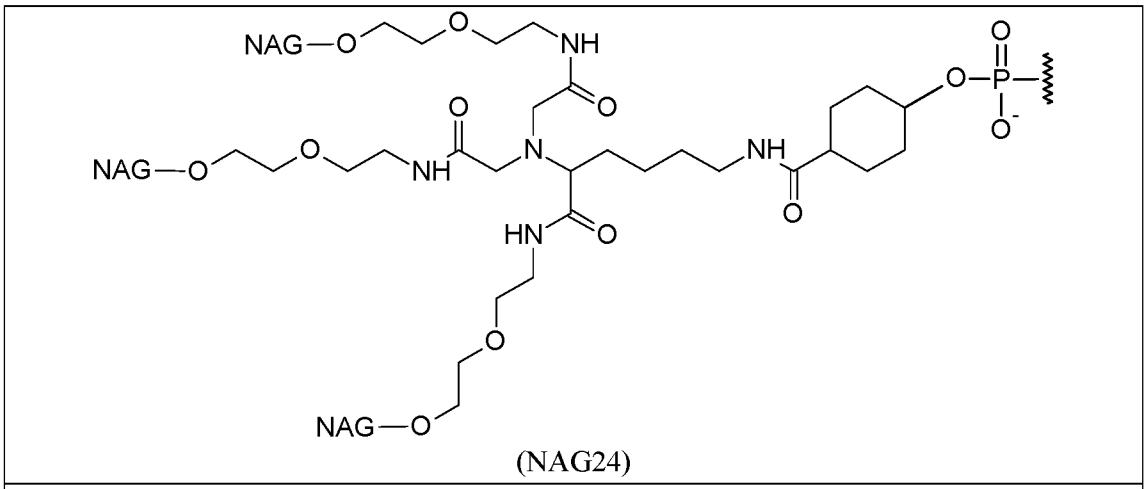

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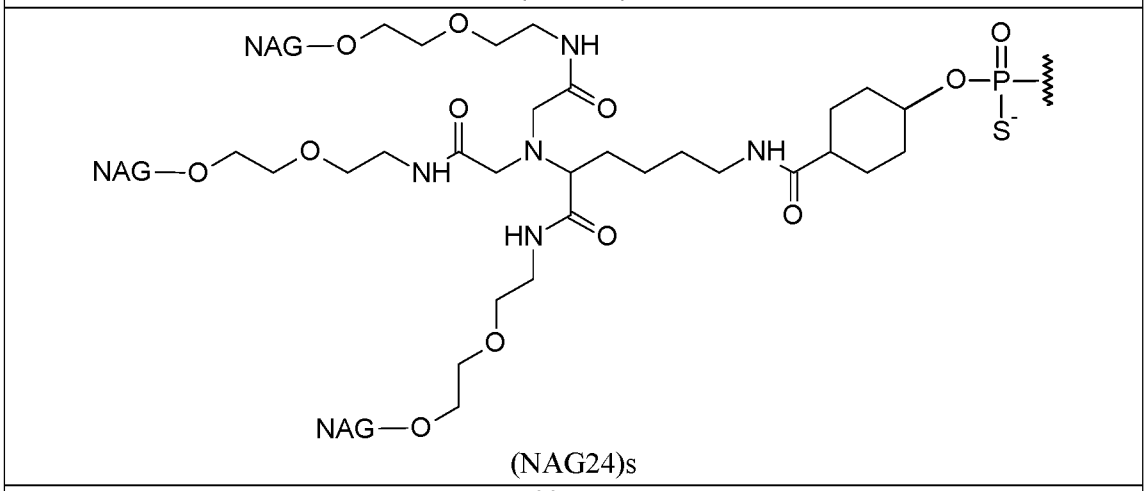

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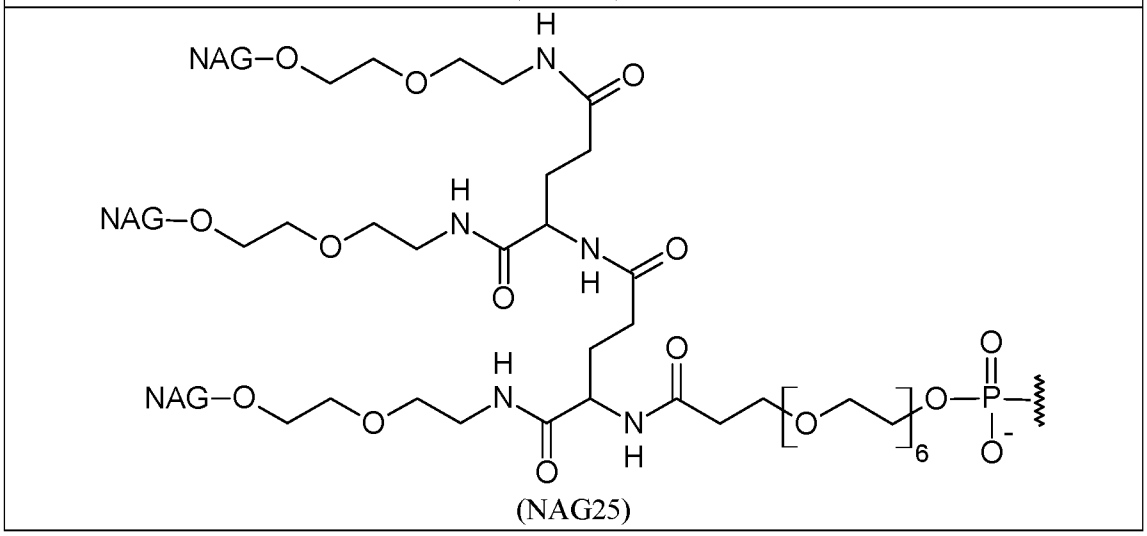

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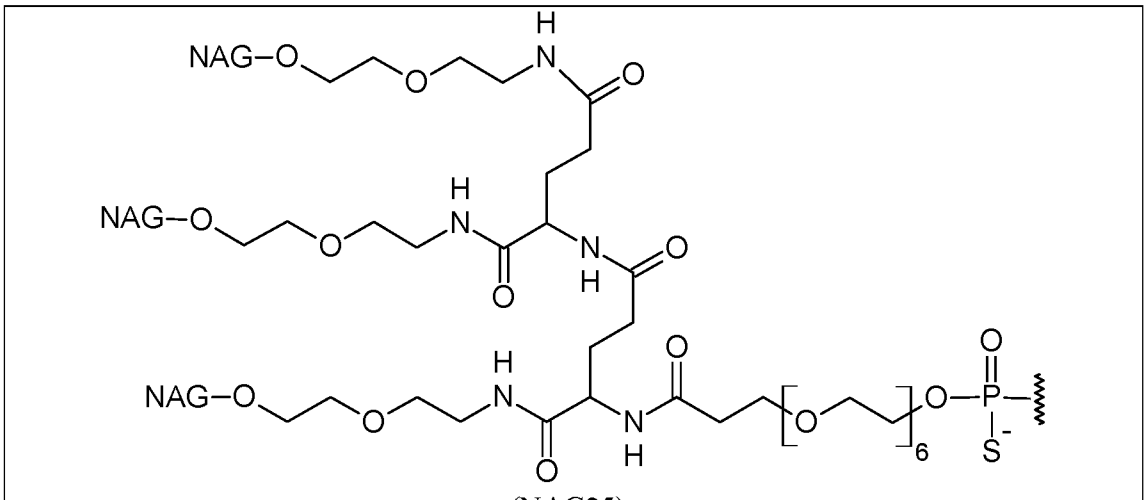

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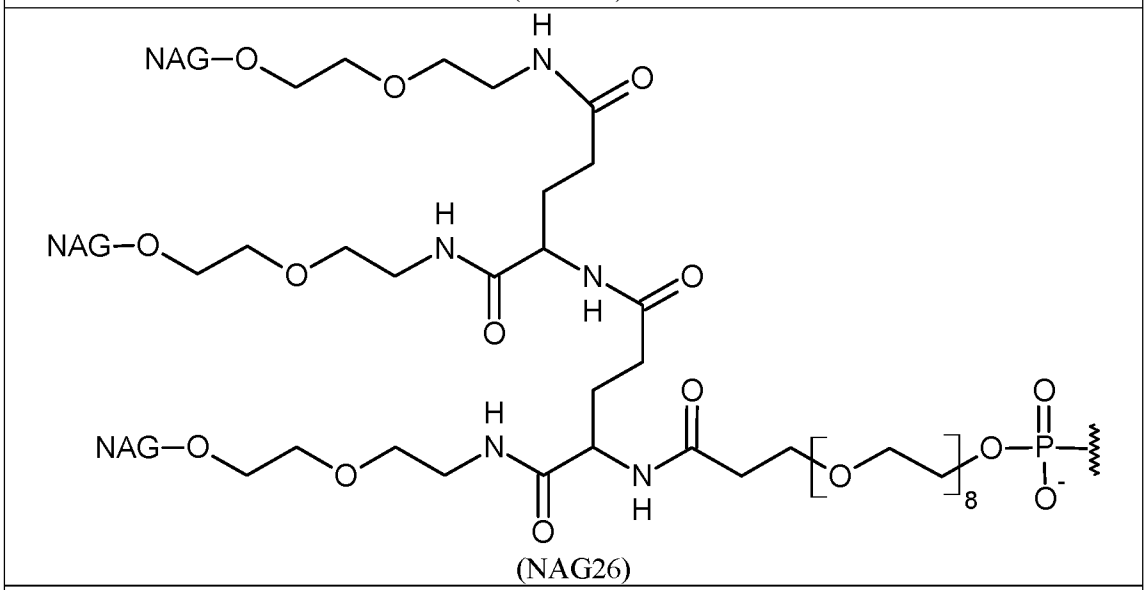
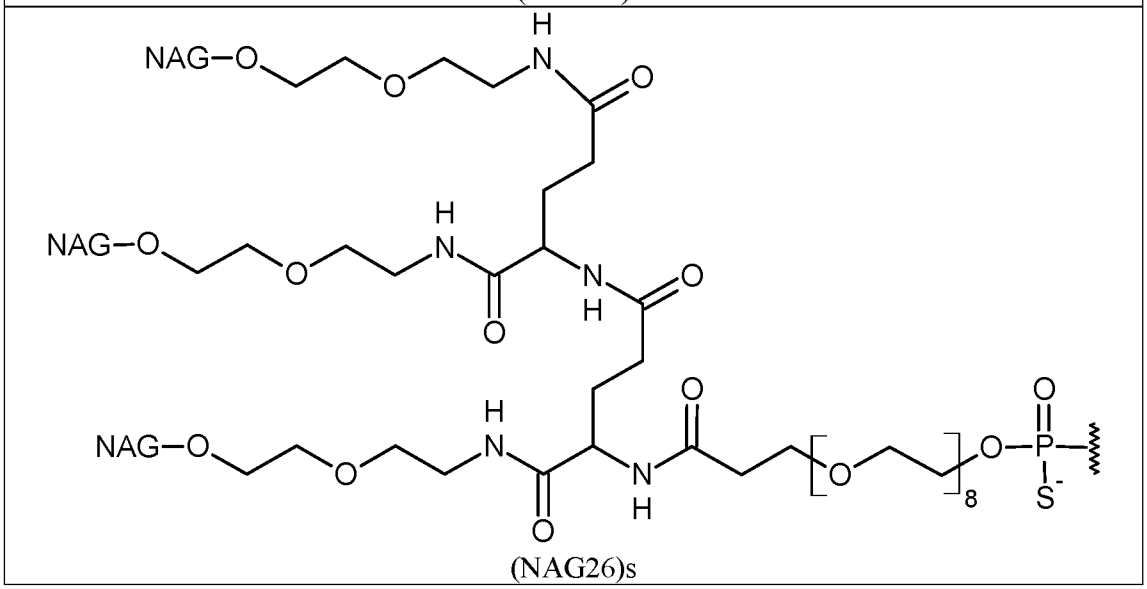


(NAG26)



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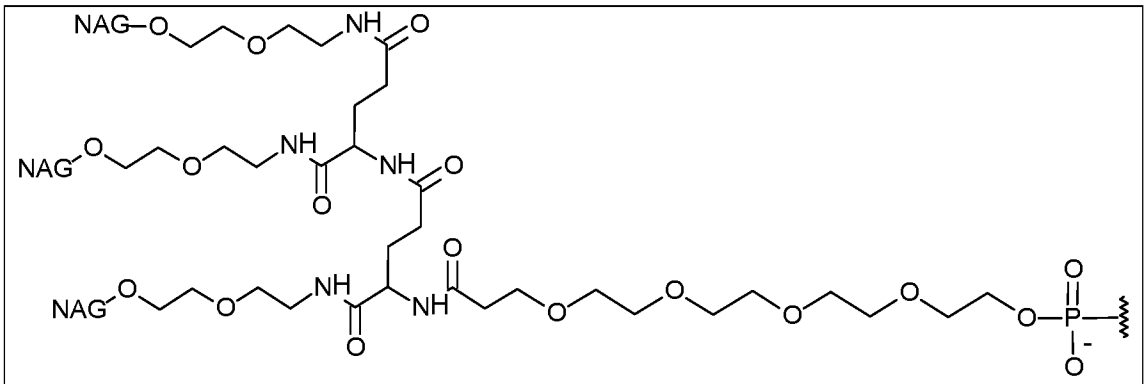

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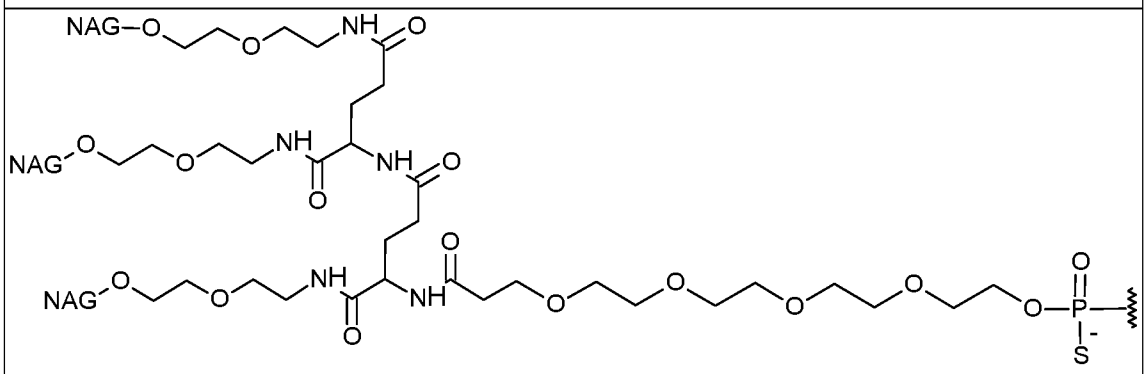

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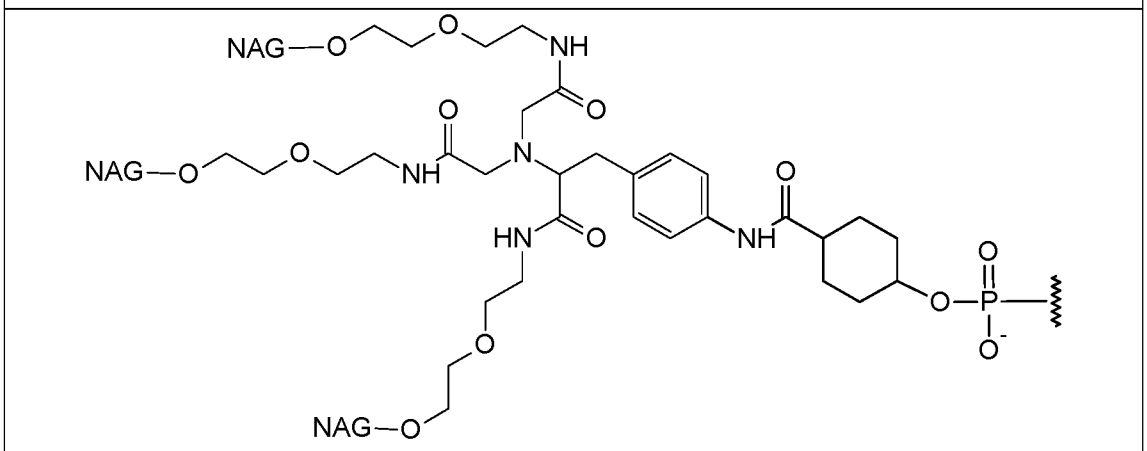
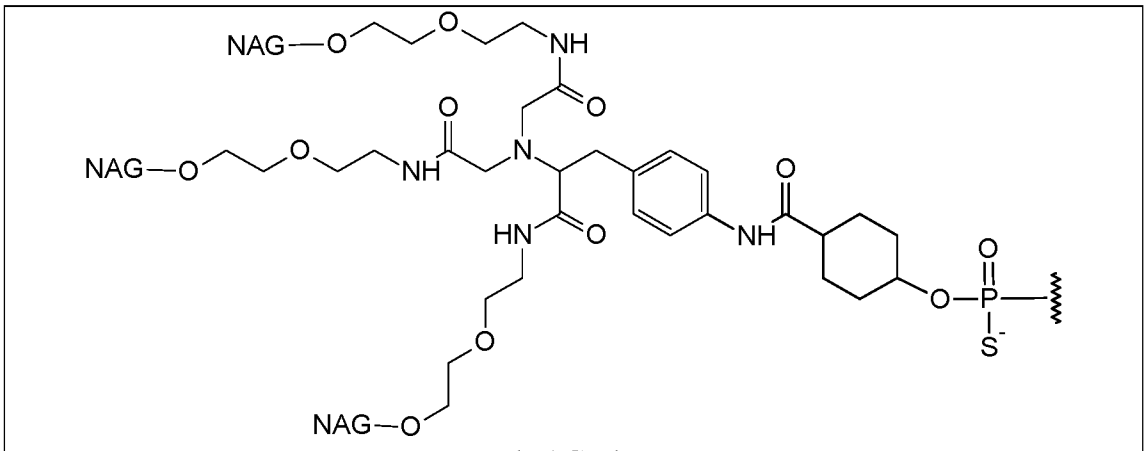


(NAG28)



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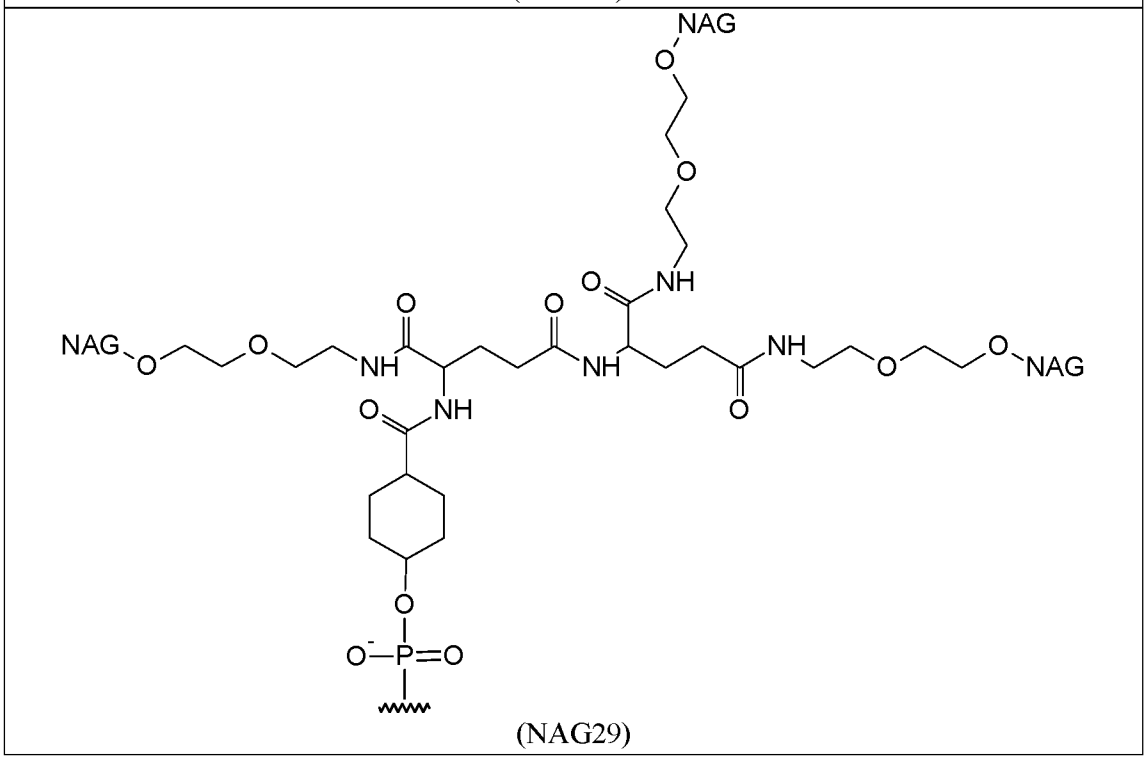

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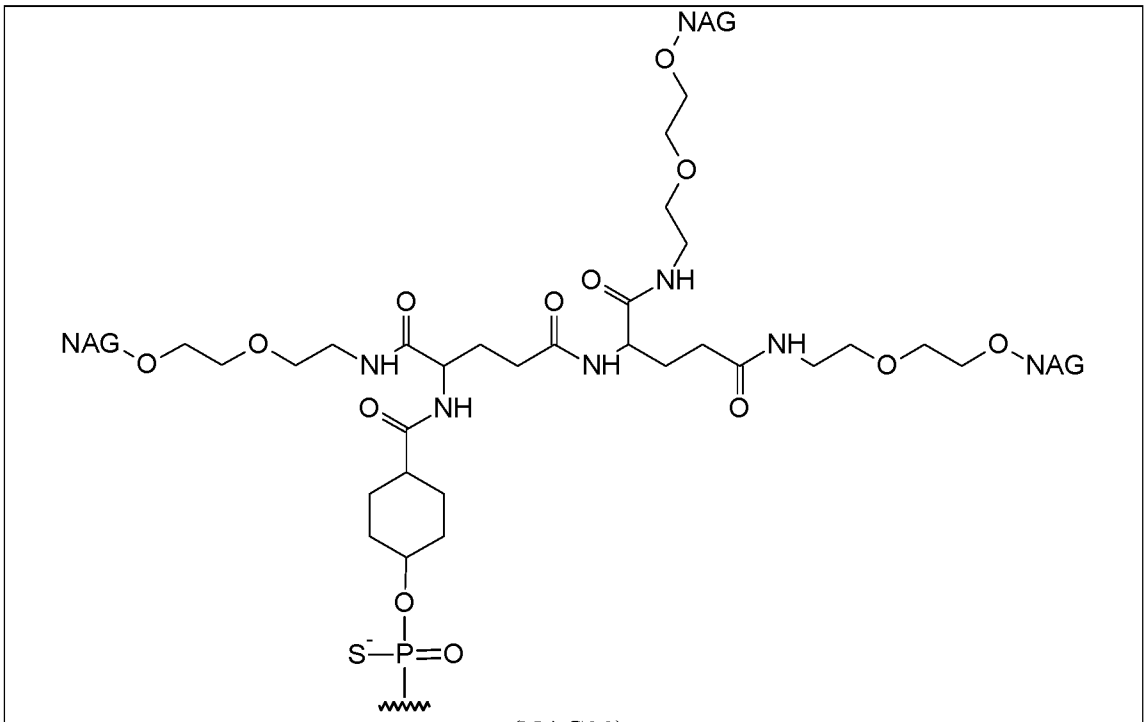
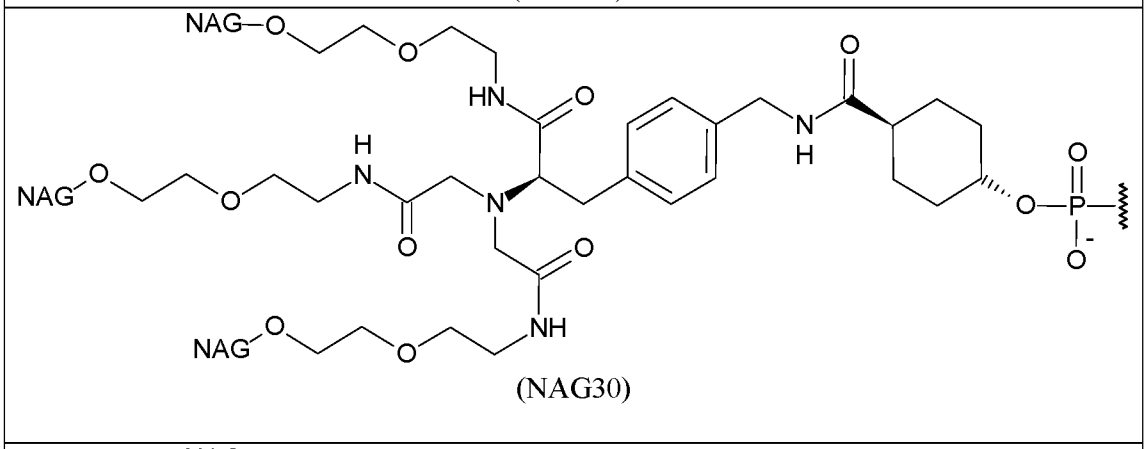


(NAG29)s



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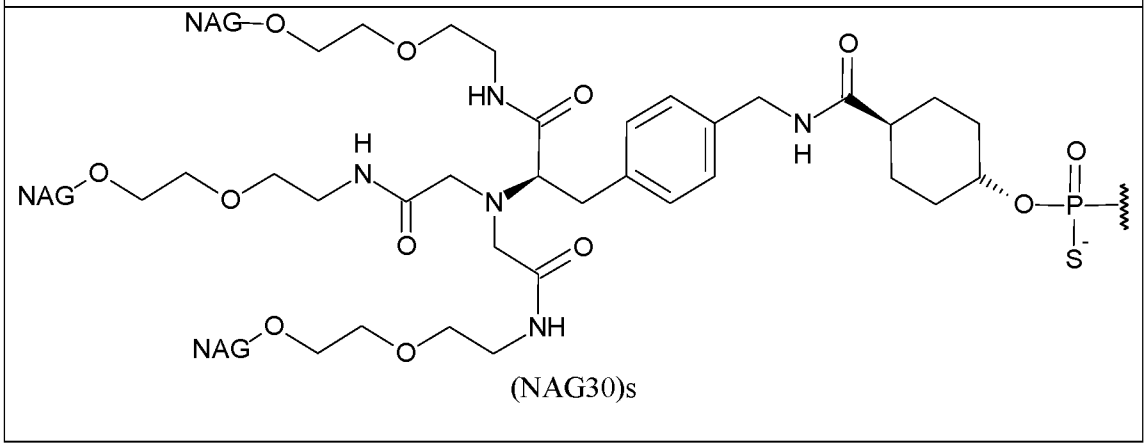

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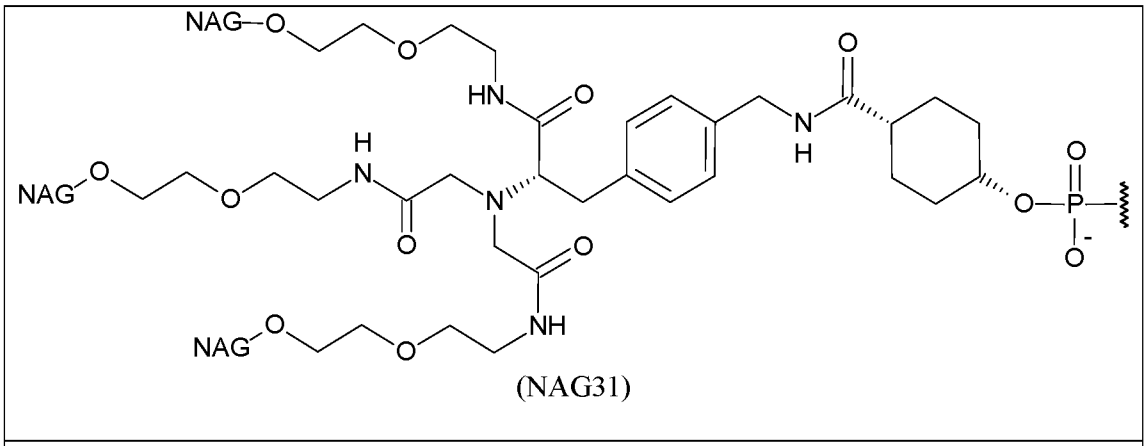
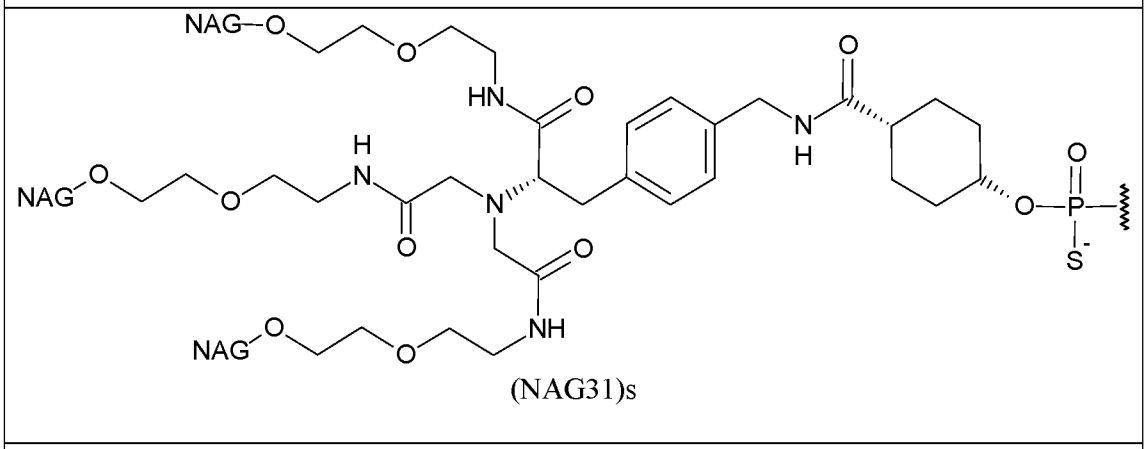
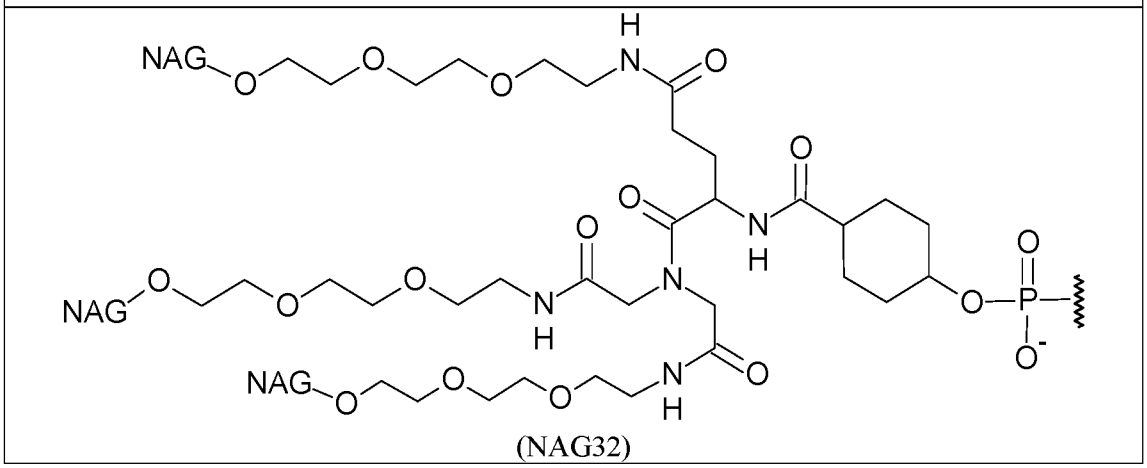


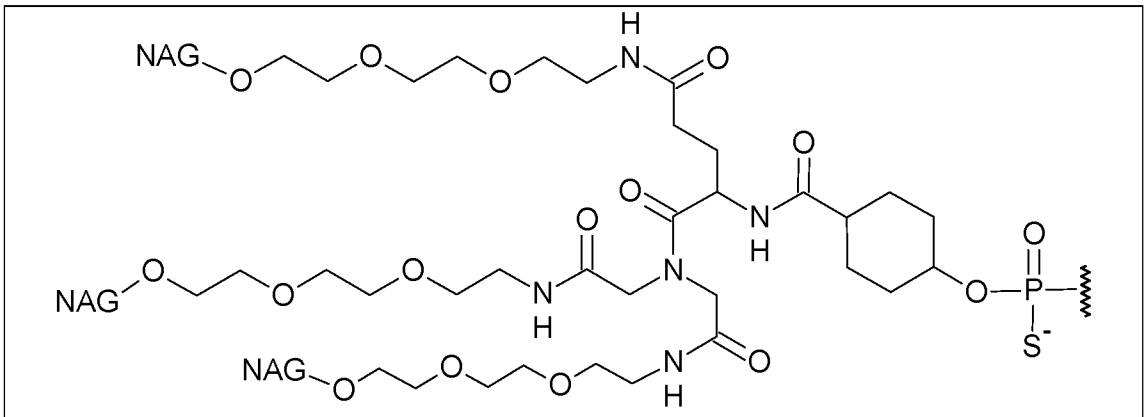
(NAG31)



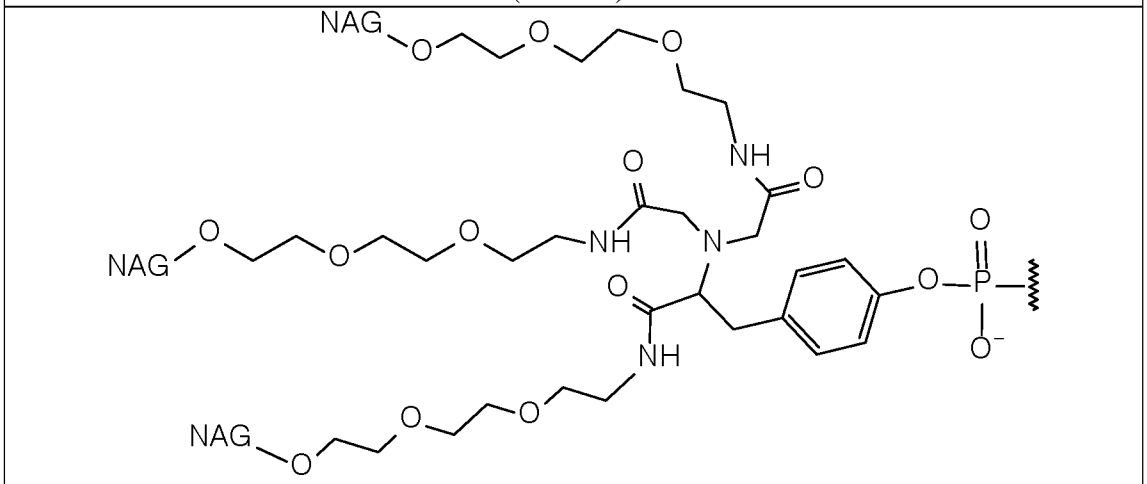
(NAG31)s



(NAG32)



(NAG32)s



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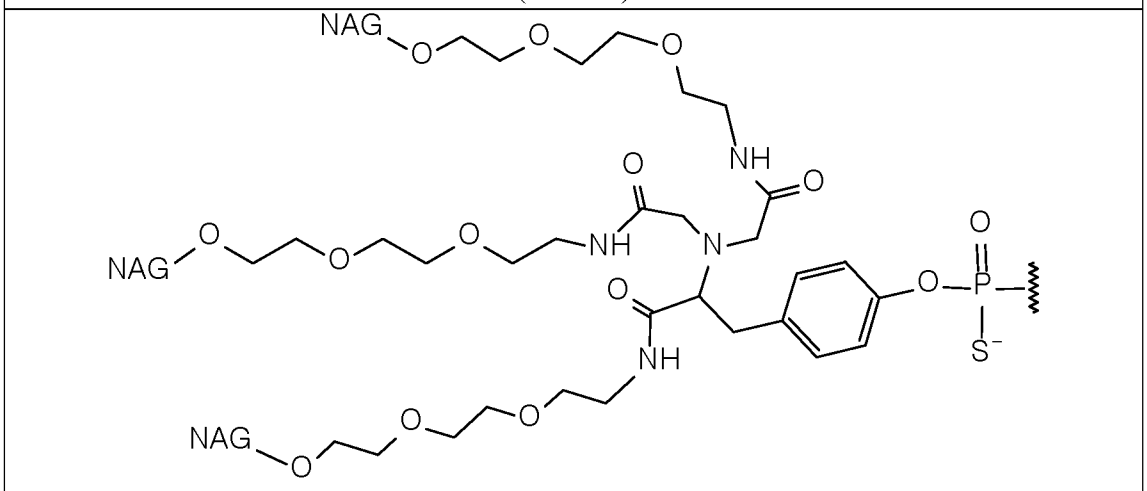
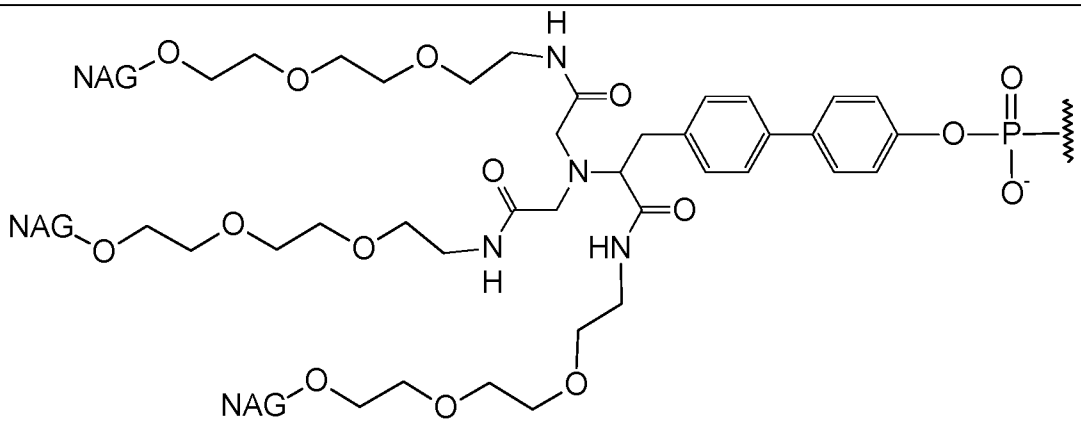
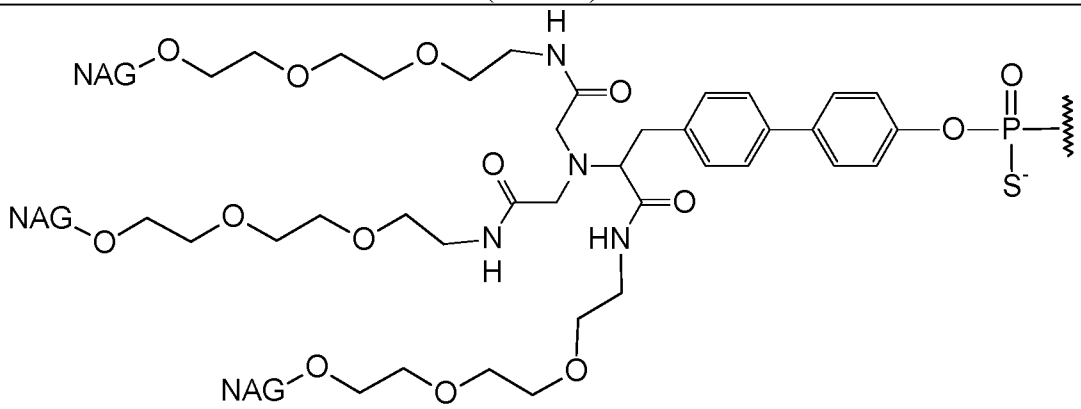


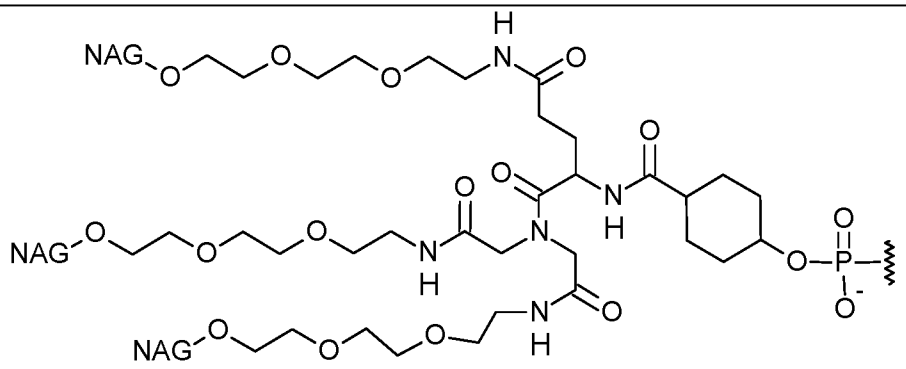
(NAG33)s



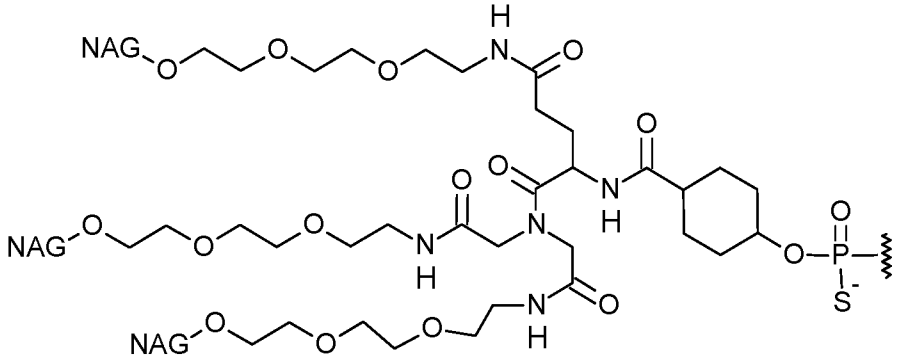
(NAG34)



(NAG34)s



(NAG35)



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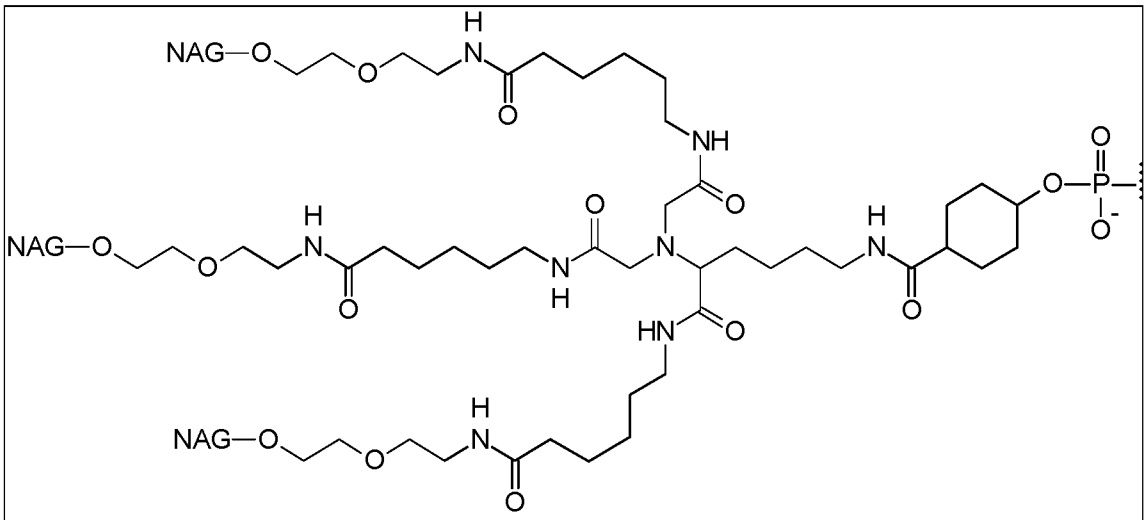
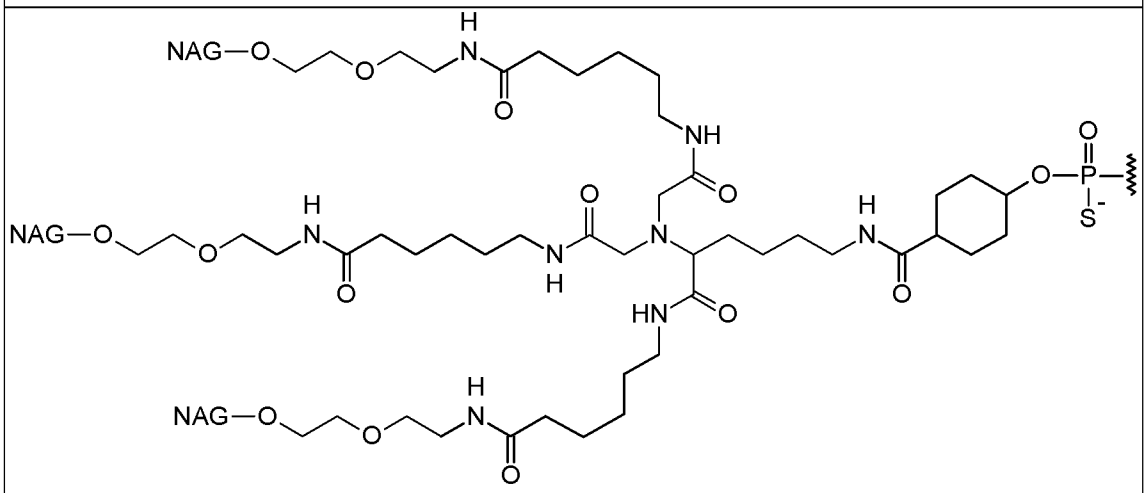


(NAG36)



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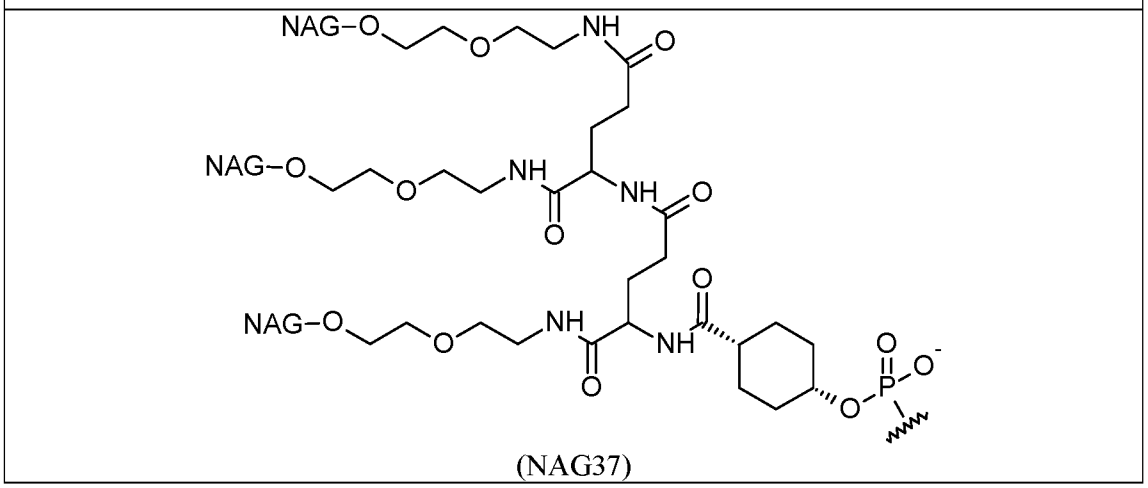
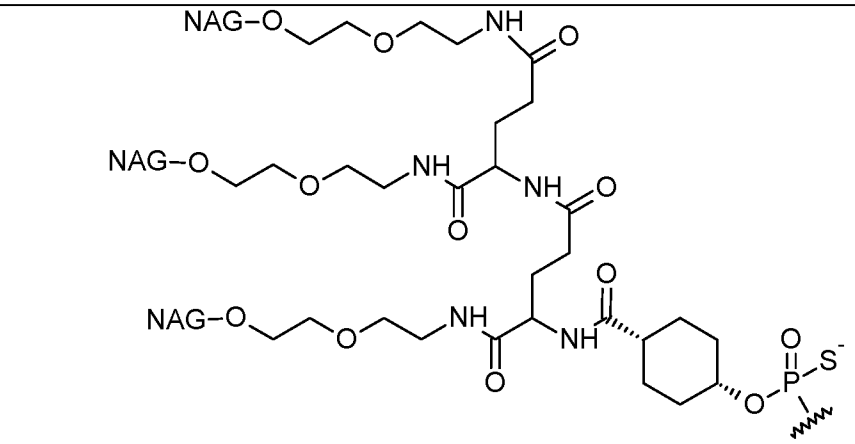
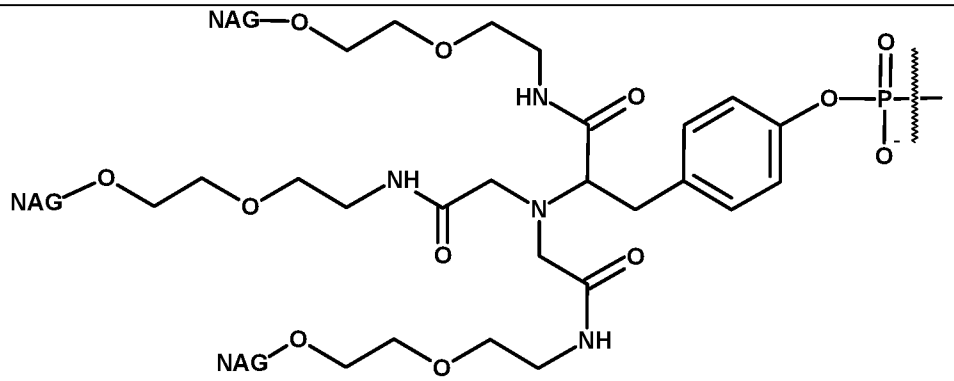


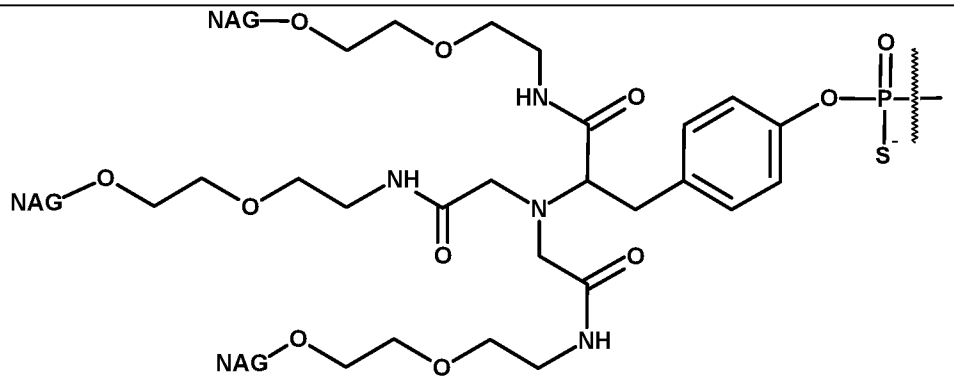
(NAG37)



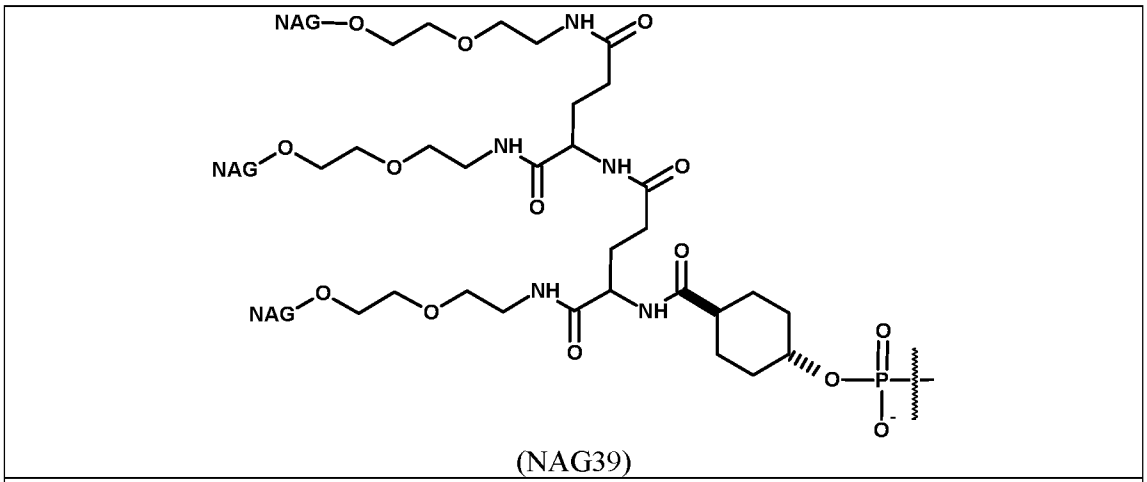
(NAG37)s



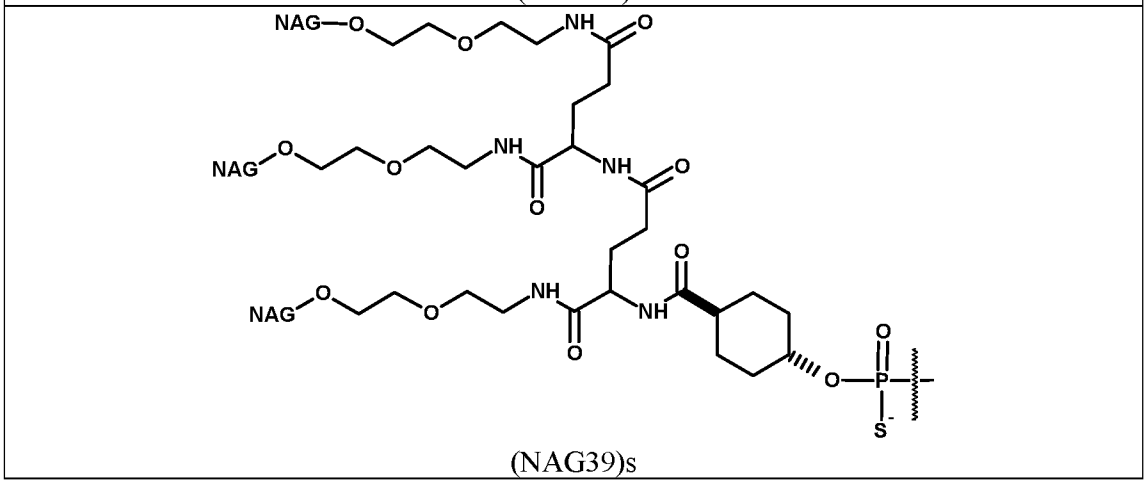
(NAG 38)



(NAG 38)s

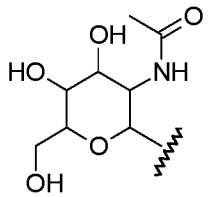


(NAG39)



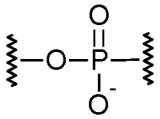
(NAG39)s

In each of the above structures in Table 6, NAG comprises an N-acetyl-galactosamine or another asialoglycoprotein receptor ligand, as would be understood by a person of ordinary skill in the art to be attached in view of the structures above and description provided herein. For example, in some embodiments, NAG in the structures provided in Table 6 is represented by the following structure:

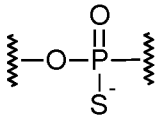


(N-acetyl-galactosamine)

Each (NAGx) may be attached to an *ASGR1* RNAi agent via a phosphate group (as in (NAG25), (NAG30), and (NAG31)), or a phosphorothioate group, (as is (NAG25)s, (NAG29)s, (NAG30)s, (NAG31)s, or (NAG37)s), or another linking group.



Phosphate group



Phosphorothioate group

Other linking groups known in the art may be used.

In some embodiments, a delivery vehicle can be used to deliver an RNAi agent to a cell or tissue. A delivery vehicle is a compound that improves delivery of the RNAi agent to a cell or tissue. A delivery vehicle can include, or consist of, but is not limited to: a polymer, such as an amphipathic polymer, a membrane active polymer, a peptide, a melittin peptide, a melittin-like peptide (MLP), a lipid, a reversibly modified polymer or peptide, or a reversibly modified membrane active polyamine.

In some embodiments, the RNAi agents can be combined with lipids, nanoparticles, polymers, liposomes, micelles, DPCs or other delivery systems available in the art. The RNAi agents can also be chemically conjugated to targeting groups, lipids (including, but not limited to cholesterol and cholesteryl derivatives), nanoparticles, polymers, liposomes, micelles, DPCs (see, for example WO 2000/053722, WO 2008/0022309, WO 2011/104169, and WO 2012/083185, WO 2013/032829, WO 2013/158141, each of which is incorporated herein by reference), or other delivery systems available in the art.

Pharmaceutical Compositions and Formulations

The *ASGR1* RNAi agents disclosed herein can be prepared as pharmaceutical compositions or formulations (also referred to herein as "medicaments"). In some embodiments, pharmaceutical compositions include at least one *ASGR1* RNAi agent. These pharmaceutical compositions are particularly useful in the inhibition of the expression of the target mRNA in a target cell, a group of cells, a tissue, or an organism. The pharmaceutical compositions can be used to treat a subject having a disease or disorder that

would benefit from reduction in the level of the target mRNA, or inhibition in expression of the target gene. The pharmaceutical compositions can be used to treat a subject at risk of developing a disease or disorder that would benefit from reduction of the level of the target mRNA or an inhibition in expression the target gene. In one embodiment, the method includes administering an *ASGR1* RNAi agent linked to a targeting ligand as described herein, to a subject to be treated. In some embodiments, one or more pharmaceutically acceptable excipients (including vehicles, carriers, diluents, and/or delivery polymers) are added to the pharmaceutical compositions including an *ASGR1* RNAi agent, thereby forming a pharmaceutical formulation suitable for *in vivo* delivery to a subject, including a human.

The pharmaceutical compositions that include an *ASGR1* RNAi agent and methods disclosed herein decrease the level of the target mRNA in a cell, group of cells, group of cells, tissue, or subject, including by administering to the subject a therapeutically effective amount of a herein described *ASGR1* RNAi agent, thereby inhibiting the expression of *ASGR1* mRNA in the subject. In some embodiments, the subject has been previously identified as having a pathogenic upregulation of the target gene in the targeted cell or tissue.

In some embodiments, the described pharmaceutical compositions including an *ASGR1* RNAi agent are used for treating or managing clinical presentations associated with elevated non-HDL-C levels, and/or elevated LDL-C levels, and/or elevated total cholesterol levels, and/or elevated TG levels, and/or over-expression of *ASGR1* mRNA. In some embodiments, a therapeutically or prophylactically effective amount of one or more of pharmaceutical compositions is administered to a subject in need of such treatment, prevention or management. In some embodiments, administration of any of the disclosed *ASGR1* RNAi agents can be used to decrease the number, severity, and/or frequency of symptoms of a disease in a subject. In some embodiments, the subject has been previously identified or diagnosed as having elevated cholesterol levels, elevated triglyceride levels, and/or some other dyslipidemia.

The described pharmaceutical compositions including an *ASGR1* RNAi agent can be used to treat at least one symptom in a subject having a disease or disorder that would benefit from reduction or inhibition in expression of *ASGR1* mRNA. In some embodiments, the

subject is administered a therapeutically effective amount of one or more pharmaceutical compositions including an *ASGR1* RNAi agent thereby treating the symptom. In other embodiments, the subject is administered a prophylactically effective amount of one or more *ASGR1* RNAi agents, thereby preventing the at least one symptom.

The route of administration is the path by which an *ASGR1* RNAi agent is brought into contact with the body. In general, methods of administering drugs, oligonucleotides, and nucleic acids, for treatment of a mammal, are well known in the art and can be applied to administration of the compositions described herein. The *ASGR1* RNAi agents disclosed herein can be administered via any suitable route in a preparation appropriately tailored to the particular route. Thus, herein described pharmaceutical compositions can be administered by injection, for example, intravenously, intramuscularly, intracutaneously, subcutaneously, intraarticularly, or intraperitoneally. In some embodiments, the herein described pharmaceutical compositions are administered via subcutaneous injection.

The pharmaceutical compositions including an *ASGR1* RNAi agent described herein can be delivered to a cell, group of cells, tissue, or subject using oligonucleotide delivery technologies known in the art. In general, any suitable method recognized in the art for delivering a nucleic acid molecule (in vitro or in vivo) can be adapted for use with the herein described compositions. For example, delivery can be by local administration, (e.g., direct injection, implantation, or topical administering), systemic administration, or subcutaneous, intravenous, intraperitoneal, or parenteral routes, including intracranial (e.g., intraventricular, intraparenchymal and intrathecal), intramuscular, transdermal, airway (aerosol), nasal, oral, rectal, or topical (including buccal and sublingual) administration. In certain embodiments, the compositions are administered by subcutaneous or intravenous infusion or injection.

Accordingly, in some embodiments, the herein described pharmaceutical compositions may comprise one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical compositions described herein can be formulated for administration to a subject.

As used herein, a pharmaceutical composition or medicament includes a pharmacologically effective amount of at least one of the described ASGR1 RNAi agents and one or more pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients (excipients) are substances other than the Active Pharmaceutical Ingredient (API, therapeutic product, e.g., *ASGR1* RNAi agent) that are intentionally included in the drug delivery system. Excipients do not exert or are not intended to exert a therapeutic effect at the intended dosage. Excipients may act to a) aid in processing of the drug delivery system during manufacture, b) protect, support or enhance stability, bioavailability or patient acceptability of the API, c) assist in product identification, and/or d) enhance any other attribute of the overall safety, effectiveness, of delivery of the API during storage or use. A pharmaceutically acceptable excipient may or may not be an inert substance.

Excipients include, but are not limited to: absorption enhancers, anti-adherents, anti-foaming agents, anti-oxidants, binders, buffering agents, carriers, coating agents, colors, delivery enhancers, delivery polymers, dextran, dextrose, diluents, disintegrants, emulsifiers, extenders, fillers, flavors, glidants, humectants, lubricants, oils, polymers, preservatives, saline, salts, solvents, sugars, suspending agents, sustained release matrices, sweeteners, thickening agents, tonicity agents, vehicles, water-repelling agents, and wetting agents.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor® ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the

injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Formulations suitable for intra-articular administration can be in the form of a sterile aqueous preparation of the drug that can be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems can also be used to present the drug for both intra-articular and ophthalmic administration.

The active compounds can be prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

The *ASGR1* RNAi agents can be formulated in compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the

dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

A pharmaceutical composition can contain other additional components commonly found in pharmaceutical compositions. Such additional components include, but are not limited to: anti-pruritics, astringents, local anesthetics, or anti-inflammatory agents (e.g., antihistamine, diphenhydramine, etc.). It is also envisioned that cells, tissues or isolated organs that express or comprise the herein defined RNAi agents may be used as "pharmaceutical compositions." As used herein, "pharmacologically effective amount," "therapeutically effective amount," or simply "effective amount" refers to that amount of an RNAi agent to produce a pharmacological, therapeutic or preventive result.

Generally, an effective amount of an active compound will be in the range of from about 0.1 to about 100 mg/kg of body weight/day, e.g., from about 1.0 to about 50 mg/kg of body weight/day. In some embodiments, an effective amount of an active compound will be in the range of from about 0.25 to about 5 mg/kg of body weight per dose. In some embodiments, an effective amount of an active ingredient will be in the range of from about 0.5 to about 4 mg/kg of body weight per dose. The amount administered will also likely depend on such variables as the overall health status of the patient, the relative biological efficacy of the compound delivered, the formulation of the drug, the presence and types of excipients in the formulation, and the route of administration. Also, it is to be understood that the initial dosage administered can be increased beyond the above upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage can be smaller than the optimum.

For treatment of disease or for formation of a medicament or composition for treatment of a disease, the pharmaceutical compositions described herein including an *ASGR1* RNAi agent can be combined with an excipient or with a second therapeutic agent or treatment including, but not limited to: a second or other RNAi agent, a small molecule drug, an antibody, an antibody fragment, peptide and/or aptamer.

The described *ASGR1* RNAi agents, when added to pharmaceutically acceptable excipients or adjuvants, can be packaged into kits, containers, packs, or dispensers. The pharmaceutical compositions described herein may be packaged in pre-filled syringes or vials.

Methods of Treatment and Inhibition of Expression

The *ASGR1* RNAi agents disclosed herein can be used to treat a subject (e.g., a human or other mammal) having a disease or disorder that would benefit from administration of the compound. In some embodiments, the RNAi agents disclosed herein can be used to treat a subject (e.g., a human) having a disease or disorder that would benefit from reduction or inhibition in expression of *ASGR1* mRNA. The subject is administered a therapeutically effective amount of any one or more of the ASGR1 RNAi agents described herein. The subject can be a human, patient, or human patient. The subject may be an adult, adolescent, child, or infant. The described pharmaceutical compositions including an *ASGR1* RNAi agent can be used to provide methods for the therapeutic treatment of diseases. Such methods include administration of a pharmaceutical composition described herein to a human being or animal.

In some embodiments, the *ASGR1* RNAi agents described herein are used to treat a subject with an *ASGR1*-related disease or disorder. An "ASGR1-related disease or disorder" refers to conditions, diseases, or disorders in which ASGR1 expression levels are altered or where elevated expression levels of ASGR1 are associated with an increased risk of developing the condition, disease or disorder. ASGR1-related diseases or disorders include, but are not limited to, obesity, metabolic syndrome, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, diabetes, cardiovascular disease, coronary artery disease, myocardial infarction, peripheral vascular disease, cerebrovascular disease and other metabolic-related disorders and diseases. In some embodiments, the described *ASGR1* RNAi agents are used to treat at least one symptom in a subject having an *ASGR1*-related disease or disorder. The subject is administered a therapeutically effective amount of any one or more of the described RNAi agents. In some embodiments, the present invention provides for the use of an *ASGR1* RNAi agent described herein for the preparation of a medicament for treating an *ASGR1*-related disease or disorder in a patient in need thereof. In other embodiments, the present invention

provides an *ASGR1* RNAi agent described herein for use in a method for treating *ASGR1*-related diseases in a patient in need thereof.

In certain embodiments, the present invention provides a method for reducing the risk of myocardial infarction in a patient in need thereof comprising administering to the patient any of the *ASGR1* RNAi agents described herein. A patient who is at risk of having a myocardial infarction may be a patient who has a history of myocardial infarction (e.g. has had a previous myocardial infarction). A patient at risk of having a myocardial infarction may also be a patient who has a familial history of myocardial infarction or who has one or more risk factors of myocardial infarction. Such risk factors include, but are not limited to, hypertension, elevated levels of non-HDL cholesterol, elevated levels of triglycerides, diabetes, obesity, or history of autoimmune diseases (e.g. rheumatoid arthritis, lupus). In one embodiment, a patient who is at risk of having a myocardial infarction is a patient who has or is diagnosed with coronary artery disease. The risk of myocardial infarction in these and other patients can be reduced by administering to the patients any of the ASGR1 RNAi agents described herein. In some embodiments, the present invention provides for the use of an *ASGR1* RNAi agent described herein for the preparation of a medicament for reducing the risk of myocardial infarction in a patient in need thereof. In other embodiments, the present invention provides an *ASGR1* RNAi agent described herein for use in a method for reducing the risk of myocardial infarction in a patient in need thereof.

In some embodiments, the present invention provides a method for reducing non-HDL cholesterol in a patient in need thereof by administering to the patient any of the *ASGR1* RNAi agents described herein. Non-HDL cholesterol is a measure of all cholesterol-containing proatherogenic lipoproteins, including LDL cholesterol, very low-density lipoprotein, intermediate-density lipoprotein, lipoprotein(a), chylomicron, and chylomicron remnants. Non-HDL cholesterol has been reported to be a good predictor of cardiovascular risk (Rana et al., Curr. Atheroscler. Rep., Vol. 14:130-134, 2012). Non-HDL cholesterol levels can be calculated by subtracting HDL cholesterol levels from total cholesterol levels. In one embodiment, a patient's LDL cholesterol levels are reduced following administration of the *ASGR1* RNAi agent. In another embodiment, a patient's lipoprotein (a) levels are reduced following administration of the *ASGR1* RNAi agent. In some embodiments, the present invention provides for the use of an *ASGR1* RNAi agent described herein for the

preparation of a medicament for reducing non-HDL cholesterol in a patient in need thereof. In other embodiments, the present invention provides an *ASGR1* RNAi agent described herein for use in a method for reducing non-HDL cholesterol in a patient in need thereof.

In some embodiments, a patient to be treated according to the methods of the invention is a patient who has elevated levels of non-HDL cholesterol (e.g. elevated serum levels of non-HDL cholesterol). Ideally, levels of non-HDL cholesterol should be about 30 mg/dL above the target for LDL cholesterol levels for any given patient. In particular embodiments, a patient is administered an *ASGR1* RNAi agent of the invention if the patient has a non-HDL cholesterol level of about 130 mg/dL or greater. In one embodiment, a patient is administered an *ASGR1* RNAi agent of the invention if the patient has a non-HDL cholesterol level of about 160 mg/dL or greater. In another embodiment, a patient is administered an *ASGR1* RNAi agent of the invention if the patient has a non-HDL cholesterol level of about 190 mg/dL or greater. In still another embodiment, a patient is administered an *ASGR1* RNAi agent of the invention if the patient has a non-HDL cholesterol level of about 220 mg/dL or greater. In certain embodiments, a patient is administered an *ASGR1* RNAi agent of the invention if the patient is at a high or very high risk of cardiovascular disease according to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (Goff et al., ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;00:000–000) and has a non-HDL cholesterol level of about 100 mg/dL or greater.

In some embodiments of the methods of the invention, a patient is administered an *ASGR1* RNAi agent described herein if they are at a moderate risk or higher for cardiovascular disease according to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (referred to herein as the "2013 Guidelines"). In certain embodiments, an *ASGR1* RNAi agent of the invention is administered to a patient if the patient's LDL cholesterol level is greater than about 160 mg/dL. In other embodiments, an *ASGR1* RNAi agent of the invention is administered to a patient if the patient's LDL cholesterol level is greater than about 130 mg/dL and the patient has a moderate risk of cardiovascular disease according to the 2013 Guidelines. In still other embodiments, an *ASGR1* RNAi agent of the invention is administered to a patient if the patient's LDL cholesterol level is greater than 100 mg/dL

and the patient has a high or very high risk of cardiovascular disease according to the 2013 Guidelines.

In some embodiments, the *ASGR1* RNAi agents are used to treat or manage a clinical presentation of a subject with an *ASGR1*-related disease or disorder. The subject is administered a therapeutically effective amount of one or more of the *ASGR1* RNAi agents or *ASGR1* RNAi agent-containing compositions described herein. In some embodiments, the method comprises administering a composition comprising an *ASGR1* RNAi agent described herein to a subject to be treated.

In some embodiments, the gene expression level and/or mRNA level of an *ASGR1* gene in a subject to whom a described *ASGR1* RNAi agent is administered is reduced by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 95%, 96%, 97%, 98%, 99%, or greater than 99% relative to the subject prior to being administered the *ASGR1* RNAi agent or to a subject not receiving the *ASGR1* RNAi agent. The gene expression level and/or mRNA level in the subject may be reduced in a cell, group of cells, and/or tissue of the subject. In some embodiments, the protein level of *ASGR1* in a subject to whom a described *ASGR1* RNAi agent has been administered is reduced by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or greater than 99% relative to the subject prior to being administered the *ASGR1* RNAi agent or to a subject not receiving the *ASGR1* RNAi agent. The protein level in the subject may be reduced in a cell, group of cells, tissue, blood, and/or other fluid of the subject. A reduction in gene expression, mRNA, or protein levels can be assessed by any methods known in the art. Reduction or decrease in *ASGR1* mRNA level and/or protein level are collectively referred to herein as a reduction or decrease in *ASGR1* or inhibiting or reducing the expression of *ASGR1*.

Cells, Tissues, Organs, and non-Human Organisms

Cells, tissues, organs, and non-human organisms that include at least one of the *ASGR1* RNAi agents described herein is contemplated. The cell, tissue, organ, or non-human organism is made by delivering the RNAi agent to the cell, tissue, organ or non-human organism.

The above provided embodiments and items are now illustrated with the following, non-limiting examples.

EXAMPLES

Example 1. Synthesis of ASGR1 RNAi agents.

ASGR1 RNAi agent duplexes shown in Table 5 (with corresponding sense and antisense strand sequences identified in Tables 3 and 4) above, were synthesized in accordance with the following:

A. *Synthesis*. The sense and antisense strands of the *ASGR1* RNAi agents were synthesized according to phosphoramidite technology on solid phase used in oligonucleotide synthesis. Depending on the scale, either a MerMade96E® (Bioautomation), a MerMade12® (Bioautomation), or an OP Pilot 100 (GE Healthcare) was used. Syntheses were performed on a solid support made of controlled pore glass (CPG, 500 Å or 600Å, obtained from Prime Synthesis, Aston, PA, USA). All RNA and 2′-modified RNA phosphoramidites were purchased from Thermo Fisher Scientific (Milwaukee, WI, USA). The 2′-O-methyl phosphoramidites included the following: (5′-O-dimethoxytrityl-N^6-(benzoyl)-2′-O-methyl-adenosine-3′-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite, 5′-O-dimethoxy-trityl-N^4-(acetyl)-2′-O-methyl-cytidine-3′-O-(2-cyanoethyl-N,N-diisopropyl-amino) phosphoramidite, (5′-O-dimethoxytrityl-N^2-(isobutyryl)-2′-O-methyl-guanosine-3′-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite, and 5′-O-dimethoxytrityl-2′-O-methyl-uridine-3′-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite. The 2′-deoxy-2′-fluoro-phosphoramidites carried the same protecting groups as the 2′-O-methyl amidites. 5′-(4,4′-Dimethoxytrityl)-2′,3′-seco-uridine-2′-benzoyl-3′-[(2- cyanoethyl)-(N,N- diisopropyl)]-phosphoramidite was also purchased from Thermo Fisher Scientific. 5′-dimethoxytrityl-2′-O-methyl-inosine-3′-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidites were purchased from Glen Research (Virginia). The inverted abasic (3′-O-dimethoxytrityl-2′-deoxyribose-5′-O-(2-cyanoethyl-N,N-

diisopropylamino) phosphoramidites were purchased from ChemGenes (Wilmington, MA, USA).

Targeting ligand containing phosphoramidites were dissolved in anhydrous dichloromethane or anhydrous acetonitrile (50 mM), while all other amidites were dissolved in anhydrous acetonitrile (50 mM or 100 mM, depending on scale) and molecular sieves (3Å) were added. 5-Benzylthio-1H-tetrazole (BTT, 250 mM in acetonitrile) or 5-Ethylthio-1H-tetrazole (ETT, 250 mM in acetonitrile) was used as activator solution. Coupling times were 12 min (RNA), 15 min (targeting ligand), 90 sec (2′OMe), and 60 sec (2′F). In order to introduce phosphorothioate linkages, a 100 mM solution of 3-phenyl 1,2,4-dithiazoline-5-one (POS, obtained from PolyOrg, Inc., Leominster, MA, USA) in anhydrous acetonitrile was employed. Unless specifically identified as a "naked" RNAi agent having no targeting ligand present, each of the *ASGR1* RNAi agent duplexes synthesized and tested in the following Examples utilized N-acetyl-galactosamine as "NAG" in the targeting ligand chemical structures represented in Table 6.

B. Cleavage and deprotection of support bound oligomer. After finalization of the solid phase synthesis, the dried solid support was treated with a 1:1 volume solution of 40 wt. % methylamine in water and 28% ammonium hydroxide solution (Aldrich) for 1.5 hours at 30°C. The solution was evaporated and the solid residue was reconstituted in water (see below).

C. Purification. Crude oligomers were purified by anionic exchange HPLC using a TSKgel SuperQ-5PW 13μm column and Shimadzu LC-20AP system. Buffer A was 20 mM Tris, pH 9.0 and contained 20% Acetonitrile and buffer B was the same as buffer A with the addition of 1.5 M sodium chloride. UV traces at 260 nm were recorded. Appropriate fractions were pooled then run on size exclusion HPLC using a GE Healthcare XK 26/40 column packed with Sephadex G-25 fine with a running buffer of filtered DI water or 100mM ammonium bicarbonate, pH 6.7 and 20% Acetonitrile.

D. Annealing. Complementary strands were mixed by combining equimolar RNA solutions (sense and antisense) in 1×Phosphate-Buffered Saline (Corning, Cellgro) to form the RNAi agents. Some RNAi agents were lyophilized and stored at −15 to −25°C. Duplex

concentration was determined by measuring the solution absorbance on a UV-Vis spectrometer in 1× Phosphate-Buffered Saline. The solution absorbance at 260 nm was then multiplied by a conversion factor and the dilution factor to determine the duplex concentration. The conversion factor used was either 0.037 mg/(mL·cm) or was calculated from an experimentally determined extinction coefficient.

Example 2. ASGR1-SEAP Mouse Model.

To assess the potency of the RNAi agents, an *ASGR1*-SEAP mouse model was used. Six to eight week old female C57BL/6 albino mice were transiently transfected *in vivo* with plasmid by hydrodynamic tail vein injection, administered at least 15 days prior to administration of an *ASGR1* RNAi agent or control. The plasmid contains the *ASGR1* cDNA sequence (GenBank NM_001671.4 (SEQ ID NO:1)) inserted into the 3' UTR of the SEAP (secreted human placental alkaline phosphatase) reporter gene. 50 μg of the plasmid containing the *ASGR1* cDNA sequence in Ringer's Solution in a total volume of 10% of the animal's body weight was injected into mice via the tail vein to create *ASGR1*-SEAP model mice. The solution was injected through a 27-gauge needle in 5-7 seconds as previously described (Zhang G et al., "High levels of foreign gene expression in hepatocytes after tail vein injection of naked plasmid DNA." Human Gene Therapy 1999 Vol. 10, p1735-1737.). Inhibition of expression of *ASGR1* by an *ASGR1* RNAi agent results in concomitant inhibition of SEAP expression, which is measured by the Phospha-Light™ SEAP Reporter Gene Assay System (Invitrogen). Prior to treatment, SEAP expression levels in serum were measured and the mice were grouped according to average SEAP levels.

Analyses: SEAP levels may be measured at various times, both before and after administration of *ASGR1* RNAi agents.

i) Serum collection: Mice were anesthetized with 2-3% isoflurane and blood samples were collected from the submandibular area into serum separation tubes (Sarstedt AG & Co., Nümbrecht, Germany). Blood was allowed to coagulate at ambient temperature for 20 min. The tubes were centrifuged at 8,000 ×g for 3 min to separate the serum and stored at 4°C.

ii) Serum SEAP levels: Serum was collected and measured by the Phospha-Light™ SEAP Reporter Gene Assay System (Invitrogen) according to the manufacturer's instructions. Serum SEAP levels for each animal was normalized to the control group of mice injected with saline in order to account for the non-treatment related decline in *ASGR1* expression with this model. First, the SEAP level for each animal at a time point was divided by the pre-treatment level of expression in that animal ("pre-treatment") in order to determine the ratio of expression "normalized to pre-treatment". Expression at a specific time point was then normalized to the control group by dividing the "normalized to pre-treatment" ratio for an individual animal by the average "normalized to pre-treatment" ratio of all mice in the normal saline control group. Alternatively, in some Examples set forth herein, the serum SEAP levels for each animal were assessed by normalizing to pre-treatment levels only.

Example 3. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing either 3.0 mg/kg (mpk) of an *ASGR1* RNAi agent or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 7.

Table 7. Dosing groups of *ASGR1*-SEAP mice of Example 3.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	3.0 mg/kg AD04634	Single injection on day 1
3	3.0 mg/kg AD04698	Single injection on day 1
4	3.0 mg/kg AD04699	Single injection on day 1
5	3.0 mg/kg AD04700	Single injection on day 1
6	3.0 mg/kg AD04701	Single injection on day 1
7	3.0 mg/kg AD04702	Single injection on day 1
8	3.0 mg/kg AD04703	Single injection on day 1
9	3.0 mg/kg AD04704	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 3, day 8, day 15, day 22, day 29, and day 36, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 8, with Average SEAP reflecting the normalized average value of SEAP:

Table 8. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 3.

	Day 3		Day 8		Day 15		Day 22	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.192	1.000	0.176	1.000	0.614	1.000	0.287
Group 2 (3.0 mg/kg AD04634)	0.757	0.404	0.282	0.164	0.235	0.202	0.316	0.243
Group 3 (3.0 mg/kg AD04698)	0.442	0.395	0.068	0.067	0.010	0.011	0.049	0.047
Group 4 (3.0 mg/kg AD04699)	0.904	0.324	0.380	0.130	0.253	0.115	0.427	0.236
Group 5 (3.0 mg/kg AD04700)	0.924	0.487	0.382	0.117	0.246	0.089	0.392	0.164
Group 6 (3.0 mg/kg AD04701)	0.480	0.263	0.234	0.135	0.133	0.085	0.362	0.244
Group 7 (3.0 mg/kg AD04702)	0.480	0.283	0.379	0.349	0.351	0.170	0.331	0.157
Group 8 (3.0 mg/kg AD04703)	0.669	0.283	0.429	0.226	0.313	0.267	0.285	0.202
Group 9 (3.0 mg/kg AD04704)	0.674	0.367	0.343	0.178	0.296	0.228	0.303	0.184

	Day 29		Day 36	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.258	1.000	0.241
Group 2 (3.0 mg/kg AD04634)	0.284	0.196	0.262	0.187
Group 3 (3.0 mg/kg AD04698)	0.071	0.078	0.094	0.101
Group 4 (3.0 mg/kg AD04699)	0.395	0.216	0.424	0.191
Group 5 (3.0 mg/kg AD04700)	0.383	0.218	0.376	0.165

Group 6 (3.0 mg/kg AD04701)	0.484	0.307	0.552	0.306
Group 7 (3.0 mg/kg AD04702)	0.360	0.121	0.264	0.257
Group 8 (3.0 mg/kg AD04703)	0.472	0.411	0.380	0.288
Group 9 (3.0 mg/kg AD04704)	0.545	0.537	0.610	0.503

Each of the *ASGR1* RNAi agents in each of the dosing groups (i.e., Groups 2 through 9) showed reduction in SEAP as compared to the saline control (Group 1) across all measured time points, which as described herein, indicates inhibition of *ASGR1* in the *ASGR1*-SEAP mouse model. For example, Group 3 showed normalized SEAP levels of 0.010 (± 0.011) on day 15, which indicates a 99% inhibition of expression at that time point after a single administration of 3.0 mg/kg of duplex AD04698.

Example 4. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing either 3.0 mg/kg of an *ASGR1* RNAi agent or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 9.

Table 9. Dosing groups of *ASGR1*-SEAP mice of Example 4.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	3.0 mg/kg AD04634	Single injection on day 1
3	3.0 mg/kg AD04705	Single injection on day 1
4	3.0 mg/kg AD04706	Single injection on day 1
5	3.0 mg/kg AD04707	Single injection on day 1
6	3.0 mg/kg AD04791	Single injection on day 1
7	3.0 mg/kg AD04792	Single injection on day 1
8	3.0 mg/kg AD04793	Single injection on day 1
9	3.0 mg/kg AD04794	Single injection on day 1
10	3.0 mg/kg AD04797	Single injection on day 1
11	3.0 mg/kg AD04800	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 4, day 8, day 15, day 22, and day 29, and SEAP

expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 10, with Average SEAP reflecting the normalized average value of SEAP:

Table 10. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 4.

	Day 4		Day 8		Day 15		Day 22	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.271	1.000	0.036	1.000	0.546	1.000	0.428
Group 2 (3.0 mg/kg AD04634)	0.505	0.105	0.357	0.066	0.333	0.079	0.276	0.076
Group 3 (3.0 mg/kg AD04705)	0.747	0.305	0.734	0.293	0.509	0.111	0.387	0.149
Group 4 (3.0 mg/kg AD04706)	0.830	0.239	0.885	0.133	0.555	0.160	0.519	0.165
Group 5 (3.0 mg/kg AD04707)	0.625	0.035	0.763	0.187	0.596	0.134	0.595	0.059
Group 6 (3.0 mg/kg AD04791)	1.236	0.622	0.834	0.197	0.650	0.148	0.713	0.030
Group 7 (3.0 mg/kg AD04792)	1.345	1.033	0.988	0.400	0.886	0.175	0.796	0.602
Group 8 (3.0 mg/kg AD04793)	1.431	1.439	0.496	0.044	0.368	0.110	0.346	0.168
Group 9 (3.0 mg/kg AD04794)	1.066	1.144	0.491	0.092	0.453	0.209	0.795	0.334
Group 10 (3.0 mg/kg AD04797)	0.764	0.617	1.156	0.366	0.939	0.412	1.113	0.490
Group 11 (3.0 mg/kg AD04800)	0.412	0.235	1.641	1.240	0.869	0.234	0.829	0.144

	Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.517
Group 2 (3.0 mg/kg AD04634)	0.308	0.200
Group 3 (3.0 mg/kg AD04705)	0.430	0.186
Group 4 (3.0 mg/kg AD04706)	0.568	0.087

Group 5 (3.0 mg/kg AD04707)	0.393	0.073
Group 6 (3.0 mg/kg AD04791)	0.654	0.131
Group 7 (3.0 mg/kg AD04792)	1.120	0.647
Group 8 (3.0 mg/kg AD04793)	0.343	0.091
Group 9 (3.0 mg/kg AD04794)	0.880	0.303
Group 10 (3.0 mg/kg AD04797)	1.344	0.375
Group 11 (3.0 mg/kg AD04800)	0.615	0.199

Example 5. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing either 0.5 mg/kg, 1.0 mg/kg, or 3.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 11.

Table 11. Dosing groups of *ASGR1*-SEAP mice of Example 5.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	3.0 mg/kg AD04634	Single injection on day 1
3	1.0 mg/kg AD04697	Single injection on day 1
4	3.0 mg/kg AD04697	Single injection on day 1
5	0.5 mg/kg AD04698	Single injection on day 1
6	1.0 mg/kg AD04698	Single injection on day 1
7	3.0 mg/kg AD04698	Single injection on day 1
8	3.0 mg/kg AD04795	Single injection on day 1
9	3.0 mg/kg AD04796	Single injection on day 1
10	3.0 mg/kg AD04798	Single injection on day 1
11	3.0 mg/kg AD04799	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 8, day 15, day 22, and day 29, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 12, with Average SEAP reflecting the normalized average value of SEAP:

Table 12. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 5.

	Day 8		Day 15		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.253	1.000	0.145	1.000	0.372	1.000	0.593
Group 2 (3.0 mg/kg AD04634)	0.323	0.032	0.351	0.050	0.343	0.055	0.451	0.252
Group 3 (1.0 mg/kg AD04697)	0.384	0.145	0.364	0.066	0.363	0.184	0.563	0.353
Group 4 (3.0 mg/kg AD04697)	0.236	0.073	0.144	0.007	0.119	0.044	0.207	0.047
Group 5 (0.5 mg/kg AD04698)	0.557	0.112	0.633	0.137	0.688	0.245	1.134	0.293
Group 6 (1.0 mg/kg AD04698)	0.331	0.030	0.301	0.041	0.242	0.010	0.560	0.109
Group 7 (3.0 mg/kg AD04698)	0.186	0.024	0.094	0.013	0.079	0.012	0.203	0.033
Group 8 (3.0 mg/kg AD04795)	0.601	0.258	0.754	0.292	0.862	0.565	1.863	1.301
Group 9 (3.0 mg/kg AD04796)	0.532	0.093	0.949	0.199	0.729	0.076	1.068	0.257
Group 10 (3.0 mg/kg AD04798)	0.643	0.154	1.310	0.700	1.063	0.323	1.252	0.251
Group 11 (3.0 mg/kg AD04799)	0.489	0.220	0.373	0.161	0.400	0.135	0.519	0.315

Example 6. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing either 1.0 mg/kg or 3.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 13.

Table 13. Dosing groups of *ASGR1*-SEAP mice of Example 6.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	1.0 mg/kg AD04634	Single injection on day 1
3	3.0 mg/kg AD04634	Single injection on day 1
4	1.0 mg/kg AD04964	Single injection on day 1
5	3.0 mg/kg AD04964	Single injection on day 1
6	1.0 mg/kg AD04698	Single injection on day 1
7	3.0 mg/kg AD04698	Single injection on day 1
8	1.0 mg/kg AD04847	Single injection on day 1
9	3.0 mg/kg AD04847	Single injection on day 1
10	1.0 mg/kg AD04701	Single injection on day 1
11	3.0 mg/kg AD04701	Single injection on day 1
12	1.0 mg/kg AD04965	Single injection on day 1
13	3.0 mg/kg AD04965	Single injection on day 1
14	3.0 mg/kg AD04700	Single injection on day 1
15	3.0 mg/kg AD04793	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Four (4) mice in each group were tested (n=4). Serum was collected on day 8, day 13, day 22, and day 29, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 14, with Average SEAP reflecting the normalized average value of SEAP:

Table 14. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 6.

	Day 8		Day 13		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.639	1.000	0.384	1.000	0.364	1.000	0.477
Group 2 (1.0 mg/kg AD04634)	0.851	0.116	0.825	0.222	0.576	0.086	0.491	0.208
Group 3 (3.0 mg/kg AD04634)	0.538	0.128	0.355	0.150	0.194	0.057	0.249	0.098
Group 4 (1.0 mg/kg AD04964)	0.608	0.217	0.564	0.138	0.358	0.090	0.402	0.244
Group 5 (3.0 mg/kg AD04964)	0.476	0.255	0.374	0.194	0.325	0.204	0.327	0.247
Group 6 (1.0 mg/kg AD04698)	0.404	0.163	0.198	0.069	0.191	0.067	0.186	0.079
Group 7 (3.0 mg/kg AD04698)	0.256	0.073	0.078	0.026	0.083	0.048	0.138	0.103
Group 8 (1.0 mg/kg AD04787)	0.307	0.129	0.138	0.056	0.145	0.068	0.210	0.119
Group 9 (3.0 mg/kg AD04787)	0.383	0.161	0.193	0.154	0.147	0.191	0.230	0.231
Group 10 (1.0 mg/kg AD04701)	0.788	0.122	0.925	0.142	0.759	0.141	0.726	0.078
Group 11 (3.0 mg/kg AD04701)	0.491	0.138	0.640	0.206	0.436	0.067	0.651	0.130
Group 12 (1.0 mg/kg AD04965)	0.813	0.248	0.900	0.209	0.643	0.124	0.904	0.504
Group 13 (3.0 mg/kg AD04965)	0.672	0.338	0.845	0.129	0.523	0.155	0.394	0.090
Group 14 (3.0 mg/kg AD04700)	0.743	0.063	0.793	0.378	0.438	0.287	0.424	0.215
Group 15 (3.0 mg/kg AD04793)	0.504	0.072	0.525	0.142	0.417	0.140	0.458	0.108

Example 7. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing either 1.0 mg/kg or 3.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 15.

Table 15. Dosing groups of *ASGR1*-SEAP mice of Example 7.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	1.0 mg/kg AD04698	Single injection on day 1
3	3.0 mg/kg AD04698	Single injection on day 1
4	1.0 mg/kg AD04847	Single injection on day 1
5	3.0 mg/kg AD04847	Single injection on day 1
6	1.0 mg/kg AD04802	Single injection on day 1
7	3.0 mg/kg AD04802	Single injection on day 1
8	1.0 mg/kg AD04975	Single injection on day 1
9	3.0 mg/kg AD04975	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Four (4) mice in each group were tested (n=4). Serum was collected on day 8, day 15, day 22, and day 29, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 16, with Average SEAP reflecting the normalized average value of SEAP:

Table 16. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 7.

	Day 8		Day 15		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.412	1.000	0.421	1.000	0.497	1.000	0.582
Group 2 (1.0 mg/kg AD04698)	0.494	0.104	0.295	0.149	0.239	0.080	0.377	0.108
Group 3 (3.0 mg/kg AD04698)	0.188	0.032	0.077	0.028	0.076	0.048	0.143	0.131
Group 4 (1.0 mg/kg AD04847)	0.517	0.196	0.304	0.129	0.297	0.109	0.533	0.184
Group 5 (3.0 mg/kg AD04847)	0.160	0.069	0.071	0.030	0.085	0.031	0.153	0.025
Group 6 (1.0 mg/kg AD04802)	0.579	0.170	0.372	0.127	0.336	0.152	0.403	0.229
Group 7 (3.0 mg/kg AD04802)	0.304	0.075	0.185	0.083	0.220	0.131	0.297	0.172
Group 8 (1.0 mg/kg AD04975)	0.487	0.069	0.338	0.069	0.453	0.295	0.689	0.537
Group 9 (3.0 mg/kg AD04975)	0.193	0.046	0.097	0.031	0.247	0.060	0.125	0.042

Example 8. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing either 1.0 mg/kg or 3.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 17.

Table 17. Dosing groups of *ASGR1*-SEAP mice of Example 8.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	1.0 mg/kg AD04847	Single injection on day 1
3	1.0 mg/kg AD04634	Single injection on day 1
4	1.0 mg/kg AD05067	Single injection on day 1
5	1.0 mg/kg AD05090	Single injection on day 1
6	1.0 mg/kg AD05065	Single injection on day 1
7	1.0 mg/kg AD05066	Single injection on day 1
8	1.0 mg/kg AD05089	Single injection on day 1
9	1.0 mg/kg AD05092	Single injection on day 1
10	1.0 mg/kg AD05093	Single injection on day 1
11	3.0 mg/kg AD05093	Single injection on day 1
12	1.0 mg/kg AD05094	Single injection on day 1
13	3.0 mg/kg AD05094	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 8, day 15, day 22, and day 29, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 18, with Average SEAP reflecting the normalized average value of SEAP:

Table 18. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 8.

	Day 8		Day 15		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.160	1.000	0.202	1.000	0.132	1.000	0.346
Group 2 (1.0 mg/kg AD04847)	0.444	0.181	0.404	0.186	0.372	0.226	0.369	0.184
Group 3 (1.0 mg/kg AD04634)	0.619	0.033	0.673	0.209	0.716	0.480	0.671	0.048
Group 4 (1.0 mg/kg AD05067)	0.679	0.059	0.454	0.129	0.200	0.174	0.416	0.557
Group 5 (1.0 mg/kg AD05090)	0.540	0.054	0.489	0.265	0.499	0.176	0.598	0.240
Group 6 (1.0 mg/kg AD05065)	0.605	0.056	0.537	0.118	0.416	0.192	0.483	0.221
Group 7 (1.0 mg/kg AD05066)	0.967	0.193	0.837	0.649	0.426	0.345	0.746	0.488
Group 8 (1.0 mg/kg AD05089)	1.017	0.434	0.547	0.041	0.446	0.134	0.406	0.071
Group 9 (1.0 mg/kg AD05092)	1.191	0.462	1.315	0.217	1.269	0.442	1.143	0.337
Group 10 (1.0 mg/kg AD05093)	1.698	0.150	1.075	0.577	1.056	0.243	0.900	0.365
Group 11 (3.0 mg/kg AD05093)	1.437	0.307	1.368	0.637	1.254	0.589	1.000	0.496
Group 12 (1.0 mg/kg AD05094)	1.838	0.167	1.367	0.548	1.455	0.552	2.236	1.451
Group 13 (3.0 mg/kg AD05094)	1.197	0.622	1.567	0.658	1.451	0.371	1.719	0.279

Example 9. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing either 1.0 mg/kg or 3.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 19.

Table 19. Dosing groups of *ASGR1*-SEAP mice of Example 9.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	1.0 mg/kg AD04847	Single injection on day 1
3	3.0 mg/kg AD04634	Single injection on day 1
4	3.0 mg/kg AD04700	Single injection on day 1
5	3.0 mg/kg AD05053	Single injection on day 1
6	3.0 mg/kg AD05096	Single injection on day 1
7	3.0 mg/kg AD05097	Single injection on day 1
8	3.0 mg/kg AD05108	Single injection on day 1
9	3.0 mg/kg AD05109	Single injection on day 1
10	3.0 mg/kg AD05110	Single injection on day 1
11	3.0 mg/kg AD05111	Single injection on day 1
12	3.0 mg/kg AD05112	Single injection on day 1
13	3.0 mg/kg AD05113	Single injection on day 1
14	3.0 mg/kg AD05114	Single injection on day 1
15	3.0 mg/kg AD05115	Single injection on day 1
16	1.0 mg/kg AD05180	Single injection on day 1
17	1.0 mg/kg AD05181	Single injection on day 1
18	1.0 mg/kg AD05182	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 8, day 13, day 22, day 29, and day 36, and SEAP

expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 20, with Average SEAP reflecting the normalized average value of SEAP:

Table 20. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 9.

	Day 8		Day 13		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.323	1.000	0.356	1.000	0.183	1.000	0.045
Group 2 (1.0 mg/kg AD04847)	0.411	0.129	0.289	0.121	0.491	0.259	0.631	0.428
Group 3 (3.0 mg/kg AD04634)	0.430	0.127	0.466	0.232	0.356	0.142	0.583	0.341
Group 4 (3.0 mg/kg AD04700)	0.550	0.021	0.597	0.139	0.826	0.228	0.770	0.131
Group 5 (3.0 mg/kg AD05053)	0.591	0.116	0.396	0.068	0.658	0.214	0.745	0.191
Group 6 (3.0 mg/kg AD05096)	0.511	0.089	0.445	0.030	0.421	0.085	0.503	0.129
Group 7 (3.0 mg/kg AD05097)	0.588	0.095	0.987	0.221	0.996	0.217	1.083	0.206
Group 8 (3.0 mg/kg AD05108)	0.253	0.126	0.155	0.093	0.132	0.074	0.134	0.091
Group 9 (3.0 mg/kg AD05109)	0.219	0.022	0.141	0.021	0.109	0.041	0.105	0.027
Group 10 (3.0 mg/kg AD05110)	0.217	0.061	0.285	0.097	0.335	0.110	0.491	0.073
Group 11 (3.0 mg/kg AD05111)	0.470	0.255	0.592	0.160	0.596	0.167	0.821	0.138
Group 12 (3.0 mg/kg AD05112)	0.600	0.173	0.862	0.252	0.905	0.517	0.992	0.343
Group 13 (3.0 mg/kg AD05113)	0.897	0.105	1.156	0.170	1.124	0.122	0.920	0.319
Group 14 (3.0 mg/kg AD05114)	0.567	0.053	0.640	0.087	0.602	0.015	0.763	0.321
Group 15 (3.0 mg/kg AD05115)	0.619	0.283	0.608	0.264	0.627	0.198	0.570	0.246
Group 16 (1.0 mg/kg AD05180)	0.491	0.111	0.337	0.152	0.466	0.084	0.573	0.152
Group 17 (1.0 mg/kg AD05181)	0.493	0.155	0.448	0.338	0.490	0.298	0.617	0.475
Group 18 (1.0 mg/kg AD05182)	0.453	0.057	0.405	0.071	0.379	0.065	0.592	0.134

Group ID	Day 36	
	Avg SEAP	Std Dev (+/-)
Group 1 (Saline)	1.000	0.188
Group 2 (1.0 mg/kg AD04847)	1.115	0.941
Group 3 (3.0 mg/kg AD04634)	0.600	0.421
Group 4 (3.0 mg/kg AD04700)	0.847	0.340
Group 5 (3.0 mg/kg AD05053)	0.649	0.226
Group 6 (3.0 mg/kg AD05096)	0.532	0.098
Group 7 (3.0 mg/kg AD05097)	1.425	0.289
Group 8 (3.0 mg/kg AD05108)	0.191	0.093
Group 9 (3.0 mg/kg AD05109)	0.181	0.089
Group 10 (3.0 mg/kg AD05110)	0.575	0.244
Group 11 (3.0 mg/kg AD05111)	0.803	0.477
Group 12 (3.0 mg/kg AD05112)	0.905	0.252
Group 13 (3.0 mg/kg AD05113)	0.789	0.207
Group 14 (3.0 mg/kg AD05114)	0.532	0.185
Group 15 (3.0 mg/kg AD05115)	0.514	0.178
Group 16 (1.0 mg/kg AD05180)	0.429	0.041
Group 17 (1.0 mg/kg AD05181)	0.428	0.322
Group 18 (1.0 mg/kg AD05182)	0.718	0.149

Example 10. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing either 1.0 mg/kg or 3.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 21.

Table 21. Dosing groups of *ASGR1*-SEAP mice of Example 10.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	1.0 mg/kg AD04847	Single injection on day 1
3	3.0 mg/kg AD05183	Single injection on day 1
4	3.0 mg/kg AD05184	Single injection on day 1
5	3.0 mg/kg AD05185	Single injection on day 1
6	3.0 mg/kg AD05186	Single injection on day 1
7	3.0 mg/kg AD05187	Single injection on day 1
8	3.0 mg/kg AD05188	Single injection on day 1
9	3.0 mg/kg AD05189	Single injection on day 1
10	3.0 mg/kg AD05190	Single injection on day 1
11	3.0 mg/kg AD05191	Single injection on day 1
12	3.0 mg/kg AD05192	Single injection on day 1
13	3.0 mg/kg AD05193	Single injection on day 1
14	3.0 mg/kg AD05194	Single injection on day 1
15	3.0 mg/kg AD05195	Single injection on day 1
16	3.0 mg/kg AD05196	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 8, day 15, day 22, day 29, and day 36, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above.

Data from the experiment are shown in the following Table 22, with Average SEAP reflecting the normalized average value of SEAP:

Table 22. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 10.

	Day 8		Day 15		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.018	1.000	0.190	1.000	0.205	1.000	0.178
Group 2 (1.0 mg/kg AD04847)	0.318	0.103	0.339	0.056	0.247	0.074	0.412	0.095
Group 3 (3.0 mg/kg AD05183)	0.106	0.015	0.043	0.025	0.062	0.017	0.062	0.009
Group 4 (3.0 mg/kg AD05184)	0.134	0.030	0.143	0.109	0.170	0.150	0.146	0.151
Group 5 (3.0 mg/kg AD05185)	0.186	0.060	0.141	0.052	0.095	0.039	0.147	0.018
Group 6 (3.0 mg/kg AD05186)	0.107	0.030	0.097	0.032	0.141	0.063	0.170	0.087
Group 7 (3.0 mg/kg AD05187)	0.255	0.132	0.264	0.138	0.420	0.204	0.520	0.341
Group 8 (3.0 mg/kg AD05188)	0.188	0.061	0.160	0.075	0.182	0.158	0.367	0.297
Group 9 (3.0 mg/kg AD05189)	0.538	0.300	0.755	0.256	0.924	0.312	0.752	0.578
Group 10 (3.0 mg/kg AD05190)	0.540	0.049	0.697	0.037	0.653	0.150	0.812	0.340
Group 11 (3.0 mg/kg AD05191)	0.489	0.293	0.769	0.706	0.686	0.636	0.550	0.566
Group 12 (3.0 mg/kg AD05192)	1.307	0.511	1.908	1.094	2.401	0.835	1.826	0.514
Group 13 (3.0 mg/kg AD05193)	0.279	0.403	0.204	0.275	0.137	0.171	0.226	0.280
Group 14 (3.0 mg/kg AD05194)	0.954	1.497	0.523	0.774	0.377	0.570	0.487	0.702
Group 15 (3.0 mg/kg AD05195)	0.153	0.228	0.137	0.187	0.130	0.151	0.094	0.098
Group 16 (3.0 mg/kg AD05196)	0.358	0.550	0.024	0.008	0.200	0.297	0.294	0.440
	Day 36							

Group ID	Avg SEAP	Std Dev (+/-)
Group 1 (Saline)	1.000	0.191
Group 2 (1.0 mg/kg AD04847)	0.456	0.114
Group 3 (3.0 mg/kg AD05183)	0.119	0.055
Group 4 (3.0 mg/kg AD05184)	0.215	0.248
Group 5 (3.0 mg/kg AD05185)	0.150	0.044
Group 6 (3.0 mg/kg AD05186)	0.195	0.069
Group 7 (3.0 mg/kg AD05187)	0.678	0.388
Group 8 (3.0 mg/kg AD05188)	0.487	0.323
Group 9 (3.0 mg/kg AD05189)	0.720	0.486
Group 10 (3.0 mg/kg AD05190)	1.114	0.559
Group 11 (3.0 mg/kg AD05191)	0.685	0.693
Group 12 (3.0 mg/kg AD05192)	3.280	1.958
Group 13 (3.0 mg/kg AD05193)	0.475	0.622
Group 14 (3.0 mg/kg AD05194)	0.908	1.380
Group 15 (3.0 mg/kg AD05195)	0.046	0.039
Group 16 (3.0 mg/kg AD05196)	0.479	0.707

Example 11. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing 1.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 23.

Table 23. Dosing groups of *ASGR1*-SEAP mice of Example 11.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	1.0 mg/kg AD05067	Single injection on day 1
3	1.0 mg/kg AD05209	Single injection on day 1
4	1.0 mg/kg AD05240	Single injection on day 1
5	1.0 mg/kg AD05256	Single injection on day 1
6	1.0 mg/kg AD05257	Single injection on day 1
7	1.0 mg/kg AD05245	Single injection on day 1
8	1.0 mg/kg AD05246	Single injection on day 1
9	1.0 mg/kg AD05210	Single injection on day 1
10	1.0 mg/kg AD05211	Single injection on day 1
11	1.0 mg/kg AD05213	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 8, day 15, day 22, day 29, and day 36, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 24, with Average SEAP reflecting the normalized average value of SEAP:

Table 24. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 11.

	Day 8		Day 15		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.378	1.000	0.326	1.000	0.308	1.000	0.264
Group 2 (1.0 mg/kg AD05067)	0.380	0.065	0.251	0.090	0.185	0.060	0.296	0.011
Group 3 (1.0 mg/kg AD05209)	0.190	0.023	0.103	0.025	0.106	0.079	0.164	0.154
Group 4 (1.0 mg/kg AD05240)	0.358	0.158	0.254	0.148	0.354	0.207	0.344	0.183
Group 5 (1.0 mg/kg AD05256)	0.237	0.155	0.135	0.081	0.147	0.092	0.108	0.052
Group 6 (1.0 mg/kg AD05257)	0.313	0.136	0.172	0.097	0.267	0.152	0.300	0.141
Group 7 (1.0 mg/kg AD05245)	0.278	0.029	0.227	0.061	0.324	0.080	0.414	0.130
Group 8 (1.0 mg/kg AD05246)	0.793	0.290	1.056	0.066	1.529	0.334	1.297	0.359
Group 9 (1.0 mg/kg AD05210)	0.451	0.018	0.394	0.082	0.585	0.075	0.509	0.100
Group 10 (1.0 mg/kg AD05211)	0.637	0.160	0.680	0.273	0.660	0.216	0.782	0.209
Group 11 (1.0 mg/kg AD05213)	0.280	0.123	0.206	0.070	0.334	0.165	0.469	0.240

	Day 36	
Group ID	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.513
Group 2 (1.0 mg/kg AD05067)	0.413	0.082
Group 3 (1.0 mg/kg AD05209)	0.210	0.175
Group 4 (1.0 mg/kg AD05240)	0.463	0.303

Group 5 (1.0 mg/kg AD05256)	0.106	0.062
Group 6 (1.0 mg/kg AD05257)	0.337	0.164
Group 7 (1.0 mg/kg AD05245)	0.469	0.214
Group 8 (1.0 mg/kg AD05246)	1.132	0.308
Group 9 (1.0 mg/kg AD05210)	0.715	0.194
Group 10 (1.0 mg/kg AD05211)	0.890	0.212
Group 11 (1.0 mg/kg AD05213)	0.658	0.459

Example 12. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing 1.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 25.

Table 25. Dosing groups of *ASGR1*-SEAP mice of Example 12.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	1.0 mg/kg AD05109	Single injection on day 1
3	1.0 mg/kg AD05193	Single injection on day 1
4	1.0 mg/kg AD05196	Single injection on day 1
5	1.0 mg/kg AD05262	Single injection on day 1
6	1.0 mg/kg AD05263	Single injection on day 1
7	1.0 mg/kg AD05264	Single injection on day 1
8	1.0 mg/kg AD05265	Single injection on day 1
9	1.0 mg/kg AD05266	Single injection on day 1
10	1.0 mg/kg AD05267	Single injection on day 1
11	1.0 mg/kg AD05268	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 8, day 15, day 23, day 29, and day 36, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 26, with Average SEAP reflecting the normalized average value of SEAP:

Table 26. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 12.

	Day 8		Day 15		Day 23		Day 29		Day 36	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.418	1.000	0.481	1.000	0.215	1.000	0.643	1.000	0.655
Group 2 (1.0 mg/kg AD05109)	0.372	0.050	0.255	0.047	0.358	0.190	0.205	0.005	0.184	0.125
Group 3 (1.0 mg/kg AD05193)	0.166	0.074	0.093	0.061	0.122	0.092	0.087	0.063	0.085	0.081
Group 4 (1.0 mg/kg AD05196)	0.177	0.034	0.142	0.049	0.219	0.088	0.191	0.098	0.132	0.055
Group 5 (1.0 mg/kg AD05262)	0.768	0.215	0.606	0.192	1.108	0.429	0.642	0.344	0.717	0.422
Group 6 (1.0 mg/kg AD05263)	0.267	0.084	0.162	0.042	0.215	0.023	0.263	0.042	0.206	0.084
Group 7 (1.0 mg/kg AD05264)	0.420	0.016	0.425	0.049	0.715	0.239	0.744	0.103	0.498	0.163
Group 8 (1.0 mg/kg AD05265)	0.561	0.280	0.703	0.391	1.105	0.732	0.793	0.532	0.652	0.412
Group 9 (1.0 mg/kg AD05266)	0.329	0.071	0.338	0.050	1.021	0.541	0.456	0.195	0.397	0.229
Group 10 (1.0 mg/kg AD05267)	0.369	0.038	0.652	0.223	1.581	0.403	0.748	0.255	0.653	0.079
Group 11 (1.0 mg/kg AD05268)	0.216	0.093	0.201	0.067	0.299	0.134	0.151	0.050	0.213	0.034

Example 13. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing 1.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 27.

Table 27. Dosing groups of *ASGR1*-SEAP mice of Example 13.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	1.0 mg/kg AD05067	Single injection on day 1
3	1.0 mg/kg AD05241	Single injection on day 1
4	1.0 mg/kg AD05242	Single injection on day 1
5	1.0 mg/kg AD05243	Single injection on day 1
6	1.0 mg/kg AD05109	Single injection on day 1
7	1.0 mg/kg AD05244	Single injection on day 1
8	1.0 mg/kg AD05247	Single injection on day 1
9	1.0 mg/kg AD05248	Single injection on day 1
10	1.0 mg/kg AD05212	Single injection on day 1
11	1.0 mg/kg AD05214	Single injection on day 1
12	1.0 mg/kg AD05206	Single injection on day 1
13	1.0 mg/kg AD05207	Single injection on day 1
14	1.0 mg/kg AD05208	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 8, day 16, day 22, day 29, and day 36, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 28, with Average SEAP reflecting the normalized average value of SEAP:

Table 28. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 13.

	Day 8		Day 16		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.252	1.000	0.134	1.000	0.375	1.000	0.454
Group 2 (1.0 mg/kg AD05067)	0.353	0.107	0.203	0.074	0.239	0.044	0.270	0.039
Group 3 (1.0 mg/kg AD05241)	0.457	0.177	0.338	0.184	0.217	0.093	0.236	0.129
Group 4 (1.0 mg/kg AD05242)	0.302	0.181	0.209	0.147	0.209	0.148	0.214	0.099
Group 5 (1.0 mg/kg AD05243)	0.379	0.133	0.141	0.022	0.111	0.040	0.134	0.033
Group 6 (1.0 mg/kg AD05109)	0.454	0.087	0.171	0.054	0.114	0.036	0.136	0.063
Group 7 (1.0 mg/kg AD05244)	0.468	0.138	0.363	0.209	0.274	0.189	0.170	0.096
Group 8 (1.0 mg/kg AD05247)	0.662	0.249	0.670	0.299	0.569	0.232	0.594	0.288
Group 9 (1.0 mg/kg AD05248)	0.597	0.127	0.325	0.252	0.276	0.182	0.246	0.241
Group 10 (1.0 mg/kg AD05212)	0.413	0.045	0.244	0.122	0.123	0.072	0.119	0.047
Group 11 (1.0 mg/kg AD05214)	0.486	0.049	0.252	0.104	0.213	0.063	0.198	0.015
Group 12 (1.0 mg/kg AD05206)	0.359	0.166	0.196	0.066	0.214	0.089	0.284	0.104
Group 13 (1.0 mg/kg AD05207)	1.109	0.103	0.484	0.223	0.381	0.275	0.404	0.247
Group 14 (1.0 mg/kg AD05208)	0.529	0.063	0.252	0.022	0.221	0.026	0.160	0.042

	Day 36	
Group ID	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.337

Group 2 (1.0 mg/kg AD05067)	0.307	0.064
Group 3 (1.0 mg/kg AD05241)	0.325	0.186
Group 4 (1.0 mg/kg AD05242)	0.164	0.019
Group 5 (1.0 mg/kg AD05243)	0.158	0.041
Group 6 (1.0 mg/kg AD05109)	0.176	0.066
Group 7 (1.0 mg/kg AD05244)	0.244	0.086
Group 8 (1.0 mg/kg AD05247)	0.804	0.531
Group 9 (1.0 mg/kg AD05248)	0.293	0.301
Group 10 (1.0 mg/kg AD05212)	0.171	0.077
Group 11 (1.0 mg/kg AD05214)	0.189	0.023
Group 12 (1.0 mg/kg AD05206)	0.416	0.127
Group 13 (1.0 mg/kg AD05207)	0.605	0.382
Group 14 (1.0 mg/kg AD05208)	0.303	0.112

Example 14. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing either 0.5 mg/kg, 1.0 mg/kg, or 3.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 29.

Table 29. Dosing groups of *ASGR1*-SEAP mice of Example 14.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	0.5 mg/kg AD05067	Single injection on day 1
3	1.0 mg/kg AD05067	Single injection on day 1
4	3.0 mg/kg AD05067	Single injection on day 1
5	0.5 mg/kg AD05183	Single injection on day 1
6	1.0 mg/kg AD05183	Single injection on day 1
7	3.0 mg/kg AD05183	Single injection on day 1
8	0.5 mg/kg AD05209	Single injection on day 1
9	1.0 mg/kg AD05209	Single injection on day 1
10	4.0 mg/kg AD05209	Single injection on day 1
11	0.5 mg/kg AD05256	Single injection on day 1
12	1.0 mg/kg AD05256	Single injection on day 1
13	3.0 mg/kg AD05256	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 8, day 15, day 22, day 29, and day 36, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 30, with Average SEAP reflecting the normalized average value of SEAP:

Table 30. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 14.

	Day 8		Day 15		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.479	1.000	0.737	1.000	0.401	1.000	0.359
Group 2 (0.5 mg/kg AD05067)	0.315	0.178	0.215	0.087	0.175	0.072	0.143	0.047
Group 3 (1.0 mg/kg AD05067)	0.265	0.136	0.129	0.071	0.139	0.025	0.165	0.029
Group 4 (3.0 mg/kg AD05067)	0.250	0.092	0.069	0.036	0.083	0.029	0.083	0.060
Group 5 (0.5 mg/kg AD05183)	0.274	0.140	0.156	0.053	0.173	0.069	0.215	0.039
Group 6 (1.0 mg/kg AD05183)	0.305	0.047	0.123	0.020	0.158	0.093	0.221	0.069
Group 7 (3.0 mg/kg AD05183)	0.182	0.060	0.052	0.028	0.069	0.036	0.070	0.045
Group 8 (0.5 mg/kg AD05209)	0.295	0.110	0.193	0.062	0.268	0.131	0.399	0.232
Group 9 (1.0 mg/kg AD05209)	0.185	0.034	0.073	0.031	0.113	0.051	0.120	0.055
Group 10 (3.0 mg/kg AD05209)	0.100	0.021	0.020	0.007	0.024	0.004	0.025	0.013
Group 11 (0.5 mg/kg AD05256)	0.618	0.069	0.334	0.087	0.397	0.128	0.430	0.312
Group 12 (1.0 mg/kg AD05256)	0.392	0.126	0.129	0.015	0.195	0.067	0.238	0.075
Group 13 (3.0 mg/kg AD05256)	0.199	0.063	0.070	0.033	0.110	0.078	0.134	0.079

	Day 36	
Group ID	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.601
Group 2 (0.5 mg/kg AD05067)	0.218	0.042

Group 3 (1.0 mg/kg AD05067)	0.238	0.046
Group 4 (3.0 mg/kg AD05067)	0.138	0.130
Group 5 (0.5 mg/kg AD05183)	0.261	0.111
Group 6 (1.0 mg/kg AD05183)	0.157	0.051
Group 7 (3.0 mg/kg AD05183)	0.069	0.068
Group 8 (0.5 mg/kg AD05209)	0.404	0.160
Group 9 (1.0 mg/kg AD05209)	0.175	0.106
Group 10 (3.0 mg/kg AD05209)	0.036	0.024
Group 11 (0.5 mg/kg AD05256)	0.484	0.298
Group 12 (1.0 mg/kg AD05256)	0.255	0.111
Group 13 (3.0 mg/kg AD05256)	0.121	0.063

As shown in Table 30 above, a dose response is observed for each of the *ASGR1* RNAi agents tested. For example, on day 22, *ASGR1* RNAi agent AD05209 showed knockdown of approximately 73% (0.268) at 0.5 mg/kg; approximately 89% (0.113) at 1.0 mg/kg; and approximately 98% (0.024) at 3.0 mg/kg administered dose.

Example 15. ***In vivo testing of ASGR1 RNAi Agents in Cynomolgus Monkeys.***

ASGR1 RNAi agents were evaluated in cynomolgus monkeys. On day 1, cynomolgus macaque (Macaca fascicularis) primates ("cynomolgus monkeys") were given a single subcutaneous injection of 0.3 mL/kg (approximately 2-3 mL volume, depending on animal mass) containing 5.0 mg/kg of *ASGR1* RNAi agent AD05126 or AD05150, formulated in saline. Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5.

Two (2) monkeys in each group were tested (n=2). Blood samples were drawn and serum samples were analyzed on days 1 (predose), 8, 15, 22, 29, 36, and 50, for alkaline phosphatase (referred to as "ALP", "ALKP", or "Alk-Phos") and standard clinical chemistry panel. As ALP is a substrate of ASGR1, reduction of ASGR1 is expected to increase ALP levels, as observed in the *ASGR1* del12 carriers in the human population. Overall, reduction of ASGR1 levels by 50% in *ASGR1* del12 carriers showed an increase in ALP levels of around 50.1%. Therefore, ALP has been shown to serve as a surrogate biomarker for monitoring reduction in ASGR1 and inhibition of an *ASGR1* gene. (Nioi et al., 2016). ALP levels in serum were measured on a Cobas® Integra 400 (Roche Diagnostics), according to the manufacturer's recommendations.

Data from the experiment are shown in the following Tables 31 and 32, which report raw ALP values (units/L) as well as ALP normalized to averaged individual pre-treatment levels.

Table 31. ALP levels from cynomolgus monkeys from Example 15 (ALP levels reported in units/L) from Cobas®.

Group ID	Mean Predose ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP	Day 50 ALP
AD05126 (Cyno A) (5.0 mg/kg)	74	88	100	120	122	115	107
AD05126 (Cyno B) (5.0 mg/kg)	115	128	151	159	160	146	159
AD05150 (Cyno A) (5.0 mg/kg)	90	100	103	110	104	111	101
AD05150 (Cyno B) (5.0 mg/kg)	105	112	136	152	165	153	161

Table 32. Normalized ALP levels from cynomolgus monkeys from Example 15 from Cobas®.

Group ID	Mean Predose ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP	Day 50 ALP
AD05126 (Cyno A) (5.0 mg/kg)	1.00	1.19	1.36	1.63	1.66	1.56	1.45
AD05126 (Cyno B) (5.0 mg/kg)	1.00	1.12	1.32	1.39	1.40	1.27	1.39
AD05150 (Cyno A) (5.0 mg/kg)	1.00	1.11	1.14	1.22	1.15	1.23	1.12
AD05150 (Cyno B) (5.0 mg/kg)	1.00	1.06	1.29	1.44	1.57	1.45	1.53

Each of cynomolgus monkeys dosed with either AD05126 or AD05150 showed in increase in ALP compared to pre-dose measurements across all measured time points, indicating a reduction in ASGR1 protein levels and inhibition of *ASGR1*.

Example 16. ***In vivo testing of ASGR1 RNAi Agents in Cynomolgus Monkeys.***

ASGR1 RNAi agents were evaluated in cynomolgus monkeys. On day 1, cynomolgus macaque (Macaca fascicularis) primates ("cynomolgus monkeys") were given a single subcutaneous injection of 0.3 mL/kg (approximately 2-3 mL volume, depending on animal mass) containing 5.0 mg/kg of *ASGR1* RNAi agent AD05186 or AD05196, formulated in saline. Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5.

Two (2) monkeys in each group were tested (n=2). Blood samples were drawn and serum samples were analyzed on days 1 (predose), 8, 15, 22, 29, 36, and 43, for ALP and standard clinical chemistry panel. As noted in Example 15, ALP serves as a surrogate biomarker for monitoring reduction in ASGR1 and inhibition of an *ASGR1* gene. ALP levels in serum were measured on a Cobas® Integra 400 (Roche Diagnostics), according to the manufacturer's recommendations.

Data from the experiment are shown in the following Tables 33 and 34, which report raw ALP values (units/L) as well as ALP normalized to averaged individual pre-treatment levels.

Table 33. ALP levels from cynomolgus monkeys from Example 16 (ALP levels reported in units/L) from Cobas®.

Group ID	Mean Predose ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP	Day 43 ALP
AD05186 (Cyno A) (5.0 mg/kg)	89	96	118	135	134	127	134
AD05186 (Cyno B) (5.0 mg/kg)	177	213	284	324	354	380	364
AD05196 (Cyno A) (5.0 mg/kg)	97	107	143	178	206	219	199
AD05196 (Cyno B) (5.0 mg/kg)	170	177	237	255	292	285	304

Table 34. Normalized ALP levels from cynomolgus monkeys from Example 16 from Cobas®.

Group ID	Mean Predose ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP	Day 43 ALP
AD05186 (Cyno A) (5.0 mg/kg)	1.00	1.08	1.33	1.52	1.51	1.43	1.51
AD05186 (Cyno B) (5.0 mg/kg)	1.00	1.21	1.61	1.84	2.01	2.15	2.06
AD05196 (Cyno A) (5.0 mg/kg)	1.00	1.10	1.47	1.84	2.12	2.26	2.05
AD05196 (Cyno B) (5.0 mg/kg)	1.00	1.04	1.40	1.50	1.72	1.68	1.79

Example 17. ***In vivo testing of ASGR1 RNAi Agents in Cynomolgus Monkeys.***

ASGR1 RNAi agents were evaluated in cynomolgus monkeys. On day 1, cynomolgus macaque (Macaca fascicularis) primates were given a single subcutaneous injection of 0.3 mL/kg (approximately 2-3 mL volume, depending on animal mass) containing 3.0 mg/kg of *ASGR1* RNAi agent AD05183 or AD05193, formulated in saline. Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5.

Two (2) monkeys in each group were tested (n=2). Blood samples were drawn and serum samples were analyzed on days 8, 15, 22, 29, 36, and 43, for ALP and standard clinical chemistry panel. As noted in Example 15, ALP serves as a surrogate biomarker for monitoring reduction in ASGR1 and inhibition of an *ASGR1* gene. ALP levels in serum were measured on a Cobas® Integra 400 (Roche Diagnostics), according to the manufacturer's recommendations.

Data from the experiment are shown in the following Tables 35 and 36, which report raw ALP values (units/L) as well as ALP normalized to averaged individual pre-treatment levels.

Table 35. ALP levels from cynomolgus monkeys from Example 17 (ALP levels reported in units/L) from Cobas®.

Group ID	Mean Predose ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP	Day 43 ALP
AD05183 (Cyno A) (3.0 mg/kg)	236	245	347	472	575	630	578
AD05183 (Cyno B) (3.0 mg/kg)	193	186	250	318	411	452	458
AD05193 (Cyno A) (3.0 mg/kg)	295	272	374	490	620	693	593
AD05193 (Cyno B) (3.0 mg/kg)	242	238	284	369	427	481	440

Table 36. Normalized ALP levels from cynomolgus monkeys from Example 17 from Cobas®.

Group ID	Mean Predose ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP	Day 43 ALP
AD05183 (Cyno A) (3.0 mg/kg)	1.00	1.04	1.47	2.00	2.44	2.67	2.45
AD05183 (Cyno B) (3.0 mg/kg)	1.00	0.97	1.30	1.65	2.13	2.35	2.38
AD05193 (Cyno A) (3.0 mg/kg)	1.00	0.92	1.27	1.66	2.10	2.35	2.01
AD05193 (Cyno B) (3.0 mg/kg)	1.00	0.98	1.17	1.52	1.76	1.99	1.82

Example 18. ***In vivo testing of ASGR1 RNAi Agents in Cynomolgus Monkeys.***

ASGR1 RNAi agents were evaluated in cynomolgus monkeys. On day 1, cynomolgus macaque (Macaca fascicularis) primates were given a single subcutaneous injection of 0.3 mL/kg (approximately 2-3 mL volume, depending on animal mass) containing 16.7 mg/mL for a total dose of 5.0 mg/kg of *ASGR1* RNAi agent AD05209, AD05195, or AD05256, formulated in saline. Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5.

Two (2) monkeys in each group were tested, except for AD05195 where only 1 monkey was dosed. Blood samples were drawn and serum samples were analyzed on days 8, 15, 22, and 29, for ALP and standard clinical chemistry panel. As noted in Example 15, ALP serves as a surrogate biomarker for monitoring reduction in ASGR1 and inhibition of an *ASGR1* gene. ALP levels in serum were measured on a Cobas® Integra 400 (Roche Diagnostics), according to the manufacturer's recommendations.

Data from the experiment are shown in the following Tables 37 and 38, which report raw ALP values (units/L) as well as ALP normalized to averaged individual pre-treatment levels.

Table 37. ALP levels from cynomolgus monkeys from Example 18 (ALP levels reported in units/L) from Cobas®.

Group ID	Mean Predose ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP
AD05209 (Cyno A) (5.0 mg/kg)	64	77	147	199	231
AD05209 (Cyno B) (5.0 mg/kg)	81	114	174	214	223
AD05195 (Cyno A) (5.0 mg/kg)	116	122	161	181	177
AD05256 (Cyno A) (5.0 mg/kg)	69	73	79	86	91
AD05256 (Cyno B) (5.0 mg/kg)	122	163	255	313	352

Table 38. Normalized ALP levels from cynomolgus monkeys from Example 18 from Cobas®.

Group ID	Mean Predose ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP
AD05209 (Cyno A) (5.0 mg/kg)	1.00	1.20	2.30	3.11	3.61
AD05209 (Cyno B) (5.0 mg/kg)	1.00	1.41	2.15	2.64	2.75
AD05195 (Cyno A) (5.0 mg/kg)	1.00	1.06	1.39	1.57	1.53
AD05256 (Cyno A) (5.0 mg/kg)	1.00	1.06	1.14	1.25	1.32
AD05256 (Cyno B) (5.0 mg/kg)	1.00	1.34	2.10	2.58	2.90

Example 19. ***In vivo testing of ASGR1 RNAi Agents in Cynomolgus Monkeys.***

ASGR1 RNAi agents were evaluated in cynomolgus monkeys. On day 1, cynomolgus macaque (Macaca fascicularis) primates were given a single subcutaneous injection of 0.3 mL/kg (approximately 2-3 mL volume, depending on animal mass) containing 10.0 mg/mL, 16.7 mg/mL, or 26.7 mg/mL, for a total dose of 3.0 mg/kg, 5.0 mg/kg, or 8.0 mg/kg, respectively, of *ASGR1* RNAi agent AD05183 formulated in saline. An additional group was dosed with 0.3 mL/kg (approximately 2-3 mL volume, depending on animal mass) with saline to be used as a control. Each of *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5.

Two (2) monkeys in each group were tested, except that one of the monkeys dosed with saline control died prior to day 15. Blood samples were drawn and serum samples were analyzed on days 8, 15, 22, 29, 36, 43, 50 and 57 for ALP and standard clinical chemistry panel. As noted in Example 15, ALP serves as a surrogate biomarker for monitoring reduction in ASGR1 and inhibition of an *ASGR1* gene. ALP levels in serum were measured on a Cobas® Integra 400 (Roche Diagnostics), according to the manufacturer's recommendations.

Data from the experiment are shown in the following Tables 39 and 40, which report raw ALP values (units/L) as well as ALP normalized to averaged individual pre-treatment levels.

Table 39. ALP levels from cynomolgus monkeys from Example 19 (ALP levels reported in units/L) from Cobas®.

Group ID	Day 1 (pre-dose) ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP	Day 43 ALP	Day 50 ALP	Day 57 ALP
Saline vehicle (Cyno A)	644	544							
Saline vehicle (Cyno B)	337	341	317	297	313	331	342	329	347
3.0 mg/kg AD05183 (Cyno A)	350	421	698	919	847	739	727	776	759
3.0 mg/kg AD05183 (Cyno B)	633	735	1053	1116	1423	1161	1181	1187	1130
5.0 mg/kg AD05183 (Cyno A)	554	681	1079	1146	1317	1184	1179	1386	1391
5.0 mg/kg AD05183 (Cyno B)	415	491	790	799	815	848	794	818	788
8.0 mg/kg AD05183 (Cyno A)	459	592	874	1006	1249	1065	1028	1251	1120
8.0 mg/kg AD05183 (Cyno B)	630	689	816	957	959	888	913	1007	959

Table 40. Normalized ALP levels from cynomolgus monkeys from Example 19 from Cobas®.

Group ID	Day 1 (pre-dose) ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP	Day 43 ALP	Day 50 ALP	Day 57 ALP
Saline vehicle (Cyno A)	1.00	0.85							
Saline vehicle (Cyno B)	1.00	1.01	0.94	0.88	0.93	0.98	1.02	0.98	1.03
3.0 mg/kg AD05183 (Cyno A)	1.00	1.20	1.99	2.62	2.42	2.11	2.08	2.22	2.17
3.0 mg/kg AD05183 (Cyno B)	1.00	1.16	1.66	1.76	2.25	1.84	1.87	1.88	1.79

Group ID	Day 1 (pre-dose) ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP	Day 43 ALP	Day 50 ALP	Day 57 ALP
5.0 mg/kg AD05183 (Cyno A)	1.00	1.23	1.95	2.07	2.38	2.14	2.13	2.50	2.51
5.0 mg/kg AD05183 (Cyno B)	1.00	1.18	1.90	1.93	1.96	2.04	1.91	1.97	1.90
8.0 mg/kg AD05183 (Cyno A)	1.00	1.29	1.90	2.19	2.72	2.32	2.24	2.72	2.44
8.0 mg/kg AD05183 (Cyno B)	1.00	1.09	1.30	1.52	1.52	1.41	1.45	1.60	1.52

Example 20. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing 1.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 41.

Table 41. Dosing groups of *ASGR1*-SEAP mice of Example 20.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	1.0 mg/kg AD05067	Single injection on day 1
3	1.0 mg/kg AD05183	Single injection on day 1
4	1.0 mg/kg AD05209	Single injection on day 1
5	1.0 mg/kg AD05256	Single injection on day 1
6	1.0 mg/kg AD05373	Single injection on day 1
7	1.0 mg/kg AD05374	Single injection on day 1
8	1.0 mg/kg AD05375	Single injection on day 1
9	1.0 mg/kg AD05376	Single injection on day 1
10	1.0 mg/kg AD05377	Single injection on day 1
11	1.0 mg/kg AD05378	Single injection on day 1
12	1.0 mg/kg AD05379	Single injection on day 1
13	1.0 mg/kg AD05380	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 8, day 15, day 22, day 29, and day 36, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 42, with Average SEAP reflecting the normalized average value of SEAP:

Table 42. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 20.

	Day 8		Day 15		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.214	1.000	0.205	1.000	0.253	1.000	0.469
Group 2 (1.0 mg/kg AD05067)	0.490	0.126	0.303	0.102	0.284	0.099	0.286	0.173
Group 3 (1.0 mg/kg AD05183)	0.404	0.138	0.205	0.109	0.216	0.093	0.311	0.089
Group 4 (1.0 mg/kg AD05209)	0.209	0.100	0.110	0.084	0.146	0.101	0.233	0.209
Group 5 (1.0 mg/kg AD05256)	0.413	0.159	0.238	0.124	0.252	0.148	0.338	0.172
Group 6 (1.0 mg/kg AD05373)	0.397	0.091	0.236	0.091	0.572	0.136	0.654	0.233
Group 7 (1.0 mg/kg AD05374)	0.266	0.051	0.248	0.148	0.281	0.069	0.443	0.204
Group 8 (1.0 mg/kg AD05375)	0.388	0.156	0.519	0.255	0.672	0.090	1.005	0.327
Group 9 (1.0 mg/kg AD05376)	0.270	0.071	0.321	0.239	0.295	0.078	0.349	0.166
Group 10 (1.0 mg/kg AD05377)	0.442	0.085	0.624	0.228	0.846	0.308	1.012	0.413
Group 11 (1.0 mg/kg AD05378)	0.304	0.080	0.203	0.097	0.280	0.117	0.315	0.079
Group 12 (1.0 mg/kg AD05379)	0.372	0.029	0.366	0.077	0.471	0.191	0.660	0.185
Group 13 (1.0 mg/kg AD05380)	0.298	0.084	0.320	0.251	0.289	0.098	0.409	0.233

	Day 36	
Group ID	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.207
Group 2 (1.0 mg/kg AD05067)	0.570	0.459

Group 3 (1.0 mg/kg AD05183)	0.574	0.343
Group 4 (1.0 mg/kg AD05209)	0.483	0.403
Group 5 (1.0 mg/kg AD05256)	0.276	0.113
Group 6 (1.0 mg/kg AD05373)	0.987	0.489
Group 7 (1.0 mg/kg AD05374)	0.634	0.357
Group 8 (1.0 mg/kg AD05375)	1.208	0.523
Group 9 (1.0 mg/kg AD05376)	0.455	0.233
Group 10 (1.0 mg/kg AD05377)	1.133	0.236
Group 11 (1.0 mg/kg AD05378)	0.635	0.184
Group 12 (1.0 mg/kg AD05379)	1.169	0.244
Group 13 (1.0 mg/kg AD05380)	0.846	0.702

Example 21. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing 1.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 43.

Table 43. Dosing groups of *ASGR1*-SEAP mice of Example 21.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	1.0 mg/kg AD05193	Single injection on day 1
3	1.0 mg/kg AD05196	Single injection on day 1
4	1.0 mg/kg AD05462	Single injection on day 1
5	1.0 mg/kg AD05603	Single injection on day 1
6	1.0 mg/kg AD05604	Single injection on day 1
7	1.0 mg/kg AD05605	Single injection on day 1
8	1.0 mg/kg AD05606	Single injection on day 1
9	1.0 mg/kg AD05607	Single injection on day 1
10	1.0 mg/kg AD05608	Single injection on day 1
11	1.0 mg/kg AD05609	Single injection on day 1
12	1.0 mg/kg AD05610	Single injection on day 1
13	1.0 mg/kg AD05624	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 8, day 15, day 22, day 29, and day 36, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 44, with Average SEAP reflecting the normalized average value of SEAP:

Table 44. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 21.

	Day 8		Day 15		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.349	1.000	0.246	1.000	0.152	1.00	0.330
Group 2 (1.0 mg/kg AD05193)	0.307	0.177	0.275	0.273	0.480	0.451	0.465	0.442
Group 3 (1.0 mg/kg AD05196)	0.176	0.072	0.120	0.052	0.181	0.053	0.186	0.107
Group 4 (1.0 mg/kg AD05462)	0.230	0.015	0.176	0.121	0.374	0.054	0.739	0.097
Group 5 (1.0 mg/kg AD05603)	0.186	0.060	0.242	0.033	0.529	0.170	0.645	0.134
Group 6 (1.0 mg/kg AD05604)	0.170	0.029	0.171	0.128	0.204	0.159	0.318	0.343
Group 7 (1.0 mg/kg AD05605)	0.149	0.026	0.127	0.036	0.222	0.036	0.304	0.018
Group 8 (1.0 mg/kg AD05606)	0.144	0.024	0.130	0.035	0.380	0.038	0.406	0.081
Group 9 (1.0 mg/kg AD05607)	0.166	0.032	0.095	0.046	0.137	0.049	0.194	0.084
Group 10 (1.0 mg/kg AD05608)	0.181	0.051	0.149	0.085	0.247	0.186	0.342	0.184
Group 11 (1.0 mg/kg AD05609)	0.120	0.008	0.118	0.031	0.223	0.047	0.210	0.109
Group 12 (1.0 mg/kg AD05610)	0.151	0.028	0.098	0.053	0.255	0.138	0.274	0.117
Group 13 (1.0 mg/kg AD05624)	0.165	0.072	0.595	0.582	0.912	1.128	0.391	0.306
	Day 36							
Group ID	**Avg SEAP**	**Std Dev (+/-)**						
Group 1 (Saline)	1.000	0.305						
Group 2 (1.0 mg/kg AD05193)	0.539	0.557						

Group 3 (1.0 mg/kg AD05196)	0.481	0.272								
Group 4 (1.0 mg/kg AD05462)	0.775	0.320								
Group 5 (1.0 mg/kg AD05603)	1.321	0.295								
Group 6 (1.0 mg/kg AD05604)	0.452	0.448								
Group 7 (1.0 mg/kg AD05605)	0.404	0.115								
Group 8 (1.0 mg/kg AD05606)	0.672	0.054								
Group 9 (1.0 mg/kg AD05607)	0.268	0.176								
Group 10 (1.0 mg/kg AD05608)	0.587	0.393								
Group 11 (1.0 mg/kg AD05609)	0.493	0.333								
Group 12 (1.0 mg/kg AD05610)	0.342	0.161								
Group 13 (1.0 mg/kg AD05624)	0.611	0.757								

Example 22. ***In vivo testing of ASGR1 RNAi Agents in Cynomolgus Monkeys.***

ASGR1 RNAi agents were evaluated in cynomolgus monkeys. On day 1, cynomolgus macaque (Macaca fascicularis) primates were given a single subcutaneous injection of 0.3 mL/kg (approximately 2-3 mL volume, depending on animal mass) containing 10.0 mg/mL, for a total dose of 3.0 mg/kg, of either *ASGR1* RNAi agent AD05209, AD05374, AD05609, or AD05692, each formulated in saline. Each of *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5.

Two (2) monkeys in each group were tested. Blood samples were drawn and serum samples were analyzed on days 8, 15, 22, 29, and 36 for ALP and standard clinical chemistry panel. As noted in Example 15, ALP serves as a surrogate biomarker for monitoring reduction in ASGR1 and inhibition of an *ASGR1* gene. ALP levels in serum were measured on a Cobas® Integra 400 (Roche Diagnostics), according to the manufacturer's recommendations.

Data from the experiment are shown in the following Tables 45 and 46, which report raw ALP values (units/L) as well as ALP normalized to the mean of the individual pre-treatment levels.

Table 45. ALP levels from cynomolgus monkeys from Example 22 (ALP levels reported in units/L) from Cobas®.

Group ID	Mean Predose ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP
3.0 mg/kg AD05209(Cyno A)	342	427	616	750	707	754
3.0 mg/kg AD05209 (Cyno B)	253	323	410	521	573	520
3.0 mg/kg AD05374 (Cyno A)	298	345	406	420	420	415
3.0 mg/kg AD05374 (Cyno B)	225	292	397	402	367	338
3.0 mg/kg AD05609 (Cyno A)	320	365	428	475	542	532
3.0 mg/kg AD05609 (Cyno B)	214	299	380	481	427	371
3.0 mg/kg AD05692 (Cyno A)	320	370	405	406	388	430
3.0 mg/kg AD05692 (Cyno B)	110	144	186	182	175	148

Table 46. Normalized ALP levels from cynomolgus monkeys from Example 22 from Cobas®.

Group ID	Mean Predose ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP
3.0 mg/kg AD05209(Cyno A)	1.00	1.25	1.80	2.19	2.07	2.20
3.0 mg/kg AD05209 (Cyno B)	1.00	1.28	1.62	2.06	2.26	2.05
3.0 mg/kg AD05374 (Cyno A)	1.00	1.16	1.36	1.41	1.41	1.39
3.0 mg/kg AD05374 (Cyno B)	1.00	1.30	1.76	1.79	1.63	1.50
3.0 mg/kg AD05609 (Cyno A)	1.00	1.14	1.34	1.49	1.70	1.66
3.0 mg/kg AD05609 (Cyno B)	1.00	1.40	1.77	2.24	1.99	1.73

Group ID	Mean Predose ALP	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP
3.0 mg/kg AD05692 (Cyno A)	1.00	1.16	1.27	1.27	1.21	1.35
3.0 mg/kg AD05692 (Cyno B)	1.00	1.31	1.69	1.65	1.59	1.35

As shown in the data presented in Tables 45 and 46 above, each of the RNAi agents showed an increase in reported ALP levels after administration in cynomolgus monkeys. For example, both of the cynomolgus monkeys dosed with 3.0 mg/kg of AD05209 had their respective ALP levels doubled compared to baseline at days 22, 29, and 36 (*see, e.g.*, Table 46 showing the ratio compared to baseline).

Example 23. ***In vivo testing of ASGR1 RNAi Agents in ASGR1-SEAP Mice.***

The *ASGR1*-SEAP mouse model described in Example 2, above, was used. At day 1, each mouse was given a single subcutaneous injection of 200 µl containing 1.0 mg/kg of an *ASGR1* RNAi agent, or 200 µl of saline without an *ASGR1* RNAi agent to be used as a control, according to the following Table 47.

Table 47. Dosing groups of *ASGR1*-SEAP mice of Example 23.

Group	RNAi Agent and Dose	Dosing Regimen
1	Saline (no RNAi agent)	Single injection on day 1
2	1.0 mg/kg AD05183	Single injection on day 1
3	1.0 mg/kg AD05209	Single injection on day 1
4	1.0 mg/kg AD05648	Single injection on day 1
5	1.0 mg/kg AD05649	Single injection on day 1
6	1.0 mg/kg AD05650	Single injection on day 1
7	1.0 mg/kg AD05651	Single injection on day 1
8	1.0 mg/kg AD05674	Single injection on day 1
9	1.0 mg/kg AD05675	Single injection on day 1
10	1.0 mg/kg AD05676	Single injection on day 1
11	1.0 mg/kg AD05740	Single injection on day 1
12	1.0 mg/kg AD05741	Single injection on day 1
13	1.0 mg/kg AD05742	Single injection on day 1
14	1.0 mg/kg AD05193	Single injection on day 1
15	1.0 mg/kg AD05692	Single injection on day 1
16	1.0 mg/kg AD05677	Single injection on day 1
17	1.0 mg/kg AD05678	Single injection on day 1
18	1.0 mg/kg AD05679	Single injection on day 1

Each of the *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand, as shown in Tables 4 and 5. The injections were performed between the skin and muscle (i.e. subcutaneous injections) into the loose skin over the neck and shoulder area. Three (3) mice in each group were tested (n=3). Serum was collected on day 8, day 15, day 22, and day 29, and SEAP expression levels were determined pursuant to the procedure set forth in Example 2, above. Data from the experiment are shown in the following Table 48, showing Average SEAP reflecting the normalized average value of SEAP normalized to pre-treatment and control, and in the following Table 49, showing Average SEAP reflecting the normalized average value of SEAP normalized to pre-treatment levels only:

Table 48. Average SEAP normalized to pre-treatment and saline control in *ASGR1*-SEAP mice from Example 23.

	Day 8		Day 15		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	1.000	0.326	1.000	0.281	1.000	0.554	1.000	0.346
Group 2 (1.0 mg/kg AD05183)	0.658	0.363	0.276	0.142	0.379	0.177	0.534	0.180
Group 3 (1.0 mg/kg AD05209)	0.290	0.104	0.272	0.236	0.300	0.302	0.467	0.387
Group 4 (1.0 mg/kg AD05648)	0.476	0.242	0.317	0.186	0.270	0.199	0.332	0.183
Group 5 (1.0 mg/kg AD05649)	0.215	0.119	0.121	0.099	0.174	0.156	0.353	0.312
Group 6 (1.0 mg/kg AD05650)	0.390	0.119	0.210	0.060	0.274	0.104	0.408	0.147
Group 7 (1.0 mg/kg AD05651)	0.316	0.198	0.189	0.116	0.343	0.154	0.943	0.275
Group 8 (1.0 mg/kg AD05674)	0.506	0.228	0.341	0.308	0.500	0.166	0.917	0.389
Group 9 (1.0 mg/kg AD05675)	0.337	0.040	0.158	0.059	0.251	0.221	0.470	0.453
Group 10 (1.0 mg/kg AD05676)	0.451	0.195	0.273	0.122	0.317	0.100	0.795	0.549
Group 11 (1.0 mg/kg AD05740)	0.345	0.217	0.258	0.170	0.266	0.201	0.368	0.247
Group 12 (1.0 mg/kg AD05741)	0.241	0.014	0.136	0.073	0.175	0.100	0.288	0.180
Group 13 (1.0 mg/kg AD05742)	0.294	0.076	0.210	0.138	0.405	0.285	0.641	0.387
Group 14 (1.0 mg/kg AD05193)	0.237	0.094	0.096	0.060	0.137	0.115	0.242	0.157
Group 15 (1.0 mg/kg AD05692)	0.468	0.285	0.304	0.325	0.545	0.497	0.718	0.902
Group 16 (1.0 mg/kg AD05677)	0.353	0.097	0.205	0.208	0.387	0.380	0.588	0.580
Group 17 (1.0 mg/kg AD05678)	0.274	0.065	0.236	0.143	0.309	0.286	0.715	0.568
Group 18 (1.0 mg/kg AD05679)	0.348	0.049	0.195	0.122	0.260	0.138	0.271	0.085

Table 49. Average SEAP normalized to pre-treatment only in *ASGR1*-SEAP mice from Example 23.

	Day 8		Day 15		Day 22		Day 29	
Group ID	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**	**Avg SEAP**	**Std Dev (+/-)**
Group 1 (Saline)	0.756	0.247	0.574	0.161	0.421	0.233	0.400	0.138
Group 2 (1.0 mg/kg AD05183)	0.497	0.275	0.159	0.081	0.160	0.075	0.214	0.072
Group 3 (1.0 mg/kg AD05209)	0.220	0.079	0.156	0.136	0.126	0.127	0.187	0.155
Group 4 (1.0 mg/kg AD05648)	0.360	0.183	0.182	0.107	0.114	0.084	0.133	0.073
Group 5 (1.0 mg/kg AD05649)	0.162	0.090	0.070	0.057	0.073	0.066	0.141	0.125
Group 6 (1.0 mg/kg AD05650)	0.295	0.090	0.120	0.034	0.115	0.044	0.163	0.059
Group 7 (1.0 mg/kg AD05651)	0.239	0.150	0.109	0.067	0.145	0.065	0.377	0.110
Group 8 (1.0 mg/kg AD05674)	0.382	0.172	0.196	0.177	0.211	0.070	0.367	0.156
Group 9 (1.0 mg/kg AD05675)	0.255	0.031	0.091	0.034	0.106	0.093	0.188	0.181
Group 10 (1.0 mg/kg AD05676)	0.341	0.147	0.157	0.070	0.133	0.042	0.318	0.220
Group 11 (1.0 mg/kg AD05740)	0.261	0.164	0.148	0.098	0.112	0.085	0.147	0.099
Group 12 (1.0 mg/kg AD05741)	0.182	0.010	0.078	0.042	0.074	0.042	0.115	0.072
Group 13 (1.0 mg/kg AD05742)	0.240	0.062	0.130	0.085	0.186	0.130	0.267	0.161
Group 14 (1.0 mg/kg AD05193)	0.194	0.077	0.059	0.037	0.063	0.052	0.101	0.065
Group 15 (1.0 mg/kg AD05692)	0.382	0.232	0.187	0.200	0.250	0.228	0.299	0.375
Group 16 (1.0 mg/kg AD05677)	0.288	0.079	0.126	0.128	0.177	0.174	0.245	0.241
Group 17 (1.0 mg/kg AD05678)	0.224	0.053	0.145	0.088	0.142	0.131	0.297	0.236
Group 18 (1.0 mg/kg AD05679)	0.263	0.037	0.112	0.070	0.109	0.058	0.113	0.035

Example 24. ***In vivo testing of ASGR1 RNAi Agents in Cynomolgus Monkeys.***

ASGR1 RNAi agents were evaluated for reduction in *ASGR1* mRNA levels in cynomolgus monkeys. On day 1, female cynomolgus macaque (Macaca fascicularis) primates ("cynomolgus monkeys") were given a single subcutaneous injection of 0.3 mL/kg (approximately 2-3 mL volume, depending on animal mass) containing 10.0 mg/mL, for a total dose of 3.0 mg/kg, of either *ASGR1* RNAi agent AD05193 or AD05209, each formulated in saline. Each of *ASGR1* RNAi agents included N-acetyl-galactosamine targeting ligands conjugated to the 5′-terminal end of the sense strand having the structure of (NAG37)s, as shown in Tables 4, 5, and 6.

Four (4) monkeys in each group were tested. On days -7 (pre-dose), 15, 29, 43, and 57, liver biopsies were taken. On the date of each biopsy collection, the cynomolgus monkeys were anesthetized and ultrasound-guided liver biopsies were performed to extract liver tissue samples. Approximately 100 mg liver samples from the median lobes were collected and snap-frozen in liquid nitrogen for RNA isolation. The biopsy samples were then homogenized, and levels of *ASGR1* mRNA in the cyno livers were measured by RT-qPCR. Resulting values were then normalized to the pre-dose (in this case, at day -7) *ASGR1* mRNA measurements using the $\Delta\Delta C_T$ method, which are reflected in the following Table 50.

Additionally, serum samples were taken on -14, -1, day 1 (pre-dose), day 8, day 15, day 22, day 29, day 36, day 43, day 57, day 71, and day 85, and ALP levels in serum for each day were measured on a Cobas® Integra 400 (Roche Diagnostics), according to the manufacturer's recommendations, which are reported in Tables 51 and 52, below.

Table 50. *ASGR1* mRNA Expression Levels Relative to Pre-Dose (Day -7) from Example 24.

	Day 15			Day 29			Day 43			Day 57		
Group	**Mean Relative ASGR1 mRNA Expression**	**Low Error**	**High Error**	**Mean Relative ASGR1 mRNA Expression**	**Low Error**	**High Error**	**Mean Relative ASGR1 mRNA Expression**	**Low Error**	**High Error**	**Mean Relative ASGR1 mRNA Expression**	**Low Error**	**High Error**
AD05193	0.292	0.057	0.071	0.284	0.128	0.233	0.248	0.383	0.151	0.598	0.295	0.197
AD05209	0.237	0.055	0.071	0.286	0.041	0.048	0.237	0.068	0.095	0.421	0.233	0.150

Table 51. Normalized ALP Levels By Group in Cynomolgus Monkeys from Example 24 (Normalized to Pre-Dose) from Cobas®.

Group ID	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP	Day 43 ALP	Day 57 ALP	Day 71 ALP	Day 85 ALP
AD05193 (3.0 mg/kg)	1.44	2.08	2.27	2.60	2.33	2.33	2.09	1.49	1.47
AD05209 (3.0 mg/kg)	1.56	1.99	2.07	2.08	2.01	1.94	1.59	1.34	1.26

Table 52. Normalized ALP Levels in Cynomolgus Monkeys from Example 24 (Normalized to Pre-Dose) from Cobas®.

Group ID	Day 8 ALP	Day 15 ALP	Day 22 ALP	Day 29 ALP	Day 36 ALP	Day 43 ALP	Day 57 ALP	Day 71 ALP	Day 85 ALP
3.0 mg/kg AD05193 (Cyno A)	1.48	2.09	2.54	2.74	2.25	1.89	1.81	1.16	1.21
3.0 mg/kg AD05193 (Cyno B)	1.51	2.61	2.39	2.88	2.54	2.44	2.15	1.54	1.53
3.0 mg/kg AD05193 (Cyno C)	1.42	1.62	1.91	1.99	1.95	2.04	2.04	1.46	1.40
3.0 mg/kg AD05193 (Cyno D)	1.37	2.00	2.24	2.77	2.60	2.97	2.34	1.82	1.73
3.0 mg/kg AD05209 (Cyno A)	1.68	1.89	2.39	2.13	2.41	1.83	1.50	1.27	1.16

3.0 mg/kg AD05209 (Cyno B)	1.40	1.66	1.50	1.31	1.17	1.17	1.05	1.00	0.96
3.0 mg/kg AD05209 (Cyno C)	1.79	2.45	2.48	2.55	2.44	2.51	1.84	1.50	1.51
3.0 mg/kg AD05209 (Cyno D)	1.36	1.94	1.91	2.32	2.01	2.23	1.95	1.60	1.43

The cynomolgus monkeys in both groups showed a significant reduction in liver-specific *ASGR1* mRNA compared to pre-treatment measurements at all measured time points. On day 43, for example, the cynomolgus monkeys of Group 1 (AD05193) had a reduction of *ASGR1* mRNA of approximately 75.2% (0.248), while cynomolgus monkeys of Group 2 (AD05209) had a reduction of approximately 76.3% (0.237), compared to pre-dose levels.

OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

CLAIMS:

1. An RNAi agent for inhibiting expression of an *ASGR1* gene, comprising:

an antisense strand comprising at least 16 consecutive nucleotides differing by 0 or 1 nucleotides from any of the antisense strand sequences provided in Table 2 or Table 3; and

a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand.

2. The RNAi agent of claim 1, wherein the antisense strand comprises nucleotides 2-18 of any of the sequences provided in Table 2 or Table 3.
3. The RNAi agent of claim 1 or 2, wherein the sense strand comprises a nucleotide sequence of at least 16 consecutive nucleotides that is at least 85% complementary to the antisense strand.
4. The RNAi agent of claim 3, wherein the sense strand comprises at least 16 consecutive nucleotides of any of the sense strand sequences provided in Table 2 or Table 4.
5. The RNAi agent of any one of claims 1-4, wherein the sense strand and antisense strand are each about 16 to about 30 nucleotides in length.
6. The RNAi agent of any one of claims 1-5, wherein the sense strand and antisense strand are each about 17 to about 26 nucleotides in length.
7. The RNAi agent of any one of claims 1-6, wherein at least one nucleotide of the sense strand and/or the antisense strand is a modified nucleotide or includes a modified internucleoside linkage.
8. The RNAi agent of any one of claims 1-6, wherein all or substantially all of the nucleotides are modified nucleotides
9. The RNAi agent of claim 7 or claim 8, wherein the modified nucleotide is a deoxyribonucleotide, an abasic nucleotide, a 2′-modified nucleotide, an inverted nucleotide, a 2′,3′-seco nucleotide mimic, a locked nucleotide, a 2'-F-arabino nucleotide, 5'-Me, 2'-fluoro nucleotide, an inosine-containing nucleotide, or combinations thereof.
10. The RNAi agent of claim 7, wherein the sense strand comprises at least one inosine-containing nucleotide.

11. The RNAi agent of claim 7, wherein the antisense strand comprises at least one 2′,3′-seco-nucleotide.
12. The RNAi agent of any one of claims 1 to 11, wherein the antisense strand comprises the nucleotide sequence of any of the antisense sequences provided in Table 2.
13. The RNAi agent of claim 12, wherein the sense strand comprises the nucleotide sequence of any of the sense sequences provided in Table 2.
14. The RNAi agent of any one of claims 1 to 11, wherein the antisense strand comprises the modified sequence of any of the modified antisense sequences provided in Table 3.
15. The RNAi agent of claim 14, wherein the sense strand comprises the modified sequence of any of the modified sense sequences provided in Table 4.
16. The RNAi agent of any one of claims 1-15, wherein the RNAi agent is conjugated to a targeting ligand.
17. The RNAi agent of claim 16, wherein the targeting ligand comprises N-acetyl-galactosamine.
18. The RNAi agent of claim 16, wherein the targeting ligand is selected from the targeting ligands in Table 6.
19. The RNAi agent of claim 16, wherein the targeting ligand is (NAG25), (NAG25)s, (NAG37), or (NAG37)s.
20. The RNAi agent of any one of claims 16-19, wherein the targeting ligand is conjugated to the 5′ end of the sense strand.
21. The RNAi agent of any one of claims 16-19, wherein the targeting ligand is conjugated to the 3′ end of the sense strand.
22. The RNAi agent of any one of claims 1-21, wherein the sense strand comprises one or two inverted abasic residues.
23. The RNAi agent of any one of claims 1 to 22, wherein the RNAi agent is any of the duplexes provided in Table 5.
24. The RNAi agent of claim 1, wherein the RNAi agent is a duplex selected from AD05126 (SEQ ID NOs:10 and 631), AD05150 (SEQ ID NOs:10 and 632), AD05183 (SEQ ID NOs:2 and 636), AD05186 (SEQ ID NOs:2 and 639), AD05193 (SEQ ID NOs:5 and 645), AD05195 (SEQ ID NOs:5 and 647), AD05196 (SEQ ID NOs:5 and 648), AD05206 (SEQ ID NOs: 28 and 658), AD05209 (SEQ ID NOs:4

and 602), AD05256 (SEQ ID NOs:2 and 674), AD05374 (SEQ ID NOs:2 and 700), AD05609 (SEQ ID NOs:7 and 708), or AD05692 (SEQ ID NOs:9 and 721).

25. The RNAi agent of claim 1, wherein the antisense strand consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

UACUCCUUGGUCAUGAUAGGU (SEQ ID NO:3);
AGCGACUUCAUCUUUCUUCCG (SEQ ID NO:6);
AGCGACUUCAUCUUUCUUCGU (SEQ ID NO:8);
ACUUCAUCUUUCUUCCCACGC (SEQ ID NO:11); or
UGAAAUAAAUUAAAGGAGAGG (SEQ ID NO:27).

26. The RNAi agent of claim 25, wherein the sense strand consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

ACCUAUCAUGACCAAGGAIUA (SEQ ID NO:12),
ACCUAUCAUGACCAAGGAGUA (SEQ ID NO:13);
ACCUAUCAUGACCAAIGAIUA (SEQ ID NO:14);
CGGAAGAAAGAUGAAGUCICU (SEQ ID NO:15);
ACGAAGAAAGAUGAAGUCICU (SEQ ID NO:16);
ACGAAGAAAGAUGAAGUCGCU (SEQ ID NO:17);
GCGUGGGAAGAAAGAUGAAGU (SEQ ID NO:18);
CGGAAGAAAGAUGAAIUCICU (SEQ ID NO:31);
CGGAAGAAAGAUGAAGUCGCU (SEQ ID NO:33); or
CCUCUCCUUUAAUUUAUUUCA (SEQ ID NO:35);

wherein I represents an inosine nucleotide.

27. The RNAi agent of claim 25 or 26, wherein all or substantially all of the nucleotides are modified nucleotides.

28. The RNAi agent of claim 27, wherein the sense strand further includes inverted abasic residues at the 3' terminal end of the nucleotide sequence, at the 5' end of the nucleotide sequence, or at both the 3' and 5' terminal ends.

29. The RNAi agent of claim 1, wherein the antisense strand comprises, consists of, or consists essentially of a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2);

usAfscUfcCfU$_{UNA}$UfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:4);
asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5);
asGfscGfaCfuucauCfuUfuCfuUfcsGfsu (SEQ ID NO:7);
asGfscsgacuucauCfuUfuCfuUfcGfsu (SEQ ID NO:9);
asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10); or
usGfsaAfaUfaAfaUfuAfaAfgGfaGfasGfsg (SEQ ID NO:28);

wherein a, c, g, and u represent 2′-O-methyl adenosine, cytidine, guanosine, or uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively; U_{UNA} represents a 2′,3′-seco-uridine; s represents a phosphorothioate linkage; and wherein all or substantially all of the nucleotides on the sense strand are modified nucleotides.

30. The RNAi agent of claim 1, wherein the sense strand comprises, consists of, or consists essentially of a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

accuaucaUfGfAfccaaggaiua (SEQ ID NO:19);
accuaucaUfGfAfccaaggagua (SEQ ID NO:20);
accuaucaUfGfAfcCaaggagua (SEQ ID NO:21);
accuaucaUfGfAfcCaaigaiua (SEQ ID NO:22);
cggaagaaAfGfAfugaagucicu (SEQ ID NO:23);
acgaagaaAfGfAfugaagucicu (SEQ ID NO:24);
acgaagaaAfGfAfugaagucgcu (SEQ ID NO:25);
gcgugggaAfGfAfaagaugaagu (SEQ ID NO:26);
gscgugggaAfGfAfaagaugaagu (SEQ ID NO:29);
accuaucaUfGfAfccaaigaiua (SEQ ID NO:30);
cggaagaaAfGfAfugaaiucicu (SEQ ID NO:32);
cggaagaaAfGfAfugaagucgcu (SEQ ID NO:34); or
ccucuccuUfUfAfauuuauuuca (SEQ ID NO:36);

wherein a, c, g, i, and u represent 2′-O-methyl adenosine, cytidine, guanosine, inosine, or uridine, respectively; and Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, cytidine, guanosine, or uridine, respectively.

31. The RNAi agent of claim 1, wherein the sense strand and antisense strand for a duplex pair that comprises, consists of, or consists essentially of a modified

nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequence pairs (5′ → 3′):

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2) and accuaucaUfGfAfccaaggaiua (SEQ ID NO:19);

usAfscUfcCfU$_{UNA}$UfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:4) and accuaucaUfGfAfccaaggagua (SEQ ID NO:20);

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2) and accuaucaUfGfAfcCaaggagua (SEQ ID NO:21);

usAfscUfcCfuUfgGfuCfaUfgAfuAfgsGfsu (SEQ ID NO:2) and accuaucaUfGfAfcCaaigaiua (SEQ ID NO:22);

asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5) and cggaagaaAfGfAfugaagucicu (SEQ ID NO:23);

asGfscGfaCfuucauCfuUfuCfuUfcsGfsu (SEQ ID NO:7) and acgaagaaAfGfAfugaagucicu (SEQ ID NO:24);

asGfscsgacuucauCfuUfuCfuUfcGfsu (SEQ ID NO:9) and acgaagaaAfGfAfugaagucgcu (SEQ ID NO:25);

asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10) and gcgugggaAfGfAfaagaugaagu (SEQ ID NO:26);

asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10) and gscgugggaAfGfAfaagaugaagu (SEQ ID NO:29);

asCfsusUfcAfuCfuUfuCfuUfcCfcAfcGfsc (SEQ ID NO:10) and accuaucaUfGfAfccaaigaiua (SEQ ID NO:30);

asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5) and cggaagaaAfGfAfugaaiucicu (SEQ ID NO:32);

asGfscGfaCfuucauCfuUfuCfuUfcsCfsg (SEQ ID NO:5) and cggaagaaAfGfAfugaagucgcu (SEQ ID NO:34); or

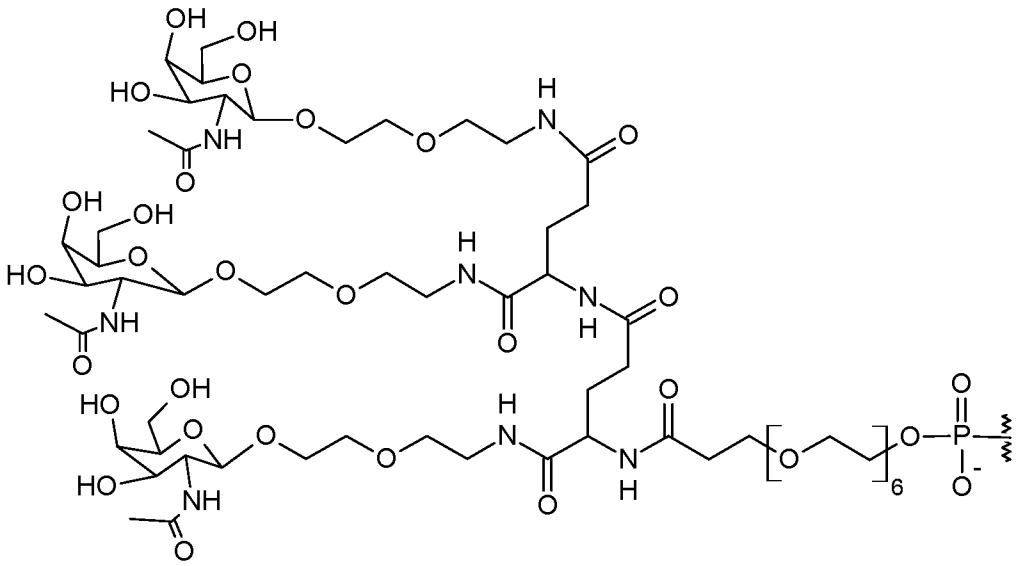
usGfsaAfaUfaAfaUfuAfaAfgGfaGfasGfsg (SEQ ID NO:28) and ccucuccuUfUfAfauuuauuuca (SEQ ID NO:36).

32. The RNAi agent of any one of claims 29 to 31, wherein the RNAi agent is conjugated to a targeting ligand at the 5’ end of the sense strand.

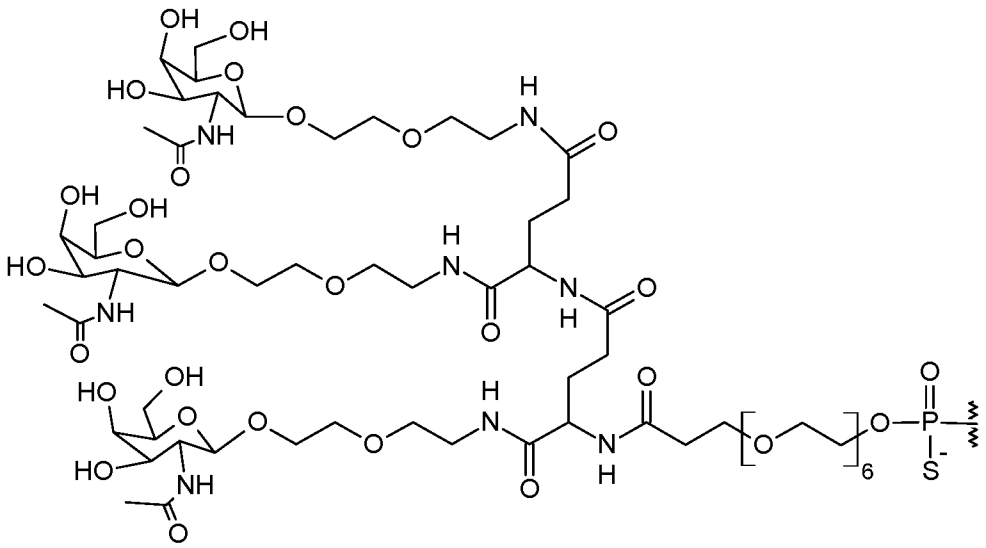
33. The RNAi agent of claim 32, wherein the targeting ligand is selected from the group consisting of:

(NAG25), (NAG25)s, (NAG37), or (NAG37)s.

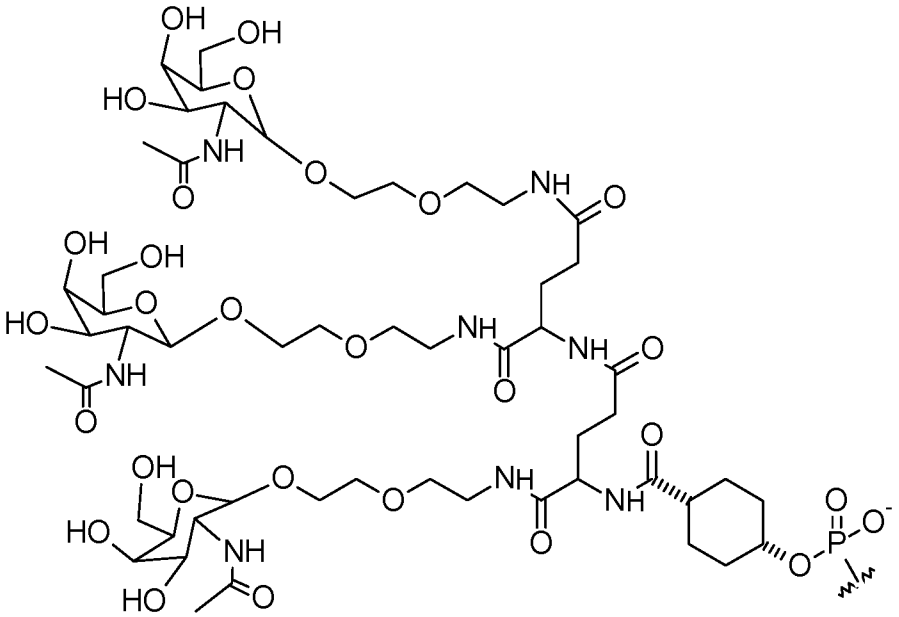
34. The RNAi agent of claim 33, wherein the targeting ligand is a tridentate ligand that includes N-acetyl-galactosamine and has the structure selected from the group consisting of:



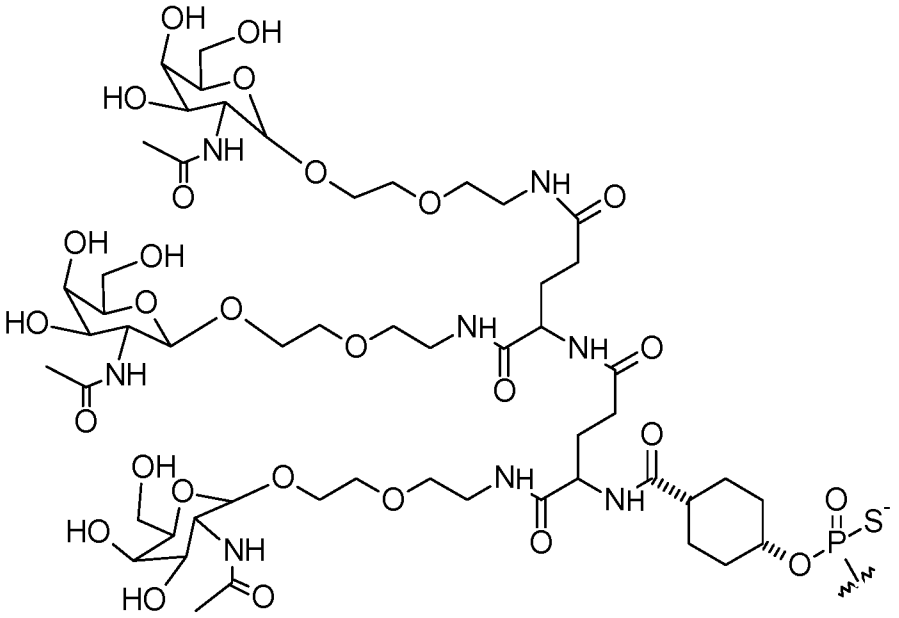
(NAG25);



(NAG25)s;



(NAG37); and



(NAG37)s.

35. A composition comprising the RNAi agent of any one of claims 1-31 and a pharmaceutically acceptable excipient.
36. The composition of claim 34, further comprising a second *ASGR1* RNAi agent comprising an antisense strand and a sense strand, wherein the antisense strand comprises nucleotides 2-18 of any of the sequences provided in Table 2 or Table 3.
37. The composition of claim 35 or 36, further comprising one or more additional therapeutics.
38. A method for inhibiting expression of an *ASGR1* gene in a cell, the method comprising administering to the cell the RNAi agent of any one of claims 1-34.
39. The method of claim 38, wherein the cell is within a human subject.
40. A method for inhibiting expression of an *ASGR1* gene in a subject, the method comprising administering to the subject the composition of any of claims 35-37.
41. A method of treating an *ASGR1*-related disease or disorder, the method comprising administering to a subject in need thereof an effective amount of the RNAi agent of any one of claims 1-34 or the composition of any one of claims 35-37.
42. The method of claim 41, wherein the ASGR1-related disease or disorder is obesity, metabolic syndrome, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, diabetes, cardiovascular disease, coronary artery disease, myocardial infarction, peripheral vascular disease, or cerebrovascular disease.
43. A method for reducing non-HDL cholesterol in a subject in need thereof, the method comprising administering to the subject an effective amount of the RNAi agent of any one of claims 1-34 or the composition of any one of claims 35-37.
44. The method of claim 43, wherein the non-HDL cholesterol is LDL cholesterol.
45. A method for reducing the risk of myocardial infarction in a subject in need thereof, the method comprising administering to the subject an effective amount of the RNAi agent of any one of claims 1-34 or the composition of any one of claims 35-37.
46. The method of claim 45, wherein the subject is diagnosed with coronary artery disease.
47. The method of claim 45, wherein the subject has elevated levels of non-HDL cholesterol.

48. The method of claim any one of claims 38-47, wherein the RNAi agent is administered at a dose of about 0.05 mg/kg to about 5.0 mg/kg of body weight of the human subject.
49. Use of the RNAi agent of any one of claims 1-34 or the composition of any one of claims 35-37 for the treatment of an *ASGR1*-related disease or disorder.
50. Use of the composition of any of claims 35-37, for the manufacture of a medicament for treatment of an *ASGR1*-related disease or disorder.
51. Use of the RNAi agent of any one of claims 1-34 for the manufacture of a medicament for reducing non-HDL cholesterol in a subject in need thereof.
52. Use of the RNAi agent of any one of claims 1-34 for the manufacture of a medicament for reducing the risk of myocardial infarction in a subject in need thereof.

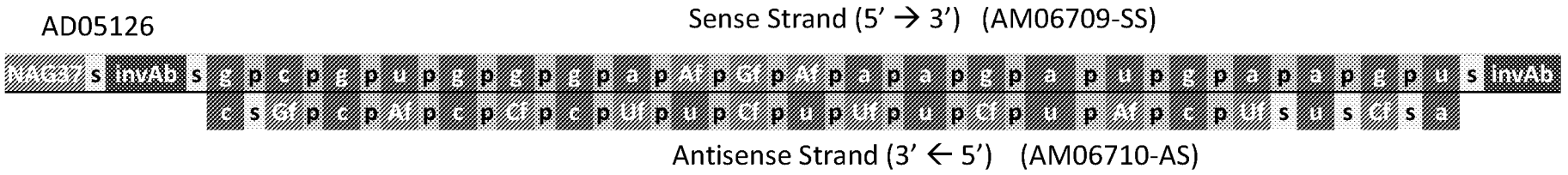


FIG. 1A

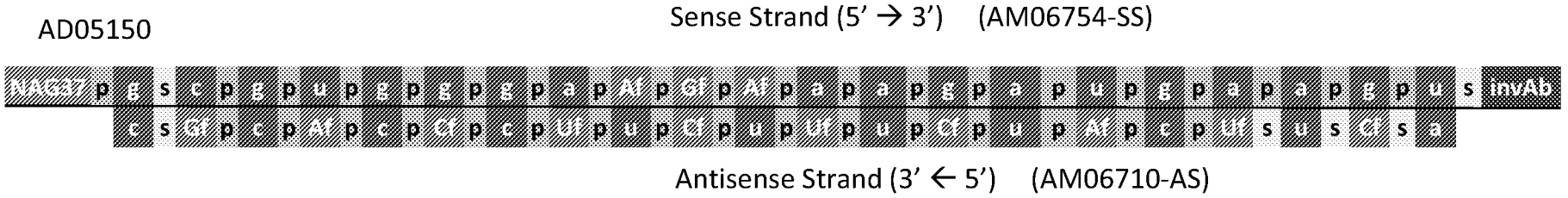


FIG. 1B

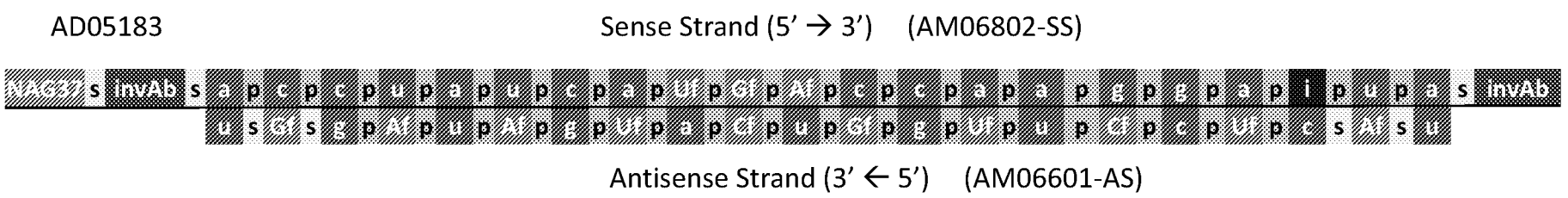


FIG. 1C

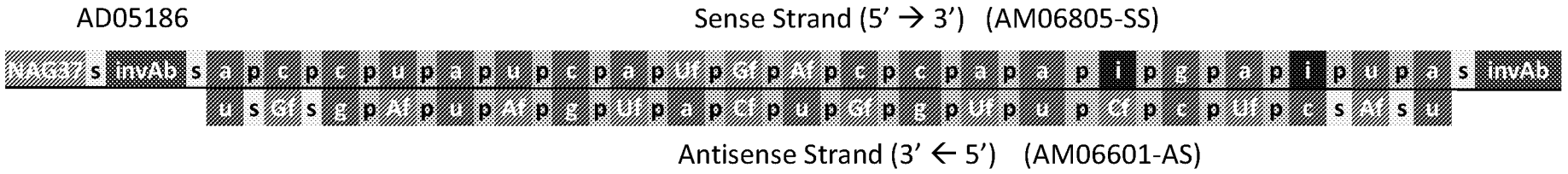


FIG. 1D

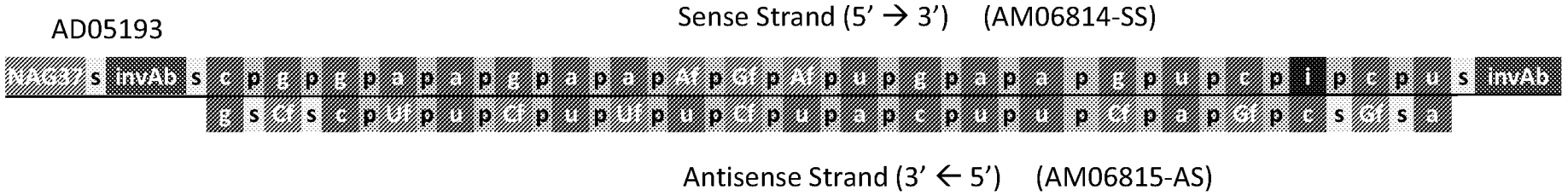


FIG. 1E

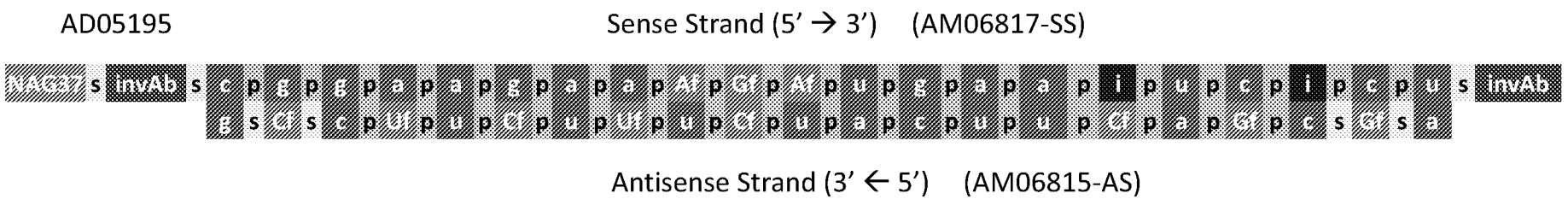
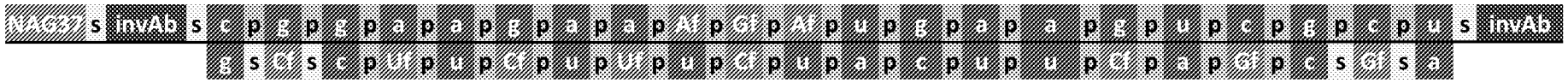


FIG. 1F

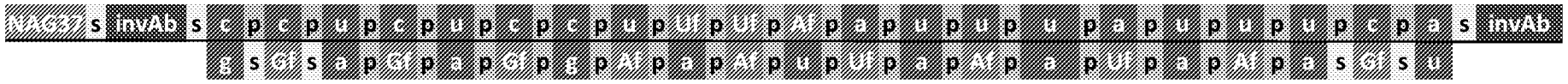
AD05196 Sense Strand (5' → 3') (AM06818-SS)



Antisense Strand (3' ← 5') (AM06815-AS)

FIG. 1G

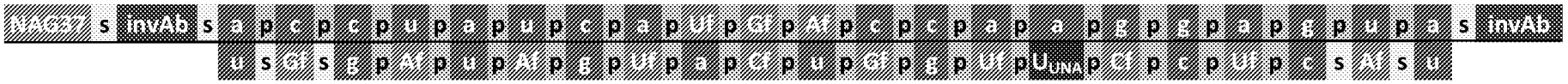
AD05206 Sense Strand (5' → 3') (AM06837-SS)



Antisense Strand (3' ← 5') (AM06838-AS)

FIG. 1H

AD05209 Sense Strand (5' → 3') (AM06600-SS)

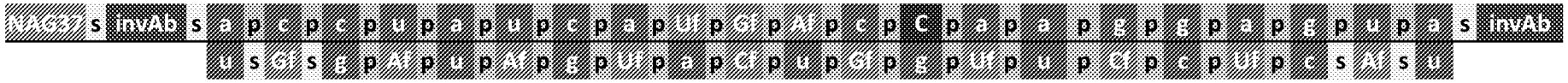


Antisense Strand (3' ← 5') (AM06851-AS)

FIG. 1I

AD05256

Sense Strand (5' → 3') (AM06930-SS)

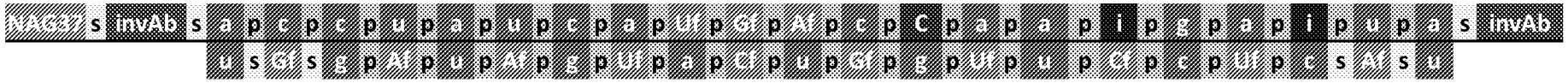


Antisense Strand (3' ← 5') (AM06601-AS)

FIG. 1J

AD05374

Sense Strand (5' → 3') (AM07110-SS)

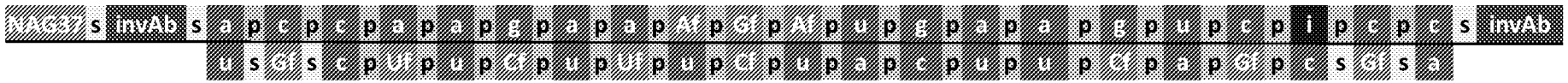


Antisense Strand (3' ← 5') (AM06601-AS)

FIG. 1K

AD05609

Sense Strand (5' → 3') (AM07395-SS)



Antisense Strand (3' ← 5') (AM07396-AS)

FIG. 1L

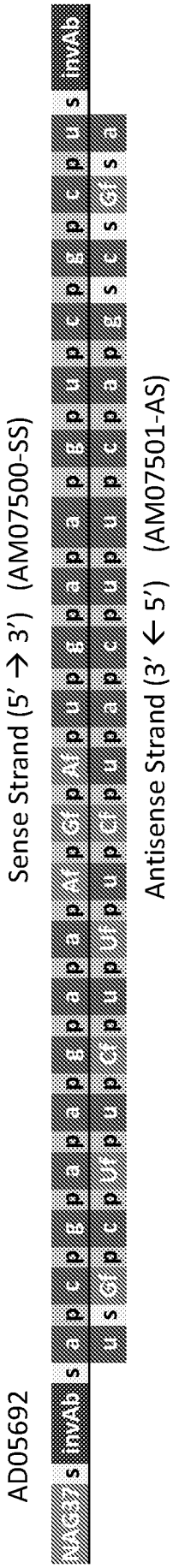

AD05692
Sense Strand (5′ → 3′) (AM07500-SS)
Antisense Strand (3′ ← 5′) (AM07501-AS)

FIG. 1M

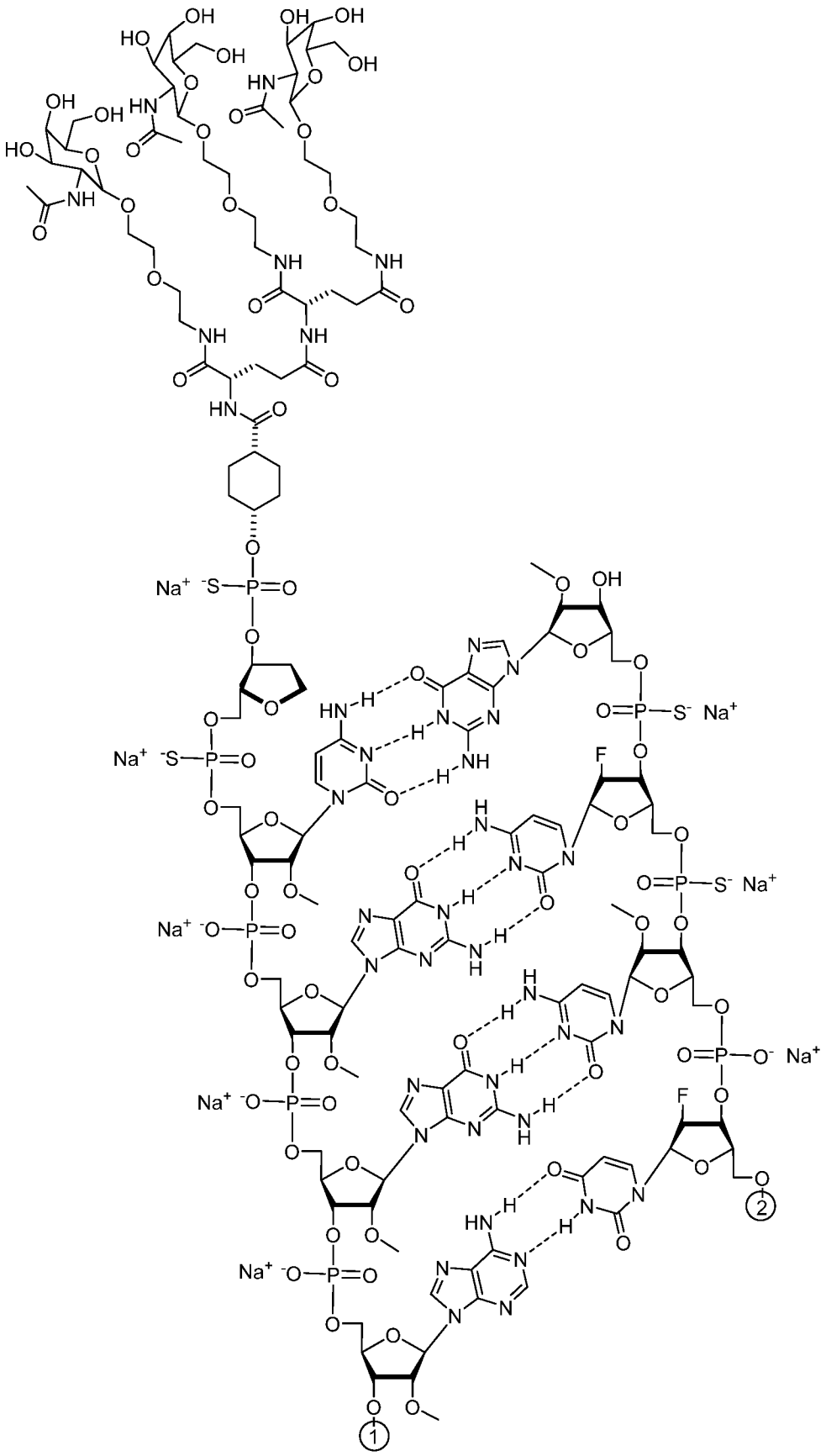


FIG. 2A

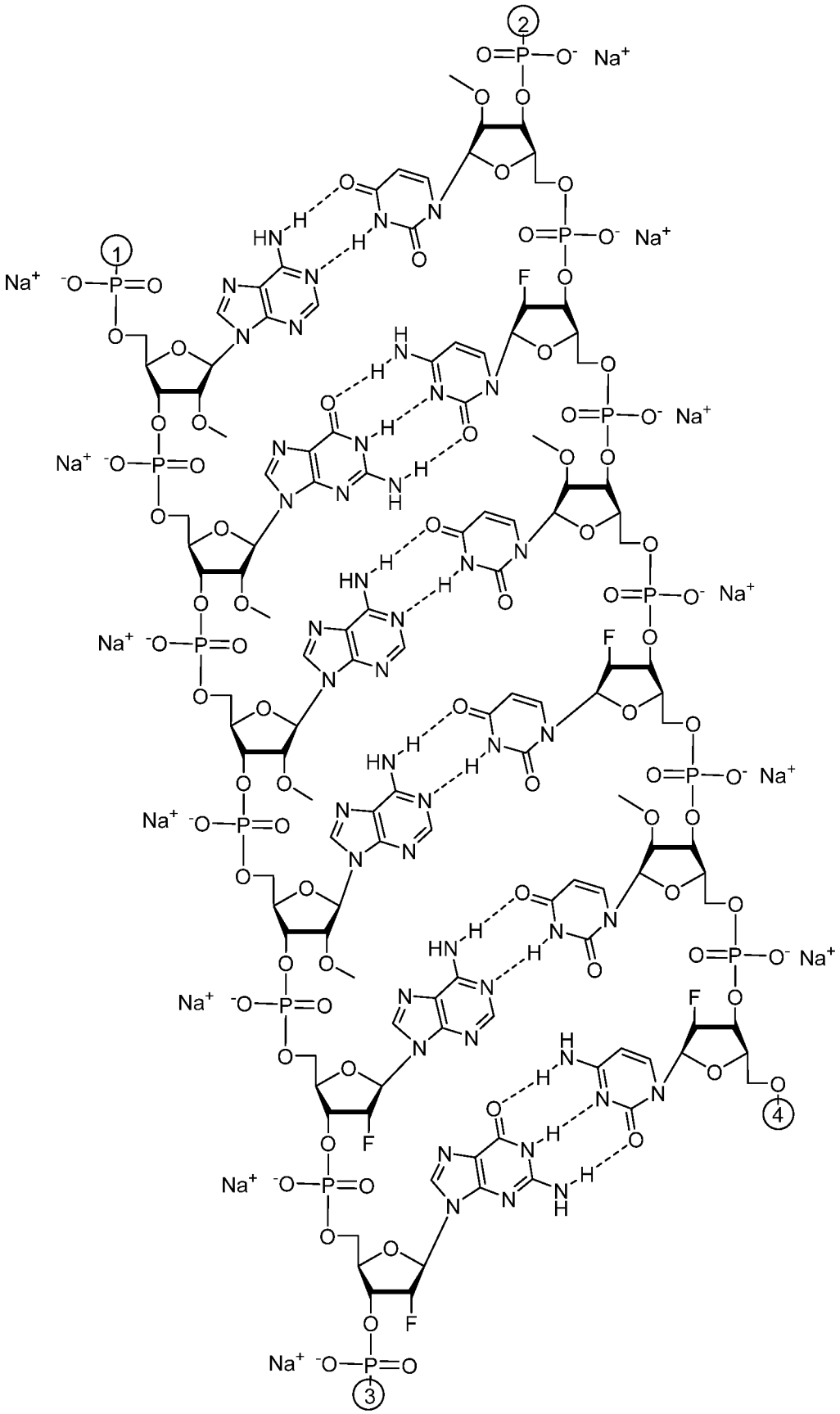


FIG. 2B

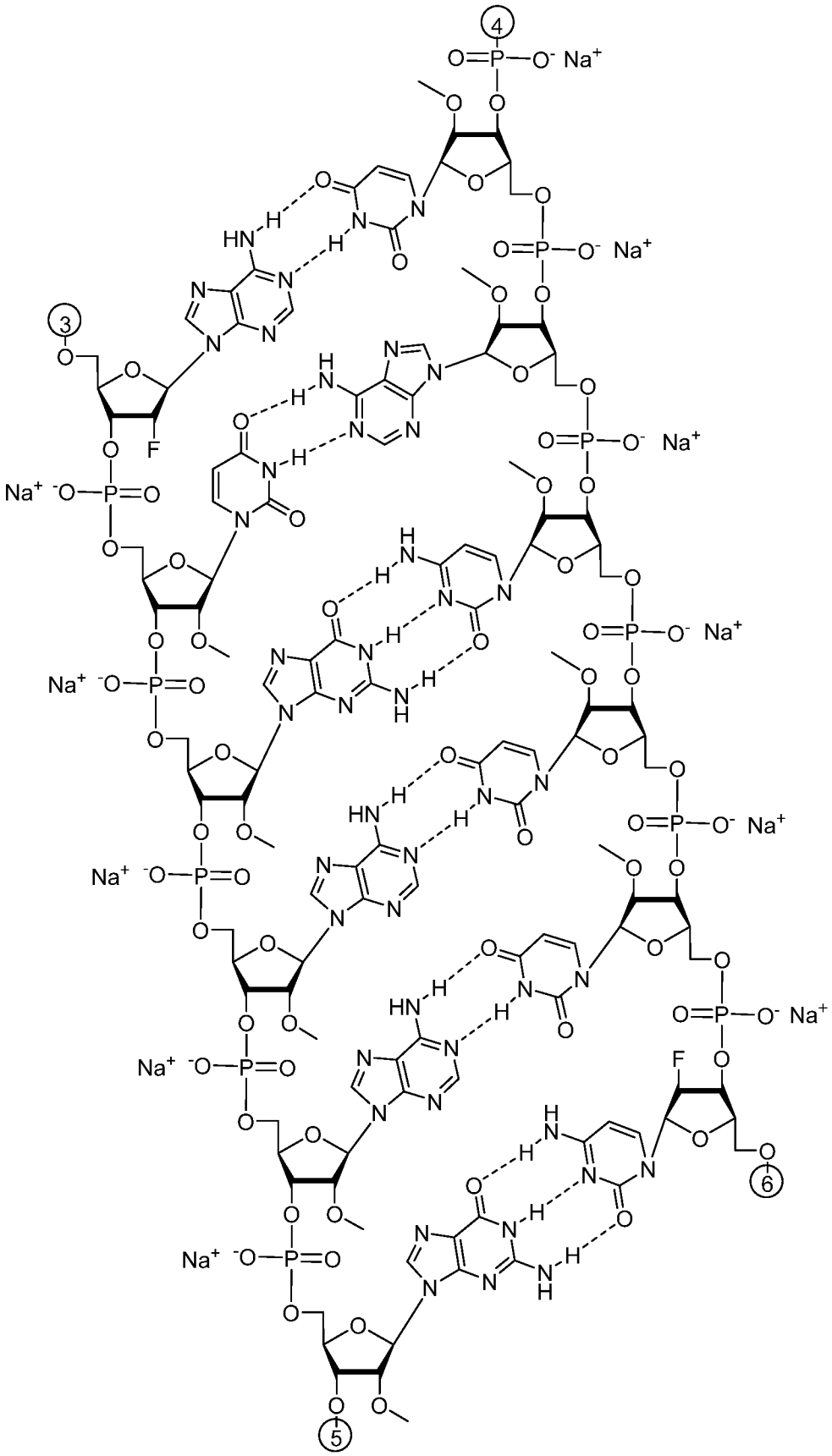


FIG. 2C

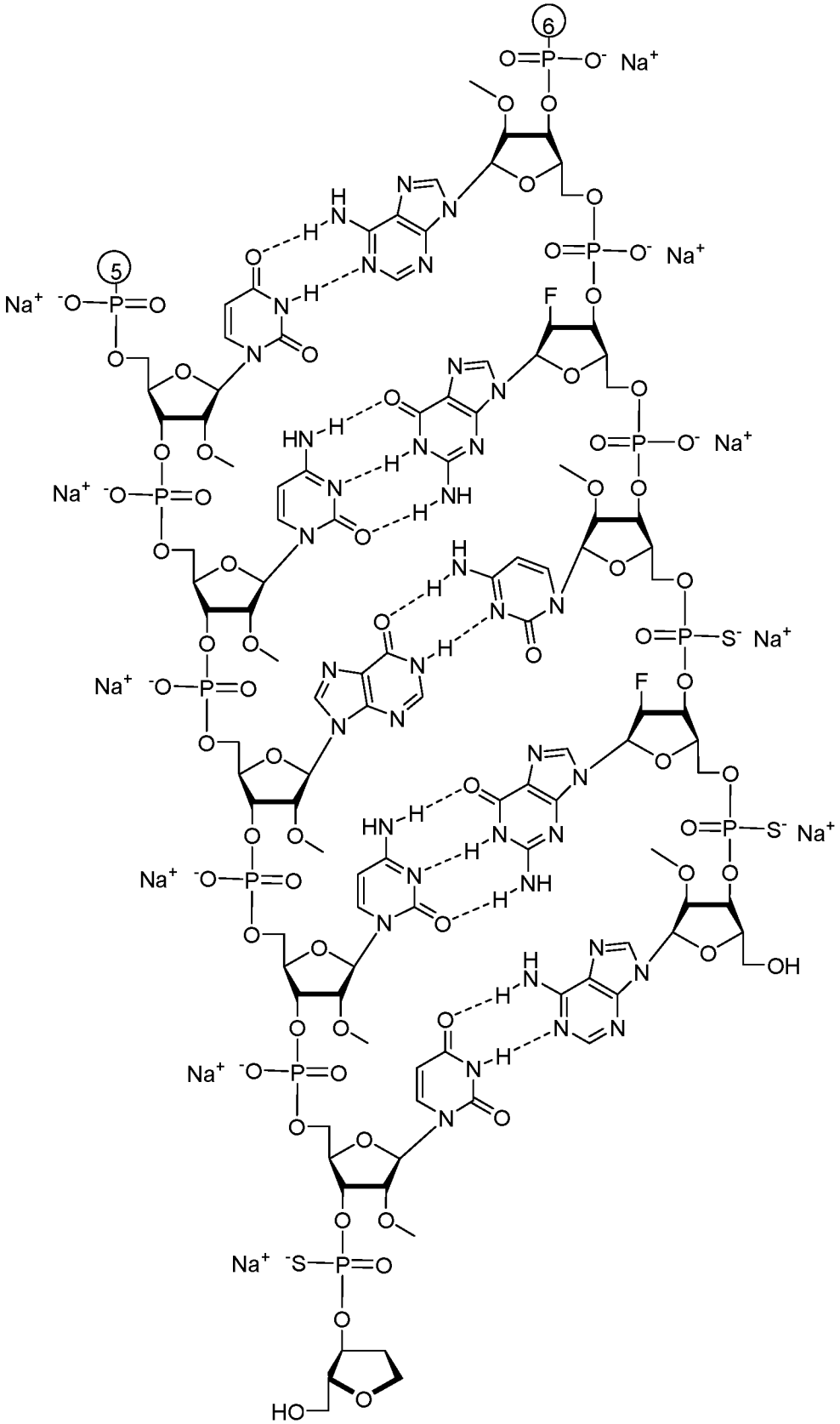


FIG. 2D

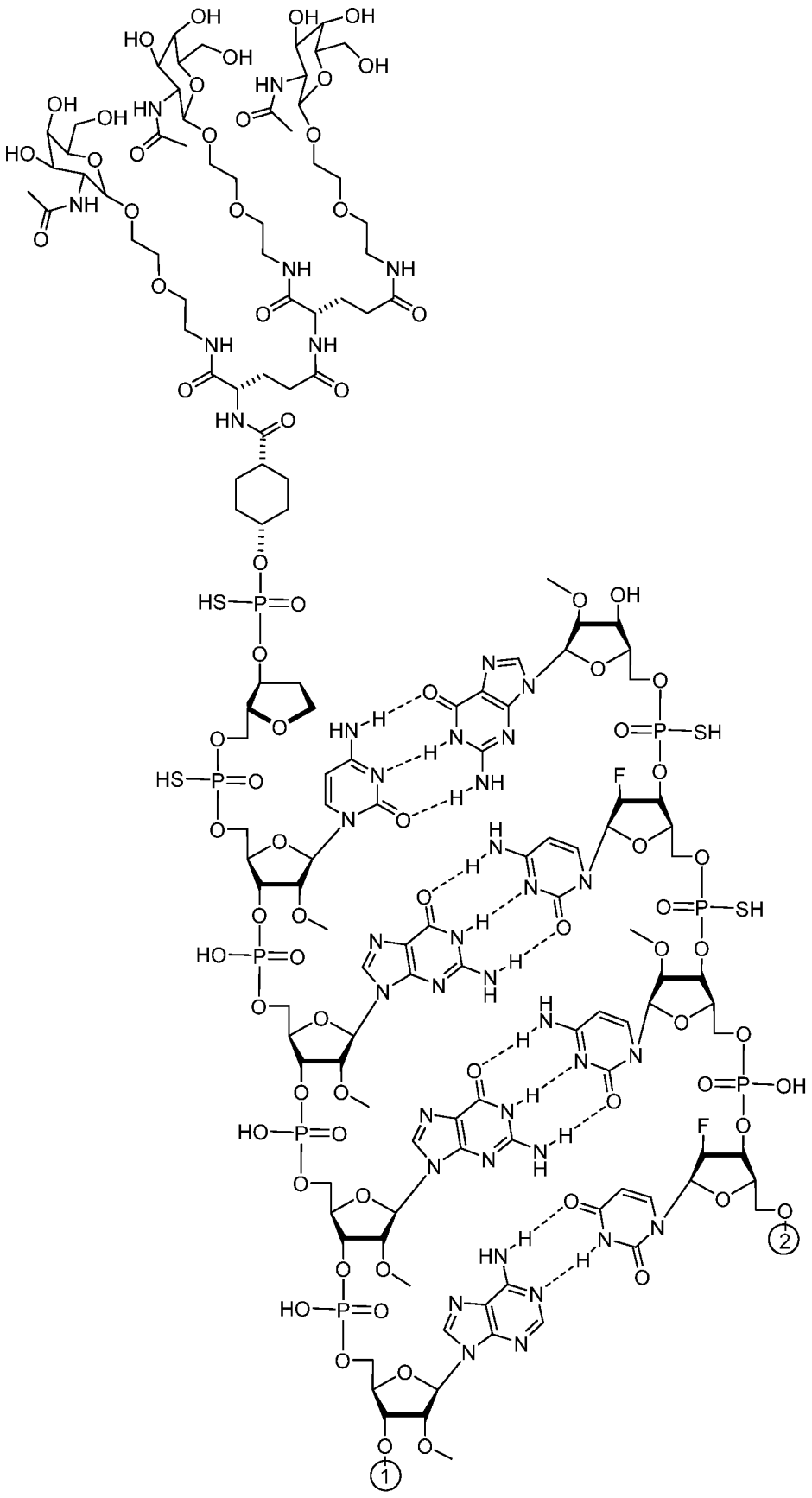


FIG. 3A

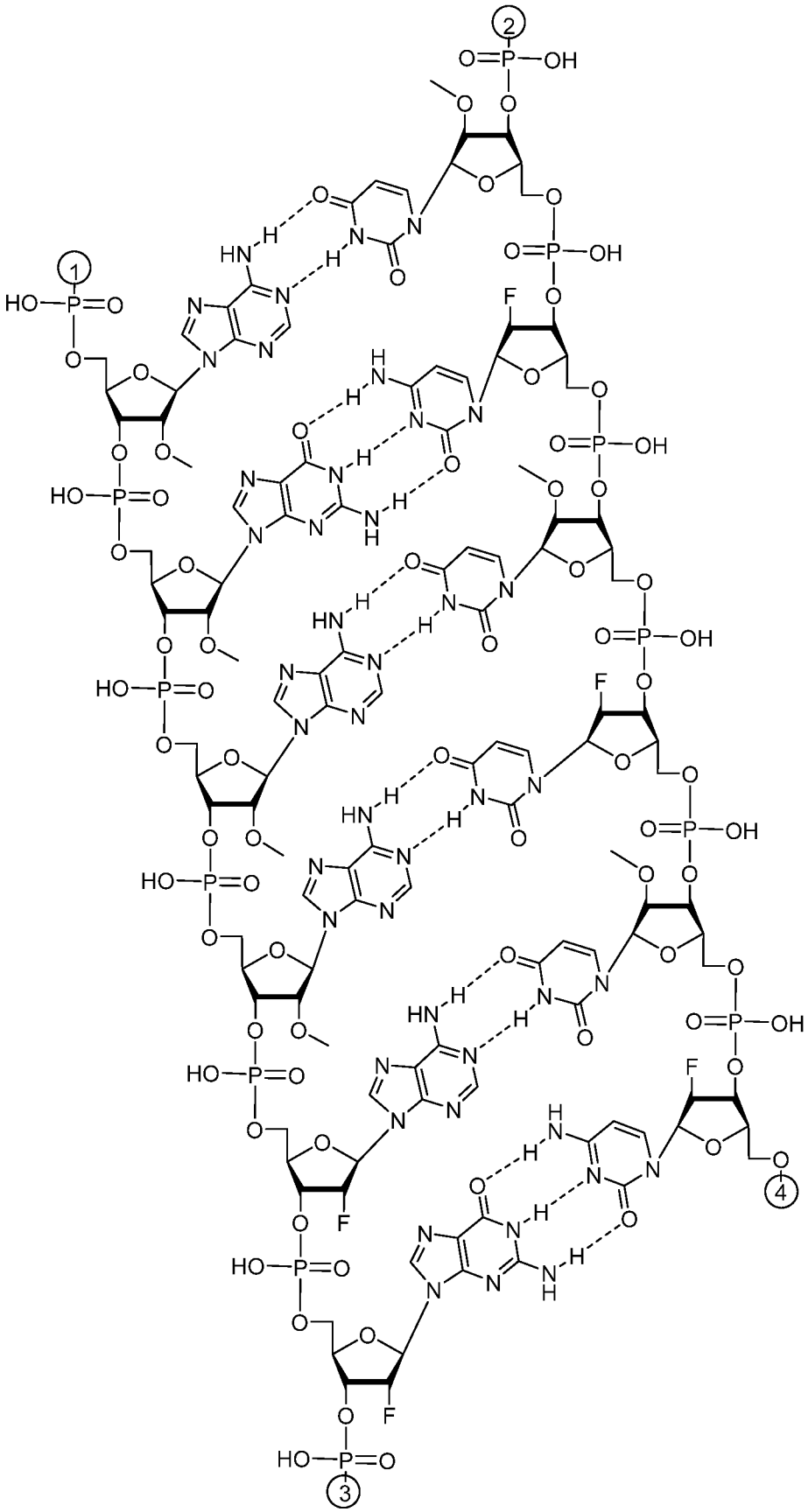


FIG. 3B

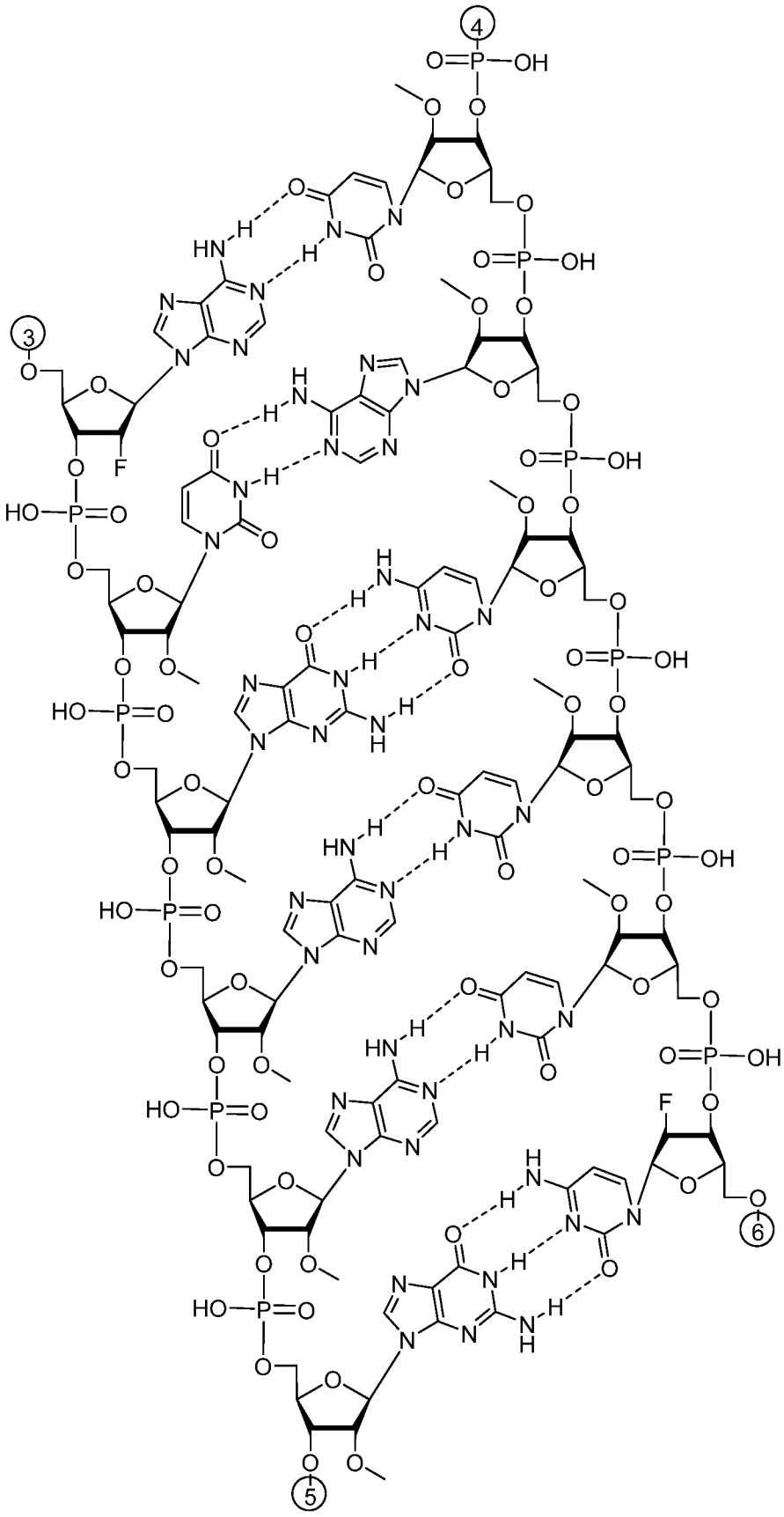


FIG. 3C

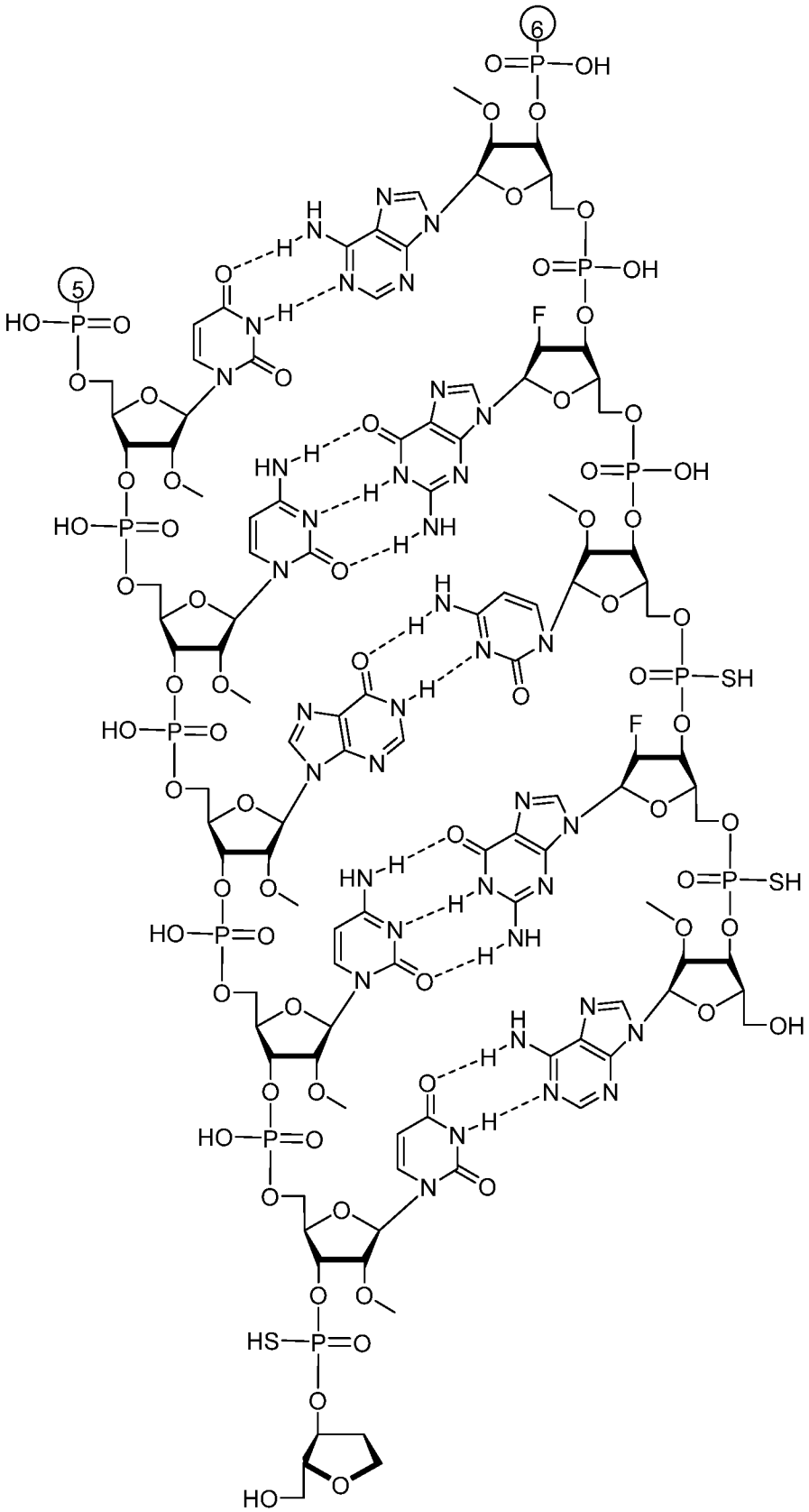


FIG. 3D

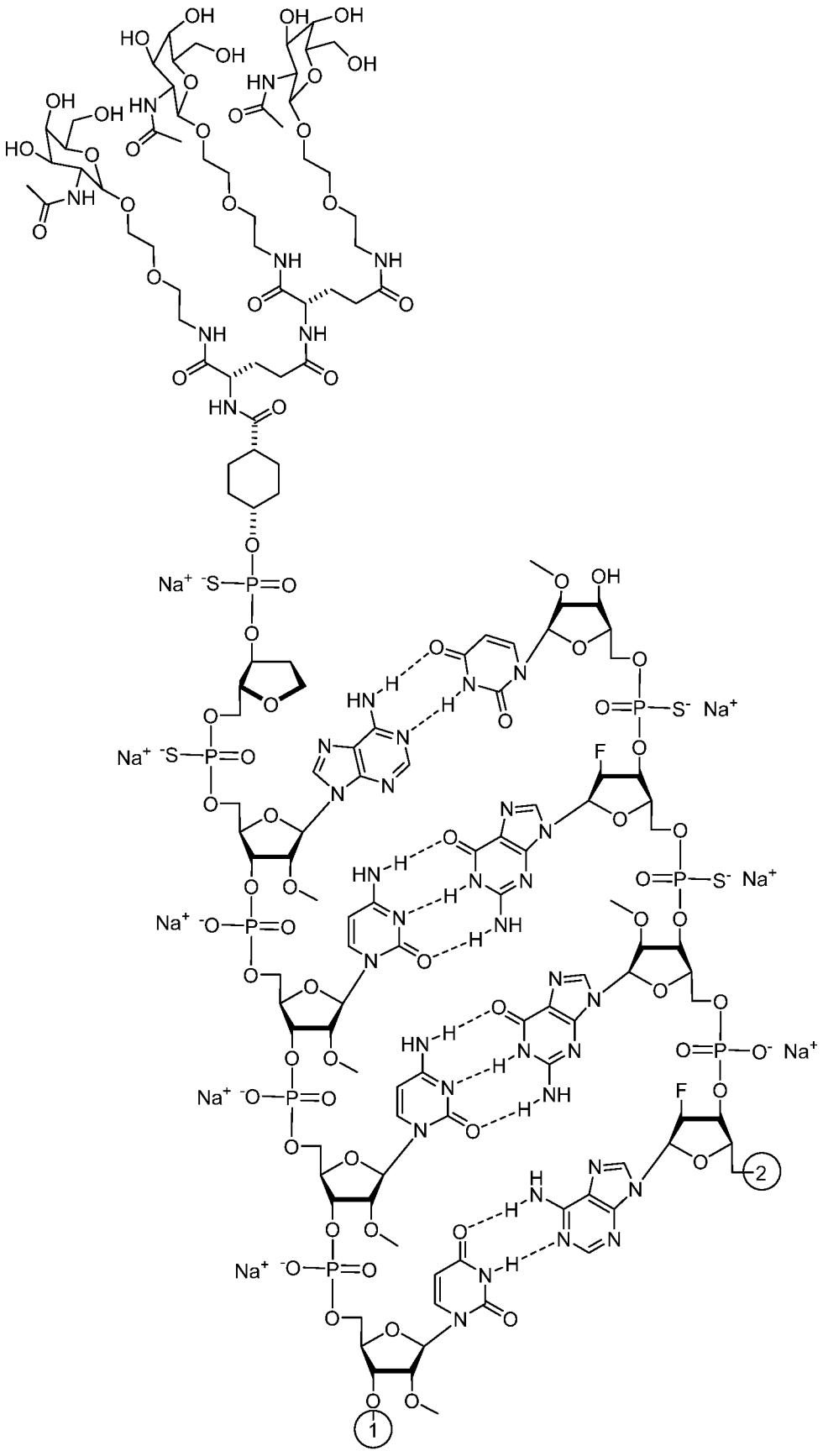


FIG. 4A

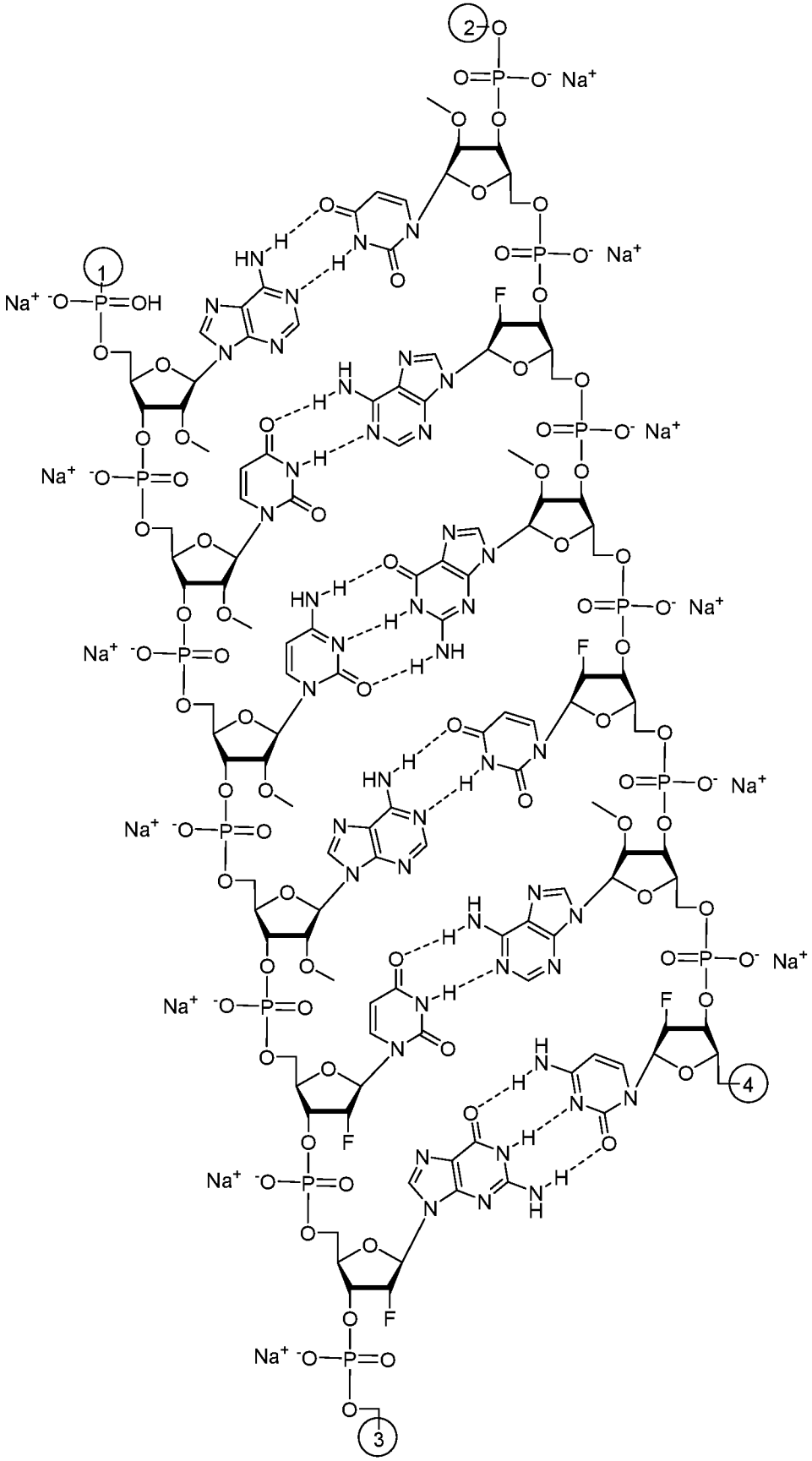


FIG. 4B

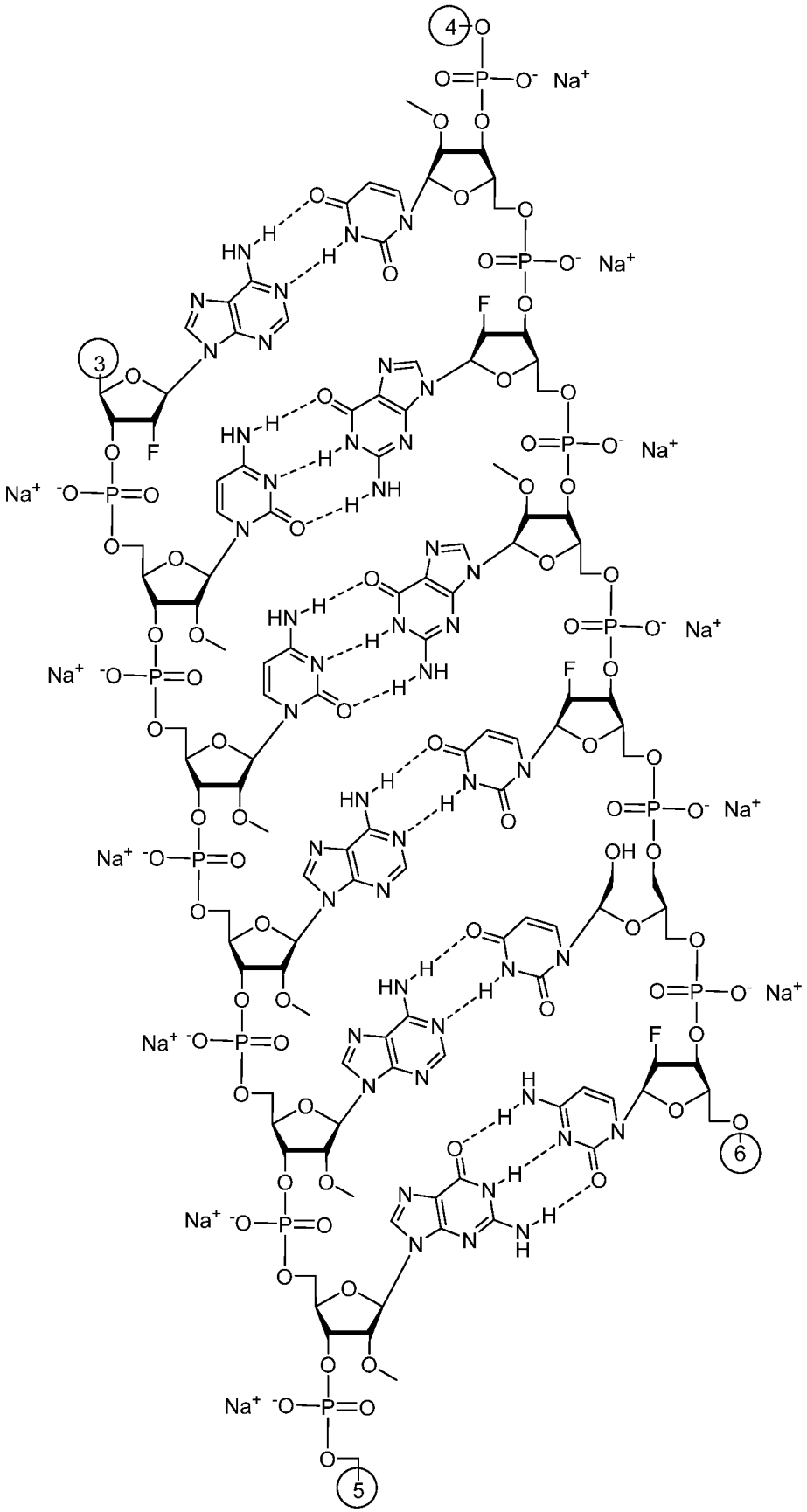


FIG. 4C

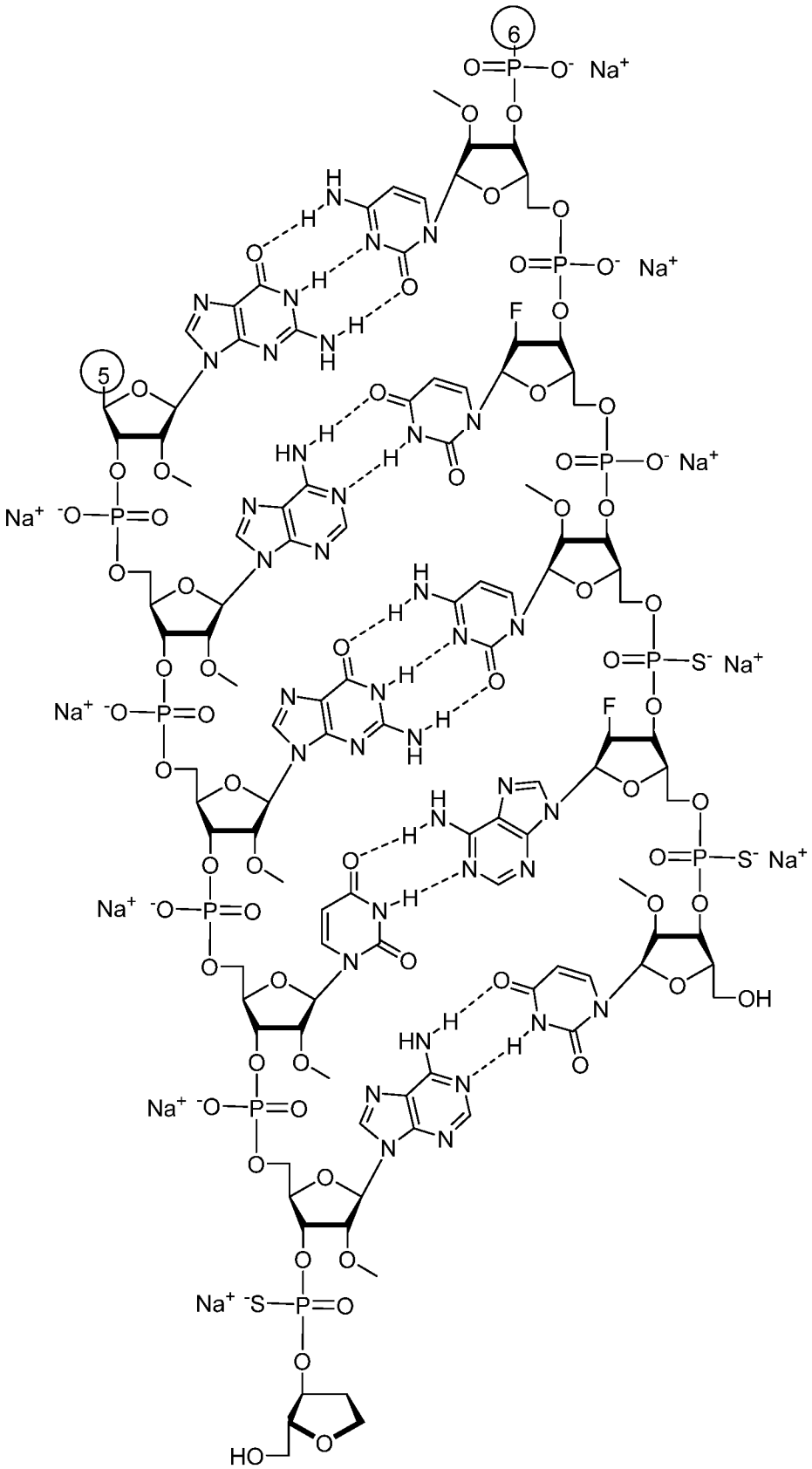


FIG. 4D

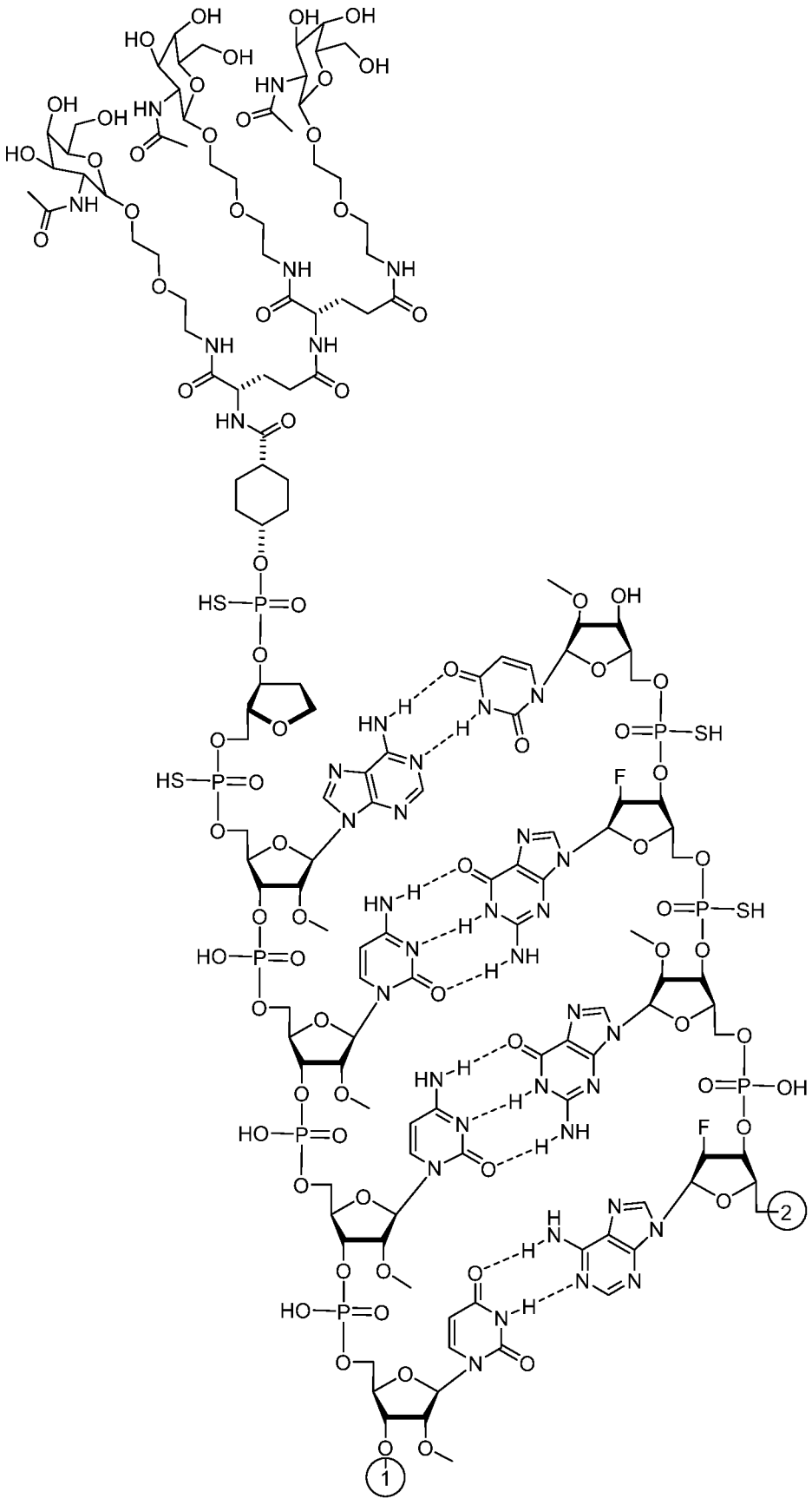


FIG. 5A

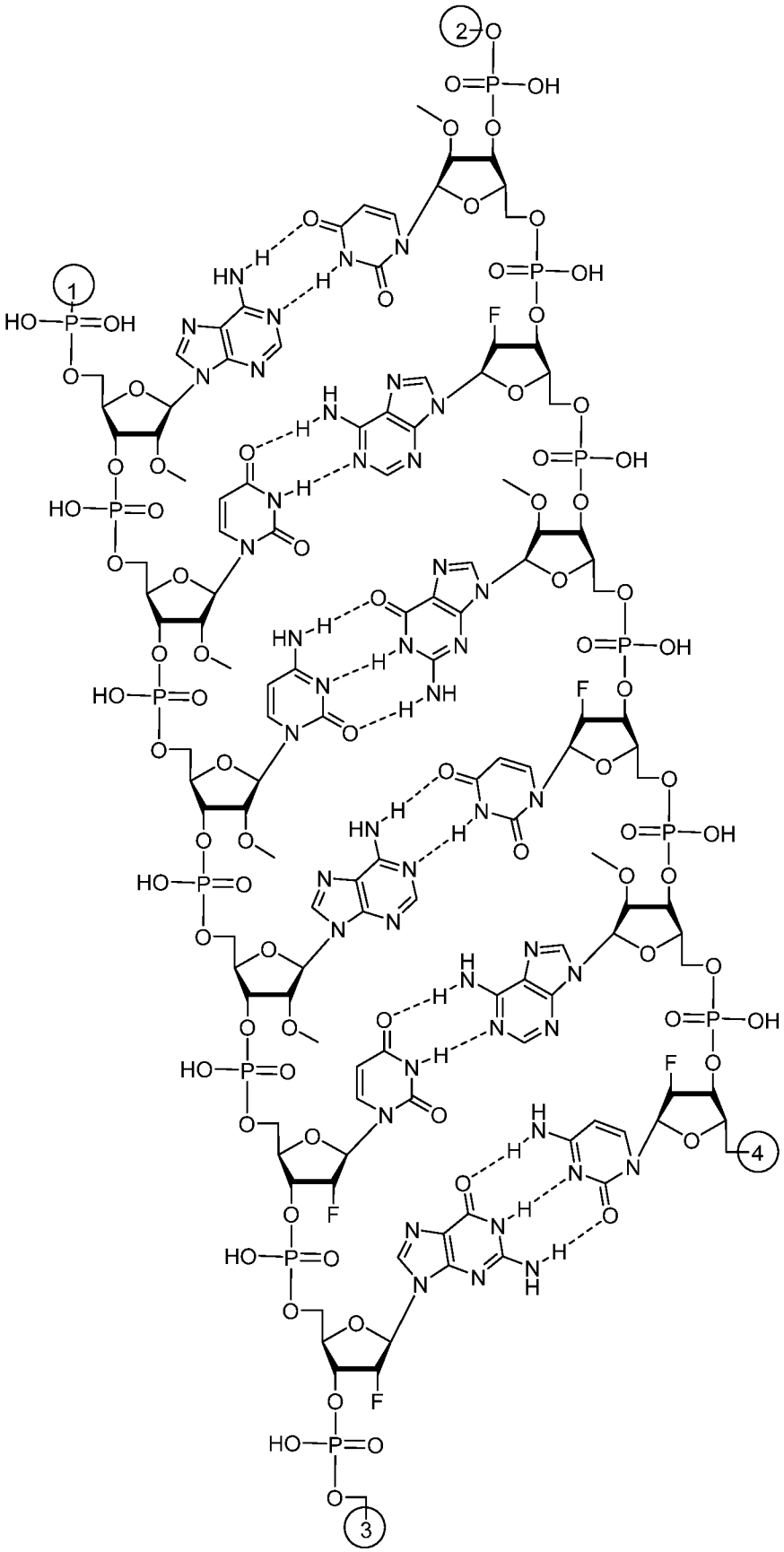


FIG. 5B

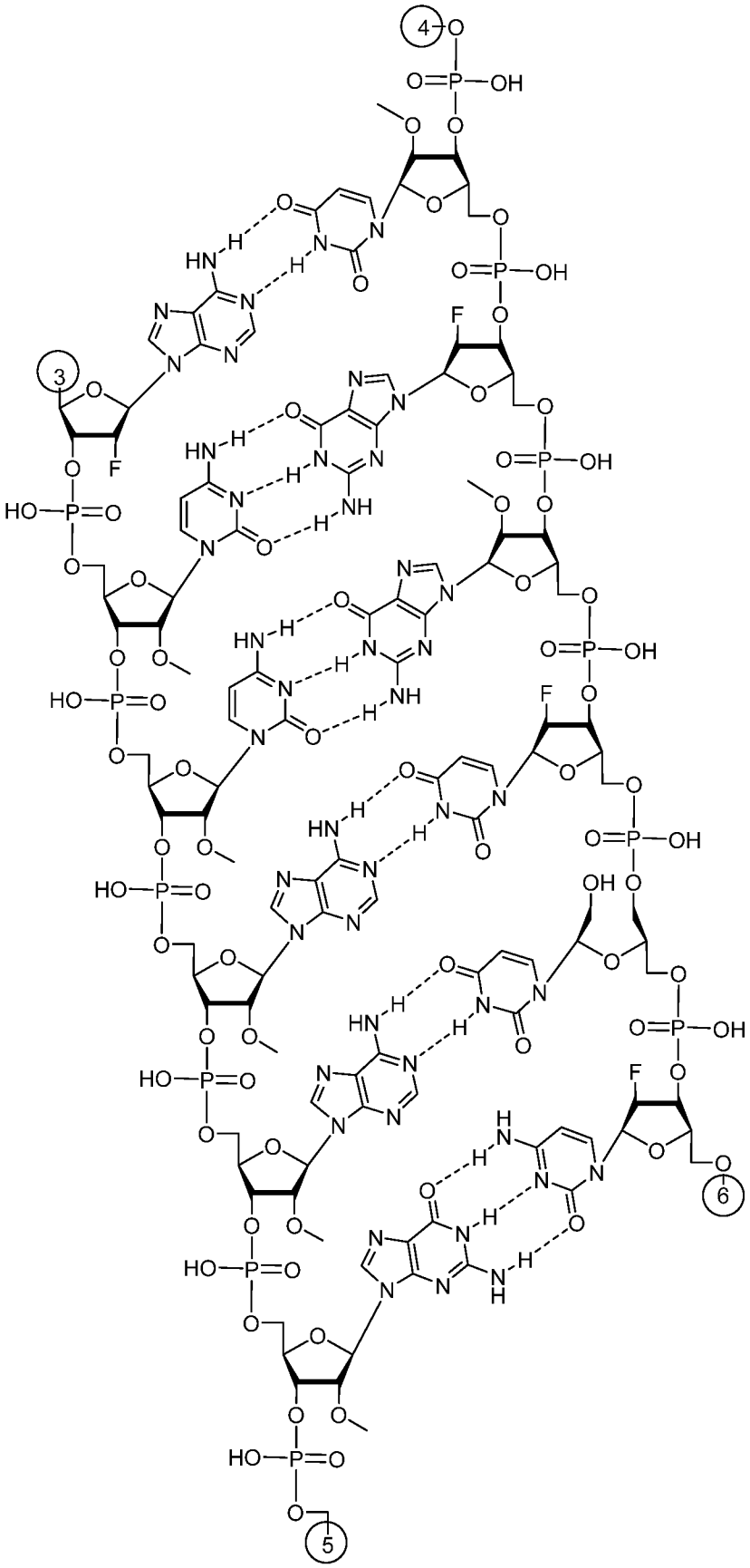


FIG. 5C

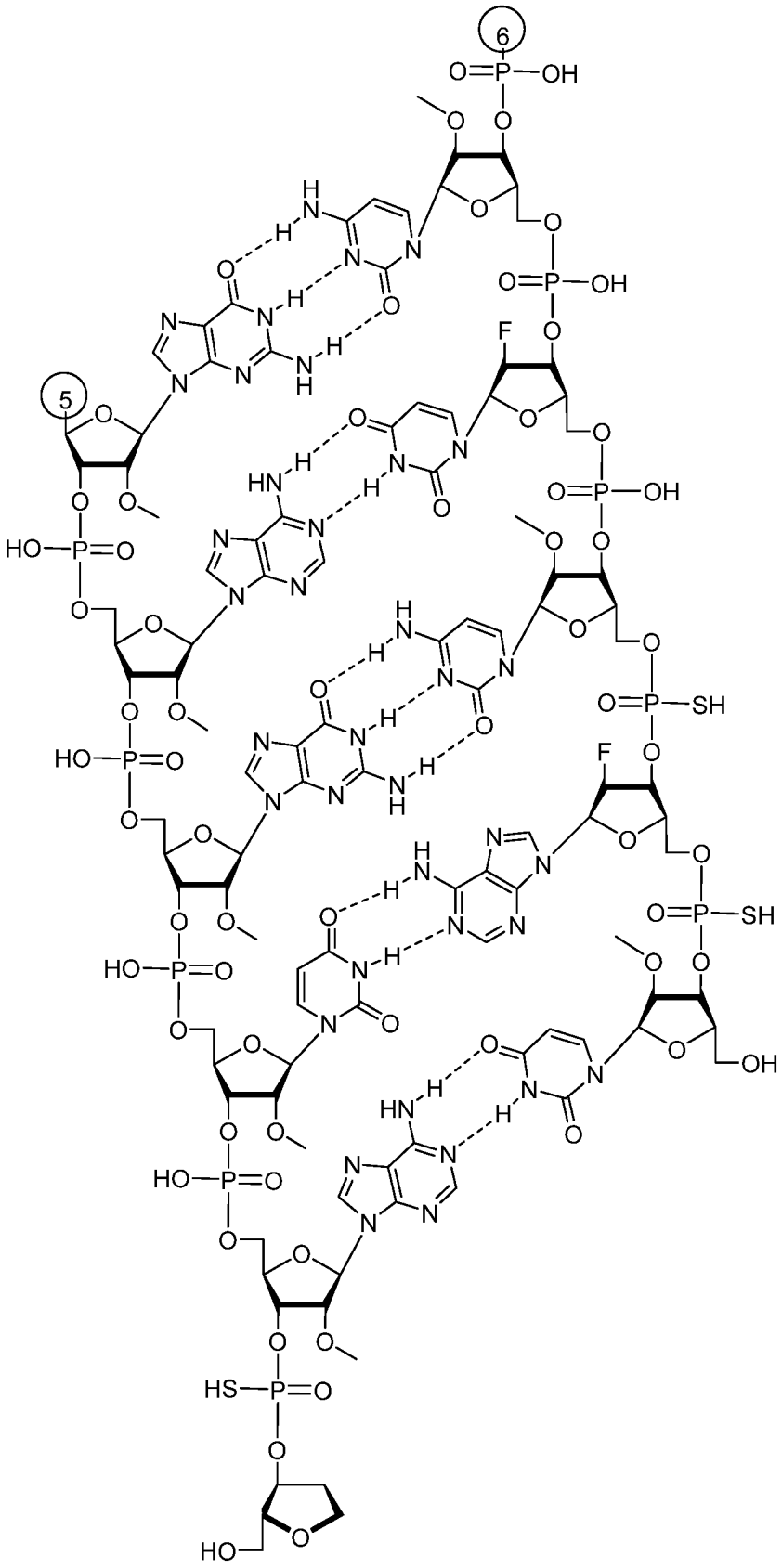


FIG. 5D