

RNAI CONSTRUCTS AND METHODS FOR INHIBITING FAM13A EXPRESSION

TECHNICAL FIELD

[0001] The present application relates to compositions and methods for modulating expression of Family with Sequence Similarity 13 Member A (FAM13A) protein. In particular, the present application relates to nucleic acid-based therapeutics for reducing *FAM13A* gene expression via RNA interference and methods of using such nucleic acid-based therapeutics.

BACKGROUND

[0002] Obesity, or excess adiposity, is recognized as a disease and is established as a major risk factor for cardiovascular disease (CVD). The most common measure of adiposity, body-mass-index (BMI), results in increased odds risk of myocardial infarction (MI). However, this association is substantially reduced after adjustment for waist-to-hip ratio (WHR), a measurement that reflects a visceral body fat distribution pattern (also known as central or abdominal obesity). WHR has been shown to be more robustly related to MI risk with individuals in the highest quintile for WHR having a 2.52-fold increase in odds ratio ($p < 0.001$), a finding that persists even after adjustment for BMI. Yusuf *et al.*, *Lancet* 366:1640-1649 (2005); Cao *et al.*, *Medicine (Baltimore)* 97, e11639 (2018); de Koning *et al.*, *Eur. Heart J.*, 28, 850-856 (2007). These data indicate that WHR is a better predictor of MI risk than BMI and that this metric overcomes some key limitations of BMI (e.g., high muscle mass).

[0003] FAM13A (also known as FAM13A1, KIAA0914, or ARHGAP48) is a cytosolic protein that has been shown to regulate AMP-activated protein kinase (AMPK) activity, and it has been linked to regulation of hepatic glucose, lipid metabolism, body fat distribution, and adipocyte function. Lin *et al.*, *iScience* 23, 100928 (2020); Fathzadeh *et al.*, *Nature Communications* 11, 1465 (2020). For example, human genetic evidence has linked FAM13A with HDL cholesterol, body mass index (BMI)-adjusted fasting insulin levels, and WHR adjusted for BMI. *In vitro*, *FAM13A* knockdown in human mesenchymal stem cells increases adipocyte differentiation and thermogenesis while overexpression causes apoptosis of pre-adipocytes and inhibits adipogenesis. Lundback *et al.*, *Diabetologia*, 2018; Tang *et al.*, *Int. J. Obesity*, 2019; Fathzadeh *et al.*, *Nat. Comm.*, 2020. Additionally, *FAM13A* KO mice are protected against diet-

induced obesity (DIO), have improved hepatic insulin sensitivity, and increased hepatocyte oxygen consumption rate. Lin *et al.*, *iScience*, 2020.

SUMMARY

[0004] The present application relates, in part, to the design and generation of RNAi constructs that target the *FAM13A* gene and reduce its expression. The sequence-specific inhibition of *FAM13A* gene expression is useful for reducing abdominal adiposity, reducing body weight, reducing fat mass, improving metabolic parameters including insulin resistance and non-alcoholic steatohepatitis (NASH), and reducing risk of myocardial infarction. Accordingly, in one embodiment, the present application provides an RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region comprising a sequence that is substantially complementary to a *FAM13A* mRNA sequence. In some embodiments, the RNAi construct is targeted only to the liver. In some embodiments, the antisense strand comprises a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of a region of the human *FAM13A* mRNA sequence (SEQ ID NO: 1) with no more than 1, 2, or 3 mismatches. In some embodiments, the antisense strand comprises a region comprising a sequence that is substantially complementary to at least 15 contiguous nucleotides within particular regions of the *FAM13A* mRNA sequence set forth in SEQ ID NO: 1, such as within nucleotides 1300-1375 or 4900-5300 of SEQ ID NO: 1. In certain embodiments, the antisense strand comprises a region comprising at least 15 contiguous nucleotides from an antisense sequence listed in **Table 1** or **Table 2**.

[0005] In some embodiments, the sense strand of the RNAi constructs described herein comprises a sequence that is sufficiently complementary to the sequence of the antisense strand to form a duplex region of about 15 to about 30 base pairs in length, about 17 to about 24 base pairs in length, or about 19 to about 21 base pairs in length. In some embodiments, the sense and antisense strands are each independently about 19 to about 30 nucleotides in length, or about 19 to about 23 nucleotides in length. In some embodiments, the RNAi constructs comprise one or two blunt ends. In other embodiments, the RNAi constructs comprise one or two nucleotide overhangs. Such nucleotide overhangs may comprise 1 to 6 unpaired nucleotides and can be located at the 3' end of the sense strand, the 3' end of the antisense strand, or the 3' end of both the sense and antisense strand. In certain embodiments, the RNAi constructs comprise an overhang of two unpaired nucleotides at the 3' end of the sense strand and the 3' end of the

antisense strand. In other embodiments, the RNAi constructs comprise an overhang of two unpaired nucleotides at the 3' end of the antisense strand and a blunt end at the 3' end of the sense strand/5' end of the antisense strand.

[0006] The disclosed RNAi constructs may comprise one or more modified nucleotides, including nucleotides having modifications to the ribose ring, nucleobase, or phosphodiester backbone. In some embodiments, the RNAi constructs comprise one or more 2'-modified nucleotides. Such 2'-modified nucleotides can include 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, 2'-O-methoxyethyl modified nucleotides, 2'-O-alkyl modified nucleotides, 2'-O-allyl modified nucleotides, bicyclic nucleic acids (BNA), deoxyribonucleotides, or combinations thereof. In one particular embodiment, the RNAi constructs comprise one or more 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, or combinations thereof. In some embodiments, all of the nucleotides in the sense and antisense strand of the RNAi construct are modified nucleotides. Abasic nucleotides may be incorporated into the disclosed RNAi constructs, for example, as the terminal nucleotide at the 3' end, the 5' end, or both the 3' end and the 5' end of the sense strand. In such embodiments, the abasic nucleotide may be inverted, *e.g.*, linked to the adjacent nucleotide through a 3'-3' internucleotide linkage or a 5'-5' internucleotide linkage.

[0007] In some embodiments, the RNAi constructs comprise at least one backbone modification, such as a modified internucleotide or internucleoside linkage. In certain embodiments, the RNAi constructs described herein comprise at least one phosphorothioate internucleotide linkage. In particular embodiments, the phosphorothioate internucleotide linkages may be positioned at the 3' or 5' ends of the sense and/or antisense strands. For instance, in some embodiments, the antisense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends. In some such embodiments, the sense strand comprises one or two phosphorothioate internucleotide linkages between the terminal nucleotides at its 3' end.

[0008] In some embodiments, the RNAi constructs of this application may target a particular region of the human *FAM13A* mRNA transcript set forth in SEQ ID NO: 1. In some embodiments, the sequence of the antisense strand may be fully complementary to the sequence of at least 15 contiguous nucleotides of the specific regions of the human *FAM13A* transcript (SEQ ID NO: 1). In some embodiments, the sequence of the antisense strand may be substantially complementary to the sequence of at least 15 contiguous nucleotides of the specific

regions of the human *FAM13A* transcript (SEQ ID NO: 1) with no more than 1, 2, or 3 mismatches between the sequence of the antisense strand and the sequence of the specific regions of the human *FAM13A* transcript. In certain embodiments, the antisense strand and/or the sense strand of the RNAi constructs may comprise or consist of a sequence from the antisense and sense sequences listed in **Table 1**. In some embodiments, the sense and antisense strands, respectively, comprise or consist of SEQ ID NOs: 15 and 559, SEQ ID NOs: 24 and 568, SEQ ID NOs: 125 and 669, SEQ ID NOs: 127 and 671, SEQ ID NOs: 222 and 766, SEQ ID NOs: 406 and 950, SEQ ID NOs: 448 and 992, SEQ ID NOs: 498 and 1042, SEQ ID NOs: 502 and 1046, SEQ ID NOs: 503 and 1047, SEQ ID NOs: 504 and 1048, SEQ ID NOs: 513 and 1057, SEQ ID NOs: 526 and 1070, SEQ ID NOs: 527 and 1071, SEQ ID NOs: 533 and 1077, or SEQ ID NOs: 534 and 1078.

[0009] In some embodiments, the RNAi construct comprises particular sequences with particular modification patterns, which are referred to as duplexes herein. In certain embodiments, the antisense strand and/or the sense strand of the RNAi constructs, with particular modification patterns, may comprise or consist of antisense and sense sequences listed in **Table 2** as particular duplexes. In some embodiments, the RNAi construct is a duplex called D-1557, D-1597, D-1612, D-1614, D-1623, D-1650, D-1667, D-1680, D-1682, D-1685, D-1686, D-1690, D-1697, D-1698, D-1699, D-1702, D-1704, D-1705, D-1709, D-1768, D-1846, D-1849, D-1853, D-1856, D-1858, D-1861, D-1862, D-1863, D-1864, D-1865, D-1866, D-1868, D-1869, D-1870, D-1871, D-1873, D-1875, D-1876, D-1877, D-1878, D-1879, D-1880, D-1881, D-1883, D-1884, D-1885, D-1886, D-1887, D-1888, D-1899, D-1896, D-1955, D-1970, D-1972, D-1975, D-1976, D-1977, D-1979, D-1980, D-1981, D-1982, D-1983, D-1984, D-1985, D-1987, D-1988, D-1989, D-1990, D-1991, D-1992, D-1993, D-1994, D-1995, D-1996, D-1997, D-1998, D-2000, D-2001, D-2002, D-2003, D-2004, D-2005, D-2012, D-2013, D-2014, D-2017, D-2021, D-2022, D-2023, D-2040, D-2044, D-2045, D-2047, D-2049, D-2051, D-2052, D-2053, D-2054, D-2058, D-2061, D-2075, D-2077, D-2079, D-2080, D-2081, D-2083, D-2090, D-2091, or D-2093. In some embodiments, the RNAi construct is a duplex observed to knock down FAM13A expression by greater than 80%.

[0010] The disclosed RNAi constructs may comprise a ligand to facilitate delivery or uptake of the RNAi constructs to specific tissues or cells, such as liver or adipose cells. In certain embodiments, the ligand targets delivery of the RNAi constructs to hepatocytes. In these and other embodiments, the ligand may comprise galactose, galactosamine, or N-acetyl-

galactosamine (GalNAc). In certain embodiments, the ligand comprises a multivalent galactose or multivalent GalNAc moiety, such as a trivalent or tetravalent galactose or GalNAc moiety. The ligand may be covalently attached to the 5' or 3' end of the sense strand of the RNAi construct, optionally through a linker. In some embodiments, the RNAi constructs comprise a ligand and linker comprising a structure according to any one of Formulas I to IX described herein. In certain embodiments, the RNAi constructs comprise a ligand and linker comprising a structure according to Formula VII. In other embodiments, the RNAi constructs comprise a ligand and linker comprising a structure according to Formula IV. In some embodiments, the ligand comprises a long-chain fatty acid such as lauric acid (C12), myristic acid (C14), palmitic acid (C16), stearic acid (C18), eicosapentaenoic acid (C20), or docosanoic acid (C22). In some embodiments, the ligand is attached through a phosphodiester or phosphorothioate linkage.

[0011] The present application also provides pharmaceutical compositions comprising any of the RNAi constructs described herein and a pharmaceutically acceptable carrier, excipient, or diluent. Such pharmaceutical compositions are particularly useful for reducing expression of the *FAM13A* gene in the cells (*e.g.*, liver or adipose cells) of a patient in need thereof. Patients who may be administered a disclosed pharmaceutical composition include patients diagnosed with or at risk of obesity, including patients displaying a high WHR and patients diagnosed with abdominal obesity. Patients who may be administered a disclosed pharmaceutical composition also can include patients diagnosed with or at risk of metabolic conditions such as fatty liver disease (*e.g.*, NAFLD, NASH, alcoholic fatty liver disease, or alcoholic steatohepatitis), insulin resistance and type 2 diabetes (T2D), hypertriglyceridemia, or hypercholesterolemia. The present application also provides methods of treating patients in need of reduction of expression of the *FAM13A* gene expression in their cells, including patients diagnosed with or at risk of obesity, abdominal obesity, fatty liver disease (*e.g.*, NAFLD, NASH, alcoholic fatty liver disease, or alcoholic steatohepatitis), insulin resistance and type 2 diabetes (T2D), hypertriglyceridemia, or hypercholesterolemia. These methods comprise administering an RNAi construct or pharmaceutical composition described herein. In some embodiments, the RNAi construct is administered with a ligand that targets the RNAi construct to the liver or hepatocytes.

[0012] The use of *FAM13A*-targeting RNAi constructs in any of the methods described herein or for preparation of medicaments for administration according to the methods described herein is specifically contemplated. For instance, the present application includes a *FAM13A*-targeting RNAi construct for use in treating, preventing, or reducing the risk of developing

obesity, abdominal obesity, fatty liver disease (*e.g.*, NAFLD, NASH, alcoholic fatty liver disease, or alcoholic steatohepatitis), insulin resistance and type 2 diabetes (T2D), hypertriglyceridemia, or hypercholesterolemia in a patient in need thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0013] **Figure 1** shows the results of a genomic analysis performed to examine the association of three common *FAM13A* variants for their association with adjusted for BMI (WHRadjBMI), triglyceride levels, HDL cholesterol levels, systolic blood pressure, and *FAM13A* expression in subcutaneous adipose tissue eQTL data.

[0014] **Figures 2A and 2B** show the results of an *in vitro* dose-response study of *Fam13a* siRNA's effects in Renca cells and primary adipocytes.

[0015] **Figures 3A-3D** show the results of an *in vivo* study of *Fam13a* siRNA's ability to knock down murine *Fam13a* mRNA expression levels in the liver and white adipose tissue of mice.

[0016] **Figures 4A-4C** show the results of an *in vivo* study of *Fam13a* siRNA's effects on body weight and fat mass of mice.

[0017] **Figure 5** is a table showing the effects of C16- and GalNAc-linked *Fam13a* siRNA in obese mice after 60 days of treatment. *Fam13a* siRNAs had significant effects on body weight, fat mass, cumulative food intake, liver weight, insulin levels, total cholesterol, LDL cholesterol, and ALT levels.

[0018] **Figure 6** is a diagram compiling the locations which of a range of human *FAM13A* siRNA triggers target on the human *FAM13A* mRNA transcript. The depicted triggers were all efficacious in reducing *FAM13A* mRNA levels and are divided in this diagram according to whether the maximum observed knockdown for that trigger fell within the range of 40-60% knockdown, 60-80% knockdown, or greater than 80% knockdown.

[0019] **Figures 7A-7R** are depictions of different modification patterns that may be applied to siRNA trigger sequences, with each figure showing a hybridized sense (top) and antisense (bottom) strand. In these figures, the solid circles correspond to 2'-O-methyl ribonucleotides, the open circles correspond to 2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotides, and the hatched circles correspond to inverted abasic deoxynucleotides. Bold lines indicate where a phosphorothioate bond is used in place of the standard phosphodiester bond between

nucleotides. Finally, arrows represent where a ligand (e.g., GalNAc or a fatty acid) may be attached to a polynucleotide.

[0020] **Figures 8A-8D** show the results of testing *FAM13A* siRNA in an AAV human *FAM13A* mouse model. Figures 8A and 8B show that a range of different members of the T-4999 and T-5043 trigger families, respectively, reduced expression of *FAM13A* mRNA in the liver. Figures 8C and 8D show that C22-conjugated members of the T-4999 and T-5043 trigger families, and to a lesser extent GalNAc-conjugated members of the T-4999 and T-5043 trigger families, were able to reduce expression of *FAM13A* mRNA in adipose tissue. In each of Figures 8A-8D, the "*" denotes those duplexes that were conjugated to C22, while those without an asterisk were conjugated to GalNAc.

[0021] **Figures 9A-9C** show the results of testing human-mouse cross reactive *FAM13A* siRNA duplexes, with knockdown noted in liver, inguinal white adipose tissue, and epididymal white adipose tissue.

[0022] **Figures 10A and 10B** show that treating diet-induced obese (DIO) mice with human-mouse cross reactive *FAM13A* siRNA duplexes prevented the increases in body weight and fat mass associated with the DIO model.

[0023] **Figures 11A-11E** show the results of treating cynomolgus monkeys with a single dose of human-cynomolgus monkey cross reactive *FAM13A* siRNA. Figures 11A and 11B show that knockdown was achieved in both liver and adipose tissue. Figures 11C-11E show that *FAM13A* siRNA treatment resulted in decreases in serum cholesterol, LDL, and HDL, respectively.

DETAILED DESCRIPTION

[0024] The present application is directed to compositions and methods for regulating the expression of the *FAM13A* gene in a cell or mammal. In some embodiments, compositions comprise RNAi constructs that target a mRNA transcribed from the *FAM13A* gene, particularly the human *FAM13A* gene, and reduce expression of the *FAM13A* protein in a cell or mammal. Such RNAi constructs are useful for for treating, preventing, or reducing the risk of developing obesity, hepatosteatois, insulin resistance and type 2 diabetes (T2D), hypertriglyceridemia, or hypercholesterolemia in a patient in need thereof.

RNAi Constructs

[0025] As used herein, the term “RNAi construct” refers to an agent comprising an RNA molecule that is capable of downregulating expression of a target gene (*e.g.*, the *FAM13A* gene) via an RNA interference mechanism when introduced into a cell. RNA interference is the process by which a nucleic acid molecule induces the cleavage and degradation of a target RNA molecule (*e.g.*, messenger RNA or mRNA molecule) in a sequence-specific manner, *e.g.*, through an RNA-induced silencing complex (RISC) pathway. In some embodiments, the RNAi construct comprises a double-stranded RNA molecule comprising two antiparallel strands of contiguous nucleotides that are sufficiently complementary to each other to hybridize to form a duplex region. “Hybridize” or “hybridization” refers to the pairing of complementary polynucleotides, typically via hydrogen bonding (*e.g.*, Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding) between complementary bases in the two polynucleotides. The strand comprising a region comprising a sequence that is substantially complementary to a target sequence (*e.g.*, target mRNA) is referred to as the “antisense strand” or “guide strand.” The “sense strand” or “passenger strand” refers to the strand that includes a region that is substantially complementary to a region of the antisense strand. In some embodiments, the sense strand may comprise a region that has a sequence that is substantially identical to the target sequence.

[0026] A double-stranded RNA molecule may include chemical modifications to ribonucleotides, including modifications to the ribose sugar, base, or backbone components of the ribonucleotides, such as those described herein or known in the art. Any such modifications, as used in a double-stranded RNA molecule (*e.g.*, siRNA, shRNA, or the like), are encompassed by the term “double-stranded RNA” for the purposes of this disclosure. Details on potential modifications to the RNAi constructs described herein are provided in the Modification and Preparation of RNAi Constructs section below.

[0027] As used herein, a first sequence is “complementary” to a second sequence if a polynucleotide comprising the first sequence can hybridize to a polynucleotide comprising the second sequence to form a duplex region under certain conditions, such as physiological conditions. Other such conditions can include moderate or stringent hybridization conditions, which are known to those of skill in the art. A first sequence is fully complementary (100% complementary) to a second sequence if a polynucleotide comprising the first sequence base pairs with a polynucleotide comprising the second sequence over the entire length of one or both

nucleotide sequences without any mismatches. A sequence is “substantially complementary” to a target sequence, or has “substantial identity to” a target sequence, if the sequence is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% complementary to a target sequence. Percent complementarity can be calculated by dividing the number of bases in a first sequence that are complementary to bases at corresponding positions in a second or target sequence by the total length of the first sequence. A sequence may also be said to be substantially complementary to another sequence if there are no more than 5, 4, 3, or 2 mismatches over a 30 base pair duplex region when the two sequences are hybridized. Generally, if any nucleotide overhangs, as defined herein, are present, the sequence of such overhangs is not considered in determining the degree of complementarity between two sequences. By way of example, a sense strand of 21 nucleotides in length and an antisense strand of 21 nucleotides in length that hybridize to form a 19 base pair duplex region with a 2- nucleotide overhang at the 3’ end of each strand would be fully complementary as the term is used herein.

[0028] In some embodiments, a region of the antisense strand comprises a sequence that is substantially or fully complementary to a region of the target RNA sequence (*e.g.*, the *FAM13A* mRNA sequence). In such embodiments, the sense strand may comprise a sequence that is fully complementary to the sequence of the antisense strand. In other such embodiments, the sense strand may comprise a sequence that is substantially complementary to the sequence of the antisense strand, *e.g.*, having 1, 2, 3, 4, or 5 mismatches in the duplex region formed by the sense and antisense strands. In certain embodiments, it is preferred that any mismatches occur within the terminal regions (*e.g.*, within 6, 5, 4, 3, or 2 nucleotides of the 5’ and/or 3’ ends of the strands). In one embodiment, any mismatches in the duplex region formed from the sense and antisense strands occur within 6, 5, 4, 3, or 2 nucleotides of the 5’ end of the antisense strand.

[0029] In certain embodiments, the sense strand and antisense strand of the double-stranded RNA may be two separate molecules that hybridize to form a duplex region but are otherwise unconnected. Such double-stranded RNA molecules formed from two separate strands are referred to as “small interfering RNAs” or “short interfering RNAs” (siRNAs). Thus, in some embodiments, the RNAi constructs comprise an siRNA.

[0030] In other embodiments, the sense strand and the antisense strand that hybridize to form a duplex region may be part of a single RNA molecule, *i.e.*, the sense and antisense strands are part of a self-complementary region of a single RNA molecule. In such cases, a single RNA molecule comprises a duplex region (also referred to as a stem region) and a loop region. The 3’

end of the sense strand is connected to the 5' end of the antisense strand by a contiguous sequence of unpaired nucleotides, which will form the loop region. The loop region is typically of a sufficient length to allow the RNA molecule to fold back on itself such that the antisense strand can base pair with the sense strand to form the duplex or stem region. The loop region can comprise from about 3 to about 25, from about 5 to about 15, or from about 8 to about 12 unpaired nucleotides. Such RNA molecules with at least partially self-complementary regions are referred to as "short hairpin RNAs" (shRNAs). In certain embodiments, the RNAi constructs comprise a shRNA. The length of a single, at least partially self-complementary RNA molecule can be from about 40 nucleotides to about 100 nucleotides, from about 45 nucleotides to about 85 nucleotides, or from about 50 nucleotides to about 60 nucleotides and comprise a duplex region and loop region each having the lengths recited herein.

[0031] In some embodiments, the RNAi constructs comprise a sense strand and an antisense strand, wherein the antisense strand comprises a region having a sequence that is substantially or fully complementary to a *FAM13A* messenger RNA (mRNA) sequence. As used herein, a "*FAM13A* mRNA sequence" refers to any messenger RNA sequence, including allelic variants and splice variants, encoding a FAM13A protein, including FAM13A protein variants or isoforms from any species (*e.g.*, non-human primate, human).

[0032] A *FAM13A* mRNA sequence also includes the transcript sequence expressed as its complementary DNA (cDNA) sequence. A cDNA sequence refers to the sequence of an mRNA transcript expressed as DNA bases (*e.g.*, guanine, adenine, thymine, and cytosine) rather than RNA bases (*e.g.*, guanine, adenine, uracil, and cytosine). Thus, the antisense strand of the RNAi constructs may comprise a region having a sequence that is substantially or fully complementary to a target *FAM13A* mRNA sequence or *FAM13A* cDNA sequence. A *FAM13A* mRNA or cDNA sequence can include, but is not limited to, any *FAM13A* mRNA or cDNA sequences in the Ensembl Genome or National Center for Biotechnology Information (NCBI) databases, including human sequences such as Ensembl transcript no. ENST00000264344.9 (SEQ ID NO: 1) and NCBI Reference sequence NM_022746.4. A *FAM13A* mRNA or cDNA sequence can also include cynomolgus monkey sequences, rhesus monkey sequences, chimpanzee sequences, rat sequences, and mouse sequences. In certain embodiments, the *FAM13A* mRNA sequence is the human transcript set forth below (SEQ ID NO: 1).

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CCTTCCAGCCATGTGGGTTTCAGCGGAAAGAGAAGCAAACCACTCTTCCTAAAATGTTAGAA  
GCTGCTCTTCGCTTACCTTGGGGCCTTTGCATTGGGAGCTGTTTTTCACATCAAAGAATATG
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TGCTGAATGGAATTTTAGTATTTTGCTGTCGTTTTAATATTTTCGTCTGGTCTTCCTCAGTT
CTTCCAGACGCTTTCTGAGAGAATGGGGGCAGGAGCTCTAGCCATCTGTCAAAGTAAAGCAG
CGGTTTCGGCTGAAAGAAGACATGAAAAAGATAGTGGCAGTGCCATTAAATGAACAGAAGGAT
TTTACCTATCAGAAGTTATTTGGAGTCAGTCTCCAAGAACTTGAACGGCAGGGGCTCACCGA
GAATGGCATTCCAGCAGTAGTGTGGAATATAGTGAATATTTGACGCAGCATGGACTTACCC
AAGAAGGTCTTTTTAGGGTGAATGGTAACGTGAAGGTGGTGAACAACCTTCGACTGAAGTTC
GAGAGTGGAGTGCCCGTGGAGCTCGGGAAGGACGGTGATGTCTGCTCAGCAGCCAGTCTGTT
GAAGCTGTTTCTGAGGGAGCTGCCTGACAGTCTGATCACCTCAGCGTTGCAGCCTCGATTCA
TTCAACTCTTTTCAGGATGGCAGAAATGATGTTTCAGGAGAGTAGCTTAAGAGACTTAATAAAA
GAGCTGCCAGACACCCACTACTGCCTCCTCAAGTACCTTTGCCAGTTCTTGACAAAAGTAGC
CAAGCATCATGTGCAGAATCGCATGAATGTTTACAATCTCGCCACTGTATTTGGGCCAAAT
GCTTTCATGTGCCACCTGGGCTTGAAGGCATGAAGGAACAGGACCTGTGCAACAAGATAATG
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CCAAAATCCAGGAGTGAGGGATCTATTGAGGCCACAGAGTACTGCAACCAGAGCTATCTGA
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CAGCAGAGGGTGCTATTAGTGCCAAGTTGGTACCCAGTTCACAGGAAGATGAAAGACCTCTG
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CTTAGAAAAGAACCATCCGATCAGCTGTAGAACAACATCTTTTTGATGTTAATAACTCTGGAG
GTCAAAGTTCAGAGGACTCAGAATCTGGAACACTATCAGCATCTTCTGCCACATCTGCCAGA
CAGCGCCGCCCGCAGTCCAAGGAGCAGGATGAAGTTCGACATGGGAGAGACAAGGGACTTAT
CAACAAAAGAAAATACTCCTTCTGGGTTCAACCACCTTGATGATTGTATTTTGAATCTCAGG
AAGTCGAAAAGGTACACAAAATACTTTTGGTTGTGCTGGAGAAAAGGAGCAAGCCTAAACGT
CAGAAATCCAGTACTAACTTTCTGAGCTTCATGACAATCAGGACGGTCTTGTGAATATGGA
AAGTCTCAATTCCACACGATCTCATGAGAGAACTGGACCTGATGATTTTGAATGGATGTCTG
ATGAAAGGAAAGGAAATGAAAAAGATGGTGGACACACTCAGCATTTTGAGAGCCCCACAATG
AAGATCCAGGAGCATCCCAGCCTATCTGACACCAAACAGCAGAGAAATCAAGATGCCGGTGA
CCAGGAGGAGAGCTTTGTCTCCGAAGTGCCCCAGTCGGACCTGACTGCATTGTGTGATGAAA
AGAAGTGGGAAGAGCCTATCCCTGCTTTCTCCTCCTGGCAGCGGGAGAACAGTGACTCTGAT
GAAGCCCACCTCTCGCCGAGGCTGGGCGCCTGATCCGTGAGCTGCTGGACGAAGACAGCGA
CCCCATGCTCTCTCCTCGGTTCTACGCTTATGGGCAGAGCAGGCAATACCTGGATGACACAG
AAGTGCTCCTTCCCCACCAAACCTCCATTCTTTTATGAGGCGGCGAAGCTCCTCTCTGGGG
TCCTATGATGATGAGCAAGAGGACCTGACACCTGCCAGCTCACACGAAGGATTCAGAGCCT
TAAAAAGAAGATCCGGAAGTTTGAAGATAGATTGGAAGAAGAGAAAGTACAGACCTTCCC
ACAGTGACAAAAGCAGCCAATCCGGAGGTTCTGAAATGGACAAAATGACCTTGCCAAATTCGGG
AGACAACCTAAAGAATCAAACTAAAGATATCTGAAGAGGACCTAACTCCCAGGATGCGGCA
GCGAAGCAACACACTCCCCAAGAGTTTTGGTTCCCAACTTGAGAAAAGAAGATGAGAAGAAGC
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AAGCTCCAGGAGAAGCGAGCGGAAAGCAGCCGCCCTGAGGACATTAAGGATATGACCAAAGA
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GACGGCCGGTAACAAAGAACGAACGGCAGGTGATGAAGCCACTATACGACAGGTACCGGCTG
GTCAAACAGATCCTCTCCCGAGCTAACACCATAACCATCATTTGGTTCCCCCTCCAGCAAGCG
GAGAAGCCCTTTGCTGCAGCCAATTATCGAGGGCGAACTGCTTCCTTCTTCAAGGAGATAA
AGGAAGAAGAGGAGGGGTGAGAAGACGATAGCAATGTGAAGCCAGACTTCATGGTCACTCTG
AAAACCGATTTTCAGTGACGATGCTTTCTGGACCAATTCGAAGATGACGCTGATGGATTTAT
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ATGCTGCCTCAATACCTGAACTCCTGGAACACCTCCAGGAAATGAGAGAAGAAAAGAAAAGG
ATTCGAAAGAACTTCGGGATTTTGAAGACAACCTTTTTCAGACAGAATGGAAGAAATGTCCA

GAAGGAAGACCGCACTCCTATGGCTGAAGAATACAGTGAATATAAGCACATAAAGGCGAAAC
 TGAGGCTCCTGGAGGTGCTCATCAGCAAGAGAGACACTGATTCCAAGTCCATGTGAGGGGCA
 TGGCCAAGCACAGGGGGCTGGCAGCTGCGGTGAGAGTTTACTGTCCCCAGAGAAAGTGACGC
 TCTGGAAGGCAGCCTTGGGGCTGGCCCTGCAAAGCATGCAGCCCTTCTGCCTCTAGACCATT
 TGGCATCGGCTCCTGTTTCCATTGCCTGCCTTAGAAACTGGCTGGAAGAAGACAATGTGACC
 TGACTTAGGCATTTTGTAAATTGGAAGTCAAGACTGCAGTATGTGCACATGCGCACGCGCAT
 GCACGCACACACACACAGTAGTGGAGCTTTCCTAACACTAGCAGAGATTAATCACTACAT
 TAGACAACACTCATCTACAGAGAATATACACTGTTCTTCCCTGGATAAAGTGAAGAAACAAGAG
 ACCATTCTCTGTCTAACTGTGATAAAAAACAAGCTCAGGACTTTATTCTATAGAGCAAACCTTG
 CTGTGGAGGGCCATGCTCTCCTTGGACCCAGTTAACTGCAAACGTGCATTGGAGCCCTATTT
 GCTGCCGCTGCCATTCTAGTGACCTTTCACAGAGCTGCGCCTTCCCTCACGTGTGTGAAAGG
 TTTTCCCCCTCAGCCCTCAGGTAGATGGAAGCTGCATCTGCCACGATGGCAGTGCATCAT
 CATCTTCAGGATGTTTCTTCAGGACTTCCCTCAGCTGACAAGGAATTTTGGTCCCTGCCTAGG
 ACCGGGTCTCTGCAGAGGACAGAGAGATGGTAAGCAGCTGTATGAATGCTGATTTTAAAC
 CAGGTCTATGGGAGAAGAGCCTGGAGATTCTTTCCTGAACACTGACTGCACTTACCAGTCTGA
 TTTTATCGTCAAACACCAAGCCAGGCTAGCATGCTCATGGCAATCTGTTTGGGGCTGTTTTG
 TTGTGGCACTAGCCAAACATAAAGGGGCTTAAGTCAGCCTGCATACAGAGGATCGGGGAGAG
 AAGGGGCTGTGTTCTCAGCCTCCTGAGTACTTACCAGAGTTTAATTTTTTAAAAAAATC
 TGCACTAAAAATCCCCAACTGACAGGTAAATGTAGCCCTCAGAGCTCAGCCCCAAGGCAGAAT
 CTAATCACACTATTTTCGAGATCATGTATAAAAAAGAAAAAAGAAAGTCATGCTGTGTGGC
 CAATTATAATTTTTTTCAAAGACTTTGTCAAAAACCTGTCTATATTAGACATTTTGGAGGGA
 CCAGGAAATGTAAGACACCAAATCCTCCATCTCTTCAGTGTGCCTGATGTCACCTCATGATT
 TGCTGTTACTTTTTTAACTCCTGCGCCAAGGACAGTGGGTTCTGTGTCCACCTTTGCTTT
 GCGAGGCCGAGCCCCAGGCATCTGCTCGCCTGCCACGGCTGACCAGAGAAGGTGCTTCAGGAG
 CTCTGCCCTTAGACGACGTGTTACAGTATGAACACACAGCAGAGGCACCCCTCGTATGTTTTGA
 AAGTTGCCTTCTGAAAGGGCACAGTTTTAAGGAAAAGAAAAAGAATGTAAACTATACTGAC
 CCGTTTTAGTTTTTAAAGGGTCGTGAGAACTGGCTGGTCCAATGGGATTTACAGCAACATT
 TTCCATTGCTGAAGTGAGGTAGCAGCTCTCTTCTGTCAGCTGAATGTTAAGGATGGGGAAAA
 AGAATGCCTTTAAGTTTGCTCTTAATCGTATGGAAGCTTGAGCTATGTGTTGGAAGTGCCCT
 GGTTTTAATCCATACACAAAGACGGTACATAATCCTACAGGTTTAAATGTACATAAAAAATAT
 AGTTTGGAAATCTTTGCTCTACTGTTTACATTGCAGATTGCTATAATTTCAAGGAGTGAGAT
 TATAAATAAAATGATGCACTTTAGGATGTTTCCATTTTGAATCTGAACATGAATCATTC
 ACATGACCAAAAATTGTGTTTTTTTTAAAAATACATGTCTAGTCTGTCTTTAATAGCTCTCT
 TAAATAAGCTATGATATTAATCAGATCATTACCAGTTAGCTTTTAAAGCACATTTGTTTAAG
 ACTATGTTTTTGGAAAAATACGCTACAGAATTTTTTTTTTAAGCTACAAATAAATGAGATGCT
 ACTAATTGTTTTGGAATCTGTTGTTTCTGCCAAAGGTAAATTAATAAAGATTTATTAGGA
 ATCCCCATTTGAATTTGTATGATTCAATAAAAGAAAACACCAAGTAAGTTATATAAAATAAA
 TTGTGTATGAGATGTTGTGTTTTCTTTGTAATTTCCACTAACTAACTAACTAATTATATT
 CTTATGGAATGGAGCCCAGAAGAAATGAGAGGAAGCCCTTTTCACTAGATCTTATTTGA
 AGAAATGTTTGTAGTCAGTCAGTCAGTGGTTTCTGGCTCTGCCGAGGGAGATGTGTTCCCC
 AGCAACCATTTCTGCAGCCAGAATCTCAAGGCACTAGAGGCGGTGTCTTAATTAATTGGCT
 TCACAAAGACAAAATGCTCTGGACTGGGATTTTTCTTTGCTGTGTTGGGAATATGTGTTTA
 TTAATTAGCACATGCCAACAAAATAAATGTCAAGAGTTATTTATAAGTGTAAAGTAACTTA
 AGAATTAAGAGTGCAGACTTATAATTTTC

[0033] A region of the antisense strand can be substantially complementary or fully complementary to at least 15 consecutive nucleotides of the *FAM13A* mRNA sequence. In certain embodiments, the region of the antisense strand comprises a sequence that is substantially

complementary to the sequence of at least 15, at least 16, at least 17, at least 18, or at least 19 contiguous nucleotides of a region of the *FAM13A* mRNA sequence (e.g., a human *FAM13A* mRNA sequence (SEQ ID NO: 1)) with no more than 1, 2, or 3 mismatches. In related embodiments, the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15, at least 16, at least 17, at least 18, or at least 19 contiguous nucleotides of a region of the *FAM13A* mRNA sequence with no more than 1 mismatch. In some embodiments, the target region of the *FAM13A* mRNA sequence to which the antisense strand comprises a region of complementarity can range from about 15 to about 30 consecutive nucleotides, from about 16 to about 28 consecutive nucleotides, from about 18 to about 26 consecutive nucleotides, from about 17 to about 24 consecutive nucleotides, from about 19 to about 30 consecutive nucleotides, from about 19 to about 25 consecutive nucleotides, from about 19 to about 23 consecutive nucleotides, or from about 19 to about 21 consecutive nucleotides. In certain embodiments, the region of the antisense strand comprising a sequence that is substantially or fully complementary to a *FAM13A* mRNA sequence may comprise at least 15 contiguous nucleotides from an antisense sequence listed in **Table 1** or **Table 2**. In other embodiments, the sequence of the antisense strand comprises at least 16, at least 17, at least 18, or at least 19 contiguous nucleotides from an antisense sequence listed in **Table 1** or **Table 2**.

[0034] In some embodiments, the region of the antisense strand comprising a sequence that is substantially or fully complementary to a *FAM13A* mRNA sequence may comprise at least 15 contiguous nucleotides from a region that is particularly susceptible to being targeted by a RNAi construct. Therefore, in some embodiments, the region of the antisense strand comprising a sequence that is substantially or fully complementary to a *FAM13A* mRNA sequence may comprise at least 15 contiguous nucleotides from within nucleotides 1300-1375, 1625-1700, 2075-2175, or 4900-5300 of the human *FAM13A* mRNA sequence set forth in SEQ ID NO: 1. In some embodiments, the region of the antisense strand comprising a sequence that is substantially or fully complementary to a *FAM13A* mRNA sequence may comprise at least 15 contiguous nucleotides from a sub-section of these regions. Therefore, in some embodiments, the sequence may comprise at least 15 contiguous nucleotides from nucleotides 1300-1350, 4900-5275, 4900-5250, 4900-5225, 4900-5200, 4900-5175, 4900-5150, 4900-5125, 4900-5100, 4900-5075, 4925-5300, 4925-5275, 4925-5250, 4925-5225, 4925-5200, 4925-5175, 4925-5150, 4925-5125, 4925-5100, 4925-5075, 4950-5300, 4950-5275, 4950-5250, 4950-5225, 4950-5200, 4950-5175, 4950-5150, 4950-5125, 4950-5100, 4950-5075, 4975-5300, 4975-5275, 4975-5250, 4975-5225, 4975-

5200, 4975-5175, 4975-5150, 4975-5125, 4975-5100, 4975-5075, 5175-3000, 5100-5300, 5125-5300, 5150-5300, 5175-5300, 5200-5300, or 5225-5300.

[0035] The sense strand of the RNAi construct typically comprises a sequence that is sufficiently complementary to the sequence of the antisense strand such that the two strands hybridize under physiological conditions to form a duplex region. A “duplex region” refers to the region in two complementary or substantially complementary polynucleotides that form base pairs with one another, either by Watson-Crick base pairing or other hydrogen bonding interaction, to create a duplex between the two polynucleotides. The duplex region of the RNAi construct should be of sufficient length to allow the RNAi construct to enter the RNA interference pathway, *e.g.*, by engaging the Dicer enzyme and/or the RISC complex. For instance, in some embodiments, the duplex region is about 15 to about 30 base pairs in length. Other lengths for the duplex region within this range are also suitable, such as about 15 to about 28 base pairs, about 15 to about 26 base pairs, about 15 to about 24 base pairs, about 15 to about 22 base pairs, about 17 to about 28 base pairs, about 17 to about 26 base pairs, about 17 to about 24 base pairs, about 17 to about 23 base pairs, about 17 to about 21 base pairs, about 19 to about 25 base pairs, about 19 to about 23 base pairs, or about 19 to about 21 base pairs. In certain embodiments, the duplex region is about 17 to about 24 base pairs in length. In other embodiments, the duplex region is about 19 to about 21 base pairs in length. In one embodiment, the duplex region is about 19 base pairs in length. In another embodiment, the duplex region is about 21 base pairs in length.

[0036] For embodiments in which the sense strand and antisense strand are two separate molecules (*e.g.*, RNAi construct comprises an siRNA), the sense strand and antisense strand need not be the same length as the length of the duplex region. For instance, one or both strands may be longer than the duplex region and have one or more unpaired nucleotides or mismatches flanking the duplex region. Thus, in some embodiments, the RNAi construct comprises at least one nucleotide overhang. As used herein, a “nucleotide overhang” refers to the unpaired nucleotide or nucleotides that extend beyond the duplex region at the terminal ends of the strands. Nucleotide overhangs are typically created when the 3' end of one strand extends beyond the 5' end of the other strand or when the 5' end of one strand extends beyond the 3' end of the other strand. The length of a nucleotide overhang is generally between 1 and 6 nucleotides, 1 and 5 nucleotides, 1 and 4 nucleotides, 1 and 3 nucleotides, 2 and 6 nucleotides, 2 and 5 nucleotides, or 2 and 4 nucleotides. In some embodiments, the nucleotide overhang comprises 1, 2, 3, 4, 5, or

6 nucleotides. In some embodiments, the nucleotide overhang comprises 1 to 4 nucleotides. In certain embodiments, the nucleotide overhang comprises 2 nucleotides. In certain other embodiments, the nucleotide overhang comprises a single nucleotide.

[0037] The nucleotides in the overhang can be ribonucleotides or modified nucleotides as described herein. In some embodiments, the nucleotides in the overhang are 2'-modified nucleotides (*e.g.*, 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides), deoxyribonucleotides, abasic nucleotides, inverted nucleotides (*e.g.*, inverted abasic nucleotides, inverted deoxyribonucleotides), or combinations thereof. For instance, in one embodiment, the nucleotides in the overhang are deoxyribonucleotides, *e.g.*, deoxythymidine. In another embodiment, the nucleotides in the overhang are 2'-O-methyl modified nucleotides, 2'-fluoro modified nucleotides, 2'-methoxyethyl modified nucleotides, or combinations thereof. In other embodiments, the overhang comprises a 5'-uridine-uridine-3' (5'-UU-3') dinucleotide. In such embodiments, the UU dinucleotide may comprise ribonucleotides or modified nucleotides, *e.g.*, 2'-modified nucleotides. In other embodiments, the overhang comprises a 5'-deoxythymidine-deoxythymidine-3' (5'-dTdT-3') dinucleotide. When a nucleotide overhang is present in the antisense strand, the nucleotides in the overhang can be complementary to the target gene sequence, form a mismatch with the target gene sequence, or comprise some other sequence (*e.g.*, polypyrimidine or polypurine sequence, such as UU, TT, AA, GG, etc.).

[0038] The nucleotide overhang can be at the 5' end or 3' end of one or both strands. For example, in one embodiment, the RNAi construct comprises a nucleotide overhang at the 5' end and the 3' end of the antisense strand. In another embodiment, the RNAi construct comprises a nucleotide overhang at the 5' end and the 3' end of the sense strand. In some embodiments, the RNAi construct comprises a nucleotide overhang at the 5' end of the sense strand and the 5' end of the antisense strand. In other embodiments, the RNAi construct comprises a nucleotide overhang at the 3' end of the sense strand and the 3' end of the antisense strand.

[0039] The RNAi constructs may comprise a single nucleotide overhang at one end of the double-stranded RNA molecule and a blunt end at the other. A "blunt end" means that the sense strand and antisense strand are fully base-paired at the end of the molecule and there are no unpaired nucleotides that extend beyond the duplex region. In some embodiments, the RNAi construct comprises a nucleotide overhang at the 3' end of the sense strand and a blunt end at the 5' end of the sense strand and 3' end of the antisense strand. In other embodiments, the RNAi construct comprises a nucleotide overhang at the 3' end of the antisense strand and a blunt end at

the 5' end of the antisense strand and the 3' end of the sense strand. In certain embodiments, the RNAi construct comprises a blunt end at both ends of the double-stranded RNA molecule. In such embodiments, the sense strand and antisense strand have the same length and the duplex region is the same length as the sense and antisense strands (*i.e.*, the molecule is double stranded over its entire length).

[0040] The sense strand and antisense strand in the RNAi constructs can each independently be about 15 to about 30 nucleotides in length, about 19 to about 30 nucleotides in length, about 18 to about 28 nucleotides in length, about 19 to about 27 nucleotides in length, about 19 to about 25 nucleotides in length, about 19 to about 23 nucleotides in length, about 19 to about 21 nucleotides in length, about 21 to about 25 nucleotides in length, or about 21 to about 23 nucleotides in length. In certain embodiments, the sense strand and antisense strand are each independently about 18, about 19, about 20, about 21, about 22, about 23, about 24, or about 25 nucleotides in length. In some embodiments, the sense strand and antisense strand have the same length but form a duplex region that is shorter than the strands such that the RNAi construct has two nucleotide overhangs. For instance, in one embodiment, the RNAi construct comprises (i) a sense strand and an antisense strand that are each 21 nucleotides in length, (ii) a duplex region that is 19 base pairs in length, and (iii) nucleotide overhangs of 2 unpaired nucleotides at both the 3' end of the sense strand and the 3' end of the antisense strand. In another embodiment, the RNAi construct comprises (i) a sense strand and an antisense strand that are each 23 nucleotides in length, (ii) a duplex region that is 21 base pairs in length, and (iii) nucleotide overhangs of 2 unpaired nucleotides at both the 3' end of the sense strand and the 3' end of the antisense strand. In other embodiments, the sense strand and antisense strand have the same length and form a duplex region over their entire length such that there are no nucleotide overhangs on either end of the double-stranded molecule. In one such embodiment, the RNAi construct is blunt ended (*e.g.*, has two blunt ends) and comprises (i) a sense strand and an antisense strand, each of which is 21 nucleotides in length, and (ii) a duplex region that is 21 base pairs in length. In another such embodiment, the RNAi construct is blunt ended (*e.g.*, has two blunt ends) and comprises (i) a sense strand and an antisense strand, each of which is 23 nucleotides in length, and (ii) a duplex region that is 23 base pairs in length. In still another such embodiment, the RNAi construct is blunt ended (*e.g.*, has two blunt ends) and comprises (i) a sense strand and an antisense strand, each of which is 19 nucleotides in length, and (ii) a duplex region that is 19 base pairs in length.

[0041] In other embodiments, the sense strand or the antisense strand is longer than the other strand and the two strands form a duplex region having a length equal to that of the shorter strand such that the RNAi construct comprises at least one nucleotide overhang. For example, in one embodiment, the RNAi construct comprises (i) a sense strand that is 19 nucleotides in length, (ii) an antisense strand that is 21 nucleotides in length, (iii) a duplex region of 19 base pairs in length, and (iv) a nucleotide overhang of 2 unpaired nucleotides at the 3' end of the antisense strand. In another embodiment, the RNAi construct comprises (i) a sense strand that is 21 nucleotides in length, (ii) an antisense strand that is 23 nucleotides in length, (iii) a duplex region of 21 base pairs in length, and (iv) a nucleotide overhang of 2 unpaired nucleotides at the 3' end of the antisense strand.

[0042] The antisense strand of the RNAi constructs can comprise or consist of the sequence of any one of the antisense sequences listed in **Table 1** or **Table 2**, the sequence of nucleotides 1-19 of any of these antisense sequences, or the sequence of nucleotides 2-19 of any of these antisense sequences. Thus, in some embodiments, the antisense strand comprises or consists of a sequence selected from SEQ ID NOs: 546-1089 or 1938-2785. In other embodiments, the antisense strand comprises or consists of a sequence of nucleotides 1-19 of any one of SEQ ID NOs: 546-1089 or 1938-2785. In still other embodiments, the antisense strand comprises or consists of a sequence of nucleotides 2-19 of any one of SEQ ID NOs: 546-1089 or 1938-2785.

[0043] In these and other embodiments, the sense strand of the RNAi constructs can comprise or consist of the sequence of any one of the sense sequences listed in **Table 1** or **Table 2**, the sequence of nucleotides 1-19 of any of these sense sequences, or the sequence of nucleotides 2-19 of any of these sense sequences. Thus, in some embodiments, the sense strand comprises or consists of a sequence selected from SEQ ID NOs: 2-545 or 1090-1937. In other embodiments, the sense strand comprises or consists of a sequence of nucleotides 1-19 of any one of SEQ ID NOs: 2-545 or 1090-1937. In still other embodiments, the sense strand comprises or consists of a sequence of nucleotides 2-19 of any one of SEQ ID NOs: 2-545 or 1090-1937.

[0044] In certain embodiments, the RNAi constructs comprise (i) a sense strand comprising or consisting of a sequence selected from 2-545 or 1090-1937 and (ii) an antisense strand comprising or consisting of a sequence selected from SEQ ID NOs: 546-1089 or 1938-2785. In some embodiments, the RNAi construct can be any of the duplex compounds listed in **Table 1** or **Table 2** (including the unmodified nucleotide sequences and/or modified nucleotide

sequences of the compounds). In certain embodiments, the RNAi construct is D-1539, D-1544, D-1545, D-1549, D-1557, D-1559, D-1573, D-1579, D-1586, D-1597, D-1607, D-1611, D-1612, D-1614, D-1623, D-1631, D-1636, D-1639, D-1640, D-1643, D-1644, D-1645, D-1646, D-1648, D-1652, D-1661, D-1667, D-1672, or D-1694.

Modification and Preparation of RNAi Constructs

[0045] The RNAi constructs disclosed herein may comprise one or more modified nucleotides. A “modified nucleotide” refers to a nucleotide that has one or more chemical modifications to the nucleoside, nucleobase, pentose ring, or phosphate group. As used herein, modified nucleotides do not encompass ribonucleotides containing adenosine monophosphate, guanosine monophosphate, uridine monophosphate, and cytidine monophosphate. However, the RNAi constructs may comprise combinations of modified nucleotides and ribonucleotides. Incorporation of modified nucleotides into one or both strands of double-stranded RNA molecules can improve the *in vivo* stability of the RNA molecules, *e.g.*, by reducing the molecules’ susceptibility to nucleases and other degradation processes. The potency of RNAi constructs for reducing expression of the target gene can also be enhanced by incorporation of modified nucleotides.

[0046] In certain embodiments, the modified nucleotides have a modification of the ribose sugar. These sugar modifications can include modifications at the 2’ and/or 5’ position of the pentose ring as well as bicyclic sugar modifications. A 2’-modified nucleotide refers to a nucleotide having a pentose ring with a substituent at the 2’ position other than OH. Such 2’-modifications include, but are not limited to, 2’-H (*e.g.*, deoxyribonucleotides), 2’-O-alkyl (*e.g.*, -O-C₁-C₁₀ or -O-C₁-C₁₀ substituted alkyl), 2’-O-allyl (-O-CH₂CH=CH₂), 2’-C-allyl, 2’-deoxy-2’-fluoro (also referred to as 2’-F or 2’-fluoro), 2’-O-methyl (-OCH₃), 2’-O-methoxyethyl (-O-(CH₂)₂OCH₃), 2’-OCF₃, 2’-O(CH₂)₂SCH₃, 2’-O-aminoalkyl, 2’-amino (*e.g.*, -NH₂), 2’-O-ethylamine, and 2’-azido. Modifications at the 5’ position of the pentose ring include, but are not limited to, 5’-methyl (R or S configuration); 5’-vinyl, and 5’-methoxy.

[0047] A “bicyclic sugar modification” refers to a modification of the pentose ring where a bridge connects two atoms of the ring to form a second ring resulting in a bicyclic sugar structure. In some embodiments the bicyclic sugar modification comprises a bridge between the 4’ and 2’ carbons of the pentose ring. Nucleotides comprising a sugar moiety with a bicyclic sugar modification are referred to herein as bicyclic nucleic acids or BNAs. Exemplary bicyclic

sugar modifications include, but are not limited to, α -L-Methyleneoxy (4'-CH₂—O-2') bicyclic nucleic acid (BNA); β -D-Methyleneoxy (4'-CH₂—O-2') BNA (also referred to as a locked nucleic acid or LNA); Ethyleneoxy (4'-(CH₂)₂—O-2') BNA; Aminooxy (4'-CH₂—O—N(R)-2', wherein R is H, C₁-C₁₂ alkyl, or a protecting group) BNA; Oxyamino (4'-CH₂—N(R)—O-2', wherein R is H, C₁-C₁₂ alkyl, or a protecting group) BNA; Methyl(methyleneoxy) (4'-CH(CH₃)—O-2') BNA (also referred to as constrained ethyl or cEt); methylene-thio (4'-CH₂—S-2') BNA; methylene-amino (4'-CH₂-N(R)-2', wherein R is H, C₁-C₁₂ alkyl, or a protecting group) BNA; methyl carbocyclic (4'-CH₂—CH(CH₃)-2') BNA; propylene carbocyclic (4'-(CH₂)₃-2') BNA; and Methoxy(ethyleneoxy) (4'-CH(CH₂OMe)-O-2') BNA (also referred to as constrained MOE or cMOE). These and other sugar-modified nucleotides that can be incorporated into the RNAi constructs are described in U.S. Patent No. 9,181,551, U.S. Patent Publication No.

2016/0122761, and Deleavey and Damha, Chemistry and Biology, Vol. 19: 937-954, 2012, all of which are hereby incorporated by reference in their entireties.

[0048] In some embodiments, the RNAi constructs comprise one or more 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, 2'-O-methoxyethyl modified nucleotides, 2'-O-alkyl modified nucleotides, 2'-O-allyl modified nucleotides, bicyclic nucleic acids (BNAs), deoxyribonucleotides, or combinations thereof. In certain embodiments, the RNAi constructs comprise one or more 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, 2'-O-methoxyethyl modified nucleotides, or combinations thereof. In some embodiments, the RNAi constructs comprise one or more 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides or combinations thereof.

[0049] Both the sense and antisense strands of the RNAi constructs can comprise one or multiple modified nucleotides. For instance, in some embodiments, the sense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more modified nucleotides. In certain embodiments, all nucleotides in the sense strand are modified nucleotides. In some embodiments, the antisense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more modified nucleotides. In other embodiments, all nucleotides in the antisense strand are modified nucleotides. In certain other embodiments, all nucleotides in the sense strand and all nucleotides in the antisense strand are modified nucleotides. In these and other embodiments, the modified nucleotides can be 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, or combinations thereof.

[0050] In certain embodiments, the modified nucleotides incorporated into one or both strands of the RNAi constructs have a modification of the nucleobase (also referred to herein as

“base”). A “modified nucleobase” or “modified base” refers to a base other than the naturally occurring purine bases adenine (A) and guanine (G) and pyrimidine bases thymine (T), cytosine (C), and uracil (U). Modified nucleobases can be synthetic or naturally occurring modifications and include, but are not limited to, universal bases, 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine (X), hypoxanthine (I), 2-aminoadenine, 6-methyladenine, 6-methylguanine, and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine.

[0051] In some embodiments, the modified base is a universal base. A “universal base” refers to a base analog that indiscriminately forms base pairs with all the natural bases in RNA and DNA without altering the double helical structure of the resulting duplex region. Universal bases are known to those of skill in the art and include, but are not limited to, inosine, C-phenyl, C-naphthyl and other aromatic derivatives, azole carboxamides, and nitroazole derivatives, such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole.

[0052] Other suitable modified bases that can be incorporated into the RNAi constructs include those described in Herdewijn, *Antisense Nucleic Acid Drug Dev.*, Vol. 10: 297–310, 2000 and Peacock *et al.*, *J. Org. Chem.*, Vol. 76: 7295–7300, 2011, both of which are hereby incorporated by reference in their entireties. The skilled person understands guanine, cytosine, adenine, thymine, and uracil may be replaced by other nucleobases, such as the modified nucleobases described above, without substantially altering the base pairing properties of a polynucleotide comprising a nucleotide bearing such replacement nucleobase.

[0053] In some embodiments, the sense and antisense strands of the RNAi constructs may comprise one or more abasic nucleotides. An “abasic nucleotide” or “abasic nucleoside” is a nucleotide or nucleoside that lacks a nucleobase at the 1' position of the ribose sugar. In certain embodiments, the abasic nucleotides are incorporated into the terminal ends of the sense and/or antisense strands of the RNAi constructs. In one embodiment, the sense strand comprises an abasic nucleotide as the terminal nucleotide at its 3' end, its 5' end, or both its 3' and 5' ends. In another embodiment, the antisense strand comprises an abasic nucleotide as the terminal

nucleotide at its 3' end, its 5' end, or both its 3' and 5' ends. In such embodiments in which the abasic nucleotide is a terminal nucleotide, it may be an inverted nucleotide – that is, linked to the adjacent nucleotide through a 3'-3' internucleotide linkage (when on the 3' end of a strand) or through a 5'-5' internucleotide linkage (when on the 5' end of a strand) rather than the natural 3'-5' internucleotide linkage. Abasic nucleotides may also comprise a sugar modification, such as any of the sugar modifications described above. In certain embodiments, abasic nucleotides comprise a 2'-modification, such as a 2'-fluoro modification, 2'-O-methyl modification, or a 2'-H (deoxy) modification. In one embodiment, the abasic nucleotide comprises a 2'-O-methyl modification. In another embodiment, the abasic nucleotide comprises a 2'-H modification (*i.e.*, a deoxy abasic nucleotide).

[0054] In certain embodiments, the RNAi constructs may comprise modified nucleotides incorporated into the sense and antisense strands according to a particular pattern, such as the patterns described in WIPO Publication No. WO 2020/123410, which is hereby incorporated by reference in its entirety. RNAi constructs having such chemical modification patterns have been shown to have improved gene silencing activity *in vivo*. In one embodiment, the RNAi construct comprises a sense strand and an antisense strand that comprise sequences that are sufficiently complementary to each other to form a duplex region of at least 15 base pairs, wherein: nucleotides at positions 2, 7, and 14 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides;

nucleotides in the sense strand at positions paired with positions 8 to 11 and 13 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides; and neither the sense strand nor the antisense strand each have more than 7 total 2'-fluoro modified nucleotides.

In other embodiments, the RNAi construct comprises a sense strand and an antisense strand that comprise sequences that are sufficiently complementary to each other to form a duplex region of at least 19 base pairs, wherein:

nucleotides at positions 2, 7, and 14 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides, nucleotides at positions 4, 6, 10, and 12 (counting from the 5' end) are optionally 2'-fluoro modified nucleotides, and all other nucleotides in the antisense strand are modified nucleotides other than 2'-fluoro modified nucleotides; and nucleotides in the sense strand at positions paired with positions 8 to 11 and 13 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides, nucleotides in the sense

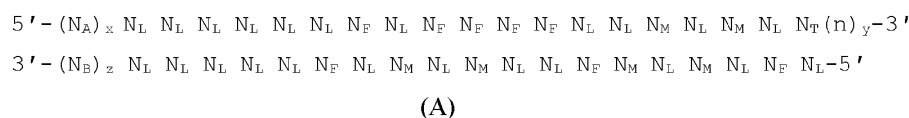
strand at positions paired with positions 3 and 5 in the antisense strand (counting from the 5' end) are optionally 2'-fluoro modified nucleotides; and all other nucleotides in the sense strand are modified nucleotides other than 2'-fluoro modified nucleotides.

[0055] In such embodiments, the modified nucleotides other than 2'-fluoro modified nucleotides can be selected from 2'-O-methyl modified nucleotides, 2'-O-methoxyethyl modified nucleotides, 2'-O-alkyl modified nucleotides, 2'-O-allyl modified nucleotides, BNAs, and deoxyribonucleotides. In these and other embodiments, the terminal nucleotide at the 3' end, the 5' end, or both the 3' end and the 5' end of the sense strand can be an abasic nucleotide or a deoxyribonucleotide. In such embodiments, the abasic nucleotide or deoxyribonucleotide may be inverted – *i.e.*, linked to the adjacent nucleotide through a 3'-3' internucleotide linkage (when on the 3' end of a strand) or through a 5'-5' internucleotide linkage (when on the 5' end of a strand) rather than the natural 3'-5' internucleotide linkage.

[0056] In any of the above-described embodiments, nucleotides at positions 2, 7, 12, and 14 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides. In other embodiments, nucleotides at positions 2, 4, 7, 12, and 14 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides. In yet other embodiments, nucleotides at positions 2, 4, 6, 7, 12, and 14 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides. In still other embodiments, nucleotides at positions 2, 4, 6, 7, 10, 12, and 14 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides. In alternative embodiments, nucleotides at positions 2, 7, 10, 12, and 14 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides. In certain other embodiments, nucleotides at positions 2, 4, 7, 10, 12, and 14 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides.

[0057] In any of the above-described embodiments, nucleotides in the sense strand at positions paired with positions 3, 8 to 11, and 13 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides. In some embodiments, nucleotides in the sense strand at positions paired with positions 5, 8 to 11, and 13 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides. In other embodiments, nucleotides in the sense strand at positions paired with positions 3, 5, 8 to 11, and 13 in the antisense strand (counting from the 5' end) are 2'-fluoro modified nucleotides.

[0058] In some embodiments, the RNAi construct comprises a structure represented by Formula (A):



[0059] In Formula (A), the top strand listed in the 5' to 3' direction is the sense strand and the bottom strand listed in the 3' to 5' direction is the antisense strand; each N_F represents a 2'-fluoro modified nucleotide; each N_M independently represents a modified nucleotide selected from a 2'-fluoro modified nucleotide, a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-O-alkyl modified nucleotide, a 2'-O-allyl modified nucleotide, a BNA, and a deoxyribonucleotide; each N_L independently represents a modified nucleotide selected from a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-O-alkyl modified nucleotide, a 2'-O-allyl modified nucleotide, a BNA, and a deoxyribonucleotide; and N_T represents a modified nucleotide selected from an abasic nucleotide, an inverted abasic nucleotide, an inverted deoxyribonucleotide, a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-O-alkyl modified nucleotide, a 2'-O-allyl modified nucleotide, a BNA, and a deoxyribonucleotide. X can be an integer from 0 to 4, provided that when x is 1, 2, 3, or 4, one or more of the N_A nucleotides is a modified nucleotide independently selected from an abasic nucleotide, an inverted abasic nucleotide, an inverted deoxyribonucleotide, a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-O-alkyl modified nucleotide, a 2'-O-allyl modified nucleotide, a BNA, and a deoxyribonucleotide. One or more of the N_A nucleotides can be complementary to nucleotides in the antisense strand. Y can be an integer from 0 to 4, provided that when y is 1, 2, 3, or 4, one or more n nucleotides are modified or unmodified overhang nucleotides that do not base pair with nucleotides in the antisense strand. Z can be an integer from 0 to 4, provided that when z is 1, 2, 3, or 4, one or more of the N_B nucleotides is a modified nucleotide independently selected from a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-O-alkyl modified nucleotide, a 2'-O-allyl modified nucleotide, a BNA, and a deoxyribonucleotide. One or more of the N_B nucleotides can be complementary to N_A nucleotides when present in the sense strand or can be overhang nucleotides that do not base pair with nucleotides in the sense strand.

[0060] In some embodiments in which the RNAi construct comprises a structure represented by Formula (A), there is a nucleotide overhang at the 3' end of the sense strand – *i.e.*, y is 1, 2, 3, or 4. In one such embodiment, y is 2. In embodiments in which there is an overhang

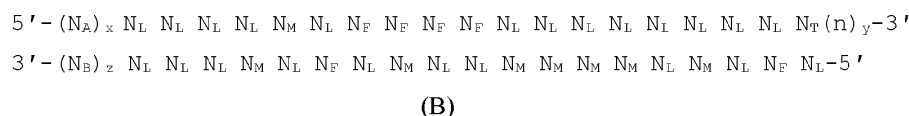
of 2 nucleotides at the 3' end of the sense strand (*i.e.*, y is 2), x is 0 and z is 2 or x is 1 and z is 2. In other embodiments in which the RNAi construct comprises a structure represented by Formula (A), the RNAi construct comprises a blunt end at the 3' end of the sense strand and the 5' end of the antisense strand (*i.e.*, y is 0). In such embodiments where there is no nucleotide overhang at the 3' end of the sense strand (*i.e.*, y is 0): (i) x is 2 and z is 4, (ii) x is 3 and z is 4, (iii) x is 0 and z is 2, (iv) x is 1 and z is 2, or (v) x is 2 and z is 2. In any of the embodiments in which x is greater than 0, the N_A nucleotide that is the terminal nucleotide at the 5' end of the sense strand can be an inverted nucleotide, such as an inverted abasic nucleotide or an inverted deoxyribonucleotide.

[0061] In certain embodiments in which the RNAi construct comprises a structure represented by Formula (A), the N_M at positions 4 and 12 in the antisense strand counting from the 5' end are each a 2'-fluoro modified nucleotide. In other embodiments, the N_M at positions 4, 6, and 12 in the antisense strand counting from the 5' end are each a 2'-fluoro modified nucleotide. In yet other embodiments, the N_M at positions 4, 6, 10, and 12 in the antisense strand counting from the 5' end are each a 2'-fluoro modified nucleotide. In alternative embodiments in which the RNAi construct comprises a structure represented by Formula (A), the N_M at positions 10 and 12 in the antisense strand counting from the 5' end are each a 2'-fluoro modified nucleotide. In related embodiments, the N_M at positions 4, 10, and 12 in the antisense strand counting from the 5' end are each a 2'-fluoro modified nucleotide. In other alternative embodiments in which the RNAi construct comprises a structure represented by Formula (A), the N_M at positions 4, 6, and 10 in the antisense strand counting from the 5' end are each a 2'-O-methyl modified nucleotide, and the N_M at position 12 in the antisense strand counting from the 5' end is a 2'-fluoro modified nucleotide. In some embodiments in which the RNAi construct comprises a structure represented by Formula (A), each N_M in the sense strand is a 2'-O-methyl modified nucleotide. In other embodiments, each N_M in the sense strand is a 2'-fluoro modified nucleotide. In still other embodiments in which the RNAi construct comprises a structure represented by Formula (A), each N_M in both the sense and antisense strands is a 2'-O-methyl modified nucleotide.

[0062] In any of the above-described embodiments in which the RNAi construct comprises a structure represented by Formula (A), each N_L in both the sense and antisense strands can be a 2'-O-methyl modified nucleotide. In these embodiments and any of the

embodiments described above, N_T in Formula (A) can be an inverted abasic nucleotide, an inverted deoxyribonucleotide, or a 2'-O-methyl modified nucleotide.

[0063] In other embodiments, the RNAi construct comprises a structure represented by Formula (B):



[0064] In Formula (B), the top strand listed in the 5' to 3' direction is the sense strand and the bottom strand listed in the 3' to 5' direction is the antisense strand; each N_F represents a 2'-fluoro modified nucleotide; each N_M independently represents a modified nucleotide selected from a 2'-fluoro modified nucleotide, a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-O-alkyl modified nucleotide, a 2'-O-allyl modified nucleotide, a BNA, and a deoxyribonucleotide; each N_L independently represents a modified nucleotide selected from a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-O-alkyl modified nucleotide, a 2'-O-allyl modified nucleotide, a BNA, and a deoxyribonucleotide; and N_T represents a modified nucleotide selected from an abasic nucleotide, an inverted abasic nucleotide, an inverted deoxyribonucleotide, a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-O-alkyl modified nucleotide, a 2'-O-allyl modified nucleotide, a BNA, and a deoxyribonucleotide. X can be an integer from 0 to 4, provided that when x is 1, 2, 3, or 4, one or more of the N_A nucleotides is a modified nucleotide independently selected from an abasic nucleotide, an inverted abasic nucleotide, an inverted deoxyribonucleotide, a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-O-alkyl modified nucleotide, a 2'-O-allyl modified nucleotide, a BNA, and a deoxyribonucleotide. One or more of the N_A nucleotides can be complementary to nucleotides in the antisense strand. Y can be an integer from 0 to 4, provided that when y is 1, 2, 3, or 4, one or more n nucleotides are modified or unmodified overhang nucleotides that do not base pair with nucleotides in the antisense strand. Z can be an integer from 0 to 4, provided that when z is 1, 2, 3, or 4, one or more of the N_B nucleotides is a modified nucleotide independently selected from a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-O-alkyl modified nucleotide, a 2'-O-allyl modified nucleotide, a BNA, and a deoxyribonucleotide. One or

more of the N_B nucleotides can be complementary to N_A nucleotides when present in the sense strand or can be overhang nucleotides that do not base pair with nucleotides in the sense strand.

[0065] In some embodiments in which the RNAi construct comprises a structure represented by Formula (B), there is a nucleotide overhang at the 3' end of the sense strand – *i.e.*, y is 1, 2, 3, or 4. In one such embodiment, y is 2. In embodiments in which there is an overhang of 2 nucleotides at the 3' end of the sense strand (*i.e.*, y is 2), x is 0 and z is 2 or x is 1 and z is 2. In other embodiments in which the RNAi construct comprises a structure represented by Formula (B), the RNAi construct comprises a blunt end at the 3' end of the sense strand and the 5' end of the antisense strand (*i.e.*, y is 0). In such embodiments where there is no nucleotide overhang at the 3' end of the sense strand (*i.e.*, y is 0): (i) x is 2 and z is 4, (ii) x is 3 and z is 4, (iii) x is 0 and z is 2, (iv) x is 1 and z is 2, or (v) x is 2 and z is 2. In any of the embodiments in which x is greater than 0, the N_A nucleotide that is the terminal nucleotide at the 5' end of the sense strand can be an inverted nucleotide, such as an inverted abasic nucleotide or an inverted deoxyribonucleotide.

[0066] In certain embodiments in which the RNAi construct comprises a structure represented by Formula (B), the N_M at positions 4, 6, 8, 9, and 16 in the antisense strand counting from the 5' end are each a 2'-fluoro modified nucleotide and the N_M at positions 7 and 12 in the antisense strand counting from the 5' end are each a 2'-O-methyl modified nucleotide. In other embodiments, the N_M at positions 4 and 6 in the antisense strand counting from the 5' end are each a 2'-fluoro modified nucleotide and the N_M at positions 7 to 9 in the antisense strand counting from the 5' end are each a 2'-O-methyl modified nucleotide. In still other embodiments, the N_M at positions 4, 6, 8, 9, and 16 in the antisense strand counting from the 5' end are each a 2'-O-methyl modified nucleotide and the N_M at positions 7 and 12 in the antisense strand counting from the 5' end are each a 2'-fluoro modified nucleotide. In alternative embodiments in which the RNAi construct comprises a structure represented by Formula (B), the N_M at positions 4, 6, 8, 9, and 12 in the antisense strand counting from the 5' end are each a 2'-O-methyl modified nucleotide and the N_M at positions 7 and 16 in the antisense strand counting from the 5' end are each a 2'-fluoro modified nucleotide. In certain other embodiments in which the RNAi construct comprises a structure represented by Formula (B), the N_M at positions 7, 8, 9, and 12 in the antisense strand counting from the 5' end are each a 2'-O-methyl modified nucleotide and the N_M at positions 4, 6, and 16 in the antisense strand counting from the 5' end are each a 2'-fluoro modified nucleotide. In these and other embodiments in which the RNAi construct comprises a

structure represented by Formula (B), the N_M in the sense strand is a 2'-fluoro modified nucleotide. In alternative embodiments, the N_M in the sense strand is a 2'-O-methyl modified nucleotide.

[0067] In any of the above-described embodiments in which the RNAi construct comprises a structure represented by Formula (B), each N_L in both the sense and antisense strands can be a 2'-O-methyl modified nucleotide. In these embodiments and any of the embodiments described above, N_T in Formula (B) can be an inverted abasic nucleotide, an inverted deoxyribonucleotide, or a 2'-O-methyl modified nucleotide.

[0068] The RNAi constructs may also comprise one or more modified internucleotide linkages. As used herein, the term "modified internucleotide linkage" refers to an internucleotide linkage other than the natural 3' to 5' phosphodiester linkage. In some embodiments, the modified internucleotide linkage is a phosphorous-containing internucleotide linkage, such as a phosphotriester, aminoalkylphosphotriester, an alkylphosphonate (*e.g.*, methylphosphonate, 3'-alkylene phosphonate), a phosphinate, a phosphoramidate (*e.g.*, 3'-amino phosphoramidate and aminoalkylphosphoramidate), a phosphorothioate, a chiral phosphorothioate, a phosphorodithioate, a thionophosphoramidate, a thionoalkylphosphonate, a thionoalkylphosphotriester, and a boranophosphate. In one embodiment, a modified internucleotide linkage is a 2' to 5' phosphodiester linkage. In other embodiments, the modified internucleotide linkage is a non-phosphorous-containing internucleotide linkage and thus can be referred to as a modified internucleoside linkage. Such non-phosphorous-containing linkages include, but are not limited to, morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane linkages ($\text{—O—Si(H)}_2\text{—O—}$); sulfide, sulfoxide and sulfone linkages; formacetyl and thioformacetyl linkages; alkene containing backbones; sulfamate backbones; methylenemethylimino ($\text{—CH}_2\text{—N(CH}_3\text{)—O—CH}_2\text{—}$) and methylenehydrazino linkages; sulfonate and sulfonamide linkages; amide linkages; and others having mixed N, O, S and CH₂ component parts. In one embodiment, the modified internucleoside linkage is a peptide-based linkage (*e.g.*, aminoethylglycine) to create a peptide nucleic acid or PNA, such as those described in U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262. Other suitable modified internucleotide and internucleoside linkages that may be employed in the RNAi constructs are described in U.S. Patent No. 6,693,187, U.S. Patent No. 9,181,551, U.S. Patent Publication No. 2016/0122761, and Deleavey and Damha, *Chemistry and Biology*, Vol. 19: 937-954, 2012, all of which are hereby incorporated by reference in their entireties.

[0069] In certain embodiments, the RNAi constructs comprise one or more phosphorothioate internucleotide linkages. The phosphorothioate internucleotide linkages may be present in the sense strand, antisense strand, or both strands of the RNAi constructs. For instance, in some embodiments, the sense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, or more phosphorothioate internucleotide linkages. In other embodiments, the antisense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, or more phosphorothioate internucleotide linkages. In still other embodiments, both strands comprise 1, 2, 3, 4, 5, 6, 7, 8, or more phosphorothioate internucleotide linkages. The RNAi constructs can comprise one or more phosphorothioate internucleotide linkages at the 3'-end, the 5'-end, or both the 3'- and 5'-ends of the sense strand, the antisense strand, or both strands. For instance, in certain embodiments, the RNAi construct comprises about 1 to about 6 or more (*e.g.*, about 1, 2, 3, 4, 5, 6 or more) consecutive phosphorothioate internucleotide linkages at the 3'-end of the sense strand, the antisense strand, or both strands. In other embodiments, the RNAi construct comprises about 1 to about 6 or more (*e.g.*, about 1, 2, 3, 4, 5, 6 or more) consecutive phosphorothioate internucleotide linkages at the 5'-end of the sense strand, the antisense strand, or both strands. In some embodiments, the antisense strand comprises at least 1 but no more than 6 phosphorothioate internucleotide linkages and the sense strand comprises at least 1 but no more than 4 phosphorothioate internucleotide linkages. In other embodiments, the antisense strand comprises at least 1 but no more than 4 phosphorothioate internucleotide linkages and the sense strand comprises at least 1 but no more than 2 phosphorothioate internucleotide linkages.

[0070] In some embodiments, the RNAi construct comprises a single phosphorothioate internucleotide linkage between the terminal nucleotides at the 3' end of the sense strand. In other embodiments, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at the 3' end of the sense strand. In one embodiment, the RNAi construct comprises a single phosphorothioate internucleotide linkage between the terminal nucleotides at the 3' end of the sense strand and a single phosphorothioate internucleotide linkage between the terminal nucleotides at the 3' end of the antisense strand. In another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at the 3' end of the antisense strand (*i.e.*, a phosphorothioate internucleotide linkage at the first and second internucleotide linkages at the 3' end of the antisense strand). In another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends of the antisense strand. In yet another embodiment, the RNAi construct

comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends of the antisense strand and two consecutive phosphorothioate internucleotide linkages at the 5' end of the sense strand. In still another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends of the antisense strand and two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at the 3' end of the sense strand. In another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends of the antisense strand and two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends of the sense strand (*i.e.*, a phosphorothioate internucleotide linkage at the first and second internucleotide linkages at both the 5' and 3' ends of the antisense strand and a phosphorothioate internucleotide linkage at the first and second internucleotide linkages at both the 5' and 3' ends of the sense strand). In yet another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends of the antisense strand and a single phosphorothioate internucleotide linkage between the terminal nucleotides at the 3' end of the sense strand. In any of the embodiments in which one or both strands comprise one or more phosphorothioate internucleotide linkages, the remaining internucleotide linkages within the strands can be the natural 3' to 5' phosphodiester linkages. For instance, in some embodiments, each internucleotide linkage of the sense and antisense strands is selected from phosphodiester and phosphorothioate, wherein at least one internucleotide linkage is a phosphorothioate.

[0071] In embodiments in which the RNAi construct comprises a nucleotide overhang, two or more of the unpaired nucleotides in the overhang can be connected by a phosphorothioate internucleotide linkage. In certain embodiments, all the unpaired nucleotides in a nucleotide overhang at the 3' end of the antisense strand and/or the sense strand are connected by phosphorothioate internucleotide linkages. In other embodiments, all the unpaired nucleotides in a nucleotide overhang at the 5' end of the antisense strand and/or the sense strand are connected by phosphorothioate internucleotide linkages. In still other embodiments, all the unpaired nucleotides in any nucleotide overhang are connected by phosphorothioate internucleotide linkages.

[0072] Incorporation of a phosphorothioate internucleotide linkage introduces an additional chiral center at the phosphorous atom in the oligonucleotide and therefore creates a diastereomer pair (Rp and Sp) at each phosphorothioate internucleotide linkage. Diastereomers or diastereoisomers are different configurations of a compound that have the same molecular formula and sequence of bonded atoms but differ in the three-dimensional orientations of their atoms in space. Unlike enantiomers, diastereomers are not mirror-images of each other. Each chiral phosphate atom can be in the “R” configuration (Rp) or the “S” configuration (Sp). In certain embodiments, the RNAi constructs may comprise one or more phosphorothioate internucleotide linkages where the chiral phosphates are selected to be primarily in either the Rp or Sp configuration. For instance, in some embodiments in which the RNAi constructs have one or more phosphorothioate internucleotide linkages, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% of the chiral phosphates are in the Sp configuration. In other embodiments in which the RNAi constructs have one or more phosphorothioate internucleotide linkages, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% of the chiral phosphates are in the Rp configuration. All the chiral phosphates in the RNAi construct can be either in the Sp configuration or the Rp configuration (*i.e.*, the RNAi construct is stereopure). In some embodiments, all the chiral phosphates in the RNAi construct are in the Sp configuration. In some embodiments, all the chiral phosphates in the RNAi construct are in the Rp configuration.

[0073] In certain embodiments, the chiral phosphates in the RNAi construct may have different configurations at different positions in the sense strand or antisense strand. In one such embodiment in which the RNAi construct comprises one or two phosphorothioate internucleotide linkages at the 5' end of the antisense strand, the chiral phosphates at the 5' end of the antisense strand may be in the Rp configuration. In another such embodiment in which the RNAi construct comprises one or two phosphorothioate internucleotide linkages at the 3' end of the antisense strand, the chiral phosphates at the 3' end of the antisense strand may be in the Sp configuration. In certain embodiments, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends of the antisense strand and two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at the 3' end of the sense strand, wherein the chiral phosphates at the 5' end of the antisense strand are in the Rp configuration, the chiral phosphates at the 3' end of the

antisense strand are in the Sp configuration, and the chiral phosphates at the 3' end of the sense strand can be either in the Rp or Sp configuration. In certain other embodiments, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends of the antisense strand and a single phosphorothioate internucleotide linkage between the terminal nucleotides at the 3' end of the sense strand, wherein the chiral phosphates at the 5' end of the antisense strand are in the Rp configuration, the chiral phosphates at the 3' end of the antisense strand are in the Sp configuration, and the chiral phosphate at the 3' end of the sense strand can be either in the Rp or Sp configuration. Methods of controlling the stereochemistry of phosphorothioate linkages during oligonucleotide synthesis are known to those skilled in the art and can include methods described in Nawrot and Rebowska, *Curr. Protoc. Nucleic Acid Chem.* 2009, Chapter 4: doi:10.1002/0471142700.nc0434s362009; Jahns *et al.*, *Nat. Commun.*, Vol. 6: 6317, 2015; Knouse *et al.*, *Science*, Vol. 361: 1234-1238, 2018; and Sakamuri *et al.*, *ChemBioChem*, Vol. 21(9): 1304-1308, 2020.

[0074] In some embodiments of the RNAi constructs, the 5' end of the sense strand, antisense strand, or both the antisense and sense strands comprises a phosphate moiety. As used herein, the term “phosphate moiety” refers to a terminal phosphate group that includes unmodified phosphates (—O—P(=O)(OH)OH) as well as modified phosphates. Modified phosphates include phosphates in which one or more of the O and OH groups are replaced with H, O, S, N(R) or alkyl (*e.g.*, C₁ to C₁₂) where R is H, an amino protecting group or unsubstituted or substituted alkyl (*e.g.*, C₁ to C₁₂). Exemplary phosphate moieties include, but are not limited to, 5'-monophosphate; 5'-diphosphate; 5'-triphosphate; 5'-guanosine cap (7-methylated or non-methylated); 5'-adenosine cap or any other modified or unmodified nucleotide cap structure; 5'-monothiophosphate (phosphorothioate); 5'-monodithiophosphate (phosphorodithioate); 5'-alpha-thiotriphosphate; 5'-gamma-thiotriphosphate, 5'-phosphoramidates; 5'-vinylphosphates; 5'-alkylphosphonates (*e.g.*, alkyl = methyl, ethyl, isopropyl, propyl, etc.); and 5'-alkyletherphosphonates (*e.g.*, alkylether = methoxymethyl, ethoxymethyl, etc.).

[0075] The modified nucleotides that can be incorporated into the RNAi constructs may have more than one chemical modification described herein. For instance, the modified nucleotide may have a modification to the ribose sugar as well as a modification to the nucleobase. By way of example, a modified nucleotide may comprise a 2' sugar modification (*e.g.*, 2'-fluoro or 2'-O-methyl) and comprise a modified base (*e.g.*, 5-methyl cytosine or

pseudouracil). In other embodiments, the modified nucleotide may comprise a sugar modification in combination with a modification to the 5' phosphate that would create a modified internucleotide or internucleoside linkage when the modified nucleotide was incorporated into a polynucleotide. For instance, in some embodiments, the modified nucleotide may comprise a sugar modification, such as a 2'-fluoro modification, a 2'-O-methyl modification, or a bicyclic sugar modification, as well as a 5' phosphorothioate group. Accordingly, in some embodiments, one or both strands of the RNAi constructs comprise a combination of 2' modified nucleotides or BNAs and phosphorothioate internucleotide linkages. In certain embodiments, both the sense and antisense strands of the RNAi constructs comprise a combination of 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, and phosphorothioate internucleotide linkages. Exemplary RNAi constructs comprising modified nucleotides and internucleotide linkages are shown in **Table 2**.

[0076] Exemplary modification patterns for RNAi constructs are shown in **Figures 7A-7R**. These patterns may be used in the context of the RNAi duplexes disclosed herein, or in the context of RNAi constructs in general. **Figures 7A-7R** each show a hybridized sense (top) and antisense (bottom) strand, in which each of the nucleotides is modified. The solid circles in **Figures 7A-7R** correspond to 2'-O-methyl ribonucleotides, while the open circles correspond to 2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotides. The hatched circles correspond to inverted abasic deoxynucleotides. Bold lines indicate where a phosphorothioate bond is used in place of the standard phosphodiester bond between nucleotides. Finally, arrows represent where a ligand (e.g., GalNAc or a fatty acid such as C22) may be attached to the RNAi construct. As demonstrated in the Examples below, these modification patterns are effective across a range of different trigger sequences in the FAM13A sequence, indicating that they are generally applicable to RNAi constructs.

[0077] The RNAi constructs can readily be made using techniques known in the art, for example, using conventional nucleic acid solid phase synthesis. The polynucleotides of the RNAi constructs can be assembled on a suitable nucleic acid synthesizer utilizing standard nucleotide or nucleoside precursors (e.g., phosphoramidites). Automated nucleic acid synthesizers are sold commercially by several vendors, including DNA/RNA synthesizers from Applied Biosystems (Foster City, CA), MerMade synthesizers from BioAutomation (Irving, TX), and OligoPilot synthesizers from GE Healthcare Life Sciences (Pittsburgh, PA). An exemplary method for synthesizing the RNAi constructs is described in Example 3.

[0078] A 2' silyl protecting group can be used in conjunction with acid labile dimethoxytrityl (DMT) at the 5' position of ribonucleosides to synthesize oligonucleotides via phosphoramidite chemistry. Final deprotection conditions are known not to significantly degrade RNA products. All syntheses can be conducted in any automated or manual synthesizer on large, medium, or small scale. The syntheses may also be carried out in multiple well plates, columns, or glass slides.

[0079] The 2'-O-silyl group can be removed via exposure to fluoride ions, which can include any source of fluoride ion, *e.g.*, those salts containing fluoride ion paired with inorganic counterions *e.g.*, cesium fluoride and potassium fluoride or those salts containing fluoride ion paired with an organic counterion, *e.g.*, a tetraalkylammonium fluoride. A crown ether catalyst can be utilized in combination with the inorganic fluoride in the deprotection reaction. Exemplary fluoride ion sources are tetrabutylammonium fluoride or aminohydrofluorides (*e.g.*, combining aqueous HF with triethylamine in a dipolar aprotic solvent, *e.g.*, dimethylformamide).

[0080] The choice of protecting groups for use on the phosphite triesters and phosphotriesters can alter the stability of the triesters towards fluoride. Methyl protection of the phosphotriester or phosphite triester can stabilize the linkage against fluoride ions and improve process yields.

[0081] Since ribonucleosides have a reactive 2' hydroxyl substituent, it can be desirable to protect the reactive 2' position in RNA with a protecting group that is orthogonal to a 5'-O-dimethoxytrityl protecting group, *e.g.*, one stable to treatment with acid. Silyl protecting groups meet this criterion and can be readily removed in a final fluoride deprotection step that can result in minimal RNA degradation.

[0082] Tetrazole catalysts can be used in the standard phosphoramidite coupling reaction. Exemplary catalysts include, *e.g.*, tetrazole, S-ethyl-tetrazole, benzylthiotetrazole, p-nitrophenyltetrazole.

[0083] As can be appreciated by the skilled artisan, further methods of synthesizing the RNAi constructs described herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Other synthetic chemistry transformations, protecting groups (*e.g.*, for hydroxyl, amino, etc. present on the bases) and protecting group methodologies (protection and deprotection) useful in synthesizing the RNAi constructs described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic

Transformations, VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof. Custom synthesis of RNAi constructs is also available from several commercial vendors, including Dharmacon, Inc. (Lafayette, CO), AxoLabs GmbH (Kulmbach, Germany), and Ambion, Inc. (Foster City, CA).

[0084] The RNAi constructs may comprise a ligand. As used herein, a "ligand" refers to any compound or molecule that is capable of interacting with another compound or molecule, directly or indirectly. The interaction of a ligand with another compound or molecule may elicit a biological response (*e.g.*, initiate a signal transduction cascade, induce receptor-mediated endocytosis) or may just be a physical association. The ligand can modify one or more properties of the double-stranded RNA molecule to which is attached, such as the pharmacodynamic, pharmacokinetic, binding, absorption, cellular distribution, cellular uptake, charge and/or clearance properties of the RNA molecule.

[0085] The ligand may comprise a serum protein (*e.g.*, human serum albumin, low-density lipoprotein, globulin), a cholesterol moiety, a vitamin (biotin, vitamin E, vitamin B₁₂), a folate moiety, a steroid, a bile acid (*e.g.*, cholic acid), a fatty acid (*e.g.*, palmitic acid, myristic acid), a carbohydrate (*e.g.*, a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid), a glycoside, a phospholipid, or antibody or binding fragment thereof (*e.g.*, antibody or binding fragment that targets the RNAi construct to a specific cell type, such as liver). Other examples of ligands include dyes, intercalating agents (*e.g.*, acridines), cross-linkers (*e.g.*, psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial endonucleases (*e.g.*, EDTA), lipophilic molecules, *e.g.*, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine), peptides (*e.g.*, antennapedia peptide, Tat peptide, RGD peptides), alkylating agents, polymers, such as polyethylene glycol (PEG) (*e.g.*, PEG-40K), polyamino acids, and polyamines (*e.g.*, spermine, spermidine).

[0086] In certain embodiments, the ligands have endosomolytic properties. The endosomolytic ligands promote the lysis of the endosome and/or transport of the RNAi construct,

or its components, from the endosome to the cytoplasm of the cell. The endosomolytic ligand may be a polycationic peptide or peptidomimetic, which shows pH-dependent membrane activity and fusogenicity. In one embodiment, the endosomolytic ligand assumes its active conformation at endosomal pH. The “active” conformation is that conformation in which the endosomolytic ligand promotes lysis of the endosome and/or transport of the RNAi construct, or its components, from the endosome to the cytoplasm of the cell. Exemplary endosomolytic ligands include the GALA peptide (Subbarao *et al.*, *Biochemistry*, Vol. 26: 2964-2972, 1987), the EALA peptide (Vogel *et al.*, *J. Am. Chem. Soc.*, Vol. 118: 1581-1586, 1996), and their derivatives (Turk *et al.*, *Biochem. Biophys. Acta*, Vol. 1559: 56-68, 2002). In one embodiment, the endosomolytic component may contain a chemical group (*e.g.*, an amino acid) which will undergo a change in charge or protonation in response to a change in pH. The endosomolytic component may be linear or branched.

[0087] In some embodiments, the ligand comprises a lipid or other hydrophobic molecule. In one embodiment, the ligand comprises a cholesterol moiety or other steroid. Cholesterol-conjugated oligonucleotides have been reported to be more active than their unconjugated counterparts (Manoharan, *Antisense Nucleic Acid Drug Development*, Vol. 12: 103-228, 2002). Ligands comprising cholesterol moieties and other lipids for conjugation to nucleic acid molecules have also been described in U.S. Patent Nos. 7,851,615; 7,745,608; and 7,833,992, all of which are hereby incorporated by reference in their entireties. In another embodiment, the ligand comprises a folate moiety. Polynucleotides conjugated to folate moieties can be taken up by cells via a receptor-mediated endocytosis pathway. Such folate-polynucleotide conjugates are described in U.S. Patent No. 8,188,247, which is hereby incorporated by reference in its entirety.

[0088] In certain embodiments, it is desirable to specifically deliver the RNAi constructs to liver cells to reduce expression of FAM13A protein specifically in the liver. Accordingly, in certain embodiments, the ligand targets delivery of the RNAi construct specifically to liver cells (*e.g.*, hepatocytes) using various approaches as described in more detail below. In certain embodiments, the RNAi constructs are targeted to liver cells with a ligand that binds to the surface-expressed asialoglycoprotein receptor (ASGR) or component thereof (*e.g.*, ASGR1, ASGR2).

[0089] In some embodiments, RNAi constructs can be specifically targeted to the liver by employing ligands that bind to or interact with proteins expressed on the surface of liver cells.

For example, in certain embodiments, the ligands may comprise antigen binding proteins (*e.g.*, antibodies or binding fragments thereof (*e.g.*, Fab, scFv)) that specifically bind to a receptor expressed on hepatocytes, such as the asialoglycoprotein receptor and the LDL receptor. In some embodiments, the ligand comprises an antibody or binding fragment thereof that specifically binds to ASGR1 and/or ASGR2. In another embodiment, the ligand comprises a Fab fragment of an antibody that specifically binds to ASGR1 and/or ASGR2. A “Fab fragment” is comprised of one immunoglobulin light chain (*i.e.*, light chain variable region (VL) and constant region (CL)) and the CH1 region and variable region (VH) of one immunoglobulin heavy chain. In another embodiment, the ligand comprises a single-chain variable antibody fragment (scFv fragment) of an antibody that specifically binds to ASGR1 and/or ASGR2. An “scFv fragment” comprises the VH and VL regions of an antibody, wherein these regions are present in a single polypeptide chain, and optionally comprising a peptide linker between the VH and VL regions that enables the Fv to form the desired structure for antigen binding. Exemplary antibodies and binding fragments thereof that specifically bind to ASGR1 that can be used as ligands for targeting the RNAi constructs to the liver are described in WIPO Publication No. WO 2017/058944, which is hereby incorporated by reference in its entirety. Other antibodies or binding fragments thereof that specifically bind to ASGR1, LDL receptor, or other liver surface-expressed proteins suitable for use as ligands in the RNAi constructs are commercially available.

[0090] In certain embodiments, it is desirable to specifically deliver the RNAi constructs to adipose tissue or adipose cells to reduce expression of FAM13A protein specifically in adipose cells. Accordingly, in certain embodiments, the ligand targets delivery of the RNAi construct specifically to adipose cells (*e.g.*, subcutaneous white adipose tissue (scWAT) or epididymal white adipose tissue (eWAT)) using various approaches as described in more detail below. In certain embodiments, the RNAi constructs are targeted to adipose tissue or cells by conjugation to long-chain fatty acids, which are saturated or unsaturated fatty acids containing between 12 and 24 carbon atoms. In some embodiments, the long-chain fatty acid is lauric acid (C12), myristic acid (C14), palmitic acid (C16), stearic acid (C18), eicosapentaenoic acid (C20), docosanoic acid (C22), or docosahexanoic acid (C24).

[0091] In certain embodiments, it is desirable to deliver the RNAi constructs systemically to reduce expression of FAM13A protein in multiple or all cell types. Accordingly, in certain embodiments, the ligand targets delivery of the RNAi construct using methods known in the art to facilitate cellular delivery of siRNA (*see, e.g.*, U.S. Patent No. 10,633,653; WO 2022/016043,

each of which is incorporated by reference in their entirety). In some embodiments, the RNAi constructs are targeted to cells by conjugation to cholesterol, α -tocopherol, or fatty acids. In some embodiments, the RNAi constructs are targeted to cells by conjugation to omega fatty acids. In certain embodiments, the RNAi constructs are targeted to cells by conjugation to long-chain fatty acids such as lauric acid (C12), myristic acid (C14), palmitic acid (C16), stearic acid (C18), eicosapentaenoic acid (C20), docosanoic acid (C22), or docosahexanoic acid (C24).

[0092] In certain embodiments, the ligand comprises a carbohydrate. A “carbohydrate” refers to a compound made up of one or more monosaccharide units having at least 6 carbon atoms (which can be linear, branched, or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Carbohydrates include, but are not limited to, the sugars (*e.g.*, monosaccharides, disaccharides, trisaccharides, tetrasaccharides, and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9 monosaccharide units), and polysaccharides, such as starches, glycogen, cellulose, and polysaccharide gums. In some embodiments, the carbohydrate incorporated into the ligand is a monosaccharide selected from a pentose, hexose, or heptose and di- and tri-saccharides including such monosaccharide units. In other embodiments, the carbohydrate incorporated into the ligand is an amino sugar, such as galactosamine, glucosamine, N-acetylgalactosamine, and N-acetylglucosamine.

[0093] In some embodiments, the ligand comprises a hexose or hexosamine. The hexose may be selected from glucose, galactose, mannose, fucose, or fructose. The hexosamine may be selected from fructosamine, galactosamine, glucosamine, or mannosamine. In certain embodiments, the ligand comprises glucose, galactose, galactosamine, or glucosamine. In one embodiment, the ligand comprises glucose, glucosamine, or N-acetylglucosamine. In another embodiment, the ligand comprises galactose, galactosamine, or N-acetyl-galactosamine. In particular embodiments, the ligand comprises N-acetyl-galactosamine. Ligands comprising glucose, galactose, and N-acetyl-galactosamine (GalNAc) are particularly effective in targeting compounds to liver cells because such ligands bind to the ASGR expressed on the surface of hepatocytes. *See, e.g.*, D’Souza and Devarajan, J. Control Release, Vol. 203: 126-139, 2015. Examples of GalNAc- or galactose-containing ligands that can be incorporated into the RNAi constructs are described in U.S. Patent Nos. 7,491,805; 8,106,022; and 8,877,917; U.S. Patent Publication No. 20030130186; and WIPO Publication No. WO 2013166155, all of which are hereby incorporated by reference in their entireties.

[0094] In certain embodiments, the ligand comprises a multivalent carbohydrate moiety. As used herein, a “multivalent carbohydrate moiety” refers to a moiety comprising two or more carbohydrate units capable of independently binding or interacting with other molecules. For example, a multivalent carbohydrate moiety comprises two or more binding domains comprised of carbohydrates that can bind to two or more different molecules or two or more different sites on the same molecule. The valency of the carbohydrate moiety denotes the number of individual binding domains within the carbohydrate moiety. For instance, the terms “monovalent,” “bivalent,” “trivalent,” and “tetravalent” with reference to the carbohydrate moiety refer to carbohydrate moieties with one, two, three, and four binding domains, respectively. The multivalent carbohydrate moiety may comprise a multivalent lactose moiety, a multivalent galactose moiety, a multivalent glucose moiety, a multivalent N-acetyl-galactosamine moiety, a multivalent N-acetyl-glucosamine moiety, a multivalent mannose moiety, or a multivalent fucose moiety. In some embodiments, the ligand comprises a multivalent galactose moiety. In other embodiments, the ligand comprises a multivalent N-acetyl-galactosamine moiety. In these and other embodiments, the multivalent carbohydrate moiety can be bivalent, trivalent, or tetravalent. In such embodiments, the multivalent carbohydrate moiety can be bi-antennary or tri-antennary. In some embodiments, the multivalent N-acetyl-galactosamine moiety is trivalent or tetravalent. In some embodiments, the multivalent galactose moiety is trivalent or tetravalent. Exemplary trivalent and tetravalent GalNAc-containing ligands for incorporation into the RNAi constructs are described in detail below.

[0095] The ligand can be attached or conjugated to the RNA molecule of the RNAi construct directly or indirectly. For instance, in some embodiments, the ligand is covalently attached directly to the sense or antisense strand of the RNAi construct. In other embodiments, the ligand is covalently attached via a linker to the sense or antisense strand of the RNAi construct. The ligand can be attached to nucleobases, sugar moieties, or internucleotide linkages of polynucleotides (*e.g.*, sense strand or antisense strand) of the RNAi constructs. Conjugation or attachment to purine nucleobases or derivatives thereof can occur at any position including, endocyclic and exocyclic atoms. In certain embodiments, the 2-, 6-, 7-, or 8-positions of a purine nucleobase are attached to a ligand. Conjugation or attachment to pyrimidine nucleobases or derivatives thereof can also occur at any position. In some embodiments, the 2-, 5-, and 6-positions of a pyrimidine nucleobase can be attached to a ligand. Conjugation or attachment to sugar moieties of nucleotides can occur at any carbon atom. Exemplary carbon atoms of a sugar

moiety that can be attached to a ligand include the 2', 3', and 5' carbon atoms. The 1' position can also be attached to a ligand, such as in an abasic nucleotide. Internucleotide linkages can also support ligand attachments. For phosphorus-containing linkages (*e.g.*, phosphodiester, phosphorothioate, phosphorodithiotate, phosphoroamidate, and the like), the ligand can be attached directly to the phosphorus atom or to an O, N, or S atom bound to the phosphorus atom. For amine- or amide-containing internucleoside linkages (*e.g.*, PNA), the ligand can be attached to the nitrogen atom of the amine or amide or to an adjacent carbon atom.

[0096] In some embodiments, the ligand may be attached to the 3' or 5' end of either the sense or antisense strand. In certain embodiments, the ligand is covalently attached to the 5' end of the sense strand. In such embodiments, the ligand is attached to the 5'-terminal nucleotide of the sense strand. In these and other embodiments, the ligand is attached at the 5'-position of the 5'-terminal nucleotide of the sense strand. In embodiments in which an inverted abasic nucleotide is the 5'-terminal nucleotide of the sense strand and linked to the adjacent nucleotide via a 5'-5' internucleotide linkage, the ligand can be attached at the 3'-position of the inverted abasic nucleotide. In other embodiments, the ligand is covalently attached to the 3' end of the sense strand. For example, in some embodiments, the ligand is attached to the 3'-terminal nucleotide of the sense strand. In certain such embodiments, the ligand is attached at the 3'-position of the 3'-terminal nucleotide of the sense strand. In embodiments in which an inverted abasic nucleotide is the 3'-terminal nucleotide of the sense strand and linked to the adjacent nucleotide via a 3'-3' internucleotide linkage, the ligand can be attached at the 5'-position of the inverted abasic nucleotide. In alternative embodiments, the ligand is attached near the 3' end of the sense strand, but before one or more terminal nucleotides (*i.e.*, before 1, 2, 3, or 4 terminal nucleotides). In some embodiments, the ligand is attached at the 2'-position of the sugar of the 3'-terminal nucleotide of the sense strand. In other embodiments, the ligand is attached at the 2'-position of the sugar of the 5'-terminal nucleotide of the sense strand.

[0097] In certain embodiments, the ligand is attached to the sense or antisense strand via a linker. A "linker" is an atom or group of atoms that covalently joins a ligand to a polynucleotide component of the RNAi construct. The linker may be from about 1 to about 30 atoms in length, from about 2 to about 28 atoms in length, from about 3 to about 26 atoms in length, from about 4 to about 24 atoms in length, from about 6 to about 20 atoms in length, from about 7 to about 20 atoms in length, from about 8 to about 20 atoms in length, from about 8 to about 18 atoms in length, from about 10 to about 18 atoms in length, and from about 12 to about

18 atoms in length. In some embodiments, the linker may comprise a bifunctional linking moiety, which generally comprises an alkyl moiety with two functional groups. One of the functional groups is selected to bind to the compound of interest (*e.g.*, sense or antisense strand of the RNAi construct) and the other is selected to bind essentially any selected group, such as a ligand as described herein. In certain embodiments, the linker comprises a chain structure or an oligomer of repeating units, such as ethylene glycol or amino acid units. Examples of functional groups that are typically employed in a bifunctional linking moiety include, but are not limited to, electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In some embodiments, bifunctional linking moieties include amino, hydroxyl, carboxylic acid, thiol, unsaturations (*e.g.*, double or triple bonds), and the like.

[0098] Linkers that may be used to attach a ligand to the sense or antisense strand in the RNAi constructs include, but are not limited to, pyrrolidine, 8-amino-3,6-dioxaoctanoic acid, succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate, 6-aminohexanoic acid, substituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl or substituted or unsubstituted C₂-C₁₀ alkynyl. Suitable substituent groups for such linkers include, but are not limited to, hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

[0099] In certain embodiments, the linkers are cleavable. A cleavable linker is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In some embodiments, the cleavable linker is cleaved at least 10 times, 20 times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, or more, or at least 100 times faster in the target cell or under a first reference condition (which can, *e.g.*, be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, *e.g.*, be selected to mimic or represent conditions found in the blood or serum).

[0100] Cleavable linkers are susceptible to cleavage agents, *e.g.*, pH, redox potential, or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, *e.g.*, oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linker by reduction; esterases; endosomes or agents that can create an acidic environment, *e.g.*, those that result in a pH of five

or lower; enzymes that can hydrolyze or degrade an acid cleavable linker by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

[0101] A cleavable linker may comprise a moiety that is susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic pH at around 5.0. Some linkers will have a cleavable group that is cleaved at a preferred pH, thereby releasing the RNA molecule from the ligand inside the cell, or into the desired compartment of the cell.

[0102] A linker can include a cleavable group that is cleavable by a particular enzyme. The type of cleavable group incorporated into a linker can depend on the cell to be targeted. For example, liver-targeting ligands can be linked to RNA molecules through a linker that includes an ester group. Liver cells are rich in esterases, and therefore the linker will be cleaved more efficiently in liver cells than in cell types that are not esterase rich. Other types of cells rich in esterases include cells of the lung, renal cortex, and testis. Linkers that contain peptide bonds can be used when targeting cells rich in peptidases, such as liver cells and synoviocytes.

[0103] In general, the suitability of a candidate cleavable linker can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate linker. It will also be desirable to also test the candidate cleavable linker for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus, one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, *e.g.*, blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. It may be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in whole animals. In some embodiments, useful candidate linkers are cleaved at least 2, 4, 10, 20, 50, 70, or 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

[0104] In other embodiments, redox cleavable linkers are utilized. Redox cleavable linkers are cleaved upon reduction or oxidation. An example of a reductively cleavable group is a disulfide linking group (-S-S-). To determine if a candidate cleavable linker is a suitable “reductively cleavable linker,” or for example is suitable for use with a particular RNAi construct

and particular ligand, one can use one or more methods described herein. For example, a candidate linker can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent known in the art, which mimics the rate of cleavage that would be observed in a cell, *e.g.*, a target cell. The candidate linkers can also be evaluated under conditions which are selected to mimic blood or serum conditions. In a specific embodiment, candidate linkers are cleaved by at most 10% in the blood. In other embodiments, useful candidate linkers are degraded at least 2, 4, 10, 20, 50, 70, or 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood (or under *in vitro* conditions selected to mimic extracellular conditions).

[0105] In yet other embodiments, phosphate-based cleavable linkers, which are cleaved by agents that degrade or hydrolyze the phosphate group, are employed to covalently attach a ligand to the sense or antisense strand of the RNAi construct. An example of an agent that hydrolyzes phosphate groups in cells are enzymes, such as phosphatases in cells. Examples of phosphate-based cleavable groups are $-O-P(O)(ORk)-O-$, $-O-P(S)(ORk)-O-$, $-O-P(S)(SRk)-O-$, $-S-P(O)(ORk)-O-$, $-O-P(O)(ORk)-S-$, $-S-P(O)(ORk)-S-$, $-O-P(S)(ORk)-S-$, $-S-P(S)(ORk)-O-$, $-O-P(O)(Rk)-O-$, $-O-P(S)(Rk)-O-$, $-S-P(O)(Rk)-O-$, $-S-P(S)(Rk)-O-$, $-S-P(O)(Rk)-S-$, and $-O-P(S)(Rk)-S-$, where Rk can be hydrogen or C₁-C₁₀ alkyl. Specific embodiments include $-O-P(O)(OH)-O-$, $-O-P(S)(OH)-O-$, $-O-P(S)(SH)-O-$, $-S-P(O)(OH)-O-$, $-O-P(O)(OH)-S-$, $-S-P(O)(OH)-S-$, $-O-P(S)(OH)-S-$, $-S-P(S)(OH)-O-$, $-O-P(O)(H)-O-$, $-O-P(S)(H)-O-$, $-S-P(O)(H)-O-$, $-S-P(S)(H)-O-$, $-S-P(O)(H)-S-$, and $-O-P(S)(H)-S-$. Another specific embodiment is $-O-P(O)(OH)-O-$. These candidate linkers can be evaluated using methods analogous to those described above.

[0106] In other embodiments, the linkers may comprise acid cleavable groups, which are groups that are cleaved under acidic conditions. In some embodiments, acid cleavable groups are cleaved in an acidic environment with a pH of about 6.5 or lower (*e.g.*, about 6.0, 5.5, 5.0, or lower), or by agents, such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes, can provide a cleaving environment for acid cleavable groups. Examples of acid cleavable linking groups include, but are not limited to, hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula $-C=NN-$, $C(O)O$, or $-OC(O)$. A specific embodiment is when the carbon attached to the oxygen of the ester (the alkoxy group) is an aryl group, substituted alkyl group, or tertiary alkyl

group such as dimethyl, pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

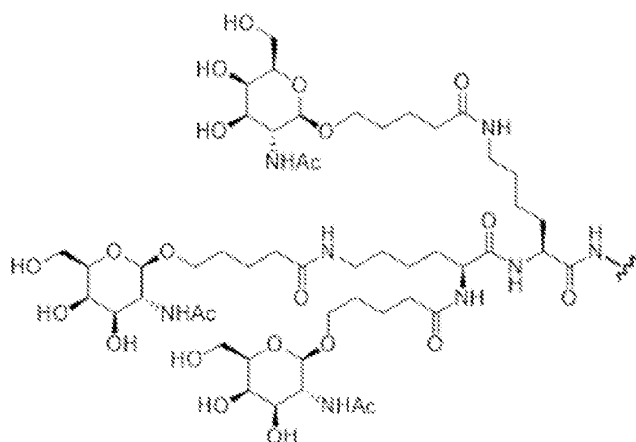
[0107] In other embodiments, the linkers may comprise ester-based cleavable groups, which are cleaved by enzymes, such as esterases and amidases in cells. Examples of ester-based cleavable groups include, but are not limited to, esters of alkylene, alkenylene and alkynylene groups. Ester cleavable groups have the general formula $-C(O)O-$, or $-OC(O)-$. These candidate linkers can be evaluated using methods analogous to those described above.

[0108] In further embodiments, the linkers may comprise peptide-based cleavable groups, which are cleaved by enzymes, such as peptidases and proteases in cells. Peptide-based cleavable groups are peptide bonds formed between amino acids to yield oligopeptides (*e.g.*, dipeptides, tripeptides) and polypeptides. Peptide-based cleavable groups include the amide group ($-C(O)NH-$). The amide group can be formed between any alkylene, alkenylene or alkynylene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide-based cleavage group is generally limited to the peptide bond (*i.e.*, the amide bond) formed between amino acids yielding peptides and proteins. Peptide-based cleavable linking groups have the general formula $-NHCHR^A C(O)NHCHR^B C(O)-$, where R^A and R^B are the side chains of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

[0109] Other types of linkers suitable for attaching ligands to the sense or antisense strands in the RNAi constructs are known in the art and can include the linkers described in U.S. Patent Nos. 7,723,509; 8,017,762; 8,828,956; 8,877,917; and 9,181,551, all of which are hereby incorporated by reference in their entireties.

[0110] In certain embodiments, the ligand covalently attached to the sense or antisense strand of the RNAi constructs comprises a GalNAc moiety, *e.g.*, a multivalent GalNAc moiety. In some embodiments, the multivalent GalNAc moiety is a trivalent GalNAc moiety and is attached to the 3' end of the sense strand. In other embodiments, the multivalent GalNAc moiety is a trivalent GalNAc moiety and is attached to the 5' end of the sense strand. In yet other embodiments, the multivalent GalNAc moiety is a tetravalent GalNAc moiety and is attached to the 3' end of the sense strand. In still other embodiments, the multivalent GalNAc moiety is a tetravalent GalNAc moiety and is attached to the 5' end of the sense strand.

[0111] In certain embodiments, the RNAi constructs comprise a ligand having the following structure ([Structure 1]):

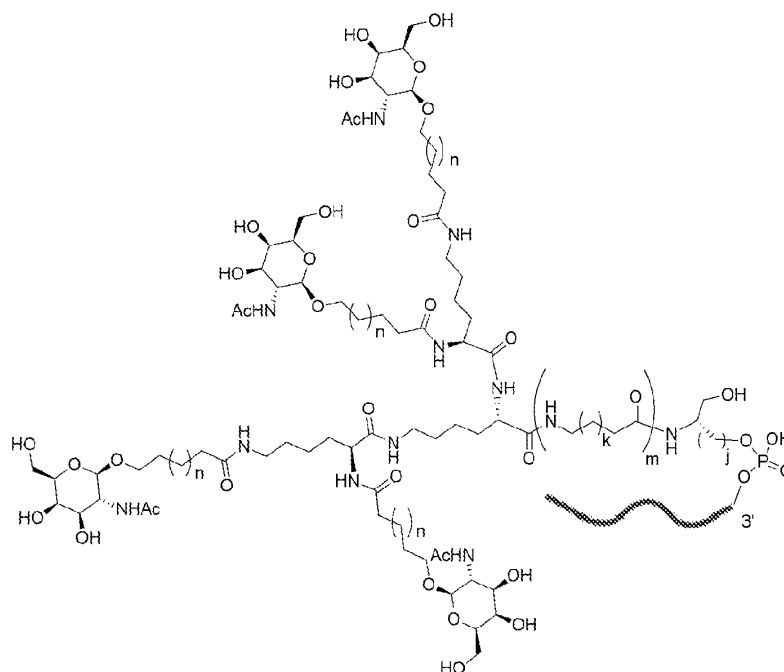


[0112] In preferred embodiments, the ligand having this structure is covalently attached to the 5' end of the sense strand (*e.g.*, to the 5' terminal nucleotide of the sense strand) via a linker, such as the linkers described herein. In one embodiment, the linker is an aminohexyl linker.

[0113] Exemplary trivalent and tetravalent GalNAc moieties and linkers that can be attached to the double-stranded RNA molecules in the RNAi constructs are provided in the structural formulas I-IX below. "Ac" in the formulas listed herein represents an acetyl group.

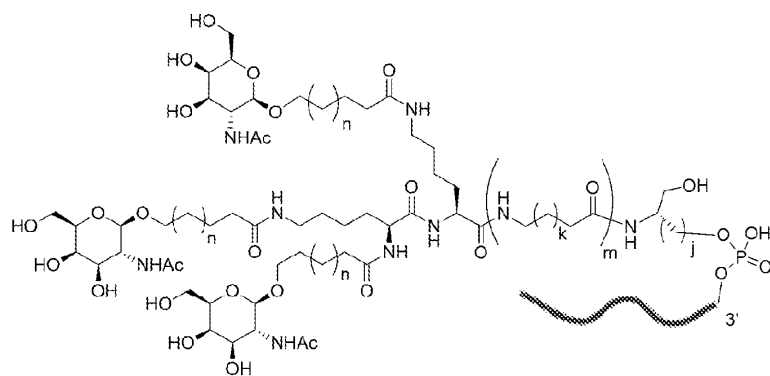
[0114] In one embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula I, wherein each *n* is independently 1 to 3, *k* is 1 to 3, *m* is 1 or 2, *j* is 1 or 2, and the ligand is attached to the 3' end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):

[0115]



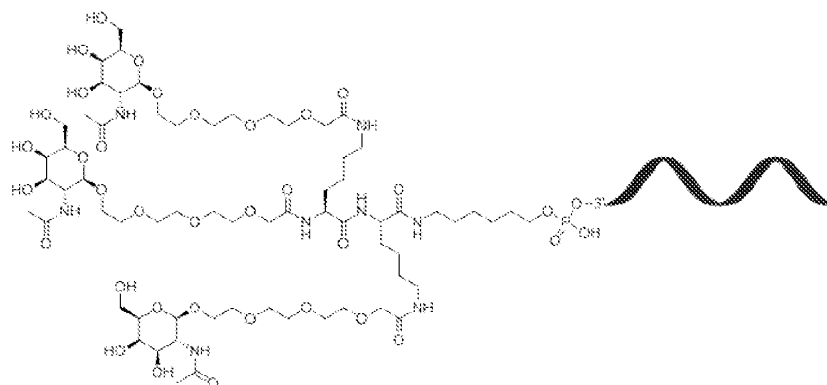
FORMULA I

[0116] In another embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula II, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2, j is 1 or 2, and the ligand is attached to the 3' end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



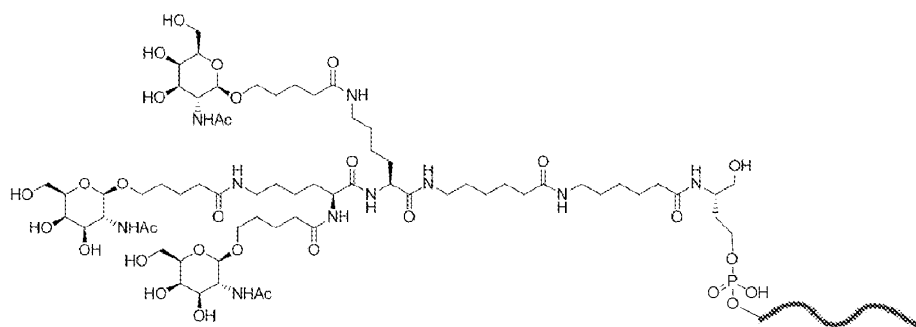
FORMULA II

[0117] In yet another embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula III, wherein the ligand is attached to the 3' end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



FORMULA III

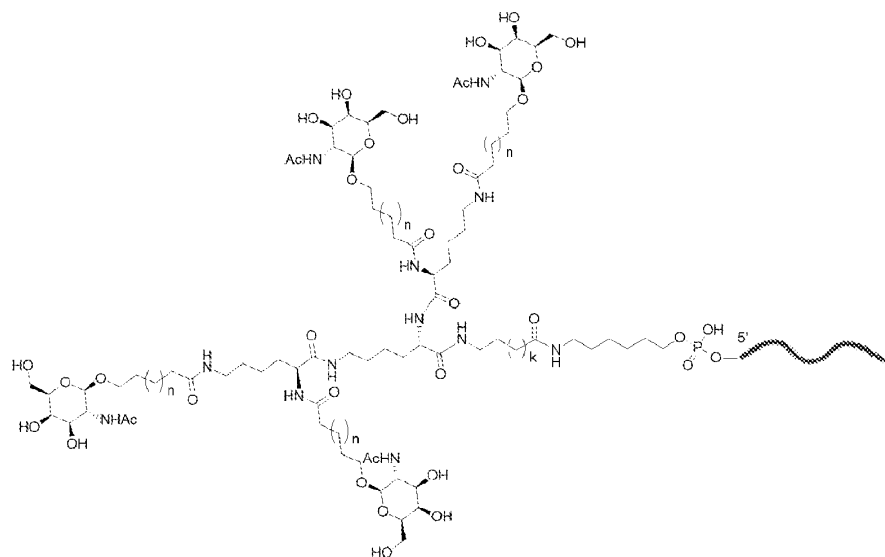
[0118] In still another embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula IV, wherein the ligand is attached to the 3' end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



FORMULA IV

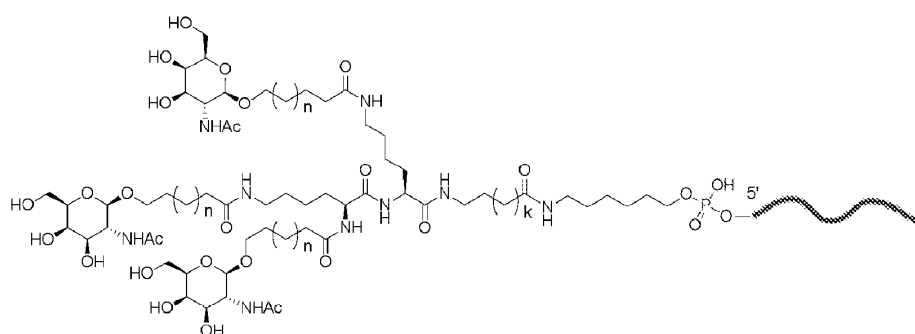
[0119] In certain embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula V, wherein each n is independently 1 to 3, k is 1 to 3, and the

ligand is attached to the 5' end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



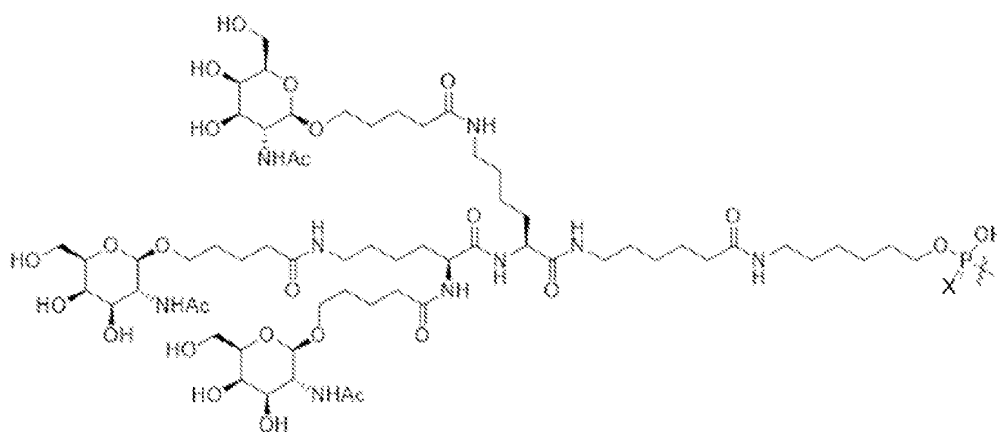
FORMULA V

[0120] In other embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula VI, wherein each n is independently 1 to 3, k is 1 to 3, and the ligand is attached to the 5' end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



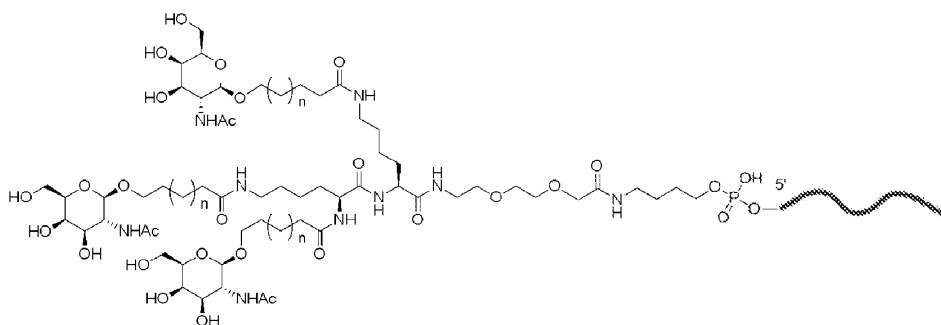
FORMULA VI

[0121] In some embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula VII, wherein X = O or S and wherein the ligand is attached to the 5' end of the sense strand of the double-stranded RNA molecule (represented by the squiggly line):



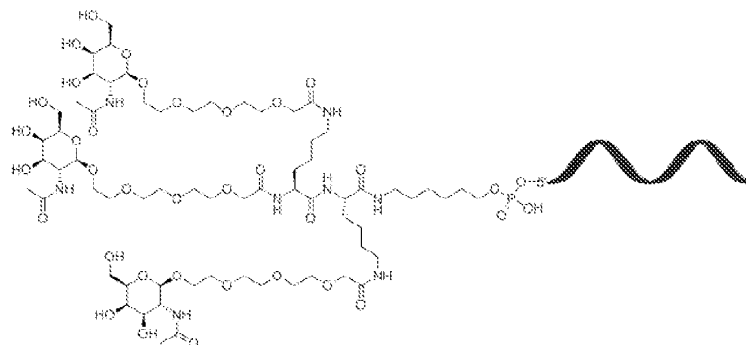
FORMULA VII

[0122] In some embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula VIII, wherein each n is independently 1 to 3 and the ligand is attached to the 5' end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



FORMULA VIII

[0123] In certain embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula IX, wherein the ligand is attached to the 5' end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



FORMULA IX

[0124] A phosphorothioate bond can be substituted for the phosphodiester bond shown in any one of Formulas I-IX to covalently attach the ligand and linker to the nucleic acid strand.

Pharmaceutical Compositions

[0125] The present application also includes pharmaceutical compositions and formulations comprising the RNAi constructs described herein and pharmaceutically acceptable carriers, excipients, or diluents. Such compositions and formulations are useful for reducing expression of the *FAM13A* gene and FAM13A protein in a patient in need thereof. Where clinical applications are contemplated, pharmaceutical compositions and formulations will be prepared in a form appropriate for the intended application. Generally, this will entail preparing compositions that are essentially free of pyrogens, as well as other impurities that could be harmful to humans or animals.

[0126] The phrases “pharmaceutically acceptable” or “pharmacologically acceptable” refer to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human. As used herein, “pharmaceutically acceptable carrier, excipient, or diluent” includes solvents, buffers, solutions, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like acceptable for use in formulating pharmaceuticals, such as pharmaceuticals suitable for administration to humans. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is

incompatible with the disclosed RNAi constructs, its use in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions, provided they do not inactivate the RNAi constructs of the compositions.

[0127] Compositions and methods for the formulation of pharmaceutical compositions depend on a number of criteria, including, but not limited to, route of administration, type and extent of disease or disorder to be treated, or dose to be administered. In some embodiments, the pharmaceutical compositions are formulated based on the intended route of delivery. For instance, in certain embodiments, the pharmaceutical compositions are formulated for parenteral delivery. Parenteral forms of delivery include intravenous, intraarterial, subcutaneous, intrathecal, intraperitoneal, or intramuscular injection or infusion. In one embodiment, the pharmaceutical composition is formulated for intravenous delivery. In such an embodiment, the pharmaceutical composition may include a lipid-based delivery vehicle. In another embodiment, the pharmaceutical composition is formulated for subcutaneous delivery. In such an embodiment, the pharmaceutical composition may include a targeting ligand (*e.g.*, a GalNAc-containing, fatty acid-containing, or antibody-containing ligand as described herein).

[0128] In some embodiments, the pharmaceutical compositions comprise an effective amount of an RNAi construct described herein. An “effective amount” is an amount sufficient to produce a beneficial or desired clinical result. In some embodiments, an effective amount is an amount sufficient to reduce *FAM13A* gene expression in a particular tissue or cell-type (*e.g.*, liver or hepatocytes or adipose tissue) of a patient. An effective amount of an RNAi construct may be from about 0.01 mg/kg body weight to about 100 mg/kg body weight, and may be administered daily, weekly, monthly, or at longer intervals. The precise determination of what would be considered an effective amount and frequency of administration may be based on several factors, including a patient’s size, age, and general condition, type of disorder to be treated (*e.g.*, fatty liver disease, liver fibrosis, or cardiovascular disease), RNAi construct employed, and route of administration.

[0129] Administration of the disclosed pharmaceutical compositions may be via any common route so long as the target tissue is available via that route. Such routes include, but are not limited to, parenteral (*e.g.*, subcutaneous, intramuscular, intraperitoneal, or intravenous), oral, nasal, buccal, intradermal, transdermal, and sublingual routes, or by direct injection into tissue (*e.g.*, liver or adipose) or delivery through the hepatic portal vein. In some embodiments, the pharmaceutical composition is administered parenterally. For instance, in certain embodiments,

the pharmaceutical composition is administered intravenously. In other embodiments, the pharmaceutical composition is administered subcutaneously.

[0130] Colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes, may be used as delivery vehicles for the RNAi constructs.

Commercially available fat emulsions that are suitable for delivering the nucleic acids include Intralipid® (Baxter International Inc.), Liposyn® (Abbott Pharmaceuticals), Liposyn®II (Hospira), Liposyn®III (Hospira), Nutrilipid (B. Braun Medical Inc.), and other similar lipid emulsions. An exemplary colloidal system for use as a delivery vehicle *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The RNAi constructs may be encapsulated within liposomes or may form complexes thereto, in particular to cationic liposomes. Alternatively, RNAi constructs may be complexed to lipids, in particular to cationic lipids. Suitable lipids and liposomes include neutral (*e.g.*, dioleoylphosphatidyl ethanolamine (DOPE), dimyristoylphosphatidyl choline (DMPC), and dipalmitoyl phosphatidylcholine (DPPC)), distearoylphosphatidyl choline, negative (*e.g.*, dimyristoylphosphatidyl glycerol (DMPG)), and cationic (*e.g.*, dioleoyltetramethylaminopropyl (DOTAP) and dioleoylphosphatidyl ethanolamine (DOTMA)). The preparation and use of such colloidal dispersion systems are well known in the art. Exemplary formulations are also disclosed in U.S. Pat. No. 5,981,505; U.S. Pat. No. 6,217,900; U.S. Pat. No. 6,383,512; U.S. Pat. No. 5,783,565; U.S. Pat. No. 7,202,227; U.S. Pat. No. 6,379,965; U.S. Pat. No. 6,127,170; U.S. Pat. No. 5,837,533; U.S. Pat. No. 6,747,014; and WIPO Publication No. WO 03/093449.

[0131] In some embodiments, the RNAi constructs are fully encapsulated in a lipid formulation, *e.g.*, to form a SNALP or other nucleic acid-lipid particle. As used herein, the term “SNALP” refers to a stable nucleic acid-lipid particle. SNALPs typically contain a cationic lipid, a non-cationic lipid, and a lipid that prevents aggregation of the particle (*e.g.*, a PEG-lipid conjugate). SNALPs are exceptionally useful for systemic applications, as they exhibit extended circulation lifetimes following intravenous injection and accumulate at distal sites (*e.g.*, sites physically separated from the administration site). The nucleic acid-lipid particles typically have a mean diameter of about 50 nm to about 150 nm, about 60 nm to about 130 nm, about 70 nm to about 110 nm, or about 70 nm to about 90 nm, and are substantially nontoxic. In addition, the nucleic acids when present in the nucleic acid-lipid particles are resistant in aqueous solution to degradation with a nuclease. Nucleic acid-lipid particles and their method of preparation are

disclosed in, *e.g.*, U.S. Patent Nos. 5,976,567; 5,981,501; 6,534,484; 6,586,410; 6,815,432; and WIPO Publication No. WO 96/40964.

[0132] The pharmaceutical compositions suitable for injectable use include, for example, sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. Generally, these preparations are sterile and fluid to the extent that easy injectability exists. Preparations 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. Appropriate solvents or dispersion media may contain, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by using a coating, such as lecithin, by maintaining the required particle size in the case of dispersion and by using surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0133] Sterile injectable solutions may be prepared by incorporating the active compounds in an appropriate amount into a solvent along with any other ingredients (for example as enumerated above) as desired, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the desired other ingredients, *e.g.*, as enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation include vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient(s) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0134] The compositions of the present application generally may be formulated in a neutral or salt form. Pharmaceutically acceptable salts include, for example, acid addition salts (formed with free amino groups) derived from inorganic acids (*e.g.*, hydrochloric or phosphoric acids), or from organic acids (*e.g.*, acetic, oxalic, tartaric, mandelic, and the like). Salts formed with the free carboxyl groups can also be derived from inorganic bases (*e.g.*, sodium, potassium, ammonium, calcium, or ferric hydroxides) or from organic bases (*e.g.*, isopropylamine,

trimethylamine, histidine, procaine and the like). Pharmaceutically acceptable salts are described in detail in Berge *et al.*, J. Pharmaceutical Sciences, Vol. 66: 1-19, 1977.

[0135] For parenteral administration in an aqueous solution, for example, the solution generally is suitably buffered, and the liquid diluent first rendered isotonic for example with sufficient saline or glucose. Such aqueous solutions may be used, for example, for intravenous, intramuscular, subcutaneous, and intraperitoneal administration. Preferably, sterile aqueous media are employed as is known to those of skill in the art, particularly in light of the present disclosure. By way of illustration, a single dose may be dissolved in 1 mL of isotonic NaCl solution and either added to 1000 mL of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA standards. In certain embodiments, a pharmaceutical composition comprises or consists of a sterile saline solution and an RNAi construct described herein. In other embodiments, a pharmaceutical composition comprises or consists of an RNAi construct described herein and sterile water (*e.g.*, water for injection, WFI). In still other embodiments, a pharmaceutical composition comprises or consists of an RNAi construct described herein and phosphate-buffered saline (PBS).

[0136] In some embodiments, the pharmaceutical compositions are packaged with or stored within a device for administration. Devices for injectable formulations include, but are not limited to, injection ports, pre-filled syringes, autoinjectors, injection pumps, on-body injectors, and injection pens. Devices for aerosolized or powder formulations include, but are not limited to, inhalers, insufflators, aspirators, and the like. Thus, some embodiments comprise administration devices comprising a disclosed pharmaceutical composition for treating or preventing one or more of the diseases or disorders described herein.

Uses For and Methods Using the Disclosed RNAi Constructs

[0137] The present application provides a method for reducing or inhibiting expression of the *FAM13A* gene, and thus the production of FAM13A protein, in a cell (*e.g.*, liver cell or adipose cell) by contacting the cell with any one of the RNAi constructs described herein. The cell may be *in vitro* or *in vivo*. Any method capable of measuring *FAM13A* mRNA or FAM13A protein can be used to assess the efficacy of the RNAi constructs. The terms "FAM13A expression" and "expression of FAM13A," as used herein, refer to the level of *FAM13A* gene

transcription, amount of *FAM13A* mRNA present, level of FAM13A translation, and amount of FAM13A protein present. Therefore, FAM13A expression can be assessed by measuring the amount or level of *FAM13A* mRNA, FAM13A protein, or another biomarker linked to FAM13A expression, such as serum or plasma levels of triglycerides, cholesterol, or insulin. The phrase “reduction in FAM13A expression,” as used herein, refers to a decrease in one or more of the level of *FAM13A* gene transcription, amount of *FAM13A* mRNA present, level of FAM13A translation, and amount of FAM13A protein present.

[0138] The reduction of FAM13A expression in cells or animals treated with an RNAi construct can be determined relative to the FAM13A expression in cells or animals not treated with the RNAi construct or treated with a control RNAi construct. For instance, in some embodiments, reduction of FAM13A expression is assessed by (a) measuring the amount or level of *FAM13A* mRNA in cells (*e.g.*, liver or adipose cells) treated with an RNAi construct, (b) measuring the amount or level of *FAM13A* mRNA in cells (*e.g.*, liver or adipose cells) treated with a control RNAi construct (*e.g.*, RNAi construct directed to an RNA molecule not expressed in cells or a RNAi construct having a nonsense or scrambled sequence) or no construct, and (c) comparing the measured *FAM13A* mRNA levels from treated cells in (a) to the measured *FAM13A* mRNA levels from control cells in (b). The *FAM13A* mRNA levels in the treated cells and controls cells can be normalized to RNA levels for a control gene (*e.g.*, 18S ribosomal RNA or housekeeping gene) prior to comparison. *FAM13A* mRNA levels can be measured by a variety of methods, including Northern blot analysis, nuclease protection assays, fluorescence *in situ* hybridization (FISH), reverse-transcriptase (RT)-PCR, real-time RT-PCR, quantitative PCR, droplet digital PCR, and the like.

[0139] In other embodiments, reduction of FAM13A expression is assessed by (a) measuring the amount or level of FAM13A protein in cells (*e.g.*, liver or adipose cells) treated with an RNAi construct, (b) measuring the amount or level of FAM13A protein in cells (*e.g.*, liver or adipose cells) treated with a control RNAi construct (*e.g.*, RNAi construct directed to an RNA molecule not expressed in cells or a RNAi construct having a nonsense or scrambled sequence) or no construct, and (c) comparing the measured FAM13A protein levels from treated cells in (a) to the measured FAM13A protein levels from control cells in (b). Methods of measuring FAM13A protein levels are known to those of skill in the art, and include Western Blots, immunoassays (*e.g.*, ELISA), and flow cytometry.

[0140] In some embodiments, the methods to assess FAM13A expression levels are performed *in vitro* in cells that natively express FAM13A (*e.g.*, liver or adipose cells) or cells that have been engineered to express FAM13A. In certain embodiments, the methods are performed *in vitro* in liver cells or adipose cells. Suitable liver cells include, but are not limited to, primary hepatocytes (*e.g.*, human or non-human primate hepatocytes), HepAD38 cells, HuH-6 cells, HuH-7 cells, HuH-5-2 cells, BNLCL2 cells, Hep3B cells, or HepG2 cells. In one embodiment, the liver cells are HuH-7 cells. In another embodiment, the liver cells are human primary hepatocytes. In yet another embodiment, the liver cells are Hep3B cells. Suitable adipose cells include cells from subcutaneous white adipose tissue (scWAT), cells from epididymal white adipose tissue (eWAT), or 3T3-L1 cells.

[0141] In other embodiments, the methods to assess FAM13A expression levels are performed *in vivo*. The RNAi constructs and any control RNAi constructs can be administered to an animal and *FAM13A* mRNA or FAM13A protein levels assessed in liver or adipose tissue harvested from the animal following treatment. Alternatively or additionally, a biomarker or functional phenotype associated with FAM13A expression can be assessed in the treated animals. For instance, people with FAM13A variants with reduced *FAM13A* expression also have reduced serum triglycerides and increased HDL cholesterol, and people with FAM13A variants with increased *FAM13A* expression also have increased triglycerides and decreased HDL cholesterol (**FIG. 1**). Additionally, FAM13A expression is significantly correlated with fasting insulin levels. Fathzadeh *et al.*, Nature Communications 11, 1465 (2020). Thus, in some embodiments the goal and result of FAM13A knockdown is to reduce serum or plasma levels of triglycerides, cholesterol, or insulin, and such reduction can be measured in animals treated with RNAi constructs to assess the functional efficacy of reducing FAM13A expression.

[0142] In certain embodiments, expression of *FAM13A* mRNA or protein is reduced in liver or adipose cells by at least 40%, at least 45%, or at least 50% by an RNAi construct. In some embodiments, expression of *FAM13A* mRNA or protein is reduced in liver or adipose cells by at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, or at least 85% by an RNAi construct. In other embodiments, the expression of *FAM13A* mRNA or protein is reduced in liver or adipose cells by about 90% or more, *e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more by an RNAi construct. The percent reduction of FAM13A expression can be measured by any of the methods described herein as well as others known in the art.

[0143] The present application provides methods for reducing or inhibiting expression of the *FAM13A* gene, and thus the production of FAM13A protein, in a patient in need thereof as well as methods of treating or preventing conditions, diseases, or disorders associated with FAM13A expression or activity. A “condition, disease, or disorder associated with FAM13A expression” refers to conditions, diseases, or disorders in which FAM13A expression levels are altered or where elevated expression levels of FAM13A are associated with an increased risk of developing the condition, disease, or disorder. A condition, disease, or disorder associated with FAM13A expression can also include conditions, diseases, or disorders resulting from aberrant changes in lipoprotein metabolism, such as changes resulting in abnormal or elevated levels of cholesterol, lipids, triglycerides, etc., or impaired clearance of these molecules. In certain embodiments, the RNAi constructs are particularly useful for treating or preventing abdominal adiposity, fatty liver disease (*e.g.*, NAFLD and NASH) and cardiovascular disease (*e.g.*, coronary artery disease and myocardial infarction), as well as reducing liver fibrosis and serum cholesterol levels.

[0144] Conditions, diseases, and disorders associated with FAM13A expression that can be treated or prevented according to the methods include, but are not limited to, fatty liver disease, such as alcoholic fatty liver disease, abdominal adiposity, alcoholic steatohepatitis, NAFLD and NASH; chronic liver disease; cirrhosis; cardiovascular disease, such as myocardial infarction, heart failure, stroke (ischemic and hemorrhagic), atherosclerosis, coronary artery disease, peripheral vascular disease (*e.g.*, peripheral artery disease), cerebrovascular disease, vulnerable plaque, and aortic valve stenosis; familial hypercholesterolemia; venous thrombosis; hypercholesterolemia; hyperlipidemia; and dyslipidemia (manifesting, *e.g.*, as elevated total cholesterol, elevated low-density lipoprotein (LDL), elevated very low-density lipoprotein (VLDL), elevated triglycerides, and/or low levels of high-density lipoprotein (HDL)).

[0145] In certain embodiments, the present application provides a method for reducing the expression of FAM13A protein in a patient in need thereof comprising administering to the patient any of the RNAi constructs described herein. The term “patient,” as used herein, refers to a mammal, including humans, and can be used interchangeably with the term “subject.” Preferably, the expression level of FAM13A in hepatocytes in the patient is reduced following administration of the RNAi construct as compared to the FAM13A expression level in a patient not receiving the RNAi construct or as compared to the FAM13A expression level in the patient prior to administration of the RNAi construct. In some embodiments, following administration of

an RNAi construct, expression of FAM13A is reduced in the patient by at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90%, *e.g.*, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. The percent reduction of FAM13A expression can be measured by any of the methods described herein as well as others known in the art.

[0146] In some embodiments, a patient in need of reduction of FAM13A expression is a patient who is at risk of having a myocardial infarction. 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 RNAi constructs described herein. Accordingly, a method for reducing the risk of myocardial infarction in a patient in need thereof comprises administering to the patient an RNAi construct described herein. In some embodiments, any of the RNAi constructs described herein may be used in the preparation of a medicament for reducing the risk of myocardial infarction in a patient in need thereof. Some embodiments comprise a *FAM13A*-targeting RNAi construct for use in a method for reducing the risk of myocardial infarction in a patient in need thereof.

[0147] In certain embodiments, a patient in need of reduction of FAM13A expression is a patient who is diagnosed with or at risk of cardiovascular disease. Thus, a method for treating or preventing cardiovascular disease in a patient in need thereof comprises administering any of the RNAi constructs. In some embodiments, any of the RNAi constructs described herein may be used in the preparation of a medicament for treating or preventing cardiovascular disease in a patient in need thereof. Some embodiments comprise a *FAM13A*-targeting RNAi construct may for use in a method for treating or preventing cardiovascular disease in a patient in need thereof. Cardiovascular disease includes, but is not limited to, myocardial infarction, heart failure, stroke (ischemic and hemorrhagic), atherosclerosis, coronary artery disease, peripheral vascular disease (*e.g.*, peripheral artery disease), cerebrovascular disease, vulnerable plaque, and aortic valve

stenosis. In some embodiments, the cardiovascular disease to be treated or prevented according to the disclosed methods is coronary artery disease. In other embodiments, the cardiovascular disease to be treated or prevented according to the disclosed methods is myocardial infarction. In yet other embodiments, the cardiovascular disease to be treated or prevented according to the disclosed methods is stroke. In still other embodiments, the cardiovascular disease to be treated or prevented according to the disclosed methods is peripheral artery disease. In certain embodiments, administration of the RNAi constructs described herein reduces the risk of non-fatal myocardial infarctions, fatal and non-fatal strokes, certain types of heart surgery (*e.g.*, angioplasty, bypass), hospitalization for heart failure, chest pain in patients with heart disease, and/or cardiovascular events in patients with established heart disease (*e.g.*, prior myocardial infarction, prior heart surgery, and/or chest pain with evidence of blocked arteries). In some embodiments, administration of the RNAi constructs described herein can be used to reduce the risk of recurrent cardiovascular events.

[0148] In some embodiments, a patient to be treated according to the disclosed methods is a patient who has a vulnerable plaque (also referred to as unstable plaque). Vulnerable plaques are a build-up of macrophages and lipids containing predominantly cholesterol that lie underneath the endothelial lining of the arterial wall. These vulnerable plaques can rupture resulting in the formation of a blood clot, which can potentially block blood flow through the artery and cause a myocardial infarction or stroke. Vulnerable plaques can be identified by methods known in the art, including, but not limited to, intravascular ultrasound and computed tomography (*see* Sahara *et al.*, European Heart Journal, Vol. 25: 2026-2033, 2004; Budhoff, J. Am. Coll. Cardiol., Vol. 48: 319-321, 2006; Hausleiter *et al.*, J. Am. Coll. Cardiol., Vol. 48: 312-318, 2006).

[0149] In other embodiments, a patient in need of reduction of FAM13A expression is a patient who has elevated blood levels of cholesterol (*e.g.*, total cholesterol, non-HDL cholesterol, or LDL cholesterol). Accordingly, in some embodiments, a method for reducing blood levels (*e.g.*, serum or plasma) of cholesterol in a patient in need thereof comprises administering to the patient any of the RNAi constructs described herein. In some embodiments, any of the RNAi constructs described herein may be used in the preparation of a medicament for reducing blood levels (*e.g.*, serum or plasma) of cholesterol in a patient in need thereof. Some embodiments comprise a *FAM13A*-targeting RNAi construct for use in a method for reducing blood levels (*e.g.*, serum or plasma) of cholesterol in a patient in need thereof. In certain embodiments, the

cholesterol reduced according to the disclosed methods is LDL cholesterol. In other embodiments, the cholesterol reduced according to the disclosed methods is non-HDL cholesterol. 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.

[0150] In some embodiments, a patient to be treated is a patient who has elevated levels of non-HDL cholesterol (*e.g.*, elevated serum or plasma 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 RNAi construct if the patient has a non-HDL cholesterol level of about 130 mg/dL or greater. In one embodiment, a patient is administered an RNAi construct if the patient has a non-HDL cholesterol level of about 160 mg/dL or greater. In another embodiment, a patient is administered an RNAi construct 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 RNAi construct if the patient has a non-HDL cholesterol level of about 220 mg/dL or greater. In certain embodiments, a patient is administered an RNAi construct 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. J Am Coll Cardiol, Vol. 63:2935-2959, 2014) and has a non-HDL cholesterol level of about 100 mg/dL or greater.

[0151] In certain embodiments, a patient is administered an RNAi construct 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 RNAi construct is administered to a patient if the patient’s LDL cholesterol level is greater than about 160 mg/dL. In other embodiments, an RNAi construct 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 RNAi construct 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.

[0152] In other embodiments, a patient in need of reduction of FAM13A expression is a patient who is diagnosed with or at risk of fatty liver disease. Thus, a method for treating, preventing, or reducing the risk of developing fatty liver disease in a patient in need thereof comprises administering to the patient any of the disclosed RNAi constructs. In some embodiments, any of the RNAi constructs described herein may be used in the preparation of a medicament for treating, preventing, or reducing the risk of developing fatty liver disease in a patient in need thereof. Other embodiments comprise a *FAM13A*-targeting RNAi construct for use in a method for treating, preventing, or reducing the risk of developing fatty liver disease in a patient in need thereof. Fatty liver disease is a condition in which fat accumulates in the liver. There are two primary types of fatty liver disease: a first type that is associated with heavy alcohol use (alcoholic steatohepatitis) and a second type that is not related to use of alcohol (nonalcoholic fatty liver disease (NAFLD)). NAFLD is typically characterized by the presence of fat accumulation in the liver but little or no inflammation or liver cell damage. NAFLD can progress to nonalcoholic steatohepatitis (NASH), which is characterized by liver inflammation and cell damage, both of which in turn can lead to liver fibrosis and eventually cirrhosis or hepatic cancer. In certain embodiments, the fatty liver disease to be treated, prevented, or reduce the risk of developing is NAFLD. In other embodiments, the fatty liver disease to be treated, prevented, or reduce the risk of developing is NASH. In still other embodiments, the fatty liver disease to be treated, prevented, or reduce the risk of developing is alcoholic steatohepatitis. In some embodiments, a patient in need of treatment or prevention for fatty liver disease or is at risk of developing fatty liver disease has been diagnosed with type 2 diabetes, a metabolic disorder, or is obese (*e.g.*, body mass index of ≥ 30.0). In other embodiments, a patient in need of treatment or prevention for fatty liver disease or is at risk of developing fatty liver disease has elevated levels of non-HDL cholesterol or triglycerides. Depending on the patient and other risk factors that patient may have, elevated levels of non-HDL cholesterol may be about 130 mg/dL or greater, about 160 mg/dL or greater, about 190 mg/dL or greater, or about 220 mg/dL or greater. Elevated triglyceride levels may be about 150 mg/dL or greater, about 175 mg/dL or greater, about 200 mg/dL or greater, or about 250 mg/dL or greater.

[0153] In certain embodiments, a patient in need of reduction of FAM13A expression is a patient who is diagnosed with or at risk of developing hepatic fibrosis or cirrhosis. Accordingly,

some embodiments comprise a method for treating, preventing, or reducing liver fibrosis in a patient in need thereof comprising administering to the patient any of the disclosed RNAi constructs. Some embodiments comprise use of any of the RNAi constructs described herein in the preparation of a medicament for treating, preventing, or reducing liver fibrosis in a patient in need thereof. Some embodiments comprise a *FAM13A*-targeting RNAi construct for use in a method for treating, preventing, or reducing liver fibrosis in a patient in need thereof. In some embodiments, a patient at risk for developing hepatic fibrosis or cirrhosis is diagnosed with NAFLD. In other embodiments, a patient at risk for developing hepatic fibrosis or cirrhosis is diagnosed with NASH. In yet other embodiments, a patient at risk for developing hepatic fibrosis or cirrhosis is diagnosed with alcoholic steatohepatitis. In still other embodiments, a patient at risk for developing hepatic fibrosis or cirrhosis is diagnosed with hepatitis. In certain embodiments, administration of a disclosed RNAi construct prevents or delays the development of cirrhosis in the patient.

[0154] In other embodiments, a patient in need of reduction of FAM13A expression is a patient who has been diagnosed with abdominal adiposity or a high waist to hip ratio (WHR). In some embodiments, the patient in need of reduction has a waist to hip ratio in excess of 0.95, in excess of 1.0, in excess of 1.05, or in excess of 1.1. Accordingly, in some embodiments, a method for reducing abdominal adiposity or WHR in a patient in need thereof comprises administering to the patient any of the RNAi constructs described herein. In some embodiments, any of the RNAi constructs described herein may be used in the preparation of a medicament for reducing abdominal adiposity or WHR in a patient in need thereof. Some embodiments comprise a *FAM13A*-targeting RNAi construct for use in a method for reducing abdominal adiposity or WHR in a patient in need thereof.

[0155] In some embodiments, patients in need of reduction of FAM13A expression are treated using RNAi constructs targeted specifically to the liver. In some embodiments, the RNAi construct is targeted by conjugation to a ligand comprising N-acetyl-galactosamine (GalNAc). Accordingly, in some embodiments, a method for reducing FAM13A levels in a patient in need thereof comprises administering to the patient any of the RNAi constructs described herein that has been conjugated to GalNAc.

Definitions of General Terms and Expressions

[0156] In order that the present disclosure can be more readily understood, certain terms are first defined. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

[0157] Units, prefixes, and symbols are denoted in their *Système International de Unites* (SI) accepted form.

[0158] As used in the present disclosure and claims, the singular forms "a," "an," and "the" include plural forms unless the context clearly dictates otherwise. Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive. The term "and/or" as used in a phrase such as "A and/or B" herein is intended to include both "A and B," "A or B," "A," and "B." Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0159] It is understood that wherever embodiments are described herein with the language "comprising," otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are also provided. In this disclosure, "comprises," "comprising," "containing" and "having" and the like can have the meaning ascribed to them in U.S. Patent law and can mean "includes," "including," and the like; "consisting essentially of" or "consists essentially" likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments.

[0160] The terms "about" or "comprising essentially of" refer to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, *i.e.*, the limitations of the measurement system. For example, "about" or "comprising essentially of" can mean within 1 or more than 1 standard deviation per the practice in the art. Alternatively, "about" or "comprising essentially of" can mean a range of up to 20%. Furthermore, particularly with respect to biological systems or processes, the terms can mean up

to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the application and claims, unless otherwise stated, the meaning of "about" or "comprising essentially of" should be assumed to be within an acceptable error range for that particular value or composition.

[0161] Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

[0162] The following examples, including the experiments conducted and the results achieved, are provided for illustrative purposes only and are not to be construed as limiting the scope of the appended claims.

EXAMPLES

Example 1: Genomic and Expression Analysis of *FAM13A*

[0163] Genomic analysis was performed to examine the association of three common *FAM13A* variants for their association with adjusted for BMI (WHRadjBMI), triglyceride levels, HDL cholesterol levels, systolic blood pressure, and *FAM13A* expression in subcutaneous adipose tissue eQTL data. The results of this analysis are presented in **FIG. 1** and show that three *FAM13A* variants associate independently with WHR adjusted for BMI.

[0164] First, the signal A variant rs57400569-A is an intronic SNP that is disease protective and is associated with increased HDL cholesterol and decreased WHR, triglycerides, and systolic blood pressure. rs57400569-A is associated with decreased *FAM13A* expression in deCODE adipose tissue eQTL data. rs57400569-A, consistent with *FAM13A* expression being correlated with disease state. The analysis also confirmed a reported association with blood pressure, while discovering previously unreported association with WHR, triglycerides, and HDL. rs57400569-A was also the top cis-eQTL variant in adipose.

[0165] Next, the signal B variant rs7657817-T is a protein coding missense variant that is associated with decreased WHR and triglycerides and increased HDL cholesterol. rs7657817-T is also disease protective, and the analysis confirmed previously reported literature associations.

[0166] Finally, the signal C variant rs9991328-T is an intronic SNP that is disease promoting and is associated with decreased HDL cholesterol and increased WHR, triglycerides, and *FAM13A* expression in deCODE adipose tissue eQTL data. Notably, rs9991328 has a

strong, reproducible Genome Wide Association Study (GWAS) association with WHR in multiple studies (5-10) with a highly significant association reported in UK Biobank data ($p = 1 \times 10^{-51}$) (5). Additionally, the *rs9991328* WHR raising allele was significantly associated with increased fasting insulin levels (a measure of insulin resistance; $p = 5.9 \times 10^{-21}$). *rs9991328*-T is disease promoting, and the analysis confirmed previously reported literature associations.

[0167] The waist-hip ratio raising alleles associate with increased triglycerides, reduced HDL cholesterol, increased systolic blood pressure, and increased FAM13A expression in subcutaneous adipose tissue.

Example 2: siRNA-mediated knockdown of murine *Fam13a* in vivo

[0168] To test the hypothesis that reduced *Fam13a* expression is associated with reduced WHR & CVD risk factors, a series of mouse *Fam13a* siRNA experiments were performed. *Fam13a* siRNAs were conjugated to a palmitate lipid (C16) or GalNAc (attached as described in Example 3 below), and these molecules were tested for their ability to reduce *Fam13a* expression in cultured cells or *in vivo* (*i.e.*, in adipose tissue or liver). These experiments were performed with commercially available mouse *Fam13a* siRNA triggers. The triggers are available from Ambion (s81721) or Dharmacon (J-041073-09), and were prepared as modified siRNA duplexes. The murine siRNA duplex sequences were:

D-0001 sense (SEQ ID NO: 2786)	GAAAGAUUCCAGGACGAU
D-0001 antisense (SEQ ID NO: 2787)	UAUCGUCCUGGAAUCUUUCUG
D-0002 sense (SEQ ID NO: 2788)	GAAUCAAGAUGGUGAAGA
D-0002 antisense (SEQ ID NO: 2789)	AUCUUCACCAUCUUGAUUCCUC
D-0003 sense (SEQ ID NO: 2790)	AGGAAUCAAGAUGGUGAAGA
D-0003 antisense (SEQ ID NO: 2791)	AUCUUCACCAUCUUGAUUCCUCU

[0169] These sequences were prepared as modified duplexes, as shown below. The nucleotide sequences of these modified duplexes apply the following notations: a, u, g, and c = corresponding 2'-O-methyl ribonucleotide; Af, Uf, Gf, and Cf = corresponding 2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide; and invAb = inverted abasic deoxynucleotide (*i.e.*, abasic deoxynucleotide linked to adjacent nucleotide via a substituent at its 3' position (a 3'-3' linkage) when on the 3' end of a strand or linked to adjacent nucleotide via a substituent at its 5' position

(a 5'-5' internucleotide linkage) when on the 5' end of a strand. Insertion of an "s" in the sequence indicates that the two adjacent nucleotides are connected by a phosphorothiodiester group (*e.g.*, a phosphorothioate internucleotide linkage). Unless indicated otherwise, all other nucleotides are connected by 3'-5' phosphodiester groups. The *Fam13a* siRNAs were conjugated to a palmitate lipid (C16) or GalNAc, using the methods provided in Example 3 below.

D-0004 sense (SEQ ID NO: 2792)	gaaagaUfuCfCfAfGfGfGacgasus{invAb}
D-0004 antisense (SEQ ID NO: 2793)	usAfsucguCfcuggAfaUfcuuucsug
D-0005 sense (SEQ ID NO: 2794)	gaaucaAfgAfUfGfGfGfugaagsas{invAb}
D-0005 antisense (SEQ ID NO: 2795)	asUfscuucAfccauCfuUfgauuccsu
D-0006 sense (SEQ ID NO: 2796)	{DCA-C6}saggaucaAfgAfUfGfGfGfugaagas{invAb}
D-0006 antisense (SEQ ID NO: 2797)	asUfscuucAfccauCfuUfgauuccsu

[0170] *In vitro Fam13a* siRNA treatment

[0171] *Fam13a* siRNA effects on *Fam13a* RNA expression levels were analyzed in murine kidney-derived (Renca cell line; ATCC CRL-2947) and adipose-derived (primary adipocytes) cultured cells. **FIGS. 2A and 2B** show the results of this *in vitro* dose-response study of *Fam13a* siRNA's effects in Renca cells and primary adipocytes.

[0172] For experiments in Renca cells, siRNAs were transfected into cells using Lipofectamine RNAiMAX transfection reagent (Thermo Fisher Scientific). Cells were plated in 96-well plates at 12,500 cells per well in 100 μ L base medium (RPMI-1640, 10% FBS, 1% Non-essential amino acids, 1% sodium pyruvate, 2% L-glutamine, and 1% penicillin-streptomycin) and incubated overnight. For transfection, 150 μ L RNAiMAX was mixed with OptiMEM (final dilution 0.3 μ L RNAiMAX per well), then 1 mM siRNA was diluted to 60 μ M in OptiMEM/RNAiMAX and then further diluted to 6 nM starting concentration. siRNAs were serially diluted 1:10 from 6 nM, 0.6 nM, 0.06 nM, and 0.006 nM. To the 100 μ L plating media, 20 μ L OptiMEM/RNAiMAX + siRNA were added for final concentrations of 1 nM, 0.1 nM, 0.01 nM, 0.001 nM, and 0 nM of each siRNA. Cells were incubated for 72 hrs. at 37 °C and 5% CO₂ then media was removed and lysed with 150 μ L Buffer RLT (Qiagen). RNA was isolated using RNeasy 96 RNA isolation protocol following manufacturer's instructions (Qiagen). Real-time PCR was performed using TaqMan® RNA-to-Ct™ 1-Step Kit following manufacturer's

instructions (ThermoFisher) with 4.25 μ L RNA and TaqMan® gene expression assays (ThermoFisher) for *Fam13a* (Mm00467910) and *Hprt* (Mm03024075).

[0173] For experiments in primary mouse adipocytes, using the method originally described by Viswanadha and Londos (Viswanadha, S. & Londos, C. Optimized conditions for measuring lipolysis in murine primary adipocytes. *J. Lipid Res.* 47, 1859–1864 (2006)), the subcutaneous WAT was isolated and dissected from male DIO mice, weighed, and immediately submerged in Krebs-Ringer bicarbonate (KRB) buffer at pH 7.4 with 4% bovine serum albumin (BSA), 500 nM adenosine, and 5 mM glucose, and the stromal vascular fraction (SVF) and primary adipocytes were separated by collagenase digestion (1 mg/mL KRB) and incubated at 37 °C with shaking at 220 rpm for 1 h. After digestion, the mixture was filtered through a 250- μ m gauze mesh into a 15-mL conical polypropylene tube and the infranatant containing the collagenase solution and the SVF was carefully removed using a long needle and syringe. The SVF was cultured as previously described by Hausman et al. (Hausman, D. B., Park, H. J. & Hausman, G. J. Isolation and culture of preadipocytes from rodent white adipose tissue. *Methods Mol. Biol.* 456, 201–219 (2008)) where the SVF containing solution was centrifuged at 200 $\times$ g for 10 min to pellet the SVF cells, resuspended in 10 mL plating medium (DMEM/F12 + 10% FBS), then filtered through a sterile 20- μ m mesh filter into a sterile 50-mL plastic centrifuge tube. SVF cells were plated in 24-well plate at 250,000 cells/well and incubated at 37 °C and 5% CO₂ overnight then the plating medium and nonadherent cells were removed, replaced with DMEM/F12 media + 5% FBS, and media was replaced every two days until cells reached confluency (5–6 days after plating). Differentiation was induced by the addition of differentiation media for 48 h (DMEM/F12 + 5% FBS + 17 nM insulin, 0.1 μ M dexamethasone, 250 μ M 3-Isobutyl-1-methylxanthine (IBMX), and 60 μ M indomethacin). After 48 h, the differentiation media was replaced by maintenance media (DMEM/F12 + 10% FBS + 17 nM insulin) for a total of 10 days with the maintenance media replaced every 2–3 days. On day 10 of differentiation, C16 conjugated siRNAs were diluted to 10 μ M in maintenance media then 10 μ M siRNA was serially diluted 1:10 from 10 μ M, 1 μ M, 100 nM, 10 nM, 1 nM, 0.1 nM, and 0.01 nM. Maintenance media was removed from the cells and replaced with 1.5 mL siRNA containing media and cells were incubated for 72 hrs. at 37 °C and 5% CO₂. After 72 hours, media was removed and cells were collected in 1 mL Qiazol (Qiagen) per well. RNA was isolated using RNeasy 96 universal tissue kit RNA isolation protocol following manufacturer's instructions (Qiagen). Real-time PCR was performed using TaqMan® RNA-to-Ct™ 1-Step Kit following

manufacturer's instructions (ThermoFisher) with 4.25 μ L RNA and TaqMan® gene expression assays (ThermoFisher) for *Fam13a* (Mm00467910) and *Ppib* (Mm00478295).

[0174] As shown in **FIGS. 2A and 2B**, each tested *Fam13a* siRNA construct reduced *Fam13a* expression in a dose-dependent manner. At the highest concentrations, 58%, 68%, or 81% reduction in *Fam13a* mRNA expression levels were observed in Renca cells. Similarly, at the highest concentrations, 49%, 75%, and 78% reduction in *Fam13a* mRNA levels were observed in primary adipocytes.

[0175] **5-day *in vivo* *Fam13a* siRNA treatment in diet-induced obese mice**

[0176] *Fam13a* siRNA effects on *Fam13a* RNA expression levels were analyzed in the high fat diet (HFD) murine model of diet-induced obesity (DIO) and insulin resistance within 5 days. Mice were placed on a HFD for 12 weeks (18 weeks old; n = 6/group). Mice were then subcutaneously administered a single injection containing a 30 mg/kg dose of C16 conjugated murine *Fam13a* siRNA, a control C16 siRNA targeting *mHprt* (C16-*Hprt* siRNA), or vehicle control. Five days post-injection, mice were sacrificed and necropsy was performed in which subcutaneous WAT, epididymal WAT, and liver tissue were obtained. *Fam13a* RNA expression levels were using RNeasy 96 universal tissue kit RNA isolation protocol following manufacturer's instructions (Qiagen). Real-time PCR was performed using TaqMan® RNA-to-Ct™ 1-Step Kit following manufacturer's instructions (ThermoFisher) with 4.25 μ L RNA and TaqMan® gene expression assays (ThermoFisher) for *Fam13a* (Mm00467910) and *Ppib* (Mm00478295). As shown in **FIGS. 3A-3D**, the *Fam13a* siRNA constructs reduced *Fam13a* RNA expression in both the liver and adipose tissue.

[0177] **30-day *in vivo* *Fam13a* siRNA treatment in diet-induced obese mice**

[0178] *Fam13a* siRNA's physiological effects were analyzed in the high fat diet (HFD) murine model of diet-induced obesity and insulin resistance after repeated siRNA injection over the course of 30 days. Mice were placed on a HFD for 12 weeks (19 weeks old; n = 7 or 8 per group). Mice were then administered a 30 mg/kg dose of a C16 conjugated murine *Fam13a* siRNA (D-0002 or D-0003), a control C16 siRNA targeting *mHprt* (C16-*Hprt* siRNA), or vehicle control (SC) once every 10 days for a total of three doses (*see* **FIG. 4A**). Body weight was measured for each mouse at the start of treatment and every 10 days thereafter until the mice were sacrificed thirty days post-injection, when necropsy was performed. Fat mass was measured for each mouse 4 days prior to the first siRNA administration and after 28 days of treatment.

[0179] **FIGS. 4B and 4C** are plots showing the results of *Fam13a* siRNA on body weight and fat mass of mice. After 30 days of treatment, both tested *Fam13a* siRNAs significantly reduced body weight by 11% and fat mass by 20% compared to the controls. These data demonstrate that the C16-conjugated siRNA triggers significantly reduced *Fam13a* expression *in vivo* in adipose tissue when conjugated to C16.

[0180] Additionally, liver weight was reduced by -25%, liver triglyceride was reduced by -31%, plasma insulin was reduced by -40%, and plasma LDL was reduced by -17%. These liver-related effects indicate that the C16-conjugated siRNA triggers also were effective in liver tissue.

[0181] **60-day *in vivo* *Fam13a* siRNA treatment in diet-induced obese mice**

[0182] An experiment was performed to compare the results using a GalNAc-conjugated *Fam13a* siRNA (which targets the siRNA specifically to the liver) head-to-head with the results using a C16-conjugated *Fam13a* siRNA (which targets the siRNA to both adipose tissue and liver). Obese mice were treated with the following molecules every 10 days for 60 days: (1) saline, (2) C16 conjugated non-targeting (NT) siRNA control (30 mg/kg), (3) C16-*Fam13a* siRNA (D-0002; 30 mg/kg), (4) C16-*Fam13a* siRNA (D-0002; 5 mg/kg), (5) GalNAc conjugated NT siRNA control (5 mg/kg), or (6) GalNAc-*Fam13a* siRNA (D-0002; 5 mg/kg).

[0183] After 60 days of treatment, both C16 and GalNAc siRNA treatments significantly reduced body weight, fat mass, liver weight, insulin, total cholesterol, LDL cholesterol, and ALT compared to their respective NT siRNA controls (**FIG. 5**). The mouse *Fam13a* x GalNAc siRNA dosed at 5 mg/kg every 10 days for 60 days in obese mice significantly reduced body weight by -15%, fat mass by -22%, liver weight by -49%, insulin by -66%, total cholesterol by -37%, LDL cholesterol by -37%, and ALT by -60%. Of therapeutic importance, GalNAc-*Fam13a* siRNA (5 mg/kg) treatment was sufficient to significantly reduce all metabolic endpoints to at least approximately the same extent as C16-*Fam13a* siRNA (30 mg/kg) treatment, which demonstrates that hepatic targeting is sufficient for efficacy of *Fam13a* siRNA in obese mice. Additionally, GalNAc-*Fam13a* siRNA significantly reduced total cholesterol to a greater extent than C16-*Fam13a* siRNA, suggesting that hepatic specific targeting may provide enhanced therapeutic benefit beyond broad targeting by a lipid conjugate and at a 6-fold lower dose.

Example 3: Selection, Design and Synthesis of Modified *FAM13A* siRNA molecules

[0184] Candidate sequences for the design of therapeutic siRNA molecules targeting the human *FAM13A* gene were identified using a bioinformatics analysis of the human *FAM13A* transcript provided herein as SEQ ID NO: 1 (Ensembl transcript no. ENST00000264344.9). The bioinformatics analysis included performing informatic analysis of SEQ ID NO: 1, including tiling SEQ ID NO: 1 by triggers of 21 nucleotides in length. To minimize the risk of off target effects, all triggers that were complementary to human micro-RNA and with less than three base pair mismatches to any identified human gene were not prepared for functional testing. In addition, sequences were selected for their ability to cross-react with human and cynomolgus monkey *FAM13A* mRNA. Based on the results of the bioinformatics analysis, sequences were selected for initial synthesis and *in vitro* testing.

[0185] **Table 1** below lists the unmodified sense and antisense sequences for duplex molecules prioritized from the bioinformatics analysis. The first nucleotide in the range of nucleotides targeted by siRNA molecules in each sequence family within the human *FAM13A* transcript (SEQ ID NO: 1) is also shown in **Table 1**.

TABLE 1: siRNA Sequences Directed to *FAM13A*

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1001	1282	CAUGUACCCCAAGUCAGCAAU	2	AUUGCUGACUUGGGGUACAUG	546
D-1002	1284	UGUACCCCAAGUCAGCAAUGU	3	ACAUUGCUGACUUGGGGUACA	547
D-1003	1285	GUACCCCAAGUCAGCAAUGUG	4	CACAUUGCUGACUUGGGGUAC	548
D-1004	1298	GCAUGUGUCUGCAACCGGAG	5	CUCCGGUUGCAGACACAUUGC	549
D-1005	1299	CAAUGUGUCUGCAACCGGAGA	6	UCUCCGGUUGCAGACACAUUG	550
D-1006	1300	AAUGUGUCUGCAACCGGAGAA	7	UUCUCCGGUUGCAGACACAUU	551
D-1007	1302	UGUGUCUGCAACCGGAGAACU	8	AGUUCUCCGGUUGCAGACACA	552
D-1008	1303	GUGUCUGCAACCGGAGAACUC	9	GAGUUCUCCGGUUGCAGACAC	553
D-1009	1304	UGUCUGCAACCGGAGAACUCU	10	AGAGUUCUCCGGUUGCAGACA	554
D-1010 D-1794	1305	GUCUGCAACCGGAGAACUCUU	11	AAGAGUUCUCCGGUUGCAGAC	555
D-1011 D-1795	1306	UCUGCAACCGGAGAACUCUUA	12	UAAGAGUUCUCCGGUUGCAGA	556
D-1012	1307	CUGCAACCGGAGAACUCUUAG	13	CUAAGAGUUCUCCGGUUGCAG	557
D-1013 D-1796	1308	UGCAACCGGAGAACUCUUAGA	14	UCUAAGAGUUCUCCGGUUGCA	558
D-1014 D-1545 D-1635 D-1639 D-1640 D-1646 D-1652	1309	GCAACCGGAGAACUCUUAGAA	15	UUCUAAGAGUUCUCCGGUUGC	559

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1657 D-1662 D-1667 D-1670 D-1676 D-1681 D-1686 D-1691 D-1847 D-1849 D-1859 D-2009 D-2018					
D-1015 D-1570	1311	AACCGGAGAACUCUUAGAAAG	16	CUUUCUAAGAGUUCUCCGGUU	560
D-1016	1322	UCUUAGAAAGAACCAUCCGAU	17	AUCGGAUGGUUCUUUCUAGA	561
D-1017	1323	CUUAGAAAGAACCAUCCGAUC	18	GAUCGGAUGGUUCUUUCUAG	562
D-1018	1324	UUAGAAAGAACCAUCCGAUCA	19	UGAUCGGAUGGUUCUUUCUAA	563
D-1019 D-1817	1326	AGAAAGAACCAUCCGAUCAGC	20	GCUGAUCGGAUGGUUCUUUCU	564
D-1020 D-1599	1328	AAAGAACCAUCCGAUCAGCUG	21	CAGCUGAUCGGAUGGUUCUUU	565
D-1021	1329	AAGAACCAUCCGAUCAGCUGU	22	ACAGCUGAUCGGAUGGUUCUU	566
D-1022 D-1818	1331	GAACCAUCCGAUCAGCUGUAG	23	CUACAGCUGAUCGGAUGGUUC	567
D-1023 D-1597 D-1694 D-1700 D-1707 D-1714 D-1721 D-1728 D-1735 D-1853 D-1873 D-2006 D-2015	1333	ACCAUCCGAUCAGCUGUAGAA	24	UUCUACAGCUGAUCGGAUGGU	568
D-1024 D-1569	1338	CCGAUCAGCUGUAGAACAACA	25	UGUUGUUCUACAGCUGAUCGG	569
D-1025 D-1543	1366	GAUGUUAAUAAACUCUGGAGGU	26	ACCUCCAGAGUUAAUAAACAU	570
D-1026	1371	UAAUAAACUCUGGAGGUCAAAG	27	CUUUGACCUCAGAGUUAAUA	571
D-1027	1373	AUAACUCUGGAGGUCAAAGUU	28	AACUUUGACCUCAGAGUUUAU	572
D-1028 D-1819	1407	AUCUGGAACACUAUCAGCAUC	29	GAUGCUGAUAGUGUUCAGAU	573
D-1029 D-1797	1472	AGGAUGAAGUUCGACAUGGGA	30	UCCCAUGUCGAACUUCAUCCU	574
D-1030	1480	GUUCGACAUGGGAGAGACAAG	31	CUUGUCUCUCCCAUGUCGAAC	575
D-1031	1483	CGACAUGGGAGAGACAAGGGA	32	UCCCUUGUCUCUCCCAUGUCG	576
D-1032	1485	ACAUGGGAGAGACAAGGGACU	33	AGUCCCUUGUCUCUCCCAUGU	577
D-1033	1487	AUGGGAGAGACAAGGGACUUA	34	UAAGUCCCUUGUCUCUCCCAU	578

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1034 D-1542	1489	GGGAGAGACAAGGGACUUAUC	35	GAUAAGUCCCUUGUCUCUCCC	579
D-1035	1490	GGAGAGACAAGGGACUUAUCA	36	UGAUAAGUCCCUUGUCUCUCC	580
D-1036	1491	GAGAGACAAGGGACUUAUCAA	37	UUGAUAAGUCCCUUGUCUCUC	581
D-1037 D-1553	1495	GACAAGGGACUUAUCAACAAA	38	UUUGUUGAUAAGUCCCUUGUC	582
D-1038 D-1589	1496	ACAAGGGACUUAUCAACAAAG	39	CUUUGUUGAUAAGUCCCUUGU	583
D-1039 D-1798	1500	GGGACUUAUCAACAAAGAAAA	40	UUUUCUUUGUUGAUAAGUCCC	584
D-1040 D-1820 D-1933 D-1939 D-1945 D-1951 D-1957 D-1963 D-1969	1514	AAGAAAAUACUCCUUCUGGGU	41	ACCCAGAAGGAGUAUUUUCUU	585
D-1041 D-1799	1520	AUACUCCUUCUGGGUUAACC	42	GGUUGAACCCAGAAGGAGUAU	586
D-1042 D-1576	1533	GUUCAACCACCUUGAUGAUUG	43	CAAUCAUCAAGGUGGUUGAAC	587
D-1043 D-1616	1534	UUCAACCACCUUGAUGAUUGU	44	ACAAUCAUCAAGGUGGUUGAA	588
D-1044 D-1575	1558	UUGAAUACUCAGGAAGUCGAA	45	UUCGACUCCUGAGUAUUCAA	589
D-1045 D-1821	1564	ACUCAGGAAGUCGAAAAGGUA	46	UACCUUUUCGACUCCUGAGU	590
D-1046	1565	CUCAGGAAGUCGAAAAGGUAC	47	GUACCUUUUCGACUCCUGAG	591
D-1047	1566	UCAGGAAGUCGAAAAGGUACA	48	UGUACCUUUUCGACUCCUGA	592
D-1048	1568	AGGAAGUCGAAAAGGUACACA	49	UGUGUACCUUUUCGACUCCU	593
D-1049	1574	UCGAAAAGGUACACAAAAUA	50	UAUUUUUGUGUACCUUUUCGA	594
D-1050	1575	CGAAAAGGUACACAAAAUAC	51	GUUUUUUGUGUACCUUUUCG	595
D-1051	1610	GAGAAAGGAGCAAGCCUAAAC	52	GUUUAGGCUUGCUCUUUCUC	596
D-1052 D-1822	1611	AGAAAGGAGCAAGCCUAAACG	53	CGUUUAGGCUUGCUCUUUCU	597
D-1053	1612	GAAAGGAGCAAGCCUAAACGU	54	ACGUUUAGGCUUGCUCUUUC	598
D-1054 D-1823	1615	AGGAGCAAGCCUAAACGUCAG	55	CUGACGUUUAGGCUUGCUCU	599
D-1055 D-1824	1616	GGAGCAAGCCUAAACGUCAGA	56	UCUGACGUUUAGGCUUGCUC	600
D-1056	1617	GAGCAAGCCUAAACGUCAGAA	57	UUCUGACGUUUAGGCUUGCUC	601
D-1057 D-1825	1618	AGCAAGCCUAAACGUCAGAAA	58	UUUCUGACGUUUAGGCUUGC	602
D-1058 D-1574	1619	GCAAGCCUAAACGUCAGAAAU	59	AUUUCUGACGUUUAGGCUUGC	603
D-1059 D-1800	1620	CAAGCCUAAACGUCAGAAAU	60	GAUUUCUGACGUUUAGGCUUG	604
D-1060 D-1801	1621	AAGCCUAAACGUCAGAAAUCC	61	GGAUUUCUGACGUUUAGGCUU	605

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1061 D-1610	1631	GUCAGAAAUCCAGUACUAAAC	62	GUUUAGUACUGGAUUUCUGAC	606
D-1062 D-1554	1632	UCAGAAAUCCAGUACUAAACU	63	AGUUUAGUACUGGAUUUCUGA	607
D-1063	1652	UUUCUGAGCUUCAUGACAAUC	64	GAUUGUCAUGAAGCU CAGAAA	608
D-1064	1658	AGCUUCAUGACAAUCAGGACG	65	CGUCCUGAUUGUCAUGAAGCU	609
D-1065	1661	UUCAUGACAAUCAGGACGGUC	66	GACCGUCCUGAUUGUCAUGAA	610
D-1066	1662	UCAUGACAAUCAGGACGGUCU	67	AGACCGUCCUGAUUGUCAUGA	611
D-1067	1663	CAUGACAAUCAGGACGGUCUU	68	AAGACCGUCCUGAUUGUCAUG	612
D-1068	1664	AUGACAAUCAGGACGGUCUUG	69	CAAGACCGUCCUGAUUGUCAU	613
D-1069	1665	UGACAAUCAGGACGGUCUUGU	70	ACAAGACCGUCCUGAUUGUCA	614
D-1070 D-1607	1666	GACAAUCAGGACGGUCUUGUG	71	CACAAGACCGUCCUGAUUGUC	615
D-1071	1667	ACAAUCAGGACGGUCUUGUGA	72	UCACAAGACCGUCCUGAUUGU	616
D-1072	1669	AAUCAGGACGGUCUUGUGAAU	73	AUUCACAAGACCGUCCUGAUU	617
D-1073	1670	AUCAGGACGGUCUUGUGAAUA	74	UAUUCACAAGACCGUCCUGAU	618
D-1074 D-1609	1671	UCAGGACGGUCUUGUGAAUAU	75	AUAUUCACAAGACCGUCCUGA	619
D-1075 D-1615 D-1695 D-1701 D-1708 D-1715 D-1722 D-1729 D-1736 D-1852 D-1867 D-2007 D-2016	1678	GGUCUUGUGAAUAUGGAAAGU	76	ACUUUCCAUAUUCACAAGACC	620
D-1076 D-1826	1693	GAAAGUCUCAAUUCCACACGA	77	UCGUGUGGAAUUGAGACUUUC	621
D-1077	1694	AAAGUCUCAAUUCCACACGAU	78	AUCGUGUGGAAUUGAGACUUU	622
D-1078	1695	AAGUCUCAAUUCCACACGAUC	79	GAUCGUGUGGAAUUGAGACUU	623
D-1079	1696	AGUCUCAAUUCCACACGAUCU	80	AGAUCGUGUGGAAUUGAGACU	624
D-1080 D-1827	1697	GUCUCAAUUCCACACGAUCUC	81	GAGAUCGUGUGGAAUUGAGAC	625
D-1081 D-1605	1698	UCUCAAUUCCACACGAUCUCA	82	UGAGAUCGUGUGGAAUUGAGA	626
D-1082	1699	CUCAAUCCACACGAUCUCAU	83	AUGAGAUCGUGUGGAAUUGAG	627
D-1083 D-1828	1700	UCAAUUCCACACGAUCUCAUG	84	CAUGAGAUCGUGUGGAAUUGA	628
D-1084 D-1829	1701	CAAUCCACACGAUCUCAUGA	85	UCAUGAGAUCGUGUGGAAUUG	629
D-1085 D-1830	1703	AUUCACACGAUCUCAUGAGA	86	UCUCAUGAGAUCGUGUGGAAU	630
D-1086 D-1831	1704	UUCACACGAUCUCAUGAGAG	87	CUCUCAUGAGAUCGUGUGGAA	631
D-1087 D-1606	1705	UCCACACGAUCUCAUGAGAGA	88	UCUCUCAUGAGAUCGUGUGGA	632
D-1088	1709	CACGAUCUCAUGAGAGAACUG	89	CAGUUCUCUCAUGAGAU CGUG	633

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1089	1714	UCUCAUGAGAGAACUGGACCU	90	AGGUCCAGUUCUCUCAUGAGA	634
D-1090 D-1832	1716	UCAUGAGAGAACUGGACCUGA	91	UCAGGUCCAGUUCUCUCAUGA	635
D-1091 D-1833	1717	CAUGAGAGAACUGGACCUGAU	92	AUCAGGUCCAGUUCUCUCAUG	636
D-1092	1742	UUGAAUGGAUGUCUGAUGAAA	93	UUUCAUCAGACAUCCAUCUCAA	637
D-1093 D-1802	1783	GGUGGACACACUCAGCAUUUU	94	AAAUGCUGAGUGUGUCCACC	638
D-1094 D-1587	1801	UUUGAGAGCCCCACAUGAAG	95	CUUCAUUGUGGGGCUUCUCAA	639
D-1095 D-1834	1832	AUCCCAGCCUAUCUGACACCA	96	UGGUGUCAGAUAGGCUGGGAU	640
D-1096 D-1835	1833	UCCCAGCCUAUCUGACACCAA	97	UUGGUGUCAGAUAGGCUGGGA	641
D-1097 D-1836	1834	CCCAGCCUAUCUGACACCAAA	98	UUUGGUGUCAGAUAGGCUGGG	642
D-1098	1835	CCAGCCUAUCUGACACCAAAC	99	GUUUGGUGUCAGAUAGGCUGG	643
D-1099	1836	CAGCCUAUCUGACACCAAACA	100	UGUUUGGUGUCAGAUAGGCUG	644
D-1100 D-1837	1856	AGCAGAGAAAUCAAGAUGCCG	101	CGGCAUCUUGAUUUCUCUGCU	645
D-1101 D-1803	1890	GAGCUUUGUCUCCGAAGUGCC	102	GGCACUUCGGAGACAAAGCUC	646
D-1102 D-1563 D-1804	1896	UGUCUCCGAAGUGCCCCAGUC	103	GACUGGGGCACUUCGGAGACA	647
D-1103	1899	CUCCGAAGUGCCCCAGUCGGA	104	UCCGACUGGGGCACUUCGGAG	648
D-1104 D-1838	1900	UCCGAAGUGCCCCAGUCGGAC	105	GUCCGACUGGGGCACUUCGGA	649
D-1105	1943	AGAACUGGGAAGAGCCUAUCC	106	GGAUAGGCUCUUCUCCAGUUCU	650
D-1106	1944	GAACUGGGAAGAGCCUAUCCC	107	GGGAUAGGCUCUUCUCCAGUUC	651
D-1107 D-1608	1952	AAGAGCCUAUCCUGCUUUCU	108	AGAAAGCAGGGAUAGGCUCUU	652
D-1108	2024	AGGCUGGGCGCCUGAUCCGUC	109	GACGGAUCAGGCGCCCAGCCU	653
D-1109	2025	GGCUGGGCGCCUGAUCCGUCA	110	UGACGGAUCAGGCGCCCAGCC	654
D-1110	2026	GCUGGGCGCCUGAUCCGUCAG	111	CUGACGGAUCAGGCGCCCAGC	655
D-1111	2027	CUGGGCGCCUGAUCCGUCAGC	112	GCUGACGGAUCAGGCGCCCAG	656
D-1112	2028	UGGGCGCCUGAUCCGUCAGCU	113	AGCUGACGGAUCAGGCGCCCA	657
D-1113	2050	CUGGACGAAGACAGCACCCC	114	GGGGUCGCGUCUUCGUCCAG	658
D-2094	2055	CGAAGACAGCGACCCAUUGCU	2807	AGCAUGGGGUCGCGUCUUCG	2808
D-1114 D-1568	2066	ACCCCAUGCUCUCUCCUGGU	115	ACCGAGGAGAGAGCAUGGGGU	659
D-1115 D-1567	2070	CAUGCUCUCUCCUGGUUCUA	116	UAGAACCGAGGAGAGAGCAUG	660
D-1116 D-1805	2071	AUGCUCUCUCCUGGUUCUAC	117	GUAGAACCGAGGAGAGAGCAU	661
D-1117	2073	GCUCUCUCCUGGUUCUACGC	118	GCGUAGAACCGAGGAGAGAGC	662
D-1118	2074	CUCUCUCCUGGUUCUACGCU	119	AGCGUAGAACCGAGGAGAGAG	663
D-1119 D-1601	2075	UCUCUCCUGGUUCUACGCUU	120	AAGCGUAGAACCGAGGAGAGA	664
D-1120	2076	CUCUCCUGGUUCUACGCUUA	121	UAAGCGUAGAACCGAGGAGAG	665
D-1121	2077	UCUCCUGGUUCUACGCUUAU	122	AUAAGCGUAGAACCGAGGAGA	666

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1122 D-1550	2078	CUCCUCGGUUCUACGCUUAUG	123	CAUAAGCGUAGAACCGAGGAG	667
D-1123	2079	UCCUCGGUUCUACGCUUAUGG	124	CCAUAAAGCGUAGAACCGAGGA	668
D-1124 D-1549 D-1643 D-1647 D-1651 D-1656 D-1661 D-1666 D-1671 D-1675 D-1680 D-1685 D-1690 D-1848 D-1860	2080	CCUCGGUUCUACGCUUAUGGG	125	CCCAUAAGCGUAGAACCGAGG	669
D-1125	2081	CUCGGUUCUACGCUUAUGGGC	126	GCCCAUAAAGCGUAGAACCGAG	670
D-1126 D-1544 D-1636 D-1648 D-1653 D-1658 D-1663 D-1668 D-1672 D-1677 D-1682 D-1687 D-1692 D-1851 D-1858 D-2010 D-2019	2144	CACCAAACUCCAUUCUUUCA	127	UGAAAGAAUGGGAGUUUGGUG	671
D-1127 D-1565 D-1641	2146	CCAAACUCCAUUCUUUCAUG	128	CAUGAAAGAAUGGGAGUUUGG	672
D-1128 D-1539	2151	CUCCCAUUCUUUCAUGAGGCG	129	CGCCUCAUGAAAGAAUGGGAG	673
D-1129	2155	CAUUCUUUCAUGAGGCGGCGA	130	UCGCCGCCUCAUGAAAGAAUG	674
D-1130	2156	AUUCUUUCAUGAGGCGGCGAA	131	UUCGCCGCCUCAUGAAAGAAU	675
D-1131	2157	UUCUUUCAUGAGGCGGCGAAG	132	CUUCGCCGCCUCAUGAAAGAA	676
D-1132	2158	UCUUUCAUGAGGCGGCGAAGC	133	GCUUCGCCGCCUCAUGAAAGA	677
D-1133	2159	CUUUUCAUGAGGCGGCGAAGCU	134	AGCUUCGCCGCCUCAUGAAAG	678
D-1134	2160	UUUCAUGAGGCGGCGAAGCUC	135	GAGCUUCGCCGCCUCAUGAAA	679
D-1135	2182	UCUCUGGGGUCCUAUGAUGAU	136	AUCAUCAUAGGACCCAGAGA	680
D-1136	2218	ACACCUGCCAGCUCACACGA	137	UCGUGUGAGCUGGGCAGGUGU	681
D-1137	2219	CACCUGCCAGCUCACACGAA	138	UUCGUGUGAGCUGGGCAGGUG	682
D-1138	2221	CCUGCCCAGCUCACACGAAGG	139	CCUUCGUGUGAGCUGGGCAGG	683
D-1139	2226	CCAGCUCACACGAAGGAUUCA	140	UGAAUCCUUCGUGAGCUGG	684

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1140 D-1806	2228	AGCUCACACGAAGGAUUCAGA	141	UCUGAAUCCUUCGUGAGAGCU	685
D-1141 D-1573 D-1638 D-1644 D-1645 D-2024 D-2025 D-2026 D-2027 D-2028 D-2029 D-2030 D-2031 D-2032 D-2033 D-2034	2263	AUCCGGAAGUUUGAAGAUAGA	142	UCUAUCUUCAAACUCCGGAU	686
D-1142 D-1547	2266	CGGAAGUUUGAAGAUAGAUUC	143	GAAUCUAUCUUCAAACUCCG	687
D-1143 D-1602	2270	AGUUUGAAGAUAGAUUCGAAG	144	CUUCGAAUCUAUCUUCAAACU	688
D-1144	2271	GUUUGAAGAUAGAUUCGAAGA	145	UCUUCGAAUCUAUCUUCAAAC	689
D-1145 D-1839	2275	GAAGAUAGAUUCGAAGAAGAG	146	CUCUUCUUCGAAUCUAUCUUC	690
D-1146 D-1807	2294	AGAAGAAGUACAGACCUUCCC	147	GGGAAGGUCUGUACUUCUUCU	691
D-1147 D-1808	2295	GAAGAAGUACAGACCUUCCCA	148	UGGAAGGUCUGUACUUCUUC	692
D-1148 D-1809	2296	AAGAAGUACAGACCUUCCAC	149	GUGGAAGGUCUGUACUUCUUC	693
D-1149 D-1810 D-1938 D-1944 D-1950 D-1956 D-1962 D-1968 D-1974 D-2035 D-2055 D-2056	2343	UCUGAAAUGGACAAAUGACCU	150	AGGUCAUUUGUCCAUUUCAGA	694
D-1150 D-1613	2344	CUGAAAUGGACAAAUGACCUU	151	AAGGUCAUUUGUCCAUUUCAG	695
D-1151 D-1598	2353	ACAAAUGACCUUGCCAAAUUC	152	GAAUUUGGCAAGGUCAUUUGU	696
D-1152 D-1811	2355	AAAUGACCUUGCCAAAUUCG	153	CGGAAUUUGGCAAGGUCAUUU	697
D-1153 D-1556	2356	AAUGACCUUGCCAAAUUCGG	154	CCGGAUUUGGCAAGGUCAUU	698

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1154 D-1595	2358	UGACCUUGCCAAAUCCGGAG	155	CUCCGGAAUUUGGCAAGGUCA	699
D-1155	2359	GACCUUGCCAAAUCCGGAGA	156	UCUCCGGAAUUUGGCAAGGUC	700
D-1156 D-1578	2360	ACCUUGCCAAAUCCGGAGAC	157	GUCUCCGGAAUUUGGCAAGGU	701
D-1157	2361	CCUUGCCAAAUCCGGAGACA	158	UGUCUCCGGAAUUUGGCAAGG	702
D-1158	2373	CCGGAGACAACUUAAGAAUC	159	GAUUCUUUAAGUUGUCUCCGG	703
D-1159	2374	CGGAGACAACUUAAGAAUCA	160	UGAUUCUUUAAGUUGUCUCCG	704
D-1160	2402	AGAUUUCUGAAGAGGACCUAA	161	UUAGGUCCUUCAGAUUUCU	705
D-1161	2413	GAGGACCUAACUCCAGGAUG	162	CAUCCUGGGAGUUAGGUCCUC	706
D-1162	2416	GACCUAACUCCAGGAUGCGG	163	CCGCAUCCUGGGAGUUAGGUC	707
D-1163 D-1812 D-1935 D-1941 D-1947 D-1953 D-1959 D-1965 D-1971	2417	ACCUAACUCCAGGAUGCGGC	164	GCCGAUCCUGGGAGUUAGGU	708
D-1164 D-1813	2432	UGCGGCAGCGAAGCAACACAC	165	GUGUGUUGCUUCGCUGCCGCA	709
D-1165	2433	GCGGCAGCGAAGCAACACACU	166	AGUGUGUUGCUUCGCUGCCGC	710
D-1166 D-1840	2437	CAGCGAAGCAACACACUCCCC	167	GGGGAGUGUGUUGCUUCGCUG	711
D-1167 D-1841	2439	GCGAAGCAACACACUCCCCAA	168	UUGGGGAGUGUGUUGCUUCGC	712
D-1168	2444	GCAACACACUCCCCAAGAGUU	169	AACUCUUGGGGAGUGUGUUGC	713
D-1169	2457	CAAGAGUUUUGGUUCCCAACU	170	AGUUGGGAACCAAACUCUUG	714
D-1170	2460	GAGUUUUGGUUCCCAACUUGA	171	UCAAGUUGGGAACCAAACUC	715
D-1171 D-1592	2462	GUUUUGGUUCCCAACUUGAGA	172	UCUCAAGUUGGGAACCAAAC	716
D-1172 D-1842	2534	UUGAAGCCACAUUGGAAUCUA	173	UAGAUAUCCAAUGUGGCUUCAA	717
D-1173	2568	CCAGGAGAAGCGAGCGGAAAG	174	CUUUCGCGUCGCUUCUCCUGG	718
D-1174 D-1581	2623	GACCAGAUUGCUAAUGAGAAA	175	UUUCUCAUUAAGCAAUCUGGUC	719
D-1175 D-1621	2632	GCUAAUGAGAAAGUGGCUCUG	176	CAGAGCCACUUCUCAUUAAGC	720
D-1176	2677	AGCAUUCAUUGGACGGCCGGUA	177	UACCGGCCGUCCAUGAAUGCU	721
D-1177	2678	GCAUUCAUUGGACGGCCGGUAA	178	UUACCGGCCGUCCAUGAAUGC	722
D-1178	2679	CAUUCAUUGGACGGCCGGUAAC	179	GUUACCGGCCGUCCAUGAAUG	723
D-1179	2680	AUUCAUUGGACGGCCGGUAACA	180	UGUUACCGGCCGUCCAUGAAU	724
D-1180	2681	UUCAUUGGACGGCCGGUAACAA	181	UUUGUUACCGGCCGUCCAUGAA	725
D-1181	2682	UCAUGGACGGCCGGUAACAAA	182	UUUGUUACCGGCCGUCCAUGA	726
D-2095	2683	CAUGGACGGCCGGUAACAAAG	2809	CUUUGUUUACCGGCCGUCCAUG	2810
D-1182	2684	AUGGACGGCCGGUAACAAAGA	183	UCUUGUUUACCGGCCGUCCAUG	727
D-1183	2685	UGGACGGCCGGUAACAAAGAA	184	UUCUUUUGUUACCGGCCGUCCA	728
D-1184	2686	GGACGGCCGGUAACAAAGAAC	185	GUUCUUUGUUACCGGCCGUCC	729
D-1185 D-1814	2688	ACGGCCGGUAACAAAGAACGA	186	UCGUUCUUUGUUACCGGCCGU	730

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1186	2689	CGGCCGGUAAACAAAGAACGAA	187	UUCGUUCUUUGUUACCGGCCG	731
D-1187 D-1815	2690	GGCCGGUAAACAAAGAACGAAC	188	GUUCGUUCUUUGUUACCGGCC	732
D-1188	2691	GCCGGUAAACAAAGAACGAACG	189	CGUUCGUUCUUUGUUACCGGC	733
D-1189	2692	CCGGUAAACAAAGAACGAACGG	190	CCGUUCGUUCUUUGUUACCGG	734
D-1190 D-1843	2693	CGGUAAACAAAGAACGAACGGC	191	GCCGUUCGUUCUUUGUUACCG	735
D-1191	2694	GGUAAACAAAGAACGAACGGCA	192	UGCCGUUCGUUCUUUGUUACC	736
D-1192	2700	AAAGAACGAACGGCAGGUGAU	193	AUACCCUGCCGUUCGUUCUUU	737
D-1193 D-1844	2719	AUGAAGCCACUACGACAGG	194	CCUGUCGUUAGUGGCUUCAU	738
D-1194	2721	GAAGCCACUACGACAGGUA	195	UACCUUCGUUAGUGGCUUC	739
D-1195	2722	AAGCCACUACGACAGGUAC	196	GUACCUUCGUUAGUGGCUU	740
D-1196	2723	AGCCACUACGACAGGUACC	197	GGUACCUUCGUUAGUGGCU	741
D-1197	2724	GCCACUACGACAGGUACCG	198	CGGUACCUUCGUUAGUGGC	742
D-1198	2725	CCACUACGACAGGUACCGG	199	CCGUACCUUCGUUAGUGG	743
D-1199 D-1845	2726	CACUACGACAGGUACCGGC	200	GCCGUACCUUCGUUAGUG	744
D-1200	2727	ACUACGACAGGUACCGGCU	201	AGCCGUACCUUCGUUAGU	745
D-1201	2753	AACAGAUCCUCUCCGAGCUA	202	UAGCUCGGGAGAGGAUCUGUU	746
D-1202	2754	ACAGAUCCUCUCCGAGCUAA	203	UUAGCUCGGGAGAGGAUCUGU	747
D-1203	2756	AGAUCUCCUCUCCGAGCUACA	204	UGUAGCUCGGGAGAGGAUCU	748
D-1204	2759	UCCUCUCCCGAGCUAACACCA	205	UGGUGUUAGCUCGGGAGAGGA	749
D-1205	2760	CCUCUCCCGAGCUAACACCAU	206	AUGGUGUUAGCUCGGGAGAGG	750
D-1206	2761	CUCUCCCGAGCUAACACCAUA	207	UAUGGUGUUAGCUCGGGAGAG	751
D-1207	2764	UCCCGAGCUAACACCAUACCC	208	GGGUAGGUGUUAGCUCGGGA	752
D-1208	2765	CCCGAGCUAACACCAUACCCA	209	UGGGUAGGUGUUAGCUCGGG	753
D-1209 D-1816	2886	GGGGUCAGAAGACGAUAGCAA	210	UUGCUAUCGUCUUCUGACCCC	754
D-1210 D-1561	2887	GGGUCAGAAGACGAUAGCAAU	211	AUUGCUAUCGUCUUCUGACCC	755
D-1211 D-1620	2889	GUCAGAAGACGAUAGCAAUGU	212	ACAUUGCUAUCGUCUUCUGAC	756
D-1212 D-1560	2890	UCAGAAGACGAUAGCAAUGUG	213	CACAUUGCUAUCGUCUUCUGA	757
D-1213 D-1559	2893	GAAGACGAUAGCAAUGUGAAG	214	CUUCACAUUGCUAUCGUCUUC	758
D-1214 D-1558	2895	AGACGAUAGCAAUGUGAAGCC	215	GGCUACAUUGCUAUCGUCU	759
D-1215 D-1604	2923	AUGGUCACUCUGAAAACCGAU	216	AUCGGUUUUCAGAGUGACCAU	760
D-1216	2924	UGGUCACUCUGAAAACCGAUU	217	AAUCGGUUUUCAGAGUGACCA	761
D-1217	2925	GGUCACUCUGAAAACCGAUUU	218	AAAUCGGUUUUCAGAGUGACC	762
D-1218 D-1541	2934	GAAAACCGAUUUCAGUGCACG	219	CGUGCACUGAAAUCGGUUUUC	763
D-1219 D-1588	2937	AACCGAUUUCAGUGCACGAUG	220	CAUCGUGCACUGAAAUCGGUU	764
D-1220 D-1619	2994	UAUUUCCCCAAUGGAUGAUAA	221	UUAUCAUCCAUUGGGGAAUA	765

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1221 D-1557 D-1642 D-1650 D-1655 D-1660 D-1665 D-1674 D-1679 D-1684 D-1689 D-1850 D-1861	3000	CCCAAUGGAUGAUAAAAUACC	222	GGUAAUUUAUCAUCCAUGGG	766
D-1222 D-1579	3002	CAAUGGAUGAUAAAAUACCAU	223	AUGGUAAUUUAUCAUCCAUG	767
D-1223	3005	UGGAUGAUAAAAUACCAUCAA	224	UUGAUGGUAAUUUAUCAUCCA	768
D-1224 D-1555	3014	AAAUACCAUCAAUAGCAGCC	225	GGCUGCAUUUUGAUGGUAAUU	769
D-1225	3043	GGGCUUUCAAAUCUCCAUGCU	226	AGCAUGGAGAUUUUGAAAGCCC	770
D-1226	3044	GGCUUUCAAAUCUCCAUGCUG	227	CAGCAUGGAGAUUUUGAAAGCCC	771
D-1227	3052	AAUCUCCAUGCUGCCUCAUA	228	UAUUGAGGCAGCAUGGAGAUU	772
D-1228	3053	AUCUCCAUGCUGCCUCAUAUAC	229	GUUUGAGGCAGCAUGGAGAU	773
D-1229	3054	UCUCCAUGCUGCCUCAUACC	230	GGUAAUUGAGGCAGCAUGGAGA	774
D-1230	3062	CUGCCUCAAUACCUGAACUCC	231	GGAGUUCAGGUAAUUGAGGCAG	775
D-1231	3082	CUGGAACACCUCAGGAAUUG	232	CAUUUCCUGGAGGUGUCCAG	776
D-1232 D-1586 D-1637 D-1649 D-1654 D-1659 D-1664 D-1669 D-1673 D-1678 D-1683 D-1688 D-1693	3133	CUUCGGGAUUUUGAAGACAAC	233	GUUGUCUUCAAAAUCCCCAAG	777
D-1233	3180	CCAGAAGGAAGACCGCACUCC	234	GGAGUGCGGUCUCCUUCUGG	778
D-1234	3183	GAAGGAAGACCGCACUCCUAU	235	AUAGGAGUGCGGUCUCCUUC	779
D-1235 D-1540	3184	AAGGAAGACCGCACUCCUAUG	236	CAUAGGAGUGCGGUCUCCUU	780
D-1236	3185	AGGAAGACCGCACUCCUAUGG	237	CCAUAGGAGUGCGGUCUCCU	781
D-1237	3186	GGAAGACCGCACUCCUAUGGC	238	GCCAUAGGAGUGCGGUCUCC	782
D-1238 D-1552	3187	GAAGACCGCACUCCUAUGGCU	239	AGCCAUAGGAGUGCGGUCUUC	783
D-1239 D-1618	3189	AGACCGCACUCCUAUGGCUGA	240	UCAGCCAUAGGAGUGCGGUCU	784
D-1240 D-1585	3192	CCGCACUCCUAUGGCUGAAGA	241	UCUUCAGCCAUAGGAGUGCGG	785
D-1241	3225	UAAGCACAUAAAGGCGAAACU	242	AGUUUCGCCUUUAUGUGCUUA	786
D-1242	3226	AAGCACAUAAAGGCGAAACUG	243	CAGUUUCGCCUUUAUGUGCUU	787

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1243	3228	GCACAUAAAGGCGAAACUGAG	244	CUCAGUUUCGCCUUUAUGUGC	788
D-1244 D-1584	3283	GAUUCCAAGUCCAUGUGAGGG	245	CCCUCACAUGGACUUGGAAUC	789
D-1245	3284	AUUCCAAGUCCAUGUGAGGGG	246	CCCCUCACAUGGACUUGGAAU	790
D-1246	3287	CCAAGUCCAUGUGAGGGGCAU	247	AUGCCCCUCACAUGGACUUGG	791
D-1247	3288	CAAGUCCAUGUGAGGGGCAUG	248	CAUGCCCCUCACAUGGACUUG	792
D-1248	3291	GUCCAUGUGAGGGGCAUGGCC	249	GGCCAUGCCCCUCACAUGGAC	793
D-1249	3327	GCAGCUGCGGUGAGAGUUUAC	250	GUAAACUCUCACCGCAGCUGC	794
D-1250	3329	AGCUGCGGUGAGAGUUUACUG	251	CAGUAAACUCUCACCGCAGCU	795
D-1251	3352	CCCAGAGAAAGUGCAGCUCUG	252	CAGAGCUGCACUUUCUCUGGG	796
D-1252	3398	CAAAGCAUGCAGCCCUUCUGC	253	GCAGAAGGGCUGCAUGCUUUG	797
D-1253	3411	CCUUCUGCCUCUAGACCAUUU	254	AAAUUGGUCUAGAGGCAGAAAG	798
D-1254	3414	UCUGCCUCUAGACCAUUUGGC	255	GCCAAAUGGUCUAGAGGCAGA	799
D-1255	3420	UCUAGACCAUUUGGCAUCGGC	256	GCCGAUGCCAAAUGGUCUAGA	800
D-1256	3421	CUAGACCAUUUGGCAUCGGCU	257	AGCCGAUGCCAAAUGGUCUAG	801
D-1257	3422	UAGACCAUUUGGCAUCGGCUC	258	GAGCCGAUGCCAAAUGGUCUA	802
D-1258	3423	AGACCAUUUGGCAUCGGCUCC	259	GGAGCCGAUGCCAAAUGGUCU	803
D-1259 D-1632	3429	UUUGGCAUCGGCUCCUGUUUC	260	GAAACAGGAGCCGAUGCCAAA	804
D-1260	3432	GGCAUCGGCUCUGUUUCCAUC	261	AUGGAAACAGGAGCCGAUGCC	805
D-1261	3436	UCGGCUCUGUUUCCAUCUGCC	262	GGCAAUGGAAACAGGAGCCGA	806
D-1262 D-1580	3438	GGCUCUGUUUCCAUCUGCCUG	263	CAGGCAAUGGAAACAGGAGCC	807
D-1263 D-1583	3498	UAGGCAUUUUGUAAUUGGAAA	264	UUUCCAAUUACAAAUGCCUA	808
D-1264 D-1582	3499	AGGCAUUUUGUAAUUGGAAAG	265	CUUCCAAUUACAAAUGCCU	809
D-1265	3503	AUUUUGUAAUUGGAAAGUCA	266	UUGACUUUCCAAUUACAAA	810
D-1266	3505	UUUGUAAUUGGAAAGUCAAGA	267	UCUUGACUUUCCAAUUACAAA	811
D-1267	3510	AAUUGGAAAGUCAAGACUGCA	268	UGCAGUCUUGACUUUCCAAU	812
D-1268	3514	GGAAGUCAAGACUGCAGUAU	269	AUACUGCAGUCUUGACUUUCC	813
D-1269	3519	GUCAAGACUGCAGUAUGUGCA	270	UGCACAUACUGCAGUCUUGAC	814
D-1270	3520	UCAAGACUGCAGUAUGUGCAC	271	GUGCACAUCUGCAGUCUUGA	815
D-2096	3536	UGCACAUUGCGCACGCGCAUGC	2811	GCAUGCGCGUGCGCAUGUGCA	2812
D-2097	3537	GCACAUUGCGCACGCGCAUGCA	2813	UGCAUGCGCGUGCGCAUGUGC	2814
D-2098	3538	CACAUGCGCACGCGCAUGCAC	2815	GUGCAUGCGCGUGCGCAUGUG	2816
D-2099	3539	ACAUGCGCACGCGCAUGCACG	2817	CGUGCAUGCGCGUGCGCAUGU	2818
D-1271	3565	ACACACACAGUAGUGGAGCUU	272	AAGCUCCACUACUGUGUGUGU	816
D-1272	3568	CACACAGUAGUGGAGCUUUC	273	GGAAAGCUCCACUACUGUGUG	817
D-1273 D-1571	3569	ACACAGUAGUGGAGCUUUCU	274	AGGAAAGCUCCACUACUGUGU	818
D-1273B	3571	ACAGUAGUGGAGCUUUCUAA	275	UUAGGAAAGCUCCACUACUGU	819
D-1274	3582	GCUUCCUAACACUAGCAGAG	276	CUCUGCUAGUGUUAGGAAAGC	820
D-1275	3589	UAAACACUAGCAGAGAUUAAUC	277	GAUUAAUCUCUGCUAGUGUUA	821
D-1276	3590	AACACUAGCAGAGAUUAAUCA	278	UGAUUAAUCUCUGCUAGUGUU	822
D-1277	3591	ACACUAGCAGAGAUUAAUCAC	279	GUGAUUAAUCUCUGCUAGUGU	823
D-1278	3594	CUAGCAGAGAUUAAUCACUAC	280	GUAGUGAUUAAUCUCUGCUAG	824
D-1279	3599	AGAGAUUAAUCACUACAUUAG	281	CUAAUGUAGUGAUUAAUCUCU	825
D-1280	3611	CUACAUUAGACAACACUCAUC	282	GAUGAGUGUUGUCUAAUGUAG	826
D-1281	3612	UACAUUAGACAACACUCAUCU	283	AGAUGAGUGUUGUCUAAUGUA	827

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1282	3614	CAUUAGACAACACUCAUCUAC	284	GUAGAUGAGUGUUGUCUAAUG	828
D-1283	3659	GGAUAAACUGAGAAACAAGAGA	285	UCUCUUGUUUCUCAGUUUACC	829
D-1284	3676	GAGACCAUUCUCUGUCUAAACU	286	AGUUAGACAGAGAAUGGUCUC	830
D-1284B	3687	CUGUCUAAACUGUGAUAAAAC	287	GUUUUUUACACAGUUAGACAG	831
D-1285	3712	UCAGGACUUUAUUCUAUAGAG	288	CUCUAUAGAAUAAAGUCCUGA	832
D-1286	3717	ACUUUAUUCUAUAGAGCAAAC	289	GUUUGCUCUAUAGAAUAAAGU	833
D-1617					
D-1287	3720	UUUAUUCUAUAGAGCAAACUUG	290	CAAGUUUGCUCUAUAGAAUAA	834
D-1626					
D-1288	3721	UAUUCUAUAGAGCAAACUUGC	291	GCAAGUUUGCUCUAUAGAAUA	835
D-1289	3723	UUCUAUAGAGCAAACUUGCUG	292	CAGCAAGUUUGCUCUAUAGAA	836
D-1290	3741	CUGUGGAGGGCCAUGCUCUCC	293	GGAGAGCAUGGCCCUCCACAG	837
D-1291	3755	GCUCUCCUUGGACCCAGUUAA	294	UUAACUGGGUCCAAGGAGAGC	838
D-1292	3757	UCUCCUUGGACCCAGUUAACU	295	AGUUAACUGGGUCCAAGGAGA	839
D-1293	3758	CUCCUUGGACCCAGUUAACUG	296	CAGUUAACUGGGUCCAAGGAG	840
D-1294	3760	CCUUGGACCCAGUUAACUGCA	297	UGCAGUUAACUGGGUCCAAGG	841
D-1295	3761	CUUGGACCCAGUUAACUGCAA	298	UUGCAGUUAACUGGGUCCAAG	842
D-1296	3764	GGACCCAGUUAACUGCAAACG	299	CGUUUGCAGUUAACUGGGUCC	843
D-1297	3765	GACCCAGUUAACUGCAAACGU	300	ACGUUUGCAGUUAACUGGGUC	844
D-1298	3766	ACCCAGUUAACUGCAAACGUG	301	CACGUUUGCAGUUAACUGGGU	845
D-1299	3767	CCCAGUUAACUGCAAACGUGC	302	GCACGUUUGCAGUUAACUGGG	846
D-1300	3768	CCAGUUAACUGCAAACGUGCA	303	UGCACGUUUGCAGUUAACUGG	847
D-1301	3769	CAGUUAACUGCAAACGUGCAU	304	AUGCACGUUUGCAGUUAACUG	848
D-1302	3772	UUAACUGCAAACGUGCAUUGG	305	CCAAUGCAGUUUGCAGUUAA	849
D-1303	3776	CUGCAAACGUGCAUUGGAGCC	306	GGCUCCAAUGCACGUUUGCAG	850
D-1304	3777	UGCAAACGUGCAUUGGAGCCC	307	GGGCUCCAAUGCACGUUUGCA	851
D-1551					
D-1305	3781	AACGUGCAUUGGAGCCCUAUU	308	AAUAGGGCUCCAAUGCACGUU	852
D-1306	3782	ACGUGCAUUGGAGCCCUAUUU	309	AAAUAGGGCUCCAAUGCACGU	853
D-1307	3784	GUGCAUUGGAGCCCUAUUUGC	310	GCAAUAGGGCUCCAAUGCAC	854
D-1308	3785	UGCAUUGGAGCCCUAUUUGCU	311	AGCAAAUAGGGCUCCAAUGCA	855
D-1309	3790	UGGAGCCCUAUUUGCUGCCGC	312	GCGGCAGCAAAUAGGGCUCCA	856
D-1310	3791	GGAGCCCUAUUUGCUGCCGCU	313	AGCGGCAGCAAAUAGGGCUCC	857
D-1311	3792	GAGCCCUAUUUGCUGCCGCU	314	CAGCGGCAGCAAAUAGGGCUC	858
D-1312	3793	AGCCCUAUUUGCUGCCGCU	315	GCAGCGGCAGCAAAUAGGGCU	859
D-1313	3807	CCGUGCCAUUCUAGUGACCU	316	AGGUCACUAGAAUGGCAGCGG	860
D-1314	3811	UGCCAUUCUAGUGACCUUUC	317	GGAAAGGUCACUAGAAUGGCA	861
D-1315	3812	GCCAUUCUAGUGACCUUCCA	318	UGGAAAGGUCACUAGAAUGGC	862
D-1316	3818	CUAGUGACCUUCCACAGAGC	319	GCUCUGUGAAAGGUCACUAG	863
D-1317	3834	AGAGCUGCGCCUCCUCACGU	320	ACGUGAGGAAGGCGCAGCUCU	864
D-1318	3840	GCGCCUUCUACAGUGUGUGA	321	UCACACACGUGAGGAAGGC	865
D-1319	3847	CCUCACGUGUGUGAAAGGUUU	322	AAACCUUUCACACACGUGAGG	866
D-1320	3848	CUCACGUGUGUGAAAGGUUU	323	AAAACCUUUCACACACGUGAG	867
D-1321	3873	UUCAGCCCUAGGUAGAUUGGA	324	UCCAUCUACCUAGAGGGCUGAA	868
D-1322	3874	UCAGCCCUAGGUAGAUUGGAA	325	UUCCAUCUACCUAGAGGGCUGA	869
D-1323	3876	AGCCCUAGGUAGAUUGGAAGC	326	GCUUCCAUCUACCUAGAGGGCU	870
D-1323B	3907	CACGAUGGCAGUGCAUCUAC	327	GAUGACUGCACUGCCAUCUGUG	871
D-1324	3932	UCAGGAUGUUUCUUCAGGACU	328	AGUCCUGAAGAAACAUCUGA	872
D-1325	3952	UUCCUCAGCUGACAAGGAAUU	329	AAUUCUUGUCAGCUGAGGAA	873

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1326	3958	AGCUGACAAGGAAUUUUGGUC	330	GACCAAAAUUCCUUGUCAGCU	874
D-1327	3968	GAAUUUUGGUCCCUGCCUAGG	331	CCUAGGCAGGGACCAAAUUC	875
D-1328	3969	AAUUUUGGUCCCUGCCUAGGA	332	UCCUAGGCAGGGACCAAAUUC	876
D-1328	3971	UUUUGGUCCCUGCCUAGGACC	333	GGUCCUAGGCAGGGACCAAAA	877
D-1329	3972	UUUGGUCCCUGCCUAGGACCG	334	CGGUCCUAGGCAGGGACCAAAA	878
D-1330	3980	CUGCCUAGGACCGGUCUACUCU	335	AGAUGACCCGGUCCUAGGCAG	879
D-1331	4008	ACAGAGAGAUGGUAAGCAGCU	336	AGCUGCUUACCAUCUCUCUGU	880
D-1548					
D-1332	4011	GAGAGAUGGUAAGCAGCUGUA	337	UACAGCUGCUUACCAUCUCUC	881
D-1333	4012	AGAGAUGGUAAGCAGCUGUAU	338	AUACAGCUGCUUACCAUCUCU	882
D-1334	4013	GAGAUGGUAAGCAGCUGUAUG	339	CAUACAGCUGCUUACCAUCUC	883
D-1335	4019	GUAAGCAGCUGUAUGAAUGCU	340	AGCAUUCAUACAGCUGCUUAC	884
D-1336	4022	AGCAGCUGUAUGAAUGCUGAU	341	AUCAGCAUUCAUACAGCUGCU	885
D-1337	4040	GAUUUUAAAACCAAGGUAUGG	342	CCAUGACCUUGGUUUUAAAUAUC	886
D-1338	4042	UUUUAAAACCAAGGUAUGGGA	343	UCCCAUGACCUUGGUUUUAAAUA	887
D-1339	4084	CUGAACACUGACUGCACUUAC	344	GUAAGUGCAGUCAGUGUUCAG	888
D-1340	4085	UGAACACUGACUGCACUUACC	345	GGUAAGUGCAGUCAGUGUUCA	889
D-1341	4098	CACUUACCAGUCUGAUUUUAU	346	AUAAAUCAGACUGGUAAGUG	890
D-1342	4103	ACCAGUCUGAUUUUAUCGUC	347	UGACGAUAAAUCAGACUGGU	891
D-1343	4104	CCAGUCUGAUUUUAUCGUCAA	348	UUGACGAUAAAUCAGACUGG	892
D-1344	4108	UCUGAUUUUAUCGUCAAACAC	349	GUGUUUGACGAUAAAUCAGA	893
D-1345	4109	CUGAUUUUAUCGUCAAACACC	350	GGUGUUUGACGAUAAAUCAG	894
D-1600					
D-1346	4110	UGAUUUUAUCGUCAAACACCA	351	UGGUGUUUGACGAUAAAUCA	895
D-1347	4111	GAUUUUUAUCGUCAAACACCAA	352	UUGGUGUUUGACGAUAAAUC	896
D-1348	4112	AUUUUUAUCGUCAAACACCAAG	353	CUUGGUGUUUGACGAUAAAUC	897
D-1349	4115	UUAUCGUCAAACACCAAGCCA	354	UGGCUUGGUGUUUGACGAUAA	898
D-1350	4116	UAUCGUCAAACACCAAGCCAG	355	CUGGCUUGGUGUUUGACGAUA	899
D-1351	4142	CAUGCUCUAGGCAUUCUGUUU	356	AAACAGAUUGCCUAGAGCAUG	900
D-1352	4147	UCAUGGCAUUCUGUUUGGGGC	357	GCCCCAAACAGAUUGCCAUUA	901
D-1353	4169	GUUUUGUUGUGGCACUAGCCA	358	UGGCUAGUGCCACAACAAAAC	902
D-1354	4170	UUUUUGUUGUGGCACUAGCCAA	359	UUGGCUAGUGCCACAACAAAAC	903
D-1355	4171	UUUGUUGUGGCACUAGCCAAA	360	UUUGGCUAGUGCCACAACAAA	904
D-1356	4172	UUGUUGUGGCACUAGCCAAAC	361	GUUUGGCUAGUGCCACAACAA	905
D-1357	4174	GUUGUGGCACUAGCCAAACAU	362	AUGUUUGGCUAGUGCCACAAC	906
D-1358	4175	UUGUGGCACUAGCCAAACAU	363	UAUGUUUGGCUAGUGCCACAAC	907
D-1359	4176	UGUGGCACUAGCCAAACAUAA	364	UUUUGUUGGCUAGUGCCACA	908
D-1360	4177	GUGGCACUAGCCAAACAUAAA	365	UUUUGUUGGCUAGUGCCAC	909
D-1361	4178	UGGCACUAGCCAAACAUAAAG	366	CUUUUUGUUGGCUAGUGCCA	910
D-1362	4179	GGCACUAGCCAAACAUAAAGG	367	CCUUUUGUUGGCUAGUGGCC	911
D-1363	4180	GCACUAGCCAAACAUAAAGGG	368	CCCUUUUUGUUGGCUAGUGC	912
D-1364	4185	AGCCAAACAUAAAGGGGCUUA	369	UAAGCCCCUUUUGUUGGCU	913
D-1365	4186	GCCAAACAUAAAGGGGCUUAA	370	UUUAGCCCCUUUUGUUGGCU	914
D-1366	4187	CCAAACAUAAAGGGGCUUAAAG	371	CUUAAAGCCCCUUUUGUUGG	915
D-1367	4188	CAAACAUAAAGGGGCUUAAAGU	372	ACUUUAGCCCCUUUUGUUGU	916
D-1368	4189	AAACAUAAAGGGGCUUAAAGUC	373	GACUUUAGCCCCUUUUGUUGU	917
D-1369	4190	AACAUAAAGGGGCUUAAAGUCA	374	UGACUUUAGCCCCUUUUGUUGU	918
D-1370	4191	ACAUAAAGGGGCUUAAAGUCAG	375	CUGACUUUAGCCCCUUUUGUUGU	919
D-1371	4193	AUAAGGGGCUUAAAGUCAGCC	376	GGCUGACUUUAGCCCCUUUUAU	920
D-1372	4194	UAAAGGGGCUUAAAGUCAGCCU	377	AGGCUGACUUUAGCCCCUUUUA	921
D-1373	4197	AGGGGCUUAAAGUCAGCCUGCA	378	UGCAGGCUGACUUUAGCCCCU	922

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1374	4205	AAGUCAGCCUGCAUACAGAGG	379	CCUCUGUAUGCAGGCUGACUU	923
D-1375	4206	AGUCAGCCUGCAUACAGAGGA	380	UCCUCUGUAUGCAGGCUGACU	924
D-1376	4210	AGCCUGCAUACAGAGGAUCGG	381	CCGAUCCUCUGUAUGCAGGCU	925
D-1377	4211	GCCUGCAUACAGAGGAUCGGG	382	CCCGAUCCUCUGUAUGCAGGC	926
D-1378	4212	CCUGCAUACAGAGGAUCGGGG	383	CCCCGAUCCUCUGUAUGCAGG	927
D-1379	4219	ACAGAGGAUCGGGGAGAGAAG	384	CUUCUCUCCCCGAUCCUCUGU	928
D-1380	4262	GAGUACUUACCAGAGUUUAU	385	AUUAAACUCUGGUAAGUACUC	929
D-2100	4297	UCUGCACUAAAAUCCCCAAC	2819	GUUUGGGGAUUUUAGUGCAGA	2820
D-1381	4298	CUGCACUAAAAUCCCCAACU	386	AGUUUGGGGAUUUUAGUGCAG	930
D-1382	4299	UGCACUAAAAUCCCCAACUG	387	CAGUUUGGGGAUUUUAGUGCA	931
D-1383	4301	CACUAAAAUCCCCAACUGAC	388	GU CAGUUUGGGGAUUUUAGUG	932
D-1384	4307	AAUCCCCAACUGACAGGUAA	389	UUACCGUGCAGUUUGGGGAUU	933
D-1385	4312	CCAAACUGACAGGUAAAUGUA	390	UACAUUUACCGUGCAGUUUGG	934
D-1386	4313	CAAACUGACAGGUAAAUGUAG	391	CUACAUUUACCGUGCAGUUUG	935
D-1387	4314	AAACUGACAGGUAAAUGUAGC	392	GCUACAUUUACCGUGCAGUUU	936
D-1388	4316	ACUGACAGGUAAAUGUAGCCC	393	GGGCUACAUUUACCGUGCAGU	937
D-1389	4359	AUCUAAAUCACACUAUUUUCG	394	CGAAAAUAGUGUGAUUUAGAU	938
D-1390	4361	CUAAAUCACACUAUUUUCGAG	395	CUCGAAAAUAGUGUGAUUUAG	939
D-1391	4362	UAAAUCACACUAUUUUCGAGA	396	UCUCGAAAAUAGUGUGAUUUU	940
D-1392	4364	AAUCACACUAUUUUCGAGAU	397	GAUCUCGAAAAUAGUGUGAUU	941
D-1393	4366	UCACACUAUUUUCGAGAUCAU	398	AUGAUCUCGAAAAUAGUGUGA	942
D-1394	4367	CACACUAUUUUCGAGAUCAUG	399	CAUGAUCUCGAAAAUAGUGUG	943
D-1395	4368	ACACUAUUUUCGAGAUCAUGU	400	ACAUGAUCUCGAAAAUAGUGU	944
D-1396	4370	ACUAUUUUCGAGAUCAUGUAU	401	AUACAUGAUCUCGAAAAUAGU	945
D-1397	4371	CUAUUUUCGAGAUCAUGUAUA	402	UAUACAUGAUCUCGAAAAUAG	946
D-1398	4373	AUUUUCGAGAUCAUGUAUAAA	403	UUUAUACAUGAUCUCGAAAAU	947
D-1399	4376	UUCGAGAUCAUGUAUAAAAAG	404	CUUUUUUAUACAUGAUCUCGAA	948
D-1400	4399	AAAAAAGAAGUCAUGCUGUGU	405	ACACAGCAUGACUUCUUUUUU	949
D-1401	4412	UGCUGUGUGGCCAAUUAUAAU	406	AUUUAUAAUUGGCCACACAGCA	950
D-1777					
D-1937					
D-1943					
D-1949					
D-1955					
D-1961					
D-1967					
D-1973					
D-2041					
D-2045					
D-2050					
D-2057					
D-2058					
D-2059					
D-2060					
D-2061					
D-2085					
D-2091					
D-1402	4476	UUGGAGGGACCAGGAAUUGUA	407	UACAUUUCCUGGUCCCUCCAA	951
D-1403	4484	ACCAGGAAUUGUAAGACACCA	408	UGGUGUCUACAUUUCCUGGU	952
D-1742					

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1404 D-1743	4485	CCAGGAAAUGUAAGACACCAA	409	UUGGUGUCUUACAUUUCCUGG	953
D-1405	4522	GUGUGCCUGAUGUCACCUCAU	410	AUGAGGUGACAUCAGGCACAC	954
D-1406	4523	UGUGCCUGAUGUCACCUCAUG	411	CAUGAGGUGACAUCAGGCACA	955
D-1407	4524	GUGCCUGAUGUCACCUCAUGA	412	UCAUGAGGUGACAUCAGGCAC	956
D-1408	4526	GCCUGAUGUCACCUCAUGAUU	413	AAUCAUGAGGUGACAUCAGGC	957
D-1409	4556	UUUUUUAACUCCUGCGCCAAG	414	CUUGGCGCAGGAGUUAAAAA	958
D-1410	4560	UUAACUCCUGCGCCAAGGACA	415	UGUCCUUGGCGCAGGAGUUA	959
D-1411	4562	AACUCCUGCGCCAAGGACAGU	416	ACUGUCCUUGGCGCAGGAGUU	960
D-1412	4563	ACUCCUGCGCCAAGGACAGUG	417	CACUGUCCUUGGCGCAGGAGU	961
D-1413	4591	UGUCCACCUUUGUGCUUUGCG	418	CGCAAAGCACAAAGGUGGACA	962
D-1414	4593	UCCACCUUUGUGCUUUGCGAG	419	CUCGCAAAGCACAAAGGUGGA	963
D-1415	4595	CACCUUUGUGCUUUGCGAGGC	420	GCCUCGCAAAGCACAAAGGUG	964
D-1416	4597	CCUUUGUGCUUUGCGAGGCCG	421	CGGCCUCGCAAAGCACAAAGG	965
D-1417	4617	GAGCCAGGCAUCUGCUCGCC	422	GGCGAGCAGAUGCCUGGGCUC	966
D-1418	4620	CCCAGGCAUCUGCUCGCCUGC	423	GCAGGCGAGCAGAUGCCUGGG	967
D-1419	4622	CAGGCAUCUGCUCGCCUGCCA	424	UGGCAGGCGAGCAGAUGCCUG	968
D-1420	4625	GCAUCUGCUCGCCUGCCACGG	425	CCGUGGCAGGCGAGCAGAUCC	969
D-1421	4638	UGCCACGGCUGACCAAGAGAAG	426	CUUCUCUGGUCAGCCGUGGCA	970
D-1422	4668	GAGCUCUGCCUAGACGACGCU	427	ACGUCGUCUAAGGCAGAGCUC	971
D-1423	4669	AGCUCUGCCUAGACGACGUG	428	CACGUCGUCUAAGGCAGAGCU	972
D-1424	4670	GCUCUGCCUAGACGACGUGU	429	ACACGUCGUCUAAGGCAGAGC	973
D-1425	4671	CUCUGCCUAGACGACGUGUU	430	AACACGUCGUCUAAGGCAGAG	974
D-1426	4672	UCUGCCUAGACGACGUGUUA	431	UAACACGUCGUCUAAGGCAGA	975
D-1427	4673	CUGCCUAGACGACGUGUUA	432	GUACACGUCGUCUAAGGCAG	976
D-1428	4675	GCCUAGACGACGUGUUAACAG	433	CUGUAACACGUCGUCUAAGGC	977
D-1429	4676	CCUAGACGACGUGUUAACAGU	434	ACUGUAACACGUCGUCUAAGG	978
D-1430	4677	CUUAGACGACGUGUUAACAGUA	435	UACUGUAACACGUCGUCUAAG	979
D-1431	4679	UAGACGACGUGUUAACAGUAUG	436	CAUACUGUAACACGUCGUCUA	980
D-1432	4682	ACGACGUGUUAACAGUAUGAAC	437	GUUCAUACUGUAACACGUCGU	981
D-1433	4703	ACACAGCAGAGGCACCCUCGU	438	ACGAGGGUGCCUCUGCUGUG	982
D-1434	4704	CACAGCAGAGGCACCCUCGUA	439	UACGAGGGUGCCUCUGCUGUG	983
D-1435	4705	ACAGCAGAGGCACCCUCGUAU	440	AUACGAGGGUGCCUCUGCUGU	984
D-1436	4706	CAGCAGAGGCACCCUCGUAUG	441	CAUACGAGGGUGCCUCUGCUG	985
D-1437	4707	AGCAGAGGCACCCUCGUAUGU	442	ACAUACGAGGGUGCCUCUGCU	986
D-1438	4708	GCAGAGGCACCCUCGUAUGUU	443	AACAUAACGAGGGUGCCUCUGC	987
D-1439	4709	CAGAGGCACCCUCGUAUGUUU	444	AAACAUACGAGGGUGCCUCUG	988
D-1440	4710	AGAGGCACCCUCGUAUGUUUU	445	AAAACAUACGAGGGUGCCUCU	989
D-1441	4711	GAGGCACCCUCGUAUGUUUUG	446	CAAAACAUACGAGGGUGCCUC	990
D-1442	4713	GGCACCCUCGUAUGUUUUGAA	447	UUCAAAACAUACGAGGGUGCC	991
D-1443 D-1744 D-1896 D-1902 D-1908 D-1914 D-1920 D-1926 D-1932 D-2062 D-2063	4717	CCCUCGUAUGUUUUGAAAGUU	448	AACUUUCAAACAUACGAGGG	992

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2089					
D-1444 D-1778	4777	AUGUAAAACUAUACUGACCCG	449	CGGGUCAGUAUAGUUUUACAU	993
D-1445	4778	UGUAAAACUAUACUGACCCGU	450	ACGGGUCAGUAUAGUUUUACA	994
D-1446 D-1590	4779	GUAAAACUAUACUGACCCGUU	451	AACGGGUCAGUAUAGUUUUAC	995
D-1447 D-1779	4780	UAAAACUAUACUGACCCGUUU	452	AAACGGGUCAGUAUAGUUUUUA	996
D-1448	4784	ACUAUACUGACCCGUUUUCAG	453	CUGAAAACGGGUCAGUAUAGU	997
D-1449	4787	AUACUGACCCGUUUUCAGUUU	454	AAACUGAAAACGGGUCAGUAU	998
D-1450 D-1745	4799	UUUCAGUUUUAAAGGGUCGUG	455	CACGACCCUUUAAAACUGAAA	999
D-1451	4800	UUCAGUUUUAAAGGGUCGUGA	456	UCACGACCCUUUAAAACUGAA	1000
D-1452 D-1746	4801	UCAGUUUUAAAGGGUCGUGAG	457	CUCACGACCCUUUAAAACUGA	1001
D-1453 D-1747	4802	CAGUUUUAAAGGGUCGUGAGA	458	UCUCACGACCCUUUAAAACUG	1002
D-1454 D-1630	4804	GUUUUAAAGGGUCGUGAGAAA	459	UUUCUCACGACCCUUUAAAAC	1003
D-1454	4805	UUUUAAAGGGUCGUGAGAAAC	460	GUUUCUCACGACCCUUUAAAA	1004
D-1455 D-1748	4806	UUUAAAGGGUCGUGAGAAACU	461	AGUUUCUCACGACCCUUUAAA	1005
D-1456	4808	UAAAGGGUCGUGAGAAACUGG	462	CCAGUUUCUCACGACCCUUUA	1006
D-1457	4809	AAAGGGUCGUGAGAAACUGGC	463	GCCAGUUUCUCACGACCCUUU	1007
D-1458 D-1780	4819	GAGAAACUGGCUGGUCCAUG	464	CAUUGGACCAGCCAGUUUCUC	1008
D-1459	4830	UGGUCCAAUGGGAUUUACAGC	465	GCUGUAAAUCCCAUUGGACCA	1009
D-1460 D-1781 D-1894 D-1900 D-1906 D-1912 D-1918 D-1924 D-1930 D-2064 D-2065 D-2066 D-2067 D-2068 D-2092	4834	CCAAUGGGAUUUACAGCAACA	466	UGUUGCUGUAAAUCCCAUUGG	1010
D-1461 D-1596	4927	UUUAAGUUUGCUCUJAAUCGU	467	ACGAUUAAGAGCAAACUAAAA	1011
D-1462 D-1594	4928	UUAAGUUUGCUCUUAUUCGUA	468	UACGAUUAAGAGCAAACUAAA	1012
D-1463 D-1782	4931	AGUUUGCUCUUAUUCGUAUGG	469	CCAUAACGAUUAAGAGCAAACU	1013
D-1464 D-1783 D-1895 D-1901	4932	GUUUGCUCUUAUUCGUAUGGA	470	UCCAUAACGAUUAAGAGCAAAC	1014

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1907 D-1913 D-1919 D-1925 D-1931 D-2069 D-2070 D-2071 D-2072 D-2073 D-2074 D-2088					
D-1465 D-1784	4933	UUUGCUCUUAAUCGUAUGGAA	471	UUCCAUACGAUUAAAGAGCAA	1015
D-1466 D-1785	4935	UGCUCUUAUCGUAUGGAAGC	472	GCUUCCAUACGAUUAAGAGCA	1016
D-1467 D-1786	4939	CUUAAUCGUAUGGAAGCUUGA	473	UCAAGCUUCCAUACGAUUAAG	1017
D-1468 D-1787	4940	UUAUUCGUAUGGAAGCUUGAG	474	CUCAAGCUUCCAUACGAUUA	1018
D-1469 D-1749	4950	GGAAGCUUGAGCUAUGUGUUG	475	CAACACAUAGCUC AAGCUUCC	1019
D-1470 D-1750	4951	GAAGCUUGAGCUAUGUGUUGG	476	CCAACACAUAGCUC AAGCUUC	1020
D-1471 D-1751	4953	AGCUUGAGCUAUGUGUUGGAA	477	UUCCAACACAUAGCUC AAGCU	1021
D-1472 D-1752	4954	GCUUGAGCUAUGUGUUGGAAG	478	CUUCCAACACAUAGCUC AAGC	1022
D-1473 D-1753	4955	CUUGAGCUAUGUGUUGGAAGU	479	ACUCCAACACAUAGCUC AAG	1023
D-1474 D-1593	4956	UUGAGCUAUGUGUUGGAAGUG	480	CACUCCAACACAUAGCUC AA	1024
D-1475 D-1631 D-1696 D-1703 D-1710 D-1717 D-1724 D-1731 D-1738 D-1857 D-2011 D-2020	4957	UGAGCUAUGUGUUGGAAGUGC	481	GCACUCCAACACAUAGCUC A	1025
D-1476 D-1754	4958	GAGCUAUGUGUUGGAAGUGCC	482	GGCACUCCAACACAUAGCUC	1026
D-1477 D-1755	4965	GUGUUGGAAGUGCCCGGUUU	483	AAACCAGGGCACUCCAACAC	1027
D-1478 D-1756	4970	GGAAGUGCCCGGUUUUAAUC	484	GAUUAAAACAGGGCACUCC	1028
D-1479	4979	CUGGUUUUAAUCCAUCACAA	485	UUGUGUAUGGAUUAAAACAG	1029
D-1480	4985	UUAAUCCAUCACAAAGACGG	486	CCGUCUUUGUGUAUGGAUUA	1030

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1481	4986	UAAUCCAUAACACAAAGACGGU	487	ACCGUCUUUGUGUAUGGAUUA	1031
D-1482	4987	AAUCCAUAACACAAAGACGGUA	488	UACCGUCUUUGUGUAUGGAUU	1032
D-1483	4988	AUCCAUAACACAAAGACGGUAC	489	GUACCGUCUUUGUGUAUGGAU	1033
D-1484 D-1788	4989	UCCAUAACACAAAGACGGUACA	490	UGUACCGUCUUUGUGUAUGGA	1034
D-1485 D-1789	4991	CAUACACAAAGACGGUACAU	491	UAUGUACCGUCUUUGUGUAUG	1035
D-1486 D-1634	4993	UACACAAAGACGGUACAUAAU	492	AUUAUGUACCGUCUUUGUGUA	1036
D-1487	4994	ACACAAAGACGGUACAUAAUC	493	GAUUAUGUACCGUCUUUGUGU	1037
D-1488 D-1546 D-2036	4995	CACAAAGACGGUACAUAAUCC	494	GGAUUAUGUACCGUCUUUGUG	1038
D-1489 D-1757 D-2037	4996	ACAAAGACGGUACAUAAUCCU	495	AGGAUUAUGUACCGUCUUUGU	1039
D-1490 D-1758 D-2038	4997	CAAAGACGGUACAUAAUCCUA	496	UAGGAUUAUGUACCGUCUUUG	1040
D-1491 D-1562 D-2039	4998	AAAGACGGUACAUAAUCCUAC	497	GUAGGAUUAUGUACCGUCUUU	1041
D-1492 D-1614 D-1697 D-1702 D-1709 D-1716 D-1723 D-1730 D-1737 D-1856 D-1863 D-1865 D-1866 D-1869 D-1872 D-1877 D-1878 D-1879 D-1880 D-1881 D-1884 D-1887 D-1978 D-1987 D-1992 D-1997 D-2002 D-2008 D-2017 D-2049	4999	AAGACGGUACAUAAUCCUACA	498	UGUAGGAUUAUGUACCGUCUU	1042

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2054 D-2090					
D-1493 D-1566	5005	GUACAUAUCCUACAGGUUUA	499	UAAACCUGUAGGAUUAUGUAC	1043
D-1494 D-1759	5008	CAUAAUCCUACAGGUUUAU	500	AUUUAAACCUGUAGGAUUAUG	1044
D-1495 D-1633	5012	AUCCUACAGGUUUAUUGUAC	501	GUACAUUUAACCUGUAGGAU	1045
D-1496 D-1564 D-2040	5042	UAGUUUGGAAUUCUUUGCUCU	502	AGAGCAAAGAAUCCAAACUA	1046
D-1497 D-1611 D-1698 D-1705 D-1712 D-1719 D-1726 D-1733 D-1740 D-1855 D-1864 D-1870 D-1875 D-1883 D-1886 D-1980 D-1984 D-1989 D-1994 D-1999 D-2004 D-2013 D-2022 D-2044 D-2048 D-2053	5043	AGUUUGGAAUUCUUUGCUCUA	503	UAGAGCAAAGAAUCCAAACU	1047
D-1498 D-1612 D-1699 D-1704 D-1711 D-1718 D-1725 D-1732 D-1739 D-1854 D-1868 D-1871 D-1876 D-1882 D-1885 D-1888	5045	UUUGGAAUUCUUUGCUCUACU	504	AGUAGAGCAAAGAAUCCAAA	1048

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1979 D-1983 D-1988 D-1993 D-1998 D-2003 D-2012 D-2021 D-2043 D-2047 D-2052					
D-1499 D-1760	5056	UUGCUCUACUGUUUACAUUGC	505	GCAAUGUAAACAGUAGAGCAA	1049
D-1500 D-1591 D-1624	5060	UCUACUGUUUACAUUGCAGAU	506	AUCUGCAAUGUAAACAGUAGA	1050
D-1501 D-1577	5062	UACUGUUUACAUUGCAGAUUG	507	CAAUCUGCAAUGUAAACAGUA	1051
D-1502	5063	ACUGUUUACAUUGCAGAUUGC	508	GCAAUCUGCAAUGUAAACAGU	1052
D-1503 D-1603	5067	UUUACAUUGCAGAUUGCUAUA	509	UAUAGCAAUCUGCAAUGUAAA	1053
D-1504 D-1629	5068	UUACAUUGCAGAUUGCUAUAA	510	UUUAGCAAUCUGCAAUGUAA	1054
D-1505 D-1628	5069	UACAUUGCAGAUUGCUAUAAU	511	AUUUAGCAAUCUGCAAUGUA	1055
D-1506	5079	AUUGCUAUAUUUCAAGGAGU	512	ACUCCUUGAAAUAUAGCAAU	1056
D-1507 D-1623 D-1846 D-1706 D-1713 D-1720 D-1727 D-1734 D-1741 D-1761 D-1846 D-1862 D-1874 D-1981 D-1985 D-1990 D-1995 D-2000 D-2005 D-2014 D-2023	5080	UUGCUAUAUUUCAAGGAGUG	513	CACUCCUUGAAAUAUAGCAA	1057
D-1508 D-1762	5114	AAUGAUGCACUUUAGGAUGUU	514	AACAUCCUAAAGUGCAUCAUU	1058
D-1509 D-1627 D-1763	5115	AUGAUGCACUUUAGGAUGUUU	515	AAACAUCCUAAAGUGCAUCAU	1059

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1510 D-1764	5154	ACAUGAAUCAUUCACAUGACC	516	GGUCAUGUGAAUGAUUCAUGU	1060
D-1511 D-1765	5155	CAUGAAUCAUUCACAUGACCA	517	UGGUCAUGUGAAUGAUUCAUG	1061
D-1512 D-1572	5194	AAAUACAUGUCUAGUCUGUCC	518	GGACAGACUAGACAUUAUUU	1062
D-1512B D-1766	5195	AAUACAUGUCUAGUCUGUCCU	519	AGGACAGACUAGACAUUAUU	1063
D-1513 D-1767	5200	AUGUCUAGUCUGUCCUUUAAU	520	AUUAAAGGACAGACUAGACAU	1064
D-1514 D-1790	5201	UGUCUAGUCUGUCCUUUAAUA	521	UAUUAAAGGACAGACUAGACA	1065
D-1515 D-1791	5203	UCUAGUCUGUCCUUUAAUAGC	522	GCUAUUAAAGGACAGACUAGA	1066
D-1516 D-1792 D-1892 D-1898 D-1904 D-1910 D-1916 D-1922 D-1928	5204	CUAGUCUGUCCUUUAAUAGCU	523	AGCUAUUAAAGGACAGACUAG	1067
D-1517	5205	UAGUCUGUCCUUUAAUAGCUC	524	GAGCUAUUAAAGGACAGACUA	1068
D-1518 D-1793	5207	GUCUGUCCUUUAAUAGCUCUC	525	GAGAGCUAUUAAAGGACAGAC	1069
D-1519 D-1768 D-1891 D-1897 D-1903 D-1909 D-1915 D-1921 D-1927 D-2075 D-2077	5247	AAUCAGAUCAUUACCAGUUAG	526	CUAACUGGUAUGAUCUGAUU	1070
D-1520 D-1769 D-1934 D-1940 D-1946 D-1952 D-1958 D-1964 D-1970 D-2076 D-2078	5249	UCAGAUCAUUACCAGUUAGCU	527	AGCUAACUGGUAUGAUCUGA	1071
D-1521	5250	CAGAUCAUUACCAGUUAGCUU	528	AAGCUAACUGGUAUGAUCUG	1072
D-1522 D-1770	5251	AGAUCAUUACCAGUUAGCUUU	529	AAAGCUAACUGGUAUGAUCU	1073

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1523 D-1771	5254	UCAUUACCAGUUAGCUUUUAA	530	UUAAAAGCUAACUGGUAUUGA	1074
D-1524 D-1622	5255	CAUUACCAGUUAGCUUUUAAA	531	UUUAAAAGCUAACUGGUAUUG	1075
D-1525 D-1772	5259	ACCAGUUAGCUUUUAAAGCAC	532	GUGCUUUAAAAGCUAACUGGU	1076
D-1526 D-1773 D-1936 D-1942 D-1948 D-1954 D-1960 D-1966 D-1972 D-2042 D-2046 D-2051 D-2079 D-2080 D-2081 D-2082 D-2083 D-2093	5274	AAGCACAUUUGUUUAAGACUA	533	UAGUCUAAACAAAUUGGCUU	1077
D-1527 D-1774 D-1893 D-1899 D-1905 D-1911 D-1917 D-1923 D-1929 D-1975 D-1976 D-1977 D-1982 D-1986 D-1991 D-1996 D-2001 D-2084	5276	GCACAUUUGUUUAAGACUAUG	534	CAUAGUCUAAACAAAUUGGC	1078
D-1528	5292	CUAUGUUUUUGGAAAAUACG	535	CGUAUUUUUCCAAAAACAUAG	1079
D-1529	5296	GUUUUUGGAAAAUACGCUAC	536	GUAGCGUAUUUUUCCAAAAAC	1080
D-1530	5300	UUGGAAAAUACGCUACAGAA	537	UUCUGUAGCGUAUUUUCCAA	1081
D-1531 D-1625	5338	AAUAAAUGAGAUGCUCUAAU	538	AUUAGUAGCAUCUAAUUUAU	1082
D-1532 D-1775	5344	UGAGAUGCUCUAAUUGUUUU	539	AAAACAAUAGUAGCAUCUCA	1083
D-1533	5362	UUUGGAAUCUGUUGUUUCUGC	540	GCAGAAACACAGAUUCCAAA	1084
D-1534	5377	UUCUGCCAAAGGUAAAUAAC	541	GUUAAUUUACCUUUGGCAGAA	1085
D-1535	5378	UCUGCCAAAGGUAAAUAACU	542	AGUUAAUUUACCUUUGGCAGA	1086

Duplex No.	Target start in SEQ ID NO: 1	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1536 D-1776	5402	GAUUUAUUCAGGAAUCCCAU	543	AUGGGGAUCCUGAAUAAAUC	1087
D-1537	5407	AUUCAGGAAUCCCAUUUGAA	544	UUCAAAUGGGGAUCCUGAAU	1088
D-1538	5412	GGAAUCCCAUUUGAAUUUGU	545	ACAAAUCAAUUGGGGAUCC	1089

[0186] **Table 2** below provides the sequences of exemplary sense and antisense strands with chemical modifications of duplexes used in experiments disclosed herein. In **Table 2**, the nucleotide sequences are listed according to the following notations: a, u, g, and c = corresponding 2'-O-methyl ribonucleotide; Af, Uf, Gf, and Cf = corresponding 2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide; and invAb = inverted abasic deoxynucleotide (*i.e.*, abasic deoxynucleotide linked to adjacent nucleotide via a substituent at its 3' position (a 3'-3' linkage) when on the 3' end of a strand or linked to adjacent nucleotide via a substituent at its 5' position (a 5'-5' internucleotide linkage) when on the 5' end of a strand. Insertion of an "s" in the sequence indicates that the two adjacent nucleotides are connected by a phosphorothiodiester group (*e.g.*, a phosphorothioate internucleotide linkage). Unless indicated otherwise, all other nucleotides are connected by 3'-5' phosphodiester groups. [DCA-C6] represents a conjugated docosanoic acid (C22). [GalNAc3] represents the GalNAc moiety shown in Formula VII. The [DCA-C6] and [GalNAc3] ligands are covalently attached to the 5' terminal nucleotide at the 5' end of the sense strand via a phosphodiester bond, or a phosphorothioate bond when an "s" follows the [GalNAc3] or [DCA-C6] notation. When an invAb nucleotide was the 5' terminal nucleotide at the 5' end of the sense strand, it was linked to the adjacent nucleotide via a 5'-5' linkage and the GalNAc or C22 moiety was covalently attached to the 3' carbon of the invAb nucleotide. Otherwise, the moiety was covalently attached to the 5' carbon of the 5' terminal nucleotide of the sense strand.

TABLE 2: Modified *FAM13A* siRNA Sequences

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1001	csasuguaCfcCfCfAfAfGfucagcaas {invAb}	1090	asUfsugcuGfacuuggGfgUfacaugs usu	1938
D-1002	usgsuaccCfcAfAfGfUfcagcaaug {invAb}	1091	asCfsauugCfugacuuGfgGfguacacs usu	1939
D-1003	gsusacccCfaAfGfUfCfagcaaug {invAb}	1092	asAfscauuGfcugacuUfgGfgguacs usu	1940
D-1004	gscsaauGfGfUfCfUfGfcaaccggas {invAb}	1093	asUfscggUfugcagaCfaCfauugcs usu	1941
D-1005	csasauguGfuCfUfGfCfaaccggags {invAb}	1094	usCfsuccGfuugcagAfcAfcaugs usu	1942

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1006	asasugugUfcUfGfCfAfaccggagas {invAb}	1095	usUfscuccGfguugcaGfaCfacauus usu	1943
D-1007	usgsugucUfgCfAfAfCfcggagaacs {invAb}	1096	asGfsuucuCfcgguugCfaGfacacacs usu	1944
D-1008	gsusgucUgCfAfAfCfCfaggagaacs {invAb}	1097	asAfsuucUfcccguUgCfagacacs usu	1945
D-1009	usgsucugCfaAfCfCfGfagagaacs {invAb}	1098	asGfsaguuCfuccguUfgCfagacacs usu	1946
D-1010	gsusgucUgCfAfAfCfGfagagaacs {invAb}	1099	asAfsaguuUfuccguUfgCfagacacs usu	1947
D-1011	uscsugcaAfCfGfGfAfgaacuuus {invAb}	1100	usAfsaguuUfuccguUfgCfagacacs usu	1948
D-1012	csusgcaAfCfGfGfAfgaacuuas {invAb}	1101	asUfsaagaGfuuccGfgUfugcags usu	1949
D-1013	usgsaacCfGfGfAfGfAfacuuuags {invAb}	1102	usCfsuaagAfguucCfGfGfagacacs usu	1950
D-1014	gsusaacGfGfAfGfAfacuuuags {invAb}	1103	usUfscuaaGfaguucCfGfGfagacacs usu	1951
D-1015	asascggAfGfAfCfUfuuagaaas {invAb}	1104	asUfsuucUfagaguuCfCfGfagacacs usu	1952
D-1016	uscsuagAfaAfGfAfAfccauccgas {invAb}	1105	asUfscggUfGfuuucUfCfuaagacs usu	1953
D-1017	csusuagaAfaAfAfCfCfauccgaus {invAb}	1106	asAfsucggAfgguucUfUfCfuaagacs usu	1954
D-1018	ususagaaAfGfAfCfCfauccgaus {invAb}	1107	usGfsaucGfagguUfUfCfuaagacs usu	1955
D-1019	asgsaaagAfaCfCfAfUfCfagacacs {invAb}	1108	asCfsugauCfGfagguUfUfCfuaagacs usu	1956
D-1020	asasagaaCfCfAfUfCfCfagacacs {invAb}	1109	asAfsugauCfGfagguUfUfCfuaagacs usu	1957
D-1021	asasgaacCfaUfCfCfGfagacacs {invAb}	1110	asCfsagcuGfagguUfGfGfagacacs usu	1958
D-1022	gsasaccaUfCfCfAfUfCfagacacs {invAb}	1111	asUfsacagCfagguUfGfGfagacacs usu	1959
D-1023	ascsgaucCfGfAfUfCfCfagacacs {invAb}	1112	usUfscuacAfgcuUfGfGfagacacs usu	1960
D-1024	cscsgaucAfgCfUfGfUfagacacs {invAb}	1113	usGfsuuguUfCfagguUfGfGfagacacs usu	1961
D-1025	gsasuguUfaUfAfAfCfCfagacacs {invAb}	1114	asCfscuccAfgaguuUfUfCfagacacs usu	1962
D-1026	usasauaaCfUfUfGfGfaggucaas {invAb}	1115	asUfsuugaCfuccagAfgUfuaagacs usu	1963
D-1027	asusaacuCfUfGfGfAfGfaggucaas {invAb}	1116	asAfsuugaCfuccagAfgUfuaagacs usu	1964
D-1028	asuscugAfaCfAfCfUfCfagacacs {invAb}	1117	asAfsugcuGfagguUfUfCfagacacs usu	1965
D-1029	asgsgaugAfaGfUfUfCfGfagacacs {invAb}	1118	usCfscuacAfgcuUfGfGfagacacs usu	1966
D-1030	gsusugcaCfaUfGfGfGfagagacaas {invAb}	1119	asUfsugucUfucccaUfgUfGfagacacs usu	1967
D-1031	csgsacauGfGfAfGfAfagacaaggs {invAb}	1120	usCfscuacAfgcuUfGfGfagacacs usu	1968
D-1032	ascsauggGfaGfAfGfAfcaaggacacs {invAb}	1121	asGfsuccUfugucUfCfCfagacacs usu	1969
D-1033	asusgggaGfaGfAfCfAfagggacuus {invAb}	1122	usAfsagucCfuuucUfUfCfagacacs usu	1970

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1034	gsgsgagaGfaCfAfAfGfGgacuuuus {invAb}	1123	asAfsuaagUfccccuugUfcUfcucccs usu	1971
D-1035	gsgsagagAfcAfAfGfGfGacuuuacs {invAb}	1124	usGfsauaaGfucccuuGfuCfucuccs usu	1972
D-1036	gsasgagaCfaAfGfGfGfGacuuuacs {invAb}	1125	usUfsgauaAfgucccuUfgUfcucucs usu	1973
D-1037	gsascaagGfgAfCfUfUfaucaacaas {invAb}	1126	usUfsuguuGfauaaguCfcCfuugucs usu	1974
D-1038	ascsaagGfaCfUfUfAfucaaaaaas {invAb}	1127	asUfsuuguUfgauaagUfcCfcuugus usu	1975
D-1039	gsgsgacuUfaUfCfAfAfcaaaagaaas {invAb}	1128	usUfsuucuUfuguugaUfaAfgucccs usu	1976
D-1040	asasgaaaAfuAfCfUfCfcuucugggs {invAb}	1129	asCfscagAfgaggaguAfuUfuucuus usu	1977
D-1041	asusacucCfuUfCfUfGfGguucaacs {invAb}	1130	asGfsuugaAfcccagaAfgGfaguau usu	1978
D-1042	gsusucacCfcAfCfCfUfugaugauus {invAb}	1131	asAfsaucaUfcaagguGfgUfugaacs usu	1979
D-1043	ususcaacCfaCfCfUfUfugaugauugs {invAb}	1132	asCfsaaucAfucaaggUfgGfuugaas usu	1980
D-1044	ususgaauAfcUfCfAfGfGgaagucgas {invAb}	1133	usUfscgacUfuccugaGfuAfuucaas usu	1981
D-1045	ascsucagGfaAfGfUfCfGaaaaggus {invAb}	1134	usAfsccuuUfucgacuUfcCfugagus usu	1982
D-1046	csuscaggAfaGfUfCfGfaaaagguas {invAb}	1135	asUfsaccuUfuucgacUfuCfcugags usu	1983
D-1047	uscsaggaAfgUfCfGfAfaaagguaacs {invAb}	1136	usGfsuaccUfuuucaGfuUfcucugas usu	1984
D-1048	asgsgaagUfcGfAfAfAfagguacacs {invAb}	1137	usGfsuguaCfcuuuucGfaCfuuccus usu	1985
D-1049	uscsgaaaAfgGfUfAfCfacaiaaauus {invAb}	1138	usAfsuuuuUfguguacCfuUfuucgas usu	1986
D-1050	csgsaaaaGfgUfAfCfAfcaiaaauas {invAb}	1139	asUfsauuuUfuguguaCfcUfuucgcs usu	1987
D-1051	gsasgaaaGfgAfGfCfAfagccuaaas {invAb}	1140	asUfsuuagGfcuugcuCfcUfuucucs usu	1988
D-1052	asgsaaagGfaGfCfAfAfagccuaaacs {invAb}	1141	asGfsuuuaGfgcuugcUfcCfuucucs usu	1989
D-1053	gsasaaggAfgCfAfAfGfGccuaaacgs {invAb}	1142	asCfsguuuAfggcuugCfuCfcuuucs usu	1990
D-1054	asgsgagcAfaGfCfCfUfaaacgucacs {invAb}	1143	asUfsgagcUfuuaaggcUfuGfcuccus usu	1991
D-1055	gsgsagcaAfgCfCfUfAfaacgucags {invAb}	1144	usCfsugacGfuuaaggCfuUfgucuccs usu	1992
D-1056	gsasgcaaGfcCfUfAfAfafagucagags {invAb}	1145	usUfscugaCfguuagGfcUfugucucs usu	1993
D-1057	asgscaagCfcUfAfAfAfagucagaaas {invAb}	1146	usUfsucugAfcguuuuAfgCfuugcus usu	1994
D-1058	gsaagccCfuAfaAfaAfcgucagaaas {invAb}	1147	asUfsuucuGfacguuuAfgGfcuugcs usu	1995
D-1059	csasagccUfaAfAfCfGfGucagaaauus {invAb}	1148	asAfsuuucUfgacguUfaGfgcuugs usu	1996
D-1060	asasgccuAfaAfaCfGfUfcagaaauus {invAb}	1149	asGfsauuuCfugacguUfuAfggcuus usu	1997
D-1061	gsuscagaAfaUfCfCfAfguacuaaas {invAb}	1150	asUfsuuagUfacuggaUfuUfcugacs usu	1998

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1062	uscsagaaAfuCfCfAfGfuacuaaacs {invAb}	1151	asGfsuuuaGfuacuggAfuUfucugas usu	1999
D-1063	ususucugAfgCfUfUfCfaugacaaus {invAb}	1152	asAfsuuguCfaugaagCfuCfagaaas usu	2000
D-1064	asgscuucAfuGfAfCfAfaucaaggacs {invAb}	1153	asGfsuccuGfauugucAfuGfaagcus usu	2001
D-1065	ususcaugAfcAfAfUfCfaggacggus {invAb}	1154	asAfsccguCfcugauuGfuCfaugaas usu	2002
D-1066	uscsaugaCfaAfUfCfAfaggacggucs {invAb}	1155	asGfsaccgUfccugauUfgUfcaugas usu	2003
D-1067	csasugacAfaUfCfAfGfgacggucus {invAb}	1156	asAfsgaccGfuccugaUfuGfucaugs usu	2004
D-1068	asusgacaAfuCfAfGfGfagcgucuuus {invAb}	1157	asAfsagacCfguccugAfuUfgucaus usu	2005
D-1069	usgsacagUfcAfGfGfAfagcgucuuus {invAb}	1158	asCfsaagaCfcguccuGfaUfugucas usu	2006
D-1070	gsascaauCfaGfGfAfCfaggucuuus {invAb}	1159	asAfscaagAfccguccUfgAfuugucs usu	2007
D-1071	ascsaaucAfgGfAfCfGfagcucuuus {invAb}	1160	usCfsaagaGfaccgucCfuGfauugus usu	2008
D-1072	asasucagGfaCfGfGfUfucugugaas {invAb}	1161	asUfsucacAfagaccgUfcCfugauus usu	2009
D-1073	asuscaggAfcGfGfUfCfuugugaas {invAb}	1162	usAfsuucacfaagaccGfuCfcugaus usu	2010
D-1074	uscsaggaCfGfUfCfUfugugaauas {invAb}	1163	asUfsauucAfcaagacCfGfUfccugas usu	2011
D-1075	gsusucuuGfuGfAfAfUfauuggaaags {invAb}	1164	asCfsuuucCfauauucAfcAfagaccs usu	2012
D-1076	gsasaaguCfuCfAfAfUfuccacacgs {invAb}	1165	usCfsguguGfgaaugAfgAfcuuucs usu	2013
D-1077	asasagucUfcAfAfUfUfccacacgas {invAb}	1166	asUfscgugUfggaauGfaGfacuuus usu	2014
D-1078	asasagucCfaAfUfUfCfcaacacgaus {invAb}	1167	asAfsucguGfuggaaUfgAfgacuuus usu	2015
D-1079	asgsucucAfaUfUfCfCfcaacgaucs {invAb}	1168	asGfsaucgUfguggaaUfuGfagacuc usu	2016
D-1080	gsuscucaAfuUfCfCfAfcaacgaucuc {invAb}	1169	asAfsagucGfuggaaAfuUfgagacs usu	2017
D-1081	uscsucaaUfuCfCfAfCfagcaucucs {invAb}	1170	usGfsagauCfuguggAfaUfugagas usu	2018
D-1082	csuscaauUfcCfAfCfAfcaucucacs {invAb}	1171	asUfsgagaUfcgugugGfaAfuugags usu	2019
D-1083	uscsaaucCfcAfCfAfCfagcaucucacs {invAb}	1172	asAfsugagAfucguguGfgAfaucags usu	2020
D-1084	csasaucCfaCfAfCfGfaucaucags {invAb}	1173	usCfsaugaGfaucgugUfgGfaauugs usu	2021
D-1085	asusuccaCfaCfGfAfUfcucaugags {invAb}	1174	usCfsucauGfagaucgUfgUfggaas usu	2022
D-1086	ususcacAfcGfAfUfCfcaucagags {invAb}	1175	asUfscucaUfgagaucGfuGfuggaas usu	2023
D-1087	uscsacacCfGfAfUfCfUfcaugagags {invAb}	1176	usCfsucucAfugagauCfGfuggas usu	2024
D-1088	csascgauCfuCfAfUfGfagagaacus {invAb}	1177	asAfsguucUfcucaugAfgAfuugags usu	2025
D-1089	uscsucauGfaGfAfGfAfagcagaccs {invAb}	1178	asGfsguccAfguucucUfcAfugagas usu	2026

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1090	uscsaugaGfaGfAfAfCfUggaaccugs {invAb}	1179	usCfsagguCfcaguucUfcUfcaugas usu	2027
D-1091	csasugagAfgAfAfCfUfggaccugas {invAb}	1180	asUfscaggUfccaguuCfuCfucaugs usu	2028
D-1092	ususgaauGfgAfUfGfUfcugaugaas {invAb}	1181	usUfsucauCFagacauCfcAfuucaas usu	2029
D-1093	gsgsuggaCfaCfAfCfUfcagcauuus {invAb}	1182	asAfssaugCfugagugUfgUfccaccs usu	2030
D-1094	ususugagAfgCfCfCfCfacaugaas {invAb}	1183	asUfsucauUfguggggCfuCfucaas usu	2031
D-1095	asuscccaGfcCfUfAfUfcugacaccs {invAb}	1184	usGfsguguCfagauagGfcUfgggas usu	2032
D-1096	uscsccagCfcUfAfUfcugacaccas {invAb}	1185	usUfsggugUfcagauaGfgCfugggas usu	2033
D-1097	csccscagCfuAfUfcUfcgacaccaas {invAb}	1186	usUfsugguGfucagauAfgGfcugggs usu	2034
D-1098	csccsagCfuAfUfcUfcgacaccaaas {invAb}	1187	asUfsuuggUfgucagaUfaGfgcuggs usu	2035
D-1099	csasgccuAfuCfUfGfAfccacaaacs {invAb}	1188	usGfssuugGfugucagAfuAfggcugs usu	2036
D-1100	asgscagaGfaAfAfUfcfaagaugccs {invAb}	1189	asGfsgcauCFuugauUfcUfcugcus usu	2037
D-1101	gsasgcuUfgUfCfUfcCfcaagugcs {invAb}	1190	asGfscacuUfcggagaCfaAfagcucs usu	2038
D-1102	usgsucucCfgAfAfGfUfgccccagus {invAb}	1191	asAfscuggGfgcacuuCfGfagacas usu	2039
D-1103	csusccgaAfgUfGfCfCfcagucggs {invAb}	1192	usCfscgacUfggggcaCfuUfcgaggs usu	2040
D-1104	usccscgaGfgGfCfCfCfcagucggas {invAb}	1193	asUfscgaCfuggggcAfcUfucggas usu	2041
D-1105	asgsaacuGfgGfAfAfGfagccuauus {invAb}	1194	asGfsauagGfcucuucCfcAfguucus usu	2042
D-1106	gsasacugGfgAfAfGfAfagccuauccs {invAb}	1195	asGfsgauaGfgcucuCfcCfaguucs usu	2043
D-1107	asasgagCfuAfUfcCfCfcugcuuucs {invAb}	1196	asGfssaaagCfagggaUfgGfcucuus usu	2044
D-1108	asgsgcugGfgCfGfCfCfcgacccgus {invAb}	1197	asAfscggaUfcaggcgCfcCfagccus usu	2045
D-1109	gsgscuggGfcGfCfCfUfgaucgucs {invAb}	1198	usGfsacggAfucaggcGfcCfcagccs usu	2046
D-1110	gscsugggCfgCfCfUfgfauccgucas {invAb}	1199	asUfsgacGfauacaggCfcCfcagccs usu	2047
D-1111	csusgggcGfcCfUfGfAfuccgucags {invAb}	1200	asCfsugacGfgaucagGfcGfcccags usu	2048
D-1112	usgsggcgCfcUfGfAfUfccgucages {invAb}	1201	asGfscugaCfaggauaGfgCfgcccas usu	2049
D-1113	csusggacGfaAfGfAfCfagcgacccs {invAb}	1202	asGfsggucGfcugucuUfcGfuccags usu	2050
D-1114	ascscccaUfgCfUfcUfcuccucggs {invAb}	1203	asCfscgagGfagagagCfaUfggggus usu	2051
D-1115	csasugcuCfuCfUfcCfucgguuucs {invAb}	1204	usAfsgaacCfaggagAfgAfgcaugs usu	2052
D-1116	asusgcucUfcUfcCfUfcgguucuas {invAb}	1205	asUfsagaaCfcgaggaGfaGfagcaus usu	2053
D-1117	gscsucucUfcCfUfcGfGguucacgs {invAb}	1206	asCfsguagAfaccgagGfaGfagagcs usu	2054

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1118	csuscucuCfcUfCfGfGfUucuaacgcs {invAb}	1207	asGfscguaGfaaccgaGfgAfgagags usu	2055
D-1119	uscusucuCfuCfGfGfUfucuaacgcs {invAb}	1208	asAfsqcguaAfgaaccgAfgGfagagags usu	2056
D-1120	csuscuccUfcGfGfUfUfcuacgcuus {invAb}	1209	usAfsagcgUfagaaccGfaGfgagags usu	2057
D-1121	uscsuccuCfGfGfUfUfcuacgcuuas {invAb}	1210	asUfsaagcGfuagaacCfGfaggagags usu	2058
D-1122	csusccucGfgUfUfcUfUfcuacgcuuas {invAb}	1211	asAfsuaagCfaguagaaCfcGfaggagags usu	2059
D-1123	uscscucgGfuUfCfUfAfcgcuuauugs {invAb}	1212	asCfsauaaGfcguagaAfcCfaggagags usu	2060
D-1124	cscsucggUfuCfUfAfcGfcuuauuggs {invAb}	1213	asCfscuauAfgcguaGfaCfcgagags usu	2061
D-1125	csuscggUfCfUfAfcGfcuuauuggs {invAb}	1214	asCfscuauAfgcguaGfaAfcgagags usu	2062
D-1126	csasccaaAfcUfCfCfCfauucuuucs {invAb}	1215	usGfsaaagAfaugggaGfuUfugggags usu	2063
D-1127	csasaaacUfcCfCfAfcUfucuuuacs {invAb}	1216	asAfsugaaAfgauggGfaGfuuggags usu	2064
D-1128	csuscccaUfuCfUfUfUfcaugaggcs {invAb}	1217	asGfscucAfcuagaaGfaUfaggagags usu	2065
D-1129	csasuuuUfuCfAfcUfGfaggcgaggcs {invAb}	1218	usCfsgccgCfcuagAfaAfgaugs usu	2066
D-1130	asusucuUfCfAfcUfGfAfgcgaggcs {invAb}	1219	usUfscgcccGfcuagAfaAfgaugs usu	2067
D-1131	ususcuuUfCfAfcUfGfAfgcgaggcs {invAb}	1220	asUfsucgcCfaggcuAfcAfaagags usu	2068
D-1132	uscscuuUfCfAfcUfGfAfgcgaggcs {invAb}	1221	asCfsuucgCfaggcuAfcAfaagags usu	2069
D-1133	csusuuuUfCfAfcUfGfAfgcgaggcs {invAb}	1222	asGfscuucGfcaggcuAfcAfaagags usu	2070
D-1134	ususcuuUfCfAfcUfGfAfgcgaggcs {invAb}	1223	asAfsqcuUfaggcuUfAfaagags usu	2071
D-1135	uscscucGfgGfUfCfCfauaugagags {invAb}	1224	asUfscuauAfuaggacCfcCfagagags usu	2072
D-1136	ascscuccGfcCfCfAfcGfcuacacgcs {invAb}	1225	usCfsguguGfagcuggGfcAfggugags usu	2073
D-1137	csasccugCfcCfAfcGfcuacacgags {invAb}	1226	usUfscgugUfagcugGfgCfaggagags usu	2074
D-1138	cscsugccCfaGfCfUfCfagacgaags {invAb}	1227	asCfsuucgUfagcugUfGfgcagags usu	2075
D-1139	cscsagcuCfaCfAfcGfaggaauucs {invAb}	1228	usGfsaaucCfuucgugUfGfgcagags usu	2076
D-1140	asgscucaCfaCfGfAfcGfaggaucags {invAb}	1229	usCfsugaaUfucucgUfGfgagagags usu	2077
D-1141	asusccgAfaGfUfUfUfGfaggaugags {invAb}	1230	usCfsuauUfucuaacUfCfaggagags usu	2078
D-1142	csgsgaagUfuUfGfAfcGfaggaauugs {invAb}	1231	asAfsauuUfucuaacAfaCfuuccgags usu	2079
D-1143	asgsuuuUfAfcUfUfUfGfaggaucgags {invAb}	1232	asUfsucgaUfucuaacUfCfaggaags usu	2080
D-1144	gsusuugaAfgAfcUfAfcGfaggaucgags {invAb}	1233	usCfsuucgAfaucuaUfUfaggaags usu	2081

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1145	gsasagauAfgAfUfUfCfgaagaagas {invAb}	1234	asUfscuucUfucgaaUcfuAfuucucs usu	2082
D-1146	asgsaagaAfgUfAfCfAfgaccuuccs {invAb}	1235	asGfsgaagGfucuguaCfuUfucucucs usu	2083
D-1147	gsasagaaGfuAfCfAfGfaccuucccs {invAb}	1236	usGfsggaaGfgucuguAfcUfucucucs usu	2084
D-1148	asasgaagUfaCfAfGfAfccuucccas {invAb}	1237	asUfsgggaAfggucugUfaCfuucucucs usu	2085
D-1149	uscsugaaAfuGfGfAfCfaaaugaccs {invAb}	1238	asGfsguacUfuuguccAfuUfucagacs usu	2086
D-1150	csusgaaaUfgGfAfCfAfaaugaccus {invAb}	1239	asAfsggucAfuugucCfaUfuucagcs usu	2087
D-1151	ascsaauGfaCfCfUfUfgccaaaus {invAb}	1240	asAfssauuGfgcaaggUfcAfuugucs usu	2088
D-1152	asasaugaCfcUfUfGfCfcaauuccs {invAb}	1241	asGfsgaaUfuggcaGfgUfcuuucs usu	2089
D-1153	asasugaaCfuUfGfCfCfaaauccgs {invAb}	1242	asCfsggaaUfuuggcaAfgGfucuuucs usu	2090
D-1154	usgsaccuUfgCfCfAfAfauccggas {invAb}	1243	asUfscggAfaauuggCfaAfggucacs usu	2091
D-1155	gsasccuGfcCfAfAfAfuuccggags {invAb}	1244	usCfsuccGfaauugGfcAfaggucs usu	2092
D-1156	ascscuugCfcAfAfAfUfuccggagas {invAb}	1245	asUfscuccGfgaaauUfgCfaaggucs usu	2093
D-1157	cscsuugCfaAfAfUfUfccggagacs {invAb}	1246	usGfsucucCfsgaaUfGfcaaggcs usu	2094
D-1158	cscsggagAfcAfAfCfUfuaaagaas {invAb}	1247	asAfssuucUfuaaguGfuCfuccggs usu	2095
D-1159	csgsgagaCfaAfCfUfUfaaagaacs {invAb}	1248	usGfsauucUfuaaguUfgUfcuccgs usu	2096
D-1160	asgsauauCfuGfAfAfGfaggaccuas {invAb}	1249	usUfsagguCfcucucAfgAfuaucucs usu	2097
D-1161	gsasggacCfuAfAfCfUfUfccaggas {invAb}	1250	asAfssuccGfggaguAfgGfuccucs usu	2098
D-1162	gsasccuaAfcUfCfCfCfaggauccgs {invAb}	1251	asCfsgcaUfcugggaGfuUfaggucs usu	2099
D-1163	ascscuaaCfuCfCfCfAfggaugcgs {invAb}	1252	asCfscgaUfccugggAfgUfuaggucs usu	2100
D-1164	usgscggAfgCfGfAfAfGcaacacas {invAb}	1253	asUfsguguUfgcuucGfuGfccgcacs usu	2101
D-1165	gscsggcaGfcGfAfAfGfcaacacas {invAb}	1254	asGfsugugUfugcuucGfcUfgccgcs usu	2102
D-1166	csasgcgaAfgCfAfAfCfacacucccs {invAb}	1255	asGfsggagUfguguugCfuUfcgcucs usu	2103
D-1167	gscsgaagCfaAfCfAfCfacuccccas {invAb}	1256	usUfsggggAfguguguUfgCfuucgcs usu	2104
D-1168	gscsaacaCfaCfUfCfCfccaagagus {invAb}	1257	asAfscucuUfggggagUfgUfguugcs usu	2105
D-1169	csasagauUfUfUfGfGfuucccaacs {invAb}	1258	asGfssuggGfaaccaaAfaCfucucgs usu	2106
D-1170	gsasguuuUfgGfUfUfCfccaacuugs {invAb}	1259	usCfsaaguUfgggaacCfaAfaucucs usu	2107
D-1171	gsusuuugGfuUfCfCfCfaacuugags {invAb}	1260	usCfssucaaGfuugggaAfcCfaaaacs usu	2108
D-1172	ususgaagCfcAfCfAfUfuggaauucs {invAb}	1261	usAfsgauCfcaaguGfgCfuucaacs usu	2109

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1173	cscsaggaGfaAfGfCfGfagcggaas {invAb}	1262	asUfsuuccGfcucgcuUfcUfccuggs usu	2110
D-1174	gsasccagAfuUfGfCfUfaaugagaas {invAb}	1263	usUfsucucAfuuaagcaAfuCfuggucs usu	2111
D-1175	gscsuaauGfaGfAfAfAfaguggcucus {invAb}	1264	asAfsgagcCfacuucUfcAfuagcs usu	2112
D-1176	asgscauuCfaUfGfGfAfCggccggus {invAb}	1265	usAfscggCfcguccaUfgAfaugcus usu	2113
D-1177	gscsauuGfaGfAfCfGgcccguas {invAb}	1266	usUfsaccGfcccuccAfuGfaaugcs usu	2114
D-1178	csasuucUfgGfAfCfGfcccguuas {invAb}	1267	asUfsuaccGfcccucCfaUfgaaugs usu	2115
D-1179	asusucAuGfgAfCfGfGfcccguacacs {invAb}	1268	usGfsuuacCfggccguCfcAfugaas usu	2116
D-1180	ususcAuGfaCfGfGfCfcccguacacs {invAb}	1269	usUfsguuaCfcccgcUfcCfaugaas usu	2117
D-1181	uscsauuGfCfGfCfCfGgguacaacs {invAb}	1270	usUfsuguuAfcccggccGfuCfcaugas usu	2118
D-1182	asusggacGfgCfCfGfGfuaacaaggs {invAb}	1271	usCfsuuuGfuaccggCfcGfuccaus usu	2119
D-1183	usgsgacGfCfCfGfGfUfaacaaggs {invAb}	1272	usUfscuuGfuuaccGfCfGuccas usu	2120
D-1184	gsgsacggCfCfGfGfUfaacaagaas {invAb}	1273	asUfsucuuUfguuaccGfgCfGuccs usu	2121
D-1185	ascsggccGfgUfAfAfCfaaagaacgs {invAb}	1274	usCfsguucUfuuguuaCfcGfgccgus usu	2122
D-1186	csgsgccGfgUfAfAfCfaaagaacgs {invAb}	1275	usUfscguUfuuguuaCfcGfgccgus usu	2123
D-1187	gsgsccgUfaAfCfAfAfagaacgaas {invAb}	1276	asUfsucguUfcuuuguUfaCfcccgs usu	2124
D-1188	gscscguUfaAfCfAfAfagaacgaacs {invAb}	1277	asGfsuucUfucuuuGfuAfcccgs usu	2125
D-1189	cscsgguUfaAfCfAfAfagaacgaacs {invAb}	1278	asCfsguucGfuucuuGfuUfaccggs usu	2126
D-1190	csgsguuaCfaAfAfGfAfagaacggs {invAb}	1279	asCfscguUfucuuuGfuUfaccggs usu	2127
D-1191	gsgsuuaCfaAfAfGfAfagaacggs {invAb}	1280	usGfscguUfucuuuGfuUfaccggs usu	2128
D-1192	asasagaaCfGfAfCfGfGfagguagas {invAb}	1281	asUfscaccUfgccguUfGfucuuus usu	2129
D-1193	asusgaagCfCfAfCfUfaUfagacaggs {invAb}	1282	asCfsugucGfuauaguGfgCfucaus usu	2130
D-1194	gsasagccAfcUfAfUfAfagacaggs {invAb}	1283	usAfscugUfGguuaGfuGfgcuucs usu	2131
D-1195	asasgccaCfuAfUfAfCfGfagagguas {invAb}	1284	asUfsaccGfGguuaUfgUfggcuus usu	2132
D-1196	asgscacUfaUfAfCfGfagagguacs {invAb}	1285	asGfsuaccUfgucguUfaGfuggcus usu	2133
D-1197	gscscacuUfaUfAfCfGfagagguacs {invAb}	1286	asGfsguacCfugucguUfaUfggucs usu	2134
D-1198	cscsacuUfaCfGfAfCfagguaccgs {invAb}	1287	asCfsgguUfGguuUfaUfaguggs usu	2135
D-1199	csascuauUfaCfGfAfCfagguaccgs {invAb}	1288	asCfscguUfGguuUfaUfaguggs usu	2136
D-1200	ascsuauUfaCfGfAfCfagguaccgs {invAb}	1289	asGfscggUfaccguUfGfauagus usu	2137

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1201	asascagaUfcCfUCfUfccccgagcus {invAb}	1290	usAfgscucGfgggagagGfaUfcuguus usu	2138
D-1202	asc sagauCfcUfCfUfCfcccgagcuas {invAb}	1291	usUfsagcuCfggggagaGfgAfucugus usu	2139
D-1203	asgsaucUfcUfCfCfCf gagcuaacs {invAb}	1292	usGfsuuagCfucgggaGfaGfgaucus usu	2140
D-1204	uscscucuCfcCfGfAfGfcuaacaccs {invAb}	1293	usGfsguguUfagcucgGfgAfgaggas usu	2141
D-1205	cscsucuCfcGfAfGfCfuAACaccas {invAb}	1294	asUfsggugUfuagcucGfgGfagaggs usu	2142
D-1206	csuscuccCfgAfGfCfUfaaacaccaus {invAb}	1295	usAf sugguGfuuagcuCf gGfgagags usu	2143
D-1207	uscscgaGfcUfAfAfCf accauaccs {invAb}	1296	asGfsguauGfguguuAGfcUfcgggas usu	2144
D-1208	cscscgagCfuAfAfCfAfccauaccs {invAb}	1297	usGfsgguaUfgguguuAfgCfucgggs usu	2145
D-1209	gsgsggucAfgAfAfGfAf cgauagcas {invAb}	1298	usUfsgcuUfcgucuuCfuGfaccccs usu	2146
D-1210	gsgsgucaGfaAfGfAfCf gauagcaas {invAb}	1299	asUfsgucuAfucgucuUfcUfgaccs usu	2147
D-1211	gsuscagaAfgAfCfGfAfuagcaaugs {invAb}	1300	asCfsauugCfuaucguCfuUfcugacs usu	2148
D-1212	usc sagaaGfaCfGfAfUf agcaaugs {invAb}	1301	asAfscauUGfcuaucgUfcUfucugas usu	2149
D-1213	gsasagacGfaUfAfGfCfaaugugaas {invAb}	1302	asUfsucACfuugcuUfcGfucucs usu	2150
D-1214	asgsacgaUfaGfCfAfAfugugaagcs {invAb}	1303	asGfscuucAfcauugcUfaUfcgucus usu	2151
D-1215	asusggucAfcUfCfUfGfaaaaccgas {invAb}	1304	asUfscggUfuucagaGfuGfaccas usu	2152
D-1216	usgsgucaCfuCfUfGfAfaaaaccgaus {invAb}	1305	asAfsucggUfuuucagAfgUfgaccas usu	2153
D-1217	gsgsucacUfcUfGfAfAfaaccgauus {invAb}	1306	asAfsaucgGfuuuucaGfaGfugaccs usu	2154
D-1218	gsasaaaCf gAfUfUfUfcagugcacs {invAb}	1307	asGfsugcaCfugaaaCf gGfuuuucs usu	2155
D-1219	asascgaUfuUfCfAfGfugcacgaus {invAb}	1308	asAfsucguGfcacugaAfaUfcgguus usu	2156
D-1220	usasuuucCfcCfAfAfUf ggaugauas {invAb}	1309	usUfsaucaUfccauugGfgGfaaauas usu	2157
D-1221	cscscaauGfgAfUfGfAfuaaaaauacs {invAb}	1310	asGfsuauUfuaucauCfcAfuugggs usu	2158
D-1222	csasauggAfuGfAfUfAfaaaauccas {invAb}	1311	asUfsgguaUfuuuauCAfuCfcauugs usu	2159
D-1223	usgsgaugAfuAfAfAfAfuaccaucas {invAb}	1312	usUfsgaugGfuauuuuAfuCfauccas usu	2160
D-1224	asasaucCfaUfCfAfAfaauncagcs {invAb}	1313	asGfscugcAfuuuugaUfgGfuauuus usu	2161
D-1225	gsgsgcuUfCfAfAfAfUfcuccaugcs {invAb}	1314	asGfscaugGfagauuGfaAfagcccs usu	2162
D-1226	gsgscuuCfaAfAfUfCfuccaugcus {invAb}	1315	asAfgscAuGfgagauUfgAfaagccs usu	2163
D-1227	asasucucCfaUfGfCfUfgccucaaus {invAb}	1316	usAfesuugaGfgcagcaUfgGfagauss usu	2164
D-1228	asuscuccAfuGfCfUfGfccucaaus {invAb}	1317	asUfsauugAfggcagcAfuGfgagaus usu	2165

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1229	usc succaUfgCfUFGfCfcucaauacs {invAb}	1318	asGfsuauuGfaggcagCfaUfggagas usu	2166
D-1230	csusgccuCfaAfUfAfCfcugaacucs {invAb}	1319	asGfsaguuCfagguauUfgAfggcags usu	2167
D-1231	csusggaaCfaCfCfUfCfcaggaaus {invAb}	1320	asAfsuuuCfuggaggUfgUfuccags usu	2168
D-1232	csusucggGfaUfUfUfUfgaagacaas {invAb}	1321	asUfsugucUfucaaaaUfcCfcgaags usu	2169
D-1233	cscsagaaGfgAfAfGfAfccgcacucs {invAb}	1322	asGfsagugCfggucuuCfcUfucuggs usu	2170
D-1234	gsasaggaAfgAfCfCfGfcacuccuas {invAb}	1323	asUfsaggaGfugcgguCfuUfccuucs usu	2171
D-1235	asasggaaGfaCfCfGfCfacuccuaus {invAb}	1324	asAfsuaggAfgugcggUfcUfuccuus usu	2172
D-1236	asgsaagAfcCfGfCfAfcuccuaugs {invAb}	1325	asCfsauagGfagugcgGfuCfuuccus usu	2173
D-1237	gsgsaagaCfcGfCfAfCfuccuauggs {invAb}	1326	asCfscuaGfgagugcGfgUfcuuccs usu	2174
D-1238	gsasagacCfGfCfAfCfUfccuauggs {invAb}	1327	asGfsccauAfggagugCfGfucuuCs usu	2175
D-1239	asgsaccgCfaCfUfCfCfuauggcugs {invAb}	1328	usCfsagccAfuaggagUfgCfggucus usu	2176
D-1240	cscsgcacUfcCfUfAfUfggcugaags {invAb}	1329	usCfsuucGfccauagGfaGfugcggs usu	2177
D-1241	usasagcaCfaUfAfAfAfggcgaaacs {invAb}	1330	asGfsuuuCfcccuaUfgUfgcuuas usu	2178
D-1242	asasgcacAfuAfAfAfGfgcgaaacus {invAb}	1331	asAfsquuuCfgccuuAfuGfugcuus usu	2179
D-1243	gscsacauAfaAfGfGfCfgaacugas {invAb}	1332	asUfscaguUfucgcuUfuAfugugcs usu	2180
D-1244	gsasuuccAfaGfUfCfCfaugugaggs {invAb}	1333	asCfscucaCfauggacUfuGfgaaucs usu	2181
D-1245	asusuccaAfgUfCfCfAfugugaggs {invAb}	1334	asCfscucAfcAuggaCfuUfggaaus usu	2182
D-1246	cscsaaguCfcAfUfGfUfgagggcas {invAb}	1335	asUfsgcccCfucacauGfgAfcuuggs usu	2183
D-1247	csasagucCfaUfGfUfGfaggggcaus {invAb}	1336	asAfsugccCfcucacaUfgGfacuugs usu	2184
D-1248	gsusccauGfuGfAfGfGfggcauggs {invAb}	1337	asGfsccauGfcccucAfcAfuggacs usu	2185
D-1249	gscsagcuGfcGfGfUfGfagaguuas {invAb}	1338	asUfsaaacUfcucaccGfcAfgcugcs usu	2186
D-1250	asgscugcGfgUfGfAfGfaguuuacus {invAb}	1339	asAfsquaaAfcucucaCfcGfcagcus usu	2187
D-1251	cscscagaGfaAfAfGfUfgcagcucus {invAb}	1340	asAfsagacUfgcacuuUfcUfcuggs usu	2188
D-1252	csasaagcAfuGfCfAfGfcccucugs {invAb}	1341	asCfsagaaGfggcugcAfuGfcuugs usu	2189
D-1253	cscsuucuGfcCfUfCfUfagaccuus {invAb}	1342	asAfsauugUfcuagagGfcAfgaaggs usu	2190
D-1254	usc sugccUfcUfAfGfAfccauuuggs {invAb}	1343	asCfscaaaUfggucuaGfaGfgcagas usu	2191
D-1255	usc suagaCfcAfUfUfUfggcaucggs {invAb}	1344	asCfscgauGfcaaaUfgUfcuagas usu	2192
D-1256	csusagacCfaUfUfUfGfgcaucggs {invAb}	1345	asGfscgaUfgccaaaUfgGfucuas usu	2193

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1257	usasgaccAfuUfUfGfGfcaucggcus {invAb}	1346	asAfsgccgAfugccaaAfuGfgucuas usu	2194
D-1258	asgsaccaUfuUfGfGfCfaucggcus {invAb}	1347	asGfsagccGfaugccaAfaUfggucus usu	2195
D-1259	ususuggcAfuCfGfGfCfuccguuus {invAb}	1348	asAfsaacaGfgagccgAfuGfccaaas usu	2196
D-1260	gsgscaucGfgCfUfCfCfuguuuccas {invAb}	1349	asUfsggaaAfcaggagCfcGfaugccs usu	2197
D-1261	uscsggcuCfcUfGfUfUfuccauugcs {invAb}	1350	asGfscaaUGfgaaacaGfgAfgccgas usu	2198
D-1262	gsgscuccUfgUfUfUfCfcauugccus {invAb}	1351	asAfsggcaAfuggaaaCfaGfgagccs usu	2199
D-1263	usasggcaUfuUfUfGfUfaauuggaas {invAb}	1352	usUfsuccaAfuuaacaAfaUfgccuas usu	2200
D-1264	asgsgcauUfuUfGfUfAfauuggaaas {invAb}	1353	asUfsuuccAfauuacaAfaAfugccus usu	2201
D-1265	asusuugUfaAfUfUfGfgaaagucas {invAb}	1354	usUfsgacuUfuccaauUfaCfaaaus usu	2202
D-1266	ususuguaAfuUfGfGfAfaagucaags {invAb}	1355	usCfsuugaCfuuucaAfuUfacaas usu	2203
D-1267	asasuuggAfaAfGfUfCfaagacugcs {invAb}	1356	usGfscaguCfuugacuUfuCfcauus usu	2204
D-1268	gsgsaaagUfcAfAfGfAfcugcaguas {invAb}	1357	asUfscagCfagucuGfaCfuuuccs usu	2205
D-1269	gsuscaagAfcUfGfCfAfguaugugcs {invAb}	1358	usGfscacaUfacugcaGfuCfuugacs usu	2206
D-1270	uscсааgаCfuGfCfAfGfuaugugcas {invAb}	1359	asUfsgcacAfuaugcAfGfUfcuugas usu	2207
D-1271	ascсacacAfcAfGfUfAfuggagcus {invAb}	1360	asAfsgcucCfacuacuGfuGfugugus usu	2208
D-1272	csascacaGfuAfGfUfGfgagcuuucs {invAb}	1361	asGfsaaagCfuccacuAfcUfgugugs usu	2209
D-1273	ascсacagUfaGfUfGfGfagcuuuccs {invAb}	1362	asGfsgaaaGfcuccacUfaCfugugus usu	2210
D-1273B	ascсaguaGfuGfGfAfGfcuuuccuas {invAb}	2821	usUfsaggaAfacuccAfcUfacugus usu	2822
D-1274	gscsuuucCfuAfAfCfAfcuagcagas {invAb}	1363	asUfscugcUfaguguuAfgGfaaagcs usu	2211
D-1275	usasacacUfaGfCfAfGfagauuaas {invAb}	1364	asAfсуаааUfcucugCfUfaGfuguas usu	2212
D-1276	asascacuAfgCfAfGfAfgauuaaucs {invAb}	1365	usGfsauuaAfucucugCfuAfguguus usu	2213
D-1277	ascсacuaGfcAfGfAfGfauuaaucas {invAb}	1366	asUfsgauuAfaucucuGfcUfagugus usu	2214
D-1278	csusagcaGfaGfAfUfUfaaucacuas {invAb}	1367	asUfsagugAfuuaaucUfcUfgcuags usu	2215
D-1279	asgsagauUfaAfUfCfAfcuacauuas {invAb}	1368	asUfsaaugUfagugauUfaAfucucus usu	2216
D-1280	csusacauUfaGfAfCfAfacacucaus {invAb}	1369	asAfсugagUfguugcUfaAfuguags usu	2217
D-1281	usascuuAfgAfCfAfAfcacucaucs {invAb}	1370	asGfsaugaGfuguuguCfuAfauguas usu	2218
D-1282	csasuugAfcAfAfCfAfcucaucas {invAb}	1371	asUfsagauGfaguguuGfuCfuaaugs usu	2219
D-1283	gsgsauaaCfuGfAfGfAfaacaagags {invAb}	1372	usCfsucuuGfuuucucAfgUfuauccs usu	2220

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1284	gsasgaccAfuUfCfUfCfugucuaacs {invAb}	1373	asGfsuuagAfcagagaAfuGfgucucs usu	2221
D-1284B	csusgucuAfaCfUfGfUfgauaaaaas {invAb}	1374	asUfsuuuuAfuacacagUfuAfgacags usu	2222
D-1285	uscsaggaCfuUfUfAfUfucuaugas {invAb}	1375	asUfscuaUfgaauaaAfgUfccugas usu	2223
D-1286	ascsuuuUfuCfUfAfUfagagcaas {invAb}	1376	asUfsuugcUfcuaUfAfaUfaaagus usu	2224
D-1287	ususauuUfaUfAfGfAfGcaaacuus {invAb}	1377	asAfsaguuUfgcucuaUfaGfaauaas usu	2225
D-1288	usasuuUfuAfGfAfGfcaaacuugs {invAb}	1378	asCfsaaguUfugcucuAfuAfgaauas usu	2226
D-1289	ususcuaUfGfAfGfCfAfaacuugcus {invAb}	1379	asAfsGcaaGfuugcuCfuAfuagaas usu	2227
D-1290	csusguggAfgGfGfCfCfaugcucucs {invAb}	1380	asGfsagagCfauggccCfuCfcacags usu	2228
D-1291	gscsucuCfuUfGfGfAfcccaguuas {invAb}	1381	usUfsaacUGfgguccaAfgGfagagcs usu	2229
D-1292	uscsuccUfGfAfCfCfCfaguuuacs {invAb}	1382	asGfsuuuacFugggucCfaAfggagas usu	2230
D-1293	csusccuUfGfAfCfCfCfaguuuacs {invAb}	1383	asAfsguuAfcuggguCfcAfaaggags usu	2231
D-1294	csusuUgGfAfCfCfAfGfuuaacugcs {invAb}	1384	usGfscaguUfaacuggGfuCfcaaggs usu	2232
D-1295	csusuggaCfcCfAfGfUfuaacugcas {invAb}	1385	usUfsgcagUfuaacugGfgUfccaggs usu	2233
D-1296	gsGsaccUfGfUfAfAfCfugcaaac {invAb}	1386	asGfsuuugCfaguuuacFufGfgguccs usu	2234
D-1297	gsascccaGfuUfAfAfCfugcaaacgs {invAb}	1387	asCfsguuUfCfaguuAfcUfgggucs usu	2235
D-1298	ascscagUfuAfAfCfUfGfcaaacgus {invAb}	1388	asAfsccguUfGfaguuAfaCfugggus usu	2236
D-1299	cscscaguUfaAfCfUfGfcaaacgugs {invAb}	1389	asCfsacguUfugcaguUfaAfcugggs usu	2237
D-1300	cscsaguUfaCfUfGfCfAfaacugcs {invAb}	1390	usGfscacgUfuugcagUfuAfacuggs usu	2238
D-1301	csasguuAfcUfGfCfAfaacugcas {invAb}	1391	asUfsgcacGfuugcaGfuUfaacugs usu	2239
D-1302	ususaacuGfCfAfAfAfCfugcauugs {invAb}	1392	asCfsaaugCfacguuUfCfaguuuacs usu	2240
D-1303	csusgcaaAfcGfUfGfCfauuggagcs {invAb}	1393	asGfscuccAfaugcacGfuUfugcags usu	2241
D-1304	usgscaaaCfGfUfGfCfAfuuggagccs {invAb}	1394	asGfsgcucCfaaugcaCfGfufugcas usu	2242
D-1305	asascgucCfaUfUfGfGfagcccuauas {invAb}	1395	asAfsuaggGfcuccaaUfgCfacguus usu	2243
D-1306	ascsgugCfuUfGfGfAfGcccuauus {invAb}	1396	asAfsauagGfguccaAfuGfcacgus usu	2244
D-1307	gsusgcaUfGfAfGfCfCcuauuugs {invAb}	1397	asCfsaaaUfGfggucCfaAfugcacs usu	2245
D-1308	usgscauuGfGfAfGfCfCcuauuugs {invAb}	1398	asGfscaaaUfagggcuCfcAfaugcas usu	2246
D-1309	usgsgagCfCfUfAfUfUfugcugccgs {invAb}	1399	asCfsggcaGfcaauaGfgGfcuccas usu	2247
D-1310	gsGsagccCfuAfUfUfUfGfcugccgs {invAb}	1400	asGfscggcAfgcauuAfgGfgcuccs usu	2248

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1311	gsasgcccUfaUfUfUfGfcugccgcus {invAb}	1401	asAfsqcgCfagcaaaUfaGfggcucs usu	2249
D-1312	asgscccuAfuUfUfGfCfugccgcugs {invAb}	1402	asCfsagcgGfcagcaaAfuAfgggcucs usu	2250
D-1313	cscsgcugCfcAfUfUfCfuagugaccs {invAb}	1403	asGfsgucaCfuagaaUfgCfagcggs usu	2251
D-1314	usgsccauUfcUfAfGfUfgaccuuucs {invAb}	1404	asGfsaaagGfucacuaGfaAfuggcas usu	2252
D-1315	gscscauGfuAfGfUfGfaccuuuccs {invAb}	1405	usGfsgaaaGfgucacuAfgAfaugcgs usu	2253
D-1316	csusagugAfcCfUfUfUfccacagags {invAb}	1406	asCfsucugUfggaaagGfuCfacuags usu	2254
D-1317	asgsagcuGfcGfCfUfuccucacgs {invAb}	1407	asCfsgugaGfgaaggcGfcAfgcucucs usu	2255
D-1318	gscsgccuUfcCfUfCfAfcgugugugs {invAb}	1408	usCfsacacAfcgugagGfaAfggcgcs usu	2256
D-1319	cscscauGfuGfUfGfUfgaaagguus {invAb}	1409	asAfsaccuUfucacacAfcGfugaggs usu	2257
D-1320	csuscacgUfgUfGfUfGfaaagguus {invAb}	1410	asAfsaaccUfuucacaCfaCfugaggs usu	2258
D-1321	ususcagcCfcUfCfAfGfGuagauggs {invAb}	1411	usCfscacuUfaccugaGfgGfcugaas usu	2259
D-1322	uscsagccCfuCfAfGfGfuagauggas {invAb}	1412	usUfscacuCfuaccugAfgGfgcugas usu	2260
D-1323	asgscccuCfaGfGfUfAfgauggaags {invAb}	1413	asCfsuuccAfucuaaccUfgAfgggcucs usu	2261
D-1323B	csascgauGfgCfAfGfUfgcagucaus {invAb}	2823	asAfsugacUfgcacugCfcAfucgugs usu	2824
D-1324	uscsaggaUfgUfUfUfCfuucaggacs {invAb}	1414	asGfsuccuGfaagaaaCfaUfccugas usu	2262
D-1325	ususcucuAfgCfUfGfAfcaaggaaus {invAb}	1415	asAfsuuccUfugucagCfuGfaggaa usu	2263
D-1326	asgsccgaCfaAfGfGfAfaauuuggus {invAb}	1416	asAfsccaaAfauccuUfgUfcagcucs usu	2264
D-1327	gsasauuuUfgGfUfCfCfugccuags {invAb}	1417	asCfsuaggCfagggaCfaAfaauucs usu	2265
D-1328	asasuuuuGfgUfCfCfCfugccuaggs {invAb}	1418	usCfscuagGfcagggacCfaAfaauus usu	2266
D-1328B	ususuuggUfcCfCfUfGfCcuaggacs {invAb}	2825	asGfsuccuAfggcaggGfaCfcaaaas usu	2826
D-1329	ususuuguCfcCfUfGfCfcuaggaccs {invAb}	1419	asGfsguccUfaggcagGfgAfccaaas usu	2267
D-1330	csusgccuAfgGfAfCfCfgggucaucs {invAb}	1420	asGfsaugaCfcggucCfuAfggcags usu	2268
D-1331	ascsagagAfgAfUfGfGfuaagcags {invAb}	1421	asGfscugcUfuaccuUfCfucugus usu	2269
D-1332	gsasgagaUfgGfUfAfAfGfcagcugus {invAb}	1422	usAfsacagUfgcuuacCfaUfcucucs usu	2270
D-1333	asgsagauGfgUfAfAfGfCagcuguas {invAb}	1423	asUfsacagCfugcuuaCfcAfucucucs usu	2271
D-1334	gsasgaugGfuAfAfGfCfagcuguauus {invAb}	1424	asAfsuacaGfcugcuUfCfauucucs usu	2272
D-1335	gsusaagcAfgCfUfGfUfauaaugcs {invAb}	1425	asGfscuuCfauacagCfuGfcuuacs usu	2273

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1336	asgscagcUfgUfAfUfGfGfaaUGCUGAS {invAb}	1426	asUfscagcAfuucAuaCfaGfcugcususu	2274
D-1337	gsasuuuuAfaAfAfCfCfaggucAUGS {invAb}	1427	asCfsaugaCfcugguUfuAfaaaucsusu	2275
D-1338	ususuuuaAfaCfCfAfGfGucaugggs {invAb}	1428	usCfscCauGfaccuggUfuUfuaaaausu	2276
D-1339	csusgaacAfcUfGfAfCfugcacuuas {invAb}	1429	asUfsaaguGfcagucaGfuGfuucagsusu	2277
D-1340	usgsaacaCfuGfAfCfUfgcacuuacs {invAb}	1430	asGfsuaagUfgcagucAfgUfguucasu	2278
D-1341	csascuuaCfcAfGfUfCfugauuuuas {invAb}	1431	asUfsaaaaUfcagacuGfgUfaagugsusu	2279
D-1342	ascscaguCfuGfAfUfUfuuaucgucs {invAb}	1432	usGfsacgaUfaaaucAfgAfcuggususu	2280
D-1343	cscsaguCfGfAfUfUfUfuauucgucas {invAb}	1433	usUfsgacgAfuaaaauCfaGfacuggsusu	2281
D-1344	uscsugauUfuUfAfUfCfGfugaacacs {invAb}	1434	asUfsguuGfacgaaAfaAfucagasusu	2282
D-1345	csusgauUfuUfAfUfCfGfuaaacacs {invAb}	1435	asGfsuguuUfgacgauAfaAfaucagsusu	2283
D-1346	usgsauuuUfaUfCfGfUfcaaacacccs {invAb}	1436	usGfsguguUfugacgaUfaAfaaucasu	2284
D-1347	gsasuuuuAfUfCfGfUfCfaaacaccas {invAb}	1437	usUfsggugUfuugacgAfuAfaaaucsusu	2285
D-1348	asusuuuaUfcGfUfCfAfaaacaccaas {invAb}	1438	asUfsugguGfuugacGfaUfaaaususu	2286
D-1349	ususaucgUfcAfAfAfCfaccagccs {invAb}	1439	usGfsgcuUfguguuGfaCfgauaasu	2287
D-1350	usasucguCfaAfAfCfAfccaagccas {invAb}	1440	asUfsggcuUfgguguUfgAfcgauasu	2288
D-1351	csasugcuCfaUfGfGfCfaaUCguus {invAb}	1441	asAfsacagAfuugccaUfgAfgcaugsusu	2289
D-1352	uscsaugcCfaAfUfCfUfguuugggs {invAb}	1442	asCfscCcaAfacagauUfgCfcaugasusu	2290
D-1353	gsusuugUfuGfUfGfGfCacuagccs {invAb}	1443	usGfsgcuGfugccacAfaCfaaaacsusu	2291
D-1354	ususuuuUfgUfGfGfCfacuagccas {invAb}	1444	usUfsggcuAfgugccaCfaAfcaaaasu	2292
D-1355	ususuguGfuGfGfCfAfcuagccaas {invAb}	1445	usUfsuggcUfaguccAfcAfacaaasu	2293
D-1356	ususguuUfgGfCfAfCfuagccaaas {invAb}	1446	asUfsuuggCfuagucCfaCfaacaasu	2294
D-1357	gsusugugGfcAfCfUfAfGccaaacacs {invAb}	1447	asUfsguuGfgcuaguGfcCfacaacsusu	2295
D-1358	ususgugcCfaCfUfAfGfCcaaaacaus {invAb}	1448	usAfsuguuUfggcuagUfgCfcacaasu	2296
D-1359	usgsuggcAfcUfAfGfCfcaaacauas {invAb}	1449	usUfsauguUfuggcuGfuGfccacasusu	2297
D-1360	gsusggcaCfuAfGfCfCfaaacuaaas {invAb}	1450	usUfsuaugUfuuggcuAfgUfgccacsusu	2298
D-1361	usgsgcacUfaGfCfCfAfaacauaaas {invAb}	1451	asUfsuuauGfuuggcUfaGfugccasu	2299
D-1362	gsgscacuAfgCfCfAfAfacauaaags {invAb}	1452	asCfsuuuaUfguuuggCfuAfgugccsusu	2300
D-1363	gscsacuGfcCfAfAfAfaacauaaags {invAb}	1453	asCfscuuuAfguuugGfcUfagugcsusu	2301

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1364	asgsccaaAfcAfUfAfAfaggggcuus {invAb}	1454	usAfsagccCfcuuuauGfuUfuggcus usu	2302
D-1365	gsccsaaaCfaUfAfAfAfaggggcuuas {invAb}	1455	usUfsaagcCfccuuuaUfgUfuuggcs usu	2303
D-1366	cscsaaacAfuAfAfAfGfgggcuuaas {invAb}	1456	asUfsuaagCfccuuuAfuGfuuuugs usu	2304
D-1367	csasaacaUfaAfAfGfGfgggcuuaags {invAb}	1457	asCfsuuaaGfccccuuUfaUfguuugs usu	2305
D-1368	asasaacuAfaAfGfGfGfgcuuaagus {invAb}	1458	asAfsuuaaAfgcccuUfuUfuguuus usu	2306
D-1369	asascuaaAfaGfGfGfGfcuuaagucs {invAb}	1459	usGfsacuuAfaagcccUfuUfauguus usu	2307
D-1370	ascsauaaAfgGfGfGfcuuaagucas {invAb}	1460	asUfsgacuUfaagcccCfuUfuaugus usu	2308
D-1371	asusaaagGfgGfCfUfUfaagucagcs {invAb}	1461	asGfscugaCfuuaagCfcCfuuuuas usu	2309
D-1372	usasaaggGfgCfUfUfAfagucagccs {invAb}	1462	asGfsgcugAfcuuaagCfcCfcuuuas usu	2310
D-1373	asgsgggcUfuAfAfGfUfcagccugcs {invAb}	1463	usGfscaggCfugacuUfaGfccccus usu	2311
D-1374	asasgucaGfcCfUfGfCfauacagags {invAb}	1464	asCfsucugUfaugcagGfcUfgacuus usu	2312
D-1375	asgsucagCfcUfGfCfAfuacagaggs {invAb}	1465	usCfscucuGfuaugcaGfgCfugacus usu	2313
D-1376	asgsccugCfaUfAfCfAfaggaucgs {invAb}	1466	asCfsgaucCfucuguaUfgCfaggcus usu	2314
D-1377	gsccscugAfuAfCfAfGfaggaucggs {invAb}	1467	asCfscgauCfcucuguAfuGfcaggcs usu	2315
D-1378	cscsugcaUfaCfAfGfAfggauccggs {invAb}	1468	asCfscgaUfccucugUfaUfgcagggs usu	2316
D-1379	ascsagagGfaUfCfGfGfggagagaas {invAb}	1469	asUfsucucUfccccgaUfcCfucugus usu	2317
D-1380	gsasguacUfuAfCfCfAfagauuuuas {invAb}	1470	asUfsuuaaCfucugguAfaGfuacucs usu	2318
D-1381	csusgcacUfaAfAfAfUfccccaaacs {invAb}	1471	asGfsuuugGfggaauUfaGfugcags usu	2319
D-1382	usgscacuAfaAfAfUfCfccccaaacus {invAb}	1472	asAfsguuuGfgggauUfuAfgugcas usu	2320
D-1383	csascuaaAfaUfCfCfCfcaaacugas {invAb}	1473	asUfscaguUfuggggaUfuUfuagugs usu	2321
D-1384	asasucccCfaAfAfCfUfGfagguuas {invAb}	1474	usUfsaccuGfucaguUfgGfggauus usu	2322
D-1385	cscsaaacUfgAfCfAfGfguaaaugus {invAb}	1475	usAfscauuUfaccuguCfaGfuuuugs usu	2323
D-1386	csasaacuGfaCfAfGfGfuuaaaguas {invAb}	1476	asUfsacauUfuaccugUfcAfguuugs usu	2324
D-1387	asasacugAfcAfGfGfUfaaauguags {invAb}	1477	asCfsuacaUfuuaacuGfuCfaguuus usu	2325
D-1388	ascsugacAfgGfUfAfAfAfauguagccs {invAb}	1478	asGfsgcuaCfauuuacCfuGfucagus usu	2326
D-1389	asuscuaaAfuCfAfCfAfcauuuuucs {invAb}	1479	asGfsaaaaUfagugAfuUfuagaus usu	2327
D-1390	csusaaaUcfaCfAfCfUfauuuucgas {invAb}	1480	asUfscgaaUfaugugUfgUfuuuags usu	2328
D-1391	usasaauCfcAfCfUfAfuuuucgags {invAb}	1481	usCfsucgaAfaauaguGfuGfauuuas usu	2329

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1392	asasucacAfcUfAfUfUfuucgagaus {invAb}	1482	asAfsucucGfaaaaaGfuGfugauus usu	2330
D-1393	uscsacacUfaUfUfUfUfcgagaucaus {invAb}	1483	asUfsgaucUfcgaaaaUfaGfugugas usu	2331
D-1394	csascacuAfuUfUfUfUfcgagaucaus {invAb}	1484	asAfsugauCfucgaaaAfuAfgugugs usu	2332
D-1395	ascscacuUfuUfUfUfUfcgagaucaugs {invAb}	1485	asCfsaugaUfcucgaaAfaUfagugus usu	2333
D-1396	ascsuauUfuCfGfAfGfaucauguas {invAb}	1486	asUfsacauGfaucucgAfaAfauagus usu	2334
D-1397	csusauuuUfcGfAfGfAfucaugauus {invAb}	1487	usAfsuacaUfgaucucGfaAfaauags usu	2335
D-1398	asusuucGfaGfAfUfCfauguauaas {invAb}	1488	usUfsuuaCfaugaucUfcGfaaaus usu	2336
D-1399	ususcgagAfuCfAfUfGfuauaaaaas {invAb}	1489	asUfsuuuuAfuacaugAfuCfucgaas usu	2337
D-1400	asasaaaaGfaAfGfUfCfaugcugugs {invAb}	1490	asCfsacagCfaugacuUfcUfuuuuus usu	2338
D-1401	usgscuguGfuGfGfCfCfaauuuaas {invAb}	1491	asUfsuuaAfuuggccAfcAfcagcas usu	2339
D-1402	usugggagGfgAfCfCfAfggaaugus {invAb}	1492	usAfscauuUfccugguCfcCfuccaas usu	2340
D-1403	ascscaggAfaAfUfGfUfaagacaccs {invAb}	1493	usGfsguguCfuacauUfuCfuggus usu	2341
D-1404	csccsaggaAfaUfGfUfAfagacaccas {invAb}	1494	usUfsggugUfcuuacaUfuUfccuggs usu	2342
D-1405	gsusgugcCfuGfAfUfGfucaccucas {invAb}	1495	asUfsgaggUfgacauCfGfGfcacacs usu	2343
D-1406	usgsugccUfgAfUfGfUfcaccucaus {invAb}	1496	asAfsugagGfugacauCfaGfgcacas usu	2344
D-1407	gsusgccuGfaUfGfUfCfaccucaugs {invAb}	1497	usCfsaugaGfgugacaUfcAfggcacs usu	2345
D-1408	gsccsugaUfgUfCfAfCfcucaugaus {invAb}	1498	asAfsucaUGfaggugaCfaUfcaggcs usu	2346
D-1409	ususuuuAfaCfUfCfCfugcgccaas {invAb}	1499	asUfsuggcGfcaggagUfuAfaaaaaas usu	2347
D-1410	ususaacuCfcUfGfCfGfccaaaggacs {invAb}	1500	usGfsuccuUfggcgcaGfgAfguaas usu	2348
D-1411	asascuccUfgCfGfCfCfaaggacags {invAb}	1501	asCfsugucCfuuggcgCfaGfgaguus usu	2349
D-1412	ascsuccuGfGfCfCfAfaaggacagus {invAb}	1502	asAfsucguCfcuuggcGfcAfggagus usu	2350
D-1413	usgsuccaCfcUfUfUfGfugcuuugcs {invAb}	1503	asGfscaaaGfcacaaaGfgUfggacas usu	2351
D-1414	uscscaccUfuUfGfUfGfucuuugcgas {invAb}	1504	asUfscgcaAfaagcacaAfaGfguggas usu	2352
D-1415	csasccuuUfgUfGfCfUfuugcgaggs {invAb}	1505	asCfscucgCfaaagcaCfaAfaaggugs usu	2353
D-1416	ccscsuuugUfgCfUfUfUfgcgaggccs {invAb}	1506	asGfsgccuUfgcaaagCfaCfaaaggs usu	2354
D-1416	ccscsuuugUfgCfUfUfUfgcgaggccs {invAb}	1507	asGfsgccuUfgcaaagCfaCfaaaggs usu	2355
D-1417	gsasgcccAfgGfCfAfUfcugcucgcs {invAb}	1508	asGfscgagCfagaugcCfuGfggcucs usu	2356
D-1418	ccscscaggCfaUfCfUfGfcucgcugcs {invAb}	1509	asCfsaggcGfagcagaUfgCfcugggs usu	2357

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1419	csasggcaUfcUfGfCfUfcgccugccs {invAb}	1510	usGfsgcagGfcgagcaGfaUfgccugs usu	2358
D-1420	gscsaucuGfcUfCfGfCfcugccacgs {invAb}	1511	asCfsguggCfaggcgaGfcAfgaugcs usu	2359
D-1421	usgscacGfgCfUfGfAfccagagaas {invAb}	1512	asUfsucucUfggucagCfcGfuggcas usu	2360
D-1422	gsasgcucUfgCfCfUfUfagacgacgs {invAb}	1513	asCfsgucgUfcuaaggCfaGfagcucs usu	2361
D-1423	asgscucGfcCfUfUfAfagcagcugus {invAb}	1514	asAfsucgucGfucuaagGfcAfgagcucs usu	2362
D-1424	gscsucugCfcUfUfAfGfagcagcugus {invAb}	1515	asCfsacguCfugucuaaGfgCfagagcs usu	2363
D-1425	csuscucGfcUfUfAfGfAfccagcugus {invAb}	1516	asAfsacgUfcgucuaAfgGfcagags usu	2364
D-1426	uscugccUfuAfGfAfCfagcaguguus {invAb}	1517	usAfsacacGfucgucuaAfaGfgcagags usu	2365
D-1427	csusgccUfaGfAfCfGfagcuguuas {invAb}	1518	asUfsaacaCfugcucUfaAfggcags usu	2366
D-1428	gscsuuaGfaCfGfAfCfuguguuacacs {invAb}	1519	asUfsguaaCfagcugUfcUfaaggcs usu	2367
D-1429	cscsuuaGfCfGfAfCfGfuguuacags {invAb}	1520	asCfsuguaAfcacgucGfuCfuaaggcs usu	2368
D-1430	csusuagaCfGfAfCfGfUfuguuacagus {invAb}	1521	usAfsucguAfacacguCfGfUfcuaags usu	2369
D-1431	usasgacGfCfUfGfUfuacagauas {invAb}	1522	asAfsuacuGfuaacacGfuCfugucuas usu	2370
D-1432	ascgacgUfgUfUfAfCfagauagaas {invAb}	1523	asUfsucauAfcuguaaCfaCfugcugus usu	2371
D-1433	ascacagCfaGfAfGfGfaccuccgs {invAb}	1524	asCfsgaggGfugccucUfgCfugugus usu	2372
D-1434	csacagcAfgAfGfGfCfaccuccgus {invAb}	1525	usAfsagcGfgugccuUfcGfugugus usu	2373
D-1435	ascacagCfaGfGfCfAfccuccguas {invAb}	1526	asUfsacgaGfggugccUfcUfgcugus usu	2374
D-1436	csagcagAfgGfCfAfCfcccucguas {invAb}	1527	asAfsuacgAfgggugcCfuCfugcugus usu	2375
D-1437	asgscagaGfgCfAfCfCfucguauas {invAb}	1528	asCfsauacGfaggugCfcUfcugcucs usu	2376
D-1438	gscsagagGfcAfCfCfCfucguauas {invAb}	1529	asAfscauaCfaggguGfcCfucugcs usu	2377
D-1439	csasgagCfaCfCfCfUfcguauuuus {invAb}	1530	asAfsacauAfcgaggUfgCfucugus usu	2378
D-1440	asgsaggCfCfCfUfcfguauuuus {invAb}	1531	asAfsaacaUfacgaggGfuGfccucucs usu	2379
D-1441	gsasggcaCfcCfUfcCfGfuauguuuus {invAb}	1532	asAfsaaaCfuaacgagGfgUfgccucs usu	2380
D-1442	gsgscaccCfuCfGfUfAfuguuuugas {invAb}	1533	usUfscaaaAfcuacgAfgGfgugccs usu	2381
D-1443	cscscucUfaUfGfUfUfuugaaagus {invAb}	1534	asAfsuuuUfaaaacaUfaCfagggcs usu	2382
D-1444	asusguuaAfaCfUfAfUfacugacccs {invAb}	1535	asGfsggucAfguauagUfuUfuacaus usu	2383
D-1445	usgsuaaaAfcUfAfUfAfucugacccgs {invAb}	1536	asCfsgggUfcaguuuGfuUfuuuacacs usu	2384
D-1446	gsusaaaaCfuAfUfAfCfugacccgus {invAb}	1537	asAfsccggUfcaguuuAfgUfuuuacacs usu	2385

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1447	usasaaacUfaUfAfCfUfgacccguus {invAb}	1538	asAfsacggGfucaguaUfaGfuuuuasu	2386
D-1448	ascsuauaCfuGfAfCfCfcguuuucas {invAb}	1539	asUfsgaaaAfcgggucAfgUfauagus	2387
D-1449	asusacugAfcCfCfGfUfuucaguus {invAb}	1540	asAfsacugAfaaacggGfuCfaguau	2388
D-1450	usususagUfuUfUfAfAfagggucgus {invAb}	1541	asAfsacgacCfcuuuaAfaCfugaaas	2389
D-1451	ususcaguUfuUfAfAfAfagggucgus {invAb}	1542	usCfsacgaCfccuuuAfaAfcugaas	2390
D-1452	uscsaguUfuUfAfAfAfGfggucgugas {invAb}	1543	asUfscacgAfcuuuAfaAfacugas	2391
D-1453	csasguuuUfaAfAfGfGfgucgugags {invAb}	1544	usCfsucacGfaccuuUfaAfaacugs	2392
D-1454	gsusuuuAfaGfGfGfUfcgugagaas {invAb}	1545	usUfsucucAfcgaccUfuUfaaaacs	2393
D-1454B	ususuuuAfgGfGfUfcgugagaaas {invAb}	2827	asUfsuucuCfacgaccCfuUfuuaaas	2828
D-1455	ususuuuAfgGfGfUfcgugagaaacs {invAb}	1546	asGfsuuucUfcacgacCfcUfuuaaas	2394
D-1456	usasaaggGfuCfGfUfGfagaaacugs {invAb}	1547	asCfsaguuUfcucacgAfcCfcuuuasu	2395
D-1457	asasaggUfcGfUfGfAfgaacuggs {invAb}	1548	asCfscaguUfucucacGfaCfcuuuasu	2396
D-1458	gsasgaaCfuGfGfCfUfgguccaau {invAb}	1549	asAfsuuggAfcagccAfgUfuucucs	2397
D-1459	usgsguucAfaUfGfGfGfauuuacags {invAb}	1550	asCfsuguaAfauccaUfuGfgaccas	2398
D-1460	cscsaagGfgAfUfUfUfacagcaacs {invAb}	1551	usGfsuugcUfguaauCfcCfauuggs	2399
D-1461	ususuaagUfuUfGfCfUfcuuuacgs {invAb}	1552	asCfsgauUfagagcaAfaCfuuaaas	2400
D-1462	ususaaguUfuGfCfUfcuuuacgus {invAb}	1553	usAfsagauUfaagagCAfaAfcuuuasu	2401
D-1463	asgsuuugCfuCfUfUfAfaucguugs {invAb}	1554	asCfsauacGfauuagAfgCfaaacus	2402
D-1464	gsusuugCfuCfUfUfAfafucguuuggs {invAb}	1555	usCfscuaCfgauuaGfaGfcaaaacs	2403
D-1465	ususugcuCfuUfAfAfUfcguuuggs {invAb}	1556	usUfscuauAfcgauuaAfgAfgcaaaas	2404
D-1466	usgscucuUfaAfUfCfGfuauggaags {invAb}	1557	asCfsuuccAfuacgauUfaAfgagcas	2405
D-1467	csusuaauCfGfUfUfGfgaagcuugs {invAb}	1558	usCfsaagCfuuccauCfGfuaaags	2406
D-1468	ususaauGfuAfUfGfGfaagcuugas {invAb}	1559	asUfscagCfuuccauAfcGfauuuasu	2407
D-1469	gsgsaagCfuGfAfGfCfuauguguus {invAb}	1560	asAfsacacAfuagcuAfaGfcuuccs	2408
D-1470	gsasagcuUfgAfGfCfUfauguguugs {invAb}	1561	asCfsaacaCfauagcuCfaAfgcuucs	2409
D-1471	asgscuugAfgCfUfAfUfguguuggs {invAb}	1562	usUfscuacCfauagCfuCfaagcus	2410
D-1472	gsusuugaGfCfUfAfUfGfuguuggaas {invAb}	1563	asUfsuccaAfcacauGfCfcaagcs	2411
D-1473	csusugagCfuAfUfGfUfguguuggaas {invAb}	1564	asCfsuuccAfacauAfgCfucaags	2412

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1474	usugagcUfaUfGfUfGfUggaagus {invAb}	1565	asAfsuucCfaacacaUfaGfcucaas usu	2413
D-1475	usgsagcuAfuGfUfGfUfuggaagugs {invAb}	1566	asCfsacuuCfcaacacAfuAfgcucas usu	2414
D-1476	gsasgcuaUfgUfGfUfUfggaagugcs {invAb}	1567	asGfscacuUfccaacaCfaUfagcucs usu	2415
D-1477	gsusguugGfaAfGfUfGfcccugguus {invAb}	1568	asAfsaccaGfggcacuUfcCfaacacs usu	2416
D-1478	gsusaucGfcCfCfUfGfuuuuuus {invAb}	1569	asAfsuuaaAfaccaggGfcAfcuuccs usu	2417
D-1479	csusgguuUfuAfAfUfCfcauacacas {invAb}	1570	usUfsguguAfuggauUfaAfaccags usu	2418
D-1480	ususaucCfaUfAfCfAfaaaagacgs {invAb}	1571	asCfsgucuUfuguguaUfgGfaauaas usu	2419
D-1481	usasaucAfuAfCfAfCfaaagacggs {invAb}	1572	asCfscgucUfuuguguAfuGfgauuas usu	2420
D-1482	asasuccaUfaCfAfCfAfaagacggus {invAb}	1573	usAfsccguCfuugugUfaUfggauus usu	2421
D-1483	asusccauAfcAfCfAfAfaagacgguas {invAb}	1574	asUfsaccgUfcuuuguGfuAfuggaus usu	2422
D-1484	uscscuaCfaCfAfAfAfgacgguaacs {invAb}	1575	usGfsuaccGfucuuugUfgUfauggas usu	2423
D-1485	csasuacaCfaAfAfGfAfCgguaacaus {invAb}	1576	usAfsuguaCfcgucuuUfgUfguaugs usu	2424
D-1486	usascacaAfaGfAfCfGfguacauaas {invAb}	1577	asUfsuauUfaccgucUfuUfguguas usu	2425
D-1487	ascsacaaAfgAfCfGfGfuacauaas {invAb}	1578	asAfsuauGfuaccguCfuUfugugus usu	2426
D-1488	csascaaaGfaCfGfGfUfacauaauacs {invAb}	1579	asGfsauuaUfguaccgUfcUfuugugs usu	2427
D-1489	ascsaaagAfcGfGfUfAfaaaauccs {invAb}	1580	asGfsgauuAfuguaccGfuCfuugugs usu	2428
D-1490	csasaagaCfGfGfUfAfaaaauccus {invAb}	1581	usAfsaggauUfauguacCfGfucuuugs usu	2429
D-1491	asasagacGfgUfAfCfAfaaaauccuas {invAb}	1582	asUfsaggaUfauaguaCfcGfucuuus usu	2430
D-1492	asasgacGfuAfCfAfUfaaaucuaacs {invAb}	1583	usGfsuaggAfuuauguAfcCfugcuus usu	2431
D-1493	gsusacauAfaUfCfCfUfacagguuus {invAb}	1584	usAfsaaccUfaguaggaUfuAfuguacs usu	2432
D-1494	csasuaaaCfcUfAfCfAfgguuuuaas {invAb}	1585	asUfsuuaaAfccuguaGfgAfuaugs usu	2433
D-1495	asusccuaCfaGfGfUfUfaaauguas {invAb}	1586	asUfsacauUfuaaaccUfgUfaggauus usu	2434
D-1496	usasguuuGfgAfAfUfUfcuuugcucs {invAb}	1587	asGfsagcaAfagaauCfcAfaacuas usu	2435
D-1497	asgsuuugGfaAfUfUfCfuugcucus {invAb}	1588	usAfsagacAfaagaauUfcCfaaacus usu	2436
D-1498	usuggaAfuUfCfUfUfugcucuaacs {invAb}	1589	asGfsuagaGfcaaagaAfuUfccaas usu	2437
D-1499	usugcucUfaCfUfGfUfuuaauugs {invAb}	1590	asCfsaaugUfaaacagUfaGfagcaas usu	2438
D-1500	uscsuacuGfuUfUfAfCfaauugcagas {invAb}	1591	asUfscugcAfauguaaAfcAfguagas usu	2439
D-1501	usascuguUfuAfCfAfUfugcagauus {invAb}	1592	asAfsaucuGfcauguAfaAfcaguas usu	2440

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1502	ascsguuUfaCfAfUfUfgcagauugs {invAb}	1593	asCfsaaucUfgcaaugUfaAfacagus usu	2441
D-1503	ususuacaUfuGfCfAfGfauugcuaus {invAb}	1594	usAfsuagcAfaucugcAfaUfguaaas usu	2442
D-1504	ususakauUfgCfAfGfAfauugcuaas {invAb}	1595	usUfsauagCfaaucugCfaAfuguaas usu	2443
D-1505	usascuauGfCfAfGfAfUfugcuaaas {invAb}	1596	asUfsuauaGfcaaucuGfCfAfauguas usu	2444
D-1506	asusugcuAfuAfAfUfUfucaaggags {invAb}	1597	asCfsuccuUfgaaaauAfuAfgcaaus usu	2445
D-1507	usugcuUfaAfUfUfUfcaaggagus {invAb}	1598	asAfsuccuUfgaaaauUfaUfagcaas usu	2446
D-1508	asasugauGfCfAfCfUfUfuaggagus {invAb}	1599	asAfscaucCfuaaaguGfCfAfucauus usu	2447
D-1509	asusgaugCfaCfUfUfUfaggauguus {invAb}	1600	asAfsacauCfcaaaagUfgCfaucaus usu	2448
D-1510	ascsgauAfuCfAfUfUfcacaugacs {invAb}	1601	asGfsucauGfugaauAfuUfcaugus usu	2449
D-1511	csasugaaUfcAfUfUfCfcaugaccs {invAb}	1602	usGfsgucaUfgugaauGfaUfcaugs usu	2450
D-1512	asasauacAfuGfUfCfUfagucugucs {invAb}	1603	asGfsacagAfcuagacAfuGfuauuus usu	2451
D-1512B	asasuacaUfgUfCfUfAfugucuguccs {invAb}	2829	asGfsgacaGfacuagaCfaUfguaus usu	2830
D-1513	asusgucuAfgUfCfUfGfuccuuuaas {invAb}	1604	asUfsuaaaGfgacagaCfuAfgacaus usu	2452
D-1514	usgsucuaGfuCfUfGfUfccuuuaas {invAb}	1605	usAfsuuaaAfggacagAfcUfagacas usu	2453
D-1515	uscsguagCfuGfUfCfUfuuaauags {invAb}	1606	asCfsuauuAfaaggacAfgAfcuagas usu	2454
D-1516	csusaguUfgUfCfCfUfuuaauagcs {invAb}	1607	asGfscuauUfaaaggacCfaGfacuags usu	2455
D-1517	usasgucuGfuCfCfUfUfuuaauagcus {invAb}	1608	asAfsagcuUfuuaaggAfcAfgacuas usu	2456
D-1518	gsuscuguCfCfUfUfUfAfaugcucus {invAb}	1609	asAfsagcuUfuuaaggAfcAfgacuas usu	2457
D-1519	asasucagAfuCfAfUfUfaccaguuaas {invAb}	1610	asUfsaacuGfguaaagAfuCfugaus usu	2458
D-1520	uscsgauCfaUfUfAfCfCfaguuagcs {invAb}	1611	asGfscuaaCfugguaaUfgAfcuagcs usu	2459
D-1521	csasgaucAfuUfAfCfCfaguuagcus {invAb}	1612	asAfsagcuAfcugguaAfuGfaucugs usu	2460
D-1522	asgsaucaUfuAfCfCfAfguuagcuus {invAb}	1613	asAfsagcuAfcugguaAfuGfaucugs usu	2461
D-1523	uscsgauCfCfAfGfUfUfagcuuuuas {invAb}	1614	usUfsaaaaGfcuaacuGfgUfaaugs usu	2462
D-1524	csasuuacCfaGfUfUfAfGcuuuuaas {invAb}	1615	usUfsuaaaAfgcuacUfgGfuaugs usu	2463
D-1525	ascscaguUfaGfCfUfUfuuaaagcas {invAb}	1616	asUfsgcuUfaaaagCfaAfcuggus usu	2464
D-1526	asasgcacAfuUfUfGfUfuuaagacus {invAb}	1617	usAfsagcuUfaaaagCfaAfcuggus usu	2465
D-1527	gsacsacuUfuGfUfUfUfaagacuus {invAb}	1618	asAfsuaguCfuuaaacAfaAfugugcs usu	2466
D-1528	csusauguUfuUfUfGfGfaaaaauacs {invAb}	1619	asGfsuauuUfuuccaaAfaAfcuagcs usu	2467

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1529	gsusuuuuGfgAfAfAfAfauacgcuas {invAb}	1620	asUfsagcgUfauuuuuCfcAfaaaacs usu	2468
D-1530	ususggaaAfaAfUfAfCfGcuacagas {invAb}	1621	usUfscuguAfgcgauUfuUfuccaas usu	2469
D-1531	asasuaaaUfgAfGfAfUfgcuacuaas {invAb}	1622	asUfsuaguAfgcaucuCfaUfuauus usu	2470
D-1532	usgsagauGfcUfAfCfUfaauuguuus {invAb}	1623	asAfsaacaAfuuaguaGfcAfucucas usu	2471
D-1533	ususugaaAfUfUfGfUfuguuucugs {invAb}	1624	asCfsagaaAfcaacagAfuUfccaaas usu	2472
D-1534	ususcugcCfaAfAfGfGfuauuuuuaas {invAb}	1625	asUfsuaauUfuaccuuUfgGfcagaa usu	2473
D-1535	uscsugccAfaAfGfGfUfaauuuuacs {invAb}	1626	asGfsuuaaUfuuaccuUfGfgcagaa usu	2474
D-1536	gsasuuuUfuCfAfGfGfaauccccas {invAb}	1627	asUfsggggAfuuccugAfaUfaauacs usu	2475
D-1537	asusucagGfaAfUfCfCfccaauugas {invAb}	1628	usUfscaaaUfggggguUfcCfugaas usu	2476
D-1538	gsgsaauCfCfAfUfUfugaauuugs {invAb}	1629	asCfsaaauUfcaaugGfgGfauccs usu	2477
D-1539	[GalNAc3] scucccaUfuCfUfUfUfc augaggcs{invAb}	1630	asGfscucAfuagaaAfaUfgggags usu	2478
D-1540	[GalNAc3] saaggaaGfaCfCfGfCfa cuccuaas{invAb}	1631	asAfsuaggAfgugcgUfcUfuccuus usu	2479
D-1541	[GalNAc3] sgaaacCfGfUfUfUfc agugcacs{invAb}	1632	asGfsugcaCfugaauCfGfuuuacs usu	2480
D-1542	[GalNAc3] sgggagaGfaCfAfAfGfg gacuaas{invAb}	1633	asAfsuaagUfcccuugUfcUfcucccs usu	2481
D-1543	[GalNAc3] sgauguuAfaUfAfAfCfu cuggaggcs{invAb}	1634	asCfscuccAfgaguuUfuAfacaacs usu	2482
D-1544	[GalNAc3] scaccaaAfcUfCfCfCfa uucuuacs{invAb}	1635	usGfsaaagAfaugggaGfuUfuggugs usu	2483
D-1545	[GalNAc3] sgcaaccGfgAfGfAfAfc ucuuagaa{invAb}	1636	usUfscuaaGfaguucuCfcGfguugcs usu	2484
D-1546	[GalNAc3] scacaaaGfaCfGfGfUfa cauaaacs{invAb}	1637	asGfsauuaUfguaccgUfcUfuugugs usu	2485
D-1547	[GalNAc3] scggaagUfuUfGfAfAfg auagauus{invAb}	1638	asAfsaucuAfuucuAfaCfuuccgs usu	2486
D-1548	[GalNAc3] sacagagAfgAfUfGfGfu aagcagcs{invAb}	1639	asGfscugcUfuaccuUfcUfucugus usu	2487
D-1549	[GalNAc3] sccucggUfuCfUfAfCfG cuuauggs{invAb}	1640	asCfscuaaAfgcguaGfaCfcgaggs usu	2488
D-1550	[GalNAc3] scuccucGfgUfUfCfUfa cgcuuaas{invAb}	1641	asAfsuaagCfugaagaaCfcGfaggags usu	2489
D-1551	[GalNAc3] sugcaaaCfGfUfGfCfAfu uggagccs{invAb}	1642	asGfsgcucCfaaugcaCfGfuugcas usu	2490
D-1552	[GalNAc3] sgaagacCfGfCfAfCfUfc cuauggcs{invAb}	1643	asGfscuauAfggagugCfGfucuuacs usu	2491
D-1553	[GalNAc3] sgacaagGfgAfCfUfUfa ucaacaas{invAb}	1644	usUfsguuGfauaaguCfcCfuugucs usu	2492
D-1554	[GalNAc3] sucagaaAfuCfCfAfGfu acuaaacs{invAb}	1645	asGfsuuuaGfuacuggAfuUfucugas usu	2493
D-1555	[GalNAc3] saauuacCfaUfCfAfAfa augcagcs{invAb}	1646	asGfscugcAfuuuugaUfgGfuauuus usu	2494
D-1556	[GalNAc3] saaugacCfuUfGfCfCfa aauccgs{invAb}	1647	asCfsggaaUfuuggcaAfgGfucauus usu	2495

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1557	[GalNAc3] sccc auGfgAfUfGfAfu aaaauacs{invAb}	1648	asGfsuauUfuauc auCfcAfuugggs usu	2496
D-1558	[GalNAc3] sagacgaUfaGfCfAfAfu gugaags{invAb}	1649	asGfscuucAfc auugcUfaUfcguc usu	2497
D-1559	[GalNAc3] sgaagacGfaUfAfGfCfa augugaas{invAb}	1650	asUfsucacAfuugc auUfcGfucuc usu	2498
D-1560	[GalNAc3] sucagaaGfaCfGfAfUfa gcaaugus{invAb}	1651	asAfscauuGfc auucgUfcUfucugas usu	2499
D-1561	[GalNAc3] sgggucaGfaAfGfAfCfG auagcaas{invAb}	1652	asUfsugcuAfuugc auUfcUfgacc usu	2500
D-1562	[GalNAc3] sgaagacGfgUfAfCfAfu aauccuas{invAb}	1653	asUfsaggaUfuaugc auCfcGfucuu usu	2501
D-1563	[GalNAc3] sugucucCfGfAfAfGfUfg ccccagus{invAb}	1654	asAfsucggGfgc auUfcGfagac usu	2502
D-1564	[GalNAc3] suaguuuGfgAfAfUfUfc uuugcucs{invAb}	1655	asGfsagcaAfaga auUfcAfauc usu	2503
D-1565	[GalNAc3] sccaaacUfcCfCfAfUfu cuuucuas{invAb}	1656	asAfsugaaAfga auUfgGfuuuggs usu	2504
D-1566	[GalNAc3] sguac auAfaUfCfCfUfa cagguuus{invAb}	1657	usAfsaaccUfga auUfgUfugac usu	2505
D-1567	[GalNAc3] scaugcuCfuCfUfCfCfu cgguucus{invAb}	1658	usAfsgaacCfga auUfgAfgauc usu	2506
D-1568	[GalNAc3] sacc caUfgCfUfCfUfc uccucggs{invAb}	1659	asCfscgagGfaga auUfggggus usu	2507
D-1569	[GalNAc3] sccgaucAfgCfUfGfUfa gaacaacs{invAb}	1660	usGfsuuguUfc auucagCfuGfauc usu	2508
D-1570	[GalNAc3] saaccggAfgAfAfCfUfc uuagaaas{invAb}	1661	asUfsuucuAfga auUfcCfcggu usu	2509
D-1571	[GalNAc3] sacacagUfaGfUfGfGfa gcuuuccs{invAb}	1662	asGfsgaaaGfca auUfcUfugug usu	2510
D-1572	[GalNAc3] sgaauacAfuGfUfCfUfa gucugucs{invAb}	1663	asGfsacagAfc auUfgUfauuu usu	2511
D-1573	[GalNAc3] sauccggAfaGfUfUfUfg aagauags{invAb}	1664	usCfsuauUfua auUfcCfcgga usu	2512
D-1574	[GalNAc3] sgcaagcCfuAfAfAfCfG ucagaaas{invAb}	1665	asUfsuucuGfca auUfgGfcuug usu	2513
D-1575	[GalNAc3] suugaauAfcUfCfAfGfg aagucgas{invAb}	1666	usUfscgacUfca auUfgUfuuca usu	2514
D-1576	[GalNAc3] sguucaacCfCfCfCfUfu gaugauus{invAb}	1667	asAfsaucaUfca auUfgUfugaac usu	2515
D-1577	[GalNAc3] suacuguUfuAfCfAfUfu gcagauus{invAb}	1668	asAfsaucuGfca auUfgUfaguc usu	2516
D-1578	[GalNAc3] saccuugCfCfAfAfAfUfu ccggagas{invAb}	1669	asUfscuccGfca auUfgCfaagg usu	2517
D-1579	[GalNAc3] scaauggAfuGfAfUfAfa aa uaccas{invAb}	1670	asUfsgguaUfua auUfgUfcuug usu	2518
D-1580	[GalNAc3] sggcuccUfgUfUfCfCfC auugccus{invAb}	1671	asAfsaggcaUfca auUfgGfgagcc usu	2519
D-1581	[GalNAc3] sgaccagAfuUfGfCfUfa augagaas{invAb}	1672	usUfscuucAfu auUfgUfcuug usu	2520
D-1582	[GalNAc3] saggc auUfuUfGfUfAfa uuggaaas{invAb}	1673	asUfsuuccAfa auUfgUfagcc usu	2521
D-1583	[GalNAc3] suaggcaUfuUfUfGfUfa auuggaas{invAb}	1674	usUfscuccAfu auUfgUfgccu usu	2522
D-1584	[GalNAc3] sgauuccAfaGfUfCfCfa ugugaggs{invAb}	1675	asCfscucaCfca auUfgUfgaau usu	2523

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1585	[GalNAc3] sccgcacUfcCfUfAfUfg gcugaags{invAb}	1676	usCfsuucAGfccauagGfaGfugcggs usu	2524
D-1586	[GalNAc3] scuucggGfaUfUfUfUfg aagacaas{invAb}	1677	asUfsugucUfucaaaaUfcCfcgaags usu	2525
D-1587	[GalNAc3] suuugagAfgCfCfCfCfa caaugaas{invAb}	1678	asUfsucauUfguggggCfuCfucaaaas usu	2526
D-1588	[GalNAc3] saaccgaUfuUfCfAfGfu gcacgaus{invAb}	1679	asAfsucguGfcacugaAfaUfcgguus usu	2527
D-1589	[GalNAc3] sacaaggGfaCfUfUfAfua caacaaas{invAb}	1680	asUfsuuguUfgauaagUfcCfcuugus usu	2528
D-1590	[GalNAc3] sguaaaaCfuAfUfAfCfu gacccgus{invAb}	1681	asAfsccggUfcagauUfUfuuaacs usu	2529
D-1591	[GalNAc3] sucuacuGfuUfUfAfCfa uugcagas{invAb}	1682	asUfscugcAfauguaaAfcAfguagas usu	2530
D-1592	[GalNAc3] sguuuugGfuUfCfCfCfa acuugags{invAb}	1683	usCfsucaAGfuugggaAfcCfaaaacs usu	2531
D-1593	[GalNAc3] suugagcUfaUfGfUfGfu uggaagus{invAb}	1684	asAfsuucCfaacacaUfaGfcucaas usu	2532
D-1594	[GalNAc3] suuaaguUfuGfCfUfCfu uaaucgus{invAb}	1685	usAfsccgauUfaagagcAfaAfcuaas usu	2533
D-1595	[GalNAc3] sugaccuUfgCfCfAfAfa uuccggas{invAb}	1686	asUfscgggAfauuuggCfaAfggucas usu	2534
D-1596	[GalNAc3] suuuagUfuUfGfCfUfc uaaucgs{invAb}	1687	asCfsgauUfagagcaAfaCfuuaaas usu	2535
D-1597	[GalNAc3] saccaucCfGfUfCfAfg cuguagas{invAb}	1688	usUfscuacAfgcugauCfGfauuggus usu	2536
D-1598	[GalNAc3] sacaaauGfaCfCfUfUfg ccaaaus{invAb}	1689	asAfsauuuGfgcaaggUfcAfuuuugus usu	2537
D-1599	[GalNAc3] saaaagCfCfUfCfCfGf aucagcus{invAb}	1690	asAfsugcUfucggauGfGfucuuus usu	2538
D-1600	[GalNAc3] scugauUfuUfCfGfUf caaacacs{invAb}	1691	asGfsuguuUfgacgauAfaAfaucags usu	2539
D-1601	[GalNAc3] sucucucCfUfGfGfUfu cuacgcus{invAb}	1692	asAfsugcUfagaaaggAfgGfagagas usu	2540
D-1602	[GalNAc3] saguuuGfaGfAfUfAfg auucgaas{invAb}	1693	asUfsucgaUfucuaucUfuCfaaacus usu	2541
D-1603	[GalNAc3] suuuacaUfuGfCfAfGfa uugcuas{invAb}	1694	usAfsuagcAfaucugcAfaUfguaaas usu	2542
D-1604	[GalNAc3] sauggucAfcUfCfUfGfa aaaccgas{invAb}	1695	asUfscggUfuucagaGfGfaccuus usu	2543
D-1605	[GalNAc3] sucucuaUfuCfCfAfCfa cgauucus{invAb}	1696	usGfsagauCfugugggAfaUfugagas usu	2544
D-1606	[GalNAc3] succacaCfGfUfCfUfc augagags{invAb}	1697	usCfsucucAfuagauCfGfugggas usu	2545
D-1607	[GalNAc3] sgacaaUfaGfGfAfCfGf gucuugus{invAb}	1698	asAfscaagAfcgguccUfgAfuugucs usu	2546
D-1608	[GalNAc3] saagagcCfuUfCfCfCfc ugcuuus{invAb}	1699	asGfsaaagCfaggauAfgGfcucuuus usu	2547
D-1609	[GalNAc3] sucaggaCfGfUfCfUfu gugaauas{invAb}	1700	asUfsauucAfaagacCfGfuccugas usu	2548
D-1610	[GalNAc3] sgucagaAfaUfCfCfAfg uacuaaas{invAb}	1701	asUfsuuagUfacuggaUfuUfcugacs usu	2549
D-1611	[GalNAc3] saguuugGfaUfUfUfCfu uugcucus{invAb}	1702	usAfsagacAfaagaaUfcCfaaacus usu	2550
D-1612	[GalNAc3] suuuggaAfuUfCfUfUfu gcucuacs{invAb}	1703	asGfsuagaGfcaagaaAfuUfccaaas usu	2551

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1613	[GalNAc3] scugaaaUfgGfAfCfAfa augaccus{invAb}	1704	asAfsgggucAfuuugucCfaUfuucags usu	2552
D-1614	[GalNAc3] saagacgGfuAfCfAfUfa auccuacs{invAb}	1705	usGfsuaggAfuuauGuAfcCfGgucuu usu	2553
D-1615	[GalNAc3] sggucuuGfuGfAfAfUfa uggaaags{invAb}	1706	asCfsuuucCfauauucAfcAfagaccs usu	2554
D-1616	[GalNAc3] suucaacCfaCfCfUfUfg augauugs{invAb}	1707	asCfsaaucAfucaaggUfgGfuugaas usu	2555
D-1617	[GalNAc3] sacuuuaUfuCfUfAfUfa gagcaas{invAb}	1708	asUfsuugcUfcauagAfaUfaaagus usu	2556
D-1618	[GalNAc3] sagaccgCfaCfUfCfCfu auggcugs{invAb}	1709	usCfsagccAfuaaggagUfgCfGgucuu usu	2557
D-1619	[GalNAc3] suauuucCfcCfAfAfUfg gaugauas{invAb}	1710	usUfsaucaUfccauugGfgGfaaauas usu	2558
D-1620	[GalNAc3] sgucagaAfgAfCfGfAfu agcaaugs{invAb}	1711	asCfsauugCfuucguCfuUfcugacs usu	2559
D-1621	[GalNAc3] sgcuaauGfaGfAfAfAfg uggcucus{invAb}	1712	asAfsgagcCfacuucUfcAfuaagcs usu	2560
D-1622	[GalNAc3] scauuacCfaGfUfUfAfg cuuuuaas{invAb}	1713	usUfsuaaaAfgcuacUfgGfuuaugs usu	2561
D-1623	[GalNAc3] suugcuaUfaAfUfUfUfc aaggagus{invAb}	1714	asAfsuccUfugaaaUfaUfagcaas usu	2562
D-1624	[GalNAc3] sucuaCuGfuUfUfAfCfa uugcagas{invAb}	1715	asUfscugcAfauguaaAfcAfguagas usu	2563
D-1625	[GalNAc3] saaaaaUfgAfGfAfUfg cuacuaas{invAb}	1716	asUfsuaguAfgcaucuCfaUfuuaus usu	2564
D-1626	[GalNAc3] suauuucUfaUfAfGfAfg caacuus{invAb}	1717	asAfsaguuUfgcucuaUfaGfaauaas usu	2565
D-1627	[GalNAc3] saugaugCfaCfUfUfUfa ggauguus{invAb}	1718	asAfsacauCfcuaaagUfgCfaucuas usu	2566
D-1628	[GalNAc3] suacauuGfcAfGfAfUfu gcuaauas{invAb}	1719	asUfsuaaGfcaucuGfcAfauguas usu	2567
D-1629	[GalNAc3] suuacauUfgCfAfGfAfu ugcuauas{invAb}	1720	usUfsauagCfaaucugCfaAfuguaas usu	2568
D-1630	[GalNAc3] sguuuuaAfaGfGfUfc gugagaas{invAb}	1721	usUfsucucAfcgacccUfuUfaaaacs usu	2569
D-1631	[GalNAc3] sugagcuAfuGfUfGfUfu ggaagugs{invAb}	1722	asCfsacuuCfcaacacAfuAfgcucas usu	2570
D-1632	[GalNAc3] suuuggcAfuCfGfGfCfu ccuguuus{invAb}	1723	asAfsaacaGfgagccgAfuGfccaaas usu	2571
D-1633	[GalNAc3] sauccuaCfaGfGfUfUfu aauguas{invAb}	1724	asUfsacauUfuaaaccUfgUfaggauas usu	2572
D-1634	[GalNAc3] suacacaAfaGfAfCfGfg uacauaas{invAb}	1725	asUfsuauGfaccgucUfuUfguguas usu	2573
D-1635	[DCA-C6] gcaaccGfgAfGfAfAfcucuuaas{invAb}	1726	usUfscuaaGfaguucuCfcGfguugcs usu	2574
D-1636	[DCA-C6] caccaaAfcUfCfCfCfauucuuuc{invAb}	1727	usGfsaaaagAfaugggaGfuUfuggugs usu	2575
D-1637	[DCA-C6] cuucggGfaUfUfUfUfgaagacaa{invAb}	1728	asUfsugucUfucaaaaUfcCfcgaags usu	2576
D-1638	[DCA-C6] auccggAfaGfUfUfUfgaagauag{invAb}	1729	usCfsuaucUfucaaacUfuCfcggauas usu	2577

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1639	[DCA-C6] aaccGfgAfGfAfAfcucuagaasus(invAb)	1730	usUfscuaaGfaguucuCfcGfguususu	2578
D-1640	[GalNAc3] saaccGfgAfGfAfAfcucuagaasus(invAb)	1731	usUfscuaaGfaguucuCfcGfguususu	2579
D-1641	[DCA-C6] ccaaacUfcCfCfAfUfucuucaus(invAb)	1732	asAfsugaaAfgaaggGfaGfuuggsusu	2580
D-1642	[DCA-C6] cccaauGfgAfUfGfAfuaaaauacs(invAb)	1733	asGfsuaauUfuaucAuCfcAfuuggsusu	2581
D-1643	[DCA-C6] ccucggUfuCfUfAfCfcgcuuauggs(invAb)	1734	asCfscauaAfgcguagAfaCfcgaggsusu	2582
D-1644	[DCA-C6] ccggAfaGfUfUfUfgaagauagasus(invAb)	1735	usCfsuaucUfucaaacUfuCfcggsusu	2583
D-1645	[GalNAc3] sccggAfaGfUfUfUfgaagauagasus(invAb)	1736	usCfsuaucUfucaaacUfuCfcggsusu	2584
D-1646	[GalNAc3] saaccggAfGfAfAfcUfcuuagaasus(invAb)	1737	usUfscuaaGfaguuCfuCfcGfguususu	2585
D-1647	[GalNAc3] sucggUfuCfUfAfCfcgcuuauggsus(invAb)	1738	asCfscauaAfgcguagAfaCfcgasusu	2586
D-1648	[GalNAc3] sccaaAfcUfcCfCfauucuuucasus(invAb)	1739	usGfsaaagAfaugggaGfuUfugggsusu	2587
D-1649	[GalNAc3] sucggGfaUfUfUfUfgaagacaasus(invAb)	1740	asUfsugucUfucaaaaUfcCfcgasusu	2588
D-1650	[GalNAc3] scaauGfgAfUfGfAfuaaauuacusus(invAb)	1741	asGfsuaauUfuaucAuCfcAfuugsusu	2589
D-1651	[GalNAc3] sucggUfuCfUfAfCfcgcuuauggsus(invAb)	1742	asCfscauaAfgcguAfgAfaCfcgasusu	2590
D-1652	[GalNAc3] saaccGfgAfGfAfAfcucuagaasus(invAb)	1743	usUfscuaaGfaguuCfuCfcGfguususu	2591
D-1653	[GalNAc3] sccaaAfcUfcCfCfauucuuucasus(invAb)	1744	usGfsaaagAfauggGfaGfuUfugggsusu	2592
D-1654	[GalNAc3] sucggGfaUfUfUfUfgaagacaasus(invAb)	1745	asUfsugucUfucaaAfaUfcCfcgasusu	2593
D-1655	[GalNAc3] scaauGfgAfUfGfAfuaaauuacusus(invAb)	1746	asGfsuaauUfuaucAfuCfcAfuugsusu	2594
D-1656	[GalNAc3] sccucggUfuCfUfAfCfcgcuuauggs(invAb)	1747	asCfscauAfafgcguagAfaCfcgaggusu	2595
D-1657	[GalNAc3] sgcaaccGfgAfGfAfAfcucuagagas(invAb)	1748	usUfscuaAfGfaguucuCfcGfguugcsusu	2596
D-1658	[GalNAc3] scaccaAfcUfcCfCfauucuuucs(invAb)	1749	usGfsaaaGfAfaugggaGfuUfugggusu	2597
D-1659	[GalNAc3] scuucggGfaUfUfUfUfgaagacaas(invAb)	1750	asUfsugucUfucaaaaUfcCfcgaagsusu	2598
D-1660	[GalNAc3] scccaauGfgAfUfGfAfuaaauuacs(invAb)	1751	asGfsuaauUfuaucAuCfcAfuugggsusu	2599
D-1661	[GalNAc3] sccucggUfuCfUfAfCfcgcuuauggs(invAb)	1752	asCfscauaAfgcguAfgAfaCfcgaggusu	2600
D-1662	[GalNAc3] sgcaaccGfgAfGfAfAfcucuagagas(invAb)	1753	usUfscuaaGfaguuCfuCfcGfguugcsusu	2601
D-1663	[GalNAc3] scaccaAfcUfcCfCfauucuuucs(invAb)	1754	usGfsaaagAfauggGfaGfuUfugggusu	2602

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1664	[GalNAc3] scuucggGfaUfUfUfUfg aagacaas{invAb}	1755	asUfsugucUfucaaAfaUfcCfcgaag susu	2603
D-1665	[GalNAc3] scccaauGfgAfUfGfAfu aaaauacs{invAb}	1756	asGfsuauuUfuaucAfuCfcAfuuggg susu	2604
D-1666	[GalNAc3] sccucggUfuCfUfAfCfG cuuauugs{invAb}	1757	asCfscuaaagcguAfgAfaCfcgaggs usu	2605
D-1667	[GalNAc3] sgcaaccGfgAfGfAfAfc ucuuagas{invAb}	1758	usUfscuaagaguUcfuCfcGfguugcs usu	2606
D-1668	[GalNAc3] scaccaAfcUfCfCfCfa uucuuucs{invAb}	1759	usGfsaaaagaauggGfaGfuUfuggugs usu	2607
D-1669	[GalNAc3] scuucggGfaUfUfUfUfg aagacaas{invAb}	1760	asUfsugucuucaaAfaUfcCfcgaags usu	2608
D-1670	[DCA-C6] aaccggAfgAfAfcUfCuuagaau s{invAb}	1761	usUfscuaaGfaguUcfuCfcGfguusu su	2609
D-1671	[DCA-C6] ucggUfuCfUfAfCfGcuuauugs us{invAb}	1762	asCfscuaaAfgcguagAfaCfcgasus u	2610
D-1672	[DCA-C6] ccaaAfcUfCfCfCfauucuuucas us{invAb}	1763	usGfsaaagAfaugggaGfuUfuggsus u	2611
D-1673	[DCA-C6] ucggGfaUfUfUfUfgaagacaau s{invAb}	1764	asUfsugucUfucaaaaUfcCfcgasus u	2612
D-1674	[DCA-C6] caauGfgAfUfGfAfuaaaauacus us{invAb}	1765	asGfsuauuUfuaucUcfuAfuugsus u	2613
D-1675	[DCA-C6] ucggUfuCfUfAfCfGcuuauugs us{invAb}	1766	asCfscuaaAfgcguAfgAfaCfcgasu su	2614
D-1676	[DCA-C6] aaccGfgAfGfAfAfcuuagaas us{invAb}	1767	usUfscuaaGfaguUcfuCfcGfguusu su	2615
D-1677	[DCA-C6] ccaaAfcUfCfCfCfauucuuucas us{invAb}	1768	usGfsaaagAfauggGfaGfuUfuggsu su	2616
D-1678	[DCA-C6] ucggGfaUfUfUfUfgaagacaau s{invAb}	1769	asUfsugucUfucaaAfaUfcCfcgasu su	2617
D-1679	[DCA-C6] caauGfgAfUfGfAfuaaaauacus us{invAb}	1770	asGfsuauuUfuaucAfuCfcAfuugsu su	2618
D-1680	[DCA-C6] ccucggUfuCfUfAfCfGcuuaugg s{invAb}	1771	asCfscuaAfAfgcguagAfaCfcgagg susu	2619
D-1681	[DCA-C6] gcaaccGfgAfGfAfAfcuuaga s{invAb}	1772	usUfscuaAfGfaguucUcfuGfguugc susu	2620
D-1682	[DCA-C6] caccAAfcUfCfCfCfauucuuuc s{invAb}	1773	usGfsaaaGfAfaugggaGfuUfuggug susu	2621
D-1683	[DCA-C6] cuucggGfaUfUfUfUfgaagacaa s{invAb}	1774	asUfsuguCfUfucaaaaUfcCfcgaag susu	2622

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1684	[DCA-C6] cccaauGfgAfUfGfAfuaaaaauacs{invAb}	1775	asGfsuauUfUfuaucAuCfcAfuugggsusu	2623
D-1685	[DCA-C6] ccucggUfuCfUfAfCfGcuuauags{invAb}	1776	asCfscauaAfgcguAfgAfaCfcgagggsusu	2624
D-1686	[DCA-C6] gcaaccGfgAfGfAfAfcucuuaags{invAb}	1777	usUfscuaaGfaguCfuCfcGfguugcsusu	2625
D-1687	[DCA-C6] caccAAfCfUfCfCfCfauucuuucs{invAb}	1778	usGfsaaagAfauggGfaGfuUfuggugsusu	2626
D-1688	[DCA-C6] cuucggGfaUfUfUfUfgaagacaa{s{invAb}}	1779	asUfsugucUfucaaAfaUfcCfcgaaggsusu	2627
D-1689	[DCA-C6] cccaauGfgAfUfGfAfuaaaaauacs{invAb}	1780	asGfsuauUfuaucAfuCfcAfuugggsusu	2628
D-1690	[DCA-C6] ccucggUfuCfUfAfCfGcuuauags{invAb}	1781	asCfscuaaagcguAfgAfaCfcgagggsusu	2629
D-1691	[DCA-C6] gcaaccGfgAfGfAfAfcucuuaags{invAb}	1782	usUfscuaagaguCfuCfcGfguugcsusu	2630
D-1692	[DCA-C6] caccAAfCfUfCfCfCfauucuuucs{invAb}	1783	usGfsaaagauggGfaGfuUfuggugsusu	2631
D-1693	[DCA-C6] cuucggGfaUfUfUfUfgaagacaa{s{invAb}}	1784	asUfsugucuucaaAfaUfcCfcgaaggsusu	2632
D-1694	[DCA-C6] accaucCfGfAfUfCfAfgcuguuaags{invAb}	1785	usUfscuacAfgcugauCfGfGfaugggsusu	2633
D-1695	[DCA-C6] ggucuuGfuGfAfAfUfauuggaaags{invAb}	1786	asCfsuuucCfauauucAfcAfagaccsusu	2634
D-1696	[DCA-C6] ugagcuAfuGfUfGfUfuggaagugs{invAb}	1787	asCfsacuuCfcaacacAfuAfgcucasusu	2635
D-1697	[DCA-C6] aagacgGfuAfcfAfUfaauccuacs{invAb}	1788	usGfsuaggAfuauguAfcCfGfucuuusu	2636
D-1698	[DCA-C6] aguuugGfaAfUfUfCfuuugcucucs{invAb}	1789	usAfsagacAfaagaauUfcCfaaacusus	2637
D-1699	[DCA-C6] uuuggaAfuUfCfUfUfugcucuacs{invAb}	1790	asGfsuagaGfcaaagaAfuUfccaaasusu	2638
D-1700	[GalNAc3] scauccgAfuCfAfGfCfuguagaasus{invAb}	1791	usUfscuacAfgcugAfuCfGfGfaugsusu	2639
D-1701	[GalNAc3] sucuuguGfaAfUfAfUfggaaagusus{invAb}	1792	asCfsuuucCfauauUfcAfcAfagagasusu	2640
D-1702	[GalNAc3] sgacggAfcAfUfAfAfuccuacacus{invAb}	1793	usGfsuaggAfuauguGfuAfcCfGfucusu	2641
D-1703	[GalNAc3] sagcuauGfuGfUfUfGfgaagugusus{invAb}	1794	asCfsacuuCfcaacAfcAfuAfgcusususu	2642

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1704	[GalNAc3] suggaaUfcUfUfGfc ucuacusus {invAb}	1795	asGfsuagaGfcaaaGfaAfuUfccasu su	2643
D-1705	[GalNAc3] suuuggaAfuUfCfUfUfu gcucuasus {invAb}	1796	usAfsbgagcAfaagaAfuUfcCfaaasu su	2644
D-1706	[GalNAc3] sgcuaaAfuUfUfCfAfa ggaguusus {invAb}	1797	asAfsuccUfugaaAfuUfaUfagcsu su	2645
D-1707	[GalNAc3] scaucCfGfUfCfAfgcu guagaasus {invAb}	1798	usUfscuacAfgcugauCfGfagcsu su	2646
D-1708	[GalNAc3] succuGfGfAfAfUfaug gaaagusus {invAb}	1799	asCfsuuucCfauauucAfcAfagasu su	2647
D-1709	[GalNAc3] sgacgGfUfCfAfUfaa ucuacusus {invAb}	1800	usGfsuaggAfuuauguAfcCfagcsu su	2648
D-1710	[GalNAc3] sagcuAfuGfUfGfUfugg aagugusus {invAb}	1801	asCfsacuuCfcaacacAfuAfgcusu su	2649
D-1711	[GalNAc3] suggaAfuUfCfUfUfugc ucuacusus {invAb}	1802	asGfsuagaGfcaaaAfuUfccasu su	2650
D-1712	[GalNAc3] suuugGfaAfuUfCfuuu gcucuasus {invAb}	1803	usAfsbgagcAfaagaauUfcCfaaasu su	2651
D-1713	[GalNAc3] sgcuaUfaAfuUfUfcaa ggaguusus {invAb}	1804	asAfsuccUfugaaaUfaUfagcsu su	2652
D-1714	[GalNAc3] scaucCfGfUfCfAfgcu guagaasus {invAb}	1805	usUfscuacAfgcugAfuCfGfagcsu su	2653
D-1715	[GalNAc3] succuGfGfAfAfUfaug gaaagusus {invAb}	1806	asCfsuuucCfauauUfcAfcAfagasu su	2654
D-1716	[GalNAc3] sgacgGfUfCfAfUfaa ucuacusus {invAb}	1807	usGfsuaggAfuuaUGfUfCfagcsu su	2655
D-1717	[GalNAc3] sagcuAfuGfUfGfUfugg aagugusus {invAb}	1808	asCfsacuuCfcaacAfcAfuAfgcusu su	2656
D-1718	[GalNAc3] suggaAfuUfCfUfUfugc ucuacusus {invAb}	1809	asGfsuagaGfcaaaGfaAfuUfccasu su	2657
D-1719	[GalNAc3] suuugGfaAfuUfCfuuu gcucuasus {invAb}	1810	usAfsbgagcAfaagaAfuUfcCfaaasu su	2658
D-1720	[GalNAc3] sgcuaUfaAfuUfUfcaa ggaguusus {invAb}	1811	asAfsuccUfugaaAfuUfaUfagcsu su	2659
D-1721	[GalNAc3] saccaucCfGfUfCfAfgcuguagas {invAb}	1812	usUfscuacAfgcugauCfGfaggu susu	2660
D-1722	[GalNAc3] sggucuuGfUfGfAfUfa uggaaags {invAb}	1813	asCfsuuucCfcauauucAfcAfagacc susu	2661
D-1723	[GalNAc3] saagacgGfUfCfAfUfa auccuacs {invAb}	1814	usGfsuagGfAfuuauguAfcCfagcuu susu	2662
D-1724	[GalNAc3] sugagcuAfuGfUfGfUfug ggaagugs {invAb}	1815	asCfsacuuCfcaacacAfuAfgcuca susu	2663
D-1725	[GalNAc3] suuuggaAfuUfCfUfUfu gcucuasus {invAb}	1816	asGfsuagAfgfcaagaAfuUfccaa susu	2664
D-1726	[GalNAc3] saguuugGfaAfuUfCfu uugcucus {invAb}	1817	usAfsbgagcAfaagaauUfcCfaaacu susu	2665
D-1727	[GalNAc3] suugcuaUfaAfuUfUfca aggagus {invAb}	1818	asAfsuccUfugaaaUfaUfagcaa susu	2666
D-1728	[GalNAc3] saccaucCfGfUfCfAfgcuguagas {invAb}	1819	usUfscuacAfgcugAfuCfGfaggu susu	2667
D-1729	[GalNAc3] sggucuuGfUfGfAfUfa uggaaags {invAb}	1820	asCfsuuucCfauauUfcAfcAfagacc susu	2668
D-1730	[GalNAc3] saagacgGfUfCfAfUfa auccuacs {invAb}	1821	usGfsuaggAfuuaUGfUfCfagcuu susu	2669
D-1731	[GalNAc3] sugagcuAfuGfUfGfUfug ggaagugs {invAb}	1822	asCfsacuuCfcaacAfcAfuAfgcuca susu	2670

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Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1760	[GalNAc3] suugcucUfaCfUfGfUfu uacauugs{invAb}	1851	asCfsaaugUfaaacagUfaGfagcaas usu	2699
D-1761	[GalNAc3] suugcuaUfaAfUfUfUfc aaggagus{invAb}	1852	asAfsuccUfugaaaUfaUfagcaas usu	2700
D-1762	[GalNAc3] saaugauGfcAfCfUfUfu aggaugus{invAb}	1853	asAfscaucCfuaaaguGfcAfucauus usu	2701
D-1763	[GalNAc3] saugaugCfaCfUfUfUfa ggauguus{invAb}	1854	asAfsacauCfcuaaagUfgCfaucAus usu	2702
D-1764	[GalNAc3] sacaugaAfuCfAfUfUfc acaugacs{invAb}	1855	asGfsucauGfugaagAfuUfcaugus usu	2703
D-1765	[GalNAc3] scaugaaUfcAfUfUfcfa caugaccs{invAb}	1856	usGfsgucaUfgugaauGfaUfcaugs usu	2704
D-1766	[GalNAc3] saauacaUfgUfCfUfAfg ucuguccs{invAb}	1857	asGfsgacaGfacuagaCfaUfguaus usu	2705
D-1767	[GalNAc3] saugucuAfgUfCfUfGfu ccuuuaas{invAb}	1858	asUfsuaaaGfgacagaCfuAfgacaus usu	2706
D-1768	[GalNAc3] saaucagAfuCfAfUfUfa ccaguas{invAb}	1859	asUfsaacuGfguaagAfuCfugaus usu	2707
D-1769	[GalNAc3] sucagauCfaUfUfAfcfc aguuaags{invAb}	1860	asGfscuaaCfugguaUfgAfcugagas usu	2708
D-1770	[GalNAc3] sagaucaUfuAfcCfAfg uuagcuus{invAb}	1861	asAfsagcuAfacugguAfaUfgaucus usu	2709
D-1771	[GalNAc3] sucauuacfcAfGfUfUfa gcuuuuas{invAb}	1862	usUfsaaaaGfcuaacuGfgUfaaugas usu	2710
D-1772	[GalNAc3] saccaguUfaGfCfUfUfu uaaagcas{invAb}	1863	asUfsgcuUfaaaaagCfaUfcuggus usu	2711
D-1773	[GalNAc3] saagcacAfuUfUfGfUfu uaagacus{invAb}	1864	usAfsqcuUfaaaacaAfuGfugcuus usu	2712
D-1774	[GalNAc3] sgacauUfuGfUfUfUfa agacuaus{invAb}	1865	asAfsuaguCfuuaaacAfaUfugugcs usu	2713
D-1775	[GalNAc3] sugagauGfcUfAfCfUfa auuguuus{invAb}	1866	asAfsaacaAfuuaagaGfcAfucucas usu	2714
D-1776	[GalNAc3] sgauuuuUfuCfAfGfGfa auccccas{invAb}	1867	asUfsggggAfuuccugAfaUfaaacs usu	2715
D-1777	[GalNAc3] sugcuguGfuGfGfCfCfa auuuaas{invAb}	1868	asUfsuaaAfuuggccAfcAfcagcas usu	2716
D-1778	[GalNAc3] sauguuaAfaCfUfAfUfa cugaccs{invAb}	1869	asGfsggucAfguaagUfuUfuacaus usu	2717
D-1779	[GalNAc3] suaaaacUfaUfAfCfUfg accguus{invAb}	1870	asAfsacggGfucaguaUfaGfuuuuas usu	2718
D-1780	[GalNAc3] sgagaaaCfuGfGfCfUfg guccaas{invAb}	1871	asAfsuaggAfcagccAfgUfuucucs usu	2719
D-1781	[GalNAc3] sccaugGfgAfuUfUfUfa cagcaacs{invAb}	1872	usGfsuugcUfguaaaUfcCfauuggs usu	2720
D-1782	[GalNAc3] saguuugCfuCfUfUfAfa ucguauus{invAb}	1873	asCfsauacGfaauaagAfgCfaaacus usu	2721
D-1783	[GalNAc3] sguuugcUfcUfUfAfAfu cguauggs{invAb}	1874	usCfscuaCfgaauaaGfaGfcaacs usu	2722
D-1784	[GalNAc3] suuugcuCfuUfAfAfUfc guauggas{invAb}	1875	usUfsccauAfcgaauaAfgAfgcaas usu	2723
D-1785	[GalNAc3] sugcucuUfaAfUfCfGfu auggaags{invAb}	1876	asCfsuuccAfuacgauUfaAfgagcas usu	2724
D-1786	[GalNAc3] scuuaaCfGfUfAfUfGfg aagcuugs{invAb}	1877	usCfsaagCfuccauCfGfuaaags usu	2725
D-1787	[GalNAc3] suuaaucGfuAfUfGfGfa agcuugas{invAb}	1878	asUfscagCfuuccauAfcGfauaas usu	2726

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1788	[GalNac3] succauaCfAcfAfAfAfG acgguacs {invAb}	1879	usGfsuaccGfucuuUfgUfagggas usu	2727
D-1789	[GalNac3] scauacaCfAcfAfGfAfGc gguacaus {invAb}	1880	usAfsuguaCfcgucuuUfgUfguaugs usu	2728
D-1790	[GalNac3] sugucuaGfUcfUfGfUfc cuuuuaus {invAb}	1881	usAfsuuaaAfggacagAfcUfagacas usu	2729
D-1791	[GalNac3] sucuaguCfUgFfCfCfUf uaaauags {invAb}	1882	asCfsuauuAfaaggacAfgAfcuagas usu	2730
D-1792	[GalNac3] scuagucUfGfUfCfCfUfu uauuagcs {invAb}	1883	asGfscuauUfaaaggacAfaGfacuags usu	2731
D-1793	[GalNac3] sgucuguCfcUfUfUfAfa uagcucus {invAb}	1884	asAfsgagcUfauuaaaGfgAfcagacs usu	2732
D-1794	[GalNac3] sgucugcAfaCfCfGfGfafa gaacucus {invAb}	1885	asAfsgaguUfcuccggUfuGfcagacs usu	2733
D-1795	[GalNac3] sucugcaAfcCfGfGfAfG aacucuu {invAb}	1886	usAfsagagUfucuccgGfuUfgcagas usu	2734
D-1796	[GalNac3] sugcaacCfGfAfGfAfa cucuuags {invAb}	1887	usCfsuaagAfguucucCfGgfuugcas usu	2735
D-1797	[GalNac3] saggaugAfaGfUfUfCfGf acaugggs {invAb}	1888	usCfsccauGfucgaacUfuCfauccus usu	2736
D-1798	[GalNac3] sgggacuUfaUfCfAfAfCf aaagaaas {invAb}	1889	usUfsuucuUfuguugaUfaAfgucccs usu	2737
D-1799	[GalNac3] sauaucCfUfCfUfGfGf guucaacs {invAb}	1890	asGfsuugaAfcccagaAfgGfaguau usu	2738
D-1800	[GalNac3] scaagccUfaAfAfCfGfUf cagaaas {invAb}	1891	asAfsuuucUfgacguuUfaGfgcuugs usu	2739
D-1801	[GalNac3] saagccuAfaAfCfGfUf cagaaaucs {invAb}	1892	asGfsauuuCfugacguUfuAfggcuus usu	2740
D-1802	[GalNac3] sgguggaCfAcfAfCfUfUf agcauuu {invAb}	1893	asAfsaaugCfugagugUfgUfccaccs usu	2741
D-1803	[GalNac3] sgagcuuUfgUfCfUfCfCf gaagugcs {invAb}	1894	asGfscacuUfcggagaCfaAfagcucs usu	2742
D-1804	[GalNac3] sugucucCfGfAfAfGfUfGf ccccagus {invAb}	1895	asAfsucggGfgcacuuCfGfagacas usu	2743
D-1805	[GalNac3] saugcucUfCfCfCfUfUf gguucuas {invAb}	1896	asUfsagaaCfcgaggaGfaGfagcaus usu	2744
D-1806	[GalNac3] sagcucaCfAcfGfAfAfGf gauucags {invAb}	1897	usCfsugaaUfccuucgUfgUfgagcus usu	2745
D-1807	[GalNac3] sagaagaAfgUfAfCfAfGf accuuccs {invAb}	1898	asGfsgaagGfucuguaCfuUfcuucus usu	2746
D-1808	[GalNac3] sgaagaaGfUfCfAfGfafa ccuucccs {invAb}	1899	usGfsggaaGfgucuguAfcUfucuucs usu	2747
D-1809	[GalNac3] saagaagUfaCfAfGfAfGf cuucccas {invAb}	1900	asUfsgggaaAfggucugUfaCfuucuu usu	2748
D-1810	[GalNac3] sucugaaAfUgGfGfAfCfafa aagaccs {invAb}	1901	asGfsgucaUfuuguccAfuUfucagas usu	2749
D-1811	[GalNac3] saaaugaCfcUfUfGfCfCf aaaauccs {invAb}	1902	asGfsgaaUfuggcaaGfgUfcuuuu usu	2750
D-1812	[GalNac3] saccuuaCfUfCfCfCfAfGf gaugcggs {invAb}	1903	asCfscgcaUfccugggAfgUfuaggus usu	2751
D-1813	[GalNac3] sugcggcAfgCfGfAfAfGf caacacas {invAb}	1904	asUfsguguUfgcuucgCfuGfccgcas usu	2752
D-1814	[GalNac3] sacggccGfGfUfAfAfCfafa aagaacgs {invAb}	1905	usCfsguucUfuuguuaCfcGfgccgus usu	2753
D-1815	[GalNac3] sggccggUfaAfCfAfAfafa gaacgaas {invAb}	1906	asUfscguUfcuuuguUfaCfcggccs usu	2754

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1816	[GalNAc3] sggggucAfgAfAfGfAfc gauagcas{invAb}	1907	usUfsgcuaUfcgucuuCfuGfaccuccs usu	2755
D-1817	[GalNAc3] sagaagAfaCfCfAfUfc cgaucags{invAb}	1908	asCfsugauCfggauGfUfuCfuuuucsu usu	2756
D-1818	[GalNAc3] sgaaccaUfcCfGfAfUfc agcuguas{invAb}	1909	asUfsacagCfugaucGfAfUfgguucsu usu	2757
D-1819	[GalNAc3] saucuggAfaCfAfCfUfa ucagcaus{invAb}	1910	asAfsugcuGfauagugUfuCfcagaus usu	2758
D-1820	[GalNAc3] saagaaaAfuAfCfUfCfc uucugggs{invAb}	1911	asCfscagAfaggaguAfuUfuucuuusu usu	2759
D-1821	[GalNAc3] sacucagGfaAfGfUfCfc gaaaaggus{invAb}	1912	usAfsccuuUfucgacuUfcCfugagus usu	2760
D-1822	[GalNAc3] sagaagGfaGfCfAfAfg ccuaaacs{invAb}	1913	asGfsuuuaGfgcuugcUfcCfuuuucsu usu	2761
D-1823	[GalNAc3] sagagcAfaGfCfCfUfa aacgucas{invAb}	1914	asUfsgacgUfuuaaggcUfuGfcuccusu usu	2762
D-1824	[GalNAc3] sggagcaAfgCfCfUfAfa acgucags{invAb}	1915	usCfsugacGfuuaaggCfuUfgcuccsu usu	2763
D-1825	[GalNAc3] sagcaagCfcUfAfAfAfc gucagaas{invAb}	1916	usUfsucugAfcguuaaGfgCfuugcus usu	2764
D-1826	[GalNAc3] sgaaaguCfuCfAfAfUfu ccacacgs{invAb}	1917	usCfsguguGfgaaugAfgAfcuuucsu usu	2765
D-1827	[GalNAc3] sgucucaAfuUfCfCfAfc acgaucus{invAb}	1918	asAfsgaucGfuguggaAfuUfgagacsu usu	2766
D-1828	[GalNAc3] sucaauCfcAfCfAfCfc aucucaus{invAb}	1919	asAfsugagAfcuguguGfgAfauugas usu	2767
D-1829	[GalNAc3] scaauucCfaCfAfCfGfa ucucaugs{invAb}	1920	usCfsaugaGfauagugUfgGfaauugs usu	2768
D-1830	[GalNAc3] sauuccaCfaCfGfAfUfc ucaugags{invAb}	1921	usCfsucaGfagauGfUfgUfggaauusu usu	2769
D-1831	[GalNAc3] suuccacAfcGfAfUfCfu caugagas{invAb}	1922	asUfscucaUfgagauGfUfgfuggaasu usu	2770
D-1832	[GalNAc3] sucaugaGfaGfAfAfCfu ggaccugs{invAb}	1923	usCfsagguCfcaguucUfcUfcaugas usu	2771
D-1833	[GalNAc3] scaugagAfgAfAfCfUfg gaccugas{invAb}	1924	asUfscaggUfccaguUfcUfcucaugs usu	2772
D-1834	[GalNAc3] saucccaGfcCfUfAfUfc ugacaccs{invAb}	1925	usGfsguguCfagauagGfcUfgggauusu usu	2773
D-1835	[GalNAc3] succcagCfcUfAfUfCfu gacaccas{invAb}	1926	usUfsggugUfcagauaGfgCfugggas usu	2774
D-1836	[GalNAc3] scccagCfuAfUfCfUfg acaccaas{invAb}	1927	usUfsugguGfucagauAfgGfcugggs usu	2775
D-1837	[GalNAc3] sagcagaGfaAfAfUfCfa agaugccs{invAb}	1928	asGfsgcauUfuugauUfcUfcugcus usu	2776
D-1838	[GalNAc3] succgaaGfuGfCfCfCfc agucggas{invAb}	1929	asUfscgaCfuggggcAfcUfucggasu usu	2777
D-1839	[GalNAc3] sgaagauAfgAfUfUfCfc aagaagas{invAb}	1930	asUfscuucUfucgaauCfuAfucuuusu usu	2778
D-1840	[GalNAc3] scagcgaAfgCfAfAfCfa cacucccs{invAb}	1931	asGfsggagUfguguugCfuUfcgcugsu usu	2779
D-1841	[GalNAc3] sgccaagCfaAfCfAfCfa cuccccas{invAb}	1932	usUfsggggAfguguguUfgCfuucgcs usu	2780
D-1842	[GalNAc3] suugaagCfcAfCfAfUfu ggaaucus{invAb}	1933	usAfsgauUfcfaaugGfgCfuucaasu usu	2781
D-1843	[GalNAc3] scgguaaCfaAfAfGfAfa cgaacggs{invAb}	1934	asCfscguCfuguucuuUfgUfuaccgs usu	2782

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1844	[GalNAc3] saugaagCfcAfCfUfAfuacgacags{invAb}	1935	asCfsugucGfuauaguGfgCfuucaususu	2783
D-1845	[GalNAc3] scacuauAfcGfAfCfAfgguaccggs{invAb}	1936	asCfscgggAfcfcugucGfuAfuagugsusu	2784
D-1846	{DCA-sC6} uugcuaUfaAfUfUfcaaggaguss{invAb}	1937	asAfcuccUfugaaauUfaUfagcaasusu	2785
D-1847	{DCA-sC6} gcaaccGfgAfGfAfAfcucuag as{invAb}	2831	usUfscuaaGfaguuCfuCfcGfguugcsusu	3085
D-1848	{DCA-sC6} ccucggUfuCfUfAfCfgcuuaggs{invAb}	2832	asCfscuaaAfgcguAfgAfaCfcgaggssusu	3086
D-1849	{DCA-sC6} gcaaccGfgAfGfAfAfcucuag as{invAb}	2833	usUfscuaagaguuCfuCfcGfguugcsusu	3087
D-1850	{DCA-sC6} caauGfgAfUfGfAfuaaaaucusus{invAb}	2834	asGf suauUfuaucuCfcAfuugssusu	3088
D-1851	{DCA-sC6} ccaaAfcUfCfCfCfauucuuucas{invAb}	2835	usGfsaaagAfaugggaGfuUfuggssusu	3089
D-1852	{DCA-sC6} ggucuuGfuGfAfUfauuggaaags{invAb}	2836	asCfsuuucCfauauucAfcAfagaccssusu	3090
D-1853	{DCA-sC6} accaucCfGfAfUfCfAfgcuguag as{invAb}	2837	usUfscuacAfgcugauCfGfauuggssusu	3091
D-1854	{DCA-sC6} uuuggaAfuUfCfUfUfugcucua cs{invAb}	2838	asGfsuagaGfcaaagaAfuUfccaaasusu	3092
D-1855	{DCA-sC6} aguuugGfaAfUfUfCfuuugcuc us{invAb}	2839	usAfsagacAfaagaauUfcCfaaacususu	3093
D-1856	{DCA-sC6} aagacgGfuAfcAfUfaauccua cs{invAb}	2840	usGfsuaggAfuauguAfcCfugcuususu	3094
D-1857	{DCA-sC6} ugagcuAfuGfUfGfUfuggaagugs{invAb}	2841	asCfsacuuCfcaacacAfuAfgcucasusu	3095
D-1858	{DCA-sC6} caccaaAfcUfCfCfCfauucuuu cs{invAb}	2842	usGfsaaagAfaugggaGfuUfuggugsusu	3096
D-1859	{DCA-sC6} gcaaccGfgAfGfAfAfcucuag as{invAb}	2843	usUfscuaaGfaguucuCfcGfguugcsusu	3097
D-1860	{DCA-sC6} ccucggUfuCfUfAfCfgcuuaggs{invAb}	2844	asCfscuaaAfgcguagAfaCfcgaggsusu	3098
D-1861	{DCA-sC6} cccaaUGfgAfUfGfAfuaaaauc us{invAb}	2845	asGf suauUfuaucuCfcAfuugggsusu	3099
D-1862	{DCA-sC6} uugcuaUfaAfUfUfcaaggag us{invAb}	2846	asAfcuccUfugaaauUfaUfagcaasusu	3100

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1863	{ DCA- C6} aagacgGfuAfCfAfUfaauccuacs {invAb}	2847	usGfsuagGfAfuuauGfuAfcCfugucuu susu	3101
D-1864	{ DCA- C6} aguuuGfAfUfUfCfuugcucus {invAb}	2848	usAfsgagcAfaagaAfUfCfCfaaacu susu	3102
D-1865	{ DCA- C6} aagacgGfuAfCfAfUfaauccuacs {invAb}	2849	usGfsuaggAfuuauGfuAfcCfugucuu susu	3103
D-1866	{ DCA- C6} aagacgGfuAfCfAfUfaauccuacs {invAb}	2850	usGfsuaggauuauGfuAfcCfugucuu usu	3104
D-1867	{ DCA- C6} ggucuuGfuGfAfAfUfauggaaags {invAb}	2851	asCfsuuuccauauUfCfAfagaccs usu	3105
D-1868	{ DCA- C6} uggaAfUfCfUfUfugcucucacus {invAb}	2852	asGfsuagaGfcaaaGfAfUfccasus u	3106
D-1869	{ DCA- C6} gacgGfuAfCfAfUfaauccuacacs {invAb}	2853	usGfsuaggAfuuauGfuAfcCfugucsu u	3107
D-1870	{ DCA- C6} uuugGfAfUfUfCfuugcucucacs {invAb}	2854	usAfsgagcAfaagaAfUfCfCfaaasu su	3108
D-1871	{ DCA- C6} uggaAfUfCfUfUfugcucucacus {invAb}	2855	asGfsuagaGfcaaaGfAfUfccasus su	3109
D-1872	{ DCA- C6} gacgGfuAfCfAfUfaauccuacacs {invAb}	2856	usGfsuaggAfuuauGfuAfcCfugucsu su	3110
D-1873	{ DCA- C6} caucCfGfAfUfCfAfgcugugaas {invAb}	2857	usUfscuacAfgcugAfUfCfGfaugsu su	3111
D-1874	{ DCA- C6} gcuauAfUfUfCfAfaggaguuus {invAb}	2858	asAfscuccUfugaaAfUfAfagcsu su	3112
D-1875	{ DCA- C6} uuuggaAfUfCfUfUfugcucucacs {invAb}	2859	usAfsgagcAfaagaAfUfCfCfaaasu su	3113
D-1876	{ DCA- C6} uggaauUfCfUfUfGfcucucacus {invAb}	2860	asGfsuagaGfcaaaGfAfUfccasus su	3114
D-1877	{ DCA- C6} gacgguAfCfAfUfAfufuccuacacs {invAb}	2861	usGfsuaggAfuuauGfuAfcCfugucsu su	3115
D-1878	{ DCA- C6} gsacgGfuAfCfAfUfaauccuacacus {invAb}	2862	usGfsuaggAfuuauGfuAfcCfugucsu su	3116
D-1879	[GalNAc3] sgsacgGfuAfCfAfUfaauccuacacus {invAb}	2863	usGfsuaggAfuuauGfuAfcCfugucsu su	3117
D-1880	{ DCA- sC6} gacgGfuAfCfAfUfaauccuacacus {invAb}	2864	usGfsuaggAfuuauGfuAfcCfugucsu su	3118
D-1881	{ DCA- sC6} aagacgGfuAfCfAfUfaauccuacs {invAb}	2865	usGfsuaggauuauGfuAfcCfugucuu usu	3119

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1882	{DCA-sC6}uggaAfuUfCfUfUfugcucuacus{invAb}	2866	asGfsuagaGfcaaaGfaAfuUfccasusu	3120
D-1883	{DCA-sC6}uuugGfaAfuUfCfuuugcucuacus{invAb}	2867	usAfsbgagcAfaagaAfuUfcCfaaasu	3121
D-1884	{DCA-sC6}gacggUfCfUfUfAfuccuacacus{invAb}	2868	usGfsuaggAfuauGfuAfcCfugucsusu	3122
D-1885	{DCA-sC6}uggaauUfCfUfUfUfGfcucuacus{invAb}	2869	asGfsuagaGfcaaaGfaAfuUfccasusu	3123
D-1886	{DCA-sC6}uuuggaAfuUfCfUfUfugcucuacus{invAb}	2870	usAfsbgagcAfaagaAfuUfcCfaaasu	3124
D-1887	{DCA-sC6}gacgGfuUfCfUfUfaauccuacacus{invAb}	2871	usGfsuaggAfuuauguUfCfugucsusu	3125
D-1888	{DCA-sC6}uggaAfuUfCfUfUfugcucuacus{invAb}	2872	asGfsuagaGfcaaaGfaAfuUfccasusu	3126
D-1889		2873		3127
D-1890		2874		3128
D-1891	[GalNAc3]saucagAfuCfAfuUfUfaccaguas{invAb}	2875	asUfSaacUfGfguaaGfuAfuCfugauususu	3129
D-1892	[GalNAc3]scuagucUfGfCfUfUfuaauagcs{invAb}	2876	asGfscuaUfUfaaaggaCfaGfacuagusu	3130
D-1893	[GalNAc3]sgcacauUfUfUfUfUfagacuaus{invAb}	2877	asAfsuagUfCfuuaaacAfaAfugugcsusu	3131
D-1894	[GalNAc3]sccaugGfgAfuUfUfUfagcaacs{invAb}	2878	usGfsuugCfUfguaaaUfCfCfauuggusu	3132
D-1895	[GalNAc3]sguuugcUfCfUfUfUfUfUfcguauugs{invAb}	2879	usCfscuaUfCfGfuaaaGfaGfcaaacusu	3133
D-1896	[GalNAc3]sccucgUfUfUfUfUfUfUfugaaagus{invAb}	2880	asAfsuuUfCfcaaaUfUfUfUfUfCfagaggusu	3134
D-1897	[GalNAc3]saucagAfuCfAfuUfUfUfaccaguas{invAb}	2881	asUfSaacuGfguaaUfGfAfuCfugauususu	3135
D-1898	[GalNAc3]scuagucUfGfCfUfUfUfuaauagcs{invAb}	2882	asGfscuaUfUfaaagGfaCfaGfacuagusu	3136
D-1899	[GalNAc3]sgcacauUfUfUfUfUfUfagacuaus{invAb}	2883	asAfsuaguCfuuaaAfcAfaAfugugcsusu	3137
D-1900	[GalNAc3]sccaugGfgAfuUfUfUfUfagcaacs{invAb}	2884	usGfsuugcUfguaaAfuCfCfCfauuggusu	3138
D-1901	[GalNAc3]sguuugcUfCfUfUfUfUfUfcguauugs{invAb}	2885	usCfscuaUfCfGfuaaAfaGfaGfcaaacusu	3139
D-1902	[GalNAc3]sccucgUfUfUfUfUfUfUfugaaagus{invAb}	2886	asAfsuuUfCfcaaaUfUfUfUfUfCfagaggusu	3140
D-1903	[GalNAc3]saucagAfuCfAfuUfUfUfaccaguas{invAb}	2887	asUfSaacugguaaUfGfAfuCfugauusu	3141
D-1904	[GalNAc3]scuagucUfGfCfUfUfUfUfuaauagcs{invAb}	2888	asGfscuaUfUfaaagGfaCfaGfacuagusu	3142
D-1905	[GalNAc3]sgcacauUfUfUfUfUfUfUfagacuaus{invAb}	2889	asAfsuagucuuuaAfcAfaAfugugcsusu	3143
D-1906	[GalNAc3]sccaugGfgAfuUfUfUfUfagcaacs{invAb}	2890	usGfsuugcuguaaAfuCfCfCfauuggusu	3144

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1907	[GalNAc3] sguuugcUfcUfUfAfAfucgaauggs{invAb}	2891	usCfscauacgauuAfaGfaGfcaacsusu	3145
D-1908	[GalNAc3] scccugUfaUfGfUfUfugaaagus{invAb}	2892	asAfscuuucaaaaCfaUfaCfagaggsusu	3146
D-1909	[GalNAc3] sucagAfuCfAfUfUfaccaguuausus{invAb}	2893	asUfSaacuGfguaaagAfuCfugasusu	3147
D-1910	[GalNAc3] sagucUfgUfCfCfUfuuaauagcusus{invAb}	2894	asGfscuauUfaaaggaCfaGfacususu	3148
D-1911	[GalNAc3] sacauUfuGfUfUfUfaagacuauusus{invAb}	2895	asAfsuaguCfuuaaacAfaAfugususu	3149
D-1912	[GalNAc3] saaugGfgAfUfUfUfaca gcaacasus{invAb}	2896	usGfSuugcUfguaaaUfcCfauususu	3150
D-1913	[GalNAc3] suugcUfcUfUfAfAfucg uauggasus{invAb}	2897	usCfscauaCfgauuaaGfaGfcaasusu	3151
D-1914	[GalNAc3] scucgUfaUfGfUfUfuugaaaguusus{invAb}	2898	asAfscuuuCfaaaacaUfaCfagagsusu	3152
D-1915	[GalNAc3] sucagAfuCfAfUfUfaccaguuausus{invAb}	2899	asUfSaacuGfguaaUfgAfuCfugasusu	3153
D-1916	[GalNAc3] sagucUfgUfCfCfUfuuaauagcusus{invAb}	2900	asGfscuauUfaaagGfaCfaGfacususu	3154
D-1917	[GalNAc3] sacauUfuGfUfUfUfaagacuauusus{invAb}	2901	asAfsuaguCfuuaaAfcAfaAfugususu	3155
D-1918	[GalNAc3] saaugGfgAfUfUfUfaca gcaacasus{invAb}	2902	usGfSuugcUfguaaAfuCfcCfauususu	3156
D-1919	[GalNAc3] suugcUfcUfUfAfAfucg uauggasus{invAb}	2903	usCfscauaCfgauuAfaGfaGfcaasusu	3157
D-1920	[GalNAc3] scucgUfaUfGfUfUfuugaaaguusus{invAb}	2904	asAfscuuuCfaaaaCfaUfaCfagagsusu	3158
D-1921	[GalNAc3] sucagauCfaUfUfAfCfcaguuausus{invAb}	2905	asUfSaacuGfguaaUfgAfuCfugasusu	3159
D-1922	[GalNAc3] sagucUfgUfCfCfUfuuaauagcusus{invAb}	2906	asGfscuauUfaaagGfaCfaGfacususu	3160
D-1923	[GalNAc3] sacauuuGfuUfUfAfAfgacuauusus{invAb}	2907	asAfsuaguCfuuaaAfcAfaAfugususu	3161
D-1924	[GalNAc3] saaugggAfuUfUfAfCfagcaacasus{invAb}	2908	usGfSuugcUfguaaAfuCfcCfauususu	3162
D-1925	[GalNAc3] suugcUfUfAfAfUfCfguauggasus{invAb}	2909	usCfscauaCfgauuAfaGfaGfcaasusu	3163
D-1926	[GalNAc3] scucguaUfgUfUfUfUfgaaaguusus{invAb}	2910	asAfscuuuCfaaaaCfaUfaCfagagsusu	3164
D-1927	[GalNAc3] sasasucagAfuCfAfUfUfaccaguusas{invAb}	2911	asUfSaacuGfgUfaaagAfuCfugauususu	3165
D-1928	[GalNAc3] scsusagucUfgUfCfCfUfuuaauagsgs{invAb}	2912	asGfscuauUfaAfaggaCfaGfacuagususu	3166
D-1929	[GalNAc3] sgscsacauUfuGfUfUfUfafaagacuasus{invAb}	2913	asAfsuaguCfuUfaaacAfaAfugugcsusu	3167
D-1930	[GalNAc3] scscsaaugGfgAfUfUfUfUfacagcaascs{invAb}	2914	usGfSuugcUfgUfaaaUfcCfauuggsusu	3168
D-1931	[GalNAc3] sgsusuugcUfcUfUfUfUfUfucguaugsgs{invAb}	2915	usCfscauaCfgUfuuaaGfaGfcaaacsusu	3169
D-1932	[GalNAc3] scscscucgUfaUfGfUfUfuugaaagsus{invAb}	2916	asAfscuuuCfaAfaacaUfaCfagaggsusu	3170
D-1933	[GalNAc3] saagaaaUfuUfCfUfCfcuucugggs{invAb}	2917	asCfscCaGfUfagagaguUfuUfuucususu	3171
D-1934	[GalNAc3] sucagauCfaUfUfAfCfcaguuaags{invAb}	2918	asGfscuaAfCfuguaaUfgAfucugasusu	3172

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1935	[GalNAc3] saccuaaCfuCfCfCfAfg gaugcggs{invAb}	2919	asCfscgcAfuUfccugggAfgUfuaggu susu	3173
D-1936	[GalNAc3] saagcacAfuUfUfGfUfu uaagacus{invAb}	2920	usAfsgucUfUfaaaciaAfuGfugcuu susu	3174
D-1937	[GalNAc3] sugcuguGfuGfGfCfCfa auuauaas{invAb}	2921	asUfsuauAfuUgugccAfcAfcagca susu	3175
D-1938	[GalNAc3] sucugaaAfuGfGfAfcfa aagaccs{invAb}	2922	asGfsgucAfuUfuguccAfuUfucaga susu	3176
D-1939	[GalNAc3] saagaaaAfuAfcUfCfc uucugggs{invAb}	2923	asCfscagAfaaggaGfuAfuUfuucuu susu	3177
D-1940	[GalNAc3] sucagauCfaUfUfAfcfc aguagcs{invAb}	2924	asGfscuaaCfugguAfaUfgAfcuca susu	3178
D-1941	[GalNAc3] saccuaaCfuCfCfCfAfg gaugcggs{invAb}	2925	asCfscgcAfuUfccugGfgAfgUfuaggu susu	3179
D-1942	[GalNAc3] saagcacAfuUfUfGfUfu uaagacus{invAb}	2926	usAfsgucuUfaaacAfaAfuGfugcuu susu	3180
D-1943	[GalNAc3] sugcuguGfuGfGfCfCfa auuauaas{invAb}	2927	asUfsuauAfuUgugCfcAfcAfcagca susu	3181
D-1944	[GalNAc3] sucugaaAfuGfGfAfcfa aagaccs{invAb}	2928	asGfsgucaUfuuguCfcAfuUfucaga susu	3182
D-1945	[GalNAc3] saagaaaAfuAfcUfCfc uucugggs{invAb}	2929	asCfscagaaaggaGfuAfuUfuucuu usu	3183
D-1946	[GalNAc3] sucagauCfaUfUfAfcfc aguagcs{invAb}	2930	asGfscuaacugguAfaUfgAfcucas usu	3184
D-1947	[GalNAc3] saccuaaCfuCfCfCfAfg gaugcggs{invAb}	2931	asCfscgcAfuUfccugGfgAfgUfuaggu usu	3185
D-1948	[GalNAc3] saagcacAfuUfUfGfUfu uaagacus{invAb}	2932	usAfsgucuuaaacAfaAfuGfugcuu usu	3186
D-1949	[GalNAc3] sugcuguGfuGfGfCfCfa auuauaas{invAb}	2933	asUfsuauaauggCfcAfcAfcagcas usu	3187
D-1950	[GalNAc3] sucugaaAfuGfGfAfcfa aagaccs{invAb}	2934	asGfsgucauuuguCfcAfuUfucagas usu	3188
D-1951	[GalNAc3] sgaaaAfuAfcUfCfcuu cugggusus{invAb}	2935	asCfscagAfaaggaAfuUfuucsu u	3189
D-1952	[GalNAc3] sagauCfaUfUfAfcfcag uuagcusu{invAb}	2936	asGfscuaaCfugguAfaUfgAfcucus u	3190
D-1953	[GalNAc3] scuaaCfuCfCfCfAfgga ugcgusus{invAb}	2937	asCfscgcAfuUfccugggAfgUfuagsu u	3191
D-1954	[GalNAc3] sgcaAfuUfUfGfUfuua agacuasus{invAb}	2938	usAfsgucuUfaaaciaAfuGfugcsu u	3192
D-1955	[GalNAc3] scuguGfuGfGfCfCfaau uauaausus{invAb}	2939	asUfsuauAfuUgugccAfcAfcagsu u	3193
D-1956	[GalNAc3] sugaaAfuGfGfAfcfaaa ugaccusus{invAb}	2940	asGfsgucaUfuuguccAfuUfucasu u	3194
D-1957	[GalNAc3] sgaaaAfuAfcUfCfcuu cugggusus{invAb}	2941	asCfscagAfaaggaGfuAfuUfuucsu su	3195
D-1958	[GalNAc3] sagauCfaUfUfAfcfcag uuagcusu{invAb}	2942	asGfscuaaCfugguAfaUfgAfcucus su	3196
D-1959	[GalNAc3] scuaaCfuCfCfCfAfgga ugcgusus{invAb}	2943	asCfscgcAfuUfccugGfgAfgUfuagsu su	3197
D-1960	[GalNAc3] sgcaAfuUfUfGfUfuua agacuasus{invAb}	2944	usAfsgucuUfaaacAfaAfuGfugcsu su	3198
D-1961	[GalNAc3] scuguGfuGfGfCfCfaau uauaausus{invAb}	2945	asUfsuauAfuUgugCfcAfcAfcagsu su	3199
D-1962	[GalNAc3] sugaaAfuGfGfAfcfaaa ugaccusus{invAb}	2946	asGfsgucaUfuuguCfcAfuUfucasu su	3200

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1963	[GalNAc3] sgaaaaUfcUfCfCfUfu cugggusus {invAb}	2947	asCfscagAfaGgaGfuAfuUfuucsusu	3201
D-1964	[GalNAc3] sagauUfuAfcCfCfAfg uuagcusus {invAb}	2948	asGfscuaaCfugguAfaUfgAfucususu	3202
D-1965	[GalNAc3] scuaacuCfcCfAfgGfGfa ugcggusus {invAb}	2949	asCfscgcaUfccugGfgAfgUfuagsusu	3203
D-1966	[GalNAc3] sgcauUfuGfUfUfUfa agacuasus {invAb}	2950	usAfsgucUfaaacAfaAfuGfugcsusu	3204
D-1967	[GalNAc3] scuguguGfgCfCfAfa uauaasus {invAb}	2951	asUfsuauAfuuggCfcAfcAfcagsusu	3205
D-1968	[GalNAc3] sugaaUGfgAfcCfAfa ugaccusus {invAb}	2952	asGfsgucaUfuuguCfcAfuUfucasusu	3206
D-1969	[GalNAc3] sasasgaaAfuAfcUfCfcuucuggsgs {invAb}	2953	asCfscagAfaGfgaguAfuUfuucuuusu	3207
D-1970	[GalNAc3] suscsagauCfaUfUfAfcfcaguuagcs {invAb}	2954	asGfscuaaCfuGfguaaUfgAfucugasusu	3208
D-1971	[GalNAc3] sascsuaaCfuCfCfCfAfggaugcgsgs {invAb}	2955	asCfscgcaUfcCfugggAfgUfuagguusu	3209
D-1972	[GalNAc3] sasasgcacAfuUfUfGfUfuuaagacs {invAb}	2956	usAfsgucUfaAfaaaAfuGfugcuusu	3210
D-1973	[GalNAc3] susgscuguGfuGfGfCfCfaauuauas {invAb}	2957	asUfsuauAfuUfggccAfcAfcagcasusu	3211
D-1974	[GalNAc3] suscsugaaAfuGfGfAfcfaaagacscs {invAb}	2958	asGfsgucaUfuUfguccAfuUfucagasusu	3212
D-1975	{DCA-C6} gcacauUfuGfUfUfUfaagacuau s {invAb}	2959	asAfsuaguCfuuaaacAfaAfugugcsusu	3213
D-1976	{DCA-sC6} gcacauUfuGfUfUfUfaagacuau s {invAb}	2960	asAfsuaguCfuuaaacAfaAfugugcsusu	3214
D-1977	[GalNAc3] sgscacauUfuGfUfUfUfaagacuau s {invAb}	2961	asAfsuaguCfuuaaacAfaAfugugcsusu	3215
D-1978	[GalNAc3] sasagacGfuAfcCfAfu faauccuacs {invAb}	2962	usGfsguaggAfuuauguAfcCfugcuusu	3216
D-1979	[GalNAc3] susuuggaAfuUfCfUfUfugcucuacs {invAb}	2963	asGfsguagaGfcaagaAfuUfccaaasusu	3217
D-1980	[GalNAc3] sasguuugGfaUfUfUfCfuuuugcucus {invAb}	2964	usAfsgagcAfaagaauUfcCfaaacususu	3218
D-1981	[GalNAc3] susugcuaUfaAfuUfUfUfcaaggagus {invAb}	2965	asAfsuccUfugaaauUfaUfagcaasusu	3219
D-1982	[GalNAc3] sascauUfuGfUfUfUfaagacuauus {invAb}	2966	asAfsuaguCfuuaaAfcAfaAfugususu	3220
D-1983	[GalNAc3] susggaAfuUfCfUfUfugcucuacus {invAb}	2967	asGfsguagaGfcaaaGfaAfuUfccasusu	3221
D-1984	[GalNAc3] susuugGfaUfUfUfCfuuuugcucuasus {invAb}	2968	usAfsgagcAfaagaUfuUfcCfaaasusu	3222
D-1985	[GalNAc3] sgscuaUfaAfuUfUfUfcaaggaguus {invAb}	2969	asAfsuccUfugaaAfuUfaUfagcsusu	3223
D-1986	[GalNAc3] sascauuUfuUfUfAfaAgacuauus {invAb}	2970	asAfsuaguCfuuaaAfcAfaAfugususu	3224
D-1987	[GalNAc3] sgscgguAfcAfuUfAfaUccuacacus {invAb}	2971	usGfsguaggAfuuaUfuAfcCfugcsusu	3225
D-1988	[GalNAc3] susggaUfCfUfUfUfGfcucuacus {invAb}	2972	asGfsguagaGfcaaaGfaAfuUfccasusu	3226
D-1989	[GalNAc3] susuuggaAfuUfCfUfUfugcucuasus {invAb}	2973	usAfsagcAfaagaAfuUfcCfaaasusu	3227

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1990	[GalNAc3] sgscuaaAfuUfUfCfAfaggaguusus {invAb}	2974	asAfsuccUfugaaAfuUfaUfagcsusu	3228
D-1991	[GalNAc3] sascuUfuGfUfUfUfaagacuauusus {invAb}	2975	asAfsuaguCfuuaaacAfaAfugususu	3229
D-1992	[GalNAc3] sgsacgGfuAfCfAfUfaa uccuacusus {invAb}	2976	usGfsuaggAfuuauguAfcCfugcususu	3230
D-1993	[GalNAc3] susggaAfuUfCfUfUfug cucuacusus {invAb}	2977	asGfsuagaGfcaaagaAfuUfccasusu	3231
D-1994	[GalNAc3] susuugGfaAfUfUfCfu ugcucuasus {invAb}	2978	usAfsagacAfaagaauUfcCfaaasusu	3232
D-1995	[GalNAc3] sgscuaUfaAfUfUfUfcaaggaguusus {invAb}	2979	asAfsuccUfugaaaUfaUfagcsusu	3233
D-1996	[GalNAc3] sascuauGfuUfUfAfAf gacuauusus {invAb}	2980	asAfsuaguCfuUfaAfaAfaaugususu	3234
D-1997	[GalNAc3] sgsacgguAfcAfUfAfAf uccuacusus {invAb}	2981	usGfsuaggAfuUfuGfuAfccgucusu	3235
D-1998	[GalNAc3] susggaUfcUfUfUfGf cucuacusus {invAb}	2982	asGfsuagaGfcaAfaGfaAfuuccasusu	3236
D-1999	[GalNAc3] susuuggaAfuUfCfUfUf ugcucuasus {invAb}	2983	usAfsagacAfaAGfaAfuUfccaaasusu	3237
D-2000	[GalNAc3] sgscuaaAfuUfUfCfAfaggaguusus {invAb}	2984	asAfsuccUfugAfaAfuUfauagcsusu	3238
D-2001	{DCA-sC6} ascauUfuGfUfUfUfaagacuauusus {invAb}	2985	asAfsuaguCfuuaaAfcAfaAfugususu	3239
D-2002	{DCA-sC6} gsacgGfuAfCfAfUfaauccuac asus {invAb}	2986	usGfsuaggAfuauGfuAfcCfugcusu	3240
D-2003	{DCA-sC6} usggaAfuUfCfUfUfugcucuac usus {invAb}	2987	asGfsuagaGfcaaaGfaAfuUfccasusu	3241
D-2004	{DCA-sC6} usuugGfaAfUfUfCfu ugcucu asus {invAb}	2988	usAfsagacAfaagaAfuUfcCfaaasusu	3242
D-2005	{DCA-sC6} gscuaUfaAfUfUfUfcaaggagu usus {invAb}	2989	asAfsuccUfugaaAfuUfaUfagcsusu	3243
D-2006	[GalNAc3] sascscuacCfGfAfUfCfA fgcuguagsas {invAb}	2990	usUfscuacAfgCfugauCfGfaggu susu	3244
D-2007	[GalNAc3] sgsucuuGfuGfAfAfU fauggaaasgs {invAb}	2991	asCfsuucCfaUfaaucAfcAfagacc susu	3245
D-2008	[GalNAc3] sasasgacGfuAfCfAfU fauuccuascs {invAb}	2992	usGfsuaggAfuUfauguAfcCfugucuu susu	3246
D-2009	[GalNAc3] sgscsaaccGfgAfGfAfA fcucuagsas {invAb}	2993	usUfscuaaGfaGfuucCfcGfguugc susu	3247
D-2010	[GalNAc3] scsascscAfcUfCfCfC fauuccuuuscs {invAb}	2994	usGfsaaagAfaUfgggaGfuUfuggu susu	3248
D-2011	[GalNAc3] susgsagcuAfuGfUfGfU fuggaagusgs {invAb}	2995	asCfsacuuCfcAfacacAfuAfgcuca susu	3249
D-2012	[GalNAc3] sususuggaAfuUfCfUfU fugcucuascs {invAb}	2996	asGfsuagaGfcaAfaagaAfuUfccaaa susu	3250
D-2013	[GalNAc3] sasgsuuugGfaAfUfUfC fuuugcucus {invAb}	2997	usAfsagacAfaAfgaauUfcCfaaacu susu	3251
D-2014	[GalNAc3] sususgcuAfaAfUfUfU fcaaggagsus {invAb}	2998	asAfsuccUfuGfaaaUfaUfagcaa susu	3252

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2015	[GalNAc3] sasccaucgAfuCfAfGfCfuguagas {invAb}	2999	usUfscuacAfgcugAfuCfggaggususu	3253
D-2016	[GalNAc3] sgsgucuuguGfaAfUfAfUfggaaags {invAb}	3000	asCfsuuucCfauauUfcAfcaagaccsusu	3254
D-2017	[GalNAc3] sasagacgguAfcAfUfAfAfuccuacs {invAb}	3001	usGfsuaggAfuauGfuAfccgucuuusu	3255
D-2018	[GalNAc3] sgscaacggAfgAfAfCfUfcuuagas {invAb}	3002	usUfscuaaGfaguUfcUfcggugcsusu	3256
D-2019	[GalNAc3] scsaccaaUfcCfCfAfUfucuuucs {invAb}	3003	usGfsaaagAfauggGfaGfuuggugsusu	3257
D-2020	[GalNAc3] susgagcuauGfuGfUfUfGfgaagugs {invAb}	3004	asCfsacuuCfcaacAfcAfuaagcucasusu	3258
D-2021	[GalNAc3] susuuggaauUfcUfUfUfGfcucuacs {invAb}	3005	asGfsuagaGfcaaaGfaAfuuccaaasu	3259
D-2022	[GalNAc3] sasguuggaAfuUfCfUfUfugcucus {invAb}	3006	usAfsagacAfaagaAfuUfccaaacususu	3260
D-2023	[GalNAc3] susugcuauAfuUfUfCfAfaggagus {invAb}	3007	asAfsuccUfugaaAfuUfauagcaasu	3261
D-2024	[GalNAc3] sauccggAfaGfUfUfUfgaagauags {invAb}	3008	usCfsuaucuucaaAfcUfUfcgggausu	3262
D-2025	[GalNAc3] sccggAfaGfUfUfUfgaagauagasus {invAb}	3009	usCfsuaucUfucaaAfcUfCfcggsusu	3263
D-2026	[GalNAc3] sccggAfaGfUfUfUfgaagauagasus {invAb}	3010	usCfsuaucUfucaaAfcUfCfcggsusu	3264
D-2027	[GalNAc3] sccggaaGfuUfUfGfAfaagauagasus {invAb}	3011	usCfsuaucUfucaaAfcUfCfcggsusu	3265
D-2028	[GalNAc3] scscggAfaGfUfUfUfgaagauagasus {invAb}	3012	usCfsuaucUfucaaAfcUfCfcggsusu	3266
D-2029	[GalNAc3] sasusccggAfaGfUfUfUfgaagauasgs {invAb}	3013	usCfsuaucUfuCfaaacUfCfcgggaususu	3267
D-2030	[GalNAc3] sasuccggAfaGfUfUfUfgaagauags {invAb}	3014	usCfsuaucUfucaaAfcUfCfcgggausu	3268
D-2031	[GalNAc3] scscggaaGfuUfUfGfAfaagauagasus {invAb}	3015	usCfsuaucUfucaaAfcUfCfcggsusu	3269
D-2032	[GalNAc3] scscggAfaGfUfUfUfgaagauagasus {invAb}	3016	usCfsuaucUfucaaAfcUfCfcggsusu	3270
D-2033	[GalNAc3] scscggaaGfuUfUfGfAfaagauagasus {invAb}	3017	usCfsuaucUfucAfaAfcUfuccggsusu	3271
D-2034	[GalNAc3] sasuccggaaGfuUfUfGfAfagauags {invAb}	3018	usCfsuaucUfucaaAfcUfuccggausu	3272
D-2035	{DCA-sC6} uscsugaaAfuGfGfAfCfaaaugacscs {invAb}	3019	asGfsgucaUfuUfguccAfuUfucagaausu	3273
D-2036	[GalNAc3] scsacaaagaCfGfUfAfCfaaaucs {invAb}	3020	asGfsauuaUfguacCfGfUfcuuugugsusu	3274
D-2037	[GalNAc3] sascaaagacGfGfUfAfAfuaaucs {invAb}	3021	asGfsgauuAfuguaCfGfUfcuuugugsusu	3275
D-2038	[GalNAc3] scsaaagacGfUfAfCfAfUfaauccus {invAb}	3022	usAfsaggauUfauguAfcCfugucuuugsusu	3276
D-2039	[GalNAc3] sasaagacggUfaCfAfUfAfauccuas {invAb}	3023	asUfsaggaUfuaugUfaCfugucuuuususu	3277
D-2040	[GalNAc3] susaguuggAfaUfUfCfUfuugcucs {invAb}	3024	asGfsagcaAfagaaUfuCfcaaacuasusu	3278
D-2041	[GalNAc3] scsuguguGfGfCfCfAfAfuaaauasus {invAb}	3025	asUfsuaauAfuUfgccAfcAfcagsusu	3279

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2042	[GalNAc3] sgsccacauUfuGfUfUfUf aagacuasus {invAb}	3026	usAfsgucUfUfaaAfcaaAfuGfugcsu su	3280
D-2043	[GalNAc3] susggaauUfcUfUfUfGf cucuacusus {invAb}	3027	asGfsuagaGfcaAfagaAfuUfccasu su	3281
D-2044	[GalNAc3] susuuggaAfuUfCfUfUf ugcucuasus {invAb}	3028	usAfsgagcAfaaGfaauUfCfcaaasu su	3282
D-2045	[GalNAc3] scsuguguGfGfCfAfAf uuauaasus {invAb}	3029	asUfsuauaAfuuggccAfcAfcagsu su	3283
D-2046	[GalNAc3] sgsccacauUfuGfUfUfUf aagacuasus {invAb}	3030	usAfsgucUfUfaaacaAfuGfugcsu su	3284
D-2047	[GalNAc3] susggaauUfcUfUfUfGf cucuacusus {invAb}	3031	asGfsuagaGfcaaaagaAfuUfccasu su	3285
D-2048	[GalNAc3] susuuggaAfuUfCfUfUf ugcucuasus {invAb}	3032	usAfsgagcAfaagaaUfCfcaaasu su	3286
D-2049	[GalNAc3] sgsacgguAfcAfUfAfAf uccuacacus {invAb}	3033	usGfsuaggAfuuauguAfcCfugcsu su	3287
D-2050	[GalNAc3] scsuguGfGfGfCfCfaa uuauaasus {invAb}	3034	asUfsuauaAfuUfggcccAfcAfcagsu su	3288
D-2051	[GalNAc3] sgsccacAfuUfUfGfUfu aagacuasus {invAb}	3035	usAfsgucUfUfaAfacaAfuGfugcsu su	3289
D-2052	[GalNAc3] susggaAfuUfCfUfUfug cucuacusus {invAb}	3036	asGfsuagaGfcaAagaAfuUfccasu su	3290
D-2053	[GalNAc3] susuugGfaAfuUfCfu ugcucuasus {invAb}	3037	usAfsgagcAfaAfgaaUfCfcaaasu su	3291
D-2054	[GalNAc3] sgsacgGfuAfcAfUfaa uccuacacus {invAb}	3038	usGfsuaggAfuUfauguAfcCfugcsu su	3292
D-2055	[GalNAc3] suscugaaUfGfAfCfAf Afaugaccs {invAb}	3039	asGfsuagaUfuuguCfcAfuucagas usu	3293
D-2056	[GalNAc3] susgaaAfuGfGfAfCfaa augaccusus {invAb}	3040	asGfsuagaUfuuguCfcAfuUfucasu su	3294
D-2057	[GalNAc3] susgcuguGfGfCfCfAf Afuuauaas {invAb}	3041	asUfsuauaAfuuggCfcAfcacagcas usu	3295
D-2058	[GalNAc3] scsuguGfuGfGfCfCfaa uuauaasus {invAb}	3042	asUfsuauaAfuuggCfcAfcAfcagsu su	3296
D-2059	[GalNAc3] susgcuguGfuGfGfCfCf auuuauaas {invAb}	3043	asUfsuauaAfuuggccAfcAfcagcas usu	3297
D-2060	[GalNAc3] scsuguguGfGfCfCfAfAf uuauaasus {invAb}	3044	asUfsuauaAfuuggCfcAfcAfcagsu su	3298
D-2061	[GalNAc3] scsuguguGfGfCfCfAfAf uuauaasus {invAb}	3045	asUfsuauaAfuGfGfCfCfAfcacagsu su	3299
D-2062	[GalNAc3] scscuccguaUfgUfUfUf Ufgaaagus {invAb}	3046	asAfsccuuCfaaaaCfaUfacgaggs usu	3300
D-2063	[GalNAc3] scsugUfaUfGfUfUfu gaaaguus {invAb}	3047	asAfsccuuCfaaaaCfaUfaCfagagsu su	3301
D-2064	[GalNAc3] scscaauggAfuUfUfAf Cfagcaacs {invAb}	3048	usGfsuugcUfguaaAfuCfccauggs usu	3302
D-2065	[GalNAc3] sasaugGfgAfUfUfUf acgaacacus {invAb}	3049	usGfsuugcUfguaaAfuCfcCfauusu su	3303
D-2066	[GalNAc3] scscaaugGfgAfUfUfUf acgaacacus {invAb}	3050	usGfsuugcUfguaaAfuCfcCfauuggs usu	3304
D-2067	[GalNAc3] sasauggAfuUfUfAfCf agcaacacus {invAb}	3051	usGfsuugcUfguaaAfuCfcCfauusu su	3305
D-2068	[GalNAc3] sasauggAfuUfUfAfCf agcaacacus {invAb}	3052	usGfsuugcUfguaAfuCfccauguusu su	3306
D-2069	[GalNAc3] sgsuuugcUfuAfAfUf Cfguauugs {invAb}	3053	usCfscuaCfguauAfaGfagcaacs usu	3307

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2070	[GalNAc3] susugcUfcUfUfAfAfucguauggasus {invAb}	3054	usCfscauaCfgauuAfaGfaGfcaasu su	3308
D-2071	[GalNAc3] sgsuuugcUfcUfUfAfAfucguauggs {invAb}	3055	usCfscauaCfgauuaaGfaGfcaacs usu	3309
D-2072	[GalNAc3] susugcucUfuAfAfUfCf guauggasus {invAb}	3056	usCfscauaCfgauuAfaGfaGfcaasu su	3310
D-2073	[GalNAc3] susugcUfcUfUfAfAfucguauggasus {invAb}	3057	usCfscauaCfgauuaaGfaGfcaasu su	3311
D-2074	[GalNAc3] susugcucUfuAfAfUfCf guauggasus {invAb}	3058	usCfscauaCfgaUfuAfaGfagcaasu su	3312
D-2075	[GalNAc3] sasaucagauCfaUfUfAfCfcaguuas {invAb}	3059	asUfsaacuGfguaaUfgAfucugauus usu	3313
D-2076	[GalNAc3] suscagaucaUfuAfCfCfAfguuagcs {invAb}	3060	asGfscuaaCfugguAfaUfgaucugas usu	3314
D-2077	[GalNAc3] suscagAfuCfAfUfUfacaguuasus {invAb}	3061	asUfsaacuGfguaaUfgAfuCfugasu su	3315
D-2078	[GalNAc3] sasgauCfaUfUfAfCfca guuagcsus {invAb}	3062	asGfscuaaCfugguAfaUfgAfucusu su	3316
D-2079	[GalNAc3] sgscacAfuUfUfGfUfuuaagacuasus {invAb}	3063	usAfsugcuUfaaacAfaAfuGfugcsu su	3317
D-2080	[GalNAc3] sasagcacAfuUfUfGfUfuuaagacus {invAb}	3064	usAfsugcuUfaaacAfaAfuGfugcuus usu	3318
D-2081	[GalNAc3] sgscacauUfuGfUfUfUfaagacuasus {invAb}	3065	usAfsugcuUfaaacAfaAfuGfugcsu su	3319
D-2082	[GalNAc3] sgscacAfuUfUfGfUfuuaagacuasus {invAb}	3066	usAfsugcuUfaaacAfaAfuGfugcsu su	3320
D-2083	[GalNAc3] sgscacauUfuGfUfUfUfaagacuasus {invAb}	3067	usAfsugcuUfaaAfcAfaAfuugcsu su	3321
D-2084	[GalNAc3] sgscacauuuGfuUfUfAfAfgacuauas {invAb}	3068	asAfsuaguCfuuaaAfcAfaaуггcs usu	3322
D-2085	{DCA-sC6} cuguGfuGfGfCfCfaauuaaau sus {invAb}	3069	asUfsuauaAfuuggccAfcAfcagsus u	3323
D-2086	[GalNAc3] sgaaucaAfgAfUfGfGfugaagsas {invAb}	3070	asUfscuucAfccauCfuUfgauucscs u	3324
D-2087	{DCA-sC6} gaaucaAfgAfUfGfGfugaagsas {invAb}	3071	asUfscuucAfccauCfuUfgauucscs u	3325
D-2088	{DCA-sC6} guuugcUfcUfUfAfAfucguauggs {invAb}	3072	usCfscauaCfgauuaaGfaGfcaacs usu	3326
D-2089	{DCA-sC6} cccucgUfaUfGfUfUfuugaaagus {invAb}	3073	asAfsuuUfCfaaaacaUfaCfгaggг susu	3327
D-2090	[GalNAc3] sgsacgguaCfaUfUfAfAfuccuacacus {invAb}	3074	usGfsuaggAfuuaFuguAfcCfгucsu su	3328
D-2091	[GalNAc3] scsuguGfuGfGfCfCfaauuaaauus {invAb}	3075	asUfsuauaAfuuggccAfcAfcagsus u	3329
D-2092	[GalNAc3] sasaugGfgAfUfUfUfacagcaacacus {invAb}	3076	usGfsuugcUfguaaaUfcCfauus u	3330
D-2093	[GalNAc3] sasagcacauUfuGfUfUfUfaagacus {invAb}	3077	usAfsugcuUfaaacAfaAfuггcuus usu	3331
D-2094	csgsaagaCfaGfCfGfAfcaccaugcs {invAb}	3078	asGfscaugGfggucgCfгUfcuucgs usu	3332
D-2095	csasuggaCfгGfCfCfGfguaacaaas {invAb}	3079	asUfsuuguUfacgggCfгUfcuugcs usu	3333

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2096	usgscacaUfgCfGfCfAfCfGcgcaugs {invAb}	3080	asCfsaugcGfGcgugcgCfaUfgugcas usu	3334
D-2097	gscsacauGfCfGfCfAfCfGcgcaugs {invAb}	3081	usGfscaugCfGcgugcGfCfAfugugcs usu	3335
D-2098	csascaugCfGfCfAfCfGfGcgcaugs {invAb}	3082	asUfsgcauGfGcgugCfGfCfAugugs usu	3336
D-2099	ascsaugcGfCfAfCfGfCfGcgcaugs {invAb}	3083	asGfsugcaUfgcgugcGfCfGfcaugs usu	3337
D-2100	uscsugcaCfuAfAfAfAfucacccaaas {invAb}	3084	asUfsuuggGfGauuuuAfgUfgcagagas usu	3338

[0187] The methods below were applied to synthesize and purify the RNAi constructs identified in **Table 1** and **Table 2**.

Synthesis

[0188] RNAi constructs were synthesized using solid phase phosphoramidite chemistry. Synthesis was performed on a MerMade synthesizer (Bioautomation). Various chemical modifications, including 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, inverted abasic nucleotides, and phosphorothioate internucleotide linkages, were incorporated into the molecules. The RNAi constructs were generally formatted to be duplexes of 19-21 base pairs when annealed with either no overhangs (double bluntmer) or one or two overhangs of 2 nucleotides at the 3' end of the antisense strand and/or the sense strand. For *in vivo* studies, the sense strands of the RNAi constructs were conjugated to either a trivalent N-acetyl-galactosamine (GalNAc) moiety or a hydrophobic moiety (*e.g.*, palmitic acid or docosanoic acid) as described further below.

[0189] The materials used in the synthesis of RNAi constructs included:

- Acetonitrile (DNA Synthesis Grade, AXO152-2505, EMD)
- Capping Reagent A (80:10:10 (v/v/v) tetrahydrofuran/lutidine/acetic anhydride, BIO221/4000, EMD)
- Capping Reagent B (16% 1-methylimidazole/tetrahydrofuran, BIO345/4000, EMD)
- Activator Solution (0.25 M 5-(ethylthio)-1H-tetrazole (ETT) in acetonitrile, BIO152/0960, EMD)
- Detritylation Reagent (3% dichloroacetic acid in dichloromethane, BIO830/4000, EMD)

- Oxidation Reagent (0.02 M iodine in 70:20:10 (v/v/v) tetrahydrofuran/pyridine/water, BIO420/4000, EMD)
- Diethylamine solution (20% DEA in acetonitrile, NC0017-0505, EMD)
- Thiolation Reagent (0.05 M 5-N-[(dimethylamino)methylene]amino-3H-1,2,4-dithiazole-3-thione (BIOSULII/160K) in pyridine)
- 5'-Aminohexyl linker phosphoramidite and 2'-methoxy and 2'-fluoro phosphoramidites of adenosine, guanosine, and cytosine (Thermo Fisher Scientific), 0.10 M in acetonitrile over Molecular Trap Packs (0.5g per 30 mL, Bioautomation)
- 2'-methoxy-uridine phosphoramidite (Thermo Fisher Scientific), 0.10 M in 90:10 (v/v) acetonitrile/DMF over Molecular Trap Packs (0.5g per 30 mL, Bioautomation)
- 2'-deoxy-reverse abasic phosphoramidite (ChemGenes), 0.10 M in acetonitrile over Molecular Trap Packs (0.5g per 30 mL, Bioautomation)
- CPG Support (Hi-Load Universal Support, 500A (BH5-3500-G1), 79.6 $\mu\text{mol/g}$, 0.126 g (10 μmol)) or 1 μmol Universal Synthesis Column, 500A, Pipette Style Body (MM5-3500-1, Bioautomation)
- Ammonium hydroxide (concentrated, J. T. Baker)

[0190] Reagent solutions, phosphoramidite solutions, and solvents were attached to the MerMade instrument. The columns containing solid support (BioAutomation, Universal Support, 500Å) were affixed to the instrument and washed with acetonitrile. The synthesis was started using the Poseidon software. The phosphoramidite and reagent solution lines were purged. The synthesis was accomplished by repetition of the deprotection/coupling/ capping /oxidation /capping synthesis cycle. To the solid support was added detritylation reagent to remove the 5'-dimethoxytrityl (DMT) protecting group. The solid support was washed with acetonitrile. To the support was added phosphoramidite (4 eq.) and activator solution (20 eq.) to couple the incoming nucleotide to the free 5'-hydroxyl group. The coupling reaction (6 min) was repeated twice. The support was washed with acetonitrile and then added capping reagents A and B to terminate any unreacted oligonucleotide chains. The support was washed with acetonitrile. To the support was added oxidation or thiolation reagent to convert the phosphite triester to the phosphate triester or phosphorothioate. The oxidation reaction was increased from 3 to 5 min. To the support was added capping reagents A and B to dehydrate the support and terminate any unreacted oligonucleotide chains. The solid support was washed with acetonitrile. After the final reaction cycle, the resin was first treated with diethylamine solution to remove the 2-cyanoethyl protecting groups from the

phosphate backbone. The support was washed with acetonitrile and the DMT group removed from antisense strands. The 5' termini of sense strands were left 5'-monomethoxytrityl (MMT) protected.

Analysis of Crude Synthesized RNAi Constructs

[0191] Crude samples were prepared for ion-pairing (IP)-LCMS by making 20-fold dilutions into water (100µL final volume). Samples were analyzed by ion-pairing (IP)-LCMS on an Agilent 1290 analytical HPLC. Samples were eluted from a Waters Xbridge BEH OST C18 column (1.7 µm, 2.1 x 50 mm) using a linear gradient of acetonitrile in 15.7 mM DIEA/50 mM HFIP over 3.5min with a flowrate of 400 µL/min.

Conjugation

[0192] To facilitate on-resin acylation or conjugation to GalNAc, the MMT group was removed by addition of deprotection solution consisting of trifluoroacetic acid with triisopropylsilane (2% each, v/v) in dichloromethane (DCM). The mixture was gently stirred and let stand for approximately 2-5 min. The mixture was initially gravity filtered until the solution no longer drained then filtered under vacuum. The process repeated 5-10 times until the filtrate was no longer colored. The resin was washed with DCM, neutralized with 5% DIEA in DCM (2 x 2 min), and washed again with DCM.

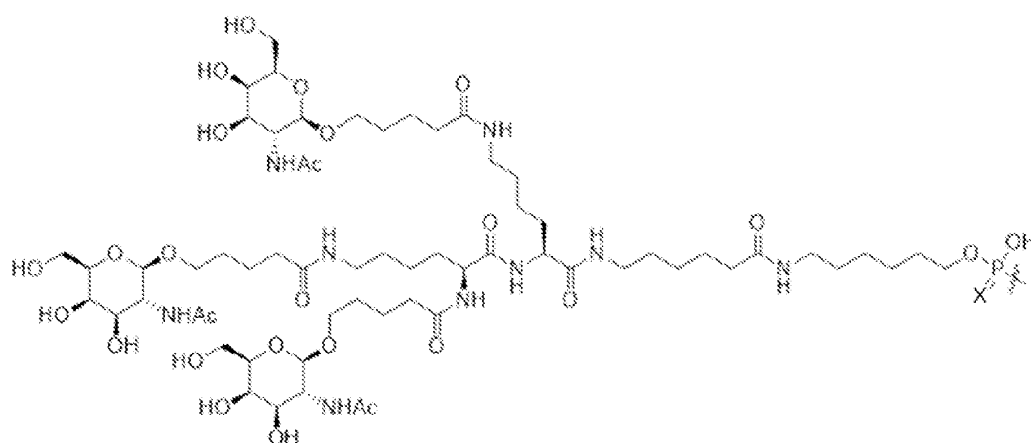
[0193] When conjugation to docosanoic acid (C22) was desired, docosanoic acid (10 molar equivalents relative to the resin) was dissolved in DCM (70 mM, 34.1 mg, 100 µmol, TCI) and TATU (500 mM DMSO) (32.2 mg, 100 µmol, ChemPep) was added (10 eq) followed by DIEA (500 mM DCM) (25.24 mg, 200 µmol, Aldrich) (20 eq). The solution was mixed and let stand to pre-activate for 5-10 min. The activated ester was added to the oligo-resin and the reaction vessels sealed. The reaction vessels were placed on a vortex mixer at 700 RPM for 14h at room temperature. The solution was drained, and the resin washed with DMF and DCM.

[0194] When conjugation to a palmitoyl group was desired, palmitic acid (10 molar equivalents relative to the resin) was dissolved in DCM (300 mM, 25.64 mg, 100 µmol, Aldrich) was transferred to a polypropylene tube (10 molar equivalents relative to the resin) and TATU (500 mM DMSO) (32.2 mg, 100 µmol, ChemPep) was added (10 eq) followed by DIEA (500 mM

DCM) (25.24 mg, 200 μ mol, Aldrich) (20 eq). The solution was mixed and let stand to pre-activate for 5-10 min. The activated ester was added to the oligo-resin and the reaction vessels sealed. The reaction vessels were placed on a vortex mixer at 700 RPM for 14h at room temperature. The solution was drained, and the resin washed with DMF and DCM.

[0195] When conjugation to GalNAc was desired, a solution of GalNAc3-Lys2-Ahx (67 mg, 40 μ mol) in DMF (0.5 mL) was prepared in a separate vial. GalNAc3-Lys2-Ahx, which has the structure shown as Formula VII below, was prepared with 1,1,3,3-tetramethyluronium tetrafluoroborate (TATU, 12.83 mg, 40 μ mol) and diisopropylethylamine (DIEA, 13.9 μ L, 80 μ mol). The activated coupling solution was added to the resin, and the column was capped and incubated at room temperature overnight. The resin was washed with DMF, DCM, and dried under vacuum.

Formula VII



[0196] In Formula VII, X = O or S. The squiggly line represents the point of attachment to the 5' terminal nucleotide of the sense strand of the RNAi construct. The GalNAc moiety was attached to the 5' carbon of the 5' terminal nucleotide of the sense strand except where an inverted abasic (invAb) deoxynucleotide was the 5' terminal nucleotide and linked to the adjacent nucleotide via a 5'-5' internucleotide linkage, in which case the GalNAc moiety was attached to the 3' carbon of the inverted abasic deoxynucleotide.

Cleavage from Resin

[0197] The columns were placed in a cleavage chuck and to the columns was added 1.2 mL of a solution containing 20% ethanol in concentrated ammonium hydroxide (1:4 v/v). The solvent was allowed to gravity drain through the solid support and filtrates collected into a 24 well plate. The cleavage process was repeated 3 times and the filtrates combined. The plate was sealed in a deprotection chuck and placed in an incubator at 55°C and let mix at 200 RPM for 20 h. The chuck/plate were let cool to room temperature and samples were taken for LCMS. The plate was placed in a Genevac HT4X and the samples concentrated for 2 hr leaving approximately 2 mL of concentrate

RP-HPLC Purification of Lipid-Conjugated Oligos

[0198] The crude oligo was purified by RP-HPLC using a Phenomenex Oligo-RP C18 column (5µm, 10 x 250 mm) with a flowrate of 6 mL/min. The mobile phase consisted of 0.02M ammonium bicarbonate with 5% acetonitrile (Buffer-A) & 75% acetonitrile (Buffer-B). The fractions were pooled for desalt as described below.

Anion Exchange Purification of Oligos

[0199] The antisense and GalNAc-conjugated sense strands were purified by anion exchange (AEX) chromatography. Oligos were eluted from a two Tosoh TSK Gel SuperQ-5PW columns in series (21 x 150 mm, 13 µm) with a flowrate of 8 mL/min. using a linear gradient of 1 M sodium bromide in 20 mM sodium phosphate, 15% acetonitrile, pH 8.5. Samples were desalted and UV quantified as described below.

Desalt

[0200] The pooled fractions were desalted by size exclusion chromatography on a GE Akta Pure using a GE Hi-Prep 26/10 column and 19.9% EtOH mobile phase. Desalted samples were analyzed by IP-LCMS, quantified by UV (Nanodrop), and lyophilized in a Genevac S3-HT12.

Final QC

[0201] Samples were analyzed by ion-pairing (IP)-LCMS on an Agilent 1290 analytical HPLC. Samples were eluted from a Waters Xbridge BEH OST C18 column (1.7 μ m, 2.1 x 50 mm) using a linear gradient of acetonitrile in 15.7 mM DIEA/50 mM HFIP over 6.5 min. with a flowrate of 400 μ L/min.

Annealing

[0202] Single strands were reconstituted in PBS at 2 mM and quantified by UV. Single strands were diluted to 1 mM in PBS and equal volumes combined to anneal the corresponding duplex. The duplex was annealed at 90°C for 5 min and allowed to cool to room temp. Duplex formation was monitored by analytical AEX and single strands titrated as necessary.

Example 4: *In Vitro* Evaluation of *FAM13A* siRNA Molecules in a Cell-Based Assay

[0203] A panel of fully chemically modified siRNAs from Example 3 were prepared and tested for potency and selectivity of *FAM13A* mRNA knockdown *in vitro*. Each siRNA duplex consisted of two strands, the sense or 'passenger' strand and the antisense or 'guide' strand.

[0204] RNA FISH (fluorescence in situ hybridization) assay was carried out to measure *FAM13A* mRNA knockdown by test siRNAs. HUH-7 cells (Sekisui Xenotech JCRB0403) were cultured in Eagle's Minimum Essential Medium (EMEM) (ATCC® 30-2003™) supplemented with 10% fetal bovine serum (FBS, Sigma) and 1% penicillin-streptomycin (P-S, Corning). siRNAs were transfected into cells by reverse transfection using Lipofectamine RNAiMAX transfection reagent (Thermo Fisher Scientific). 1 μ L of test siRNAs (in 10 data points for dose with 1:3 dilution starting at 500 nM final concentration) or phosphate-buffered saline (PBS) vehicle and 4 μ L of plain EMEM without supplements were added to PDL-coated CellCarrier-384 Ultra assay plates (PerkinElmer) by a Bravo automated liquid handling platform (Agilent). 5 μ L of Lipofectamine RNAiMAX (Thermo Fisher Scientific), pre-diluted in plain EMEM without supplements (0.06 μ L of RNAiMAX in 5 μ L EMEM), was then dispensed into the assay plates by a Multidrop Combi reagent dispenser (Thermo Fisher Scientific). After 20-minute incubation of the siRNA/RNAiMAX mixture at room temperature (RT), 30 μ L of HepG2 cells (2000 cells per well) in EMEM supplemented with 10% FBS and 1% P-S were added to the transfection

complex using a Multidrop Combi reagent dispenser. The assay plates were incubated at RT for 20 mins prior to being placed in an incubator. Cells were incubated for 72 hrs. at 37 °C and 5% CO₂.

[0205] The RNA FISH assay was performed 72 hours after siRNA transfection, using the manufacturer's assay reagents and protocol (QuantiGene® ViewRNA HC Screening Assay from Thermo Fisher Scientific) on an in-house assembled automated FISH assay platform. In brief, cells were fixed in 4% formaldehyde (Thermo Fisher Scientific) for 15 mins at RT, permeabilized with detergent for 3 mins at RT and then treated with protease solution for 10 mins at RT. Target-specific probes (ThermoFisher VA6-3175340-VC) or vehicle (target probe diluent without target probes as negative control) were incubated for 3 hours, whereas preamplifiers, amplifiers, and label probes were incubated for 1 hour each. All hybridization steps were carried out at 40 °C in a Cytomat 2 C-LIN automated incubator (Thermo Fisher Scientific).

[0206] After hybridization reactions, cells were stained for 30 mins with Hoechst and CellMask Blue (Thermo Fisher Scientific) and then imaged on an Opera Phenix high-content screening system (PerkinElmer). The images were analyzed using a Columbus image data storage and analysis system (PerkinElmer) to obtain the mean spot count per cell. The mean spot count per cell was normalized using the high (PBS with target probes) and low (PBS without target probes) control wells. The high and low controls have normalized values of 100 and 0, respectively. The normalized values against the test siRNA concentrations were fitted to a 4-parameter sigmoidal model using Genedata Screener data analysis software (Genedata, Basel, Switzerland) to obtain IC₅₀ values and maximum activity.

[0207] To verify and compare results, some of the siRNA duplexes were analyzed more than once using the above assay.

[0208] The results of the assays are shown in **Table 3**. *FAM13A* knockdown provides a percentage of knockdown compared to control samples. Where an siRNA duplex was tested more than once, each test is shown as a separate row in **Table 3** as different "runs" of the assay. Negative values indicate a decrease in *FAM13A* mRNA levels. Undefined means the Genedata Screener software could not fit a curve.

TABLE 3: *In vitro* inhibition of human *FAM13A* mRNA in Hep3B cells

Duplex No.	Run No.	IC ₅₀ (nM)	Max <i>FAM13A</i> knockdown (%)
1001		5.74	-49.1
1002		5.95	-46.1

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1003		> 500	-40.0
1004		3.49	-38.7
1005	Run 1	Undefined	-33.0
1005	Run 2	6.51	-43.9
1005	Run 3	1.97	-50.6
1006		> 500	-1.6
1007		2.4	-53.3
1008		1.36	-52.7
1009		> 500	-15.3
1010		16.5	-65.7
1011		5.85	-65.5
1012		13	-51.9
1013	Run 1	5.44	-67.8
1013	Run 2	4.93	-63.9
1014		4.4	-72.9
1015		3.99	-74.7
1016		2.33	-67.0
1017		3.34	-75.8
1018		6.84	-31.9
1019		2.59	-78.9
1020		5.91	-81.0
1021		4.43	-52.3
1022		5.48	-70.1
1023		4.08	-80.3
1024		2.47	-77.4
1025		6.26	-81.4
1026		Undefined	-38.7
1027		> 500	-2.1
1028		3.77	-81.2
1029		3.51	-70.5
1030		16	-50.6
1031		2.67	-43.7
1032		> 500	-25.7
1033		Undefined	-37.0
1034		3.92	-74.3
1035	Run 1	1.95	-41.4
1035	Run 2	9.61	-31.8
1036		Undefined	-39.3
1037		1.23	-77.7
1038	Run 1	4.72	-80.8
1038	Run 2	6.55	-76.5
1038	Run 3	4.56	-71.9
1039		14.1	-69.2
1040		2.55	-82.9

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1041		3.91	-71.3
1042		8.71	-72.6
1043		2.46	-78.6
1044		4.49	-77.6
1045		1.47	-79.6
1046		5.89	-65.6
1047		6.16	-73.2
1048		4.7	-69.8
1049		6.59	-76.0
1050		5.19	-86.4
1051		6.74	-68.7
1052		3.77	-69.5
1053		18.9	-62.2
1054		5.86	-72.6
1055		Undefined	-60.1
1056		5.25	-55.4
1057		4.01	-76.3
1058		4.31	-74.9
1059		10.5	-71.2
1060		4.44	-65.1
1061		11.2	-82.2
1062		5.75	-95.0
1063		16.5	-68.1
1064		11.3	-56.1
1065		7.73	-55.6
1066		> 500	-18.5
1067		4.9	-68.4
1068		Undefined	-36.8
1069		20.2	-72.1
1070		3.7	-84.3
1071		2.78	-52.0
1072		2.72	-75.8
1073		> 500	-9.7
1074		4.12	-76.3
1075		1.62	-81.9
1076		5.71	-78.7
1077		2.92	-60.1
1078		3.14	-71.9
1079		4.53	-49.4
1080		8.67	-79.1
1081		3.97	-82.1
1082		2.73	-75.3
1083		2.48	-72.7
1084		2.45	-60.5

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1085		2.93	-63.7
1086		11.8	-81.7
1087		8.19	-77.0
1088		Undefined	-28.5
1089		> 500	4.8
1090		3.22	-75.1
1091		3.5	-82.7
1092		2.81	-70.1
1093		7.01	-66.3
1094	Run 1	27.7	-70.5
1094	Run 2	28	-80.9
1094	Run 3	6.51	-72.5
1095		14.2	-76.8
1096		2.98	-81.7
1097		3.39	-79.6
1098		6.78	-56.7
1099		> 500	-10.8
1100		2.42	-74.3
1101		3.49	-64.2
1102	Run 1	19.9	-54.2
1102	Run 2	18.8	-73.3
1102	Run 3	26.2	-70.0
1103		8.52	-59.5
1104		5.59	-79.1
1105		6.73	-38.8
1106		3.44	-44.4
1107		6.25	-88.4
1108		17.6	-42.5
1109		2.7	-44.7
1110		> 500	-23.1
1111		> 500	28.7
1112		4.27	-49.4
1113		4.03	-54.1
1114		5.59	-79.4
1115		15.8	-76.0
1116		6.72	-70.9
1117		52.3	-48.3
1118	Run 1	7.89	-58.9
1118	Run 2	1.42	-46.1
1119		5.51	-78.9
1120		4.28	-39.5
1121		> 500	0.0
1122		3.2	-74.3
1123		> 18.5	-24.6

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1124		2.95	-80.7
1125		8.53	-37.6
1126		1.86	-85.5
1127		3.94	-82.0
1128		2.92	-83.9
1129		> 500	-20.2
1130		> 500	7.8
1131		> 500	-22.7
1132		> 500	-0.8
1133		1.36	-38.9
1134		28.9	-55.7
1135		Undefined	-57.6
1136		> 500	-18.4
1137		> 167	-19.0
1138		9.39	-51.8
1139		> 500	-21.7
1140		2.61	-70.0
1141		1.48	-75.0
1142		3.9	-93.1
1143		3.55	-85.1
1144		6.44	-54.5
1145		3.35	-89.3
1146		27.9	-65.8
1147		1.83	-64.6
1148		4.16	-63.8
1149		3.07	-61.7
1150		3.65	-79.0
1151		12.3	-80.2
1152		7.56	-69.6
1153		6.31	-87.0
1154		4.23	-80.4
1155		24.9	-50.3
1156		6.43	-72.3
1157		> 500	3.9
1158		4.07	-76.2
1159		2.42	-78.5
1160		3.8	-31.4
1161		46.6	-43.0
1162		Undefined	-39.5
1163		6.17	-70.2
1164		20.5	-65.9
1165		19	-56.7
1166	Run 1	3.29	-72.1
1166	Run 2	3.27	-75.1

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1167		3.88	-79.2
1168		18.2	-58.5
1169		> 500	-15.2
1170		8.32	-58.4
1171		1.71	-84.5
1172		5.3	-90.7
1173		Undefined	-31.5
1174		3.51	-73.5
1175		12.8	-85.8
1176		> 500	8.5
1177		> 500	6.5
1178		> 500	11.2
1179	Run 1	> 500	11.6
1179	Run 2	Undefined	-34.1
1180		Undefined	-52.7
1181		10.2	-46.4
1182		26.2	-42.9
1183		5.71	-50.8
1184		> 500	21.2
1185		5.34	-65.0
1186		6.12	-47.3
1187		12.1	-64.8
1188		4.44	-45.4
1189		6.12	-42.4
1190		3.52	-74.4
1191		3.77	-67.5
1192		> 500	7.5
1193		16.6	-73.9
1194		33.4	-40.3
1195		9.77	-42.8
1196		> 500	-3.6
1197		9.38	-39.0
1198		9.41	-55.6
1199		6.51	-64.1
1200		> 500	-37.7
1201		> 500	-19.0
1202		> 167	-24.0
1203		11.6	-58.5
1204		0.593	-44.6
1205		6.19	-41.3
1206		3.99	-65.8
1207		7.26	-49.6
1208		3.91	-50.1
1209		2.55	-65.0

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1210		3.24	-84.2
1211		7.45	-77.8
1212		2.09	-82.1
1213		5.31	-83.7
1214		3.75	-84.4
1215		7.38	-84.0
1216		2.48	-74.3
1217		3.61	-56.6
1218		1.22	-79.7
1219	Run 1	5.07	-93.2
1219	Run 2	1.84	-88.2
1219	Run 3	11.1	-87.5
1220		3.89	-88.0
1221		1.97	-89.0
1222		12.9	-80.1
1223		57.4	-31.0
1224		2.42	-94.2
1225		3.62	-85.0
1226		3.12	-87.7
1227		1.62	-71.5
1228		> 500	-29.3
1229		> 500	-10.4
1230		5.23	-37.0
1231		> 500	8.4
1232		1.35	-78.4
1233		Undefined	-29.0
1234		4.38	-42.8
1235		3.42	-80.9
1236		7.33	-59.6
1237		8.96	-51.5
1238		2.27	-82.2
1239		2.74	-83.0
1240		2.33	-77.5
1241		2.77	-76.6
1242		6.71	-63.5
1243		2.29	-86.4
1244		46.8	-72.2
1245		18	-57.2
1246		> 500	20.7
1247		> 500	-0.9
1248		> 500	-20.0
1249		2.99	-57.3
1250		4.38	-72.3
1251		4.87	-53.2

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1252		2.3	-44.6
1253		3.27	-66.6
1254		Undefined	-53.4
1255		3.68	-51.2
1256		3.2	-57.2
1257		21.6	-57.7
1258		> 500	-15.1
1259		9.5	-76.0
1260		2.47	-67.7
1261		2.41	-63.4
1262		12.3	-78.3
1263		11.7	-83.0
1264		2.02	-77.8
1265		6.7	-62.0
1266		3.99	-70.0
1267		5.48	-69.7
1268		4.6	-55.0
1269		Undefined	-31.8
1270		5.58	-64.8
1271		6.02	-59.9
1272		2.32	-57.8
1273	Run 1	5.34	-78.2
1273	Run 2	4.11	-72.8
1274		1.88	-62.2
1275		2.35	-72.0
1276		1.57	-72.1
1277		3.79	-79.0
1278		1.81	-73.0
1279		1.81	-71.1
1280		1.44	-64.8
1281		1.95	-67.7
1282		4.44	-71.4
1283		2.71	-77.3
1284	Run 1	3.55	-67.3
1284	Run 2	3.28	-72.0
1285		8.75	-66.3
1286		4.65	-78.9
1287		10.3	-76.5
1288		4.76	-74.0
1289		5.13	-68.5
1290		> 500	-22.5
1291		15.6	-52.2
1292		2.3	-37.6
1293		5.38	-63.6

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1294		> 500	-25.6
1295		6.02	-60.4
1296		5.31	-83.4
1297		1.62	-73.4
1298		Undefined	-30.6
1299		2.32	-63.6
1300		1.19	-54.6
1301		1.78	-64.7
1302		4.79	-55.9
1303		1.83	-57.3
1304		9.89	-75.5
1305		4.19	-69.5
1306		3.65	-74.3
1307		12.6	-55.7
1308		12.6	-61.5
1309		2.83	-50.6
1310		4.94	-55.4
1311		1.74	-50.9
1312		4.25	-58.2
1313		5.44	-71.6
1314		2.28	-78.4
1315		3.42	-73.2
1316		8.48	-43.1
1317		Undefined	-39.4
1318		9.04	-51.5
1319		4.55	-58.6
1320		5.69	-63.2
1321		Undefined	-37.6
1322		4.82	-56.4
1323	Run 1	Undefined	-49.9
1323	Run 2	> 500	-8.8
1324		9.43	-50.7
1325		16.3	-51.9
1326		15.8	-42.6
1327		7.09	-54.5
1328	Run 1	22.5	-63.9
1328	Run 2	34.1	-47.5
1329		> 500	27.5
1330		4.47	-39.0
1331		11.6	-83.7
1332		5.14	-56.8
1333		3.43	-44.6
1334		2.79	-65.6
1335	Run 1	5.17	-55.2

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1335	Run 2	5.78	-58.2
1336	Run 1	5.63	-54.8
1336	Run 2	Undefined	-50.7
1337		13.9	-68.8
1338		13	-61.6
1339		12.7	-66.6
1340		2.85	-68.3
1341	Run 1	3.41	-68.1
1341	Run 2	1.97	-64.3
1342	Run 1	0.113	-76.1
1342	Run 2	3.75	-81.6
1343		3.08	-78.4
1344		14.1	-87.2
1345		2.92	-84.4
1346		9.04	-84.3
1347		6.71	-75.3
1348		11.4	-75.0
1349		8.35	-57.0
1350	Run 1	9.86	-79.2
1350	Run 2	6.72	-74.6
1351		6.46	-72.8
1352	Run 1	Undefined	-31.0
1352	Run 2	23.5	-36.5
1353		8.35	-57.1
1354		Undefined	-32.8
1355		> 500	-1.4
1356		> 500	-19.1
1357		Undefined	-53.8
1358		10.9	-63.6
1359		7.91	-57.3
1360		10.5	-63.8
1361		3.53	-37.2
1362		> 500	-3.7
1363		> 500	-19.6
1364	Run 1	Undefined	-36.2
1364	Run 2	40.9	-40.0
1365		26.2	-50.3
1366	Run 1	4.25	-50.8
1366	Run 2	1.76	-52.4
1367		> 500	23.8
1368		Undefined	-39.2
1369		> 500	-32.2
1370		16.3	-49.5
1371		Undefined	-51.8

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1372		43.5	-73.6
1373		4.18	-60.3
1374		11.9	-62.0
1375		9.86	-61.2
1376		7.68	-61.3
1377		4.8	-50.1
1378	Run 1	2.32	-61.0
1378	Run 2	1.91	-65.2
1379		7.06	-59.1
1380		14.4	-64.5
1381	Run 1	Undefined	-31.4
1381	Run 2	> 500	-3.3
1382		6.69	-36.3
1383		> 500	-14.2
1384		24.7	-72.1
1385		7.57	-65.4
1386		5.78	-80.7
1387		13	-60.6
1388		18.1	-71.0
1389		6.48	-72.6
1390		1.79	-68.7
1391		3.7	-77.4
1392		7.54	-74.5
1393		2.25	-66.4
1394		4.24	-69.7
1395		2.06	-64.5
1396	Run 1	1.01	-69.3
1396	Run 2	0.597	-71.2
1397		2.63	-70.2
1398		5.5	-74.8
1399		1.93	-70.0
1400		3.14	-74.4
1401		9.12	-70.5
1402		Undefined	-43.8
1403		8.46	-70.3
1404		9.15	-75.0
1405		14.5	-63.9
1406		4.89	-60.6
1407		5.41	-52.0
1408	Run 1	2.46	-42.3
1408	Run 2	1.75	-67.0
1409		19.5	-64.5
1410		> 500	-28.7
1411		> 500	-14.2

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1412		> 500	-3.4
1413		4.59	-58.6
1414		Undefined	-43.9
1415		Undefined	-54.5
1416	Run 1	> 500	22.8
1416	Run 2	> 500	13.1
1417		> 500	0.5
1418		> 500	43.6
1419		77.3	-64.7
1420	Run 1	> 500	9.3
1420	Run 2	> 500	-4.3
1421	Run 1	7.54	-47.1
1421	Run 2	26.3	-43.0
1422		4.9	-53.3
1423		2.06	-54.0
1424		Undefined	-49.9
1425		3.79	-55.6
1426		Undefined	-45.5
1427		0.569	-46.2
1428		7.11	-72.7
1429		0.653	-63.3
1430		1.07	-66.8
1431		4.47	-70.9
1432		7.62	-63.1
1433		15.8	-66.5
1434		4.22	-64.0
1435		5.61	-57.6
1436		Undefined	-45.5
1437		Undefined	-39.1
1438		32.2	-69.4
1439		4.03	-48.3
1440		Undefined	-40.6
1441	Run 1	13.7	-45.1
1441	Run 2	Undefined	-61.3
1442		1.48	-57.2
1443		4.08	-70.3
1444		6.59	-68.0
1445		5.2	-44.5
1446	Run 1	16.2	-77.6
1446	Run 2	18	-82.3
1447		3.61	-64.6
1448		8.4	-44.0
1449		> 500	-21.8
1450		28.4	-67.6

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1451		8.59	-57.0
1452		7.12	-62.2
1453		3.53	-62.4
1454	Run 1	16.5	-76.5
1454	Run 2	6.29	-51.7
1455		3.26	-61.8
1456		2.62	-58.2
1457		9.92	-55.2
1458		6.52	-80.4
1459	Run 1	1.57	-64.4
1459	Run 2	4.65	-63.4
1460		3.82	-61.8
1461		4.83	-80.9
1462		3.11	-82.0
1463		3.2	-78.5
1464		3.85	-72.9
1465		2.94	-79.1
1466		2.73	-70.7
1467		2.78	-67.1
1468		3.24	-64.2
1469		8.53	-71.2
1470		7.92	-73.5
1471		4.63	-67.0
1472		7.7	-66.0
1473		5.15	-67.9
1474		7.04	-76.4
1475		3.17	-74.5
1476		1.86	-72.8
1477		6.87	-62.9
1478		19.1	-61.4
1479		3.31	-79.0
1480		5.12	-74.9
1481		2.39	-74.5
1482		7.5	-69.0
1483		3.6	-70.0
1484		1.97	-72.2
1485		5.47	-79.8
1486		6.5	-73.7
1487		5.19	-59.7
1488		1.78	-81.0
1489		1.99	-61.5
1490		0.976	-60.4
1491		2.58	-73.5
1492		0.878	-81.6

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1493		3.86	-81.7
1494		2.53	-64.3
1495		3.27	-75.3
1496		1.24	-90.2
1497		1.26	-81.8
1498		1.44	-86.2
1499		1.14	-69.0
1500	Run 1	1.85	-75.9
1500	Run 2	1.07	-71.1
1500	Run 3	1.73	-80.0
1501		1.31	-81.6
1502		1.91	-71.2
1503		4.05	-77.5
1504		3.64	-75.5
1505		1.22	-76.0
1506		0.925	-57.1
1507	Run 1	2.22	-74.5
1507	Run 2	2.84	-72.6
1507	Run 3	3.58	-64.9
1508		3.57	-73.6
1509	Run 1	2.55	-76.4
1509	Run 2	3.9	-72.5
1510	Run 1	0.449	-73.0
1510	Run 2	0.715	-65.6
1511		3.23	-74.2
1512	Run 1	2.08	-77.9
1512	Run 2	2.54	-62.8
1513		4.14	-68.2
1514	Run 1	5.72	-67.8
1514	Run 2	5.64	-77.0
1515		2.7	-75.4
1516		2.5	-66.4
1517		2.83	-66.8
1518	Run 1	1.91	-66.6
1518	Run 2	5.63	-70.0
1518	Run 3	3.13	-76.4
1519		3.52	-63.2
1520		1.05	-70.7
1521		1.41	-56.4
1522		2.37	-68.2
1523		0.935	-68.4
1524	Run 1	4.41	-75.7
1524	Run 2	0.914	-70.3
1525		3.18	-62.3

Duplex No.	Run No.	IC50 (nM)	Max <i>FAM13A</i> knockdown (%)
1526		4.5	-66.1
1527		1.93	-73.6
1528		1.35	-79.4
1529		1.8	-72.2
1530	Run 1	0.598	-58.8
1530	Run 2	1.12	-69.6
1531		1.59	-76.4
1532		2.1	-67.7
1533		2.56	-41.1
1534		5.96	-57.4
1535	Run 1	1.75	-61.3
1535	Run 2	0.449	-58.7
1536		14.7	-66.5
1537		0.47	-44.4
1538		2.27	-45.6

Example 5: *In vivo* Efficacy of siRNA Molecules in an AAV Human FAM13A Mouse Model

[0209] To assess the efficacy of the *FAM13A* siRNA molecules, the top performing *FAM13A* siRNA molecules from the *in vitro* activity assays described in Example 4 were evaluated for *in vivo* efficacy and durability in a C57BL/6 mouse model. Broadly, the *FAM13A* siRNA molecules were administered to mice expressing a portion of the human *FAM13A* gene. For these experiments, the sense strand in each tested siRNA molecule was conjugated to the trivalent GalNAc moiety shown in Formula VII or to docosanoic acid (C22), using the methods described in Example 3. In some experiments, *FAM13A* siRNA molecules were evaluated for *in vivo* efficacy and durability with altered chemical modification patterns.

[0210] The mouse model used was an AAV human FAM13A mouse model. In advance of siRNA injection, 10-12-week-old C57BL/6 mice (The Jackson Laboratory) were fed standard chow (Harlan, 2020× Teklad global soy protein-free extruded rodent diet). Female C57Bl6 mice 10-14 weeks old were intravenously (i.v.) injected with an adeno-associated virus (AAV) engineered to coexpress both eGFP and a portion of the human *FAM13A* gene transcript. The construct used was: AAV-hFAM13A-1 (encoding nucleotides 1200-2900 of SEQ ID NO: 1; "AAV1"), AAV-hFAM13A-2 (encoding nucleotides 2800-4500 of SEQ ID NO: 1; "AAV2"), AAV-hFAM13A-3 (encoding nucleotides 4400-6100 of SEQ ID NO: 1; "AAV3"), AAV-hFAM13A-9span (encoding selected portions of SEQ ID NO: 1 that contain SEQ ID NOs: 15,

24, 125, 127, 222, 233, 481, 498, 503, 504, and 513, connected by linkers; "AAV-9span"), or AAV-FAM13A-22span (encoding selected portions of SEQ ID NO: 1 that contain SEQ ID NOs: 15, 24, 41, 125, 127, 150, 164, 222, 233, 406, 448, 466, 470, 481, 498, 503, 504, 513, 523, 526, 527, 533, and 534, connected by linkers; "AAV-22span").

[0211] Each mouse was injected with a single AAV at a dose of 1×10^{12} genome copies (GC) per animal. Two weeks following AAV injection, mice received a single subcutaneous (s.c.) injection of buffer (PBS) or the *FAM13A* siRNA molecule at a dose of 0.5 mg/kg, 1 mg/kg, 3 mg/kg, 5 mg/kg, 15 mg/kg, or 20 mg/kg body weight in PBS (n = 3 or 4 mice per group, as indicated below).

[0212] Liver and subcutaneous white adipose tissue (ScWAT) were collected 2 or 4 weeks following siRNA administration and analyzed. RNA from harvested animal tissues was processed for qPCR analysis. RNA was isolated from 50-100 mg tissue using RNeasy 96 universal tissue kit RNA isolation protocol following manufacturer's instructions (Qiagen) or using a KingFisher Apex system and the MagMAX mirVana Total RNA Isolation Kit according to the manufacturer's instructions (ThermoFisher). Real-time PCR was performed using TaqMan® RNA-to-Ct™ 1-Step Kit following manufacturer's instructions (ThermoFisher) with 50 ng RNA per reaction and the following primer probe sets: (1) eGFP1 Forward primer: CTATGTGCAGGAGAGAACCATC (Sense; SEQ ID NO: 2798); Reverse primer: GCCCTTCAGCTCGATTCTATT (Antisense; SEQ ID NO: 2799); Probe: 5'-6FAM-TACAAGACCCGCGCTGAAGTCAAG TAMRA-3' (Sense; SEQ ID NO: 2800); (2) eGFP2 Forward primer: TCATCTGCACCACTGGAAAG (Sense; SEQ ID NO: 2801); Reverse primer: CTGCTTCATATGGTCTGGGTATC (Antisense; SEQ ID NO: 2802); Probe: 5'-6FAM CCAACACTGGTCACTACCCCTCACC TAMRA-3' (Sense; SEQ ID NO: 2803); (3) BGH Forward primer: 5'-GCCAGCCATCTGTTGT-3' (SEQ ID NO: 2804); Reverse primer: 5'-GGAGTGGCACCTTCCA-3' (SEQ ID NO: 2805); Probe: 5'-6FAM-TCCCCCGTGCCTTCCTTGACC TAMRA-3' (Sense; SEQ ID NO: 2806); and (4) *mPpib* TaqMan® gene expression assay (Mm00478295 Thermo Fisher). Knockdown of mRNA levels were quantified using primer sets targeting either the eGFP sequence in the 5' end of the construct (*i.e.*, eGFP primer set #1 or eGFP primer set #2) or the bovine growth hormone polyadenylation signal present in the viral mRNA (BGHpA primer set) at the 3' end of construct. The knockdown efficiency of the siRNA triggers was determined using semi-quantitative real-time polymerase chain reactions on a QuantStudio 7 Flex real time thermocycler. Gene

expression was calculated using the $\Delta\Delta C_t$ approach while utilizing cyclophilin (PPIB) as the reference gene. A percentage change in human *FAM13A* mRNA in liver or ScWAT for each animal was calculated relative to the level of human *FAM13A* mRNA in the liver or ScWAT of control animals. The control animals used to calculate the percentage change expressed the same human *FAM13A* mRNA but received the buffer only injection in place of an siRNA injection.

[0213] Results of the studies in the AAV-FAM13A mouse model with different *FAM13A* siRNA molecules are shown in **Tables 4-17** below. Data are expressed as average percent change from control at week 4 or 6 of each study (*i.e.*, 2 or 4 weeks after siRNA injection as indicated) for each treatment group (n = 3 or 4 animals/group as indicated). The trigger family refers to the first nucleotide in the range of nucleotides of SEQ ID NO: 1 that is targeted by a given siRNA molecule. If a *FAM13A* siRNA molecule has the same trigger family designation as another *FAM13A* siRNA molecule but differs in duplex number, then the two molecules have the same core sequence (*i.e.*, the siRNA molecules target the same region of the *FAM13A* transcript) but differ in chemical modification pattern as detailed in **Table 2**. A chart of a subset of this data is also shown in **FIGS. 8A-8D**.

TABLE 4 – siRNA Efficacy in Liver 4 Weeks Following siRNA Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1545	1309	1	3	AAV1	GalNAc	-42.71 $\pm$ 5.394	-42.27 $\pm$ 6.616	-43.14 $\pm$ 7.444
D-1570	1311	1	4	AAV1	GalNAc	-19.4 $\pm$ 22.73	-20.06 $\pm$ 23.37	-11.63 $\pm$ 22.15
D-1569	1338	1	4	AAV1	GalNAc	-11.79 $\pm$ 13.66	-9.43 $\pm$ 15.27	-2.923 $\pm$ 19.6
D-1543	1366	1	4	AAV1	GalNAc	6.133 $\pm$ 27.89	-6.135 $\pm$ 26.59	-0.283 $\pm$ 29.62
D-1542	1489	1	4	AAV1	GalNAc	35.76 $\pm$ 43.79	-9.96 $\pm$ 10.4	-3.553 $\pm$ 24.72
D-1553	1495	1	4	AAV1	GalNAc	23.78 $\pm$ 27.21	-19.31 $\pm$ 9.899	-22.28 $\pm$ 11.59
D-1576	1533	1	4	AAV1	GalNAc	24.96 $\pm$ 21.55	23.82 $\pm$ 31.71	-10.03 $\pm$ 7.092
D-1575	1558	1	4	AAV1	GalNAc	33.74 $\pm$ 49.25	13.87 $\pm$ 59.23	-6.078 $\pm$ 39.15
D-1574	1619	1	4	AAV1	GalNAc	40.25 $\pm$ 54.93	-34.08 $\pm$ 31.01	-36.47 $\pm$ 25.89
D-1554	1632	1	4	AAV1	GalNAc	-6.793 $\pm$ 44.9	-31.49 $\pm$ 35.05	-35.24 $\pm$ 28.19
D-1563	1896	1	4	AAV1	GalNAc	29.29 $\pm$ 45.3	-8.05 $\pm$ 32.28	-13.19 $\pm$ 25.73
D-1568	2066	1	4	AAV1	GalNAc	21.07 $\pm$ 48.89	-13.38 $\pm$ 36.29	-18.64 $\pm$ 22.78
D-1567	2070	1	4	AAV1	GalNAc	-23.67 $\pm$ 22.87	-21.89 $\pm$ 19.75	-29.35 $\pm$ 12.26
D-1550	2078	1	4	AAV1	GalNAc	-25.78 $\pm$ 25.17	-15.87 $\pm$ 29.37	-19.85 $\pm$ 24.99
D-1549	2080	1	4	AAV1	GalNAc	-44.66 $\pm$ 24.88	-37.31 $\pm$ 28.36	-33.42 $\pm$ 23.16
D-1544	2144	1	4	AAV1	GalNAc	-28.04 $\pm$ 10.28	-23.07 $\pm$ 13.65	-36.02 $\pm$ 7.789
D-1565	2146	1	4	AAV1	GalNAc	-1.398 $\pm$ 16.51	3.045 $\pm$ 16.82	-17.82 $\pm$ 16.44
D-1539	2151	1	3	AAV1	GalNAc	-32.85 $\pm$ 3.319	-27.82 $\pm$ 3.752	-35.23 $\pm$ 5.315
D-1573	2263	1	4	AAV1	GalNAc	-39.7 $\pm$ 15.67	-37.2 $\pm$ 17.08	-60.35 $\pm$ 10.09
D-1547	2266	1	4	AAV1	GalNAc	26.08 $\pm$ 32.18	5.21 $\pm$ 30.99	-37.34 $\pm$ 10.9
D-1556	2356	1	4	AAV1	GalNAc	62.47 $\pm$ 17.62	38.02 $\pm$ 19.36	-6.388 $\pm$ 11.61
D-1578	2360	1	4	AAV1	GalNAc	13.18 $\pm$ 30.52	-6.565 $\pm$ 26.66	-36.01 $\pm$ 14.96

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1581	2623	1	4	AAV1	GalNAc	-1.75 $\pm$ 5.865	-22.66 $\pm$ 7.519	-57.66 $\pm$ 5.097
D-1561	2887	1	4	AAV1	GalNAc	16.06 $\pm$ 19.7	-2.823 $\pm$ 18.4	-40.04 $\pm$ 5.249
D-1561	2887	1	3	AAV2	GalNAc	-23.87 $\pm$ 27.24	-20.19 $\pm$ 29.58	-36.03 $\pm$ 9.772
D-1620	2889	1	3	AAV1	GalNAc	40.81 $\pm$ 24.72	15.21 $\pm$ 24.44	-39.23 $\pm$ 10.53
D-1620	2889	1	3	AAV2	GalNAc	52.21 $\pm$ 70.23	47.44 $\pm$ 78.78	-39.71 $\pm$ 28.42
D-1560	2890	1	3	AAV2	GalNAc	-17.63 $\pm$ 29.61	-12.89 $\pm$ 40.28	-19.9 $\pm$ 24.63
D-1559	2893	1	3	AAV2	GalNAc	-27.2 $\pm$ 15.47	-25.82 $\pm$ 14.26	-38.13 $\pm$ 14.9
D-1558	2895	1	4	AAV2	GalNAc	-4.058 $\pm$ 33.95	-1.795 $\pm$ 34.36	-18.15 $\pm$ 26.74
D-1604	2923	1	4	AAV2	GalNAc	-18.23 $\pm$ 34.59	-14.74 $\pm$ 36.79	-27.4 $\pm$ 32.69
D-1541	2934	1	4	AAV2	GalNAc	-24.22 $\pm$ 24.87	-17.93 $\pm$ 26.09	-32.21 $\pm$ 24.58
D-1588	2937	1	4	AAV2	GalNAc	-6.588 $\pm$ 17.49	-2.385 $\pm$ 20.55	-20.34 $\pm$ 14.32
D-1619	2994	1	4	AAV2	GalNAc	-4.965 $\pm$ 29.63	-0.955 $\pm$ 31.88	-16.1 $\pm$ 23.98
D-1557	3000	1	4	AAV2	GalNAc	-38.01 $\pm$ 36.01	-38.72 $\pm$ 32.87	-45.02 $\pm$ 26.58
D-1579	3002	1	4	AAV2	GalNAc	-29.78 $\pm$ 13.38	-23.06 $\pm$ 12.39	-29.02 $\pm$ 11.54
D-1555	3014	1	4	AAV2	GalNAc	-33.3 $\pm$ 38.16	-33.52 $\pm$ 35.11	-27.61 $\pm$ 45.38
D-1586	3133	1	3	AAV2	GalNAc	-14.15 $\pm$ 24.03	-14.48 $\pm$ 32.6	-32.73 $\pm$ 22.7
D-1540	3184	1	4	AAV2	GalNAc	49.01 $\pm$ 85.72	47.35 $\pm$ 84.39	-15.39 $\pm$ 48
D-1552	3187	1	4	AAV2	GalNAc	-23.01 $\pm$ 40.18	-23.16 $\pm$ 41.09	-57.91 $\pm$ 23.56
D-1618	3189	1	4	AAV2	GalNAc	-15.8 $\pm$ 32.14	-11.32 $\pm$ 38.42	-55.8 $\pm$ 15.9
D-1585	3192	1	4	AAV2	GalNAc	-23.44 $\pm$ 22.34	-25.44 $\pm$ 24.5	-32.71 $\pm$ 15.77
D-1584	3283	1	4	AAV2	GalNAc	51.7 $\pm$ 81.84	48.43 $\pm$ 75.58	-28.35 $\pm$ 32.39
D-1580	3438	1	3	AAV2	GalNAc	37.73 $\pm$ 23.51	37.64 $\pm$ 14.87	-41.3 $\pm$ 12.94
D-1583	3498	1	4	AAV2	GalNAc	61.43 $\pm$ 51.09	70.94 $\pm$ 52.52	-40.57 $\pm$ 15.94
D-1582	3499	1	4	AAV2	GalNAc	3.543 $\pm$ 40.05	5.378 $\pm$ 33.08	-50.74 $\pm$ 20.44
D-1571	3569	1	4	AAV2	GalNAc	87.02 $\pm$ 48.83	105.1 $\pm$ 53.36	-23.29 $\pm$ 23.41
D-1551	3777	1	4	AAV2	GalNAc	32.18 $\pm$ 41.17	38.02 $\pm$ 52.05	-37.14 $\pm$ 25.23
D-1548	4008	1	4	AAV2	GalNAc	55.32 $\pm$ 23.06	52.73 $\pm$ 30.99	-42 $\pm$ 8.405
D-1600	4109	1	4	AAV2	GalNAc	-0.87 $\pm$ 54.04	4.31 $\pm$ 64.12	-53.28 $\pm$ 23.72

TABLE 5 – siRNA Dose-Response in Liver 2 Weeks Following siRNA Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1545	1309	0.5	4	AAV1	GalNAc	32.32 $\pm$ 41.77	27.47 $\pm$ 45.03	60.59 $\pm$ 56.66
D-1545	1309	1	3	AAV1	GalNAc	-43.11 $\pm$ 49.6	-43.36 $\pm$ 48.77	-21.68 $\pm$ 72.64
D-1545	1309	3	3	AAV1	GalNAc	-38.58 $\pm$ 8.37	-38.32 $\pm$ 8.48	-4.04 $\pm$ 17.42
D-1635	1309	5	4	AAV1	C22	-33.1 $\pm$ 36.41	-38.7 $\pm$ 34.27	-36.57 $\pm$ 31.56
D-1635	1309	15	4	AAV1	C22	-9.79 $\pm$ 18.62	-11.38 $\pm$ 16.78	-6.75 $\pm$ 28.58
D-1639	1309	5	4	AAV1	C22	40.4 $\pm$ 22.62	31.4 $\pm$ 25.97	19.65 $\pm$ 19.04
D-1639	1309	15	4	AAV1	C22	-3.26 $\pm$ 22.12	-8.76 $\pm$ 21.44	-8.45 $\pm$ 16.66
D-1640	1309	0.5	4	AAV1	GalNAc	-28.7 $\pm$ 46.06	-32.11 $\pm$ 44.06	-2.33 $\pm$ 58.61
D-1640	1309	1	4	AAV1	GalNAc	-46.12 $\pm$ 29.63	-47.19 $\pm$ 29.99	-19.78 $\pm$ 50.46
D-1640	1309	3	3	AAV1	GalNAc	-45.55 $\pm$ 4.81	-46.32 $\pm$ 6.37	-19.31 $\pm$ 10.39
D-1549	2080	0.5	3	AAV1	GalNAc	-8.73 $\pm$ 17.94	-11.9 $\pm$ 18.81	-10.33 $\pm$ 22.34
D-1549	2080	1	3	AAV1	GalNAc	-60.51 $\pm$ 24.19	-53.49 $\pm$ 11.13	-52.03 $\pm$ 14.74
D-1549	2080	3	3	AAV1	GalNAc	-47.02 $\pm$ 17.61	-47.06 $\pm$ 20.21	-47.44 $\pm$ 14.68
D-1643	2080	5	3	AAV1	C22	9.49 $\pm$ 25.88	-0.76 $\pm$ 26.26	-11.85 $\pm$ 13.08

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1643	2080	15	3	AAV1	C22	6.1 $\pm$ 41.35	2.91 $\pm$ 39.69	-6.65 $\pm$ 37.28
D-1544	2144	0.5	4	AAV1	GalNAc	-34.12 $\pm$ 38.75	-39.14 $\pm$ 36.58	-10.02 $\pm$ 46.03
D-1544	2144	1	4	AAV1	GalNAc	-5.52 $\pm$ 24.49	-3.87 $\pm$ 28.72	23.6 $\pm$ 37.54
D-1544	2144	3	3	AAV1	GalNAc	-52.79 $\pm$ 51.1	-54.53 $\pm$ 49.23	-28.81 $\pm$ 78.9
D-1636	2144	5	4	AAV1	C22	-15.47 $\pm$ 42.39	-23.31 $\pm$ 36.14	-16.14 $\pm$ 34.22
D-1636	2144	15	4	AAV1	C22	-43.75 $\pm$ 19.47	-44.85 $\pm$ 17.58	-39.17 $\pm$ 18.75
D-1539	2151	1	4	AAV1	GalNAc	13.36 $\pm$ 33.44	4.59 $\pm$ 30.4	-0.61 $\pm$ 23.31
D-1539	2151	3	4	AAV1	GalNAc	-15.59 $\pm$ 26.47	-16.46 $\pm$ 26.89	-15.8 $\pm$ 20.8
D-1573	2263	0.5	3	AAV1	GalNAc	-2.52 $\pm$ 64.76	-5.55 $\pm$ 66.02	3.78 $\pm$ 43.72
D-1573	2263	1	3	AAV1	GalNAc	-36.45 $\pm$ 14.44	-36.88 $\pm$ 13.96	-35.55 $\pm$ 7.81
D-1573	2263	3	4	AAV1	GalNAc	-16.91 $\pm$ 14.29	-16.85 $\pm$ 11.81	-19.48 $\pm$ 14.82
D-1638	2263	5	3	AAV1	C22	6.18 $\pm$ 39.91	1.64 $\pm$ 38.82	0.64 $\pm$ 24.22
D-1638	2263	15	4	AAV1	C22	-14.48 $\pm$ 14.06	-15.34 $\pm$ 16.81	-32.49 $\pm$ 23.85
D-1644	2263	5	3	AAV1	C22	-4.49 $\pm$ 28.46	-8.13 $\pm$ 28.85	-9.74 $\pm$ 20.2
D-1644	2263	15	3	AAV1	C22	-40.62 $\pm$ 32.29	-41.72 $\pm$ 34.15	-45.04 $\pm$ 28.65
D-1645	2263	0.5	3	AAV1	GalNAc	17.05 $\pm$ 15.72	13.25 $\pm$ 12.64	5.3 $\pm$ 8.75
D-1645	2263	1	3	AAV1	GalNAc	11.58 $\pm$ 11.59	12 $\pm$ 9.78	19.45 $\pm$ 15.6
D-1645	2263	3	4	AAV1	GalNAc	-30.31 $\pm$ 8.48	-31.96 $\pm$ 5.84	-34.08 $\pm$ 16.03
D-1557	3000	1	3	AAV2	GalNAc	3.82 $\pm$ 37.62	-4.13 $\pm$ 31.55	5.9 $\pm$ 34.59
D-1557	3000	3	3	AAV2	GalNAc	9.8 $\pm$ 49.78	6.24 $\pm$ 48.34	27.57 $\pm$ 48.71
D-1642	3000	15	3	AAV2	C22	-60.07 $\pm$ 23.8	-58.2 $\pm$ 24.84	-52.11 $\pm$ 26.5
D-1586	3133	1	4	AAV2	GalNAc	-9.95 $\pm$ 20.45	-7.39 $\pm$ 16.97	-6.25 $\pm$ 21.94
D-1586	3133	3	3	AAV2	GalNAc	-46.14 $\pm$ 14.71	-42.98 $\pm$ 17.58	-39.14 $\pm$ 15.32
D-1637	3133	15	3	AAV2	C22	-17.3 $\pm$ 10.47	-17.27 $\pm$ 10.65	-16.31 $\pm$ 9.96

TABLE 6 – siRNA Efficacy in Liver 4 Weeks Following siRNA Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1599	1328	1	4	AAV1	GalNAc	-45.95 $\pm$ 34.12	-51.22 $\pm$ 29.38	-43.47 $\pm$ 38.85
D-1597	1333	1	4	AAV1	GalNAc	-62.57 $\pm$ 20.24	-64.15 $\pm$ 18.92	-62.8 $\pm$ 14.32
D-1589	1496	1	4	AAV1	GalNAc	14.3 $\pm$ 63.6	10.78 $\pm$ 62.99	-4.3 $\pm$ 34.03
D-1616	1534	1	4	AAV1	GalNAc	-11.65 $\pm$ 14.21	-16.95 $\pm$ 16.59	-11.05 $\pm$ 10.43
D-1610	1631	1	4	AAV1	GalNAc	-48.26 $\pm$ 55.95	-52.2 $\pm$ 51.51	-53.22 $\pm$ 49.44
D-1607	1666	1	4	AAV1	GalNAc	-49.8 $\pm$ 32.9	-51.01 $\pm$ 30.93	-54.32 $\pm$ 27.54
D-1609	1671	1	4	AAV1	GalNAc	-4.39 $\pm$ 32.6	-17.13 $\pm$ 26.03	-19.54 $\pm$ 26.39
D-1615	1678	1	4	AAV1	GalNAc	-41.13 $\pm$ 53.81	-49.28 $\pm$ 45.76	-45.21 $\pm$ 48.78
D-1605	1698	1	4	AAV1	GalNAc	-33.95 $\pm$ 19.59	-36.11 $\pm$ 16.39	-36.42 $\pm$ 16.43
D-1606	1705	1	4	AAV1	GalNAc	-17.39 $\pm$ 28.54	-19.93 $\pm$ 31.05	-25.46 $\pm$ 25.93
D-1587	1801	1	4	AAV1	GalNAc	45.99 $\pm$ 35.41	32.63 $\pm$ 29.48	14.33 $\pm$ 25.53
D-1608	1952	1	4	AAV1	GalNAc	21.23 $\pm$ 45.64	18.69 $\pm$ 46.27	12.11 $\pm$ 38.75
D-1601	2075	1	4	AAV1	GalNAc	3.48 $\pm$ 52.45	11.81 $\pm$ 55.2	-28.69 $\pm$ 27.8
D-1602	2270	1	4	AAV1	GalNAc	-31.34 $\pm$ 30.1	-29.49 $\pm$ 32.27	-29.03 $\pm$ 29.76
D-1613	2344	1	4	AAV1	GalNAc	-16.52 $\pm$ 26.48	-5.98 $\pm$ 37.64	-16.72 $\pm$ 16.64
D-1598	2353	1	3	AAV1	GalNAc	-6.46 $\pm$ 79.75	2.57 $\pm$ 87.09	-11.44 $\pm$ 74.95
D-1595	2358	1	3	AAV1	GalNAc	-17.2 $\pm$ 28.13	-8.88 $\pm$ 30.22	-8.88 $\pm$ 30.22
D-1592	2462	1	4	AAV1	GalNAc	-19.82 $\pm$ 24.34	-16.13 $\pm$ 26.34	98.03 $\pm$ 8.2

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1621	2632	1	4	AAV1	GalNAc	-13.73 $\pm$ 45.73	-9.86 $\pm$ 49.02	64.93 $\pm$ 59.16
D-1620	2889	1	4	AAV2	GalNAc	-37.46 $\pm$ 43.63	-40.78 $\pm$ 35.94	-45.42 $\pm$ 32.5
D-1604	2923	1	4	AAV2	GalNAc	39.14 $\pm$ 72.97	25.32 $\pm$ 61.13	15.5 $\pm$ 48.93
D-1588	2937	1	3	AAV2	GalNAc	6.07 $\pm$ 22.94	5.99 $\pm$ 30.89	-5.12 $\pm$ 13.34
D-1619	2994	1	4	AAV2	GalNAc	39.67 $\pm$ 48.64	44.18 $\pm$ 65.89	18.49 $\pm$ 38.81
D-1618	3189	1	4	AAV2	GalNAc	10.19 $\pm$ 27.42	3.71 $\pm$ 24.64	0.48 $\pm$ 24.64
D-1632	3429	1	4	AAV2	GalNAc	45.62 $\pm$ 34.77	41.55 $\pm$ 34.47	23.62 $\pm$ 31.38
D-1617	3717	1	4	AAV2	GalNAc	38.84 $\pm$ 47.24	37.53 $\pm$ 45.21	19 $\pm$ 42.75
D-1626	3720	1	4	AAV2	GalNAc	-6.37 $\pm$ 40.83	-11.26 $\pm$ 36.19	-17.84 $\pm$ 31.67
D-1600	4109	1	4	AAV2	GalNAc	27.89 $\pm$ 36.42	22.01 $\pm$ 32.66	12.46 $\pm$ 28.14
D-1590	4779	1	3	AAV3	GalNAc	-33.73 $\pm$ 13	-38.93 $\pm$ 12.77	6 $\pm$ 19.5
D-1630	4804	1	4	AAV3	GalNAc	-14.77 $\pm$ 6.49	-12.14 $\pm$ 2.53	-30.29 $\pm$ 35.81
D-1596	4927	1	4	AAV3	GalNAc	-42.19 $\pm$ 18.45	-41.27 $\pm$ 17.05	-42.41 $\pm$ 18.48
D-1594	4928	1	4	AAV3	GalNAc	-2.76 $\pm$ 27.16	-1.57 $\pm$ 31.74	-39.67 $\pm$ 30.85
D-1593	4956	1	4	AAV3	GalNAc	8.35 $\pm$ 10.98	14.89 $\pm$ 12.4	36.47 $\pm$ 110.18
D-1631	4957	1	4	AAV3	GalNAc	-57.28 $\pm$ 10.53	-54.33 $\pm$ 14.16	-61.59 $\pm$ 11.91
D-1634	4993	1	4	AAV3	GalNAc	-34.13 $\pm$ 23.86	-29.69 $\pm$ 22.95	-42.05 $\pm$ 16.41
D-1614	4999	1	4	AAV3	GalNAc	-72.8 $\pm$ 18.55	-70.72 $\pm$ 19.27	-75.89 $\pm$ 15.31
D-1633	5012	1	4	AAV3	GalNAc	-44.29 $\pm$ 14.87	-41.01 $\pm$ 14.68	-47.43 $\pm$ 12.41
D-1611	5043	1	4	AAV3	GalNAc	-67.5 $\pm$ 14.12	-64.75 $\pm$ 15.77	-70.05 $\pm$ 12.45
D-1612	5045	1	4	AAV3	GalNAc	-57.91 $\pm$ 11.94	-56.76 $\pm$ 12.24	-72.15 $\pm$ 19.53
D-1591	5060	1	4	AAV3	GalNAc	-37.88 $\pm$ 21.07	-36.57 $\pm$ 20.16	-43.71 $\pm$ 19.3
D-1603	5067	1	4	AAV3	GalNAc	-27.08 $\pm$ 12.11	-21.28 $\pm$ 12.91	-29.76 $\pm$ 9.66
D-1629	5068	1	4	AAV3	GalNAc	-25.94 $\pm$ 28.07	-22.16 $\pm$ 29.33	-27.4 $\pm$ 24.84
D-1628	5069	1	4	AAV3	GalNAc	-36.64 $\pm$ 25.96	-33.81 $\pm$ 25.97	-37.94 $\pm$ 22.7
D-1623	5080	1	4	AAV3	GalNAc	-34.14 $\pm$ 2.45	-29.15 $\pm$ 4.19	-40.61 $\pm$ 6.41
D-1627	5115	1	4	AAV3	GalNAc	-9.14 $\pm$ 24.05	-4.67 $\pm$ 24.43	-12.81 $\pm$ 27.17
D-1622	5255	1	4	AAV3	GalNAc	-36.04 $\pm$ 17.88	-33.61 $\pm$ 19.59	-34.26 $\pm$ 15.69
D-1625	5338	1	4	AAV3	GalNAc	-26.25 $\pm$ 35.36	-24.19 $\pm$ 36.13	-29.8 $\pm$ 29.64

TABLE 7 – siRNA Efficacy in Liver and Adipose Tissue 4 Weeks Following siRNA Injection*

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	Carrier	Tissue	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1597	1333	3	4	GalNAc	Liver	-56.3 $\pm$ 21.55	-55.72 $\pm$ 21.86	-51.8 $\pm$ 24.69
D-1545	1309	3	3	GalNAc	Liver	-38.49 $\pm$ 7.6	-38.32 $\pm$ 10.46	-35.9 $\pm$ 12.63
D-1640	1309	3	4	GalNAc	Liver	-27.46 $\pm$ 16.52	-30.18 $\pm$ 15.06	-26.35 $\pm$ 9.34
D-1646	1309	3	4	GalNAc	Liver	-33.27 $\pm$ 15.52	-35.26 $\pm$ 16.91	-36.1 $\pm$ 11.18
D-1652	1309	3	4	GalNAc	Liver	-37.03 $\pm$ 10.19	-37.27 $\pm$ 11.97	-40.53 $\pm$ 10.69
D-1657	1309	3	4	GalNAc	Liver	-42.36 $\pm$ 27.93	-44.67 $\pm$ 25.92	-47.49 $\pm$ 20.08
D-1662	1309	3	4	GalNAc	Liver	-49.31 $\pm$ 3.2	-49.12 $\pm$ 3.99	-36.17 $\pm$ 6.86
D-1667	1309	3	4	GalNAc	Liver	-64.41 $\pm$ 14.9	-64.39 $\pm$ 13.81	-53.08 $\pm$ 18.99
D-1549	2080	3	3	GalNAc	Liver	-42.27 $\pm$ 1.69	-37.74 $\pm$ 6.96	-36.56 $\pm$ 12.45
D-1647	2080	3	4	GalNAc	Liver	-9.81 $\pm$ 14.47	-14.38 $\pm$ 34.58	-15 $\pm$ 35.29
D-1651	2080	3	4	GalNAc	Liver	-14.14 $\pm$ 38.82	-15.22 $\pm$ 33.33	-7.23 $\pm$ 42.67
D-1656	2080	3	4	GalNAc	Liver	-26.48 $\pm$ 28.43	-45.17 $\pm$ 17.46	-46.61 $\pm$ 18.99

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	Carrier	Tissue	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1661	2080	3	4	GalNAc	Liver	-57.19 $\pm$ 35.09	-57.87 $\pm$ 34.18	-46.61 $\pm$ 38.09
D-1666	2080	3	4	GalNAc	Liver	-10.47 $\pm$ 28.04	-23.11 $\pm$ 34.64	-21.77 $\pm$ 37.38
D-1544	2144	3	4	GalNAc	Liver	-43.5 $\pm$ 14.87	-40.65 $\pm$ 14.86	-27.59 $\pm$ 20.88
D-1648	2144	3	4	GalNAc	Liver	-53.99 $\pm$ 29.24	-53.2 $\pm$ 28.75	-46.51 $\pm$ 30.91
D-1653	2144	3	4	GalNAc	Liver	-36.13 $\pm$ 14.87	-34.76 $\pm$ 16.33	-25.79 $\pm$ 18.55
D-1658	2144	3	4	GalNAc	Liver	-39.78 $\pm$ 25.74	-34.7 $\pm$ 27.83	-32.37 $\pm$ 17.93
D-1663	2144	3	4	GalNAc	Liver	-27.73 $\pm$ 16.32	-24.24 $\pm$ 16.47	-23.95 $\pm$ 12.37
D-1668	2144	3	4	GalNAc	Liver	-29.31 $\pm$ 14.33	-30.61 $\pm$ 11.87	-19.7 $\pm$ 18.95
D-1635	1309	20	4	C22	Liver	-31.24 $\pm$ 27.79	-31.05 $\pm$ 29.03	-23.73 $\pm$ 19.73
D-1639	1309	20	4	C22	Liver	-43.19 $\pm$ 40.95	-36.31 $\pm$ 47.36	-40.72 $\pm$ 42.52
D-1670	1309	20	4	C22	Liver	-18.18 $\pm$ 16.92	-8.04 $\pm$ 17.92	-16.58 $\pm$ 9.32
D-1676	1309	20	4	C22	Liver	-22.36 $\pm$ 34.59	-17.1 $\pm$ 39.02	-11.76 $\pm$ 38.63
D-1681	1309	20	3	C22	Liver	-47.73 $\pm$ 7.7	-52.39 $\pm$ 10.5	-55.07 $\pm$ 10.11
D-1686	1309	20	3	C22	Liver	-46.26 $\pm$ 7.27	-46.39 $\pm$ 8.07	-44.22 $\pm$ 16.43
D-1691	1309	20	4	C22	Liver	-32.27 $\pm$ 13.41	-24.45 $\pm$ 15.05	-28.15 $\pm$ 14.13
D-1635	1309	20	4	C22	Adipose	7.94 $\pm$ 65.35	9.18 $\pm$ 74.04	-9.4 $\pm$ 78.81
D-1639	1309	20	4	C22	Adipose	-61.2 $\pm$ 32.62	-61.1 $\pm$ 33.16	-61.15 $\pm$ 36.91
D-1670	1309	20	4	C22	Adipose	-56.88 $\pm$ 23.59	-51.24 $\pm$ 33.29	-59.98 $\pm$ 24.89
D-1676	1309	20	4	C22	Adipose	63.2 $\pm$ 100.25	42.97 $\pm$ 75.56	24.61 $\pm$ 57.61
D-1681	1309	20	3	C22	Adipose	29.33 $\pm$ 103.09	19.17 $\pm$ 93.9	-9.62 $\pm$ 76.91
D-1686	1309	20	3	C22	Adipose	-79.73 $\pm$ 13.34	-80.1 $\pm$ 13.72	-80.3 $\pm$ 11.86
D-1691	1309	20	4	C22	Adipose	-18.98 $\pm$ 17.2	-20.98 $\pm$ 11.52	-26.98 $\pm$ 11.76

* Table 7 contains data only from mice infected with the AAV1 viral construct

TABLE 8 – siRNA Efficacy in Liver and Adipose Tissue 4 Weeks Following siRNA Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Tissue	Avg. % Change in mRNA $\pm$ STD		
							eGFP-1	eGFP-2	BGHpA
D-1597	1333	1	4	AAV1	GalNAc	Liver	-37.5 $\pm$ 14.1	-30.9 $\pm$ 13.3	-47.3 $\pm$ 6.1
D-1615	1678	1	4	AAV1	GalNAc	Liver	-37.9 $\pm$ 18	-34.7 $\pm$ 19.1	-38.8 $\pm$ 17.8
D-1631	4957	1	4	AAV3	GalNAc	Liver	-32.1 $\pm$ 10.7	-26.1 $\pm$ 17.3	-38.3 $\pm$ 15.5
D-1614	4999	1	4	AAV3	GalNAc	Liver	-53.2 $\pm$ 12.8	-49.7 $\pm$ 17	-56.2 $\pm$ 9
D-1611	5043	1	4	AAV3	GalNAc	Liver	-34.3 $\pm$ 33.8	-33.3 $\pm$ 32	-44.5 $\pm$ 21.2
D-1612	5045	1	4	AAV3	GalNAc	Liver	-31.1 $\pm$ 27.1	-30.1 $\pm$ 27.3	-34.5 $\pm$ 18.5
D-1597	1333	3	4	AAV1	GalNAc	Liver	-72.3 $\pm$ 10.6	-69.5 $\pm$ 12.8	-72.2 $\pm$ 7.4
D-1615	1678	3	4	AAV1	GalNAc	Liver	-65.5 $\pm$ 6.1	-63.2 $\pm$ 7	-63.9 $\pm$ 4.7
D-1631	4957	3	4	AAV3	GalNAc	Liver	-68 $\pm$ 6.9	-65.3 $\pm$ 7.7	-65.5 $\pm$ 7.2
D-1614	4999	3	4	AAV3	GalNAc	Liver	-67.3 $\pm$ 2.4	-64.9 $\pm$ 2.6	-65.2 $\pm$ 0.6
D-1611	5043	3	4	AAV3	GalNAc	Liver	-66.8 $\pm$ 17.1	-65.2 $\pm$ 17.7	-66.4 $\pm$ 14.9
D-1612	5045	3	4	AAV3	GalNAc	Liver	-83 $\pm$ 13	-82.2 $\pm$ 14	-82.6 $\pm$ 14.2
D-1694	1333	20	4	AAV1	C22	Liver	-73.3 $\pm$ 9.4	-71.3 $\pm$ 10.4	-72.2 $\pm$ 3.7
D-1695	1678	20	4	AAV1	C22	Liver	-51.9 $\pm$ 33.7	-51 $\pm$ 33.5	-56.8 $\pm$ 29.8
D-1696	4957	20	4	AAV3	C22	Liver	-34.7 $\pm$ 29.7	-34.3 $\pm$ 31.1	-43.6 $\pm$ 21.4
D-1697	4999	20	4	AAV3	C22	Liver	-3.3 $\pm$ 53.7	1.1 $\pm$ 55.4	-18.9 $\pm$ 43.9
D-1698	5043	20	4	AAV3	C22	Liver	-32.6 $\pm$ 15.1	-31 $\pm$ 15.9	-43.7 $\pm$ 10.3

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Tissue	Avg. % Change in mRNA $\pm$ STD		
							eGFP-1	eGFP-2	BGHpA
D-1699	5045	20	4	AAV3	C22	Liver	-18.6 $\pm$ 16.2	-18.7 $\pm$ 13.7	-28.2 $\pm$ 11.7
D-1694	1333	20	4	AAV1	C22	Adipose	-66.4 $\pm$ 8	-67.6 $\pm$ 9.6	-75.2 $\pm$ 7
D-1695	1678	20	4	AAV1	C22	Adipose	-19 $\pm$ 55.4	-17.5 $\pm$ 59.3	-43.7 $\pm$ 43
D-1696	4957	20	4	AAV3	C22	Adipose	-75.6 $\pm$ 34.8	-75.3 $\pm$ 34.7	-78.1 $\pm$ 27.5
D-1697	4999	20	4	AAV3	C22	Adipose	-79.7 $\pm$ 5.8	-78.5 $\pm$ 6.4	-73.2 $\pm$ 9.1
D-1698	5043	20	4	AAV3	C22	Adipose	-69 $\pm$ 21.9	-67.5 $\pm$ 25.3	-68.4 $\pm$ 19.7
D-1699	5045	20	4	AAV3	C22	Adipose	-72.2 $\pm$ 15.9	-69.1 $\pm$ 19.5	-54.4 $\pm$ 17.1

TABLE 9 – siRNA Efficacy in Liver and Adipose Tissue 4 Weeks Following siRNA Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Tissue	Avg. % Change in mRNA $\pm$ STD		
							eGFP-1	eGFP-2	BGHpA
D-1557	3000	3	4	AAV2	GalNAc	Liver	-52.1 $\pm$ 15.3	-51.3 $\pm$ 15.8	-46.9 $\pm$ 19.4
D-1650	3000	3	4	AAV2	GalNAc	Liver	-54.1 $\pm$ 10	-53.1 $\pm$ 10.5	-52.4 $\pm$ 15.2
D-1655	3000	3	4	AAV2	GalNAc	Liver	-44.6 $\pm$ 9.6	-42.8 $\pm$ 10	-42.3 $\pm$ 7.1
D-1660	3000	3	4	AAV2	GalNAc	Liver	-39.3 $\pm$ 8.9	-42.9 $\pm$ 3.7	-43.4 $\pm$ 8.3
D-1665	3000	3	4	AAV2	GalNAc	Liver	-20.5 $\pm$ 22	-19.6 $\pm$ 21.1	-22.1 $\pm$ 17.8
D-1586	3133	3	4	AAV2	GalNAc	Liver	-38.6 $\pm$ 9.4	-36.8 $\pm$ 8.5	-40 $\pm$ 2.3
D-1649	3133	3	4	AAV2	GalNAc	Liver	-43.4 $\pm$ 5.6	-37.6 $\pm$ 6.5	-42.5 $\pm$ 12.4
D-1654	3133	3	4	AAV2	GalNAc	Liver	-27.4 $\pm$ 46.7	-22 $\pm$ 49.3	-20.8 $\pm$ 46.1
D-1659	3133	3	4	AAV2	GalNAc	Liver	-41.5 $\pm$ 2.9	-36.8 $\pm$ 5.7	-42.1 $\pm$ 6.3
D-1664	3133	3	4	AAV2	GalNAc	Liver	-43.7 $\pm$ 14.8	-41.6 $\pm$ 15.9	-45.5 $\pm$ 12.1
D-1669	3133	3	4	AAV2	GalNAc	Liver	-45.7 $\pm$ 27.1	-40.7 $\pm$ 29.6	-46.4 $\pm$ 28.6
D-1623	5080	3	4	AAV3	GalNAc	Liver	-27.1 $\pm$ 25.9	-22.4 $\pm$ 30.4	-27.1 $\pm$ 24.9
D-1643	2080	20	4	AAV1	C22	Liver	-14.9 $\pm$ 19.5	-14.6 $\pm$ 21.1	-11.6 $\pm$ 17.1
D-1671	2080	20	4	AAV1	C22	Liver	-20.1 $\pm$ 23.6	-20.5 $\pm$ 23.4	-17 $\pm$ 25.9
D-1675	2080	20	4	AAV1	C22	Liver	-32.6 $\pm$ 11.2	-31.9 $\pm$ 14	-19.5 $\pm$ 15.8
D-1680	2080	20	4	AAV1	C22	Liver	-52.1 $\pm$ 13.6	-50 $\pm$ 12.9	-42.1 $\pm$ 11.9
D-1685	2080	20	4	AAV1	C22	Liver	-54 $\pm$ 25.8	-53.5 $\pm$ 26.2	-46.7 $\pm$ 29
D-1690	2080	20	4	AAV1	C22	Liver	-40 $\pm$ 10.9	-36.2 $\pm$ 8.7	-33.9 $\pm$ 13.3
D-1636	2144	20	4	AAV1	C22	Liver	-48.8 $\pm$ 30	-44.2 $\pm$ 33.6	-40.9 $\pm$ 33.7
D-1672	2144	20	4	AAV1	C22	Liver	-11 $\pm$ 16.5	-7.5 $\pm$ 16.9	-20 $\pm$ 6.3
D-1677	2144	20	4	AAV1	C22	Liver	-23.6 $\pm$ 9.1	-20.2 $\pm$ 7.2	-17.5 $\pm$ 9.3
D-1682	2144	20	4	AAV1	C22	Liver	-14.4 $\pm$ 9.8	-13 $\pm$ 9.2	-29.9 $\pm$ 5.7
D-1687	2144	20	4	AAV1	C22	Liver	-59.5 $\pm$ 33.4	-61 $\pm$ 32.4	-74.3 $\pm$ 18.5
D-1692	2144	20	4	AAV1	C22	Liver	-60.5 $\pm$ 21.6	-60.1 $\pm$ 23.3	-73 $\pm$ 6.7
D-1846	5080	20	4	AAV3	C22	Liver	-76.6 $\pm$ 36	-79.6 $\pm$ 29.9	-83.5 $\pm$ 27.2
D-1643	2080	20	4	AAV1	C22	Adipose	-53.4 $\pm$ 23.5	-55.1 $\pm$ 23.9	-65.8 $\pm$ 16.6
D-1671	2080	20	4	AAV1	C22	Adipose	-74.9 $\pm$ 7.5	-79.2 $\pm$ 5	-76.1 $\pm$ 10.3
D-1675	2080	20	4	AAV1	C22	Adipose	-64.9 $\pm$ 14.4	-67.8 $\pm$ 14.9	-71 $\pm$ 13.7
D-1680	2080	20	4	AAV1	C22	Adipose	-69.6 $\pm$ 26.1	-66.3 $\pm$ 29	-83.1 $\pm$ 11.1
D-1685	2080	20	4	AAV1	C22	Adipose	-70.2 $\pm$ 32	-67.3 $\pm$ 35.7	-80.4 $\pm$ 20
D-1690	2080	20	4	AAV1	C22	Adipose	-81.5 $\pm$ 11.6	-82.6 $\pm$ 10.5	-82.1 $\pm$ 16.7
D-1636	2144	20	4	AAV1	C22	Adipose	-65.7 $\pm$ 40.7	-60 $\pm$ 47.4	-78.5 $\pm$ 26.6
D-1672	2144	20	4	AAV1	C22	Adipose	-63.3 $\pm$ 21.1	-65.6 $\pm$ 19.9	-59.1 $\pm$ 27.6
D-1677	2144	20	4	AAV1	C22	Adipose	-44.2 $\pm$ 19.2	-35.8 $\pm$ 26	-56.6 $\pm$ 18.2
D-1682	2144	20	4	AAV1	C22	Adipose	-85.5 $\pm$ 7.7	-81.1 $\pm$ 8.9	-78.3 $\pm$ 14

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Tissue	Avg. % Change in mRNA $\pm$ STD		
							eGFP-1	eGFP-2	BGHpA
D-1687	2144	20	4	AAV1	C22	Adipose	-52.1 $\pm$ 15.3	-51.3 $\pm$ 15.8	-46.9 $\pm$ 19.4
D-1692	2144	20	4	AAV1	C22	Adipose	-54.1 $\pm$ 10	-53.1 $\pm$ 10.5	-52.4 $\pm$ 15.2
D-1846	5080	20	4	AAV3	C22	Adipose	-44.6 $\pm$ 9.6	-42.8 $\pm$ 10	-42.3 $\pm$ 7.1

TABLE 10 – siRNA Efficacy in Liver 4 Weeks Following siRNA Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1597	1333	3	4	1	GalNAc	-57.5 $\pm$ 17.2	-54.9 $\pm$ 17.5	-55.1 $\pm$ 15.5
D-1721	1333	3	4	1	GalNAc	-35.5 $\pm$ 4	-31.5 $\pm$ 8.3	-34 $\pm$ 3.1
D-1728	1333	3	4	1	GalNAc	-32.5 $\pm$ 18.5	-28.1 $\pm$ 18.5	-36.8 $\pm$ 13.8
D-1735	1333	3	4	1	GalNAc	-36.3 $\pm$ 11.7	-35 $\pm$ 7.2	-36.3 $\pm$ 8.6
D-1707	1333	3	4	1	GalNAc	-37.8 $\pm$ 10.4	-39.3 $\pm$ 9.7	-34.5 $\pm$ 4.1
D-1714	1333	3	4	1	GalNAc	-50.6 $\pm$ 18.8	-49.1 $\pm$ 19.4	-45.8 $\pm$ 18
D-1700	1333	3	4	1	GalNAc	-44.5 $\pm$ 15.2	-40.9 $\pm$ 17.9	-45.8 $\pm$ 18.5
D-1615	1678	3	4	1	GalNAc	-53.7 $\pm$ 19.8	-52 $\pm$ 20.9	-47.8 $\pm$ 14.9
D-1722	1678	3	4	1	GalNAc	-45.8 $\pm$ 22	-40.4 $\pm$ 24.7	-46.9 $\pm$ 14.7
D-1729	1678	3	4	1	GalNAc	-31.8 $\pm$ 15.6	-27.5 $\pm$ 16.4	-43.2 $\pm$ 4.9
D-1736	1678	3	4	1	GalNAc	-51.7 $\pm$ 8.2	-50.6 $\pm$ 7.3	-43.2 $\pm$ 5.4
D-1708	1678	3	4	1	GalNAc	-36.1 $\pm$ 9.7	-32.3 $\pm$ 11.1	-35.2 $\pm$ 9.7
D-1715	1678	3	4	1	GalNAc	-28.1 $\pm$ 28.8	-22.6 $\pm$ 30.8	-32.9 $\pm$ 21
D-1701	1678	3	4	1	GalNAc	-27.8 $\pm$ 20.9	-25.6 $\pm$ 18.1	-17 $\pm$ 18.8
D-1631	4957	3	4	3	GalNAc	-55.3 $\pm$ 18.1	-56.1 $\pm$ 19.4	-52.7 $\pm$ 18.3
D-1724	4957	3	4	3	GalNAc	-62.3 $\pm$ 8.1	-62.5 $\pm$ 7	-59.1 $\pm$ 7.3
D-1731	4957	3	4	3	GalNAc	-64 $\pm$ 11.9	-59.9 $\pm$ 14.4	-58.9 $\pm$ 15.6
D-1738	4957	3	4	3	GalNAc	-42.1 $\pm$ 9.4	-40.2 $\pm$ 11.3	-46.7 $\pm$ 9
D-1710	4957	3	4	3	GalNAc	-57.9 $\pm$ 6.3	-57.3 $\pm$ 6.3	-49.7 $\pm$ 4.3
D-1717	4957	3	4	3	GalNAc	-61.4 $\pm$ 24.8	-58.5 $\pm$ 28.6	-59.3 $\pm$ 23.8
D-1703	4957	3	4	3	GalNAc	-61.2 $\pm$ 10	-62.1 $\pm$ 9	-54.3 $\pm$ 12.5
D-1614	4999	3	4	3	GalNAc	-71 $\pm$ 21.5	-70.7 $\pm$ 21.7	-73.5 $\pm$ 16.8
D-1723	4999	3	4	3	GalNAc	-70.8 $\pm$ 3.4	-70 $\pm$ 2.2	-60.8 $\pm$ 1.5
D-1730	4999	3	4	3	GalNAc	-72.4 $\pm$ 15	-72.5 $\pm$ 16.2	-67.2 $\pm$ 11.7
D-1737	4999	3	4	3	GalNAc	-71.5 $\pm$ 3.9	-74.5 $\pm$ 5	-65.1 $\pm$ 1.5
D-1709	4999	3	4	3	GalNAc	-73 $\pm$ 5	-71.6 $\pm$ 5.3	-67.5 $\pm$ 6.2
D-1716	4999	3	4	3	GalNAc	-76 $\pm$ 4	-75.5 $\pm$ 4.2	-69.4 $\pm$ 4.1
D-1702	4999	3	4	3	GalNAc	-72.7 $\pm$ 4.9	-72.1 $\pm$ 4.7	-67.9 $\pm$ 2.1
D-1611	5043	3	4	3	GalNAc	-71.6 $\pm$ 11.4	-69.4 $\pm$ 12	-65.2 $\pm$ 10.6
D-1726	5043	3	4	3	GalNAc	-59.8 $\pm$ 17.1	-57.3 $\pm$ 18.3	-58.8 $\pm$ 13.7
D-1733	5043	3	4	3	GalNAc	-70.8 $\pm$ 8.1	-68.3 $\pm$ 9.2	-64.3 $\pm$ 8.7
D-1740	5043	3	4	3	GalNAc	-61.6 $\pm$ 10.8	-57.9 $\pm$ 12.3	-56.6 $\pm$ 6.9
D-1712	5043	3	4	3	GalNAc	-67.8 $\pm$ 9	-64.7 $\pm$ 10.4	-69.6 $\pm$ 6.3
D-1719	5043	3	4	3	GalNAc	-69.4 $\pm$ 6.2	-68.9 $\pm$ 5.6	-68.1 $\pm$ 3.3
D-1705	5043	3	4	3	GalNAc	-81.4 $\pm$ 4.9	-77.9 $\pm$ 8.8	-79.7 $\pm$ 8.6
D-1612	5045	3	3	3	GalNAc	-67.5 $\pm$ 15.5	-69.6 $\pm$ 14.1	-75.3 $\pm$ 7.4
D-1725	5045	3	4	3	GalNAc	-64.8 $\pm$ 5.2	-66.7 $\pm$ 5.4	-67.1 $\pm$ 3.8
D-1732	5045	3	4	3	GalNAc	-66 $\pm$ 9.9	-64.2 $\pm$ 10.6	-69.5 $\pm$ 5.7
D-1739	5045	3	4	3	GalNAc	-66.8 $\pm$ 12.9	-65.5 $\pm$ 14.7	-67.6 $\pm$ 11

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1711	5045	3	4	3	GalNAc	-75.7 $\pm$ 6.7	-75.8 $\pm$ 5.1	-71.5 $\pm$ 5.1
D-1718	5045	3	4	3	GalNAc	-76.6 $\pm$ 4.1	-75.7 $\pm$ 4.4	-75.6 $\pm$ 2.8
D-1704	5045	3	4	3	GalNAc	-80.1 $\pm$ 12.2	-80.1 $\pm$ 12.1	-79.9 $\pm$ 12.4
D-1623	5080	3	4	3	GalNAc	-72.9 $\pm$ 7.6	-72.6 $\pm$ 7.1	-75.9 $\pm$ 7.1
D-1727	5080	3	4	3	GalNAc	-59 $\pm$ 3.6	-53.4 $\pm$ 12.7	-49.3 $\pm$ 20.9
D-1734	5080	3	4	3	GalNAc	-59.6 $\pm$ 7.4	-60.3 $\pm$ 7	-61.2 $\pm$ 6.2
D-1741	5080	3	4	3	GalNAc	-59.9 $\pm$ 4.8	-59.4 $\pm$ 4.1	-61 $\pm$ 5.8
D-1713	5080	3	4	3	GalNAc	-67.9 $\pm$ 11.1	-67.5 $\pm$ 8.7	-69 $\pm$ 4.9
D-1720	5080	3	4	3	GalNAc	-55.3 $\pm$ 6.4	-57 $\pm$ 6.5	-60.7 $\pm$ 5.6
D-1706	5080	3	4	3	GalNAc	-66.2 $\pm$ 9	-67.7 $\pm$ 7.8	-69.1 $\pm$ 6.7

TABLE 11– siRNA Efficacy in Liver and Adipose Tissue 4 Weeks Following siRNA Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Tissue	Avg. % Change in mRNA $\pm$ STD		
							eGFP-1	eGFP-2	BGHpA
D-1714	1333	3	4	1	GalNAc	Liver	-50.6 $\pm$ 13.9	-49.2 $\pm$ 14.5	-46.6 $\pm$ 17.4
D-1615	1678	3	4	1	GalNAc	Liver	-52.5 $\pm$ 11.4	-53.1 $\pm$ 10.4	-57.9 $\pm$ 6.1
D-1736	1678	3	4	1	GalNAc	Liver	-44.9 $\pm$ 8.9	-43.1 $\pm$ 9.7	-50 $\pm$ 7.7
D-1648	2144	3	4	1	GalNAc	Liver	-39.4 $\pm$ 13	-37.3 $\pm$ 13.2	-38.5 $\pm$ 10.9
D-1557	3000	3	4	2	GalNAc	Liver	-45.8 $\pm$ 11	-44.6 $\pm$ 12.7	-46.8 $\pm$ 13.2
D-1650	3000	3	4	2	GalNAc	Liver	-32.2 $\pm$ 30.3	-27.5 $\pm$ 32.7	-35.5 $\pm$ 20.2
D-1664	3133	3	4	2	GalNAc	Liver	-38.4 $\pm$ 23.9	-31.8 $\pm$ 26.2	-46.1 $\pm$ 11.7
D-1614	4999	3	4	3	GalNAc	Liver	-66.3 $\pm$ 13	-59.8 $\pm$ 14.3	-58.7 $\pm$ 13.9
D-1723	4999	3	4	3	GalNAc	Liver	-65.3 $\pm$ 16.8	-58.7 $\pm$ 19	-58.5 $\pm$ 14.9
D-1737	4999	3	4	3	GalNAc	Liver	-57.2 $\pm$ 22.1	-51.3 $\pm$ 21	-47.9 $\pm$ 15.1
D-1730	4999	3	4	3	GalNAc	Liver	-61 $\pm$ 24.9	-56.6 $\pm$ 25.7	-48.8 $\pm$ 24
D-1709	4999	3	4	3	GalNAc	Liver	-73 $\pm$ 6.3	-67.4 $\pm$ 8	-68.1 $\pm$ 16.8
D-1716	4999	3	4	3	GalNAc	Liver	-64.8 $\pm$ 14.9	-57.1 $\pm$ 19.5	-56.6 $\pm$ 10.9
D-1702	4999	3	3	3	GalNAc	Liver	-55.6 $\pm$ 13.3	-45.7 $\pm$ 15.6	-50.4 $\pm$ 7.6
D-1879	4999	3	4	3	GalNAc	Liver	-70.1 $\pm$ 10.9	-62.6 $\pm$ 13.7	-55.6 $\pm$ 15.7
D-1611	5043	3	4	3	GalNAc	Liver	-77.2 $\pm$ 9.6	-78.2 $\pm$ 9.1	-69.5 $\pm$ 13.8
D-1733	5043	3	4	3	GalNAc	Liver	-75.3 $\pm$ 9.1	-75.7 $\pm$ 9.3	-69.2 $\pm$ 10.8
D-1719	5043	3	4	3	GalNAc	Liver	-70.9 $\pm$ 14	-71.2 $\pm$ 12.7	-70.9 $\pm$ 9.4
D-1705	5043	3	4	3	GalNAc	Liver	-75.7 $\pm$ 10.3	-76.7 $\pm$ 9.8	-74.4 $\pm$ 7.9
D-1612	5045	3	3	3	GalNAc	Liver	-72.1 $\pm$ 6	-71.2 $\pm$ 5.3	-65.2 $\pm$ 7.2
D-1711	5045	3	4	3	GalNAc	Liver	-73 $\pm$ 3.8	-72.4 $\pm$ 3.4	-70.4 $\pm$ 4.4
D-1718	5045	3	4	3	GalNAc	Liver	-75.4 $\pm$ 14.3	-75.4 $\pm$ 14.5	-70.1 $\pm$ 16.3
D-1704	5045	3	4	3	GalNAc	Liver	-76.4 $\pm$ 5.3	-73.9 $\pm$ 6.2	-71.6 $\pm$ 5.6
D-1876	5045	20	4	3	C22	Liver	-31 $\pm$ 19.2	-34 $\pm$ 17.4	-38 $\pm$ 14.6
D-1623	5080	3	3	3	GalNAc	Liver	-71.4 $\pm$ 3.3	-65.6 $\pm$ 4.9	-65.9 $\pm$ 2.3
D-1706	5080	3	4	3	GalNAc	Liver	-64.9 $\pm$ 12.7	-63.6 $\pm$ 16.6	-64.9 $\pm$ 8.5
D-1873	1333	20	4	1	C22	Liver	-37.5 $\pm$ 21.5	-33 $\pm$ 24.6	-53.8 $\pm$ 12.3
D-1695	1678	20	4	1	C22	Liver	-22 $\pm$ 15.4	-22.4 $\pm$ 13.1	-31.6 $\pm$ 12.9
D-1867	1678	20	3	1	C22	Liver	-48.2 $\pm$ 10.4	-49.7 $\pm$ 6.3	-51.4 $\pm$ 5.3
D-1672	2144	20	4	1	C22	Liver	-48 $\pm$ 17.3	-47.1 $\pm$ 17.8	-49.6 $\pm$ 15.8
D-1642	3000	20	4	2	C22	Liver	-38 $\pm$ 15.5	-35.7 $\pm$ 16.1	-36.2 $\pm$ 9.4
D-1674	3000	20	3	2	C22	Liver	-44.8 $\pm$ 11.5	-45.9 $\pm$ 9	-45.3 $\pm$ 15.1

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Tissue	Avg. % Change in mRNA $\pm$ STD		
							eGFP-1	eGFP-2	BGHpA
D-1688	3133	20	4	2	C22	Liver	-41 $\pm$ 28.5	-32.2 $\pm$ 32.9	-47.4 $\pm$ 21.9
D-1697	4999	20	4	3	C22	Liver	-22.4 $\pm$ 23	-14 $\pm$ 27.2	-15.4 $\pm$ 25.6
D-1865	4999	20	4	3	C22	Liver	-16.8 $\pm$ 47.2	-4.9 $\pm$ 53.2	-14.1 $\pm$ 33.6
D-1863	4999	20	4	3	C22	Liver	-0.6 $\pm$ 33.2	16.7 $\pm$ 46.2	1.2 $\pm$ 32.6
D-1866	4999	20	4	3	C22	Liver	-11.7 $\pm$ 61.1	-2.2 $\pm$ 65.8	-7.8 $\pm$ 45.2
D-1869	4999	20	4	3	C22	Liver	-78 $\pm$ 7.7	-73.1 $\pm$ 9.9	-66.4 $\pm$ 9.2
D-1872	4999	20	4	3	C22	Liver	-65.6 $\pm$ 11.2	-56.5 $\pm$ 14.2	-54.4 $\pm$ 12.2
D-1877	4999	20	4	3	C22	Liver	-68.4 $\pm$ 7.9	-60.1 $\pm$ 12.1	-58 $\pm$ 11.8
D-1878	4999	20	3	3	C22	Liver	-58.2 $\pm$ 9.1	-49.9 $\pm$ 8.6	-52.2 $\pm$ 7.5
D-1698	5043	20	4	3	C22	Liver	-72.2 $\pm$ 15	-72.8 $\pm$ 15.1	-70.5 $\pm$ 18.3
D-1864	5043	20	4	3	C22	Liver	-35.4 $\pm$ 11.3	-39.2 $\pm$ 8.5	-41.2 $\pm$ 12.7
D-1870	5043	20	4	3	C22	Liver	-30.4 $\pm$ 11.4	-25.1 $\pm$ 9.3	-32.1 $\pm$ 8.7
D-1875	5043	20	4	3	C22	Liver	-61.5 $\pm$ 19.5	-61.1 $\pm$ 20.5	-60.9 $\pm$ 18.2
D-1699	5045	20	4	3	C22	Liver	-40.1 $\pm$ 10.8	-42.4 $\pm$ 10.7	-38.2 $\pm$ 9.6
D-1868	5045	20	4	3	C22	Liver	-52.7 $\pm$ 11.7	-45.4 $\pm$ 11.3	-48.7 $\pm$ 8.4
D-1871	5045	20	4	3	C22	Liver	-65.4 $\pm$ 5.2	-65.3 $\pm$ 4	-66.8 $\pm$ 5.2
D-1846	5080	20	4	3	C22	Liver	-25.8 $\pm$ 17.6	-12.7 $\pm$ 20.8	-22.9 $\pm$ 17.3
D-1874	5080	20	4	3	C22	Liver	-41.6 $\pm$ 10.4	-36.9 $\pm$ 11.9	-40.6 $\pm$ 7.5
D-1873	1333	20	4	1	C22	Adipose	37.4 $\pm$ 68	31.4 $\pm$ 63.8	6.3 $\pm$ 35.5
D-1695	1678	20	4	1	C22	Adipose	-19.2 $\pm$ 12.7	-28 $\pm$ 12.9	-25.3 $\pm$ 7.2
D-1867	1678	20	3	1	C22	Adipose	-67.3 $\pm$ 35.7	-69.4 $\pm$ 35.3	-71.5 $\pm$ 24.1
D-1672	2144	20	4	1	C22	Adipose	-43 $\pm$ 26.1	-43.1 $\pm$ 31.7	-32.6 $\pm$ 37.7
D-1642	3000	20	4	2	C22	Adipose	-37.2 $\pm$ 40.5	-30.3 $\pm$ 45.9	-15.8 $\pm$ 61.1
D-1674	3000	20	3	2	C22	Adipose	-70.7 $\pm$ 19.9	-68.6 $\pm$ 21.7	-71.4 $\pm$ 19.9
D-1688	3133	20	4	2	C22	Adipose	-39.6 $\pm$ 18.4	-39.7 $\pm$ 21.7	-28.9 $\pm$ 44.3
D-1697	4999	20	4	3	C22	Adipose	-85.9 $\pm$ 7.3	-89.5 $\pm$ 5.6	-81.5 $\pm$ 8.1
D-1865	4999	20	4	3	C22	Adipose	-78.6 $\pm$ 25.5	-78.2 $\pm$ 29.5	-81.7 $\pm$ 21
D-1863	4999	20	4	3	C22	Adipose	-84.6 $\pm$ 8.1	-87.1 $\pm$ 6.9	-72.9 $\pm$ 15.4
D-1866	4999	20	4	3	C22	Adipose	-88.5 $\pm$ 10.9	-91.6 $\pm$ 6.7	-86.6 $\pm$ 13.3
D-1869	4999	20	4	3	C22	Adipose	-90 $\pm$ 8.2	-92.4 $\pm$ 6.7	-85.3 $\pm$ 10.6
D-1872	4999	20	4	3	C22	Adipose	-66.2 $\pm$ 15.1	-75.9 $\pm$ 9.4	-72.9 $\pm$ 11.9
D-1877	4999	20	4	3	C22	Adipose	-73.7 $\pm$ 6.7	-79.6 $\pm$ 5	-62.8 $\pm$ 14.3
D-1878	4999	20	3	3	C22	Adipose	-85.2 $\pm$ 12	-88.8 $\pm$ 9.3	-84.7 $\pm$ 10.5
D-1698	5043	20	4	3	C22	Adipose	-93 $\pm$ 9	-91.5 $\pm$ 11.3	-91.4 $\pm$ 10.7
D-1864	5043	20	4	3	C22	Adipose	-87.6 $\pm$ 7.4	-86.7 $\pm$ 7.2	-84.6 $\pm$ 9.5
D-1870	5043	20	4	3	C22	Adipose	-81.6 $\pm$ 15.5	-81 $\pm$ 16.7	-80.5 $\pm$ 14
D-1875	5043	20	4	3	C22	Adipose	-85.6 $\pm$ 9.1	-86.9 $\pm$ 8.2	-81.3 $\pm$ 12.9
D-1699	5045	20	4	3	C22	Adipose	-78.8 $\pm$ 9.5	-78.7 $\pm$ 10.6	-79.8 $\pm$ 7.7
D-1868	5045	20	4	3	C22	Adipose	-82 $\pm$ 9	-79.4 $\pm$ 11.7	-79.6 $\pm$ 9.2
D-1871	5045	20	4	3	C22	Adipose	-90 $\pm$ 15.1	-91.9 $\pm$ 12	-90.9 $\pm$ 12.9
D-1876	5045	20	4	3	C22	Adipose	-76 $\pm$ 24.4	-76.9 $\pm$ 22.6	-75.2 $\pm$ 25.4
D-1846	5080	20	4	3	C22	Adipose	-82.9 $\pm$ 8.8	-87.2 $\pm$ 7.7	-75.9 $\pm$ 14.9
D-1874	5080	20	4	3	C22	Adipose	-71.2 $\pm$ 9.7	-72.8 $\pm$ 8.8	-74.2 $\pm$ 5.7

TABLE 12– siRNA Efficacy in Liver and Adipose Tissue 4 Weeks Following siRNA Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Tissue	Avg. % Change in mRNA $\pm$ STD		
							eGFP-1	eGFP-2	BGHpA
D-1686	1309	20	4	1	C22	Liver	-39.9 $\pm$ 38.8	-39.9 $\pm$ 40.6	-51 $\pm$ 29.2
D-1691	1309	20	4	1	C22	Liver	-40.1 $\pm$ 18.4	-40 $\pm$ 16.9	-49.8 $\pm$ 10.6
D-1635	1309	20	4	1	C22	Liver	-38.4 $\pm$ 30.6	-38.8 $\pm$ 29.3	-45.9 $\pm$ 19.5
D-1694	1333	20	4	1	C22	Liver	-25 $\pm$ 20.4	-26 $\pm$ 21.8	-43.4 $\pm$ 13.7
D-1695	1678	20	4	1	C22	Liver	-11.9 $\pm$ 10.8	-14 $\pm$ 11.7	-19.5 $\pm$ 17.5
D-1643	2080	20	4	1	C22	Liver	-44.2 $\pm$ 17.3	-44.1 $\pm$ 17.4	-46.2 $\pm$ 11.4
D-1672	2144	20	4	1	C22	Liver	-58.5 $\pm$ 9.6	-55.6 $\pm$ 9.9	-52 $\pm$ 10.2
D-1636	2144	20	4	1	C22	Liver	-65.3 $\pm$ 31.3	-66.3 $\pm$ 30.2	-63.4 $\pm$ 32.9
D-1847	1309	20	4	1	C22	Liver	-43 $\pm$ 14.5	-39.9 $\pm$ 17.1	-49.9 $\pm$ 12.1
D-1849	1309	20	4	1	C22	Liver	-23.5 $\pm$ 13.9	-19.6 $\pm$ 14.1	-14.8 $\pm$ 11.6
D-1859	1309	20	4	1	C22	Liver	-33.1 $\pm$ 15.6	-33.3 $\pm$ 13.8	-36.9 $\pm$ 15.7
D-1853	1333	20	4	1	C22	Liver	-42.2 $\pm$ 22.9	-41 $\pm$ 19.8	-44.1 $\pm$ 20.7
D-1852	1678	20	4	1	C22	Liver	-51.2 $\pm$ 21.2	-44.9 $\pm$ 23.4	-38 $\pm$ 21.7
D-1860	2080	20	4	1	C22	Liver	-14.1 $\pm$ 23.1	-11.5 $\pm$ 21.8	-5.5 $\pm$ 34.2
D-1851	2144	20	4	1	C22	Liver	-61.6 $\pm$ 15.8	-55.8 $\pm$ 17.8	-52.5 $\pm$ 16.3
D-1858	2144	20	4	1	C22	Liver	-47.6 $\pm$ 10.8	-44.7 $\pm$ 10.2	-46.2 $\pm$ 1.9
D-1666	4999	20	4	3	C22	Liver	-35 $\pm$ 11.7	-35.7 $\pm$ 11.2	-38.6 $\pm$ 11.7
D-1872	4999	20	4	3	C22	Liver	-78.4 $\pm$ 5.1	-76.2 $\pm$ 6.1	-71.3 $\pm$ 4.3
D-1877	4999	20	4	3	C22	Liver	-84.6 $\pm$ 1.7	-82.1 $\pm$ 1.9	-79.9 $\pm$ 2.4
D-1697	4999	20	4	3	C22	Liver	-40.9 $\pm$ 9.3	-37.5 $\pm$ 10.5	-38.9 $\pm$ 8.3
D-1846	5080	20	4	3	C22	Liver	-43.3 $\pm$ 6.8	-43.8 $\pm$ 6.3	-40 $\pm$ 4.5
D-1881	4999	20	4	3	C22	Liver	-80.2 $\pm$ 2.7	-77.3 $\pm$ 3.3	-71 $\pm$ 2.8
D-1887	4999	20	4	3	C22	Liver	-83.2 $\pm$ 3.3	-80.2 $\pm$ 3.8	-75.6 $\pm$ 4.5
D-1880	4999	20	4	3	C22	Liver	-83.6 $\pm$ 2.7	-82.1 $\pm$ 2.8	-81.5 $\pm$ 2.9
D-1884	4999	20	4	3	C22	Liver	-88 $\pm$ 2.9	-85.5 $\pm$ 3.2	-86 $\pm$ 2.3
D-1856	4999	20	4	3	C22	Liver	-82.3 $\pm$ 4.5	-79.7 $\pm$ 5	-74.3 $\pm$ 5.8
D-1862	5080	20	4	3	C22	Liver	-72.3 $\pm$ 3.5	-69.3 $\pm$ 4.1	-65 $\pm$ 3.8
D-1869	4999	20	4	3	C22	Liver	-78.8 $\pm$ 2.7	-73.6 $\pm$ 2.9	-68.7 $\pm$ 1
D-1869	4999	10	4	3	C22	Liver	-72 $\pm$ 3.1	-69.4 $\pm$ 2.9	-67.1 $\pm$ 3.3
D-1869	4999	5	4	3	C22	Liver	-63.3 $\pm$ 6.4	-60.9 $\pm$ 6.8	-57.3 $\pm$ 7
D-1709	4999	3	4	3	GalNAc	Liver	-81.1 $\pm$ 4	-77.1 $\pm$ 4.7	-75.4 $\pm$ 5.2
D-1709	4999	1	4	3	GalNAc	Liver	-42.9 $\pm$ 7	-39 $\pm$ 7.6	-43.8 $\pm$ 7.5
D-1709	4999	0.5	4	3	GalNAc	Liver	-60.9 $\pm$ 6	-58.1 $\pm$ 5.9	-57.8 $\pm$ 5.8
D-1774	5276	3	4	3	GalNAc	Liver	-66.1 $\pm$ 4.5	-59.6 $\pm$ 5.6	-57.6 $\pm$ 4.7
D-1975	5276	20	4	3	C22	Liver	-73.5 $\pm$ 3.6	-70.7 $\pm$ 3.5	-65.4 $\pm$ 3.3
D-1976	5276	20	3	3	C22	Liver	-80.2 $\pm$ 0.4	-76.7 $\pm$ 0.3	-69.3 $\pm$ 0.7
D-1870	5043	20	4	3	C22	Liver	-49 $\pm$ 11.5	-47.6 $\pm$ 11.6	-49.4 $\pm$ 11
D-1698	5043	20	4	3	C22	Liver	-10.2 $\pm$ 15.9	-13.2 $\pm$ 16	-27.4 $\pm$ 9.6
D-1875	5043	20	4	3	C22	Liver	-41.9 $\pm$ 9	-40.1 $\pm$ 10.4	-44.8 $\pm$ 6.9
D-1868	5045	20	4	3	C22	Liver	-33 $\pm$ 10.8	-32.2 $\pm$ 11.1	-35.7 $\pm$ 9.5
D-1871	5045	20	4	3	C22	Liver	-26 $\pm$ 7.2	-27.4 $\pm$ 7.4	-27.7 $\pm$ 6.2
D-1876	5045	20	4	3	C22	Liver	-32 $\pm$ 3.2	-25.4 $\pm$ 2.7	-29.9 $\pm$ 3.8
D-1699	5045	20	4	3	C22	Liver	-22.6 $\pm$ 16.4	-20.2 $\pm$ 16.8	-21.4 $\pm$ 15.4
D-1883	5043	20	4	3	C22	Liver	-64.8 $\pm$ 6.2	-63.2 $\pm$ 6.4	-64.8 $\pm$ 6
D-1886	5043	20	4	3	C22	Liver	-73.5 $\pm$ 5.6	-70.4 $\pm$ 6.6	-70.9 $\pm$ 6.2
D-1855	5045	20	4	3	C22	Liver	-61 $\pm$ 5.4	-57.8 $\pm$ 6.1	-53.2 $\pm$ 2.9
D-1888	5045	20	4	3	C22	Liver	-68.3 $\pm$ 3.5	-65.1 $\pm$ 2.8	-67.2 $\pm$ 2.4
D-1882	5045	20	4	3	C22	Liver	-69.1 $\pm$ 3.3	-64.7 $\pm$ 5	-63.7 $\pm$ 4.1
D-1885	5045	20	4	3	C22	Liver	-66 $\pm$ 1.9	-62.4 $\pm$ 2.1	-59 $\pm$ 2

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Tissue	Avg. % Change in mRNA $\pm$ STD		
							eGFP-1	eGFP-2	BGHpA
D-1611	5043	3	4	3	GalNAc	Liver	-70.5 $\pm$ 6.1	-71.5 $\pm$ 6.1	-70.3 $\pm$ 5.7
D-1611	5043	1	4	3	GalNAc	Liver	-17.9 $\pm$ 13.6	-21.3 $\pm$ 15.3	-28.7 $\pm$ 8.1
D-1611	5043	0.5	4	3	GalNAc	Liver	5.7 $\pm$ 5.4	-3.3 $\pm$ 4.3	-5.7 $\pm$ 6.5
D-1718	5045	3	4	3	GalNAc	Liver	-63.1 $\pm$ 1.5	-56.3 $\pm$ 1.9	-62.1 $\pm$ 1.1
D-1718	5045	1	4	3	GalNAc	Liver	-37.8 $\pm$ 21.9	-30.9 $\pm$ 26.4	-33.7 $\pm$ 19.9
D-1718	5045	0.5	4	3	GalNAc	Liver	-21 $\pm$ 13.3	-16.5 $\pm$ 16.5	-21.2 $\pm$ 16.9
D-1866	4999	20	4	3	C22	Adipose	-94.3 $\pm$ 1.3	-93.9 $\pm$ 1.3	-90.9 $\pm$ 1.4
D-1873	4999	20	4	3	C22	Adipose	-94.3 $\pm$ 1.7	-93.7 $\pm$ 1.8	-89.8 $\pm$ 3.3
D-1877	4999	20	4	3	C22	Adipose	-95 $\pm$ 1.7	-94.7 $\pm$ 1.8	-94.9 $\pm$ 1.7
D-1697	4999	20	4	3	C22	Adipose	-96.9 $\pm$ 1.2	-96.6 $\pm$ 1.4	-96.1 $\pm$ 1.5
D-1846	5080	20	4	3	C22	Adipose	-92.2 $\pm$ 2.4	-90.8 $\pm$ 3	-90.9 $\pm$ 2.6
D-1881	4999	20	4	3	C22	Adiposc	-97.3 $\pm$ 0.7	-97.2 $\pm$ 0.7	-96.6 $\pm$ 0.9
D-1887	4999	20	4	3	C22	Adipose	-93.9 $\pm$ 4	-93.2 $\pm$ 4.7	-95.8 $\pm$ 2.3
D-1880	4999	20	4	3	C22	Adipose	-96.1 $\pm$ 1.8	-95.6 $\pm$ 2	-96.3 $\pm$ 1.4
D-1884	4999	20	4	3	C22	Adipose	-98.6 $\pm$ 0.5	-98.5 $\pm$ 0.6	-98.4 $\pm$ 0.5
D-1856	4999	20	4	3	C22	Adipose	-98.3 $\pm$ 0.6	-98.1 $\pm$ 0.7	-97.5 $\pm$ 0.9
D-1862	5080	20	4	3	C22	Adipose	-96.1 $\pm$ 1.2	-95.7 $\pm$ 1.5	-95.4 $\pm$ 1.2
D-1869	4999	20	4	3	C22	Adipose	-93.9 $\pm$ 1.6	-92.5 $\pm$ 2.2	-92.8 $\pm$ 0.5
D-1869	4999	10	4	3	C22	Adipose	-95.5 $\pm$ 1.3	-94.8 $\pm$ 1.6	-95.6 $\pm$ 1.3
D-1869	4999	5	4	3	C22	Adipose	-87.7 $\pm$ 4.9	-86.2 $\pm$ 5.1	-88.6 $\pm$ 4.1
D-1975	5276	20	4	3	C22	Adipose	-95.9 $\pm$ 1.4	-95.2 $\pm$ 1.4	-95.9 $\pm$ 1.3
D-1976	5276	20	3	3	C22	Adipose	-94.1 $\pm$ 2.4	-93.1 $\pm$ 2.6	-92.2 $\pm$ 2.7
D-1870	5043	20	4	3	C22	Adipose	-84.4 $\pm$ 6.6	-85.6 $\pm$ 6.3	-83.9 $\pm$ 6.8
D-1698	5043	20	4	3	C22	Adiposc	-70.8 $\pm$ 5.6	-71.8 $\pm$ 5.3	-63.4 $\pm$ 7.9
D-1875	5043	20	4	3	C22	Adipose	-87.5 $\pm$ 4	-88.9 $\pm$ 3.5	-83.6 $\pm$ 6.1
D-1868	5045	20	4	3	C22	Adipose	-72.1 $\pm$ 13.2	-73.5 $\pm$ 13.3	-68.2 $\pm$ 10.6
D-1871	5045	20	4	3	C22	Adipose	-61.6 $\pm$ 12.1	-64 $\pm$ 11.3	-62.7 $\pm$ 6.2
D-1876	5045	20	4	3	C22	Adipose	-82.3 $\pm$ 5.1	-82.5 $\pm$ 5.1	-71.8 $\pm$ 6.4
D-1699	5045	20	4	3	C22	Adipose	-81.5 $\pm$ 4.5	-82.6 $\pm$ 4.6	-65.5 $\pm$ 10.1
D-1883	5043	20	4	3	C22	Adipose	-90 $\pm$ 5.9	-90.7 $\pm$ 5.7	-85.9 $\pm$ 8.2
D-1886	5043	20	4	3	C22	Adipose	-84.9 $\pm$ 7.6	-84 $\pm$ 7.9	-81.7 $\pm$ 9.8
D-1855	5045	20	4	3	C22	Adipose	-76.9 $\pm$ 8.7	-77.7 $\pm$ 8.4	-68.8 $\pm$ 5.7
D-1888	5045	20	4	3	C22	Adipose	-82.1 $\pm$ 3	-83.1 $\pm$ 3	-70.2 $\pm$ 5
D-1882	5045	20	4	3	C22	Adipose	-74.7 $\pm$ 6.7	-74.7 $\pm$ 6.7	-59.7 $\pm$ 9.4
D-1885	5045	20	4	3	C22	Adipose	-86.1 $\pm$ 1.6	-86.8 $\pm$ 1.6	-78.6 $\pm$ 3

TABLE 13 – siRNA Efficacy in Liver 4 Weeks Following siRNA Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1933	1514	3	4	1	GalNAc	3.7 $\pm$ 14.8	12.5 $\pm$ 17	2.9 $\pm$ 18.1
D-1939	1514	3	4	1	GalNAc	18.7 $\pm$ 10.1	23.6 $\pm$ 11.5	21.7 $\pm$ 15.2
D-1945	1514	3	4	1	GalNAc	-33.5 $\pm$ 16.6	-26.5 $\pm$ 18.2	-25.2 $\pm$ 9.8
D-1951	1514	3	4	1	GalNAc	7.5 $\pm$ 65.3	15.5 $\pm$ 67.9	4.3 $\pm$ 46.6
D-1957	1514	3	4	1	GalNAc	12.1 $\pm$ 38.9	17.4 $\pm$ 37.8	5.6 $\pm$ 35.6
D-1963	1514	3	4	1	GalNAc	-7.4 $\pm$ 45.8	4.7 $\pm$ 55.1	-11.4 $\pm$ 41.8
D-1969	1514	3	4	1	GalNAc	-12.6 $\pm$ 14.6	-6.2 $\pm$ 11.6	-7.7 $\pm$ 12

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1820	1514	3	4	1	GalNAc	-24.8 $\pm$ 19	-14.5 $\pm$ 27.1	-17.8 $\pm$ 21.1
D-1938	2343	3	4	1	GalNAc	-37.7 $\pm$ 14.9	-32.9 $\pm$ 17.1	-13.3 $\pm$ 22.1
D-1944	2343	3	4	1	GalNAc	-35 $\pm$ 3.2	-26 $\pm$ 7.1	-21 $\pm$ 16.2
D-1950	2343	3	4	1	GalNAc	-18.4 $\pm$ 11	-9.8 $\pm$ 10.8	-9.8 $\pm$ 7.6
D-1956	2343	3	4	1	GalNAc	-48.5 $\pm$ 43	-42.3 $\pm$ 51.4	-40.4 $\pm$ 49.1
D-1962	2343	3	4	1	GalNAc	-10.4 $\pm$ 19.6	2.8 $\pm$ 27.4	-10.1 $\pm$ 19.3
D-1968	2343	3	4	1	GalNAc	-44.2 $\pm$ 16.5	-36.9 $\pm$ 20	-27 $\pm$ 21.7
D-1974	2343	3	4	1	GalNAc	-52.5 $\pm$ 5.8	-46.5 $\pm$ 4.2	-33.5 $\pm$ 6.4
D-1810	2343	3	4	1	GalNAc	-42.8 $\pm$ 41.3	-38.5 $\pm$ 44.2	-30 $\pm$ 47.6
D-1935	2417	3	4	1	GalNAc	-20.7 $\pm$ 16.2	-13.1 $\pm$ 23.6	-34.4 $\pm$ 16.2
D-1941	2417	3	4	1	GalNAc	-27.7 $\pm$ 27.6	-24.9 $\pm$ 29.4	-28.4 $\pm$ 29.4
D-1947	2417	3	4	1	GalNAc	-24 $\pm$ 41.1	-18.9 $\pm$ 46.2	-28.4 $\pm$ 32.2
D-1953	2417	3	4	1	GalNAc	-48.3 $\pm$ 21.8	-40.7 $\pm$ 25.3	-54.8 $\pm$ 16.5
D-1959	2417	3	4	1	GalNAc	-31.3 $\pm$ 10.2	-27.3 $\pm$ 8.9	-42.4 $\pm$ 9.6
D-1965	2417	3	4	1	GalNAc	-30.7 $\pm$ 13.8	-25.7 $\pm$ 13.8	-33.8 $\pm$ 12
D-1971	2417	3	4	1	GalNAc	-25 $\pm$ 22	-10.9 $\pm$ 28.5	-25.4 $\pm$ 33
D-1812	2417	3	4	1	GalNAc	-29.2 $\pm$ 17.7	-27 $\pm$ 17.8	-39 $\pm$ 14
D-1937	4412	3	3	3	GalNAc	-74 $\pm$ 6.9	-70.8 $\pm$ 6.4	-66.4 $\pm$ 6.8
D-1943	4412	3	4	3	GalNAc	-68 $\pm$ 12.7	-64.2 $\pm$ 15	-66.3 $\pm$ 11
D-1949	4412	3	4	3	GalNAc	-54.8 $\pm$ 7.8	-52.2 $\pm$ 6.7	-55.5 $\pm$ 5.7
D-1955	4412	3	4	3	GalNAc	-84.5 $\pm$ 1.6	-82.6 $\pm$ 2.2	-76.7 $\pm$ 3.5
D-1961	4412	3	4	3	GalNAc	-78 $\pm$ 12	-75.7 $\pm$ 13.3	-73 $\pm$ 13.1
D-1967	4412	3	4	3	GalNAc	-72.2 $\pm$ 24	-70 $\pm$ 25.1	-64.3 $\pm$ 22.4
D-1973	4412	3	4	3	GalNAc	-62.5 $\pm$ 7.3	-56.8 $\pm$ 7.3	-58.2 $\pm$ 3
D-1777	4412	3	4	3	GalNAc	-74 $\pm$ 17.9	-72.8 $\pm$ 20	-72 $\pm$ 20.7
D-1934	5249	3	4	3	GalNAc	-10.6 $\pm$ 25.9	-4.4 $\pm$ 25.7	-21.6 $\pm$ 24.3
D-1940	5249	3	4	3	GalNAc	-41.4 $\pm$ 11.5	-39.9 $\pm$ 9.3	-46.1 $\pm$ 10.9
D-1946	5249	3	4	3	GalNAc	-45.9 $\pm$ 12.7	-43.7 $\pm$ 13.7	-50 $\pm$ 7.2
D-1952	5249	3	4	3	GalNAc	-72.6 $\pm$ 10.9	-72.3 $\pm$ 11.8	-74.3 $\pm$ 12.6
D-1958	5249	3	4	3	GalNAc	-45.9 $\pm$ 26.4	-44.7 $\pm$ 27.7	-56.1 $\pm$ 17.1
D-1964	5249	3	4	3	GalNAc	-56.3 $\pm$ 19.1	-56.1 $\pm$ 17.1	-60.4 $\pm$ 12.1
D-1970	5249	3	4	3	GalNAc	-79.4 $\pm$ 15	-79.3 $\pm$ 14.9	-80.1 $\pm$ 14
D-1769	5249	3	4	3	GalNAc	-67.2 $\pm$ 3.2	-64.9 $\pm$ 4.7	-72.2 $\pm$ 3.8
D-1936	5274	3	4	3	GalNAc	-61.7 $\pm$ 13	-60.9 $\pm$ 13.1	-67.3 $\pm$ 10.4
D-1942	5274	3	4	3	GalNAc	-51.7 $\pm$ 36.3	-50.8 $\pm$ 37.5	-63.6 $\pm$ 19.5
D-1948	5274	3	4	3	GalNAc	-70.5 $\pm$ 8.4	-67.8 $\pm$ 11	-71.7 $\pm$ 6.5
D-1954	5274	3	4	3	GalNAc	-71.9 $\pm$ 8.4	-70.6 $\pm$ 9.6	-74 $\pm$ 6.1
D-1960	5274	3	4	3	GalNAc	-69.7 $\pm$ 15.5	-67.5 $\pm$ 16.3	-77.9 $\pm$ 5.6
D-1966	5274	3	4	3	GalNAc	-76.8 $\pm$ 12.6	-74.1 $\pm$ 14	-76.2 $\pm$ 11.3
D-1972	5274	3	4	3	GalNAc	-79.7 $\pm$ 8.6	-77.4 $\pm$ 10	-77 $\pm$ 10.5
D-1773	5274	3	4	3	GalNAc	-69.5 $\pm$ 13.7	-66.8 $\pm$ 14.1	-73.9 $\pm$ 11.7
D-1709	4999	3	4	3	GalNAc	-86.7 $\pm$ 8.9	-85.2 $\pm$ 9.8	-84 $\pm$ 10.7
D-1705	5043	3	4	3	GalNAc	-78.5 $\pm$ 2.3	-77.1 $\pm$ 2.2	-75.3 $\pm$ 2.7
D-1597	1333	3	4	9-span	GalNAc	-81.3 $\pm$ 6.9	-81.6 $\pm$ 7.7	-81.6 $\pm$ 6.7
D-1709	4999	3	4	9-span	GalNAc	-93.4 $\pm$ 2.5	-93.7 $\pm$ 2	-94.5 $\pm$ 1.9
D-1705	5043	3	4	9-span	GalNAc	-94.4 $\pm$ 0.4	-94.2 $\pm$ 0.5	-94.7 $\pm$ 0.4

TABLE 14 – siRNA Efficacy in Liver and Adipose Tissue 4 Weeks Following siRNA

Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Tissue	Carrier	Avg. % Change in mRNA $\pm$ STD		
							eGFP-1	eGFP-2	BGHpA
D-1709	4999	3	4	22-span	Liver	GalNAc	-80.8 $\pm$ 12	-81.6 $\pm$ 9.7	-85.7 $\pm$ 8.9
D-1887	4999	20	4	22-span	Liver	C22	-85.6 $\pm$ 2.1	-85.9 $\pm$ 2.7	-88.9 $\pm$ 1.7
D-1702	4999	3	4	22-span	Liver	GalNAc	-83.6 $\pm$ 8.3	-84.3 $\pm$ 7.4	-88.3 $\pm$ 5.2
D-1884	4999	20	4	22-span	Liver	C22	-79.5 $\pm$ 2.9	-80.2 $\pm$ 3.4	-85.1 $\pm$ 2.2
D-1978	4999	3	4	22-span	Liver	GalNAc	-85.9 $\pm$ 3.8	-86.4 $\pm$ 3.4	-89.8 $\pm$ 3
D-1879	4999	3	4	22-span	Liver	GalNAc	-81.3 $\pm$ 3	-82.6 $\pm$ 2.1	-87.1 $\pm$ 0.7
D-2002	4999	20	4	22-span	Liver	C22	-88.5 $\pm$ 5.5	-88.5 $\pm$ 5.4	-92.1 $\pm$ 3.2
D-1987	4999	3	4	22-span	Liver	GalNAc	-85.9 $\pm$ 5.6	-86.4 $\pm$ 5.2	-91.6 $\pm$ 2.2
D-1992	4999	3	4	22-span	Liver	GalNAc	-82.7 $\pm$ 11.3	-84 $\pm$ 9.9	-88.1 $\pm$ 5.8
D-1997	4999	3	4	22-span	Liver	GalNAc	-84.7 $\pm$ 7.1	-84.8 $\pm$ 6.2	-88.1 $\pm$ 6.2
D-1705	5043	3	4	22-span	Liver	GalNAc	-82.3 $\pm$ 8.1	-82.4 $\pm$ 8.1	-84.2 $\pm$ 7
D-1886	5043	20	4	22-span	Liver	C22	-86.2 $\pm$ 11.9	-87.3 $\pm$ 10.7	-87.9 $\pm$ 8.7
D-1980	5043	3	4	22-span	Liver	GalNAc	-76.9 $\pm$ 20.9	-77.6 $\pm$ 19	-
D-1984	5043	3	4	22-span	Liver	GalNAc	-77.3 $\pm$ 8	-78.5 $\pm$ 7.6	-82.3 $\pm$ 6.2
D-2004	5043	20	3	22-span	Liver	C22	-65.8 $\pm$ 11.7	-69.4 $\pm$ 10	-73.7 $\pm$ 7.7
D-1989	5043	3	4	22-span	Liver	GalNAc	-82.8 $\pm$ 9.6	-83.4 $\pm$ 8	-84.3 $\pm$ 7.3
D-1994	5043	3	4	22-span	Liver	GalNAc	-79.1 $\pm$ 3.3	-79.5 $\pm$ 2.2	-83 $\pm$ 2.2
D-1999	5043	3	4	22-span	Liver	GalNAc	-66.2 $\pm$ 27.4	-67.7 $\pm$ 25.4	-
D-1704	5045	3	4	22-span	Liver	GalNAc	-83 $\pm$ 10.2	-83.9 $\pm$ 10.1	-88.6 $\pm$ 5.4
D-1885	5045	20	4	22-span	Liver	C22	-89.1 $\pm$ 5.5	-90.3 $\pm$ 4.9	-90.1 $\pm$ 7
D-1979	5045	3	4	22-span	Liver	GalNAc	-92.3 $\pm$ 3.3	-93 $\pm$ 3	-93.7 $\pm$ 2.4
D-1983	5045	3	4	22-span	Liver	GalNAc	-71.8 $\pm$ 8.3	-74.6 $\pm$ 7.4	-83.6 $\pm$ 4.8
D-2003	5045	20	4	22-span	Liver	C22	-86.7 $\pm$ 6.2	-88.5 $\pm$ 5.2	-90.2 $\pm$ 4.8
D-1988	5045	3	4	22-span	Liver	GalNAc	-84.4 $\pm$ 16.7	-85 $\pm$ 15.7	-89.6 $\pm$ 9.9
D-1993	5045	3	4	22-span	Liver	GalNAc	-85 $\pm$ 7.4	-86.1 $\pm$ 6.7	-89.9 $\pm$ 4
D-1998	5045	3	4	22-span	Liver	GalNAc	-95.3 $\pm$ 1.8	-95.6 $\pm$ 1.4	-96 $\pm$ 1.5
D-1623	5080	3	4	22-span	Liver	GalNAc	-77.5 $\pm$ 13.5	-78.8 $\pm$ 14.7	-82.5 $\pm$ 10.1
D-1862	5080	20	4	22-span	Liver	C22	-79 $\pm$ 16	-81.1 $\pm$ 14.7	-83 $\pm$ 11.3
D-1981	5080	3	4	22-span	Liver	GalNAc	-82.2 $\pm$ 14.2	-83.2 $\pm$ 13.7	-86.4 $\pm$ 10.4
D-1985	5080	3	4	22-span	Liver	GalNAc	-90.3 $\pm$ 5.4	-91.3 $\pm$ 4.7	-91.5 $\pm$ 4.2
D-2005	5080	20	4	22-span	Liver	C22	-88.9 $\pm$ 8	-89.4 $\pm$ 7.3	-90.3 $\pm$ 5.3
D-1990	5080	3	4	22-span	Liver	GalNAc	-81.7 $\pm$ 8.7	-84.1 $\pm$ 7.3	-86.1 $\pm$ 5.4
D-1995	5080	3	4	22-span	Liver	GalNAc	-80.9 $\pm$ 8.8	-84 $\pm$ 7.1	-82.8 $\pm$ 7.6
D-2000	5080	3	4	22-span	Liver	GalNAc	-78.3 $\pm$ 6.4	-81.5 $\pm$ 6.2	-81.9 $\pm$ 4.5
D-1955	4412	3	4	22-span	Liver	GalNAc	-74.8 $\pm$ 8.4	-76.7 $\pm$ 7.7	-78.3 $\pm$ 9.3
D-1970	5249	3	4	22-span	Liver	GalNAc	-66.9 $\pm$ 24	-71.3 $\pm$ 21.6	-74.5 $\pm$ 14.7
D-1972	5274	3	4	22-span	Liver	GalNAc	-77 $\pm$ 10.9	-78.1 $\pm$ 9.6	-80.5 $\pm$ 9.2
D-1774	5276	3	3	22-span	Liver	GalNAc	-73.8 $\pm$ 10	-74.7 $\pm$ 9.7	-77.9 $\pm$ 10.6
D-1976	5276	20	4	22-span	Liver	C22	-83.6 $\pm$ 6.4	-83.9 $\pm$ 6.9	-87.9 $\pm$ 5.6
D-1977	5276	3	4	22-span	Liver	GalNAc	-89.5 $\pm$ 1.5	-89.2 $\pm$ 1.4	-90.7 $\pm$ 1.1
D-1982	5276	3	4	22-span	Liver	GalNAc	-75.7 $\pm$ 6.9	-74.6 $\pm$ 7.8	-80.5 $\pm$ 5.3
D-2001	5276	20	4	22-span	Liver	C22	-83.7 $\pm$ 4.4	-83.5 $\pm$ 4.9	-86.7 $\pm$ 3
D-1986	5276	3	4	22-span	Liver	GalNAc	-69.6 $\pm$ 9.2	-71.4 $\pm$ 7.8	-77.6 $\pm$ 7.3
D-1991	5276	3	4	22-span	Liver	GalNAc	-83.7 $\pm$ 5.2	-83 $\pm$ 5.4	-86.6 $\pm$ 4.1

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Tissue	Carrier	Avg. % Change in mRNA $\pm$ STD		
							eGFP-1	eGFP-2	BGHpA
D-1996	5276	3	4	22-span	Liver	GalNAc	-83.3 $\pm$ 11.2	-84.3 $\pm$ 11.2	-85.9 $\pm$ 8.9
D-2017	1333	3	4	22-span	Liver	GalNAc	-93.1 $\pm$ 2	-92.7 $\pm$ 2	-94.7 $\pm$ 1.8
D-1597	1333	3	4	22-span	Liver	GalNAc	-87.6 $\pm$ 4.2	-87.6 $\pm$ 3.7	-89.1 $\pm$ 3.5
D-1853	1333	20	4	22-span	Liver	C22	-87.2 $\pm$ 3.1	-86.5 $\pm$ 3.1	-89.4 $\pm$ 2.6
D-1667	1309	3	4	22-span	Liver	GalNAc	-84.2 $\pm$ 10.2	-84.3 $\pm$ 9.6	-86.5 $\pm$ 10.6
D-1849	1309	20	4	22-span	Liver	C22	-91.1 $\pm$ 8.5	-91 $\pm$ 7.9	-92.3 $\pm$ 6.2
D-1636	2144	3	4	22-span	Liver	GalNAc	-78.2 $\pm$ 5.2	-77.8 $\pm$ 5.3	-77.7 $\pm$ 4.4
D-1858	2144	20	4	22-span	Liver	C22	-85.5 $\pm$ 6.7	-85.4 $\pm$ 6.1	-90.7 $\pm$ 2.5
D-1650	3000	3	4	22-span	Liver	GalNAc	-87.5 $\pm$ 6	-87 $\pm$ 5.9	-89.6 $\pm$ 4.4
D-2035	3000	20	4	22-span	Liver	C22	-50.4 $\pm$ 29.9	-48.7 $\pm$ 30.8	-46.6 $\pm$ 30.8
D-1557	3000	3	4	22-span	Liver	GalNAc	-85.3 $\pm$ 14.9	-85.2 $\pm$ 14.5	-88.3 $\pm$ 10.7
D-1861	3000	20	4	22-span	Liver	C22	-92.8 $\pm$ 3.2	-92.2 $\pm$ 3.4	-94.3 $\pm$ 2.2
D-1709	4999	3	4	22-span	Adipose	GalNAc	54.7 $\pm$ 86.1	53.3 $\pm$ 88.7	59.4 $\pm$ 77
D-1887	4999	20	4	22-span	Adipose	C22	-85.4 $\pm$ 10.7	-85.3 $\pm$ 10	-88.2 $\pm$ 7.5
D-1702	4999	3	4	22-span	Adipose	GalNAc	-38.1 $\pm$ 72.9	-45 $\pm$ 62.5	-34.8 $\pm$ 83
D-1884	4999	20	4	22-span	Adipose	C22	-90.2 $\pm$ 1.9	-90.2 $\pm$ 1.6	-92.3 $\pm$ 1.9
D-1978	4999	3	4	22-span	Adipose	GalNAc	11.8 $\pm$ 77.3	6.2 $\pm$ 70.4	7.8 $\pm$ 84.9
D-1879	4999	3	4	22-span	Adipose	GalNAc	-14.4 $\pm$ 28.1	-19 $\pm$ 28	-6.3 $\pm$ 26.8
D-2002	4999	20	4	22-span	Adipose	C22	-92.9 $\pm$ 5.2	-93.1 $\pm$ 5.4	-95.3 $\pm$ 3
D-1987	4999	3	4	22-span	Adipose	GalNAc	73.5 $\pm$ 135.8	79 $\pm$ 140.5	68.6 $\pm$ 125.8
D-1992	4999	3	4	22-span	Adipose	GalNAc	-21.1 $\pm$ 86.3	-17.9 $\pm$ 86.4	-20.7 $\pm$ 86
D-1997	4999	3	4	22-span	Adipose	GalNAc	-5.5 $\pm$ 40.6	-7.8 $\pm$ 43.4	-7.4 $\pm$ 46.8
D-1705	5043	3	4	22-span	Adipose	GalNAc	6.6 $\pm$ 93.3	2.5 $\pm$ 81	-2.2 $\pm$ 89.2
D-1886	5043	20	4	22-span	Adipose	C22	-91.4 $\pm$ 5.8	-90.7 $\pm$ 6	-90.8 $\pm$ 7.3
D-1980	5043	3	4	22-span	Adipose	GalNAc	-1.1 $\pm$ 45.8	-12.7 $\pm$ 40.1	1.1 $\pm$ 48
D-1984	5043	3	4	22-span	Adipose	GalNAc	-30.8 $\pm$ 60.8	-28.8 $\pm$ 60.2	-34.7 $\pm$ 51.4
D-2004	5043	20	3	22-span	Adipose	C22	-90.9 $\pm$ 7.3	-91 $\pm$ 6	-92.8 $\pm$ 5.6
D-1989	5043	3	4	22-span	Adipose	GalNAc	-29.2 $\pm$ 64	-36 $\pm$ 54.6	-18.9 $\pm$ 74.2
D-1994	5043	3	4	22-span	Adipose	GalNAc	160.7 $\pm$ 277.8	170.5 $\pm$ 276.8	144.6 $\pm$ 227.8
D-1999	5043	3	4	22-span	Adipose	GalNAc	43.8 $\pm$ 119.1	49.5 $\pm$ 123.3	50.5 $\pm$ 127.9
D-1704	5045	3	4	22-span	Adipose	GalNAc	-45.7 $\pm$ 33.2	-45.7 $\pm$ 35.2	-46 $\pm$ 29.9
D-1885	5045	20	4	22-span	Adipose	C22	-97 $\pm$ 2.2	-97 $\pm$ 1.9	-96.7 $\pm$ 3
D-1979	5045	3	4	22-span	Adipose	GalNAc	-60.8 $\pm$ 31.4	-58.4 $\pm$ 37	-65.6 $\pm$ 25.6
D-1983	5045	3	4	22-span	Adipose	GalNAc	-31.4 $\pm$ 68.4	-24.2 $\pm$ 78.3	-34.1 $\pm$ 65.3
D-2003	5045	20	4	22-span	Adipose	C22	-92.5 $\pm$ 5.1	-92.8 $\pm$ 4.5	-94.6 $\pm$ 3.6
D-1988	5045	3	4	22-span	Adipose	GalNAc	125 $\pm$ 249.1	108.8 $\pm$ 235.9	162.6 $\pm$ 294.1
D-1993	5045	3	4	22-span	Adipose	GalNAc	-27 $\pm$ 97	-31.1 $\pm$ 85.3	-24.5 $\pm$ 101.3
D-1998	5045	3	4	22-span	Adipose	GalNAc	17.7 $\pm$ 133.4	6.3 $\pm$ 116.3	14.3 $\pm$ 134.1
D-1623	5080	3	4	22-span	Adipose	GalNAc	-25.3 $\pm$ 71.6	-29.6 $\pm$ 65.9	-23.2 $\pm$ 76.9
D-1862	5080	20	4	22-span	Adipose	C22	-92.1 $\pm$ 4.3	-91.8 $\pm$ 4.8	-94.6 $\pm$ 3.7
D-1981	5080	3	4	22-span	Adipose	GalNAc	-1.8 $\pm$ 67.6	-8.1 $\pm$ 63.5	0.5 $\pm$ 72.2
D-1985	5080	3	4	22-span	Adipose	GalNAc	-21.9 $\pm$ 83	-25.4 $\pm$ 79	-24.5 $\pm$ 86.3
D-2005	5080	20	4	22-span	Adipose	C22	-85.9 $\pm$ 9.7	-86.8 $\pm$ 8.5	-92.3 $\pm$ 5.5
D-1990	5080	3	4	22-span	Adipose	GalNAc	-4.1 $\pm$ 104	-5.1 $\pm$ 100.6	-2 $\pm$ 107.4
D-1995	5080	3	4	22-span	Adipose	GalNAc	-23.7 $\pm$ 41.3	-29.9 $\pm$ 39.2	-28.1 $\pm$ 41.4

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Tissue	Carrier	Avg. % Change in mRNA $\pm$ STD		
							eGFP-1	eGFP-2	BGHpA
D-2000	5080	3	4	22-span	Adipose	GalNAc	-71.9 $\pm$ 15.2	-73.3 $\pm$ 14.4	-69.7 $\pm$ 18.6
D-1955	4412	3	4	22-span	Adipose	GalNAc	-36.7 $\pm$ 62.3	-36.3 $\pm$ 61.6	-34.6 $\pm$ 68.6
D-1970	5249	3	4	22-span	Adipose	GalNAc	-51.1 $\pm$ 48.8	-48.6 $\pm$ 52.8	-54.4 $\pm$ 47.3
D-1972	5274	3	4	22-span	Adipose	GalNAc	-37 $\pm$ 22.6	-28.7 $\pm$ 27.9	-37.3 $\pm$ 21
D-1774	5276	3	3	22-span	Adipose	GalNAc	171 $\pm$ 226.8	165.7 $\pm$ 214.9	168.2 $\pm$ 242.3
D-1976	5276	20	4	22-span	Adipose	C22	-82.7 $\pm$ 15.8	-82.9 $\pm$ 15	-87.8 $\pm$ 11.5
D-1977	5276	3	4	22-span	Adipose	GalNAc	-21.3 $\pm$ 82.3	-14.2 $\pm$ 87.6	-23.4 $\pm$ 78.2
D-1982	5276	3	4	22-span	Adipose	GalNAc	164.9 $\pm$ 233.4	167.4 $\pm$ 228.3	157.3 $\pm$ 227.8
D-2001	5276	20	4	22-span	Adipose	C22	-92.3 $\pm$ 2.3	-91.7 $\pm$ 2.6	-95.2 $\pm$ 1.4
D-1986	5276	3	4	22-span	Adipose	GalNAc	80.1 $\pm$ 94	67.7 $\pm$ 71.1	77.4 $\pm$ 85.6
D-1991	5276	3	4	22-span	Adipose	GalNAc	-47.7 $\pm$ 10.6	-47.9 $\pm$ 11.6	-47.2 $\pm$ 11.1
D-1996	5276	3	4	22-span	Adipose	GalNAc	251.3 $\pm$ 448.9	228.4 $\pm$ 404.2	294.1 $\pm$ 491.1
D-2017	1333	3	4	22-span	Adipose	GalNAc	-51.1 $\pm$ 20.6	-49.3 $\pm$ 23	-48.6 $\pm$ 24.1
D-1597	1333	3	4	22-span	Adipose	GalNAc	58.2 $\pm$ 158.7	46.4 $\pm$ 139.6	44.4 $\pm$ 138.8
D-1853	1333	20	4	22-span	Adipose	C22	-50.4 $\pm$ 2.9	-51.3 $\pm$ 2	-65.9 $\pm$ 7.5
D-1667	1309	3	4	22-span	Adipose	GalNAc	154.6 $\pm$ 218.9	143.5 $\pm$ 199.5	163 $\pm$ 206.2
D-1849	1309	20	4	22-span	Adipose	C22	-71.6 $\pm$ 27.5	-70 $\pm$ 30	-79.5 $\pm$ 23.8
D-1636	2144	3	4	22-span	Adipose	GalNAc	-69.5 $\pm$ 25.7	-69.3 $\pm$ 23.4	-77.5 $\pm$ 19.5
D-1858	2144	20	4	22-span	Adipose	C22	-66.2 $\pm$ 18.2	-63.6 $\pm$ 22.3	-81.7 $\pm$ 10.5
D-1650	3000	3	4	22-span	Adipose	GalNAc	121 $\pm$ 235.1	104.5 $\pm$ 202.1	179.8 $\pm$ 319.6
D-2035	3000	20	4	22-span	Adipose	C22	-65 $\pm$ 28.1	-62.1 $\pm$ 29.7	-66.4 $\pm$ 31.9
D-1557	3000	3	4	22-span	Adipose	GalNAc	67.1 $\pm$ 166.8	93.7 $\pm$ 184	74.4 $\pm$ 166.2
D-1861	3000	20	4	22-span	Adipose	C22	-96 $\pm$ 5.4	-95.3 $\pm$ 6.4	-97 $\pm$ 3.6

TABLE 15 – siRNA Efficacy in Liver 4 Weeks Following siRNA Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1614	4999	1	4	3	GalNAc	-40.7 $\pm$ 17.9	-39.6 $\pm$ 15.7	-41.1 $\pm$ 19.3
D-1611	5043	1	4	3	GalNAc	-31.7 $\pm$ 28	-32.7 $\pm$ 26	-48.1 $\pm$ 20.5
D-1742	4484	1	4	3	GalNAc	-3.9 $\pm$ 22.4	-0.9 $\pm$ 17.6	-23.5 $\pm$ 16.7
D-1743	4485	1	4	3	GalNAc	-35.7 $\pm$ 39.2	-33.8 $\pm$ 43.6	-45.2 $\pm$ 26.3
D-1744	4717	1	4	3	GalNAc	-44.9 $\pm$ 30.1	-49.8 $\pm$ 23.9	-45.9 $\pm$ 12.8
D-1745	4799	1	4	3	GalNAc	-15 $\pm$ 25.8	-21.9 $\pm$ 24	-4.6 $\pm$ 31
D-1746	4801	1	4	3	GalNAc	-29.3 $\pm$ 49.2	-32.5 $\pm$ 46.5	-31.7 $\pm$ 38.3
D-1747	4802	1	4	3	GalNAc	14.7 $\pm$ 53.5	16 $\pm$ 55.1	14.9 $\pm$ 46
D-1748	4806	1	4	3	GalNAc	33.3 $\pm$ 51.8	21.9 $\pm$ 46.2	-11.2 $\pm$ 21.5
D-1749	4950	1	4	3	GalNAc	-26.3 $\pm$ 7.9	-22.5 $\pm$ 7.1	-32.4 $\pm$ 10.3
D-1750	4951	1	4	3	GalNAc	-15.7 $\pm$ 33.3	-9.4 $\pm$ 36.4	-33.6 $\pm$ 22.4
D-1751	4953	1	4	3	GalNAc	7.4 $\pm$ 34.9	12.5 $\pm$ 35.5	-15.3 $\pm$ 33.1
D-1752	4954	1	4	3	GalNAc	-5.1 $\pm$ 35.9	-2.1 $\pm$ 35.1	-25.5 $\pm$ 23.3

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1753	4955	1	4	3	GalNAc	6.2 $\pm$ 38.7	13.5 $\pm$ 38.1	14.8 $\pm$ 55.2
D-1754	4958	1	4	3	GalNAc	-21 $\pm$ 18.5	-19.8 $\pm$ 13.2	-35.3 $\pm$ 4.6
D-1755	4965	1	4	3	GalNAc	12.9 $\pm$ 31.8	7.1 $\pm$ 27.4	7.3 $\pm$ 24.2
D-1756	4970	1	4	3	GalNAc	23.6 $\pm$ 25.4	25.9 $\pm$ 26	17.3 $\pm$ 23.6
D-1757	4996	1	4	3	GalNAc	-15.5 $\pm$ 17.8	-10.8 $\pm$ 22	-27.5 $\pm$ 9.6
D-1758	4997	1	4	3	GalNAc	6.9 $\pm$ 13.4	8.3 $\pm$ 13.3	-24.1 $\pm$ 13.7
D-1759	5008	1	4	3	GalNAc	70.4 $\pm$ 77	79.3 $\pm$ 88.9	14.4 $\pm$ 36.1
D-1760	5056	1	4	3	GalNAc	-5.1 $\pm$ 19.6	-2 $\pm$ 18.9	-42.6 $\pm$ 7
D-1761	5080	1	4	3	GalNAc	9.2 $\pm$ 33.4	15.1 $\pm$ 33	-37.6 $\pm$ 4.3
D-1762	5114	1	4	3	GalNAc	-27.6 $\pm$ 26.5	-21.7 $\pm$ 27	-47.8 $\pm$ 13.6
D-1763	5115	1	4	3	GalNAc	24.8 $\pm$ 64.5	25.4 $\pm$ 60.1	-2.1 $\pm$ 28.1
D-1764	5154	1	4	3	GalNAc	8.7 $\pm$ 50.5	15.7 $\pm$ 57.8	-4.1 $\pm$ 32.8
D-1765	5155	1	4	3	GalNAc	28.9 $\pm$ 64.5	40.4 $\pm$ 72.9	3.6 $\pm$ 35.5
D-1766	5195	1	4	3	GalNAc	28.3 $\pm$ 40.2	28.8 $\pm$ 32.9	52.2 $\pm$ 56.6
D-1767	5200	1	4	3	GalNAc	77.3 $\pm$ 52.2	82.7 $\pm$ 68.3	46.4 $\pm$ 48.2
D-1614	4999	1	4	3	GalNAc	-83.8 $\pm$ 2.8	-82.2 $\pm$ 2.6	-73.4 $\pm$ 3.8
D-1611	5043	1	4	3	GalNAc	-50.5 $\pm$ 5.6	-50 $\pm$ 9	-50 $\pm$ 3.7
D-1768	5247	1	4	3	GalNAc	-55.7 $\pm$ 3.3	-53.3 $\pm$ 4.1	-49.9 $\pm$ 4.3
D-1769	5249	1	4	3	GalNAc	-56.7 $\pm$ 10	-53.6 $\pm$ 9.5	-52.2 $\pm$ 2.4
D-1770	5251	1	4	3	GalNAc	-33.4 $\pm$ 10	-31.6 $\pm$ 10.2	-38.9 $\pm$ 8.5
D-1771	5254	1	4	3	GalNAc	-32.5 $\pm$ 16.7	-28.3 $\pm$ 20.6	-30.7 $\pm$ 8.4
D-1772	5259	1	4	3	GalNAc	-42.9 $\pm$ 22.8	-39.9 $\pm$ 23.9	-44.1 $\pm$ 18.5
D-1773	5274	1	4	3	GalNAc	-52.4 $\pm$ 16.3	-46.6 $\pm$ 21.8	-62.1 $\pm$ 8.1
D-1774	5276	1	4	3	GalNAc	-51.9 $\pm$ 23.5	-50.2 $\pm$ 23.8	-44 $\pm$ 37.8
D-1775	5344	1	4	3	GalNAc	1.8 $\pm$ 46.5	8.3 $\pm$ 63.6	8.3 $\pm$ 38.4
D-1776	5402	1	4	3	GalNAc	-33.2 $\pm$ 37	-21.4 $\pm$ 44.9	-26.9 $\pm$ 44.4
D-1777	4412	1	4	3	GalNAc	-51.3 $\pm$ 10.8	-46.8 $\pm$ 9.3	-51 $\pm$ 7.5
D-1778	4777	1	4	3	GalNAc	-28.5 $\pm$ 43.7	-17.5 $\pm$ 55.4	-33.7 $\pm$ 35.1
D-1779	4780	1	4	3	GalNAc	-19 $\pm$ 26.9	-4.3 $\pm$ 26.2	-16 $\pm$ 21.4
D-1780	4819	1	4	3	GalNAc	-18.8 $\pm$ 39.4	-4.3 $\pm$ 46.1	-1.9 $\pm$ 45.2
D-1781	4834	1	4	3	GalNAc	-63.4 $\pm$ 8.6	-58.4 $\pm$ 12.7	-60 $\pm$ 12.2
D-1782	4931	1	4	3	GalNAc	-41.3 $\pm$ 12.2	-34.9 $\pm$ 12.7	-23.6 $\pm$ 10.1
D-1783	4932	1	4	3	GalNAc	-59.1 $\pm$ 10.8	-57.2 $\pm$ 11.4	-52.7 $\pm$ 8.6
D-1784	4933	1	4	3	GalNAc	-33.6 $\pm$ 7.4	-31.2 $\pm$ 9.6	-17.7 $\pm$ 9.5
D-1785	4935	1	4	3	GalNAc	-27 $\pm$ 31.3	-14.9 $\pm$ 37.2	-22.9 $\pm$ 27.1
D-1786	4939	1	4	3	GalNAc	-34.6 $\pm$ 17.4	-34.6 $\pm$ 17.1	-32.2 $\pm$ 23.8
D-1787	4940	1	4	3	GalNAc	0.6 $\pm$ 31.7	-12 $\pm$ 20.3	-5.1 $\pm$ 13.9
D-1788	4989	1	4	3	GalNAc	-42.4 $\pm$ 25.6	-38.8 $\pm$ 23.8	-30.5 $\pm$ 18.8
D-1789	4991	1	4	3	GalNAc	-37.1 $\pm$ 8.7	-30.7 $\pm$ 8.1	-17.2 $\pm$ 6.8
D-1790	5201	1	4	3	GalNAc	-22.6 $\pm$ 50.6	-17.1 $\pm$ 54.8	-11.9 $\pm$ 52.9
D-1791	5203	1	4	3	GalNAc	-19 $\pm$ 34.6	-17.9 $\pm$ 35.4	-2.2 $\pm$ 51.2
D-1792	5204	1	4	3	GalNAc	-55.4 $\pm$ 6.5	-49.7 $\pm$ 6.7	-31 $\pm$ 12.8
D-1793	5207	1	4	3	GalNAc	-46 $\pm$ 13.6	-42.6 $\pm$ 18.7	-26.8 $\pm$ 22.9
D-1597	1333	1	4	1	GalNAc	-7.1 $\pm$ 14.9	-3.7 $\pm$ 15.6	-10.5 $\pm$ 13.8
D-1544	2144	1	4	1	GalNAc	-26.1 $\pm$ 20.1	-22.6 $\pm$ 14	-32.8 $\pm$ 16.4
D-1794	1305	1	4	1	GalNAc	-9.6 $\pm$ 21.6	-2.6 $\pm$ 18.8	-19.9 $\pm$ 17.5
D-1795	1306	1	4	1	GalNAc	2.7 $\pm$ 27.1	7.9 $\pm$ 32.2	4.2 $\pm$ 26.5
D-1796	1308	1	4	1	GalNAc	-8.8 $\pm$ 26.4	-5.8 $\pm$ 23.5	-20.8 $\pm$ 18.6
D-1797	1472	1	4	1	GalNAc	0.6 $\pm$ 49.8	0.3 $\pm$ 54.3	-20.3 $\pm$ 38.7

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1798	1500	1	4	1	GalNAc	-4.6 $\pm$ 8.9	-3.9 $\pm$ 9.5	-19.3 $\pm$ 18
D-1809	2296	1	4	1	GalNAc	12.4 $\pm$ 65.3	15 $\pm$ 64.7	21.4 $\pm$ 78.9
D-1810	2343	1	4	1	GalNAc	-30 $\pm$ 20.2	-28.8 $\pm$ 20.4	-38.3 $\pm$ 13.1
D-1811	2355	1	4	1	GalNAc	-20.1 $\pm$ 39.6	-20.6 $\pm$ 32.7	-18.9 $\pm$ 30.3
D-1812	2417	1	4	1	GalNAc	-42.3 $\pm$ 12.1	-38.8 $\pm$ 12.2	-45.6 $\pm$ 4.9
D-1813	2432	1	4	1	GalNAc	-28.6 $\pm$ 22.1	-22.1 $\pm$ 27.3	-36.7 $\pm$ 14.5
D-1814	2688	1	4	1	GalNAc	21.5 $\pm$ 13	23.6 $\pm$ 14.6	-6.8 $\pm$ 10.2
D-1815	2690	1	4	1	GalNAc	-21.3 $\pm$ 19.1	-18.3 $\pm$ 17.1	-34.5 $\pm$ 9.8
D-1816	2886	1	4	1	GalNAc	-23.6 $\pm$ 42.2	-18.2 $\pm$ 45.8	-49.4 $\pm$ 24.2
D-1817	1326	1	4	1	GalNAc	-14.2 $\pm$ 21	-13.1 $\pm$ 16	-36.1 $\pm$ 9.9
D-1818	1331	1	4	1	GalNAc	11.5 $\pm$ 72	12.7 $\pm$ 62.6	-21.3 $\pm$ 35.1
D-1819	1407	1	4	1	GalNAc	-20.5 $\pm$ 12.3	-17.4 $\pm$ 20.2	-35.4 $\pm$ 5.6
D-1597	1333	1	4	1	GalNAc	-29.9 $\pm$ 43.6	-36.7 $\pm$ 36	-40.4 $\pm$ 31.5
D-1544	2144	1	4	1	GalNAc	16.9 $\pm$ 24.5	10.7 $\pm$ 23.7	1.5 $\pm$ 30
D-1820	1514	1	4	1	GalNAc	-26 $\pm$ 41.7	-23.6 $\pm$ 41.8	-26.4 $\pm$ 37.4
D-1821	1564	1	4	1	GalNAc	16.7 $\pm$ 67	12.9 $\pm$ 68.8	105.3 $\pm$ 51.2
D-1822	1611	1	4	1	GalNAc	58.7 $\pm$ 72	57.7 $\pm$ 80	45.4 $\pm$ 67.1
D-1823	1615	1	4	1	GalNAc	27.2 $\pm$ 21.2	38.5 $\pm$ 23.9	24.7 $\pm$ 30.4
D-1824	1616	1	4	1	GalNAc	-17.8 $\pm$ 56.8	-13.7 $\pm$ 59.5	-12.9 $\pm$ 59.4
D-1825	1618	1	4	1	GalNAc	-20.6 $\pm$ 35.1	-21.3 $\pm$ 35	-31.1 $\pm$ 22
D-1826	1693	1	4	1	GalNAc	-28.1 $\pm$ 32.7	-13.8 $\pm$ 32.7	-34.2 $\pm$ 30.4
D-1827	1697	1	4	1	GalNAc	0.8 $\pm$ 18.9	-1.8 $\pm$ 19.2	4.9 $\pm$ 41.3
D-1828	1700	1	4	1	GalNAc	32.6 $\pm$ 24.6	33 $\pm$ 14	15.6 $\pm$ 19.4
D-1829	1701	1	4	1	GalNAc	17.8 $\pm$ 50.2	11.2 $\pm$ 46.5	2.7 $\pm$ 40.7
D-1830	1703	1	4	1	GalNAc	51.5 $\pm$ 39	44.7 $\pm$ 43.9	32.3 $\pm$ 35.8
D-1831	1704	1	4	1	GalNAc	9.4 $\pm$ 36.6	9.7 $\pm$ 36.7	-5.9 $\pm$ 23.2
D-1832	1716	1	4	1	GalNAc	21.8 $\pm$ 29.4	29.7 $\pm$ 25.6	25.8 $\pm$ 28.6
D-1833	1717	1	4	1	GalNAc	24.7 $\pm$ 45.7	33.3 $\pm$ 42.4	27.2 $\pm$ 34.9
D-1834	1832	1	4	1	GalNAc	91.8 $\pm$ 94.3	125.8 $\pm$ 122.3	80.5 $\pm$ 91.5
D-1835	1833	1	4	1	GalNAc	72.7 $\pm$ 75.1	98.8 $\pm$ 91.9	72.8 $\pm$ 71.2
D-1836	1834	1	4	1	GalNAc	4 $\pm$ 25.5	3.4 $\pm$ 27.5	7.3 $\pm$ 26.1
D-1837	1856	1	4	1	GalNAc	-8.2 $\pm$ 8.8	-10.2 $\pm$ 9.3	-16.2 $\pm$ 15.9
D-1838	1900	1	4	1	GalNAc	35.2 $\pm$ 35.2	42.4 $\pm$ 32.3	13.6 $\pm$ 28.3
D-1839	2275	1	4	1	GalNAc	54.8 $\pm$ 62.1	57.1 $\pm$ 67.4	9.3 $\pm$ 30.7
D-1840	2437	1	4	1	GalNAc	80 $\pm$ 18.3	79.2 $\pm$ 26.8	79.4 $\pm$ 22.8
D-1841	2439	1	4	1	GalNAc	49.2 $\pm$ 23.8	43.4 $\pm$ 12.9	42.3 $\pm$ 19.9
D-1842	2534	1	4	1	GalNAc	24.1 $\pm$ 22.7	12.5 $\pm$ 17.4	16.7 $\pm$ 10.3
D-1843	2693	1	4	1	GalNAc	87.7 $\pm$ 40.7	83.7 $\pm$ 39.7	62.3 $\pm$ 32.7
D-1844	2719	1	4	1	GalNAc	24.4 $\pm$ 44.4	26.8 $\pm$ 38.5	19.9 $\pm$ 22.8
D-1845	2726	1	4	1	GalNAc	26.8 $\pm$ 46.2	29.3 $\pm$ 49.8	25.5 $\pm$ 43.9

TABLE 16 – siRNA Efficacy in Liver 4 Weeks Following siRNA Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1744	4717	3	4	3	GalNAc	-62.6 $\pm$ 19.9	-61.8 $\pm$ 21.1	-63 $\pm$ 14
D-1896	4717	3	4	3	GalNAc	-81.8 $\pm$ 6.7	-81.3 $\pm$ 7.2	-75.2 $\pm$ 9.1

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHPA
D-1902	4717	3	4	3	GalNAc	-59.6 $\pm$ 14.4	-59.4 $\pm$ 15.3	-62.5 $\pm$ 8.5
D-1908	4717	3	4	3	GalNAc	-67.3 $\pm$ 9.2	-65.2 $\pm$ 11.5	-60.4 $\pm$ 15
D-1781	4834	3	4	3	GalNAc	-64.9 $\pm$ 8.5	-65 $\pm$ 6.9	-60.9 $\pm$ 3.9
D-1894	4834	3	4	3	GalNAc	-66.9 $\pm$ 10.7	-65.6 $\pm$ 10.5	-61 $\pm$ 8
D-1900	4834	3	4	3	GalNAc	-54.2 $\pm$ 25.6	-56.4 $\pm$ 26	-57 $\pm$ 13.9
D-1906	4834	3	4	3	GalNAc	-64.2 $\pm$ 10.8	-62.9 $\pm$ 11	-64.9 $\pm$ 7.8
D-1783	4932	3	4	3	GalNAc	-79.1 $\pm$ 8.3	-79.3 $\pm$ 7.9	-74.5 $\pm$ 4.7
D-1895	4932	3	4	3	GalNAc	-75.3 $\pm$ 17.4	-74.1 $\pm$ 17.5	-64.9 $\pm$ 13.2
D-1901	4932	3	4	3	GalNAc	-50.8 $\pm$ 7.8	-47.6 $\pm$ 9.7	-57.1 $\pm$ 6.7
D-1907	4932	3	4	3	GalNAc	-74.6 $\pm$ 11.3	-73.9 $\pm$ 12.4	-70.6 $\pm$ 15
D-1614	4999	3	4	3	GalNAc	-72.2 $\pm$ 10.1	-71.9 $\pm$ 10.2	-63.3 $\pm$ 10.6
D-1611	5043	3	4	3	GalNAc	-66.7 $\pm$ 24.4	-67.8 $\pm$ 22.8	-70.6 $\pm$ 17.9
D-1792	5204	3	4	3	GalNAc	-55.6 $\pm$ 9.1	-52.9 $\pm$ 7.6	-62.9 $\pm$ 6.5
D-1892	5204	3	4	3	GalNAc	-54.2 $\pm$ 12.8	-53.1 $\pm$ 14.4	-56.1 $\pm$ 11.1
D-1898	5204	3	4	3	GalNAc	-69.1 $\pm$ 3.8	-68.5 $\pm$ 3.2	-66.8 $\pm$ 2.3
D-1904	5204	3	4	3	GalNAc	-39.5 $\pm$ 13	-39.3 $\pm$ 14.2	-49.1 $\pm$ 11
D-1768	5247	3	4	3	GalNAc	-67.2 $\pm$ 7.6	-69.4 $\pm$ 7	-69.4 $\pm$ 8.7
D-1891	5247	3	4	3	GalNAc	-37.2 $\pm$ 16	-39.3 $\pm$ 15.8	-57.1 $\pm$ 11.9
D-1897	5247	3	4	3	GalNAc	-61.7 $\pm$ 9.1	-60.4 $\pm$ 9.6	-67.2 $\pm$ 6.4
D-1903	5247	3	4	3	GalNAc	-39.3 $\pm$ 28.3	-38.4 $\pm$ 30.2	-56.1 $\pm$ 16.5
D-1774	5276	3	4	3	GalNAc	-70 $\pm$ 20.2	-70.5 $\pm$ 18.8	-68.2 $\pm$ 21.8
D-1893	5276	3	4	3	GalNAc	-59.4 $\pm$ 11.7	-56.8 $\pm$ 12.6	-61.5 $\pm$ 7.3
D-1899	5276	3	4	3	GalNAc	-73.8 $\pm$ 6.3	-72.9 $\pm$ 7.9	-72.4 $\pm$ 5.3
D-1905	5276	3	4	3	GalNAc	-59.7 $\pm$ 8.2	-59.1 $\pm$ 8.2	-61.8 $\pm$ 3.6
D-1914	4717	3	4	3	GalNAc	-55.9 $\pm$ 5.1	-51 $\pm$ 6	-64.9 $\pm$ 12.9
D-1920	4717	3	4	3	GalNAc	-61.8 $\pm$ 10.6	-58.2 $\pm$ 13	-59.2 $\pm$ 7.6
D-1926	4717	3	4	3	GalNAc	-40.6 $\pm$ 25	-39.3 $\pm$ 19.9	-52.3 $\pm$ 11.1
D-1932	4717	3	4	3	GalNAc	-69.5 $\pm$ 8.3	-68.7 $\pm$ 6.7	-67.6 $\pm$ 7.4
D-1912	4834	3	4	3	GalNAc	-25.9 $\pm$ 30.2	-7.6 $\pm$ 46.6	-43.6 $\pm$ 20.4
D-1918	4834	3	4	3	GalNAc	-71.9 $\pm$ 40.5	-71.3 $\pm$ 41	-69.3 $\pm$ 41.3
D-1924	4834	3	4	3	GalNAc	-27.1 $\pm$ 27	-29.6 $\pm$ 21.3	-36.2 $\pm$ 18.8
D-1930	4834	3	4	3	GalNAc	-62.5 $\pm$ 17.3	-64.9 $\pm$ 17.4	-64.3 $\pm$ 15.7
D-1913	4932	3	4	3	GalNAc	-55.9 $\pm$ 12.3	-47.5 $\pm$ 11.4	-53.1 $\pm$ 12.5
D-1919	4932	3	4	3	GalNAc	-38 $\pm$ 37.3	-34.7 $\pm$ 44.3	-55.1 $\pm$ 22.1
D-1925	4932	3	4	3	GalNAc	-56.9 $\pm$ 9.8	-51.5 $\pm$ 11.8	-58.3 $\pm$ 8.8
D-1931	4932	3	4	3	GalNAc	-62.1 $\pm$ 14.1	-63.2 $\pm$ 10.2	-58.1 $\pm$ 14.8
D-1614	4999	3	4	3	GalNAc	-76.1 $\pm$ 7	-78.2 $\pm$ 5.6	-73.3 $\pm$ 9.8
D-1611	5043	3	4	3	GalNAc	-46.6 $\pm$ 8	-47.3 $\pm$ 7.3	-52.1 $\pm$ 11.5
D-1910	5204	3	4	3	GalNAc	-30.7 $\pm$ 40.6	-33.5 $\pm$ 39.2	-41.1 $\pm$ 35.3
D-1916	5204	3	4	3	GalNAc	-59.5 $\pm$ 8.3	-59.6 $\pm$ 10.9	-59.3 $\pm$ 4.4
D-1922	5204	3	4	3	GalNAc	-16.2 $\pm$ 25.6	-20 $\pm$ 22.8	-24.5 $\pm$ 22.7
D-1928	5204	3	4	3	GalNAc	-61.8 $\pm$ 6.1	-58.5 $\pm$ 8	-56.4 $\pm$ 15.8
D-1909	5247	3	4	3	GalNAc	-59 $\pm$ 20.7	-60.6 $\pm$ 16.4	-65.7 $\pm$ 12.5
D-1915	5247	3	4	3	GalNAc	-52.8 $\pm$ 20.8	-37.6 $\pm$ 29.6	-66 $\pm$ 11.9
D-1921	5247	3	4	3	GalNAc	-54.4 $\pm$ 13.4	-48.2 $\pm$ 19.7	-66 $\pm$ 12.1

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1927	5247	3	4	3	GalNAc	-47.4 $\pm$ 21.1	-35.6 $\pm$ 31.6	-57.9 $\pm$ 17.4
D-1911	5276	3	4	3	GalNAc	-49.6 $\pm$ 22.2	-47.1 $\pm$ 24.8	-60.6 $\pm$ 18.2
D-1917	5276	3	4	3	GalNAc	-79.6 $\pm$ 17.6	-77.6 $\pm$ 19.8	-76.4 $\pm$ 17.7
D-1923	5276	3	4	3	GalNAc	-63.8 $\pm$ 17.3	-61.4 $\pm$ 19.7	-59.5 $\pm$ 21.4
D-1929	5276	3	4	3	GalNAc	-69 $\pm$ 10.5	-68.8 $\pm$ 10	-59 $\pm$ 11.2

TABLE 17 – siRNA Efficacy in Liver 4 Weeks Following siRNA Injection

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1709	4999	3	4	22span	GalNAc	-83.2 $\pm$ 8.6	-82.9 $\pm$ 9.3	-83.7 $\pm$ 7.5
D-2008	4999	3	4	22span	GalNAc	-62.7 $\pm$ 8.7	-65.6 $\pm$ 11.3	-76.2 $\pm$ 7.4
D-2017	4999	3	4	22span	GalNAc	-66.4 $\pm$ 15.5	-66.4 $\pm$ 16.1	-72.6 $\pm$ 11.5
D-2049	4999	3	4	22span	GalNAc	-78.6 $\pm$ 11.1	-79.7 $\pm$ 10.1	-85.5 $\pm$ 5.7
D-2054	4999	3	4	22span	GalNAc	-82.6 $\pm$ 6.2	-82.4 $\pm$ 5.9	-87.3 $\pm$ 3.8
D-1704	5045	3	4	22span	GalNAc	-81.1 $\pm$ 8.4	-81.8 $\pm$ 6.9	-83.3 $\pm$ 6
D-2012	5045	3	4	22span	GalNAc	-91.6 $\pm$ 1.1	-91.3 $\pm$ 0.8	-90.4 $\pm$ 1.2
D-2021	5045	3	4	22span	GalNAc	-84.5 $\pm$ 6.7	-85.3 $\pm$ 5.2	-84.8 $\pm$ 6.3
D-2043	5045	3	4	22span	GalNAc	-74 $\pm$ 12.9	-74.7 $\pm$ 11.1	-79.2 $\pm$ 8.6
D-2047	5045	3	4	22span	GalNAc	-80.1 $\pm$ 13.4	-81 $\pm$ 11.1	-81.6 $\pm$ 11.4
D-2052	5045	3	4	22span	GalNAc	-84.2 $\pm$ 5.9	-84.1 $\pm$ 6.5	-83.3 $\pm$ 4.9
D-1623	5080	3	4	22span	GalNAc	-59.6 $\pm$ 11.3	-62.9 $\pm$ 11.1	-62.9 $\pm$ 11
D-2014	5080	3	4	22span	GalNAc	-89.1 $\pm$ 10.6	-88.8 $\pm$ 9.1	-88.5 $\pm$ 9.8
D-2023	5080	3	4	22span	GalNAc	-89.1 $\pm$ 6.5	-88.2 $\pm$ 6.2	-87.6 $\pm$ 5.3
D-2036	4995	3	4	22span	GalNAc	-59.3 $\pm$ 40.7	-60.4 $\pm$ 39.2	-66 $\pm$ 29.9
D-2037	4996	3	4	22span	GalNAc	-42.8 $\pm$ 23.2	-48.5 $\pm$ 16.9	-42.5 $\pm$ 20.2
D-2038	4997	3	4	22span	GalNAc	76.6 $\pm$ 62.9	105.4 $\pm$ 74.5	88.1 $\pm$ 60.4
D-2039	4998	3	4	22span	GalNAc	-43.5 $\pm$ 27.1	-43.6 $\pm$ 30.2	-56.6 $\pm$ 19
D-2040	5042	3	4	22span	GalNAc	-83.5 $\pm$ 10.5	-83.8 $\pm$ 9.5	-84.3 $\pm$ 7.2
D-1705	5043	3	4	22span	GalNAc	-86.5 $\pm$ 5.5	-86.9 $\pm$ 5.4	-90.5 $\pm$ 4.1
D-2013	5043	3	4	22span	GalNAc	-77.8 $\pm$ 15.6	-78.8 $\pm$ 15.2	-85.1 $\pm$ 10.8
D-2022	5043	3	4	22span	GalNAc	-79.2 $\pm$ 5.7	-80.3 $\pm$ 5	-87.6 $\pm$ 3.7
D-2044	5043	3	4	22span	GalNAc	-72.4 $\pm$ 32.6	-70.3 $\pm$ 37.2	-82 $\pm$ 21.7
D-2048	5043	3	4	22span	GalNAc	-64.1 $\pm$ 18.9	-66.2 $\pm$ 18.5	-76.3 $\pm$ 10.2
D-2053	5043	3	4	22span	GalNAc	-83.7 $\pm$ 5	-84.9 $\pm$ 4.9	-89.8 $\pm$ 3.2
D-2042	5274	3	4	22span	GalNAc	-58.7 $\pm$ 23.5	-62.9 $\pm$ 21.2	-74.4 $\pm$ 14.3
D-2046	5274	3	4	22span	GalNAc	-51.9 $\pm$ 37.4	-55.9 $\pm$ 32.1	-70.4 $\pm$ 18.9
D-2051	5274	3	4	22span	GalNAc	-71.2 $\pm$ 14.4	-72.6 $\pm$ 13	-82.1 $\pm$ 8.2
D-2079	5274	3	4	22span	GalNAc	-83.4 $\pm$ 6.6	-84.7 $\pm$ 5.8	-89.1 $\pm$ 5.1
D-2080	5274	3	4	22span	GalNAc	-84.7 $\pm$ 4.6	-85.2 $\pm$ 4.4	-90.1 $\pm$ 2.6
D-2081	5274	3	4	22span	GalNAc	-83.1 $\pm$ 11	-83.7 $\pm$ 10.8	-88.5 $\pm$ 8.3
D-2082	5274	3	4	22span	GalNAc	-60.4 $\pm$ 18.6	-61.8 $\pm$ 18	-75 $\pm$ 9.5
D-2083	5274	3	4	22span	GalNAc	-72.3 $\pm$ 21.8	-73.2 $\pm$ 20.8	-82.2 $\pm$ 11.4
D-2059	4412	3	4	22span	GalNAc	-53.8 $\pm$ 19	-52.8 $\pm$ 26	-68.3 $\pm$ 10.9
D-2058	4412	3	4	22span	GalNAc	-76.9 $\pm$ 18.2	-76.6 $\pm$ 20.2	-83.9 $\pm$ 11.5
D-2060	4412	3	4	22span	GalNAc	-62.4 $\pm$ 17.8	-60.8 $\pm$ 18.1	-74.6 $\pm$ 11.4

siRNA Duplex	Trigger Family	Dose (mg/kg)	N	AAV No.	Carrier	Avg. % Change in mRNA $\pm$ STD		
						eGFP-1	eGFP-2	BGHpA
D-1774	5276	3	4	22span	GalNAc	-59.9 $\pm$ 14.9	-59.8 $\pm$ 15.9	-74 $\pm$ 6.8
D-2084	5276	3	4	22span	GalNAc	-46.3 $\pm$ 25.2	-47.5 $\pm$ 23.2	-65.6 $\pm$ 13.1
D-1955	4412	3	4	22span	GalNAc	-88.2 $\pm$ 5.2	-87.8 $\pm$ 5.5	-88.1 $\pm$ 4.7
D-2091	4412	3	4	22span	GalNAc	-89.2 $\pm$ 2.4	-89.4 $\pm$ 2.9	-90.6 $\pm$ 1
D-2061	4412	3	4	22span	GalNAc	-93.3 $\pm$ 3	-93.5 $\pm$ 2.9	-93.6 $\pm$ 3.1
D-2041	4412	3	4	22span	GalNAc	-60.5 $\pm$ 18.9	-60.7 $\pm$ 18.9	-69 $\pm$ 13.4
D-2045	4412	3	4	22span	GalNAc	-80 $\pm$ 12	-80.2 $\pm$ 10	-82.6 $\pm$ 10.5
D-2050	4412	3	4	22span	GalNAc	-56.1 $\pm$ 55.5	-58.3 $\pm$ 50.9	-62.3 $\pm$ 44.7
D-2057	4412	3	4	22span	GalNAc	-76.7 $\pm$ 14.4	-78.8 $\pm$ 11.8	-76.9 $\pm$ 12.4
D-1970	5249	3	4	22span	GalNAc	-82.4 $\pm$ 13	-83.5 $\pm$ 11.9	-82.9 $\pm$ 13
D-2076	5249	3	4	22span	GalNAc	-60.6 $\pm$ 11.6	-65 $\pm$ 9.7	-66.8 $\pm$ 10.1
D-2078	5249	3	4	22span	GalNAc	-72.6 $\pm$ 17.4	-74 $\pm$ 16.1	-70.8 $\pm$ 20.2
D-1768	5247	3	4	22span	GalNAc	-83.6 $\pm$ 10.3	-83.8 $\pm$ 10	-83.3 $\pm$ 9.6
D-2075	5247	3	4	22span	GalNAc	-88.6 $\pm$ 10	-89.2 $\pm$ 9.1	-87.8 $\pm$ 11
D-2077	5247	3	4	22span	GalNAc	-93 $\pm$ 2.2	-92.7 $\pm$ 2.6	-94.5 $\pm$ 1
D-1597	1333	3	4	22span	GalNAc	-83.4 $\pm$ 9.3	-83.3 $\pm$ 9.2	-86.8 $\pm$ 7.4
D-2006	1333	3	4	22span	GalNAc	-79.3 $\pm$ 9.7	-79.2 $\pm$ 9.6	-79.7 $\pm$ 9.9
D-2015	1333	3	4	22span	GalNAc	-65.3 $\pm$ 12.8	-66 $\pm$ 12.1	-72 $\pm$ 8.2
D-2090	4999	3	4	22span	GalNAc	-94.5 $\pm$ 1.8	-94 $\pm$ 2.1	-94.6 $\pm$ 1.6
D-2093	5274	3	4	22span	GalNAc	-81.6 $\pm$ 13	-79.6 $\pm$ 15.1	-86.9 $\pm$ 7.1
D-1899	5276	3	4	22span	GalNAc	-78.5 $\pm$ 10.1	-78.2 $\pm$ 9.9	-83.4 $\pm$ 5.9

[0214] Testing of *FAM13A*-directed siRNA molecules within the AAV human *FAM13A* mouse model showed that a variety of different regions within *FAM13A* mRNA can be targeted to effectively reduce *FAM13A* expression. As shown in FIG. 6, the effective siRNA triggers targeted regions throughout the *FAM13A* mRNA transcript (SEQ ID NO: 1). In the above tables, the region targeted by the siRNA is specified by the trigger family, which refers to the first nucleotide in the range of nucleotides of SEQ ID NO: 1 that is targeted by a given siRNA molecule.

[0215] Trigger families that achieved a maximum knockdown of between 40-60% relative to vehicle control (for at least one probe set with at least one duplex) were T-1328, T-1631, T-1666, T-2343, T-2417, T-2623, T-2886, T-2887, T-2889, T-3133, T-3187, T-3189, T-3498, T-3499, T-4008, T-4109, T-4485, T-4927, T-4989, T-4993, T-4996, T-4998, T-5060, and T-5114.

[0216] Trigger families that achieved a maximum knockdown of between 60-80% relative to vehicle control (for at least one probe set with at least one duplex) were T-1678, T-2263, T-4834, T-4932, T-4957, T-4995, and T-5204. Exemplary duplexes within these families

that proved effective in reducing *FAM13A* expression by 60-80% included D-1615, D-1695, and D-1867 from trigger family T-1678; D-1573 from trigger family T-2263; D-1781, D-1894, D-1906, D-1918, and D-1930 from trigger family T-4834; D-1783, D-1895, D-1907, and D-1931 from trigger family T-4932; D-1631, D-1696, D-1703, D-1717, D-1724, and D-1731 from trigger family T-4957; D-2036 from T-4995; and D-1792, D-1898, and D-1928 from trigger family T-5204.

[0217] Trigger families that achieved greater than 80% knockdown relative to vehicle control (for at least one probe set with at least one duplex) were T-1309, T-1333, T-2080, T-2144, T-3000, T-4412, T-4717, T-4999, T-5042, T-5043, T-5045, T-5080, T-5247, T-5249, T-5274, and T-5276. Exemplary duplexes within these families that proved effective in reducing *FAM13A* expression by greater than 80% included D-1667, D-1686, and D-1849 from trigger family T-1309; D-1597, D-1853, and D-2017 from trigger family T-1333; D-1680, D-1685, and D-1690 from trigger family T-2080; D-1682 and D-1858 from trigger family T-2144; D-1557, D-1650, and D-1861 from trigger family T-3000; D-1955 from trigger family T-4412; D-1896 from trigger family T-4717; D-1614, D-1697, D-1702, D-1709, D-1856, D-1863, D-1865, D-1866, D-1869, D-1873, D-1877, D-1878, D-1879, D-1880, D-1881, D-1884, D-1887, D-1987, D-1992, D-1997, and D-2002 from trigger family T-4999; D-2040 from trigger family T-5042; D-1698, D-1705, D-1864, D-1870, D-1875, D-1883, D-1886, D-1980, D-1984, D-1989, D-1994, and D-2004 from trigger family T-5043; D-1699, D-1612, D-1704, D-1868, D-1871, D-1876, D-1885, D-1888, D-1979, D-1983, D-1988, D-1993, D-1998, and D-2003 from trigger family T-5045; D-1623, D-1846, D-1862, D-1981, D-1985, D-1990, D-1995, D-2000, and D-2005 from trigger family T-5080; D-1768, D-2075, and D-2077 from trigger family T-5247; D-1970 from trigger family T-5249; D-1972 from trigger family T-5274; and D-1975, D-1991, D-1976, D-1977, D-1982, D-1996, and D-2001 from trigger family T-5276.

[0218] In testing a range of different modification patterns for some trigger families, it was found that some triggers consistently facilitated high levels of knockdown of *FAM13A* knockdown. For example, 31 different modification patterns were tested in the above AAV-based experiments using the T-4999 trigger family sequence (D-1614, D-1697, D-1702, D-1709, D-1716, D-1723, D-1730, D-1737, D-1856, D-1863, D-1865, D-1866, D-1869, D-1872, D-1877, D-1878, D-1879, D-1880, D-1881, D-1884, D-1887, D-1978, D-1987, D-1992, D-1997, D-2002, D-2008, D-2017, D-2049, D-2054, and D-2090; see **Table 2** for sense and antisense sequences, and modification patterns used, in these duplexes). Each of these duplexes utilized a different

modification pattern in the context of the same sense and antisense sequences (SEQ ID NOs: 498 and 1042). Of these duplexes, 25 modification patterns were observed to facilitate greater than 80% knockdown of *FAM13A* mRNA in at least one assay, and the remaining 6 were observed to facilitate between 60% and 80% knockdown in at least one assay. These data indicate that the T-4999 trigger family is a particularly effective and reliable trigger for reducing *FAM13A* expression.

[0219] Another effective and reliable trigger family is the T-5043 trigger family. For this family, 25 different modification patterns were tested in the above AAV-based experiments (D-1611, D-1698, D-1705, D-1712, D-1719, D-1726, D-1733, D-1740, D-1855, D-1864, D-1870, D-1875, D-1883, D-1886, D-1980, D-1984, D-1989, D-1994, D-1999, D-2004, D-2013, D-2022, D-2044, D-2048, and D-2053; see **Table 2** for sense and antisense sequences, and modification patterns used, in these duplexes). Each of these duplexes utilized a different modification pattern in the context of the same sense and antisense sequences (SEQ ID NOs: 503 and 1047). Of these duplexes, 16 modification patterns were observed to facilitate greater than 80% knockdown of *FAM13A* mRNA in at least one assay, 8 were observed to facilitate between 60% and 80% knockdown in at least one assay, and 1 was observed to facilitate between 40% and 60% knockdown of *FAM13A* mRNA in at least one assay.

[0220] A third particularly effective trigger family is the T-5045 trigger family (whose target sequence largely overlaps with the T-5043 trigger family). For this family, 25 different modification patterns were tested in the above AAV-based experiments (D-1612, D-1699, D-1704, D-1711, D-1718, D-1725, D-1732, D-1739, D-1868, D-1871, D-1876, D-1882, D-1885, D-1888, D-1979, D-1983, D-1988, D-1993, D-1998, D-2003, D-2012, D-2021, D-2043, D-2047, and D-2052; see **Table 2** for sense and antisense sequences, and modification patterns used, in these duplexes). Each of these duplexes utilized a different modification pattern in the context of the same sense and antisense sequences (SEQ ID NOs: 504 and 1048). Of these duplexes, 18 modification patterns were observed to facilitate greater than 80% knockdown of *FAM13A* mRNA in at least one assay, and 7 were observed to facilitate between 60% and 80% knockdown in at least one assay.

[0221] Other trigger families that were able to show effective knockdown with multiple modification patterns included the T-1309, T-1333, T-2144, T-3000, T-5080, and T-5226 trigger families.

[0222] From a broad perspective, testing a wide range of triggers across the *FAM13A* transcript revealed that which regions of the transcript were susceptible to RNAi-mediated knockdown. **FIG. 6** is a diagram compiling the locations of where different effective trigger families target the *FAM13A* mRNA transcript (as provided in SEQ ID NO: 1), along with categorizing the maximal degree to which those trigger families were able to knock down FAM13A expression in the above AAV-based assays. The triggers were divided according to whether the maximum observed knockdown for that trigger fell within the range of 40-60% knockdown, 60-80% knockdown, or greater than 80% knockdown.

[0223] As shown in **FIG. 6**, one region of the human *FAM13A* mRNA transcript that is particularly susceptible to RNAi-based knockdown is the portion between nucleotides 4900 and 5300 of the *FAM13A* mRNA transcript. Within this small region, 24 distinct trigger families were identified that facilitated knockdown of FAM13A, most of which were validated with multiple different duplexes having different modification patterns. These families included 12 trigger families that facilitated greater than 80% knockdown, 5 families that facilitated between 60% and 80% knockdown, and 7 families that facilitated between 40% and 60% knockdown. This unexpected concentration of successful targets indicates that targeting between nucleotides 4900 and 5300 is a particularly useful strategy for knocking down FAM13A expression.

[0224] Other regions that also were susceptible at multiple target locations included nucleotides 1300-1375, nucleotides 1625-1700, and nucleotides 2075-2175. Therefore, these data also indicate that targeting any of these regions is a useful strategy for knocking down FAM13A expression.

[0225] These AAV-based experiments also tested the effectiveness of conjugating different ligands to siRNA duplexes in facilitating knockdown in different tissues. **Figures 8A-8D** and **Table 14** show the results of testing *FAM13A* siRNA from the T-4999 and T-5043 families, when the duplexes had been conjugated to either GalNAc (Formula VII) or the fatty acid C22. In these figures, the "*" denotes those duplexes that were conjugated to C22, while those without an asterisk were conjugated to GalNAc. Knockdown data was gathered both the liver and adipose tissue, after systemic administration. GalNAc-conjugated duplexes were administered at 3mg/kg, while C22 conjugated triggers were administered at 20 mg/kg. All of the tested T-4999 and T-5043 duplexes were able to reduce expression of FAM13A in the liver. In the adipose tissue, the GalNAc-conjugated triggers were less effective in reducing FAM13A expression, with some having no detectable effect. In contrast, the C22-conjugated triggers

consistently facilitated reduction of FAM13A expression in adipose tissue to a similar degree as they facilitated in the liver. Examination of these data in combination with studies of weight, fat mass, and metabolic characterization (see Examples 2, 6, and 7) indicates that GalNAc targeting is surprisingly able to achieve similar results to C22 targeting, despite having less effect on FAM13A expression in biologically significant adipose tissue.

[0226] The above data also allows for comparison of linkages used to attach C22 to siRNA duplexes. The two tested linkages are through a phosphodiester bond (PO) and through a phosphorothioate bond (PS). Unexpectedly, linking C22 with PS led to significantly better knockdown than linking with PO. This was observed through comparison of pairs of duplexes, which only differ in their conjugation method. For example, one T-4999 trigger family pair showed an increase of 43% in knockdown when switching from PO to PS linkage (compare D-1697 (PO; 37% KD) and D-1856 (PS; 80% KD)). Another T-4999 trigger family pair showed a more modest increase of 6% in knockdown when switching from PO to PS linkage (compare D-1869 (PO; 74% KD) and D-1887 (PS; 80% KD)). A T-5080 trigger family pair showed an increase of 25% in knockdown when switching from PO to PS linkage (compare D-1846 (PO; 44% KD) and D-1862 (PS; 69% KD)). A T-5043 trigger family pair showed an increase of 45% in knockdown when switching from PO to PS linkage (compare D-1698 (PO; 13% KD) and D-1855 (PS; 58% KD)). Another T-5043 trigger family pair showed an increase of 30% in knockdown when switching from PO to PS linkage (compare D-1875 (PO; 40% KD) and D-1886 (PS; 70% KD)). And a T-5045 trigger family pair showed an increase of 38% in knockdown when switching from PO to PS linkage (compare D-1871 (PO; 27% KD) and D-1882 (PS; 65% KD)). These and other data in Tables 4-17 above show that linking C22 to a siRNA duplex with PS unexpectedly and consistently led to significantly better knockdown than linking to that same siRNA duplex with PO.

Example 6: *In Vivo* Knockdown of Endogenous Murine *Fam13a* in Obesity Model

[0227] To determine which human siRNA duplexes (see Examples 4 and 5) would be suitable for testing with endogenous murine *Fam13a* knockdown experiments, effective trigger families (see Examples 4 and 5 above) were reviewed for cross-reactivity with murine *Fam13a* mRNA. This review found that the T-4999 trigger family aligned with the murine *Fam13a* sequence for all except one base of its sequence. Hypothesizing that this might be sufficient to still show knockdown activity, experiments were undertaken to assess the efficacy of T-4999

FAM13A siRNA molecules on endogenous murine *Fam13a* mRNA in the diet-induced obesity (DIO) model in C57BL/6 mice.

[0228] Three duplexes from the T-4999 trigger family were chosen for this assay: D-1709 (GalNAc conjugated via PS), D-1869 (C22 conjugated via PO), and D-1887 (C22 conjugated via PS). Duplexes D-2086 (GalNAc conjugated via PS) and D-2087 (C22 conjugated via PS), which target human FAM13A but were not predicted to bind mouse FAM13A, were used as negative controls. D-2086 (GalNAc conjugated via PS) and D-2087 (C22 conjugated via PS), two duplexes that fully match the murine *Fam13a* mRNA sequence, were also tested.

[0229] Male C57BL6 mice were fed a diet containing high fat content (Research Diets D12492, 60% kcal derived from fat) beginning at 5 weeks of age. When the mice reached 19 weeks of age (14 weeks on the high-fat diet), the mice received a subcutaneous injection of buffer (PBS) or the FAM13A siRNA molecule at a dose of 3mg/kg body mass or 20mg/kg body mass in PBS (n = 8 mice per group). Body mass was measured continuously throughout the study. Body composition was measured by NMR (EchoMRI 3n1 Body Composition Analyzer) at baseline (2 days prior to injection) and on day 25 post-injection. Liver and subcutaneous white adipose tissue (ScWAT) were collected 4 weeks following siRNA administration and analyzed.

[0230] RNA from harvested animal tissues was processed for qPCR analysis. RNA was isolated from 50-100 mg tissue using RNeasy 96 universal tissue kit RNA isolation protocol following manufacturer's instructions (Qiagen). Real-time PCR was performed using TaqMan® RNA-to-Ct™ 1-Step Kit following manufacturer's instructions (ThermoFisher) with 50 ng RNA per reaction and a primer probe set complementary to the murine *Fam13a* mRNA. A percentage change in murine *Fam13a* mRNA in liver or ScWAT for each animal was calculated relative to the level of murine *Fam13a* mRNA in the liver or ScWAT of animals administered PBS buffer control.

[0231] Results of these studies are shown in **FIGS. 9A-9C** and **FIGS. 10A-10B**. These figures show the level of knockdown achieved in each mouse's liver, inguinal WAT, and epididymal WAT. Each of the non-targeting control siRNA duplexes displayed expression levels the same as buffer -only control mice (in all three tissues).

[0232] In the liver, all the *Fam13a*-directed duplexes effectively reduced expression of murine *Fam13a* (**FIG. 9A**). The GalNAc-linked duplexes, D-2086 and D-1709, reduced *Fam13a* expression in the liver equivalently (by 62% and 63%, respectively). This showed that the T-4999 duplex (D-1709) was effective despite having one mismatch with the target sequence. Each

of the C22-linked duplexes also facilitated *Fam13a* knockdown in the liver, with D-2087 resulting in 76% knockdown, D-1869 resulting in 55% knockdown, and D-1887 resulting in 69% knockdown.

[0233] In inguinal WAT, the C22-linked duplexes were more effective than the GalNAc-linked duplexes in reducing murine *Fam13a* expression. The GalNAc-linked duplexes, D-2086 and D-1709, reduced expression in the liver by 8% and 19%, respectively. In contrast, the C22-linked duplexes resulted in *Fam13a* knockdown at similar levels to that achieved in the liver: D-2087 resulted in 66% knockdown, D-1869 resulted in 60% knockdown, and D-1887 resulted in 62% knockdown.

[0234] In epididymal WAT, less knockdown was observed than in the other two tissue types. Neither of the GalNAc-linked duplexes resulted in significant knockdown of murine *Fam13a*. In contrast, the C22-linked duplexes resulted in some *Fam13a* knockdown: D-2087 resulted in 22% knockdown, D-1869 resulted in 26% knockdown, and D-1887 resulted in 26% knockdown.

[0235] FIG. 10A shows the effects of siRNA treatment on the body weight of the DIO mice. Untreated and control treated mice had a 5-8% increase in body weight over the course of the experiment. Treatment with any of the *Fam13a* duplexes decreased or prevented that weight gain. The GalNAc-linked duplexes, D-2086 and D-1709, limited the weight gain to 2% and 4%, respectively. The C22-linked duplexes also limited the weight gain, with D-2087 actually resulting in a 1% weight loss for the mice, D-1869 limiting the gain to 2%, and D-1887 limiting the gain to 3%.

[0236] FIG. 10B shows the effects of siRNA treatment on the fat mass of the DIO mice. Untreated and control treated mice had an 8-9% increase in fat mass over the course of the experiment. Treatment with any of the *Fam13a* duplexes decreased or prevented that weight gain. The GalNAc-linked duplexes, D-2086 and D-1709, limited the weight gain to 6% and 4%, respectively. The C22-linked duplexes also limited the weight gain, with D-2087 actually resulting in a 2% weight loss for the mice, D-1869 limiting the gain to 3%, and D-1887 limiting the gain to 3%.

[0237] These data provide further support for *FAM13A* siRNA (and the T-4999 trigger family specifically) being used for a variety of purposes, such as reducing abdominal adiposity, reducing body weight, reducing fat mass, improving metabolic parameters including insulin resistance and non-alcoholic steatohepatitis (NASH), and reducing risk of myocardial infarction.

Example 7: FAM13A siRNA in Nonhuman Primates

[0238] To assess the efficacy of the FAM13A siRNA molecules in a nonhuman primate model, top performing FAM13A siRNA molecules from the *in vitro* and *in vivo* activity assays described in Examples 4 and 5 were evaluated for *in vivo* efficacy using cynomolgus monkeys. In particular, triggers from the T-4999 and T-5043 families were selected. Because the selected triggers target a sequence present in both human and cynomolgus FAM13A mRNA, it was expected that they would also be effective in knocking down endogenous cynomolgus FAM13A.

[0239] For these experiments, the sense strand in each tested siRNA molecule was conjugated to the trivalent GalNAc moiety shown in Formula VII or to docosanoic acid (C22), using the methods described in Example 3. Accordingly, the experiment used the T-4999 duplexes T-1709 (GalNAc conjugated via PS) and D-1887 (C22 conjugated via PS), and the T-5043 duplexes D-1705 (GalNAc conjugated via PS) and D-1886 (C22 conjugated via PS).

[0240] The study design is provided in **Table 18** below. Briefly, there were N=3 animals per treatment group (naïve and non-naïve, female, lean cynomolgus monkeys, Cambodian origin, 3 years old). A single subcutaneous dose was administered in the mid-scapular region to each animal. Liver tissue biopsies were collected pre-dose on day -14 or day -11, and post-dose on days 14, 30, and 45 (relative to dosing on day 0). Adipose tissue biopsies were collected pre-dose on day -14 or day -11 (omental fat), and post-dose on days 14 (falciform fat), 30 (omental fat), and 45 (omental and falciform fat). Blood for clinical chemistry analysis was collected via femoral vein on days -14 (prior to biopsy), -7, 7, 14 (prior to biopsy), 20, 25, 30 (prior to biopsy), 35, and 45 (prior to necropsy). Animals were fasted on days -14, 14, and 30 due to the tissue biopsy collection procedures.

TABLE 18 – NHP Study Design

Group	Animals	siRNA Duplex	Trigger Family	Carrier	Dose Route	Dose Level (mg/kg)	Dose Conc. (mg/mL)
1	3	D-1709	4999	GalNAc	SC	3	0.6
2	3	D-1887	4999	C22	SC	20	4
3	3	D-1705	5043	GalNAc	SC	3	0.6
4	3	D-1886	5043	C22	SC	20	4

[0241] For analysis of FAM13A knockdown level in liver and adipose tissue, the total RNA was isolated from 10 to 20 mg tissue for each tissue sample from each time point. A cDNA

sample was then prepared from each total RNA sample and diluted 1:10 for ddPCR analysis. A cynomolgus *FAM13A* primer/probe set and a cynomolgus PPIB primer/probe set was used in the analysis. The percent mRNA knockdown was calculated relative to the pre-dose *FAM13A* expression level for each individual animal and then averaged across timepoints.

[0242] The data on knockdown of *FAM13A* mRNA levels in the liver is shown in **FIG. 11A**. The most effective duplex in the liver was D-1709, the GalNAc-conjugated siRNA from the T-4999 trigger family. In the liver, the single dose of D-1709 reduced *FAM13A* mRNA levels by an average of 81% by day 14, and the knockdown was maintained at day 30 (77%) and day 45 (80%) without any subsequent treatment. The duplex D-1887, which is identical to D-1709 aside from being C22-conjugated, was almost as effective as D-1709 (albeit at a higher dose). The single dose of D-1887 reduced *FAM13A* mRNA levels by an average of 68% by day 14, and the knockdown was increased on day 30 (71%) and day 45 (75%) without any subsequent treatment.

[0243] **FIG. 11A** also shows the liver knockdown achieved by two duplexes from the T-5043 trigger family. The single dose of D-1705 (GalNAc) reduced *FAM13A* mRNA levels by an average of 58% by day 14, and the knockdown was maintained at day 30 (52%) and day 45 (48%) without any subsequent treatment. However, the knockdown was much higher in two of the animals, as one of the three treated animals was a possible outlier that exhibited minimal knockdown. The other duplex in the T-5043 family, D-1886 (C22), reduced *FAM13A* mRNA levels by an average of 45% by day 14, but the knockdown levels decreased by day 30 (35%) and day 45 (8.4%).

[0244] **FIG. 11B** shows the data on knockdown of *FAM13A* mRNA in the adipose tissue. The most effective duplexes in the adipose tissue were D-1887 (T-4999; C22) and D-1886 (T-5043; C22). The single dose of D-1887 reduced *FAM13A* mRNA levels by an average of 83% by day 14, and the knockdown was maintained on day 30 (80%) and day 45 (75%) without any subsequent treatment. Similarly, the single dose of D-1886 reduced *FAM13A* mRNA levels by an average of 79% by day 14, and the knockdown was maintained on day 30 (64%) and day 45 (83%) without any subsequent treatment. The two GalNAc conjugated duplexes demonstrated a lag time in silencing activity but were also effective in knocking down *FAM13A*. The single dose of D-1709 reduced *FAM13A* mRNA levels by an average of 11% by day 14, and the knockdown increased at day 30 (45%) and day 45 (56%) without any subsequent treatment. The single dose of D-1705 had minimal effects on *FAM13A* mRNA levels at day 14 (decreased 19%) and day 30 (increased 15%), but an average knockdown of 55% was observed on day 45.

[0245] **FIGS. 11C-11E** show results of the clinical chemistry analysis performed on blood serum samples from the treated animals. For all of the tested duplexes, there was a consistent approximately 20% or greater decrease in serum cholesterol (**FIG. 11C**), serum LDL (**FIG. 11D**), and serum HDL (**FIG. 11E**) between 20 and 30 days after siRNA treatment. These decreases are consistent with the effects of FAM13A-targeted siRNA on the blood chemistry of mice (see **Example 2** and **FIG. 5**). Accordingly, these data provide further support for FAM13A siRNA (and the T-4999 and T-5043 trigger families specifically) being used for a variety of purposes, such as reducing abdominal adiposity, reducing body weight, reducing fat mass, improving metabolic parameters including insulin resistance and non-alcoholic steatohepatitis (NASH), and reducing risk of myocardial infarction.

[0246] Further evidence for the efficacy of FAM13A siRNA in treatment of such conditions will be gathered through the use of obese cynomolgus monkeys. These animals will be monitored after the administration of the T-4999 duplexes T-1709 (GalNAc conjugated via PS) and D-1887 (C22 conjugated via PS), and the T-5043 duplexes D-1705 (GalNAc conjugated via PS) and D-1886 (C22 conjugated via PS). The weight, fat mass, blood chemistry, and other metabolic parameters will be monitored and correlated with the knockdown of FAM13A expression in both the liver and adipose tissue.

CLAIMS

What is claimed:

1. An RNAi construct comprising a sense strand and an antisense strand, wherein the sense strand comprises a sequence that is sufficiently complementary to the sequence of the antisense strand to form a duplex region, and
wherein the antisense strand comprises:
 - (a) a region that has substantial identity to at least 15 contiguous nucleotides within nucleotides 1300-1375 or 4900-5300 of the *FAM13A* mRNA sequence set forth in SEQ ID NO: 1, such that there are no more than 2 mismatches between the antisense strand's region of substantial identity and the contiguous nucleotides; or
 - (b) a region that has substantial identity to at least 15 contiguous nucleotides from an antisense sequence listed in Table 1 or Table 2, such that there are no more than 2 mismatches between the antisense strand's region of substantial identity and the contiguous nucleotides.
2. An RNAi construct of claim 1, wherein the antisense strand comprises (a) a region that consists of at least 15 contiguous nucleotides within nucleotides 1300-1375 or 4900-5300 of the *FAM13A* mRNA sequence set forth in SEQ ID NO: 1, or (b) a region that consists of at least 15 contiguous nucleotides from an antisense sequence listed in Table 1 or Table 2.
3. The RNAi construct of claim 1, wherein the antisense strand comprises a region comprising a sequence that is substantially complementary to at least 15 contiguous nucleotides within nucleotides 4950-5100 of the *FAM13A* mRNA sequence set forth in SEQ ID NO: 1.
4. The RNAi construct of claim 3, wherein the antisense strand comprises a region comprising a sequence that is substantially complementary to at least 15 contiguous nucleotides within nucleotides 4975-5075 of the *FAM13A* mRNA sequence set forth in SEQ ID NO: 1.

5. The RNAi construct of claim 1, wherein the antisense strand comprises a region comprising a sequence that is substantially complementary to at least 15 contiguous nucleotides within nucleotides 5225-5300 of the *FAM13A* mRNA sequence set forth in SEQ ID NO: 1.
6. The RNAi construct of any one of claims 1 to 5, wherein the sense strand and antisense strand form a duplex region of about 15 to about 30 base pairs in length.
7. The RNAi construct of claim 6, wherein the duplex region is about 17 to about 24 base pairs in length.
8. The RNAi construct of claim 6, wherein the duplex region is about 19 to about 21 base pairs in length.
9. The RNAi construct of any one of claims 1 to 8, wherein the sense strand and the antisense strand are each independently about 19 to about 30 nucleotides in length.
10. The RNAi construct of claim 9, wherein the sense strand and the antisense strand are each independently about 19 to about 23 nucleotides in length.
11. The RNAi construct of any one of claims 1 to 10, wherein the RNAi construct comprises one or two blunt ends.
12. The RNAi construct of any one of claims 1 to 10, wherein the RNAi construct comprises one or two nucleotide overhangs of 1 to 4 unpaired nucleotides.
13. The RNAi construct of claim 12, wherein the nucleotide overhang has 2 unpaired nucleotides.
14. The RNAi construct of claim 12 or 13, wherein the RNAi construct comprises a nucleotide overhang at the 3' end of the sense strand, the 3' end of the antisense strand, or the 3' end of both the sense strand and the antisense strand.
15. The RNAi construct of any one of claims 1 to 14, wherein the RNAi construct comprises one or more modified nucleotides.

16. The RNAi construct of claim 15, wherein the one or more modified nucleotides are 2'-modified nucleotides.
17. The RNAi construct of claim 15, wherein the one or more modified nucleotides are 2'-fluoro modified nucleotides, a 2'-O-methyl modified nucleotides, a 2'-O-methoxyethyl modified nucleotides, 2'-O-alkyl modified nucleotides, 2'-O-allyl modified nucleotides, bicyclic nucleic acid (BNA), deoxyribonucleotides, or combinations thereof.
18. The RNAi construct of any of claims 15 to 17, wherein all the nucleotides in the sense and antisense strands are modified nucleotides.
19. The RNAi construct of claim 18, wherein the modified nucleotides are 2'-O-methyl modified nucleotides, 2'-fluoro modified nucleotides, or a combination thereof.
20. The RNAi construct of any one of claims 1 to 19, wherein the sense strand comprises an abasic nucleotide as the terminal nucleotide at its 3' end, its 5' end, or both its 3' and 5' ends.
21. The RNAi construct of claim 20, wherein the abasic nucleotide is linked to the adjacent nucleotide through a 3'-3' internucleotide linkage or a 5'-5' internucleotide linkage.
22. The RNAi construct of any one of claims 1 to 21, wherein the sense strand, the antisense strand, or both the sense and antisense strands comprise one or more phosphorothioate internucleotide linkages.
23. The RNAi construct of claim 22, wherein the antisense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends.
24. The RNAi construct of claim 22 or 23, wherein the sense strand comprises a single phosphorothioate internucleotide linkage between the terminal nucleotides at the 3' end.
25. The RNAi construct of claim 22 or 23, wherein the sense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at the 3' end.

26. The RNAi construct of any one of claims 1 to 25, wherein the antisense strand comprises or consists of a sequence selected from the antisense sequences listed in Table 1 or Table 2.
27. The RNAi construct of any one of claims 1 to 26, wherein the sense strand comprises or consists of a sequence selected from the sense sequences listed in Table 1 or Table 2.
28. The RNAi construct of any one of claims 1 to 27, wherein the sense and antisense strands, respectively, comprise or consist of SEQ ID NOs: 15 and 559, SEQ ID NOs: 24 and 568, SEQ ID NOs: 125 and 669, SEQ ID NOs: 127 and 671, SEQ ID NOs: 222 and 766, SEQ ID NOs: 406 and 950, SEQ ID NOs: 448 and 992, SEQ ID NOs: 498 and 1042, SEQ ID NOs: 502 and 1046, SEQ ID NOs: 503 and 1047, SEQ ID NOs: 504 and 1048, SEQ ID NOs: 513 and 1057, SEQ ID NOs: 526 and 1070, SEQ ID NOs: 527 and 1071, SEQ ID NOs: 533 and 1077, or SEQ ID NOs: 534 and 1078.
29. The RNAi construct of claim 28, wherein the sense and antisense strands, respectively, comprise or consist of SEQ ID NOs: 24 and 568, SEQ ID NOs: 406 and 950, SEQ ID NOs: 498 and 1042, SEQ ID NOs: 503 and 1047, SEQ ID NOs: 504 and 1048, SEQ ID NOs: 513 and 1057, SEQ ID NOs: 527 and 1071, or SEQ ID NOs: 534 and 1078.
30. The RNAi construct of claim 28, wherein the sense and antisense strands, respectively, comprise or consist of SEQ ID NOs: 498 and 1042.
31. The RNAi construct of any one of claims 1 to 27, wherein the RNAi construct is D-1557, D-1597, D-1612, D-1614, D-1623, D-1650, D-1667, D-1680, D-1682, D-1685, D-1686, D-1690, D-1697, D-1698, D-1699, D-1702, D-1704, D-1705, D-1709, D-1768, D-1846, D-1849, D-1853, D-1856, D-1858, D-1861, D-1862, D-1863, D-1864, D-1865, D-1866, D-1868, D-1869, D-1870, D-1871, D-1873, D-1875, D-1876, D-1877, D-1878, D-1879, D-1880, D-1881, D-1883, D-1884, D-1885, D-1886, D-1887, D-1888, D-1899, D-1896, D-1955, D-1970, D-1972, D-1975, D-1976, D-1977, D-1979, D-1980, D-1981, D-1982, D-1983, D-1984, D-1985, D-1987, D-1988, D-1989, D-1990, D-1991, D-1992, D-1993, D-1994, D-1995, D-1996, D-1997, D-1998, D-2000, D-2001, D-2002, D-2003, D-2004, D-2005, D-2012, D-2013, D-2014, D-2017, D-2021, D-2022, D-2023, D-2040, D-2044, D-2045, D-2047, D-2049, D-2051, D-2052, D-2053, D-2054, D-2058, D-2061, D-2075, D-2077, D-2079, D-2080, D-2081, D-2083, D-2090, D-2091, or D-2093.

32. The RNAi construct of any one of claims 1 to 27, wherein the RNAi construct is D-1492, D-1614, D-1697, D-1702, D-1709, D-1716, D-1723, D-1730, D-1737, D-1856, D-1863, D-1865, D-1866, D-1869, D-1872, D-1877, D-1878, D-1879, D-1880, D-1881, D-1884, D-1887, D-1978, D-1987, D-1992, D-1997, D-2002, D-2008, D-2017, D-2049, D-2054, or D-2090.
33. The RNAi construct of any one of claims 1 to 27, wherein the sense and antisense strands, respectively, comprise or consist of SEQ ID NOs: 1800 and 2648 (D-1709) or SEQ ID NOs: 2861 and 3115 (D-1887).
34. The RNAi construct of any one of claims 1 to 33, wherein the RNAi construct further comprises a ligand.
35. The RNAi construct of claim 34, wherein the ligand comprises a cholesterol moiety, a vitamin, a steroid, a bile acid, a folate moiety, a fatty acid, a carbohydrate, a glycoside, or antibody or antigen-binding fragment thereof.
36. The RNAi construct of claim 34, wherein the ligand comprises galactose, galactosamine, or N-acetyl-galactosamine.
37. The RNAi construct of claim 36, wherein the ligand comprises a multivalent galactose moiety or multivalent N-acetyl-galactosamine moiety.
38. The RNAi construct of claim 37, wherein the multivalent galactose moiety or multivalent N-acetyl-galactosamine moiety is trivalent or tetravalent.
39. The RNAi construct of claim 35, wherein the ligand is a long-chain fatty acid.
40. The RNAi construct of claim 39, wherein the long-chain fatty acid is lauric acid (C12), myristic acid (C14), palmitic acid (C16), stearic acid (C18), eicosapentaenoic acid (C20), docosanoic acid (C22), or docosahexanoic acid (C24).
41. The RNAi construct of claim 40, wherein the long-chain fatty acid is docosanoic acid (C22).
42. The RNAi construct of any one of claims 34 to 41, wherein the ligand is covalently attached to the sense strand optionally through a linker.

43. The RNAi construct of claim 42, wherein the ligand is covalently attached to the 5' end of the sense strand.
44. The RNAi construct of any of claims 34 to 43, wherein the ligand is attached through a phosphodiester or phosphorothioate linkage.
45. A pharmaceutical composition comprising the RNAi construct of any one of claims 1 to 44 and a pharmaceutically acceptable carrier or excipient.
46. A method for reducing the expression of FAM13A protein in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 44 or the pharmaceutical composition of claim 45.
47. The method of claim 46, wherein the expression level of FAM13A in hepatocytes is reduced in the patient following administration of the RNAi construct or pharmaceutical composition as compared to the FAM13A expression level in a patient not receiving the RNAi construct or pharmaceutical composition.
48. The method of claim 46 or claim 47, wherein the expression level of FAM13A in adipocytes is reduced in the patient following administration of the RNAi construct or pharmaceutical composition as compared to the FAM13A expression level in a patient not receiving the RNAi construct or pharmaceutical composition.
49. The method of any of claims 46 to 48, wherein the patient is diagnosed with or at risk for obesity, abdominal obesity, NASH, hepatosteatosis, insulin resistance, type 2 diabetes, hypertriglyceridemia, or hypercholesterolemia.
50. A method for reducing the body weight or fat mass of a patient comprising administering to the patient the RNAi construct of any one of claims 1 to 44 or the pharmaceutical composition of claim 45.
51. The method of any of claims 46 to 50, wherein the patient has a high waist to hip ratio.
52. The method of claim 50, wherein the waist to hip ratio is greater than 1.0.
53. The method of claim 50 or 51, wherein the patient has been diagnosed with abdominal obesity.

54. The method of any of claims 46 to 53, wherein the RNAi construct or pharmaceutical composition is administered to the patient via a parenteral route of administration.
55. The method of claim 54, wherein the parenteral route of administration is intravenous or subcutaneous.
56. An RNAi construct of any one of claims 1 to 44 for use in treating, preventing, or reducing the risk of developing obesity, abdominal obesity, NASH, hepatosteatosis, insulin resistance, type 2 diabetes, hypertriglyceridemia, or hypercholesterolemia in a patient in need thereof.
57. Use of an RNAi construct of any one of claims 1 to 44 in the preparation of a medicament for treating, preventing, or reducing the risk of developing obesity, abdominal obesity, NASH, hepatosteatosis, insulin resistance, type 2 diabetes, hypertriglyceridemia, or hypercholesterolemia in a patient in need thereof.
58. A method of reducing body weight or fat mass by administering an RNAi construct comprising a sense strand, an antisense strand, and a ligand that targets delivery to hepatocytes, wherein the antisense sense strand has a sequence that is complementary to a FAM13 mRNA sequence.
59. The method of claim 58, wherein the FAM13A mRNA sequence is a human mRNA sequence.
60. The method of claim 58, wherein the antisense strand comprises a region comprising a sequence that is substantially complementary to at least 15 contiguous nucleotides within nucleotides 1300-1375 or 4900-5300 of the *FAM13A* mRNA sequence set forth in SEQ ID NO: 1.
61. The method of claim 58, wherein the antisense strand comprises a region comprising a sequence that is substantially complementary to a *FAM13A* mRNA sequence, and wherein said region comprises at least 15 contiguous nucleotides from an antisense sequence listed in Table 1 or Table 2.

62. The method of claim 60, wherein the antisense strand comprises a region comprising a sequence that is substantially complementary to at least 15 contiguous nucleotides within nucleotides 4950-5100 of the *FAM13A* mRNA sequence set forth in SEQ ID NO: 1.
63. The method of claim 62, wherein the antisense strand comprises a region comprising a sequence that is substantially complementary to at least 15 contiguous nucleotides within nucleotides 4975-5075 of the *FAM13A* mRNA sequence set forth in SEQ ID NO: 1.
64. The method of claim 60, wherein the antisense strand comprises a region comprising a sequence that is substantially complementary to at least 15 contiguous nucleotides within nucleotides 5225-5300 of the *FAM13A* mRNA sequence set forth in SEQ ID NO: 1.
65. The method of any one of claims 58 to 64, wherein the sense strand comprises a sequence that is sufficiently complementary to the sequence of the antisense strand to form a duplex region of about 15 to about 30 base pairs in length.
66. The method of claim 65, wherein the duplex region is about 17 to about 24 base pairs in length.
67. The method of claim 66, wherein the duplex region is about 19 to about 21 base pairs in length.
68. The method of any one of claims 58 to 67, wherein the sense strand and the antisense strand are each independently about 19 to about 30 nucleotides in length.
69. The method of claim 68, wherein the sense strand and the antisense strand are each independently about 19 to about 23 nucleotides in length.
70. The method of any one of claims 58 to 69, wherein the RNAi construct comprises one or two blunt ends.
71. The method of any one of claims 58 to 69, wherein the RNAi construct comprises one or two nucleotide overhangs of 1 to 4 unpaired nucleotides.
72. The method of claim 71, wherein the nucleotide overhang has 2 unpaired nucleotides.

73. The method of claim 71 or 72, wherein the RNAi construct comprises a nucleotide overhang at the 3' end of the sense strand, the 3' end of the antisense strand, or the 3' end of both the sense strand and the antisense strand.
74. The method of any one of claims 58 to 73, wherein the RNAi construct comprises one or more modified nucleotides.
75. The method of claim 74, wherein the one or more modified nucleotides are 2'-modified nucleotides.
76. The method of claim 74, wherein the one or more modified nucleotides are 2'-fluoro modified nucleotides, a 2'-O-methyl modified nucleotides, a 2'-O-methoxyethyl modified nucleotides, 2'-O-alkyl modified nucleotides, 2'-O-allyl modified nucleotides, bicyclic nucleic acid (BNA), deoxyribonucleotides, or combinations thereof.
77. The method of any of claims 74 to 76, wherein all the nucleotides in the sense and antisense strands are modified nucleotides.
78. The method of claim 77, wherein the modified nucleotides are 2'-O-methyl modified nucleotides, 2'-fluoro modified nucleotides, or a combination thereof.
79. The method of any one of claims 58 to 78, wherein the sense strand comprises an abasic nucleotide as the terminal nucleotide at its 3' end, its 5' end, or both its 3' and 5' ends.
80. The method of claim 79, wherein the abasic nucleotide is linked to the adjacent nucleotide through a 3'-3' internucleotide linkage or a 5'-5' internucleotide linkage.
81. The method of any one of claims 58 to 80, wherein the sense strand, the antisense strand, or both the sense and antisense strands comprise one or more phosphorothioate internucleotide linkages.
82. The method of claim 81, wherein the antisense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends.
83. The method of claim 81 or 82, wherein the sense strand comprises a single phosphorothioate internucleotide linkage between the terminal nucleotides at the 3' end.

84. The method of claim 81 or 82, wherein the sense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at the 3' end.
85. The method of any one of claims 58 to 84, wherein the antisense strand comprises or consists of a sequence selected from the antisense sequences listed in Table 1 or Table 2.
86. The method of any one of claims 58 to 85, wherein the sense strand comprises or consists of a sequence selected from the sense sequences listed in Table 1 or Table 2.
87. The method of any one of claims 58 to 86, wherein the sense and antisense strands, respectively, comprise or consist of SEQ ID NOs: 15 and 559, SEQ ID NOs: 24 and 568, SEQ ID NOs: 125 and 669, SEQ ID NOs: 127 and 671, SEQ ID NOs: 222 and 766, SEQ ID NOs: 406 and 950, SEQ ID NOs: 448 and 992, SEQ ID NOs: 498 and 1042, SEQ ID NOs: 502 and 1046, SEQ ID NOs: 503 and 1047, SEQ ID NOs: 504 and 1048, SEQ ID NOs: 513 and 1057, SEQ ID NOs: 526 and 1070, SEQ ID NOs: 527 and 1071, SEQ ID NOs: 533 and 1077, or SEQ ID NOs: 534 and 1078.
88. The method of claim 87, wherein the sense and antisense strands, respectively, comprise or consist of SEQ ID NOs: 24 and 568, SEQ ID NOs: 406 and 950, SEQ ID NOs: 498 and 1042, SEQ ID NOs: 503 and 1047, SEQ ID NOs: 504 and 1048, SEQ ID NOs: 513 and 1057, SEQ ID NOs: 527 and 1071, or SEQ ID NOs: 534 and 1078.
89. The method of claim 87, wherein the sense and antisense strands, respectively, comprise or consist of SEQ ID NOs: 498 and 1042.
90. The method of any one of claims 58 to 86, wherein the RNAi construct is D-1557, D-1597, D-1612, D-1614, D-1623, D-1650, D-1667, D-1680, D-1682, D-1685, D-1686, D-1690, D-1697, D-1698, D-1699, D-1702, D-1704, D-1705, D-1709, D-1768, D-1846, D-1849, D-1853, D-1856, D-1858, D-1861, D-1862, D-1863, D-1864, D-1865, D-1866, D-1868, D-1869, D-1870, D-1871, D-1873, D-1875, D-1876, D-1877, D-1878, D-1879, D-1880, D-1881, D-1883, D-1884, D-1885, D-1886, D-1887, D-1888, D-1899, D-1896, D-1955, D-1970, D-1972, D-1975, D-1976, D-1977, D-1979, D-1980, D-1981, D-1982, D-1983, D-1984, D-1985, D-1987, D-1988, D-1989, D-1990, D-1991, D-1992, D-1993, D-1994, D-1995, D-1996, D-1997, D-1998, D-2000, D-2001, D-2002, D-2003, D-2004, D-2005, D-2012, D-2013, D-2014, D-2017, D-2021, D-2022, D-2023, D-2040, D-2044, D-

2045, D-2047, D-2049, D-2051, D-2052, D-2053, D-2054, D-2058, D-2061, D-2075, D-2077, D-2079, D-2080, D-2081, D-2083, D-2090, D-2091, or D-2093.

91. The method of any one of claims 58 to 86, wherein the RNAi construct is D-1492, D-1614, D-1697, D-1702, D-1709, D-1716, D-1723, D-1730, D-1737, D-1856, D-1863, D-1865, D-1866, D-1869, D-1872, D-1877, D-1878, D-1879, D-1880, D-1881, D-1884, D-1887, D-1978, D-1987, D-1992, D-1997, D-2002, D-2008, D-2017, D-2049, D-2054, or D-2090.
92. The method of any one of claims 58 to 86, wherein the sense and antisense strands, respectively, comprise or consist of SEQ ID NOs: 1800 and 2648 (D-1709) or SEQ ID NOs: 2861 and 3115 (D-1887).
93. An RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region comprising a sequence that is substantially complementary to at least 15 contiguous nucleotides within a target polynucleotide, wherein the RNAi construct is conjugated to a fatty acid molecule, and wherein the fatty acid is attached through a phosphorothioate linkage.
94. The RNAi construct of claim 93, wherein the fatty acid is C22.
95. An RNAi construct of claim 93 or claim 94, wherein the antisense strand comprises a region comprising a sequence that is substantially complementary to at least 15 contiguous nucleotides within nucleotides 1300-1375 or 4900-5300 of the *FAM13A* mRNA sequence set forth in SEQ ID NO: 1.
96. An RNAi construct of claim 93 or 94, wherein the antisense strand comprises a region comprising a sequence that is substantially complementary to a *FAM13A* mRNA sequence, and wherein said region comprises at least 15 contiguous nucleotides from an antisense sequence listed in Table 1 or Table 2.
97. A non-therapeutic or cosmetic method for reducing the body weight or fat mass of an individual comprising applying or administering the RNAi construct of any one of claims 1 to 44 to that individual.