

RNAi CONSTRUCTS AND METHODS FOR INHIBITING MARC1 EXPRESSION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/065,190, filed August 13, 2020, and U.S. Provisional Application No. 63/214,016, filed June 23, 2021, both of which are hereby incorporated by reference in their entireties.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

[0002] The present application contains a Sequence Listing, which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. The computer readable format copy of the Sequence Listing, which was created on August 3, 2021, is named A-2664-WO-PCT_ ST25 and is 1,064 kilobytes in size.

FIELD OF THE INVENTION

[0003] The present invention relates to compositions and methods for modulating liver expression of mitochondrial amidoxime-reducing component 1 (mARC1) protein. In particular, the present invention relates to nucleic acid-based therapeutics for reducing *MARC1* gene expression via RNA interference and methods of using such nucleic acid-based therapeutics to reduce circulating lipid levels and to treat or prevent fatty liver disease and liver fibrosis.

BACKGROUND OF THE INVENTION

[0004] Comprising a spectrum of hepatic pathologies, nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world, the prevalence of which doubled in the last 20 years and now is estimated to affect approximately 20-30% of the world population. In some individuals the accumulation of ectopic fat in the liver, called steatosis, triggers inflammation and hepatocellular injury leading to a more advanced stage of disease called, nonalcoholic steatohepatitis (NASH). NASH is defined as lipid accumulation with evidence of cellular damage, inflammation, and different degrees of scarring or fibrosis. As of 2015, 75-100 million Americans are predicted to have NAFLD, whereas NASH accounts for approximately 10-30% of NAFLD diagnoses.

[0005] The mARC1 protein is a molybdenum-containing protein in the mitochondrial outer membrane that catalyzes the reduction of N-oxygenated molecules (Klein *et al.*, J Biol Chem, Vol. 287(51):42795-42803, 2012; Ott *et al.*, J Biol Inorg Chem, Vol. 20(2):265-275, 2015). It is a highly effective counterpart to one of the most prominent biotransformation enzymes, CYP450, and is involved in activation of amidoxime prodrugs as well as inactivation of other drugs containing N-hydroxylated functional groups (Neve *et al.*, PLoS One, Vol. 10(9):e0138487, 2015; Ott *et al.*, 2015, *supra*). Recently, predicted loss-of-function variants in the *MARC1* gene have been reported to be associated with decreased blood levels of cholesterol and liver enzymes, reduced liver fat, and protection from cirrhosis. See Emdin *et al.*, bioRxiv 594523; [//doi.org/10.1101/594523](https://doi.org/10.1101/594523), 2019; and Emdin *et al.*, PLoS Genet, Vol. 16(4): e1008629, 2020. Specifically, the A165T missense variant in the mARC1 coding region was associated with protection from all-cause cirrhosis, lower levels of hepatic fat on computed tomographic imaging and lower odds of physician-diagnosed fatty liver as well as lower blood levels of alanine transaminase, alkaline phosphatase, total cholesterol, and LDL cholesterol levels in an analysis of 12,361 all-cause cirrhosis cases and 790,095 controls from eight cohorts (Emdin *et al.*, 2020, *supra*). Additional *MARC1* alleles (M187K missense mutation and R200Ter truncation mutation) that associated with lower cholesterol levels, liver enzyme levels and reduced risk of cirrhosis were also identified (Emdin *et al.*, 2020, *supra*). These data suggest that deficiency of the mARC1 enzyme protects against chronic liver disease and cirrhosis. Accordingly, therapeutics targeting mARC1 function represent a novel approach to reducing cholesterol levels (e.g. non-HDL cholesterol or LDL-cholesterol levels) and liver fibrosis, and treating or preventing liver diseases, particularly NAFLD and NASH.

SUMMARY OF THE INVENTION

[0006] The present invention is based, in part, on the design and generation of RNAi constructs that target the *MARC1* gene and reduce its expression in liver cells. The sequence-specific inhibition of *MARC1* gene expression is useful for treating or preventing conditions associated with elevated lipid levels and liver fat, such as cardiovascular disease and fatty liver disease. Accordingly, in one embodiment, the present invention provides an RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having a sequence that is substantially complementary to a mARC1 mRNA sequence. For instance, 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 mARC1 mRNA sequence (SEQ ID NO: 1) with no more than 1, 2, or 3 mismatches. In certain embodiments, the antisense strand comprises a region having at least 15 contiguous nucleotides from an antisense sequence listed in Table 1 or Table 2.

[0007] 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. In these and other embodiments, the sense and antisense strands are each independently about 19 to about 30 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.

[0008] The RNAi constructs of the invention 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 RNAi constructs of the invention, 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.

[0009] 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.

[0010] In certain embodiments, the antisense strand and/or the sense strand of the RNAi constructs of the invention may comprise or consist of a sequence from the antisense and sense sequences listed in Table 1 or Table 2. In certain such embodiments, the RNAi construct may be any one of the duplex compounds listed in any one of Tables 1 to 24. In some embodiments, the RNAi construct is D-1044, D-1061, D-1062, D-1067, D-1083, D-1090, D-1092, D-1093, D-1095, D-1138, D-1139, D-1143, D-1170, D-1177, D-1180, D-1191, D-1245, D-2000, D-2002, D-2003, D-2004, D-2011, D-2026, D-2028, D-2032, D-2033, D-2034, D-2035, D-2036, D-2042, D-2044, D-2045, D-2046, D-2050, D-2078, D-2079, D-2081, D-2182, D-2196, D-2238, D-2241, D-2243, D-2246, D-2255, D-2356, D-2258, D-2301, D-2316, D-2317, D-2329, D-2332, D-2341, D-2344, D-2357, D-2399, or D-2510. In certain embodiments, the RNAi construct is D-2079, D-2081, D-2196, D-2238, D-2241, D-2255, D-2258, D-2317, D-2332, D-2357, or D-2399.

[0011] In some embodiments, the RNAi constructs of the invention may target a particular region of the human mARC1 mRNA transcript (e.g. the human mARC1 mRNA transcript sequence set forth in SEQ ID NO: 1). For instance, in certain 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 complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1205 to 1250 of SEQ ID NO: 1. In other embodiments, the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1209 to 1239 of SEQ ID NO: 1. In yet other embodiments, the antisense strand comprises a region having a sequence that is substantially

complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1345 to 1375 of SEQ ID NO: 1. In still other embodiments, the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 2039 to 2078 of SEQ ID NO: 1. In certain other embodiments, the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 2048 to 2074 of SEQ ID NO: 1. In any of the above 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 mARC1 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 mARC1 transcript. In some such embodiments in which a mismatch occurs between the sequence of the antisense strand and the sequence of the target mARC1 mRNA sequence, the mismatch may be located between the target mARC1 mRNA sequence and the nucleotide at position 6 and/or position 8 from the 5' end of the antisense strand. In other 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 mARC1 transcript (SEQ ID NO: 1).

[0012] The RNAi constructs of the invention may further comprise a ligand to facilitate delivery or uptake of the RNAi constructs to specific tissues or cells, such as liver 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 having a structure according to any one of Formulas I to IX described herein. In certain embodiments, the RNAi constructs comprise a ligand and linker having a structure according to Formula VII. In other embodiments, the RNAi constructs comprise a ligand and linker having a structure according to Formula IV.

[0013] The present invention 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

MARC1 gene in the cells (e.g. liver cells) of a patient in need thereof. Patients who may be administered a pharmaceutical composition of the invention can include patients diagnosed with or at risk of cardiovascular disease, fatty liver disease, liver fibrosis, or cirrhosis and patients with elevated blood levels of cholesterol (e.g. total cholesterol, non-HDL cholesterol, or LDL-cholesterol). Accordingly, the present invention includes methods of treating, preventing, or reducing the risk of developing fatty liver disease (e.g. NAFLD, NASH, alcoholic fatty liver disease, or alcoholic steatohepatitis), liver fibrosis, or cardiovascular disease in a patient in need thereof comprising administering an RNAi construct or pharmaceutical composition described herein. In certain embodiments, the present invention provides methods for reducing blood levels (serum or plasma) of cholesterol (e.g. total cholesterol, non-HDL cholesterol, or LDL-cholesterol) in a patient in need thereof comprising administering an RNAi construct or pharmaceutical composition described herein.

[0014] The use of *mARC1*-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 invention includes a *mARC1*-targeting RNAi construct for use in a method for treating, preventing, or reducing the risk of developing fatty liver disease (e.g. NAFLD, NASH, alcoholic fatty liver disease, or alcoholic steatohepatitis), liver fibrosis, or cardiovascular disease in a patient in need thereof. The present invention also includes a *mARC1*-targeting RNAi construct for use in a method for reducing blood levels (serum or plasma) of cholesterol (e.g. total cholesterol, non-HDL cholesterol, or LDL-cholesterol) in a patient in need thereof.

[0015] The present invention also encompasses the use of a *mARC1*-targeting RNAi construct in the preparation of a medicament for treating, preventing, or reducing the risk of developing fatty liver disease (e.g. NAFLD, NASH, alcoholic fatty liver disease, or alcoholic steatohepatitis), liver fibrosis, or cardiovascular disease in a patient in need thereof. In certain embodiments, the present invention provides the use of a *mARC1*-targeting RNAi construct in the preparation of a medicament for reducing blood levels (serum or plasma) of cholesterol (e.g. total cholesterol, non-HDL cholesterol, or LDL-cholesterol) in a patient in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] **Figure 1** shows the nucleotide sequence of a transcript of the human *MARC1* gene (Ensembl transcript no. ENST00000366910.9; SEQ ID NO: 1). The transcript sequence is depicted as the complementary DNA (cDNA) sequence with thymine bases replacing uracil bases.

[0017] **Figures 2A and 2B** are bar graphs showing liver expression of mARC1 mRNA (**Figure 2A**) and mARC2 mRNA (**Figure 2B**) in ob/ob mice receiving subcutaneous injections of buffer, mARC1 siRNA (duplex no. D-1000), or a control siRNA (duplex no. D-1002) once every two weeks for six weeks. mRNA levels were assessed by qPCR at six weeks and are expressed relative to mRNA levels in animals receiving buffer only injections.

[0018] **Figures 3A-3H** are graphs depicting serum levels of total cholesterol (CHOL; **Figure 3A**), LDL cholesterol (LDL; **Figure 3B**), HDL cholesterol (HDL; **Figure 3C**), triglycerides (TG; **Figure 3D**), alanine aminotransferase (ALT; **Figure 3E**), aspartate aminotransferase (AST; **Figure 3F**), C-reactive protein (CRP; **Figure 3G**), and tissue inhibitor of metalloproteinases-1 (TIMP-1; **Figure 3H**) in ob/ob mice receiving subcutaneous injections of buffer, mARC1 siRNA (duplex no. D-1000), or a control siRNA (duplex no. D-1002) once every two weeks for six weeks. Serum levels of the different analytes were measured using a clinical analyzer at the six-week time point. Mean values $\pm$ standard error of the mean (SEM) are shown. * = $p < 0.05$; ** = $p < 0.01$ vs. buffer control group.

[0019] **Figures 4A and 4B** are graphs showing liver levels of triglycerides (liver TG; **Figure 4A**) or total cholesterol (liver TC; **Figure 4B**) at six weeks in ob/ob mice receiving subcutaneous injections of buffer, mARC1 siRNA (duplex no. D-1000), or a control siRNA (duplex no. D-1002) once every two weeks for six weeks. Mean values $\pm$ SEM are shown. *** = $p < 0.001$ vs. buffer control group.

[0020] **Figures 5A and 5B** are bar graphs showing liver expression of mARC1 mRNA (**Figure 5A**) and mARC2 mRNA (**Figure 5B**) in c57BL/6 mice on a standard chow diet (chow control) or a 0.2% cholesterol diet (TD190883). Mice on the 0.2% cholesterol diet received subcutaneous injections of buffer (TD190883 control), mARC1 siRNA (duplex no. D-1000), or a control siRNA (duplex no. D-1002) once every two weeks for 24 weeks. mRNA levels were assessed by qPCR at 24 weeks and are expressed relative to mRNA levels in the chow control animals.

[0021] Figures 6A-6F are graphs depicting serum levels of aspartate aminotransferase (AST; **Figure 6A**), alanine aminotransferase (ALT; **Figure 6B**), total cholesterol (**Figure 6C**), LDL cholesterol (LDL-c; **Figure 6D**), HDL cholesterol (HDL-c; **Figure 6E**), and triglycerides (**Figure 6F**) in c57BL/6 mice on a standard chow diet (chow control) or a 0.2% cholesterol diet (TD190883). Mice on the 0.2% cholesterol diet received subcutaneous injections of buffer (TD190883 control), mARC1 siRNA (duplex no. D-1000), or a control siRNA (duplex no. D-1002) once every two weeks for 24 weeks. Serum levels of the different analytes were measured using a clinical analyzer at the indicated time post dosing. Mean values $\pm$ standard error of the mean (SEM) are shown. * = $p < 0.05$; ** = $p < 0.01$, *** = $p < 0.001$ vs. TD190883 control group.

[0022] Figures 7A-7D are graphs showing body weight (**Figure 7A**), liver weight (**Figure 7B**), liver levels of triglycerides (**Figure 7C**) and liver levels of total cholesterol (**Figure 7D**) at 24 weeks in c57BL/6 mice on a standard chow diet (chow control) or a 0.2% cholesterol diet (TD190883). Mice on the 0.2% cholesterol diet received subcutaneous injections of buffer (TD190883 control), mARC1 siRNA (duplex no. D-1000), or a control siRNA (duplex no. D-1002) once every two weeks for 24 weeks. Mean values $\pm$ SEM are shown.

[0023] Figures 8A-8F are antisense strand and sense strand serum concentration-time profiles in cynomolgus macaque monkeys following a single 3 mg/kg s.c. dose of GalNAc-conjugated mARC1 siRNA molecules D-2241 (**Figures 8A and 8B**), D-2081 (**Figures 8C and 8D**), and D-2258 (**Figures 8E and 8F**). Figures 8A, 8C, and 8E depict the concentration-time profiles from 0.083 to 24 hours post dose, whereas Figures 8B, 8D, and 8F depict the concentration-time profiles from 0.083 to 1056 hours post dose.

DETAILED DESCRIPTION

[0024] The present invention is directed to compositions and methods for regulating the expression of the *MARCI* gene in a cell or mammal. In some embodiments, compositions of the invention comprise RNAi constructs that target a mRNA transcribed from the *MARCI* gene, particularly the human *MARCI* gene, and reduce expression of the mARC1 protein in a cell or mammal. Such RNAi constructs are useful for reducing serum lipid levels (e.g., total cholesterol and LDL-cholesterol levels), treating or preventing various forms of cardiovascular disease and fatty liver disease, such as NAFLD and NASH, and reducing liver fibrosis and the risk of progression to cirrhosis.

[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. *MARCI* 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 having 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.

[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 considered to be 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 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 considered to 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. mARC1 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 of the invention 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 of the invention 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 of the invention 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 mARC1 messenger RNA (mRNA) sequence. As used herein, a “mARC1 mRNA sequence” refers to any messenger RNA sequence, including allelic variants and splice variants, encoding a mARC1 protein, including mARC1 protein variants or isoforms from any species (e.g. non-human primate, human). The *MARC1* gene (also known as *MTARC1* or *MOSCI*) encodes the mitochondrial amidoxime reducing component 1 enzyme (also known as MOCO sulphurase C-terminal domain containing 1 enzyme). In humans, the *MARC1* gene is found on chromosome 1 at locus 1q41.

[0032] A mARC1 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 of the invention may comprise a region having a sequence that is substantially or fully complementary to a target mARC1 mRNA sequence or mARC1 cDNA sequence. A mARC1 mRNA or cDNA sequence can include, but is not limited to, any mARC1 mRNA or cDNA sequences in the Ensembl Genome or National Center for Biotechnology Information (NCBI) databases, such as human sequences: Ensembl transcript no. ENST00000366910.9 (Figure 1, SEQ ID NO: 1) and NCBI Reference sequence NM_022746.4; cynomolgus monkey sequences: NCBI Reference sequences XR_001490722.1, XR_001490722.1, XR_001490723.1, XR_001490726.1, XR_273285.2, XM_005540901.2, XR_273286.2, XM_005540898.2, and XM_005540899.2; rhesus monkey sequences: NCBI Reference sequences XM_015115809.2,

XM_015115815.2, XM_001102192.4, and XM_001102284.3; chimpanzee sequences: NCBI Reference sequences XM_009441519.3, XM_001172926.4, and XM_009441521.3; rat sequences: NCBI Reference sequence XM_017598938.1; and mouse sequences: NCBI Reference sequence XM_006497192.4. In certain embodiments, the mARC1 mRNA sequence is the human transcript set forth in Figure 1 (SEQ ID NO: 1).

[0033] A region of the antisense strand can be substantially complementary or fully complementary to at least 15 consecutive nucleotides of the mARC1 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 mARC1 mRNA sequence (e.g. a human mARC1 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 mARC1 mRNA sequence with no more than 1 mismatch. In embodiments in which the sequence of the antisense strand is not fully complementary to the target mARC1 mRNA sequence and contains a mismatch, the mismatch may occur between the target mARC1 mRNA sequence and the nucleotide at position 6 and/or position 8 from the 5' end of the antisense strand. In some embodiments, the target region of the mARC1 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 mARC1 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] 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.

[0035] 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 one particular embodiment, 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.

[0036] 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.).

[0037] 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.

[0038] 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).

[0039] The sense strand and antisense strand in the RNAi constructs of the invention 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.

[0040] 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.

[0041] The antisense strand of the RNAi constructs of the invention 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: 671-1339, 2072-2803, 2906-3061, or 3321-3655. In other embodiments, the antisense strand comprises or consists of a sequence of nucleotides 1-19 of any one of SEQ ID NOs: 671-1339, 2072-2803, 2906-3061, or 3321-3655. In still other embodiments, the antisense strand comprises or consists of a sequence of nucleotides 2-19 of any one of SEQ ID NOs: 671-1339, 2072-2803, 2906-3061, or 3321-3655. In certain embodiments, the antisense strand comprises or consists of a sequence selected from SEQ ID NO: 715; SEQ ID NO: 725; SEQ ID NO: 732; SEQ ID NO: 733; SEQ ID NO: 737; SEQ ID NO: 738; SEQ ID NO: 739; SEQ ID NO: 745; SEQ ID NO: 754; SEQ ID NO: 757; SEQ ID NO: 758; SEQ ID NO: 761; SEQ ID NO: 762; SEQ ID NO: 763; SEQ ID NO: 764; SEQ ID NO: 766; SEQ ID NO: 767; SEQ ID NO: 768; SEQ ID NO: 770; SEQ ID NO: 782; SEQ ID NO: 784; SEQ ID NO: 801; SEQ ID NO: 809; SEQ ID NO: 810; SEQ ID NO: 811; SEQ ID NO: 814; SEQ ID NO: 818; SEQ ID NO: 821; SEQ ID NO: 837; SEQ ID NO: 841; SEQ ID NO: 842; SEQ ID NO: 845; SEQ ID NO: 847; SEQ ID NO: 848; SEQ ID NO: 850; SEQ ID NO: 851; SEQ ID NO: 855; SEQ ID NO: 856; SEQ ID NO: 860; SEQ ID NO: 861; SEQ ID NO: 862; SEQ ID NO: 865; SEQ ID NO: 875; SEQ ID NO: 884; SEQ ID NO: 886; SEQ ID NO: 891; SEQ ID NO: 899; SEQ ID NO: 901; SEQ ID NO: 907; SEQ ID NO: 914; SEQ ID NO: 916; SEQ ID NO: 920; SEQ ID NO: 927; SEQ ID NO: 937; SEQ ID NO: 1056; SEQ ID NO: 1057; SEQ ID NO: 1058; SEQ ID NO: 1059; SEQ ID NO: 1078; SEQ ID NO: 2917; SEQ ID NO: 2919; SEQ ID NO: 2926; SEQ ID NO: 2946; SEQ ID NO: 2949; SEQ ID NO: 2951; SEQ ID

NO: 2953; and SEQ ID NO: 2956. In some embodiments, the antisense strand comprises or consists of a sequence selected from SEQ ID NO: 715; SEQ ID NO: 732; SEQ ID NO: 733; SEQ ID NO: 737; SEQ ID NO: 738; SEQ ID NO: 739; SEQ ID NO: 745; SEQ ID NO: 754; SEQ ID NO: 757; SEQ ID NO: 761; SEQ ID NO: 762; SEQ ID NO: 763; SEQ ID NO: 764; SEQ ID NO: 766; SEQ ID NO: 767; SEQ ID NO: 784; SEQ ID NO: 801; SEQ ID NO: 809; SEQ ID NO: 810; SEQ ID NO: 811; SEQ ID NO: 814; SEQ ID NO: 841; SEQ ID NO: 842; SEQ ID NO: 845; SEQ ID NO: 848; SEQ ID NO: 851; SEQ ID NO: 856; SEQ ID NO: 860; SEQ ID NO: 862; SEQ ID NO: 914; SEQ ID NO: 916; SEQ ID NO: 927; SEQ ID NO: 937; SEQ ID NO: 1056; SEQ ID NO: 1057; SEQ ID NO: 1058; SEQ ID NO: 1059; SEQ ID NO: 1078; SEQ ID NO: 2917; SEQ ID NO: 2919; SEQ ID NO: 2926; SEQ ID NO: 2946; SEQ ID NO: 2949; SEQ ID NO: 2951; SEQ ID NO: 2953; and SEQ ID NO: 2956. In other embodiments, the antisense strand comprises or consists of a sequence selected from SEQ ID NO: 715; SEQ ID NO: 732; SEQ ID NO: 733; SEQ ID NO: 738; SEQ ID NO: 754; SEQ ID NO: 761; SEQ ID NO: 763; SEQ ID NO: 764; SEQ ID NO: 766; SEQ ID NO: 809; SEQ ID NO: 810; SEQ ID NO: 814; SEQ ID NO: 841; SEQ ID NO: 848; SEQ ID NO: 851; SEQ ID NO: 862; SEQ ID NO: 916; SEQ ID NO: 1057; SEQ ID NO: 1078; SEQ ID NO: 2919; SEQ ID NO: 2926; SEQ ID NO: 2946; SEQ ID NO: 2949; SEQ ID NO: 2953; and SEQ ID NO: 2956.

[0042] In these and other embodiments, the sense strand of the RNAi constructs of the invention 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: 2-670, 1340-2071, 2804-2905, or 3062-3320. In other embodiments, the sense strand comprises or consists of a sequence of nucleotides 1-19 of any one of SEQ ID NOs: 2-670, 1340-2071, 2804-2905, or 3062-3320. In still other embodiments, the sense strand comprises or consists of a sequence of nucleotides 2-19 of any one of SEQ ID NOs: 2-670, 1340-2071, 2804-2905, or 3062-3320. In certain embodiments, the sense strand comprises or consists of a sequence selected from SEQ ID NO: 46; SEQ ID NO: 56; SEQ ID NO: 63; SEQ ID NO: 64; SEQ ID NO: 68; SEQ ID NO: 69; SEQ ID NO: 70; SEQ ID NO: 76; SEQ ID NO: 85; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 92; SEQ ID NO: 93; SEQ ID NO: 94; SEQ ID NO: 95; SEQ ID NO: 97; SEQ ID NO: 98; SEQ ID NO: 99; SEQ ID NO: 101; SEQ ID NO: 113; SEQ ID NO: 115; SEQ ID NO: 132; SEQ ID

NO: 140; SEQ ID NO: 141; SEQ ID NO: 142; SEQ ID NO: 145; SEQ ID NO: 149; SEQ ID NO: 152; SEQ ID NO: 168; SEQ ID NO: 172; SEQ ID NO: 173; SEQ ID NO: 176; SEQ ID NO: 178; SEQ ID NO: 179; SEQ ID NO: 181; SEQ ID NO: 182; SEQ ID NO: 186; SEQ ID NO: 187; SEQ ID NO: 191; SEQ ID NO: 192; SEQ ID NO: 193; SEQ ID NO: 196; SEQ ID NO: 206; SEQ ID NO: 215; SEQ ID NO: 217; SEQ ID NO: 222; SEQ ID NO: 230; SEQ ID NO: 232; SEQ ID NO: 238; SEQ ID NO: 245; SEQ ID NO: 247; SEQ ID NO: 251; SEQ ID NO: 258; SEQ ID NO: 268; SEQ ID NO: 387; SEQ ID NO: 388; SEQ ID NO: 389; SEQ ID NO: 390; SEQ ID NO: 391; SEQ ID NO: 392; SEQ ID NO: 409; SEQ ID NO: 2808; and SEQ ID NO: 2820. In certain other embodiments, the sense strand comprises or consists of a sequence selected from SEQ ID NO: 46; SEQ ID NO: 63; SEQ ID NO: 64; SEQ ID NO: 68; SEQ ID NO: 69; SEQ ID NO: 70; SEQ ID NO: 76; SEQ ID NO: 85; SEQ ID NO: 88; SEQ ID NO: 92; SEQ ID NO: 93; SEQ ID NO: 94; SEQ ID NO: 95; SEQ ID NO: 97; SEQ ID NO: 98; SEQ ID NO: 115; SEQ ID NO: 132; SEQ ID NO: 140; SEQ ID NO: 141; SEQ ID NO: 142; SEQ ID NO: 145; SEQ ID NO: 172; SEQ ID NO: 173; SEQ ID NO: 176; SEQ ID NO: 179; SEQ ID NO: 182; SEQ ID NO: 187; SEQ ID NO: 191; SEQ ID NO: 193; SEQ ID NO: 245; SEQ ID NO: 247; SEQ ID NO: 258; SEQ ID NO: 268; SEQ ID NO: 387; SEQ ID NO: 388; SEQ ID NO: 389; SEQ ID NO: 390; SEQ ID NO: 391; SEQ ID NO: 392; SEQ ID NO: 409; SEQ ID NO: 2808; and SEQ ID NO: 2820. In yet other embodiments, the sense strand comprises or consists of a sequence selected from SEQ ID NO: 46; SEQ ID NO: 63; SEQ ID NO: 64; SEQ ID NO: 69; SEQ ID NO: 85; SEQ ID NO: 92; SEQ ID NO: 94; SEQ ID NO: 95; SEQ ID NO: 97; SEQ ID NO: 140; SEQ ID NO: 141; SEQ ID NO: 145; SEQ ID NO: 172; SEQ ID NO: 179; SEQ ID NO: 182; SEQ ID NO: 193; SEQ ID NO: 247; SEQ ID NO: 388; SEQ ID NO: 390; SEQ ID NO: 391; SEQ ID NO: 409; SEQ ID NO: 2808; and SEQ ID NO: 2820.

[0043] In certain embodiments of the invention, the RNAi constructs comprise (i) a sense strand comprising or consisting of a sequence selected from 2-670, 1340-2071, 2804-2905, or 3062-3320 and (ii) an antisense strand comprising or consisting of a sequence selected from SEQ ID NOs: 671-1339, 2072-2803, 2906-3061, or 3321-3655. In some embodiments, the RNAi constructs comprise (i) a sense strand comprising or consisting of a sequence selected from SEQ ID NO: 46; SEQ ID NO: 56; SEQ ID NO: 63; SEQ ID NO: 64; SEQ ID NO: 68; SEQ ID NO: 69; SEQ ID NO: 70; SEQ ID NO: 76; SEQ ID NO: 85; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 92; SEQ ID NO: 93; SEQ ID NO: 94; SEQ ID NO: 95; SEQ ID NO: 97; SEQ ID NO:

98; SEQ ID NO: 99; SEQ ID NO: 101; SEQ ID NO: 113; SEQ ID NO: 115; SEQ ID NO: 132; SEQ ID NO: 140; SEQ ID NO: 141; SEQ ID NO: 142; SEQ ID NO: 145; SEQ ID NO: 149; SEQ ID NO: 152; SEQ ID NO: 168; SEQ ID NO: 172; SEQ ID NO: 173; SEQ ID NO: 176; SEQ ID NO: 178; SEQ ID NO: 179; SEQ ID NO: 181; SEQ ID NO: 182; SEQ ID NO: 186; SEQ ID NO: 187; SEQ ID NO: 191; SEQ ID NO: 192; SEQ ID NO: 193; SEQ ID NO: 196; SEQ ID NO: 206; SEQ ID NO: 215; SEQ ID NO: 217; SEQ ID NO: 222; SEQ ID NO: 230; SEQ ID NO: 232; SEQ ID NO: 238; SEQ ID NO: 245; SEQ ID NO: 247; SEQ ID NO: 251; SEQ ID NO: 258; SEQ ID NO: 268; SEQ ID NO: 387; SEQ ID NO: 388; SEQ ID NO: 389; SEQ ID NO: 390; SEQ ID NO: 391; SEQ ID NO: 392; SEQ ID NO: 409; SEQ ID NO: 2808; and SEQ ID NO: 2820 and (ii) an antisense strand comprising or consisting of a sequence selected from SEQ ID NO: 715; SEQ ID NO: 725; SEQ ID NO: 732; SEQ ID NO: 733; SEQ ID NO: 737; SEQ ID NO: 738; SEQ ID NO: 739; SEQ ID NO: 745; SEQ ID NO: 754; SEQ ID NO: 757; SEQ ID NO: 758; SEQ ID NO: 761; SEQ ID NO: 762; SEQ ID NO: 763; SEQ ID NO: 764; SEQ ID NO: 766; SEQ ID NO: 767; SEQ ID NO: 768; SEQ ID NO: 770; SEQ ID NO: 782; SEQ ID NO: 784; SEQ ID NO: 801; SEQ ID NO: 809; SEQ ID NO: 810; SEQ ID NO: 811; SEQ ID NO: 814; SEQ ID NO: 818; SEQ ID NO: 821; SEQ ID NO: 837; SEQ ID NO: 841; SEQ ID NO: 842; SEQ ID NO: 845; SEQ ID NO: 847; SEQ ID NO: 848; SEQ ID NO: 850; SEQ ID NO: 851; SEQ ID NO: 855; SEQ ID NO: 856; SEQ ID NO: 860; SEQ ID NO: 861; SEQ ID NO: 862; SEQ ID NO: 865; SEQ ID NO: 875; SEQ ID NO: 884; SEQ ID NO: 886; SEQ ID NO: 891; SEQ ID NO: 899; SEQ ID NO: 901; SEQ ID NO: 907; SEQ ID NO: 914; SEQ ID NO: 916; SEQ ID NO: 920; SEQ ID NO: 927; SEQ ID NO: 937; SEQ ID NO: 1056; SEQ ID NO: 1057; SEQ ID NO: 1058; SEQ ID NO: 1059; SEQ ID NO: 1078; SEQ ID NO: 2917; SEQ ID NO: 2919; SEQ ID NO: 2926; SEQ ID NO: 2946; SEQ ID NO: 2949; SEQ ID NO: 2951; SEQ ID NO: 2953; and SEQ ID NO: 2956. In other embodiments, the RNAi constructs comprise (i) a sense strand comprising or consisting of a sequence selected from SEQ ID NO: 46; SEQ ID NO: 63; SEQ ID NO: 64; SEQ ID NO: 68; SEQ ID NO: 69; SEQ ID NO: 70; SEQ ID NO: 76; SEQ ID NO: 85; SEQ ID NO: 88; SEQ ID NO: 92; SEQ ID NO: 93; SEQ ID NO: 94; SEQ ID NO: 95; SEQ ID NO: 97; SEQ ID NO: 98; SEQ ID NO: 115; SEQ ID NO: 132; SEQ ID NO: 140; SEQ ID NO: 141; SEQ ID NO: 142; SEQ ID NO: 145; SEQ ID NO: 172; SEQ ID NO: 173; SEQ ID NO: 176; SEQ ID NO: 179; SEQ ID NO: 182; SEQ ID NO: 187; SEQ ID NO: 191; SEQ ID NO: 193; SEQ ID NO: 245; SEQ ID NO: 247; SEQ ID NO: 258;

SEQ ID NO: 268; SEQ ID NO: 387; SEQ ID NO: 388; SEQ ID NO: 389; SEQ ID NO: 390; SEQ ID NO: 391; SEQ ID NO: 392; SEQ ID NO: 409; SEQ ID NO: 2808; and SEQ ID NO: 2820 and (ii) an antisense strand comprising or consisting of a sequence selected from SEQ ID NO: 715; SEQ ID NO: 732; SEQ ID NO: 733; SEQ ID NO: 737; SEQ ID NO: 738; SEQ ID NO: 739; SEQ ID NO: 745; SEQ ID NO: 754; SEQ ID NO: 757; SEQ ID NO: 761; SEQ ID NO: 762; SEQ ID NO: 763; SEQ ID NO: 764; SEQ ID NO: 766; SEQ ID NO: 767; SEQ ID NO: 784; SEQ ID NO: 801; SEQ ID NO: 809; SEQ ID NO: 810; SEQ ID NO: 811; SEQ ID NO: 814; SEQ ID NO: 841; SEQ ID NO: 842; SEQ ID NO: 845; SEQ ID NO: 848; SEQ ID NO: 851; SEQ ID NO: 856; SEQ ID NO: 860; SEQ ID NO: 862; SEQ ID NO: 914; SEQ ID NO: 916; SEQ ID NO: 927; SEQ ID NO: 937; SEQ ID NO: 1056; SEQ ID NO: 1057; SEQ ID NO: 1058; SEQ ID NO: 1059; SEQ ID NO: 1078; SEQ ID NO: 2917; SEQ ID NO: 2919; SEQ ID NO: 2926; SEQ ID NO: 2946; SEQ ID NO: 2949; SEQ ID NO: 2951; SEQ ID NO: 2953; and SEQ ID NO: 2956. In still other embodiments, the RNAi constructs comprise (i) a sense strand comprising or consisting of a sequence selected from SEQ ID NO: 46; SEQ ID NO: 63; SEQ ID NO: 64; SEQ ID NO: 69; SEQ ID NO: 85; SEQ ID NO: 92; SEQ ID NO: 94; SEQ ID NO: 95; SEQ ID NO: 97; SEQ ID NO: 140; SEQ ID NO: 141; SEQ ID NO: 145; SEQ ID NO: 172; SEQ ID NO: 179; SEQ ID NO: 182; SEQ ID NO: 193; SEQ ID NO: 247; SEQ ID NO: 388; SEQ ID NO: 390; SEQ ID NO: 391; SEQ ID NO: 409; SEQ ID NO: 2808; and SEQ ID NO: 2820 and (ii) an antisense strand comprising or consisting of a sequence selected from SEQ ID NO: 715; SEQ ID NO: 732; SEQ ID NO: 733; SEQ ID NO: 738; SEQ ID NO: 754; SEQ ID NO: 761; SEQ ID NO: 763; SEQ ID NO: 764; SEQ ID NO: 766; SEQ ID NO: 809; SEQ ID NO: 810; SEQ ID NO: 814; SEQ ID NO: 841; SEQ ID NO: 848; SEQ ID NO: 851; SEQ ID NO: 862; SEQ ID NO: 916; SEQ ID NO: 1057; SEQ ID NO: 1078; SEQ ID NO: 2919; SEQ ID NO: 2926; SEQ ID NO: 2946; SEQ ID NO: 2949; SEQ ID NO: 2953; and SEQ ID NO: 2956.

[0044] In certain embodiments, the RNAi constructs of the invention comprise: (i) a sense strand comprising or consisting of the sequence of SEQ ID NO: 46 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 715; (ii) a sense strand comprising or consisting of the sequence of SEQ ID NO: 63 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 732; (iii) a sense strand comprising or consisting of the sequence of SEQ ID NO: 64 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 733; (iv) a sense strand comprising or consisting of the sequence of SEQ ID NO: 69 and an antisense strand

comprising or consisting of the sequence of SEQ ID NO: 738; (v) a sense strand comprising or consisting of the sequence of SEQ ID NO: 85 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 754; (vi) a sense strand comprising or consisting of the sequence of SEQ ID NO: 92 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 761; (vii) a sense strand comprising or consisting of the sequence of SEQ ID NO: 94 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 763; (viii) a sense strand comprising or consisting of the sequence of SEQ ID NO: 95 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 764; (ix) a sense strand comprising or consisting of the sequence of SEQ ID NO: 97 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 766; (x) a sense strand comprising or consisting of the sequence of SEQ ID NO: 140 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 809; (xi) a sense strand comprising or consisting of the sequence of SEQ ID NO: 141 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 810; (xii) a sense strand comprising or consisting of the sequence of SEQ ID NO: 145 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 814; (xiii) a sense strand comprising or consisting of the sequence of SEQ ID NO: 172 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 841; (xiv) a sense strand comprising or consisting of the sequence of SEQ ID NO: 179 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 848; (xv) a sense strand comprising or consisting of the sequence of SEQ ID NO: 182 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 851; (xvi) a sense strand comprising or consisting of the sequence of SEQ ID NO: 193 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 862; or (xvii) a sense strand comprising or consisting of the sequence of SEQ ID NO: 247 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 916.

[0045] In certain other embodiments, the RNAi constructs of the invention comprise: (i) a sense strand comprising or consisting of the sequence of SEQ ID NO: 409 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 1078; (ii) a sense strand comprising or consisting of the sequence of SEQ ID NO: 388 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 1057; (iii) a sense strand comprising or consisting of the sequence of SEQ ID NO: 2808 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 2926; (iv) a sense strand comprising or consisting of the sequence of SEQ ID

NO: 2820 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 2946; (v) a sense strand comprising or consisting of the sequence of SEQ ID NO: 391 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 2949; (vi) a sense strand comprising or consisting of the sequence of SEQ ID NO: 390 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 2956; (vii) a sense strand comprising or consisting of the sequence of SEQ ID NO: 179 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 2919; (viii) a sense strand comprising or consisting of the sequence of SEQ ID NO: 388 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 2953; or (ix) a sense strand comprising or consisting of the sequence of SEQ ID NO: 388 and an antisense strand comprising or consisting of the sequence of SEQ ID NO: 1057.

[0046] In some embodiments, the RNAi constructs of the invention comprise: (i) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2009 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2741; (ii) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2011 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2743; (iii) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2012 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2744; (iv) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2013 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2745; (v) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2020 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2752; (vi) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2035 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2767; (vii) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2037 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2769; (viii) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2041 and an antisense strand comprising or consisting of the sequence of modified nucleotides

according to SEQ ID NO: 2773; (ix) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2042 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2774; (x) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2043 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2775; (xi) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2044 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2776; (xii) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2045 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2777; (xiii) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2051 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2783; (xiv) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2053 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2785; (xv) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2054 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2786; (xvi) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2055 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2787; or (xvii) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2059 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2791.

[0047] In other embodiments, the RNAi constructs of the invention comprise: (i) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3078 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3337; (ii) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3080 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3339; (iii) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID

NO: 3163 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3441; (iv) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3183 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3469; (v) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3076 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3472; (vi) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3077 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3484; (vii) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 2051 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3545; (viii) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3080 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3481; (ix) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3188 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3339; (x) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3080 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3476; or (xi) a sense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3223 and an antisense strand comprising or consisting of the sequence of modified nucleotides according to SEQ ID NO: 3517.

[0048] The RNAi construct of the invention can be any of the duplex compounds listed in Tables 1 to 24 (including the unmodified nucleotide sequences and/or modified nucleotide sequences of the compounds). In some embodiments, the RNAi construct is any of the duplex compounds listed in Table 1. In other embodiments, the RNAi construct is any of the duplex compounds listed in Table 2 (including the unmodified nucleotide sequences and/or modified nucleotide sequences of the compounds). In certain embodiments, the RNAi construct is D-1044, D-1061, D-1062, D-1067, D-1083, D-1090, D-1092, D-1093, D-1095, D-1138, D-1139, D-1143, D-1170, D-1177, D-1180, D-1191, D-1245, D-2000, D-2002, D-2003, D-2004, D-2011, D-2026, D-2028,

D-2032, D-2033, D-2034, D-2035, D-2036, D-2042, D-2044, D-2045, D-2046, D-2050, D-2078, D-2079, D-2081, D-2182, D-2196, D-2238, D-2241, D-2243, D-2246, D-2255, D-2258, D-2301, D-2316, D-2317, D-2329, D-2332, D-2341, D-2344, D-2356, D-2357, D-2399, or D-2510. In certain other embodiments, the RNAi construct is D-2079, D-2081, D-2196, D-2238, D-2241, D-2255, D-2258, D-2317, D-2332, D-2357, or D-2399.

[0049] In certain embodiments, the RNAi constructs of the invention may target a particular region of the human mARC1 transcript sequence. As described in Example 4 and summarized in Table 23, it was found that certain RNAi constructs with antisense strands designed to have a sequence complementary to certain regions of the human mARC1 transcript (SEQ ID NO: 1) exhibited superior *in vivo* knockdown activity of human mARC1 mRNA as compared to RNAi constructs with antisense strands complementary to other regions of the transcript. Thus, in some embodiments of the invention, RNAi constructs that are particularly suitable for inhibiting expression of a human *MARC1* gene in a cell comprise a sense strand and an antisense strand that hybridize to form a duplex region of about 15 to about 30 base pairs in length, wherein the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1205 to 1250 of SEQ ID NO: 1. In one embodiment, the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1209 to 1239 of SEQ ID NO: 1. In another embodiment, the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1211 to 1236 of SEQ ID NO: 1. In some such embodiments, the antisense strand has a sequence that is substantially complementary with no more than 1, 2, or 3 mismatches to the sequence of at least 15 contiguous nucleotides of nucleotides 1205 to 1250, nucleotides 1209 to 1239, or nucleotides 1211 to 1236 of SEQ ID NO: 1. In other embodiments, the antisense strand has a sequence that is fully complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1205 to 1250, nucleotides 1209 to 1239, or nucleotides 1211 to 1236 of SEQ ID NO: 1. RNAi constructs targeting nucleotides 1205 to 1250 of the human mARC1 transcript include, but are not limited to, D-2063, D-2066, D-2076, D-2077, D-2078, D-2080, D-2081, D-2108, D-2113, D-2142, D-2240, D-2241, D-2243, D-2245, D-2246, D-2248, D-2250, D-2251, D-2253, D-2255, D-2256, D-2258, D-2259, D-2261, D-2264, D-2265, D-2268, D-2269, D-2270, D-2271, D-2301, D-2309, D-2311, D-2312, D-2314, D-2316, D-2317,

D-2319, D-2321, D-2322, D-2324, D-2326, D-2327, D-2329, D-2331, D-2332, D-2334, D-2336, D-2337, D-2339, D-2341, D-2342, D-2344, D-2346, D-2347, D-2349, D-2351, D-2352, D-2354, D-2356, D-2357, D-2376, D-2380, D-2393, D-2395, D-2396, D-2431, D-2436, D-2437, D-2440, D-2441, D-2444, D-2445, D-2447, D-2453, D-2518, D-2519, D-2520, D-2521, D-2522, D-2523, D-2524, D-2525, D-2526, D-2527, D-2528, D-2529, D-2530, D-2531, D-2532, D-2533, D-2534, and D-2535. In some embodiments, the RNAi construct targeting nucleotides 1205 to 1250 of the human mARC1 transcript is D-2063, D-2066, D-2076, D-2077, D-2078, D-2080, D-2081, D-2108, D-2113, D-2142, or D-2301. In certain embodiments, RNAi constructs targeting nucleotides 1205 to 1250, particularly nucleotides 1211 to 1236, of SEQ ID NO: 1 comprise an antisense strand comprising the sequence of 5' - CAUCUAAUAUCCAG - 3' (SEQ ID NO: 3656).

[0050] In other embodiments, the RNAi constructs of the invention comprise a sense strand and an antisense strand that hybridize to form a duplex region of about 15 to about 30 base pairs in length, wherein the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1345 to 1375 of SEQ ID NO: 1. In one embodiment, the antisense strand comprises a sequence that is substantially complementary with no more than 1, 2, or 3 mismatches to the sequence of at least 15 contiguous nucleotides of nucleotides 1345 to 1375 of SEQ ID NO: 1. In another embodiment, the antisense strand comprises a sequence that is fully complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1345 to 1375 of SEQ ID NO: 1. Exemplary RNAi constructs targeting nucleotides 1345 to 1375 of the human mARC1 transcript include, but are not limited to, D-2042, D-2043, D-2047, D-2052, D-2158, D-2162, D-2169, D-2182, D-2183, D-2184, D-2185, D-2186, D-2187, D-2189, D-2211, D-2213, D-2304, D-2305, D-2306, D-2307, D-2308, D-2384, D-2384, D-2385, D-2386, D-2387, D-2388, D-2389, D-2390, D-2391, D-2392, D-2399, D-2400, D-2401, D-2402, D-2403, D-2488, D-2494, D-2500, D-2506, D-2512, D-2538, D-2539, D-2540, and D-2541. In some embodiments, the RNAi construct targeting nucleotides 1345 to 1375 of the human mARC1 transcript is D-2042, D-2043, D-2047, D-2052, D-2304, D-2305, D-2306, D-2307, or D-2308. In certain embodiments, RNAi constructs targeting nucleotides 1345 to 1375, particularly nucleotides 1350 to 1375, of SEQ ID NO: 1 comprise an antisense strand comprising the sequence of 5' - UGGGACAUUGAAGCA - 3' (SEQ ID NO: 3657).

[0051] In still other embodiments, RNAi constructs of the invention comprise a sense strand and an antisense strand that hybridize to form a duplex region of about 15 to about 30 base pairs in length, wherein the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 2039 to 2078 of SEQ ID NO: 1. In one embodiment, the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 2048 to 2074 of SEQ ID NO: 1. In some such embodiments, the antisense strand has a sequence that is substantially complementary with no more than 1, 2, or 3 mismatches to the sequence of at least 15 contiguous nucleotides of nucleotides 2039 to 2078 or nucleotides 2048 to 2074 of SEQ ID NO: 1. In other embodiments, the antisense strand has a sequence that is fully complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 2039 to 2078 or nucleotides 2048 to 2074 of SEQ ID NO: 1. RNAi constructs targeting nucleotides 2039 to 2078 of the human mARC1 transcript include, but are not limited to, D-2045, D-2065, D-2079, D-2082, D-2105, D-2106, D-2137, D-2143, D-2166, D-2173, D-2193, D-2242, D-2247, D-2252, D-2257, D-2260, D-2262, D-2266, D-2272, D-2273, D-2302, D-2303, D-2310, D-2313, D-2315, D-2318, D-2320, D-2323, D-2325, D-2328, D-2330, D-2333, D-2335, D-2338, D-2340, D-2343, D-2345, D-2348, D-2350, D-2353, D-2355, D-2358, D-2394, D-2397, D-2454, D-2455, D-2456, D-2457, D-2458, D-2459, D-2460, D-2463, D-2465, D-2465, D-2468, D-2470, D-2472, D-2473, D-2477, D-2487, D-2493, D-2499, D-2505, D-2511, D-2552, D-2553, D-2554, D-2555, D-2556, and D-2557. In certain embodiments, the RNAi construct targeting nucleotides 2039 to 2078 of the human mARC1 transcript is D-2045, D-2065, D-2079, D-2082, D-2105, D-2106, D-2137, D-2143, D-2302, or D-2303. In certain other embodiments, RNAi constructs targeting nucleotides 2039 to 2078, particularly nucleotides 2048 to 2074, of SEQ ID NO: 1 comprise an antisense strand comprising the sequence of 5' - AUCAGAUCUUAGAGU - 3' (SEQ ID NO: 3658).

[0052] The RNAi constructs of the invention 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.

[0053] 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.

[0054] 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 of the invention 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.

[0055] 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 one particular embodiment, the RNAi constructs comprise one or more 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides or combinations thereof.

[0056] 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.

[0057] In certain embodiments, the modified nucleotides incorporated into one or both of the strands of the RNAi constructs of the invention 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.

[0058] 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 of 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.

[0059] Other suitable modified bases that can be incorporated into the RNAi constructs of the invention 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 is well aware that 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.

[0060] 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).

[0061] In certain embodiments, the RNAi constructs of the invention 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 of the invention 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.

[0062] In other embodiments, the RNAi construct of the invention 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.

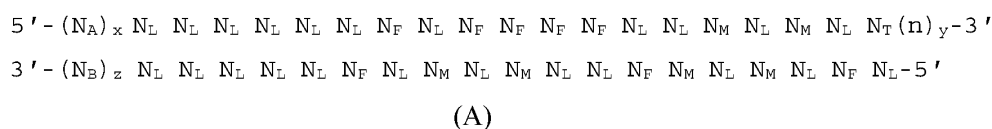
[0063] In such embodiments, the modified nucleotides other than 2'-fluoro modified nucleotides can be selected from 2'-O-methyl modified nucleotides, 2'-O-methoxyethyl modified

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.

[0064] 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.

[0065] 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.

[0066] In some embodiments, the RNAi construct of the invention comprises a structure represented by Formula (A):



[0067] 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.

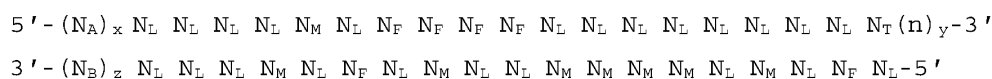
[0068] In some embodiments in which the RNAi construct comprises a structure represented by Formula (A), there is a nucleotide overhang at the 3' end of the sense strand – i.e. y is 1, 2, 3, or 4. In one such embodiment, y is 2. In embodiments in which there is an overhang of 2 nucleotides at the 3' 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.

[0069] 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.

[0070] 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.

[0071] In other embodiments of the invention, the RNAi construct of the invention comprises a structure represented by Formula (B):



(B)

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] The RNAi constructs of the invention 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 ($—O—Si(H)_2—O—$); sulfide, sulfoxide and sulfone linkages; formacetyl and thioformacetyl linkages; alkene containing backbones; sulfamate backbones; methylenemethylimino ($—CH_2—N(CH_3)—O—CH_2—$) and methylenehydrazino linkages; sulfonate and sulfonamide linkages; amide linkages; and others having mixed N, O, S and CH_2 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 of the invention 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.

[0077] In certain embodiments, the RNAi constructs of the invention 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 one particular embodiment, 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 another particular embodiment, 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.

[0078] 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.

[0079] 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.

[0080] 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 of the invention 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 one particular embodiment, all the chiral phosphates in the RNAi construct are in the Sp configuration. In another particular embodiment, all the chiral phosphates in the RNAi construct are in the Rp configuration.

[0081] 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.

[0082] In some embodiments of the RNAi constructs of the invention, 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.).

[0083] The modified nucleotides that can be incorporated into the RNAi constructs of the invention 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 of the invention 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 of the invention 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.

[0084] The RNAi constructs of the invention 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 of the invention is described in Example 2.

[0085] 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.

[0086] 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).

[0087] 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.

[0088] 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.

[0089] Tetrazole catalysts can be used in the standard phosphoramidite coupling reaction. Exemplary catalysts include, e.g., tetrazole, S-ethyl-tetrazole, benzylthiotetrazole, p-nitrophenyltetrazole.

[0090] 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).

[0091] The RNAi constructs of the invention 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.

[0092] 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).

[0093] In certain embodiments, the ligands have endosomolytic properties. The endosomolytic ligands promote the lysis of the endosome and/or transport of the RNAi construct of the invention, 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 of the invention, 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.

[0094] 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.

[0095] In certain embodiments, it is desirable to specifically deliver the RNAi constructs of the invention to liver cells to reduce expression of mARC1 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).

[0096] 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 one particular embodiment, 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 of the invention 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 of the invention are commercially available.

[0097] 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.

[0098] 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 of the invention 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.

[0099] 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 one particular embodiment, the multivalent N-acetyl-galactosamine moiety is trivalent or tetravalent. In another particular embodiment, the multivalent galactose moiety is trivalent or tetravalent. Exemplary trivalent and tetravalent GalNAc-containing ligands for incorporation into the RNAi constructs of the invention are described in detail below.

[0100] 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 of the invention. 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.

[0101] 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.

[0102] 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.

[0103] Linkers that may be used to attach a ligand to the sense or antisense strand in the RNAi constructs of the invention 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.

[0104] 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).

[0105] 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.

[0106] 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.

[0107] 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.

[0108] 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).

[0109] 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).

[0110] 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.

[0111] 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.

[0112] 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.

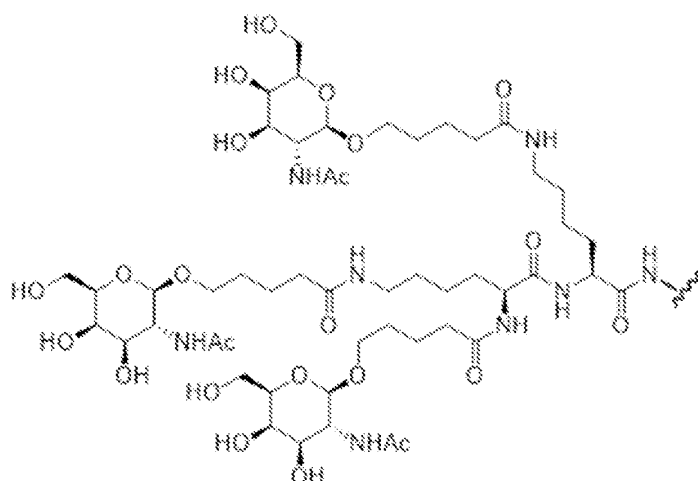
[0113] In further embodiments, the linkers may comprise peptide-based cleavable groups, which are cleaved by enzymes, such as peptidases and proteases in cells. Peptide-based cleavable groups are peptide bonds formed between amino acids to yield oligopeptides (e.g., dipeptides, tripeptides etc.) and 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 $-NHCHR^AC(O)NHCHR^BC(O)-$, 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.

[0114] Other types of linkers suitable for attaching ligands to the sense or antisense strands in the RNAi constructs of the invention 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.

[0115] In certain embodiments, the ligand covalently attached to the sense or antisense strand of the RNAi constructs of the invention 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.

[0116] In certain embodiments, the RNAi constructs of the invention comprise a ligand having the following structure ([Structure 1]):

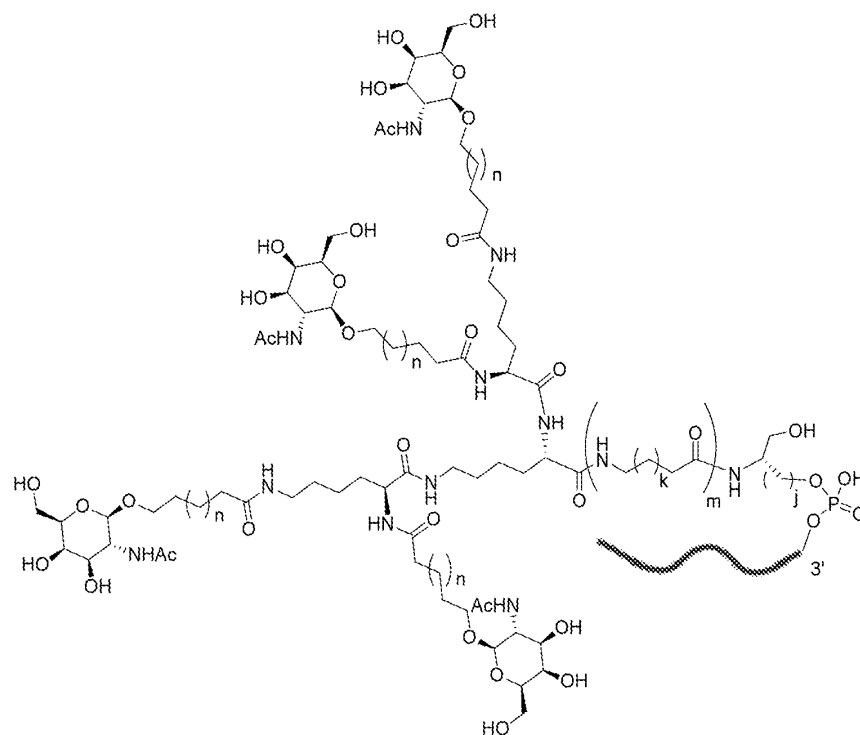


In preferred embodiments, the ligand having this structure is covalently attached to the 5' end of the sense strand (e.g. to the 5' terminal nucleotide of the sense strand) via a linker, such as the linkers described herein. In one embodiment, the linker is an aminohexyl linker.

[0117] Exemplary trivalent and tetravalent GalNAc moieties and linkers that can be attached to the double-stranded RNA molecules in the RNAi constructs of the invention are provided in the structural formulas I-IX below. "Ac" in the formulas listed herein represents an acetyl group.

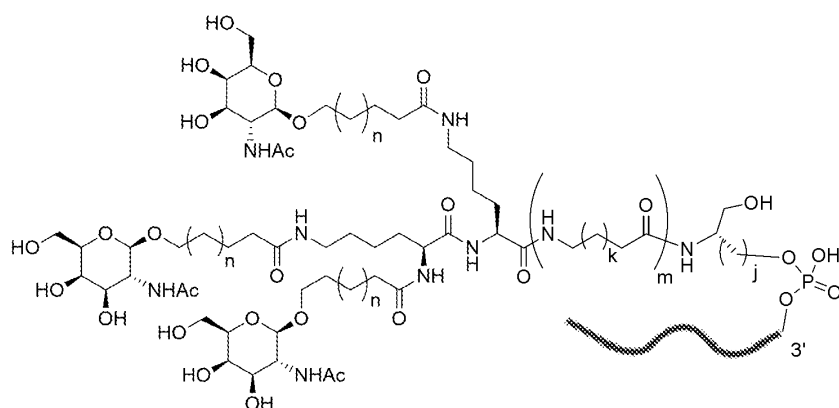
[0118] In one embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula I, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2, j

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):



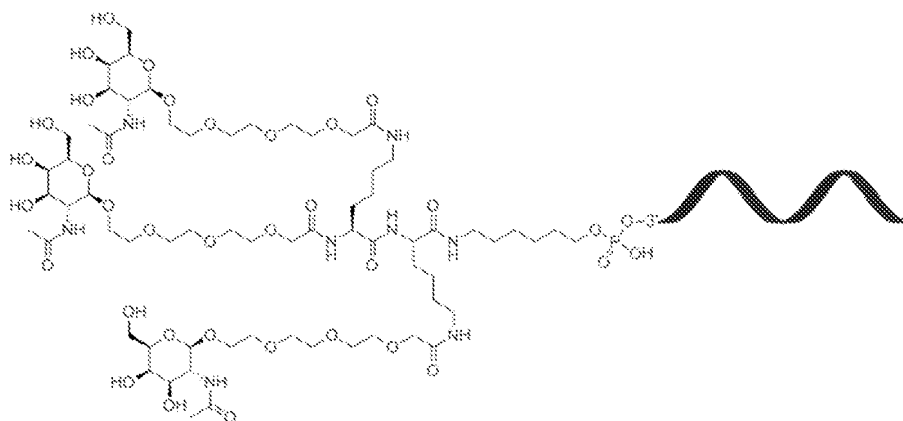
FORMULA I

[0119] 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):



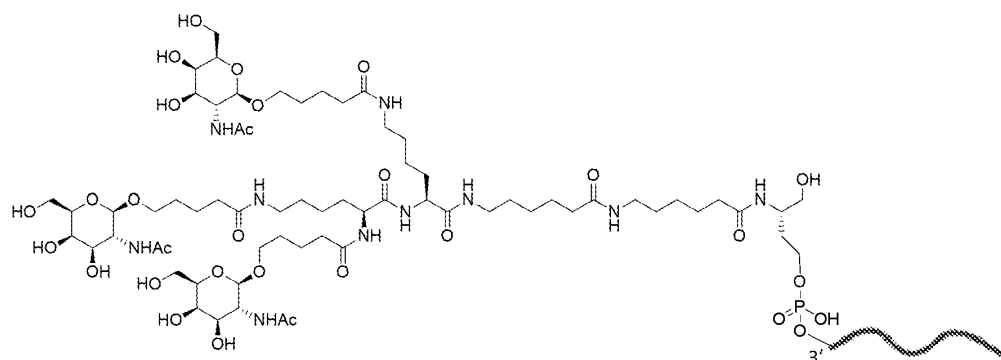
FORMULA II

[0120] 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):



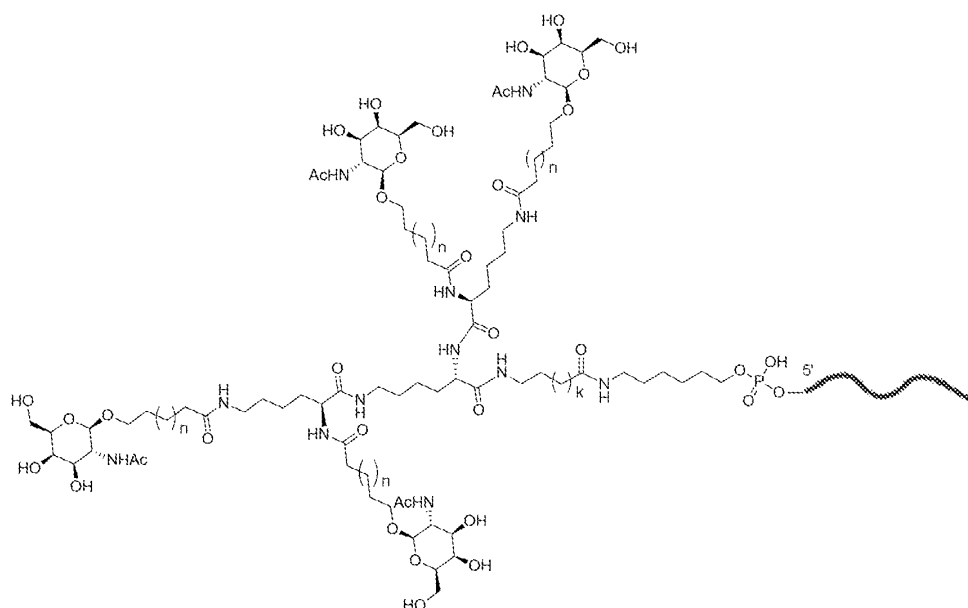
FORMULA III

[0121] 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):



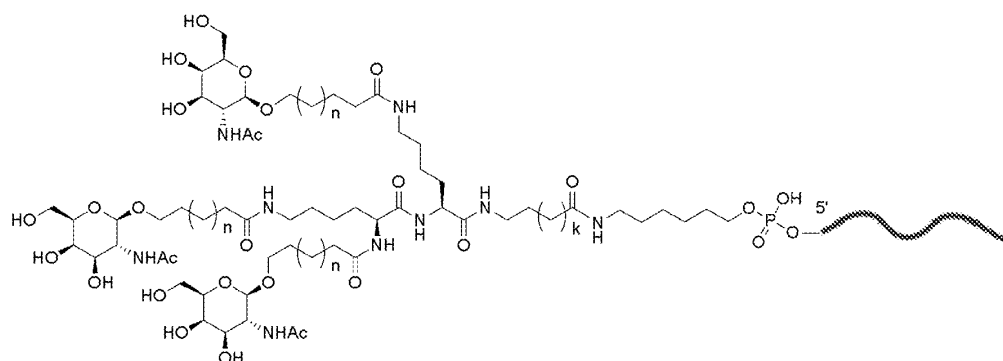
FORMULA IV

[0122] 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):



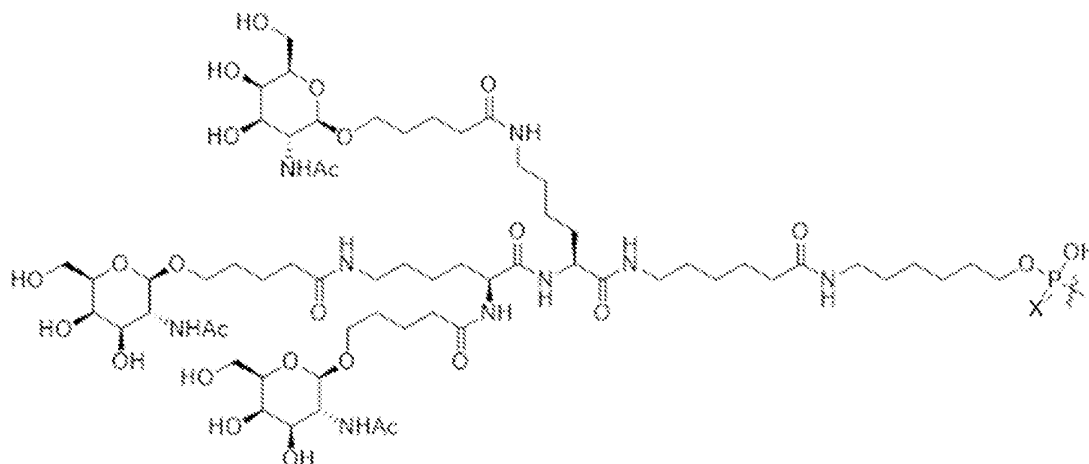
FORMULA V

[0123] 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):



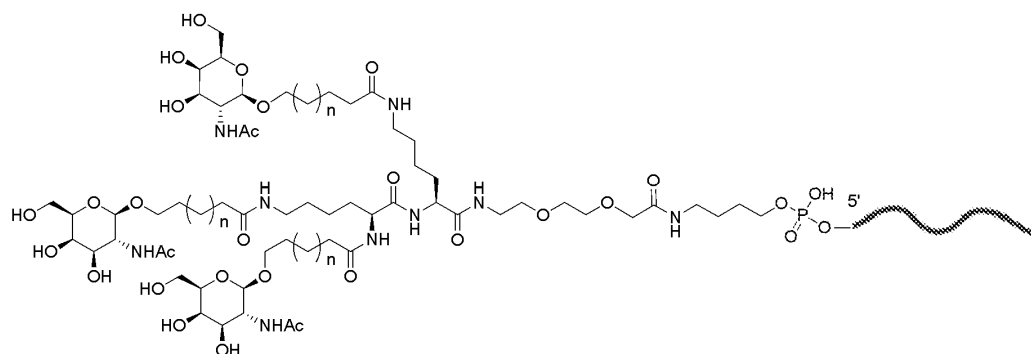
FORMULA VI

[0124] In one particular embodiment, 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):



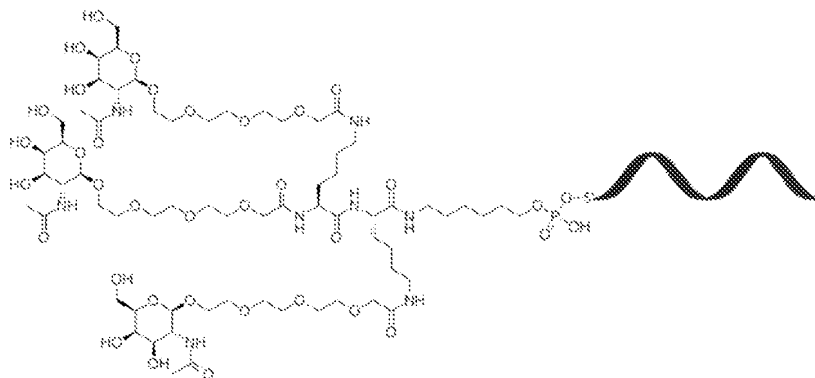
FORMULA VII

[0125] 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

[0126] 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

[0127] 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.

[0128] The present invention 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 *MARCI* gene 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.

[0129] 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 RNAi constructs of the present invention, 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.

[0130] 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. GalNAc-containing or antibody-containing ligands described herein).

[0131] 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 *MARCI* gene expression in a particular tissue or cell-type (e.g. liver or hepatocytes) of a patient. An effective amount of an RNAi construct of the invention 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), particular RNAi construct employed, and route of administration.

[0132] Administration of the pharmaceutical compositions of the present invention 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 liver tissue 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.

[0133] 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 of the invention. Commercially available fat emulsions that are suitable for delivering the nucleic acids of the invention 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 of the invention may be encapsulated within liposomes or may form complexes thereto, in particular to cationic liposomes. Alternatively, RNAi constructs of the invention 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.

[0134] In some embodiments, the RNAi constructs of the invention 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.

[0135] 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 the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. 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.

[0136] 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.

[0137] The compositions of the present invention 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.

[0138] 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 of the invention comprises or consists of a sterile saline solution and an RNAi construct described herein. In other embodiments, a pharmaceutical composition of the invention 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 of the invention comprises or consists of an RNAi construct described herein and phosphate-buffered saline (PBS).

[0139] In some embodiments, the pharmaceutical compositions of the invention 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, the present invention includes administration devices comprising a pharmaceutical composition of the invention for treating or preventing one or more of the diseases or disorders described herein.

[0140] The present invention provides a method for reducing or inhibiting expression of the *MARC1* gene, and thus the production of mARC1 protein, in a cell (e.g. liver cell) by contacting the cell with any one of the RNAi constructs described herein. The cell may be *in vitro* or *in vivo*. mARC1 expression can be assessed by measuring the amount or level of mARC1 mRNA, mARC1 protein, or another biomarker linked to mARC1 expression, such as serum levels of cholesterol, LDL-cholesterol, or liver enzymes, such as alanine aminotransferase (ALT). The reduction of mARC1 expression in cells or animals treated with an RNAi construct of the invention can be determined relative to the mARC1 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 mARC1 expression is assessed by (a) measuring the amount or level of mARC1 mRNA in liver cells treated with an RNAi construct of the invention, (b) measuring the amount or level of mARC1 mRNA in liver cells treated with a control RNAi construct (e.g. RNAi construct directed to an RNA molecule not expressed in liver cells or a RNAi construct having a nonsense or scrambled sequence) or no construct, and (c) comparing the measured mARC1 mRNA levels from treated cells in (a) to the measured mARC1 mRNA levels from control cells in (b). The mARC1 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. mARC1 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.

[0141] In other embodiments, reduction of mARC1 expression is assessed by (a) measuring the amount or level of mARC1 protein in liver cells treated with an RNAi construct of the invention, (b) measuring the amount or level of mARC1 protein in liver cells treated with a control RNAi construct (e.g. RNAi construct directed to an RNA molecule not expressed in liver cells or a RNAi construct having a nonsense or scrambled sequence) or no construct, and (c) comparing

the measured mARC1 protein levels from treated cells in (a) to the measured mARC1 protein levels from control cells in (b). Methods of measuring mARC1 protein levels are known to those of skill in the art, and include Western Blots, immunoassays (e.g. ELISA), and flow cytometry. Any method capable of measuring mARC1 mRNA or mARC1 protein can be used to assess the efficacy of the RNAi constructs of the invention.

[0142] In some embodiments, the methods to assess mARC1 expression levels are performed *in vitro* in cells that natively express mARC1 (e.g. liver cells) or cells that have been engineered to express mARC1. In certain embodiments, the methods are performed *in vitro* in liver 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.

[0143] In other embodiments, the methods to assess mARC1 expression levels are performed *in vivo*. The RNAi constructs and any control RNAi constructs can be administered to an animal and mARC1 mRNA or mARC1 protein levels assessed in liver tissue harvested from the animal following treatment. Alternatively or additionally, a biomarker or functional phenotype associated with mARC1 expression can be assessed in the treated animals. For instance, *MARC1* loss of function variants have been associated with reduced serum total cholesterol, LDL-cholesterol, and liver enzyme levels (*see* Emdin *et al.*, PLoS Genet, Vol. 16(4): e1008629, 2020). Thus, serum or plasma levels of cholesterol, LDL-cholesterol, or liver enzymes (e.g. ALT) can be measured in animals treated with RNAi constructs of the invention to assess the functional efficacy of reducing mARC1 expression. Exemplary methods for measuring serum or plasma cholesterol or enzyme levels are described in Examples 1, 4, and 5.

[0144] In certain embodiments, expression of mARC1 mRNA or protein is reduced in liver cells by at least 40%, at least 45%, or at least 50% by an RNAi construct of the invention. In some embodiments, expression of mARC1 mRNA or protein is reduced in liver 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 of the invention. In other embodiments, the expression of mARC1 mRNA or protein is reduced in liver cells by about 90% or more, e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or

more by an RNAi construct of the invention. The percent reduction of mARC1 expression can be measured by any of the methods described herein as well as others known in the art.

[0145] The present invention provides methods for reducing or inhibiting expression of the *MARC1* gene, and thus the production of mARC1 protein, in a patient in need thereof as well as methods of treating or preventing conditions, diseases, or disorders associated with mARC1 expression or activity. A “condition, disease, or disorder associated with mARC1 expression” refers to conditions, diseases, or disorders in which mARC1 expression levels are altered or where elevated expression levels of mARC1 are associated with an increased risk of developing the condition, disease or disorder. A condition, disease, or disorder associated with mARC1 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. Recent genetic studies have reported an association between loss-of-function variants in the *MARC1* gene and decreased blood levels of cholesterol and liver enzymes, reduced liver fat, and protection from cirrhosis (Spracklen *et al.*, Hum Mol Genet., Vol. 26(9):1770-178, 2017; Emdin *et al.*, bioRxiv 594523; //doi.org/10.1101/594523, 2019; and Emdin *et al.*, PLoS Genet, Vol. 16(4): e1008629, 2020)). See Emdin *et al.*, bioRxiv 594523; //doi.org/10.1101/594523, 2019; and Emdin *et al.*, PLoS Genet, Vol. 16(4): e1008629, 2020). Thus, in certain embodiments, the RNAi constructs of the invention are particularly useful for treating or preventing 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.

[0146] Conditions, diseases, and disorders associated with mARC1 expression that can be treated or prevented according to the methods of the invention include, but are not limited to, fatty liver disease, such as alcoholic fatty liver disease, 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)).

[0147] In certain embodiments, the present invention provides a method for reducing the expression of mARC1 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 mARC1 in hepatocytes in the patient is reduced following administration of the RNAi construct as compared to the mARC1 expression level in a patient not receiving the RNAi construct or as compared to the mARC1 expression level in the patient prior to administration of the RNAi construct. In some embodiments, following administration of an RNAi construct of the invention, expression of mARC1 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 mARC1 expression can be measured by any of the methods described herein as well as others known in the art. In certain embodiments, the percent reduction of mARC1 expression is determined by assessing levels of a serum or plasma biomarker, such as total cholesterol, LDL-cholesterol, or liver enzyme (e.g. ALT) levels, in the patient according to methods described herein.

[0148] In some embodiments, a patient in need of reduction of mARC1 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, the present invention provides a method for reducing the risk of myocardial infarction in a patient in need thereof comprising administering to the patient an RNAi construct described herein. In some embodiments, the present invention includes use of any of the RNAi constructs described herein in the preparation of a medicament for reducing the risk of myocardial infarction in a

patient in need thereof. In other embodiments, the present invention provides a mARC1-targeting RNAi construct for use in a method for reducing the risk of myocardial infarction in a patient in need thereof.

[0149] In certain embodiments, a patient in need of reduction of mARC1 expression is a patient who is diagnosed with or at risk of cardiovascular disease. Thus, the present invention includes a method for treating or preventing cardiovascular disease in a patient in need thereof by administering any of the RNAi constructs of the invention. In some embodiments, the present invention includes use of any of the RNAi constructs described herein in the preparation of a medicament for treating or preventing cardiovascular disease in a patient in need thereof. In other embodiments, the present invention provides a mARC1-targeting RNAi construct 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 methods of the invention is coronary artery disease. In other embodiments, the cardiovascular disease to be treated or prevented according to the methods of the invention is myocardial infarction. In yet other embodiments, the cardiovascular disease to be treated or prevented according to the methods of the invention is stroke. In still other embodiments, the cardiovascular disease to be treated or prevented according to the methods of the invention 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 according to the methods of the invention can be used to reduce the risk of recurrent cardiovascular events.

[0150] In some embodiments, a patient to be treated according to the methods of the invention 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).

[0151] In other embodiments, a patient in need of reduction of mARC1 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, the present invention provides a method for reducing blood levels (e.g. serum or plasma) of cholesterol in a patient in need thereof comprising administering to the patient any of the RNAi constructs described herein. In some embodiments, the present invention includes use of any of the RNAi constructs described herein in the preparation of a medicament for reducing blood levels (e.g. serum or plasma) of cholesterol in a patient in need thereof. In other embodiments, the present invention provides a mARC1-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 methods of the invention is LDL cholesterol. In other embodiments, the cholesterol reduced according to the methods of the invention 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.

[0152] In some embodiments, a patient to be treated according to the methods of the invention is a patient who has elevated levels of non-HDL cholesterol (e.g. elevated serum 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 of the invention if the patient has a non-HDL cholesterol level of about 130 mg/dL or greater. In one embodiment, a patient is administered an

RNAi construct of the invention if the patient has a non-HDL cholesterol level of about 160 mg/dL or greater. In another embodiment, a patient is administered an RNAi construct of the invention if the patient has a non-HDL cholesterol level of about 190 mg/dL or greater. In still another embodiment, a patient is administered an RNAi construct of the invention if the patient has a non-HDL cholesterol level of about 220 mg/dL or greater. In certain embodiments, a patient is administered an RNAi construct of the invention if the patient is at a high or very high risk of cardiovascular disease according to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (Goff *et al.*, ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol, Vol. 63:2935-2959, 2014) and has a non-HDL cholesterol level of about 100 mg/dL or greater.

[0153] In certain embodiments of the methods of the invention, 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 of the invention is administered to a patient if the patient’s LDL cholesterol level is greater than about 160 mg/dL. In other embodiments, an RNAi construct of the invention is administered to a patient if the patient’s LDL cholesterol level is greater than about 130 mg/dL and the patient has a moderate risk of cardiovascular disease according to the 2013 Guidelines. In still other embodiments, an RNAi construct of the invention is administered to a patient if the patient’s LDL cholesterol level is greater than 100 mg/dL and the patient has a high or very high risk of cardiovascular disease according to the 2013 Guidelines.

[0154] In other embodiments, a patient in need of reduction of mARC1 expression is a patient who is diagnosed with or at risk of fatty liver disease. Thus, the present invention includes a method for treating, preventing, or reducing the risk of developing fatty liver disease in a patient in need thereof comprising administering to the patient any of the RNAi constructs of the invention. In some embodiments, the present invention includes use of any of the RNAi constructs described herein in the preparation of a medicament for treating, preventing, or reducing the risk of developing fatty liver disease in a patient in need thereof. In other embodiments, the present invention provides a mARC1-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 according to the methods of the invention is NAFLD. In other embodiments, the fatty liver disease to be treated, prevented, or reduce the risk of developing according to the methods of the invention is NASH. In still other embodiments, the fatty liver disease to be treated, prevented, or reduce the risk of developing according to the methods of the invention is alcoholic steatohepatitis. In some embodiments, a patient in need of treatment or prevention for fatty liver disease according to the methods of the invention 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 according to the methods of the invention or is at risk of developing fatty liver disease has elevated levels of non-HDL cholesterol or triglycerides. Depending on the particular 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.

[0155] In certain embodiments, a patient in need of reduction of mARC1 expression is a patient who is diagnosed with or at risk of developing hepatic fibrosis or cirrhosis. Accordingly, the present invention encompasses a method for treating, preventing, or reducing liver fibrosis in a patient in need thereof comprising administering to the patient any of the RNAi constructs of the invention. In some embodiments, the present invention includes 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. In other embodiments, the present invention provides a mARC1-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 an RNAi construct of the invention prevents or delays the development of cirrhosis in the patient. [0156] 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. Inhibition of mARC1 Expression in Ob/Ob Animals Regulates Lipid Levels

[0157] Genetic studies have reported an association between the A165T missense mutation in the *MARC1* gene and reduced serum low-density lipoprotein (LDL)-cholesterol and total cholesterol levels (Spracklen *et al.*, Hum Mol Genet., Vol. 26(9):1770-178, 2017; Emdin *et al.*, bioRxiv 594523; //doi.org/10.1101/594523, 2019; and Emdin *et al.*, PLoS Genet, Vol. 16(4): e1008629, 2020)). This mutation as well as other loss of function variants of the *MARC1* gene have also been recently associated with lower levels of hepatic fat, reduced liver enzyme levels, and reduced risk of cirrhosis (Emdin *et al.*, 2019 and Emdin *et al.*, 2020). To evaluate whether inhibition of mARC1 expression could reduce serum cholesterol levels as observed in human carriers of the *MARC1* A165T variant allele, aged obese mice (ob/ob) were administered an siRNA molecule targeting the mouse *Marc1* gene or a control siRNA molecule. Ob/ob mice are obese and have elevated lipid levels, and therefore these mice are often used as a model of type II diabetes and other metabolic disorders.

[0158] 18-20-week-old male ob/ob animals (The Jackson Laboratory) were fed standard chow (Harlan, 2020× Teklad global soy protein-free extruded rodent diet). Mice received, by subcutaneous injection, buffer (phosphate-buffered saline) alone (n = 8), mARC1-targeted siRNA (duplex no. D-1000; n = 8), or a control siRNA (duplex no. D-1002; n = 8) at 3 mg/kg body weight in 0.2 ml buffer once every two weeks for six weeks. The siRNA molecules were synthesized and conjugated to a trivalent GalNAc moiety (structure shown in Formula VII) as described in Example 2 below. The structure of each of the siRNA molecules is provided in

Tables 1 and 2 below. Animals were fasted and harvested on week 6 for further analysis. Liver total RNA from harvested animals was processed for qPCR analysis and serum parameters were measured by clinical analyzer (AU400 Chemistry Analyzer, Olympus). mRNA levels were first normalized to 18S ribosomal RNA levels in each liver sample, and then compared to the expression levels in the buffer alone group. Data were presented as relative fold over expression in the buffer alone group. Liver tissues were homogenized and extracted by isopropanol for total cholesterol and total triglyceride measurement (ThermoFisher, Infinity cholesterol and Infinity triglyceride reagents). All animal housing conditions and research protocols were approved by the Amgen Institutional Animal Care and Use Committee (IACUC). Mice were housed in a specified-pathogen free, AAALAC, Intl-accredited facility in ventilated microisolators. Procedures and housing rooms were positively pressured and regulated on a 12:12 dark: light cycle. All animals received reverse-osmosis purified water ad libitum via an automatic watering system.

[0159] Animals treated with the mARC1-targeted siRNA exhibited approximately an 80% reduction of mARC1 expression in the liver as compared to animals receiving buffer only injections (Figure 2A). The reduction in mARC1 expression by the siRNA molecule was specific as liver expression of mARC2 mRNA was not affected (Figure 2B). Treatment with the mARC1-targeted siRNA reduced serum high-density lipoprotein (HDL), LDL, and total cholesterol levels as well as serum levels of alanine aminotransferase (ALT) and C-reactive protein (CRP) (Figures 3A-3H). Triglyceride levels in the liver were also reduced in ob/ob animals receiving the mARC1-targeted siRNA (Figures 4A and 4B). Liver expression of fibrosis genes in animals receiving the mARC1-targeted siRNA were not significantly altered as compared to buffer-injected animals in this animal model (data not shown).

[0160] The results of this series of experiments show that specific inhibition of mARC1 expression in the liver with a mARC1-targeted siRNA molecule reduces serum cholesterol, LDL-cholesterol, ALT levels, and liver triglycerides, demonstrating a causal effect of mARC1 in lipid regulation in hepatocytes. The observed reductions in serum cholesterol, LDL-cholesterol, and ALT levels in the ob/ob animals treated with the mARC1-targeted siRNA are consistent with the reduced levels of these analytes observed in human carriers of the of the *MARC1* A165T variant allele. Thus, inhibition of mARC1 expression with siRNA molecules, such as those described herein, may be useful to reduce cholesterol and triglyceride levels in patients with

hypercholesterolemia or hyperlipidemic disorders and may be therapeutic for other liver disorders, such as nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, alcoholic fatty liver disease, alcoholic steatohepatitis, liver fibrosis, and cirrhosis.

Example 2. Design and Synthesis of mARC1 siRNA Molecules

[0161] Candidate sequences for the design of therapeutic siRNA molecules targeting the human *MARC1* gene were identified using a bioinformatics analysis of the human *MARC1* transcript, the sequence of which is provided herein as SEQ ID NO: 1 (Ensembl transcript no. ENST00000366910.9; see Figure 1). Sequences were analyzed using an in-house siRNA design algorithm and selected if certain criteria were met. The bioinformatics analysis was conducted in two phases. In the first phase, sequences were evaluated for various features, including cross-reactivity with *MARC1* transcripts from cynomolgus monkeys (*Macaca fascicularis*; NCBI Reference Sequence Nos.: XR_001490722.1, XR_001490722.1, XR_001490723.1, XR_001490726.1, XR_273285.2, XM_005540901.2, XR_273286.2, XM_005540898.2, and XM_005540899.2), sequence identity to other human, cynomolgus monkey, and rodent gene sequences, and for overlap with known human single nucleotide polymorphisms. In the second phase, selection criteria were adjusted to include sequences with specificity for only the human *MARC1* transcript and to evaluate sequences for seed region matches to human microRNA (miRNA) sequences to predict off-target effects. Based on the results of the bioinformatics analysis, 665 sequences were selected for initial synthesis and *in vitro* testing.

[0162] RNAi constructs were synthesized using solid phase phosphoramidite chemistry. Synthesis was performed on a MerMade12 or MerMade192X (Bioautomation) instrument. 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 a trivalent N-acetyl-galactosamine (GalNAc) moiety as described further below.

Materials

- [0163] Acetonitrile (DNA Synthesis Grade, AXO152-2505, EMD)
- [0164] Capping Reagent A (80:10:10 (v/v/v) tetrahydrofuran/lutidine/acetic anhydride, BIO221/4000, EMD)
- [0165] Capping Reagent B (16% 1-methylimidazole/tetrahydrofuran, BIO345/4000, EMD)
- [0166] Activator Solution (0.25 M 5-(ethylthio)-1H-tetrazole (ETT) in acetonitrile, BIO152/0960, EMD)
- [0167] Detritylation Reagent (3% dichloroacetic acid in dichloromethane, BIO830/4000, EMD)
- [0168] Oxidation Reagent (0.02 M iodine in 70:20:10 (v/v/v) tetrahydrofuran/pyridine/water, BIO420/4000, EMD)
- [0169] Diethylamine solution (20% DEA in acetonitrile, NC0017-0505, EMD)
- [0170] Thiolation Reagent (0.05 M 5-N-[(dimethylamino)methylene]amino-3H-1,2,4-dithiazole-3-thione (BIOSULII/160K) in pyridine)
- [0171] 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)
- [0172] 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)
- [0173] 2'-deoxy-reverse abasic phosphoramidite (ChemGenes), 0.10 M in acetonitrile over Molecular Trap Packs (0.5g per 30 mL, Bioautomation)
- [0174] 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)
- [0175] Ammonium hydroxide (concentrated, J. T. Baker)

Synthesis

[0176] Reagent solutions, phosphoramidite solutions, and solvents were attached to the MerMade12 or MerMade192X instrument. Solid support was added to each column (4 mL SPE tube with top and bottom frit for 10 μmol), and the columns were affixed to the instrument. The columns were washed twice with acetonitrile. The phosphoramidite and reagent solution lines were purged. The synthesis was initiated using the Poseidon software. The synthesis was

accomplished by repetition of the deprotection/coupling/oxidation/capping synthesis cycle. Specifically, 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 and activator solution followed by incubation to couple the incoming nucleotide to the free 5'-hydroxyl group. 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. To the support was added capping reagents A and B to terminate any unreacted oligonucleotide chains. The support was washed with acetonitrile. After the final reaction cycle, the resin was washed with diethylamine solution to remove the 2-cyanoethyl protecting groups. The support was washed with acetonitrile and dried under vacuum.

GalNAc conjugation

[0177] Sense strands for conjugation to a trivalent GalNAc moiety (structure shown in Formula VII below) were prepared with a 5'-aminohexyl linker. After automated synthesis, the column was removed from the instrument and transferred to a vacuum manifold in a hood. The 5'-monomethoxytrityl (MMT) protecting group was removed from the solid support by successive treatments with 2 mL aliquots of 1% trifluoroacetic acid (TFA) in dichloromethane (DCM) with vacuum filtration. When the orange/yellow color was no longer observable in the eluent, the resin was washed with dichloromethane. The resin was washed with 5 mL of 10% diisopropylethylamine in N,N-dimethylformamide (DMF). In a separate vial a solution of GalNAc3-Lys2-Ahx (67 mg, 40 μ mol) in DMF (0.5 mL), the structure and synthesis of which is described 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.

Cleavage

[0178] The synthesis columns were removed from the synthesizer or vacuum manifold and transferred to a cleavage apparatus. To the solid support was added 4 x 1 mL (for 10 μ mol) or 4 x 250 μ L (for 1 μ mol) of concentrated ammonium hydroxide. The eluent was collected by gravity

or light vacuum filtration into a 24- or 96-well deep well plate, respectively. The plate was sealed, bolted into a cleavage chuck (Bioautomation), and the mixture was heated at 55°C for 4h. The plate was moved to the freezer and cooled for 20 minutes before opening the cleavage chuck in the hood.

Analysis and Purification

[0179] A portion of the cleavage solution was analyzed and purified by anion exchange chromatography. The pooled fractions were desalted by size exclusion chromatography and analyzed by ion pair-reversed phase high-performance liquid chromatograph-mass spectrometry (HPLC-MS). The pooled fractions were lyophilized to obtain a white amorphous powder.

Analytical anion exchange chromatography (AEX):

[0180] Column: Thermo DNAPac PA200RS (4.6 x 50 mm, 4µm)

[0181] Instrument: Agilent 1100 HPLC

[0182] Buffer A: 20 mM sodium phosphate, 10% acetonitrile, pH 8.5

[0183] Buffer B: 20 mM sodium phosphate, 10% acetonitrile, pH 8.5, 1 M sodium bromide

[0184] Flow rate: 1 mL/min at 40°C

[0185] Gradient: 20-65% B in 6.2 min

Preparative anion exchange chromatography (AEX):

[0186] Column: Tosoh TSK Gel SuperQ-5PW, 21 x 150 mm, 13 µm

[0187] Instrument: Agilent 1200 HPLC

[0188] Buffer A: 20 mM sodium phosphate, 10% acetonitrile, pH 8.5

[0189] Buffer B: 20 mM sodium phosphate, 10% acetonitrile, pH 8.5, 1 M sodium bromide

[0190] Flow rate: 8 mL/min

[0191] Injection volume: 5 mL

[0192] Gradient: 35-55% B over 40 min for sense strands and 50-100% B over 40 min for antisense strands

Preparative size exclusion chromatography (SEC):

[0193] Column: 3 x GE Hi-Prep 26/10 in series

[0194] Instrument: GE AKTA Pure

[0195] Buffer: 20% ethanol in water

[0196] Flow Rate: 10 mL/min

[0197] Injection volume: 45 mL using sample loading pump

Ion Pair-Reversed Phase (IP-RP) HPLC:

[0198] Column: Water Xbridge BEH OST C18, 2.5 μ m, 2.1 x 50 mm

[0199] Instrument: Agilent 1100 HPLC

[0200] Buffer A: 15.7 mM DIEA, 50 mM hexafluoroisopropanol (HFIP) in water

[0201] Buffer B: 15.7 mM DIEA, 50 mM HFIP in 50:50 water/acetonitrile

[0202] Flow rate: 0.5 mL/min

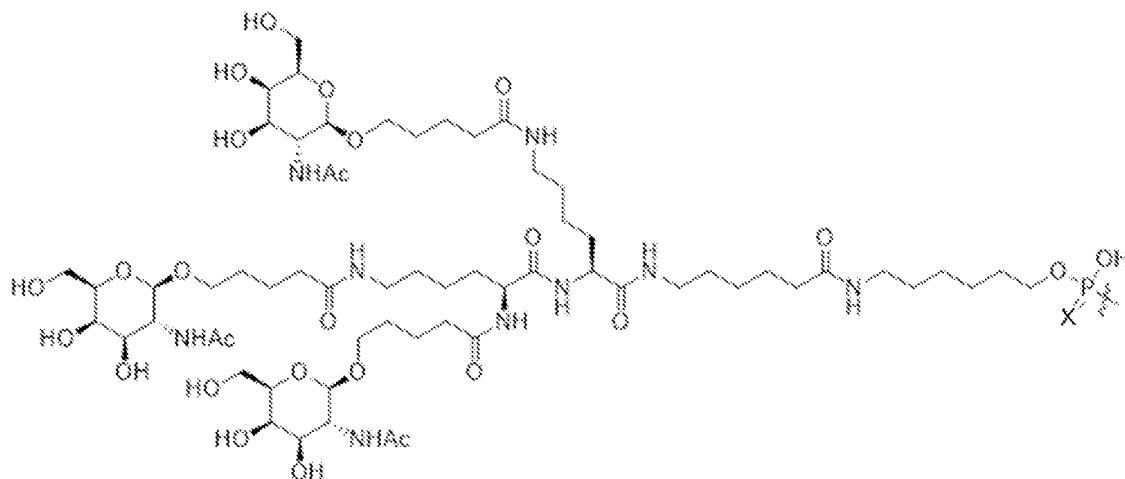
[0203] Gradient: 10-30% B over 6 min

Annealing

[0204] A small amount of the sense strand and the antisense strand were weighed into individual vials. To the vials was added phosphate buffered saline (PBS, Gibco) to an approximate concentration of 2 mM based on the dry weight. The actual sample concentration was measured on the NanoDrop One (ssDNA, extinction coefficient = 33 μ g/OD260). The two strands were then mixed in an equimolar ratio, and the sample was heated for 5 minutes in a 90°C incubator and allowed to cool slowly to room temperature. The sample was analyzed by AEX. The duplex was registered and submitted for *in vitro* and *in vivo* testing as described in more detail in Examples 3 and 4 below.

Preparation of GalNAc3-Lys2-Ahx

Formula VII



wherein 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.

[0205] To a 50 mL falcon tube was added Fmoc-Ahx-OH (1.13 g, 3.19 mmol) in DCM (30 mL) followed by DIEA (2.23 mL, 12.78 mmol). The solution was added to 2-Cl Trityl chloride resin (3.03 g, 4.79 mmol) in a 50 mL centrifuge tube and loaded onto a shaker for 2 h. The solvent was drained and the resin was washed with 17:2:1 DCM/MeOH/DIEA (30 ml x2), DCM (30 mL x4) and dried. The loading was determined to be 0.76 mmol/g with UV spectrophotometric detection at 290 nm.

[0206] 3 g of the loaded 2-Cl Trityl resin was suspended in 20% 4-methylpiperidine in DMF (20 mL), and after 30 min the solvent was drained. The process was repeated one more time, and the resin was washed with DMF (30 mL x3) and DCM (30 mL x3).

[0207] To a solution of Fmoc-Lys(ivDde)-OH (3.45 g, 6 mmol) in DMF (20 mL) was added TATU (1.94 g, 6 mmol) followed by DIEA (1.83 mL, 10.5 mmol). The solution was then added to the above deprotected resin, and the suspension was set on a shaker overnight. The solvent was drained and the resin was washed with DMF (30 mL x3) and DCM (30 mL x3).

[0208] The resin was treated with 20% 4-methylpiperidine in DMF (15 mL) and after 10 min the solvent was drained. The process was repeated one more time and the resin was washed with DMF (15 mL x4) and DCM (15 mL x4).

[0209] To a solution of Fmoc-Lys(Fmoc)-OH (3.54 g, 6 mmol) in DMF (20 mL) was added TATU (1.94 g, 6 mmol) followed by DIEA (1.83 mL, 10.5 mmol). The solution was then added to the above deprotected resin and the suspension was set on a shaker overnight. The solvent was drained and the resin was washed with DMF (30 mL x3) and DCM (30 mL x3).

[0210] The resin was treated with 5% hydrazine in DMF (20 mL) and after 5 min, the solvent was drained. The process was repeated four more times and the resin was washed with DMF (30 mL x4) and DCM (30 mL x 4).

[0211] To a solution of 5-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanoic acid (4.47 g, 10 mmol) in DMF (40 mL) was added TATU (3.22 g, 10 mmol), and the solution was stirred for 5 min. DIEA (2.96 mL, 17 mmol) was added to the solution, and the mixture was then added to the resin above. The suspension was kept at room temperature overnight and the solvent was drained. The resin was washed with DMF (3 x 30 mL) and DCM (3 x 30 mL).

[0212] The resin was treated with 1% TFA in DCM (30 mL with 3% triisopropylsilane) and after 5 min, the solvent was drained. The process was repeated three more times, and the combined filtrate was concentrated in vacuo. The residue was triturated with diethyl ether (50 mL) and the suspension was filtered and dried to give the crude product. The crude product was purified with reverse phase chromatography and eluted with 0-20% of MeCN in water. The fractions were combined and lyophilized to give the product as a white solid.

[0213] Table 1 below lists the unmodified sense and antisense sequences for molecules prioritized from the bioinformatics analysis. The range of nucleotides targeted by siRNA molecules in each sequence family within the human *MARCI* transcript (SEQ ID NO: 1) is also shown in Table 1. Duplex nos. D-1000 to D-1003 were designed to target the *Marc1* mouse transcript and do not cross-react with the human *MARCI* transcript. Table 2 provides the

sequences of the sense and antisense strands with chemical modifications. Based on activity in *in vitro* cell-based assays and *in vivo* mouse studies as described in Examples 3 and 4, respectively, sequences targeting specific regions of the human *MARC1* transcript were selected for structure-activity relationship (SAR) studies. 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. [GalNAc3] represents the GalNAc moiety shown in Formula VII, which was 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] 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 moiety was covalently attached to the 3' carbon of the invAb nucleotide. Otherwise, the GalNAc moiety was covalently attached to the 5' carbon of the 5' terminal nucleotide of the sense strand.

Table 1. Unmodified mARC1 siRNA sequences

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1000	—	GAGCAAGCACUAUAUGGAAU	2	UUCCAUAUAGUGCUUGCUCGG	671
D-1001	—	AGAAGUUCUCGGCAAUGAU	3	UCAUUUGCCGAGAACUUCUGG	672
D-1002	—	GAGCAAGCUGAAUUUGGAAU	4	UUCCAAUUUCAGCUUGCUCGG	673
D-1003	—	AGAAGUUCAGCGCUAAUGAU	5	UCAUUAGCGCUGAACUUCUGG	674
D-1004	40-60	GAAGGACGCACUGCUCUGAU	6	AAUCAGAGCAGUGCGUCCUUCUU	675
D-1005	42-62	AGGACGCACUGCUCUGAUUG	7	ACAAUCAGAGCAGUGCGUCCUUU	676
D-1006	43-63	GGACGCACUGCUCUGAUUGG	8	ACCAAUCAGAGCAGUGCGUCCUU	677
D-1007	45-65	ACGCACUGCUCUGAUUGGCC	9	AGGCCAAUCAGAGCAGUGCGUUU	678
D-1008	50-70	CUGCUCUGAUUGGCCCCGAA	10	AUUCGGGGCCAAUCAGAGCAGUU	679
D-1009	51-71	UGCUCUGAUUGGCCCCGGAAG	11	ACUUCGGGGCCAAUCAGAGCAUU	680
D-1010	52-72	GCUCUGAUUGGCCCCGAAGG	12	ACCUUCGGGGCCAAUCAGAGCUU	681

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1011	99-119	CGGGGCCAAAGGCCGCACCU	13	AAGGUGCGGCCUUUGGCCCGUU	682
D-1012	100-120	GGGGCCAAAGGCCGCACCU	14	AAAGGUGCGGCCUUUGGCCCGUU	683
D-1013	103-123	GCCAAAGGCCGCACCUUCCC	15	AGGGAAGGUGCGGCCUUUGGCUU	684
D-1014	104-124	CCAAAGGCCGCACCUUCCCC	16	AGGGGAAGGUGCGGCCUUUGGCUU	685
D-1015	163-183	CGCCACCUCGCGGAGAAGCC	17	UGGCUUCUCCGCGAGGUGGCGUU	686
D-1016	164-184	GCCACCUCGCGGAGAAGCCA	18	AUGGCUUCUCCGCGAGGUGGCUU	687
D-1017	165-185	CCACCUCGCGGAGAAGCCAG	19	ACUGGCUUCUCCGCGAGGUGGCUU	688
D-1018	167-187	ACCUCGCGGAGAAGCCAGCC	20	UGGCUUGGCUUCUCCGCGAGGUUU	689
D-1019	473-493	UGAUAACCAGGAGGGAAAC	21	UGUUUCCCUCCUGGUUGAUCUU	690
D-1020	475-495	AUCAACCAGGAGGGAAACAU	22	AAUGUUUCCCUCCUGGUUGAUUU	691
D-1021	476-496	UCAACCAGGAGGGAAACAU	23	ACAUGUUUCCCUCCUGGUUGAUU	692
D-1022	477-497	CAACCAGGAGGGAAACAU	24	ACCAUGUUUCCCUCCUGGUUGUU	693
D-1023	478-498	AACCAGGAGGGAAACAU	25	AACCAUGUUUCCCUCCUGGUUUU	694
D-1024	479-499	ACCAGGAGGGAAACAU	26	UAACCAUGUUUCCCUCCUGGUUU	695
D-1025	501-521	UGCUCGCCAGGAACCUCGCC	27	AGGCGAGGUUCCUGGCGAGCAUU	696
D-1026	503-523	CUCGCCAGGAACCUCGCCUG	28	ACAGGCGAGGUUCCUGGCGAGUU	697
D-1027	510-530	GGAACCUCGCCUGGUCCUGA	29	AUCAGGACCAGGCGAGGUUCCUU	698
D-1028	512-532	AACCUCGCCUGGUCCUGAUU	30	AAAUACAGGACCAGGCGAGGUUUU	699
D-1029	513-533	ACCUCGCCUGGUCCUGAUUU	31	AAAAUCAGGACCAGGCGAGGUUU	700
D-1030	514-534	CCUCGCCUGGUCCUGAUUU	32	AGAAAUCAGGACCAGGCGAGGUU	701
D-1031	515-535	CUCGCCUGGUCCUGAUUU	33	AGGAAAUCAGGACCAGGCGAGUU	702
D-1032	519-539	CCUGGUCCUGAUUUCCUGA	34	AUCAGGGAAAUACAGGACCAGGUU	703
D-1033	558-578	GACUCUCAGUGCAGCCUACA	35	AUGUAGGCUGCACUGAGAGUCUU	704
D-1034	560-580	CUCUCAGUGCAGCCUACACA	36	UUGUGUAGGCUGCACUGAGAGUU	705
D-1035	561-581	UCUCAGUGCAGCCUACACAA	37	UUUGUGUAGGCUGCACUGAGAUU	706
D-1036	562-582	CUCAGUGCAGCCUACACAAA	38	AUUUGUGUAGGCUGCACUGAGUU	707
D-1037	563-583	UCAGUGCAGCCUACACAAAG	39	ACUUUGUGUAGGCUGCACUGAUU	708
D-1038	596-616	CUAUCAAAACGCCACCACAA	40	UUGUGGUGGGCGUUUUGAUAGUU	709
D-1039	597-617	UAUCAAAACGCCACCACAA	41	UUUGUGGUGGGCGUUUUGAUUU	710
D-1040	598-618	AUCAAAACGCCACCACAAA	42	AUUUGUGGUGGGCGUUUUGAUUU	711
D-1041	599-619	UCAAAACGCCACCACAAAU	43	AAUUUGUGGUGGGCGUUUUGAUU	712
D-1042	602-622	AAACGCCACCACAAAU	44	AUGCAUUUGUGGUGGGCGUUUUU	713
D-1043	603-623	AACGCCACCACAAAU	45	ACUGCAUUUGUGGUGGGCGUUUU	714
D-1044; D-2004; D-2165; D-2172	684-704	CCAGUGGAUAACCAGCUUCC	46	AGGAAGCUGGUUAUCCACUGGUU	715
D-1045	685-705	CAGUGGAUAACCAGCUUCCU	47	AAGGAAGCUGGUUAUCCACUGUU	716
D-1046	687-707	GUGGAUAACCAGCUUCCUGA	48	UUCAGGAAGCUGGUUAUCCACUU	717
D-1047	690-710	GAUAACCAGCUUCCUGAAGU	49	AACUUCAGGAAGCUGGUUAUCUU	718
D-1048	764-784	AUCAAAUAGCAGACUUGUUC	50	AGAACAAGUCUGCUAUUUUGAUUU	719
D-1049	766-786	CAAAUAGCAGACUUGUCCG	51	UCGGAACAAGUCUGCUAUUUUGUU	720
D-1050	767-787	AAAUAGCAGACUUGUCCGA	52	AUCGGAACAAGUCUGCUAUUUUUU	721
D-1051	951-971	UGAGCUUCUUAUUGGUGACG	53	ACGUCACCAUAAGAAGCUAAU	722
D-1052	953-973	AGCUUCUUAUUGGUGACGUG	54	ACACGUCACCAUAAGAAGCUUU	723
D-1053	954-974	GCUUCUUAUUGGUGACGUGG	55	UCCACGUCACCAUAAGAAGCUU	724

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1054; D-2029	956-976	UUCUUAUUGGUGACGUGGAA	56	AUCCACGUCACCAUAAGAAUU	725
D-1055	962-982	UUGGUGACGUGGAACUGAAA	57	UUUUCAGUCCACGUCACCAUU	726
D-1056	963-983	UGGUGACGUGGAACUGAAAA	58	AUUUUCAGUCCACGUCACCAUU	727
D-1057	964-984	GGUGACGUGGAACUGAAAAG	59	ACUUUUCAGUCCACGUCACCUU	728
D-1058	965-985	GUGACGUGGAACUGAAAAGG	60	ACCUUUCAGUCCACGUCACUU	729
D-1059	991-1011	GCUUGUCCAGAUCAUUUU	61	UAAAAUGCAUCUGGAACAAGCUU	730
D-1060	995-1015	GUUCCAGAUCAUUUAACC	62	UGGUUAAAAUGCAUCUGGAACUU	731
D-1061; D-2002; D-2228	996-1016	UUCAGAUCAUUUAACCA	63	AUGGUUAAAAUGCAUCUGGAUU	732
D-1062; D-2003	1003-1023	UGCAUUUAACACAGUGGA	64	AUCCACUGUGGUUAAAAUGCAUU	733
D-1063	1004-1024	GCAUUUAACACAGUGGAC	65	AGUCCACUGUGGUUAAAAUGCUU	734
D-1064	1033-1053	GGUGUCAUGAGCAGGAAGGA	66	UCCUCCUGCUCAUGACACCUU	735
D-1065	1051-1071	GAACCGCUGGAAACACUGAA	67	AUUCAGUGUUCCAGCGGUUCUU	736
D-1066; D-2005	1056-1076	GCUGGAAACACUGAAGAGUU	68	UACUCUUCAGUGUUCCAGCUU	737
D-1067; D-2035	1059-1079	GGAAACACUGAAGAGUUAUC	69	AGAUAAACUCUUCAGUGUUCCUU	738
D-1068; D-2006	1060-1080	GAAACACUGAAGAGUUAUCG	70	ACGAUAAACUCUUCAGUGUUUCUU	739
D-1069	1061-1081	AAACACUGAAGAGUUAUCGC	71	AGCGAUAAACUCUUCAGUGUUUUU	740
D-1070; D-2007	1062-1082	AACACUGAAGAGUUAUCGCC	72	UGGCGAUAAACUCUUCAGUGUUUU	741
D-1071	1063-1083	ACACUGAAGAGUUAUCGCCA	73	AUGGCGAUAAACUCUUCAGUGUUU	742
D-1072	1064-1084	CACUGAAGAGUUAUCGCCAG	74	ACUGGCGAUAAACUCUUCAGUGUU	743
D-1073	1065-1085	ACUGAAGAGUUAUCGCCAGU	75	AACUGGCGAUAAACUCUUCAGUUU	744
D-1074; D-2025	1066-1086	CUGAAGAGUUAUCGCCAGUG	76	ACACUGGCGAUAAACUCUUCAGUU	745
D-1075	1067-1087	UGAAGAGUUAUCGCCAGUGU	77	AACACUGGCGAUAAACUCUUCUU	746
D-1076	1068-1088	GAAGAGUUAUCGCCAGUGUG	78	UCACACUGGCGAUAAACUCUUCUU	747
D-1077	1071-1091	GAGUUAUCGCCAGUGUGACC	79	AGGUCACACUGGCGAUAAACUU	748
D-1078	1072-1092	AGUUAUCGCCAGUGUGACCC	80	AGGGUCACACUGGCGAUAAACUU	749
D-1079	1073-1093	GUUAUCGCCAGUGUGACCCU	81	AAGGGUCACACUGGCGAUAAACUU	750
D-1080	1074-1094	UUAUCGCCAGUGUGACCCUU	82	AAAGGGUCACACUGGCGAUAAUU	751
D-1081	1078-1098	CGCCAGUGUGACCCUUCAGA	83	UUCUGAAGGGUCACACUGGCGUU	752
D-1082	1079-1099	GCCAGUGUGACCCUUCAGAA	84	AUUCUGAAGGGUCACACUGGCUU	753
D-1083; D-2050	1081-1101	CAGUGUGACCCUUCAGAACG	85	UCGUUCUGAAGGGUCACACUGUU	754
D-1084	1082-1102	AGUGUGACCCUUCAGAACGA	86	UUCGUUCUGAAGGGUCACACUUU	755
D-1085	1083-1103	GUGUGACCCUUCAGAACGAA	87	UUUCGUUCUGAAGGGUCACACUU	756
D-1086; D-2049	1084-1104	UGUGACCCUUCAGAACGAAA	88	AUUUCGUUCUGAAGGGUCACAUU	757
D-1087; D-2027	1085-1105	GUGACCCUUCAGAACGAAAG	89	ACUUUCGUUCUGAAGGGUCACUU	758

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1088	1086-1106	UGACCCUUCAGAACGAAAGU	90	AACUUUCGUUCUGAAGGGUCAUU	759
D-1089	1087-1107	GACCCUUCAGAACGAAAGUU	91	UACUUUCGUUCUGAAGGGUCUU	760
D-1090; D-2026	1088-1108	ACCCUUCAGAACGAAAGUUA	92	AUAACUUUCGUUCUGAAGGGUUU	761
D-1091; D-2031	1089-1109	CCCUUCAGAACGAAAGUUUAU	93	UAUAACUUUCGUUCUGAAGGGUU	762
D-1092; D-2032; D-2229	1090-1110	CCUUCAGAACGAAAGUUUAUA	94	AUAUAACUUUCGUUCUGAAGGUU	763
D-1093; D-2033; D-2230	1091-1111	CUUCAGAACGAAAGUUUAUAU	95	AAUAUAACUUUCGUUCUGAAGUU	764
D-1094	1092-1112	UUCAGAACGAAAGUUUAUAUG	96	ACAUUAACUUUCGUUCUGAAUU	765
D-1095; D-2028; D-2227	1093-1113	UCAGAACGAAAGUUUAUAUGG	97	UCCAUAUAACUUUCGUUCUGAUU	766
D-1096; D-2001; D-2163; D-2170	1094-1114	CAGAACGAAAGUUUAUAUGGA	98	UCCAUAUAACUUUCGUUCUGUU	767
D-1097; D-2030	1103-1123	AGUUAUAUGGAAAAUCACCA	99	AUGGUGAUUUUCCAUAUAACUUU	768
D-1098	1105-1125	UUUAUAUGGAAAAUCACCACU	100	AAGUGGUGAUUUUCCAUAUAUUU	769
D-1099; D-2057; D-2489; D-2501; D-2507	768-788	AAUAGCAGACUUGUUCGAC	101	AGUCGGAACAAGUCUGCUAUUUU	770
D-1100	769-789	AUAGCAGACUUGUUCGACC	102	AGGUCGGAACAAGUCUGCUAUUU	771
D-1101	770-790	UAGCAGACUUGUUCGACCC	103	UGGGUCGGAACAAGUCUGCUAUU	772
D-1102	771-791	AGCAGACUUGUUCGACCCA	104	UUGGGUCGGAACAAGUCUGCUUU	773
D-1103	772-792	GCAGACUUGUUCGACCCAA	105	AUUGGGUCGGAACAAGUCUGCUU	774
D-1104	773-793	CAGACUUGUUCGACCCAAG	106	ACUUGGGUCGGAACAAGUCUGUU	775
D-1105	774-794	AGACUUGUUCGACCCAAGG	107	UCCUUGGGUCGGAACAAGUCUUU	776
D-1106	775-795	GACUUGUUCGACCCAAGGA	108	AUCCUUGGGUCGGAACAAGUCUU	777
D-1107	776-796	ACUUGUUCGACCCAAGGAC	109	AGUCCUUGGGUCGGAACAAGUUU	778
D-1108	777-797	CUUGUUCGACCCAAGGACC	110	UGGUCCUUGGGUCGGAACAAGUU	779
D-1109	781-801	UCCGACCCAAGGACCAGAU	111	AAUCUGGUCCUUGGGUCGGAUUU	780
D-1110	790-810	AAGGACCAGAUUGCUCUACUC	112	UGAGUAAGCAAUCUGGUCCUUU	781
D-1111; D-2039	793-813	GACCAGAUUGCUCUACUCAGA	113	AUCUGAGUAAGCAAUCUGGUUU	782
D-1112	795-815	CCAGAUUGCUCUACUCAGACA	114	AUGUCUGAGUAAGCAAUCUGGUU	783
D-1113; D-2024; D-2167; D-2174	796-816	CAGAUUGCUCUACUCAGACAC	115	AGUGUCUGAGUAAGCAAUCUGUU	784

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1114	797-817	AGAUUGC UUACUCAGACACC	116	UGGUGUCUGAGUAAGCAAUCUUU	785
D-1115	798-818	GAUUGC UUACUCAGACACCA	117	AUGGUGUCUGAGUAAGCAAUCUU	786
D-1116	799-819	AUUGC UUACUCAGACACCAG	118	ACUGGUGUCUGAGUAAGCAAUUU	787
D-1117	802-822	GCUUACUCAGACACCAGCCC	119	UGGGCUGGUGUCUGAGUAAGCUU	788
D-1118	804-824	UUACUCAGACACCAGCCAU	120	AAUGGGCUGGUGUCUGAGUAAUU	789
D-1119	851-871	CGGAUCUCAACUCCAGGCUA	121	AUAGCCUGGAGUUGAGAUCCGUU	790
D-1120	852-872	GGAUUCUCAACUCCAGGCUAG	122	UCUAGCCUGGAGUUGAGAUCCUU	791
D-1121	853-873	GAUCUCAACUCCAGGCUAGA	123	AUCUAGCCUGGAGUUGAGAUUU	792
D-1122	854-874	AUCUCAACUCCAGGCUAGAG	124	UCUCUAGCCUGGAGUUGAGAUUU	793
D-1123	859-879	AACUCCAGGCUAGAGAAGAA	125	UUUCUUCUCUAGCCUGGAGUUUU	794
D-1124	872-892	AGAAGAAAGUUAAAGCAACC	126	UGGUUGC UUUAACUUUCUUCUUU	795
D-1125	873-893	GAAGAAAGUUAAAGCAACCA	127	UUGGUUGC UUUAACUUUCUUCUU	796
D-1126	874-894	AAGAAAGUUAAAGCAACCAA	128	AUUGGUUGC UUUAACUUUCUUUU	797
D-1127	875-895	AGAAAGUUAAAGCAACCAAC	129	AGUUGGUUGC UUUAACUUUCUUU	798
D-1128	876-896	GAAAGUUAAAGCAACCAACU	130	AAGUUGGUUGC UUUAACUUUCUU	799
D-1129	877-897	AAAGUUAAAGCAACCAACUU	131	AAAGUUGGUUGC UUUAACUUUUU	800
D-1130; D-2037	878-898	AAGUUAAAGCAACCAACUUC	132	UGAAGUUGGUUGC UUUAACUUUU	801
D-1131	879-899	AGUUAAGCAACCAACUUA	133	AUGAAGUUGGUUGC UUUAACUUU	802
D-1132	880-900	GUUAAGCAACCAACUUCAG	134	ACUGAAGUUGGUUGC UUUAACUU	803
D-1133	883-903	AAAGCAACCAACUUCAGGCC	135	AGGCCUGAAGUUGGUUGC UUUUU	804
D-1134	885-905	AGCAACCAACUUCAGGCCCA	136	UUGGGCCUGAAGUUGGUUGC UUU	805
D-1135	887-907	CAACCAACUUCAGGCCCAU	137	UAUUGGGCCUGAAGUUGGUUGUU	806
D-1136	888-908	AACCAACUUCAGGCCCAUA	138	AUAUUGGGCCUGAAGUUGGUUUU	807
D-1137	890-910	CCAACUUCAGGCCCAUAUU	139	AAAUUUGGGCCUGAAGUUGGUU	808
D-1138; D-2034; D-2231	891-911	CAACUUCAGGCCCAUAUUG	140	ACAAUAUUGGGCCUGAAGUUGUU	809
D-1139; D-2036; D-2232	893-913	ACUUCAGGCCCAUAUUGUA	141	UUACAAUAUUGGGCCUGAAGUUU	810
D-1140; D-2038; D-2161; D-2168	894-914	CUUCAGGCCCAUAUUGUAA	142	AUUACAAUAUUGGGCCUGAAGUU	811
D-1141	895-915	UUCAGGCCCAUAUUGUAAU	143	AAUUAACAAUAUUGGGCCUGAAUU	812
D-1142	896-916	UCAGGCCCAUAUUGUAAUU	144	AAAUUAACAAUAUUGGGCCUGAUU	813
D-1143; D-2000	898-918	AGGCCCAUAUUGUAAUUUC	145	UGAAAUUAACAAUAUUGGGCCUUU	814
D-1144	899-919	GGCCCAUAUUGUAAUUUCA	146	AUGAAAUUAACAAUAUUGGGCCUU	815
D-1145	949-969	GAUGAGCUUCUUAUUGGUGA	147	AUCACCAUAAGAAGCUCAUUU	816
D-1146	950-970	AUGAGCUUCUUAUUGGUGAC	148	AGUCACCAUAAGAAGCUCAUUU	817
D-1147; D-2041	1107-1127	AUAUGGAAAAUACCACUCU	149	AAGAGUGGUGAUUUUCCAUAUUU	818
D-1148	1108-1128	UAUGGAAAAUACCACUCUU	150	AAAGAGUGGUGAUUUUCCAUAUU	819
D-1149	1109-1129	AUGGAAAAUACCACUCUUU	151	AAAAGAGUGGUGAUUUUCCAUAUU	820

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1150; D-2060; D-2207; D-2215	1110-1130	UGGAAAAUCACCACUCUUUG	152	ACAAAGAGUGGUGAUUUUCCAUI	821
D-1151	1144-1164	CUGGAAAACCCAGGGACCAU	153	AAUGGUCCCUGGGUUUUCCAGUU	822
D-1152	1146-1166	GGAAAACCCAGGGACCAUCA	154	UUGAUGGUCCCUGGGUUUUCCUU	823
D-1153	1147-1167	GAAAACCCAGGGACCAUCAA	155	UUUGAUGGUCCCUGGGUUUUCCUU	824
D-1154	1152-1172	CCCAGGGACCAUCAAGUGG	156	ACCACUUUGAUGGUCCCUGGGUU	825
D-1155	1153-1173	CCAGGGACCAUCAAGUGGG	157	UCCACUUUGAUGGUCCCUGGUU	826
D-1156	1156-1176	GGGACCAUCAAGUGGGAGA	158	AUCUCCACUUUGAUGGUCCCUU	827
D-1157	1170-1190	GGGAGACCCUGUGUACCUUGC	159	AGCAGGUACACAGGGUCUCCCUU	828
D-1158	1182-1202	GUACCUUGUGGGCCAGUAAU	160	AAUUACUGGCCACGAGGUACUU	829
D-1159	1187-1207	UGCUGGGCCAGUAAUGGGAA	161	AUUCACUUACUGGCCACGAAU	830
D-1160	1239-1259	AAAUGUUCUAAAAUGACA	162	UUUGCAUUUUUGAGAACAUUUUU	831
D-1161	1240-1260	AAUGUUCUAAAAUGACAA	163	AUUGCAUUUUUGAGAACAUUUUU	832
D-1162	1250-1270	AAAUGACAACACUUGAAGC	164	UGCUUCAAGUGUUGCAUUUUUU	833
D-1163; D-2009	1251-1271	AAAUGACAACACUUGAAGCA	165	AUGCUUCAAGUGUUGCAUUUUUU	834
D-1164	1252-1272	AAUGACAACACUUGAAGCAU	166	AAUGCUUCAAGUGUUGCAUUUU	835
D-1165	1254-1274	UGACAACACUUGAAGCAUGG	167	ACCAUGCUUCAAGUGUUGCAUU	836
D-1166; D-2058; D-2210; D-2218	1255-1275	GACAACACUUGAAGCAUGGU	168	AACCAUGCUUCAAGUGUUGUCUU	837
D-1167	1256-1276	ACAACACUUGAAGCAUGGUG	169	ACACCAUGCUUCAAGUGUUGUUU	838
D-1168; D-2010	1260-1280	CACUUGAAGCAUGGUGUUUC	170	UGAAACACCAUGCUUCAAGUGUU	839
D-1169	1262-1282	CUUGAAGCAUGGUGUUUCAG	171	UCUGAAACACCAUGCUUCAAGUU	840
D-1170; D-2046	1343-1363	CUGGUGUCUCAAGCUUCAA	172	AUUGAAGCAUUGAGACACCAGUU	841
D-1171; D-2013	1344-1364	UGGUGUCUCAAGCUUCAAU	173	AAUUGAAGCAUUGAGACACCAUU	842
D-1172; D-2304	1345-1365	GGUGUCUCAAGCUUCAAUG	174	ACAUUGAAGCAUUGAGACACCUU	843
D-1173; D-2305; D-2494; D-2506; D-2512	1346-1366	GUGUCUCAAGCUUCAAUGU	175	AACAUUGAAGCAUUGAGACACUU	844
D-1174; D-2047	1347-1367	UGUCUCAAGCUUCAAUGUC	176	AGACAUUGAAGCAUUGAGACAUU	845
D-1175; D-2306	1349-1369	UCUCAAGCUUCAAUGUCCC	177	UGGGACAUUGAAGCAUUGAGAUU	846
D-1176; D-2052; D-2203;	1350-1370	CUCAAUGCUUCAAUGUCCCA	178	AUGGGACAUUGAAGCAUUGAGUU	847

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2211					
D-1177; D-2042; D-2162; D-2169; D-2183; D-2184; D-2185; D-2186; D-2187; D-2291; D-2292; D-2293; D-2294; D-2295; D-2296; D-2297; D-2298; D-2299; D-2388	1352-1372	CAAUGCUUCAUGUCCAGU	179	AACUGGGACAUUGAAGCAUUGUU	848
D-1178; D-2308	1354-1374	AUGCUUCAUGUCCAGUGC	180	UGCACUGGGACAUUGAAGCAUUU	849
D-1179; D-2043; D-2205; D-2213	1355-1375	UGCUUCAUGUCCAGUGCA	181	UUGCACUGGGACAUUGAAGCAUU	850
D-1180; D-2044	1429-1449	AAUGACAAGACAGGAUUCUG	182	UCAGAAUCCUGUCUUGUCAUUUU	851
D-1181	1430-1450	AUGACAAGACAGGAUUCUGA	183	UUCAGAAUCCUGUCUUGUCAUUU	852
D-1182; D-2014	1432-1452	GACAAGACAGGAUUCUGAAA	184	UUUUCAGAAUCCUGUCUUGUCUU	853
D-1183	1435-1455	AAGACAGGAUUCUGAAAACU	185	AAGUUUUCAGAAUCCUGUCUUUU	854
D-1184; D-2053; D-2209; D-2217	1438-1458	ACAGGAUUCUGAAAACUCCC	186	AGGGAGUUUUCAGAAUCCUGUUU	855
D-1185; D-2008	1456-1476	CCCGUUUAACUGAUUAUGGA	187	UUGCAUAAUCAGUUAAACGGGUU	856
D-1186	1460-1480	UUUAACUGAUUAUGGAAUAG	188	ACUAUCCAUAAUCAGUUAAAUU	857
D-1187	1461-1481	UUAACUGAUUAUGGAAUAGU	189	AACUAUCCAUAAUCAGUUAAUU	858
D-1188	1463-1483	AACUGAUUAUGGAAUAGUUC	190	AGAACUAUCCAUAAUCAGUUUU	859
D-1189; D-2040	1464-1484	ACUGAUUAUGGAAUAGUUCU	191	AAGAACUAUCCAUAAUCAGUUU	860
D-1190; D-2062	1465-1485	CUGAUUAUGGAAUAGUUCUU	192	AAAGAACUAUCCAUAAUCAGUU	861
D-1191; D-2011	1467-1487	GAUUAUGGAAUAGUUCUUUC	193	AGAAAGAACUAUCCAUAAUCUU	862

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1192; D-2012	1468-1488	AUUUAUGGAAUAGUUCUUUCU	194	AAGAAAGAACUUAUCCAUAUUUU	863
D-1193	1522-1542	UUGCAUCCUGUCACUACCAC	195	AGUGGUAGUGACAGGAUGCAAUU	864
D-1194; D-2051	1650-1670	CACCCCAAUAUGGCUUGAA	196	AUCCAGCCAUUUUUGGGGUGUU	865
D-1195	1652-1672	CCCCAAUAUGGCUUGAAUG	197	ACAUUCCAGCCAUUUUUGGGGUU	866
D-1196	1688-1708	CUCAAGCCCCGGGCUAGCUU	198	AAAGCUAGCCCCGGGCUUGAGUU	867
D-1197	1689-1709	UCAAGCCCCGGGCUAGCUUU	199	AAAAGCUAGCCCCGGGCUUGAUU	868
D-1198	1691-1711	AAGCCCCGGGCUAGCUUUUG	200	UCAAAGCUAGCCCCGGGCUUUU	869
D-1199	1692-1712	AGCCCCGGGCUAGCUUUUGA	201	UUCAAAAGCUAGCCCCGGGCUUU	870
D-1200	1693-1713	GCCCCGGGCUAGCUUUUGAA	202	UUUCAAAAGCUAGCCCCGGGCUU	871
D-1201	1695-1715	CCCGGGCUAGCUUUUGAAU	203	AAUUUCAAAAGCUAGCCCCGGGCUU	872
D-1202	1699-1719	GGCUAGCUUUUGAAUUGGCA	204	AUGCCAUUUCAAAGCUAGCCUU	873
D-1203	1718-1738	AUAAAGACUGAGGUGACCUU	205	AAAGGUCACCUAGUCUUUAUUU	874
D-1204; D-2055	1747-1767	CUGCAGAUUAUUUUUCCA	206	AUGGAAAUUAUAUCUGCAGUU	875
D-1205	1752-1772	GAUAUUAAUUUUCCAUAAGAU	207	AAUCUAUGGAAAUUAUAUCUU	876
D-1206	1753-1773	AUAUUAAUUUUCCAUAAGAU	208	AGAUCUAUGGAAAUUAUAUUU	877
D-1207	1757-1777	UAAUUUUCCAUAAGAUUGGA	209	AUCCAGAUCUAUGGAAAUUAUU	878
D-1208	1758-1778	AAUUUUCCAUAAGAUUGGAU	210	AAUCCAGAUCUAUGGAAAUUUU	879
D-1209	1759-1779	AUUUUCCAUAAGAUUGGAUC	211	AGAUCAGAUCUAUGGAAAUUU	880
D-1210	1761-1781	UUUCCAUAAGAUUGGAUCUG	212	ACAGAUCCAGAUCUAUGGAAAUU	881
D-1211	1788-1808	UGCUUCUCAGACAGCAUUGG	213	UCCAAUGCUGUCUGAGAAGCAUU	882
D-1212	1789-1809	GCUUCUCAGACAGCAUUGGA	214	AUCCAAUGCUGUCUGAGAAGCUU	883
D-1213; D-2059; D-2206; D-2214	1794-1814	UCAGACAGCAUUGGAUUUCC	215	AGGAAAUCCAAUGCUGUCUGAUU	884
D-1214	1795-1815	CAGACAGCAUUGGAUUUCCU	216	UAGGAAAUCCAAUGCUGUCUGUU	885
D-1215; D-2061; D-2208; D-2216; D-2267	1796-1816	AGACAGCAUUGGAUUUCCUA	217	UUAGGAAAUCCAAUGCUGUCUUU	886
D-1216	1810-1830	UUCCUAAAGGUGCUCAGGAG	218	ACUCCUGAGCACCUUUAGGAAUU	887
D-1217	1849-1869	AGGACCCUGGAUCCUUGCC	219	UGGCAAGGAUCCAGGGGUCCUUU	888
D-1218	1854-1874	CCCUGGAUCCUUGCCAUUCC	220	AGGAAUGGCAAGGAUCCAGGUU	889
D-1219	1856-1876	CUGGAUCCUUGCCAUUCCCC	221	AGGGGAAUGGCAAGGAUCCAGUU	890
D-1220; D-2054	1858-1878	GGAUCCUUGCCAUUCCCCUC	222	UGAGGGGAAUGGCAAGGAUCCUU	891
D-1221	1859-1879	GAUCCUUGCCAUUCCCCUCA	223	AUGAGGGGAAUGGCAAGGAUCCUU	892
D-1222	1862-1882	CCUUGCCAUUCCCCUCAGCU	224	UAGCUGAGGGGAAUGGCAAGGUU	893
D-1223	1863-1883	CUUGCCAUUCCCCUCAGCUA	225	UUAGCUGAGGGGAAUGGCAAGUU	894
D-1224	1866-1886	GCCAUUCCCCUCAGCUAAUG	226	UCAUUAGCUGAGGGGAAUGGCUU	895
D-1225	1868-1888	CAUUCCCCUCAGCUAAUGAC	227	AGUCAUUAGCUGAGGGGAAUGUU	896

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1226	1886-1906	ACGGAGUGCUCCUUCUCCAG	228	ACUGGAGAAGGAGCACUCCGUUU	897
D-1227	1976-1996	GAAAACCUUUAAAGGGGGAA	229	UUUCCCCUUUAAAGGUUUUCUU	898
D-1228; D-2015	2004-2024	CAUAUGUCAGUUGUUUAAAA	230	AUUUUAAACAACUGACAUAUGUU	899
D-1229	2010-2030	UCAGUUGUUUAAAACCCAAU	231	UAUUGGGUUUUAAACAACUGAUU	900
D-1230; D-2016	2012-2032	AGUUGUUUAAAACCCAAUUAU	232	AAUAUUGGGUUUUAAACAACUUU	901
D-1231	41-61	AAGGACGCACUGCUCUGAUU	233	AAAUCAAGAGCAGUGCGUCCUUUU	902
D-1232	1690-1710	CAAGCCCCGGGCUAGCUUUU	234	AAAAAGCUAGCCCGGGGCUUGUU	903
D-1233	1694-1714	CCCCGGGCUAGCUUUUGAAA	235	AUUUCAAAAGCUAGCCCGGGGUU	904
D-1234	1723-1743	GACUGAGGUGACCUUCAGGA	236	UCCUGAAGGUCACCUCAGUCUU	905
D-1235	1754-1774	UAUUAAUUUUCCAUAAGAUCU	237	AAGAUCUAUGGAAAAUUAAUAUU	906
D-1236; D-2048	1760-1780	UUUUCCAUAGAUCUGGAUCU	238	AAGAUCCAGAUCAUUGGAAAAUU	907
D-1237	1791-1811	UUCUCAGACAGCAUUGGAUU	239	AAAUCCAUGCUGUCUGAGAAUU	908
D-1238	1809-1829	UUUCCUAAAGGUGCUCAGGA	240	AUCCUGAGCACCUUUAGGAAAUU	909
D-1239	1855-1875	CCUGGAUCCUUGCCAUUCCC	241	AGGGAAUGGCAAGGAUCCAGUU	910
D-1240	1861-1881	UCCUUGCCAUCUCCCUACGC	242	AGCUGAGGGGAAUGGCAAGGAUU	911
D-1241	1867-1887	CCAUUCUCCUACAGCUAAUGA	243	AUCAUUAGCUGAGGGGAAUGGUU	912
D-1242	1977-1997	AAAACCUUUAAAGGGGGAAA	244	UUUUCCCCUUUAAAGGUUUUUU	913
D-1243; D-2017; D-2204; D-2212	2014-2034	UUGUUUAAAACCCAAUAUCU	245	UAGAUAUUGGGUUUUAAACAAUU	914
D-1244	2055-2075	CUCUAAGAUCUGAUGAAGUA	246	AUACUUAUCAGAUCCUAGAGUU	915
D-1245; D-2045; D-2166; D-2173	2057-2077	CUAAGAUCUGAUGAAGUAUA	247	AUAUACUUAUCAGAUCCUAGUU	916
D-1246; D-2303	2058-2078	UAAGAUCUGAUGAAGUAUAU	248	AAUAUACUUAUCAGAUCCUUAUU	917
D-1247; D-2056	2059-2079	AAGAUCUGAUGAAGUAUAUU	249	AAAUUAUACUUAUCAGAUCCUUU	918
D-1248; D-2018	2066-2086	GAUGAAGUAUAUUUUUAUU	250	AAAUAAAAAUUAUCUUAUCUU	919
D-1249; D-2019	2079-2099	UUUUAUUGCCAUUUUGUCCU	251	AAGGACAAAAUGGCAAUAAAAUU	920
D-1250	2080-2100	UUUAUUGCCAUUUUGUCCUU	252	AAAGGACAAAAUGGCAAUAAAAUU	921
D-1251	2081-2101	UUUAUUGCCAUUUUGUCCUUU	253	AAAAGGACAAAAUGGCAAUAAUU	922
D-1252; D-2020	2083-2103	AUUGCCAUUUUGUCCUUUGA	254	AUCAAGGACAAAAUGGCAAUUU	923
D-1253; D-2021	2105-2125	AUAUUGGGAAGUUGACUAAA	255	AUUUAGUCAACUCCCAUAUUU	924
D-1254	2109-2129	UGGGAAGUUGACUAAACUUG	256	UCAAGUUUAGUCAACUCCCAUU	925
D-1255	2110-2130	GGGAAGUUGACUAAACUUGA	257	UUCAAGUUUAGUCAACUCCCUU	926
D-1256;	2111-2131	GGAAGUUGACUAAACUUGAA	258	UUUCAAGUUUAGUCAACUCCUU	927

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2022; D-2164; D-2171					
D-1257; D-2023	2144-2164	ACUGUGAAUAAAUGGAAGCU	259	UAGCUUCCAUUUUUAUUCACAGUUU	928
D-1258	2148-2168	UGAAUAAAUGGAAGCUACUU	260	AAAGUAGCUUCCAUUUUAUUCUU	929
D-1259	2152-2172	UAAUUGGAAGCUACUUUGAC	261	AGUCAAGUAGCUUCCAUUUUAUU	930
D-1260	2153-2173	AAAUGGAAGCUACUUUGACU	262	UAGUCAAGUAGCUUCCAUUUUUU	931
D-1261	2159-2179	AAGCUACUUUGACUAGUUUC	263	UGAAACUAGUCAAGUAGCUUUU	932
D-1262	2160-2180	AGCUACUUUGACUAGUUUCA	264	AUGAAACUAGUCAAGUAGCUUU	933
D-1263	1888-1908	GGAGUGCUCCUUCUCCAGUU	265	AAACUGGAGAAGGAGCACUCCUU	934
D-1264	1979-1999	AACCUUUAAAGGGGGAAAAG	266	ACUUUUCCCCCUUUAAAGGUUUU	935
D-1265	1980-2000	ACCUUUAAAGGGGGAAAAGG	267	UCCUUUUCCCCCUUUAAAGGUUU	936
D-1266; D-2145; D-2492; D-2504; D-2510	2082-2102	UAUUGCCAUUUUGUCCUUUG	268	UCAAGGACAAAAUGGCAUAUU	937
D-1267	2112-2132	GAAGUUGACUAAACUUGAAA	269	UAUUCAAGUUUAGUCAACUUCUU	938
D-1268	2113-2133	AAGUUGACUAAACUUGAAAA	270	UAUUUCAAGUUUAGUCAACUUUU	939
D-1269	2161-2181	GCUACUUUGACUAGUUUCAG	271	UCUGAAACUAGUCAAGUAGCUU	940
D-1270	557-577	UGACUCUCAGUGCAGCCUAC	272	UGUAGGCUGCACUGAGAGUCAUU	941
D-1271	604-624	ACGCCACCACAAAUGCAGU	273	AACUGCAUUUGUGGUGGGCGUUU	942
D-1272	683-703	CCCAGUGGAUAACAGCUUC	274	AGAAGCUGGUUAUCCACUGGGUU	943
D-1273	763-783	CAUCAAAUAGCAGACUUGUU	275	AAACAAGUCUGCUAUUUUGAUGUU	944
D-1274	765-785	UCAAAUAGCAGACUUGUCC	276	AGGAACAAGUCUGCUAUUUUGAUU	945
D-1275	864-884	CAGGCUAGAGAAGAAAGUUA	277	UUAACUUUCUUCUCUAGCCUGUU	946
D-1276; D-2064	865-885	AGGCUAGAGAAGAAAGUUA	278	UUUAAACUUUCUUCUCUAGCCUUU	947
D-1277	889-909	ACCAACUUCAGGCCCAAUAU	279	AAUAUUGGGCCUGAAGUUGGUUU	948
D-1278	952-972	GAGCUUCUUUAUUGGUGACGU	280	AACGUCACCAUAAGAAGCUCUU	949
D-1279	955-975	CUUCUUUAUUGGUGACGUGGA	281	UUCACGUCACCAUAAGAAGUU	950
D-1280	957-977	UCUUAUUGGUGACGUGGAAC	282	AGUUCACGUCACCAUAAGAUAU	951
D-1281	961-981	AUUGGUGACGUGGAACUGAA	283	UUUCAGUUCACGUCACCAAUUU	952
D-1282; D-2144	992-1012	CUUGUCCAGAUUCAUUUUUA	284	UUAAAAUGCAUCUGGAACAAGUU	953
D-1283	994-1014	UGUCCAGAUUCAUUUUUAAAC	285	AGUUAAAAUGCAUCUGGAACAUAU	954
D-1284; D-2074	1057-1077	CUGGAAACACUGAAGAGUUA	286	AUAACUCUUCAGUGUUUCCAGUU	955
D-1285; D-2125	1058-1078	UGGAAACACUGAAGAGUUUAU	287	AAUAACUCUUCAGUGUUUCCAUAU	956
D-1286; D-2138	1069-1089	AAGAGUUAUCGCCAGUGUGA	288	AUCACACUGGCGAUAAACUUUUU	957
D-1287	1070-1090	AGAGUUAUCGCCAGUGUGAC	289	AGUCACACUGGCGAUAAACUUUU	958
D-1288; D-2140	1104-1124	GUUAUAUGGAAAAUACCAC	290	AGUGGUGAUUUUCCAUAUAACUU	959

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1289	1141-1161	GUGCUGGAAAACCCAGGGAC	291	AGUCCCUGGGUUUUCAGCACUU	960
D-1290	1142-1162	UGCUGGAAAACCCAGGGACC	292	UGGUCCCUGGGUUUUCAGCAUU	961
D-1291	1143-1163	GCUGGAAAACCCAGGGACCA	293	AUGGUCCCUGGGUUUUCAGCUU	962
D-1292	1148-1168	AAAACCCAGGGACCAUCAA	294	AUUUGAUGGUCCCUGGGUUUUUU	963
D-1293	1149-1169	AAACCCAGGGACCAUCAAG	295	ACUUUGAUGGUCCCUGGGUUUUU	964
D-1294	1150-1170	AACCCAGGGACCAUCAAGU	296	AACUUUGAUGGUCCCUGGGUUUU	965
D-1295	1151-1171	ACCCAGGGACCAUCAAGUG	297	ACACUUUGAUGGUCCCUGGGUUU	966
D-1296	1168-1188	GUGGGAGACCCUGUGUACCU	298	AAGGUACACAGGGUCUCCCAUU	967
D-1297	1188-1208	GCUGGGCCAGUAAUGGGAAC	299	AGUUCCCAUUACUGGCCAGCUU	968
D-1298; D-2067	1248-1268	CAAAAUGACAACACUUGAA	300	AUUCAAGUGUUGUCAUUUUUGUU	969
D-1299; D-2119; D-2491; D-2503; D-2509	1253-1273	AUGACAACACUUGAAGCAUG	301	ACAUGCUUCAAGUGUUGUCAUUU	970
D-1300	1261-1281	ACUUGAAGCAUGGUGUUUCA	302	AUGAAACACCAUGCUUCAAGUUU	971
D-1301	1306-1326	AAAUUUGUGAUUUUACAUU	303	AAAUGUGAAAAUCACAAUUUUU	972
D-1302; D-2307	1353-1373	AAUGCUUCAAGUCCAGUG	304	ACACUGGGACAUAUGAAGCAUUU	973
D-1303	1428-1448	AAAUGACAAGACAGGAUUCU	305	AAGAAUCCUGUCUUGUCAUUUUU	974
D-1304; D-2149	1469-1489	UUAUGGAUAGUUCUUCUC	306	AGAGAAAGAACUAUCCAUAUUU	975
D-1305	1470-1490	UAUGGAUAGUUCUUCUCC	307	AGGAGAAAGAACUAUCCAUAUU	976
D-1306	1474-1494	GAAUAGUUCUUCUCCUGCU	308	AAGCAGGAGAAAGAACUAUUCUU	977
D-1307	1475-1495	AAUAGUUCUUCUCCUGCUU	309	AAAGCAGGAGAAAGAACUAUUUU	978
D-1308	1523-1543	UGCAUCCUGUCACUACCACU	310	AAGUGGUAGUGACAGGAUGCAUU	979
D-1309	1524-1544	GCAUCCUGUCACUACCACUC	311	AGAGUGGUAGUGACAGGAUGCUU	980
D-1310; D-2139	1696-1716	CCGGGCUAGCUUUUGAAUG	312	ACAUUUCAAAGCUAGCCCGGUU	981
D-1311; D-2073	1697-1717	CGGGCUAGCUUUUGAAUGG	313	ACCAUUUCAAAGCUAGCCCGUU	982
D-1312	1721-1741	AAGACUGAGGUGACCUUCAG	314	ACUGAAGGUCACCUCAGUCUUUU	983
D-1313	1728-1748	AGGUGACCUUCAGGAAGCAC	315	AGUGCUUCCUGAAGGUCACCUUU	984
D-1314	1764-1784	CCAUAGAUCUGGAUCUGGCC	316	AGGCCAGAUCCAGAUCAUUGGUU	985
D-1315; D-2130	1805-1825	UGGAUUUCCUAAAGGUGCUC	317	UGAGCACCUUUAGGAAAUCCAUU	986
D-1316	1807-1827	GAUUUCCUAAAGGUGCUCAG	318	ACUGAGCACCUUUAGGAAAUCCU	987
D-1317	1811-1831	UCCUAAAGGUGCUCAGGAGG	319	UCCUCCUGAGCACCUUUAGGAUU	988
D-1318	1846-1866	UGGAGGACCCUGGAUCCUU	320	AAAGGAUCCAGGGGUCCUCCAU	989
D-1319	1847-1867	GGAGGACCCUGGAUCCUUG	321	ACAAGGAUCCAGGGGUCCUCCU	990
D-1320	1848-1868	GAGGACCCUGGAUCCUUGC	322	AGCAAGGAUCCAGGGGUCCUCCU	991
D-1321	1887-1907	CGGAGUGCUCCUUCUCCAGU	323	AACUGGAGAAGGAGCACUCCGUU	992
D-1322	39-59	AGAAGGACGCACUGCUCUGA	324	AUCAGAGCAGUGCGUCCUUCUUU	993
D-1323	53-73	CUCUGAUUGGCCCGGAAGGG	325	ACCCUUCGGGGCCAAUCAGAGUU	994
D-1324	54-74	UCUGAUUGGCCCGGAAGGGU	326	AACCCUUCGGGGCCAAUCAGAUU	995

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1325	55-75	CUGAUUGGCCCGGAAGGGUU	327	AAACCCUUCGGGCCAAUCAGUU	996
D-1326	102-122	GGCCAAAGGCCGACCUUCC	328	AGGAAGGUGCGCCUUGGCCUU	997
D-1327	168-188	CCUCGCGGAGAAGCCAGCCA	329	AUGGCUGGCUUCUCCGCGAGGUU	998
D-1328	174-194	GGAGAAGCCAGCCAUGGGCG	330	ACGCCCAUGGCUGGCUUCUCCUU	999
D-1329	175-195	GAGAAGCCAGCCAUGGGCGC	331	AGCGCCCAUGGCUGGCUUCUCCUU	1000
D-1330	474-494	GAUCAACCAGGAGGGAAACA	332	AUGUUUCCCUCCUGGUUGAUUU	1001
D-1331	499-519	ACUGCUCGCCAGGAACCUCG	333	ACGAGGUUCCUGGCGAGCAGUUU	1002
D-1332	504-524	UCGCCAGGAACCUCGCCUGG	334	ACCAGGCGAGGUUCCUGGCGAUU	1003
D-1333	506-526	GCCAGGAACCUCGCCUGGUC	335	AGACCAGGCGAGGUUCCUGGCUU	1004
D-1334	511-531	GAACCUCCGCCUGGUCCUGAU	336	AAUCAGGACCAGGCGAGGUUCCUU	1005
D-1335	545-565	AUGGUGACACCCUGACUCUC	337	UGAGAGUCAGGGUGUCACCAUUU	1006
D-1336	546-566	UGGUGACACCCUGACUCUCA	338	AUGAGAGUCAGGGUGUCACCAUU	1007
D-1337	550-570	GACACCCUGACUCUCAGUGC	339	UGCACUGAGAGUCAGGGUGUCUU	1008
D-1338; D-2085	553-573	ACCCUGACUCUCAGUGCAGC	340	AGCUGCACUGAGAGUCAGGGUUU	1009
D-1339	680-700	CCGCCAGUGGAUAACCAGC	341	AGCUGGUUAUCCACUGGGCGGUU	1010
D-1340	720-740	CCGCCUGGUGCACUUCGAGC	342	AGCUCGAAGUGCACCAGGCGGUU	1011
D-1341	721-741	CGCCUGGUGCACUUCGAGCC	343	AGGCUCGAAGUGCACCAGGCGUU	1012
D-1342	722-742	GCCUGGUGCACUUCGAGCCU	344	AAGGCUCGAAGUGCACCAGGCUU	1013
D-1343	723-743	CCUGGUGCACUUCGAGCCUC	345	UGAGGCUCGAAGUGCACCAGGUU	1014
D-1344	724-744	CUGGUGCACUUCGAGCCUCA	346	AUGAGGCUCGAAGUGCACCAGUU	1015
D-1345	725-745	UGGUGCACUUCGAGCCUCAC	347	UGUGAGGCUCGAAGUGCACC AUU	1016
D-1346	726-746	GGUGCACUUCGAGCCUCACA	348	AUGUGAGGCUCGAAGUGCACC UU	1017
D-1347	727-747	GUGCACUUCGAGCCUCACAU	349	AAUGUGAGGCUCGAAGUGCACUU	1018
D-1348	728-748	UGCACUUCGAGCCUCACAUG	350	ACAUGUGAGGCUCGAAGUGCAUU	1019
D-1349	729-749	GCACUUCGAGCCUCACAUGC	351	AGCAUGUGAGGCUCGAAGUGCUU	1020
D-1350	730-750	CACUUCGAGCCUCACAUGCG	352	UCGCAUGUGAGGCUCGAAGUGUU	1021
D-1351	731-751	ACUUCGAGCCUCACAUGCGA	353	AUCGCAUGUGAGGCUCGAAGUUU	1022
D-1352	732-752	CUUCGAGCCUCACAUGCGAC	354	AGUCGCAUGUGAGGCUCGAAGUU	1023
D-1353	733-753	UUCGAGCCUCACAUGCGACC	355	AGGUCGCAUGUGAGGCUCGAAUU	1024
D-1354	734-754	UCGAGCCUCACAUGCGACCG	356	UCGGUCGCAUGUGAGGCUCGAUU	1025
D-1355	735-755	CGAGCCUCACAUGCGACCGA	357	AUCGGUCGCAUGUGAGGCUCGUU	1026
D-1356	738-758	GCCUCACAUGCGACCGAGAC	358	AGUCUCGGUCGCAUGUGAGGC UU	1027
D-1357	825-845	CUUGAUCCUUUCUGAGGCGU	359	AACGCCUCAGAAAGGAUCAAGUU	1028
D-1358	847-867	CUGGCGGAUCUCAACUCCAG	360	ACUGGAGUUGAGAUCCGCCAGUU	1029
D-1359	848-868	UGGCGGAUCUCAACUCCAGG	361	ACCUGGAGUUGAGAUCCGCCAUU	1030
D-1360	923-943	GCGAUGUCUAUGCAGAGGAU	362	AAUCCUCUGCAUAGACAUCGCUU	1031
D-1361	925-945	GAUGUCUAUGCAGAGGAUUC	363	AGAAUCCUCUGCAUAGACAUCUU	1032
D-1362	927-947	UGUCUAUGCAGAGGAUUCUU	364	AAAGAAUCCUCUGCAUAGACA UU	1033
D-1363; D-2084	928-948	GUCUAUGCAGAGGAUUCUUG	365	ACAAGAAUCCUCUGCAUAGACUU	1034
D-1364	929-949	UCUAUGCAGAGGAUUCUUGG	366	ACCAAGAAUCCUCUGCAUAGAUU	1035
D-1365	930-950	CUAUGCAGAGGAUUCUUGGG	367	UCCCAAGAAUCCUCUGCAUAGUU	1036
D-1366	984-1004	GGUGAUGGCUUGUCCAGAU	368	AAUCUGGAACAAGCCAUCACCUU	1037
D-1367;	985-1005	GUGAUGGCUUGUCCAGAU	369	ACAUCUGGAACAAGCCAUCACUU	1038

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2083; D-2244; D-2249					
D-1368	989-1009	UGGCUUGUCCAGAUGCAUU	370	AAAUGCAUCUGGAACAAGCCAUU	1039
D-1369	1005-1025	CAUUUUAACCACAGUGGACC	371	AGGUCCACUGUGGUUAAAAUGUU	1040
D-1370	1007-1027	UUUUAACCACAGUGGACCCA	372	AUGGGUCCACUGUGGUUAAAAUU	1041
D-1371	1008-1028	UUUAACCACAGUGGACCCAG	373	UCUGGGUCCACUGUGGUUAAAAUU	1042
D-1372	1118-1138	CACCACUCUUUGGGCAGUAU	374	AAUACUGCCCAAAGAGUGGUGUU	1043
D-1373	1119-1139	ACCACUCUUUGGGCAGUAUU	375	AAAUACUGCCCAAAGAGUGGUUU	1044
D-1374	1125-1145	CUUUGGGCAGUAUUUUGUGC	376	AGCACAAAAUACUGCCCAAAGUU	1045
D-1375; D-2071	1126-1146	UUUGGGCAGUAUUUUGUGCU	377	AAGCACAAAAUACUGCCCAAUUU	1046
D-1376	1127-1147	UUGGGCAGUAUUUUGUGCUG	378	ACAGCACAAAAUACUGCCCAAUU	1047
D-1377	1128-1148	UGGGCAGUAUUUUGUGCUGG	379	UCCAGCACAAAAUACUGCCCAUU	1048
D-1378	1130-1150	GGCAGUAUUUUGUGCUGGAA	380	UUUCCAGCACAAAAUACUGCCUU	1049
D-1379	1135-1155	UAUUUUGUGCUGGAAAACCC	381	UGGGUUUUCAGCACAAAAUAUU	1050
D-1380	1136-1156	AUUUUGUGCUGGAAAACCCA	382	AUGGGUUUUCAGCACAAAAUUU	1051
D-1381; D-2154	1206-1226	ACCGUAUGUCCUGGAAUAUU	383	UAAUAUUCAGGACAUACGGUUU	1052
D-1382; D-2066	1207-1227	CCGUAUGUCCUGGAAUAUUA	384	AUAAUAUUCAGGACAUACGGUU	1053
D-1383; D-2063	1209-1229	GUAUGUCCUGGAAUAUUAGA	385	AUCUAAUAUUCAGGACAUACUU	1054
D-1384; D-2142	1210-1230	UAUGUCCUGGAAUAUUAGAU	386	AAUCUAAUAUUCAGGACAUUU	1055
D-1385; D-2301; D-2441; D-2445	1211-1231	AUGUCCUGGAAUAUUAGAUG	387	ACAUCUAAUAUUCAGGACAUUU	1056
D-1386; D-2081; D-2245; D-2250; D-2312; D-2317; D-2322; D-2327; D-2332; D-2337; D-2342; D-2347; D-2352; D-2357; D-2396	1212-1232	UGUCCUGGAAUAUUAGAUGC	388	AGCAUCUAAUAUUCAGGACAUU	1057
D-1387; D-2080; D-2246;	1213-1233	GUCCUGGAAUAUUAGAUGCC	389	AGGCAUCUAAUAUUCAGGACUU	1058

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2251; D-2264; D-2276; D-2277; D-2278; D-2279; D-2280; D-2281; D-2282; D-2283; D-2284; D-2285; D-2286; D-2287; D-2288; D-2289; D-2311; D-2316; D-2321; D-2326; D-2331; D-2336; D-2341; D-2346; D-2351; D-2356; D-2395					
D-1388; D-2078; D-2248; D-2253; D-2265; D-2309; D-2314; D-2319; D-2324; D-2329; D-2334; D-2339; D-2344; D-2349; D-2354; D-2393	1214-1234	UCCUGGAAUUAUAGAUGCCU	390	AAGGCAUCUAAUUAUCCAGGAUU	1059
D-1389; D-2077	1215-1235	CCUGGAAUUAUAGAUGCCUU	391	AAAGGCAUCUAAUUAUCCAGGUU	1060
D-1390; D-2076	1216-1236	CUGGAAUUAUAGAUGCCUUU	392	AAAAGGCAUCUAAUUAUCCAGUU	1061

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1391; D-2150	1269-1289	CAUGGUGUUUCAGAACUGAG	393	UCUCAGUUCUGAAACACCAUGUU	1062
D-1392	1270-1290	AUGGUGUUUCAGAACUGAGA	394	AUCUCAGUUCUGAAACACCAUUU	1063
D-1393	1271-1291	UGGUGUUUCAGAACUGAGAC	395	AGUCUCAGUUCUGAAACACCAUU	1064
D-1394	1272-1292	GGUGUUUCAGAACUGAGACC	396	AGGUCUCAGUUCUGAAACACCUU	1065
D-1395; D-2131	1935-1955	GAGGAGAAGAAAAGUGAUUC	397	UGAAUCACUUUUUCUCCUCUU	1066
D-1396; D-2070; D-2471	1939-1959	AGAAGAAAAGUGAUUCAGUG	398	UCACUGAAUCACUUUUUCUUCUU	1067
D-1397; D-2151	1940-1960	GAAGAAAAGUGAUUCAGUGA	399	AUCACUGAAUCACUUUUUCUUCUU	1068
D-1398	1943-1963	GAAAAGUGAUUCAGUGAUUU	400	AAAAUCACUGAAUCACUUUUUCUU	1069
D-1399; D-2141	1945-1965	AAAGUGAUUCAGUGAUUUCA	401	AUGAAAUCACUGAAUCACUUUUU	1070
D-1400; D-2069	1970-1990	ACUACUGAAAACCUUUAAG	402	ACUUUAAAGGUUUUCAGUAGUUU	1071
D-1401; D-2068	1972-1992	UACUGAAAACCUUUAAGGG	403	ACCCUUUAAAGGUUUUCAGUAUU	1072
D-1402; D-2065	2048-2068	UGUAUAACUCUAAGAUCUGA	404	AUCAGAUCUUAGAGUUUAUACUU	1073
D-1403; D-2302; D-2493; D-2505; D-2511	2050-2070	UAUAACUCUAAGAUCUGAUG	405	UCAUCAGAUCUUAGAGUUUAUUAU	1074
D-1404; D-2143	2051-2071	AUAACUCUAAGAUCUGAUGA	406	UUCAUCAGAUCUUAGAGUUUAUUU	1075
D-1405; D-2082; D-2313; D-2318; D-2323; D-2328; D-2333; D-2338; D-2343; D-2348; D-2353; D-2358; D-2397; D-2470	2052-2072	UAACUCUAAGAUCUGAUGAA	407	AUUAUCAGAUCUUAGAGUUUAUU	1076
D-1406; D-2137	2053-2073	AACUCUAAGAUCUGAUGAAG	408	ACUUAUCAGAUCUUAGAGUUUUU	1077
D-1407; D-2079; D-2247;	2054-2074	ACUCUAAGAUCUGAUGAAGU	409	UACUUAUCAGAUCUUAGAGUUU	1078

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2252; D-2266; D-2310; D-2315; D-2320; D-2325; D-2330; D-2335; D-2340; D-2345; D-2350; D-2355; D-2394					
D-1408	57-77	GAUUGGCCCGGAAGGGUUA	410	AUGAACCCUUCGGGCCAAUCUU	1079
D-1409	89-109	CCUUUGGGCUCGGGGCCAAA	411	AUUUGGCCCCGAGCCCAAAGGUU	1080
D-1410	92-112	UUGGGCUCGGGGCCAAAGGC	412	AGCCUUUGGCCCCGAGCCCAAUU	1081
D-1411	112-132	CGCACCUCUCCCCAGCGGCC	413	AGGCCGUCGGGGGAAGGUGCGUU	1082
D-1412	159-179	CCGCCGCCACCUCGCGGAGA	414	UUCUCCGCGAGGUGGCGGCGUU	1083
D-1413	205-225	UCCGCGCUGGCGCGCUUUGU	415	AACAAAGCGCGCCAGCGCGGAUU	1084
D-1414	206-226	CCGCGCUGGCGCGCUUUGUC	416	AGACAAAGCGCGCCAGCGCGUU	1085
D-1415	207-227	CGCGCUGGCGCGCUUUGUCC	417	AGGACAAAGCGCGCCAGCGCGUU	1086
D-1416; D-2091	215-235	CGCGCUUUGUCCUCCUCGCG	418	ACGCGAGGAGGACAAAGCGCGUU	1087
D-1417	216-236	GCGCUUUGUCCUCCUCGCGC	419	UGCGCGAGGAGGACAAAGCGCUU	1088
D-1418	217-237	CGCUUUGUCCUCCUCGCGCA	420	UUGCGCGAGGAGGACAAAGCGUU	1089
D-1419	218-238	GCUUUGUCCUCCUCGCGCAA	421	AUUGCGCGAGGAGGACAAAGCUU	1090
D-1420; D-2093	219-239	CUUUGUCCUCCUCGCGCAAU	422	AAUUGCGCGAGGAGGACAAAGUU	1091
D-1421; D-2095	220-240	UUUGUCCUCCUCGCGCAAUC	423	AGAUUGCGCGAGGAGGACAAAUU	1092
D-1422	222-242	UGUCCUCCUCGCGCAAUCCC	424	AGGGAUUGCGCGAGGAGGACAUU	1093
D-1423	223-243	GUCCUCCUCGCGCAAUCCCG	425	ACGGGAUUGCGCGAGGAGGACUU	1094
D-1424	224-244	UCCUCCUCGCGCAAUCCCGG	426	ACCGGAUUGCGCGAGGAGGAUU	1095
D-1425	225-245	CCUCCUCGCGCAAUCCCGGC	427	AGCCGGGAUUGCGCGAGGAGGUU	1096
D-1426	229-249	CUCGCGCAAUCCCGGCCCGG	428	ACCGGGCCGGGAUUGCGCGAGUU	1097
D-1427	232-252	GCGCAAUCCCGGCCCGGGUG	429	ACACCCGGGCCGGGAUUGCGCUU	1098
D-1428	233-253	CGCAAUCCCGGCCCGGGUGG	430	ACCACCCGGGCCGGGAUUGCGUU	1099
D-1429	234-254	GCAAUCCCGGCCCGGGUGGC	431	AGCCACCCGGGCCGGGAUUGCUU	1100
D-1430	242-262	GGCCCGGUGGCUUGGGGUU	432	AAACCCGAGCCACCCGGGCCUU	1101
D-1431	243-263	GCCCGGUGGCUUGGGGUUUG	433	ACAACCCGAGCCACCCGGGCCUU	1102
D-1432	244-264	CCCGGGUGGCUUGGGGUUUGC	434	AGCAACCCGAGCCACCCGGGUU	1103
D-1433	254-274	UCGGGGUUGCCGCGUGGGC	435	AGCCAGCGCGGAACCCGAUU	1104
D-1434	258-278	GGUUGCCGCGUGGGCCUGA	436	AUCAGGCCAGCGCGGAACCUU	1105
D-1435	262-282	GCCGCGUGGGCCUGACCGC	437	AGCGGUCAGGCCAGCGCGGUU	1106
D-1436	265-285	GCGCUGGGCCUGACCGCGGU	438	AACCGCGGUCAGGCCAGCGCUU	1107
D-1437	269-289	UGGGCCUGACCGCGUGGCG	439	ACGCCACCGCGGUCAGGCCAUU	1108

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1438	270-290	GGGCCUGACCGCGGUGGCGC	440	AGCGCCACCGCGGUCAGGCCUU	1109
D-1439; D-2122	484-504	GAGGGAAACAUGGUUACUGC	441	AGCAGUAACCAUGUUUCCUCUU	1110
D-1440	487-507	GGAAACAUGGUUACUGCUCG	442	ACGAGCAGUAACCAUGUUUCCUU	1111
D-1441; D-2092	488-508	GAAACAUGGUUACUGCUCGC	443	AGCGAGCAGUAACCAUGUUUCCUU	1112
D-1442	489-509	AAACAUGGUUACUGCUCGCC	444	UGGCGAGCAGUAACCAUGUUUUU	1113
D-1443	490-510	AACAUGGUUACUGCUCGCCA	445	AUGGCGAGCAGUAACCAUGUUUU	1114
D-1444	491-511	ACAUGGUUACUGCUCGCCAG	446	ACUGGCGAGCAGUAACCAUGUUU	1115
D-1445	496-516	GUUACUGCUCGCCAGGAACC	447	AGGUUCCUGGCGAGCAGUAACUU	1116
D-1446	531-551	UUCCUGACCGUGCGAUGGUG	448	UCACCAUCGAGGUCAGGAAUU	1117
D-1447	538-558	ACCUGCGAUGGUGACACCCU	449	AAGGGUGUCACCAUCGCAGGUUU	1118
D-1448	566-586	GUGCAGCCUACACAAAGGAC	450	AGUCCUUUGUGUAGGCUGCACUU	1119
D-1449	567-587	UGCAGCCUACACAAAGGACC	451	AGGUCCUUUGUGUAGGCUGCACUU	1120
D-1450	569-589	CAGCCUACACAAAGGACCUA	452	AUAGGUCCUUUGUGUAGGCUGUU	1121
D-1451; D-2086	570-590	AGCCUACACAAAGGACCUAC	453	AGUAGGUCCUUUGUGUAGGCUUU	1122
D-1452	571-591	GCCUACACAAAGGACCUACU	454	UAGUAGGUCCUUUGUGUAGGCUU	1123
D-1453	572-592	CCUACACAAAGGACCUACUA	455	AUAGUAGGUCCUUUGUGUAGGUU	1124
D-1454	573-593	CUACACAAAGGACCUACUAC	456	AGUAGUAGGUCCUUUGUGUAGUU	1125
D-1455; D-2110	576-596	CACAAAGGACCUACUACUGC	457	AGCAGUAGUAGGUCCUUUGUGUU	1126
D-1456	581-601	AGGACCUACUACUGCCUAUC	458	UGAUAGGCAGUAGUAGGUCCUUU	1127
D-1457	582-602	GGACCUACUACUGCCUAUCA	459	UUGAUAGGCAGUAGUAGGUCCUU	1128
D-1458; D-2134	584-604	ACCUACUACUGCCUAUCAA	460	UUUUGAUAGGCAGUAGUAGGUUU	1129
D-1459; D-2135	587-607	UACUACUGCCUAUCAAACG	461	ACGUUUUGAUAGGCAGUAGUAUU	1130
D-1460; D-2098	589-609	CUACUGCCUAUCAAACGCC	462	AGGCGUUUUGAUAGGCAGUAGUU	1131
D-1461	594-614	GCCUAUCAAACGCCACCA	463	AUGGUGGGCGUUUUGAUAGGCUU	1132
D-1462	610-630	ACCACAAUGCAGUGCACAA	464	AUUGUGCACUGCAUUUGUGUUU	1133
D-1463	612-632	CACAAUGCAGUGCACAAAGU	465	AACUUGUGCACUGCAUUUGUGUU	1134
D-1464	614-634	CAAAUGCAGUGCACAAAGUGC	466	UGCACUUGUGCACUGCAUUUGUU	1135
D-1465	617-637	AUGCAGUGCACAAAGUGCAGA	467	AUCUGCACUUGUGCACUGCAUUU	1136
D-1466	621-641	AGUGCACAAGUGCAGAGUGC	468	UGCACUCUGCACUUGUGCACUUU	1137
D-1467	626-646	ACAAGUGCAGAGUGCACGGC	469	AGCCGUGCACUCUGCACUUGUUU	1138
D-1468	627-647	CAAGUGCAGAGUGCACGGCC	470	AGGCCGUGCACUCUGCACUUGUU	1139
D-1469	631-651	UGCAGAGUGCACGGCCUGGA	471	AUCCAGGCCGUGCACUCUGCAUU	1140
D-1470	634-654	AGAGUGCACGGCCUGGAGAU	472	UAUCUCCAGGCCGUGCACUCUUU	1141
D-1471	635-655	GAGUGCACGGCCUGGAGAU	473	AUAUCUCCAGGCCGUGCACUCUU	1142
D-1472	647-667	UGGAGAUAGAGGCGAGGGAC	474	AGUCCUGCCCUCAUCCCAUU	1143
D-1473	701-721	UCCUGAAGUCACAGCCCUAC	475	AGUAGGGCUGUGACUUCAGGAUU	1144
D-1474	703-723	CUGAAGUCACAGCCCUACCG	476	ACGGUAGGGCUGUGACUUCAGUU	1145
D-1475	705-725	GAAGUCACAGCCCUACCGCC	477	AGGCGGUAGGGCUGUGACUUCUU	1146
D-1476	739-759	CCUCACAUGCGACCGAGACG	478	ACGUCUCGGUCGCAUGUGAGGUU	1147

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1477	740-760	CUCACAUGCGACCGAGACGU	479	AACGUCUCGGUCGCAUGUGAGUU	1148
D-1478	741-761	UCACAUGCGACCGAGACGUC	480	AGACGUCUCGGUCGCAUGUGAUU	1149
D-1479	742-762	CACAUGCGACCGAGACGUCC	481	AGGACGUCUCGGUCGCAUGUGUU	1150
D-1480	743-763	ACAUGCGACCGAGACGUCCU	482	AAGGACGUCUCGGUCGCAUGUUU	1151
D-1481	746-766	UGCGACCGAGACGUCCUCAU	483	AAUGAGGACGUCUCGGUCGCAUU	1152
D-1482	747-767	GCGACCGAGACGUCCUCAUC	484	UGAUGAGGACGUCUCGGUCGCUU	1153
D-1483	751-771	CCGAGACGUCCUCAUCAAU	485	UAAUUUGAUGAGGACGUCUCGGUU	1154
D-1484	752-772	CGAGACGUCCUCAUCAAUA	486	AUAUUUGAUGAGGACGUCUCGUU	1155
D-1485	754-774	AGACGUCCUCAUCAAUAGC	487	UGCUAUUUGAUGAGGACGUCUUU	1156
D-1486	759-779	UCCUCAUCAAUAGCAGACU	488	AAGUCUGCUAUUUUGAUGAGGAUU	1157
D-1487; D-2099	761-781	CUCAUCAAUAGCAGACUUG	489	ACAAGUCUGCUAUUUUGAUGAGUU	1158
D-1488	809-829	CAGACACCAGCCAUUCUUG	490	UCAAGAAUGGGCUGGUGUCUGUU	1159
D-1489; D-2100	810-830	AGACACCAGCCAUUCUUGA	491	AUCAAGAAUGGGCUGGUGUCUUU	1160
D-1490	811-831	GACACCAGCCAUUCUUGAU	492	AAUCAAGAAUGGGCUGGUGUCUU	1161
D-1491; D-2101	816-836	CAGCCAUUCUUGAUCCUUU	493	AAAAGGAUCAAGAAUGGGCUGUU	1162
D-1492; D-2112	820-840	CCAUCUUGAUCCUUUCUGA	494	AUCAGAAAGGAUCAAGAAUGGUU	1163
D-1493; D-2102	934-954	GCAGAGGAUUCUUGGGAUGA	495	AUCAUCCAAGAAUCCUCUGCUU	1164
D-1494	941-961	AUUCUUGGGAUGAGCUUCUU	496	UAAGAAGCUCAUCCCAAGAAUUU	1165
D-1495	944-964	CUUGGGAUGAGCUUCUUAUU	497	AAAUAGAAGCUCAUCCCAAGUU	1166
D-1496	947-967	GGGAUGAGCUUCUUAUUGGU	498	AACCAAUAGAAGCUCAUCCCUU	1167
D-1497	948-968	GGGAUGAGCUUCUUAUUGGUG	499	UCACCAAUAGAAGCUCAUCCUU	1168
D-1498	970-990	GUGGAACUGAAAAGGGUGAU	500	AAUCACCCUUUUCAGUUCACUU	1169
D-1499	971-991	UGGAACUGAAAAGGGUGAUG	501	ACAUCACCCUUUUCAGUUCACUU	1170
D-1500	973-993	GAACUGAAAAGGGUGAUGGC	502	AGCCAUCACCCUUUUCAGUUCUU	1171
D-1501	976-996	CUGAAAAGGGUGAUGGCUUG	503	ACAAGCCAUCACCCUUUUCAGUU	1172
D-1502	977-997	UGAAAAGGGUGAUGGCUUGU	504	AACAAGCCAUCACCCUUUUCAUU	1173
D-1503; D-2096	978-998	GAAAAGGGUGAUGGCUUGUU	505	AAACAAGCCAUCACCCUUUUCUU	1174
D-1504; D-2097	979-999	AAAAGGGUGAUGGCUUGUUC	506	AGAACAAGCCAUCACCCUUUUUU	1175
D-1505	1018-1038	GUGGACCCAGACACCGGUGU	507	AACACCGGUGUCUGGGUCCACUU	1176
D-1506	1019-1039	UGGACCCAGACACCGGUGUC	508	UGACACCGGUGUCUGGGUCCAUU	1177
D-1507	1020-1040	GGACCCAGACACCGGUGUCA	509	AUGACACCGGUGUCUGGGUCCUU	1178
D-1508	1022-1042	ACCCAGACACCGGUGUCAUG	510	UCAUGACACCGGUGUCUGGGUUU	1179
D-1509	1024-1044	CCAGACACCGGUGUCAUGAG	511	ACUCAUGACACCGGUGUCUGGUU	1180
D-1510	1029-1049	CACCGGUGUCAUGAGCAGGA	512	UUCUGCUCAUGACACCGGUGUU	1181
D-1511	1036-1056	GUCAUGAGCAGGAAGGAACC	513	AGGUUCCUCCUGCUCAUGACUU	1182
D-1512	1039-1059	AUGAGCAGGAAGGAACCGCU	514	AAGCGGUUCCUCCUGCUCAUUU	1183
D-1513	1045-1065	AGGAAGGAACCGCUGGAAAC	515	UGUUUCCAGCGGUUCCUCCUUU	1184
D-1514	1046-1066	GGAAGGAACCGCUGGAAACA	516	AUGUUUCCAGCGGUUCCUCCUU	1185
D-1515;	1047-1067	GAAGGAACCGCUGGAAACAC	517	AGUGUUUCCAGCGGUUCCUUCUU	1186

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2088					
D-1516	1189-1209	CUGGGCCAGUAAUGGGAACC	518	AGGUUCCCAUUACUGGCCAGUU	1187
D-1517	1191-1211	GGGCCAGUAAUGGGAACCGU	519	UACGGUCCCAUUACUGGCCUU	1188
D-1518	1192-1212	GGCCAGUAAUGGGAACCGUA	520	AUACGGUCCCAUUACUGGCCUU	1189
D-1519	1193-1213	GCCAGUAAUGGGAACCGUAU	521	AAUACGGUCCCAUUACUGGCCUU	1190
D-1520	1194-1214	CCAGUAAUGGGAACCGUAUG	522	ACAUACGGUCCCAUUACUGGUU	1191
D-1521	1195-1215	CAGUAAUGGGAACCGUAUGU	523	AACAUACGGUCCCAUUACUGUU	1192
D-1522	1196-1216	AGUAAUGGGAACCGUAUGUC	524	AGACAUACGGUCCCAUUACUUU	1193
D-1523	1201-1221	UGGGAACCGUAUGUCCUGGA	525	UUCAGGACAUACGGUCCCAUU	1194
D-1524	1203-1223	GGAACCGUAUGUCCUGGAAU	526	UAUUCAGGACAUACGGUCCUU	1195
D-1525; D-2113; D-2376; D-2380	1219-1239	GAAUAUUAGAUGCCUUUUA	527	UUUAAAAGGCAUCUAAUAUUCUU	1196
D-1526; D-2108; D-2440; D-2444	1227-1247	GAUGCCUUUUAAAAAUGUUC	528	AGAACAUUUUUAAAAGGCAUCUU	1197
D-1527	1275-1295	GUUUCAGAACUGAGACCUCU	529	UAGAGGUCUCAGUUCUGAAACUU	1198
D-1528	1278-1298	UCAGAACUGAGACCUCUACA	530	AUGUAGAGGUCUCAGUUCUGAUU	1199
D-1529	1283-1303	ACUGAGACCUCUACAUUUUUC	531	AGAAAAUGUAGAGGUCUCAGUUU	1200
D-1530	1284-1304	CUGAGACCUCUACAUUUUCU	532	AAGAAAAUGUAGAGGUCUCAGUU	1201
D-1531	1285-1305	UGAGACCUCUACAUUUUCUU	533	AAAGAAAAUGUAGAGGUCUCAUU	1202
D-1532; D-2146	1313-1333	UGAUUUUCACAUUUUUCGUC	534	AGACGAAAAAUGUGAAAAUCAUU	1203
D-1533; D-2111; D-2374; D-2375; D-2379; D-2383	1314-1334	GAUUUUCACAUUUUUCGUCU	535	AAGACGAAAAAUGUGAAAAUCUU	1204
D-1534	1315-1335	AUUUUCACAUUUUUCGUCUU	536	AAAGACGAAAAAUGUGAAAAUUU	1205
D-1535	1317-1337	UUUCACAUUUUUCGUCUUUU	537	AAAAAGACGAAAAAUGUGAAAUU	1206
D-1536	1318-1338	UUCACAUUUUUCGUCUUUUG	538	ACAAAAGACGAAAAAUGUGAAUU	1207
D-1537	1319-1339	UCACAUUUUUCGUCUUUUGG	539	UCCAAAAGACGAAAAAUGUGAUU	1208
D-1538	1321-1341	ACAUUUUUCGUCUUUUGGAC	540	AGUCCAAAAGACGAAAAAUGUUU	1209
D-1539	1325-1345	UUUUCGUCUUUUGGACUUCU	541	AAGAAGUCCAAAAGACGAAAAUU	1210
D-1540	1326-1346	UUUCGUCUUUUGGACUUCUG	542	ACAGAAGUCCAAAAGACGAAAAU	1211
D-1541	1327-1347	UUCGUCUUUUGGACUUCUGG	543	ACCAGAAGUCCAAAAGACGAAUU	1212
D-1542	1328-1348	UCGUCUUUUGGACUUCUGGU	544	AACCAGAAGUCCAAAAGACGAUU	1213
D-1543	1332-1352	CUUUUGGACUUCUGGUGUCU	545	AAGACACCAGAAGUCCAAAAGUU	1214
D-1544	1335-1355	UUGGACUUCUGGUGUCUCAA	546	AUUGAGACACCAGAAGUCCAAUU	1215
D-1545	1337-1357	GGACUUCUGGUGUCUCAAUG	547	ACAUUGAGACACCAGAAGUCCUU	1216
D-1546	1338-1358	GACUUCUGGUGUCUCAAUGC	548	AGCAUUGAGACACCAGAAGUCUU	1217
D-1547	1341-1361	UUCUGGUGUCUCAAUGCUUC	549	UGAAGCAUUGAGACACCAGAAUU	1218
D-1548	1356-1376	GCUUCAUUGUCCAGUGCAA	550	UUUGCACUGGGACAUUGAAGCUU	1219

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1549; D-2075	1362-1382	AUGUCCCAGUGCAAAAAGUA	551	UUACUUUUUGCACUGGGACAUUU	1220
D-1550	1363-1383	UGUCCCAGUGCAAAAAGUAA	552	UUUACUUUUUGCACUGGGACAUU	1221
D-1551; D-2152	1364-1384	GUCCCAGUGCAAAAAGUAAA	553	AUUUACUUUUUGCACUGGGACUU	1222
D-1552; D-2157	1365-1385	UCCCAGUGCAAAAAGUAAAG	554	UCUUUACUUUUUGCACUGGGAUU	1223
D-1553	1369-1389	AGUGCAAAAAGUAAAGAAAU	555	UAUUUCUUUACUUUUUGCACUUU	1224
D-1554	1382-1402	AAGAAUAUAGUCUCAAUAA	556	AUUUAUUGAGACUAUAUUUCUUUU	1225
D-1555; D-2136; D-2438; D-2442	1385-1405	AAAUUAAGUCUCAUAACUU	557	UAAGUUAUUGAGACUAUAUUUUU	1226
D-1556; D-2156	1387-1407	AUAUAGUCUCAUAACUUAG	558	ACUAAGUUAUUGAGACUAUAUUU	1227
D-1557	1388-1408	UAUAGUCUCAUAACUUAGU	559	UACUAAGUUAUUGAGACUAUAUU	1228
D-1558	1389-1409	AUAGUCUCAUAACUUAGUA	560	AUACUAAGUUAUUGAGACUAUUU	1229
D-1559	1390-1410	UAGUCUCAUAACUUAGUAG	561	ACUACUAAGUUAUUGAGACUAUU	1230
D-1560	1391-1411	AGUCUCAUAACUUAGUAGG	562	UCCUACUAAGUUAUUGAGACUUU	1231
D-1561	1395-1415	UCAUAACUUAGUAGGACUU	563	AAAGUCCUACUAAGUUAUUGAUU	1232
D-1562	1396-1416	CAUAACUUAGUAGGACUUC	564	UGAAGUCCUACUAAGUUAUUGUU	1233
D-1563	1398-1418	AUAACUUAGUAGGACUUCAG	565	ACUGAAGUCCUACUAAGUUAUUU	1234
D-1564	1400-1420	AACUUAGUAGGACUUCAGUA	566	UUACUGAAGUCCUACUAAGUUUU	1235
D-1565	1401-1421	ACUUAGUAGGACUUCAGUAA	567	AUUACUGAAGUCCUACUAAGUUU	1236
D-1566	1403-1423	UUAGUAGGACUUCAGUAAGU	568	AACUUACUGAAGUCCUACUAUUU	1237
D-1567	1404-1424	UAGUAGGACUUCAGUAAGUC	569	UGACUUACUGAAGUCCUACUAUU	1238
D-1568	1405-1425	AGUAGGACUUCAGUAAGUCA	570	AUGACUUACUGAAGUCCUACUUU	1239
D-1569	1407-1427	UAGGACUUCAGUAAGUCACU	571	AAGUGACUUACUGAAGUCCUAAU	1240
D-1570	1427-1447	UAAAUGACAAGACAGGAUUC	572	AGAAUCCUGUCUUGUCAUUUUU	1241
D-1571	1441-1461	GGAUUCUGAAAACUCCCGU	573	AACGGGGAGUUUUCAGAAUCCUU	1242
D-1572	1442-1462	GAUUCUGAAAACUCCCGUU	574	AAACGGGGAGUUUUCAGAAUCUU	1243
D-1573	1444-1464	UUCUGAAAACUCCCGUUUA	575	UUAAACGGGGAGUUUUCAGAAUU	1244
D-1574	1445-1465	UCUGAAAACUCCCGUUUAA	576	AUUAAACGGGGAGUUUUCAGAUU	1245
D-1575	1446-1466	CUGAAAACUCCCGUUUAAC	577	AGUUAAACGGGGAGUUUUCAGUU	1246
D-1576; D-2107	1447-1467	UGAAAACUCCCGUUUAACU	578	AAGUUAAACGGGGAGUUUUCAUU	1247
D-1577	1449-1469	AAAACUCCCGUUUAACUGA	579	AUCAGUUAACGGGGAGUUUUUU	1248
D-1578	1452-1472	ACUCCCGUUUAACUGAUUA	580	AUAAUCAGUUAACGGGGAGUUU	1249
D-1579	1453-1473	CUCCCGUUUAACUGAUUAU	581	AAUAAUCAGUUAACGGGGAGUU	1250
D-1580; D-2155	1454-1474	UCCCGUUUAACUGAUUAUG	582	ACAUAAUCAGUUAACGGGGAUU	1251
D-1581; D-2116; D-2490; D-2502; D-2508	1455-1475	CCCCGUUUAACUGAUUAUGG	583	UCCAUAUCAGUUAACGGGGUU	1252

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1582	1484-1504	UUCUCCUGCUUCUCCGUUUA	584	AUAAACGGAGAAGCAGGAGAAUU	1253
D-1583	1485-1505	UCUCCUGCUUCUCCGUUUAU	585	AAUAAACGGAGAAGCAGGAGAAUU	1254
D-1584; D-2120	1486-1506	CUCCUGCUUCUCCGUUUAUC	586	AGAUAAACGGAGAAGCAGGAGUU	1255
D-1585	1488-1508	CCUGCUUCUCCGUUUAUCUA	587	AUAGAUAAACGGAGAAGCAGGUU	1256
D-1586	1491-1511	GCUUCUCCGUUUAUCUACCA	588	UUGGUAGAUAAACGGAGAAGCUU	1257
D-1587	1492-1512	CUUCUCCGUUUAUCUACCAA	589	AUUGGUAGAUAAACGGAGAAGUU	1258
D-1588	1493-1513	UUCUCCGUUUAUCUACCAAG	590	UCUUGGUAGAUAAACGGAGAAGUU	1259
D-1589	1494-1514	UCUCCGUUUAUCUACCAAGA	591	AUCUUGGUAGAUAAACGGAGAUU	1260
D-1590	1495-1515	CUCCGUUUAUCUACCAAGAG	592	ACUCUUGGUAGAUAAACGGAGUU	1261
D-1591	1496-1516	UCCGUUUAUCUACCAAGAGC	593	AGCUCUUGGUAGAUAAACGGAUU	1262
D-1592	1498-1518	CGUUUAUCUACCAAGAGCGC	594	UGCGCUCUUGGUAGAUAAACGUU	1263
D-1593	1501-1521	UUAUCUACCAAGAGCGCAGA	595	AUCUGCGCUCUUGGUAGAUAAUU	1264
D-1594	1503-1523	AUCUACCAAGAGCGCAGACU	596	AAGUCUGCGCUCUUGGUAGAUUU	1265
D-1595; D-2072; D-2439; D-2443	1506-1526	UACCAAGAGCGCAGACUUGC	597	UGCAAGUCUGCGCUCUUGGUUU	1266
D-1596; D-2087	1507-1527	ACCAAGAGCGCAGACUUGCA	598	AUGCAAGUCUGCGCUCUUGGUUU	1267
D-1597; D-2147	1509-1529	CAAGAGCGCAGACUUGCAUC	599	AGAUGCAAGUCUGCGCUCUUGUU	1268
D-1598	1510-1530	AAGAGCGCAGACUUGCAUCC	600	AGGAUGCAAGUCUGCGCUCUUUU	1269
D-1599	1512-1532	GAGCGCAGACUUGCAUCCUG	601	ACAGGAUGCAAGUCUGCGCUCUU	1270
D-1600	1514-1534	GCGCAGACUUGCAUCCUGUC	602	UGACAGGAUGCAAGUCUGCGCUU	1271
D-1601	1515-1535	CGCAGACUUGCAUCCUGUCA	603	AUGACAGGAUGCAAGUCUGCGUU	1272
D-1602; D-2121	1517-1537	CAGACUUGCAUCCUGUCACU	604	UAGUGACAGGAUGCAAGUCUGUU	1273
D-1603	1521-1541	CUUGCAUCCUGUCACUACCA	605	AUGGUAGUGACAGGAUGCAAGUU	1274
D-1604	1525-1545	CAUCCUGUCACUACCACUCG	606	ACGAGUGGUAGUGACAGGAUGUU	1275
D-1605	1527-1547	UCCUGUCACUACCACUCGUU	607	UAACGAGUGGUAGUGACAGGAUU	1276
D-1606; D-2090	1528-1548	CCUGUCACUACCACUCGUUA	608	AUAACGAGUGGUAGUGACAGGUU	1277
D-1607	1529-1549	CUGUCACUACCACUCGUUAG	609	UCUAACGAGUGGUAGUGACAGUU	1278
D-1608	1530-1550	UGUCACUACCACUCGUUAGA	610	AUCUAACGAGUGGUAGUGACAUU	1279
D-1609	1534-1554	ACUACCACUCGUUAGAGAAA	611	AUUUCUCUAACGAGUGGUAGUUU	1280
D-1610	1572-1592	AAGAGUGGGUGGGCUGGAAG	612	UCUCCAGCCCACCCACUCUUUU	1281
D-1611; D-2124	1596-1616	UCCUAGAAUGUGUUAUUGCC	613	AGGCAAUAAACAUUCUAGGAUU	1282
D-1612	1597-1617	CCUAGAAUGUGUUAUUGCCC	614	AGGGCAAUAAACAUUCUAGGUU	1283
D-1613	1602-1622	AAUGUGUUAUUGCCCCUGUU	615	AAACAGGGGCAAUAAACAUUUU	1284
D-1614	1605-1625	GUGUUAUUGCCCCGUUUAU	616	AAUGAACAGGGGCAAUAAACUU	1285
D-1615	1608-1628	UUAUUGCCCCGUUUAUAGAG	617	ACUCAUGAACAGGGGCAAUAAUU	1286
D-1616	1610-1630	AUUGCCCCGUUUAUAGAGGU	618	UACCUCAUGAACAGGGGCAAUUU	1287
D-1617	1634-1654	AAUGAAAAUUAUUUGCACC	619	AGGUGCAUUUAAUUUUCAUUUU	1288
D-1618	1635-1655	AUGAAAAUUAUUUGCACCC	620	AGGGUGCAUUUAAUUUUCAUUU	1289

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1619	1639-1659	AAAUUAAUUGCACCCCAA	621	AUUUGGGGUGCAAUUUAAUUUUU	1290
D-1620	1641-1661	AUUAAUUGCACCCCAAUA	622	AUAUUUGGGGUGCAAUUUAAUUU	1291
D-1621	1642-1662	UUAAUUGCACCCCAAUAU	623	AAUAAUUGGGGUGCAAUUUAAUU	1292
D-1622	1645-1665	AAUUGCACCCCAAUAUGGC	624	AGCCAUUUUGGGGUGCAAUUUU	1293
D-1623	1646-1666	AUUGCACCCCAAUAUGGCU	625	AAGCCAUUUUGGGGUGCAAUUU	1294
D-1624	1658-1678	AUAUGGCUUGAAUGCCACUU	626	AAAGUGGCAUUCAGCCAUUUU	1295
D-1625	1665-1685	UGGAAUGCCACUUCUUUUU	627	AAAAAGGGAAGUGGCAUCCAUU	1296
D-1626; D-2089	1676-1696	UUCUUUUUCUUCUAGGCC	628	AGGCUUGAGAAGAAAAGGGAAUU	1297
D-1627	1684-1704	UCUUCUCAAGCCCCGGGCUA	629	AUAGCCCCGGGCUUGAGAAGAUU	1298
D-1628	1687-1707	UCUCAAGCCCCGGGCUAGCU	630	AAGCUAGCCCCGGGCUUGAGAUU	1299
D-1629	1704-1724	GCUUUUGAAUUGGCAUAAAG	631	UCUUUAUGCCAUUUCAAAGCUU	1300
D-1630	1707-1727	UUUGAAUUGGCAUAAAGACU	632	AAGUCUUUAUGCCAUUUCAAUUU	1301
D-1631	1712-1732	AAUGGCAUAAAGACUGAGGU	633	AACCUCAGUCUUUAUGCCAUUUU	1302
D-1632; D-2123	1714-1734	UGGCAUAAAGACUGAGGUGA	634	AUCACCUCAGUCUUUAUGCCAUU	1303
D-1633; D-2094	1716-1736	GCAUAAAGACUGAGGUGACC	635	AGGUCACCUCAGUCUUUAUGCUU	1304
D-1634	1741-1761	GAAGCACUGCAGAUUUAAU	636	AAUUAUAUCUGCAGUGCUUCUU	1305
D-1635; D-2103	1813-1833	CUAAAGGUGCUCAGGAGGAU	637	AAUCCUCCUGAGCACCUUUAGUU	1306
D-1636	1817-1837	AGGUGCUCAGGAGGAUGGUU	638	AAACCAUCCUCCUGAGCACCUUU	1307
D-1637	1819-1839	GUGCUCAGGAGGAUGGUUGU	639	AACAACCAUCCUCCUGAGCACUU	1308
D-1638	1827-1847	GAGGAUGGUUGUGUAGUCAU	640	AAUGACUACACAACCAUCCUCUU	1309
D-1639	1828-1848	AGGAUGGUUGUGUAGUCAUG	641	ACAUGACUACACAACCAUCCUUU	1310
D-1640	1829-1849	GGAUGGUUGUGUAGUCAUGG	642	UCCAUGACUACACAACCAUCCUU	1311
D-1641	1835-1855	UUGUGUAGUCAUGGAGGACC	643	AGGUCCUCCAUGACUACCAAUU	1312
D-1642	1843-1863	UCAUGGAGGACCCUGGAUC	644	AGAUCCAGGGGUCCUCCAUGAUU	1313
D-1643	1869-1889	AUUCUCCUCAGCUAAUGACG	645	ACGUCAUUAAGCUGAGGGGAUUU	1314
D-1644	1870-1890	UUCUCCUCAGCUAAUGACGG	646	UCCGUCAUUAAGCUGAGGGGAUU	1315
D-1645	1871-1891	UCCUCCUCAGCUAAUGACGGA	647	AUCCGUCAUUAAGCUGAGGGGAUU	1316
D-1646	1876-1896	UCAGCUAAUGACGGAGUGCU	648	AAGCACUCCGUCAUUAAGCUGAUU	1317
D-1647	1914-1934	GAAAAAGUUCUGAAUUCUGU	649	AACAGAAUUCAGAAUUUUUUCUU	1318
D-1648	1919-1939	AGUUCUGAAUUCUGUGGAGG	650	UCCUCCACAGAAUUCAGAACUUU	1319
D-1649	1955-1975	AGUGAUUUCAGAUAGACUAC	651	AGUAGUCUAUCUGAAAUCACUUU	1320
D-1650	1959-1979	AUUUCAGAUAGACUACUGAA	652	UUUCAGUAGUCUAUCUGAAAUUU	1321
D-1651; D-2148	1963-1983	CAGAUAGACUACUGAAAACC	653	AGGUUUUCAGUAGUCUAUCUGUU	1322
D-1652	1967-1987	UAGACUACUGAAAACCUUUA	654	UUAAAGGUUUUCAGUAGUCUAUU	1323
D-1653	1968-1988	AGACUACUGAAAACCUUUA	655	UUUAAAGGUUUUCAGUAGUCUUU	1324
D-1654; D-2114	1996-2016	AAGGAAAGCAUAGUCAGUU	656	AAACUGACAUAGCUUUCCUUU	1325
D-1655; D-2115; D-2377; D-2381	1997-2017	AGGAAAGCAUAGUCAGUUG	657	ACAACUGACAUAGCUUUCCUUU	1326

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D-1656; D-2117	1998-2018	GGAAAGCAUAUGUCAGUUGU	658	AACAACUGACAUAUGCUUUCCUU	1327
D-1657; D-2104	2000-2020	AAAGCAUAUGUCAGUUGUUU	659	UAAACAACUGACAUAUGCUUUUU	1328
D-1658	2001-2021	AAGCAUAUGUCAGUUGUUUA	660	UUAAACAACUGACAUAUGCUUUU	1329
D-1659	2002-2022	AGCAUAUGUCAGUUGUUUAA	661	UUUAAACAACUGACAUAUGCUUU	1330
D-1660	2019-2039	UAAAACCCAAUAUCUAAUUU	662	AAAAAUAGAUUUGGGUUUUUU	1331
D-1661	2022-2042	AACCCAAUAUCUAAUUUUUA	663	UUAAAAAUAGAUUUGGGUUUU	1332
D-1662; D-2105	2039-2059	UUAACUGAUUGUAUAACUCU	664	UAGAGUUUAACAAUCAGUAAUU	1333
D-1663; D-2106	2040-2060	UAACUGAUUGUAUAACUCUA	665	UUAGAGUUUAACAAUCAGUAAU	1334
D-1664; D-2153	2042-2062	ACUGAUUGUAUAACUCUAAG	666	UCUUAGAGUUUAACAAUCAGUUU	1335
D-1665	2043-2063	CUGAUUGUAUAACUCUAAGA	667	AUCUUAGAGUUUAACAAUCAGUU	1336
D-1666	2045-2065	GAUUGUAUAACUCUAAGAUC	668	AGAUCUUAGAGUUUAACAAUCUU	1337
D-1667; D-2118; D-2378; D-2382	2086-2106	GCCAUUUUGUCCUUUGAUUA	669	AUAAUCAAGGACAAAUGGCUU	1338
D-1668	2093-2113	UGUCCUUUGAUUAUUAUUGGG	670	UCCCAUAUAUAUCAAAGGACAUU	1339
D-2179	682-704	CCAGUGGAUAACCAGCUUCC	46	AGGAAGCUGGUUAUCCACUGGUG	2914
D-2192	684-704	CCAGUGGAUAACCAGCUUCC	46	AGGAAGCUGGUUAUCCACUGG	2922
D-2177	1092-1114	CAGAACGAAAGUUAUAUGGA	98	UUCCAUAUAACUUUCGUUCUGUG	2912
D-2190	1094-1114	CAGAACGAAAGUUAUAUGGA	98	UUCCAUAUAACUUUCGUUCUG	2920
D-2462	1092-1114	CAGAACGAAAGUUAUAUGGA	98	UUCCAUAUAACUUUCGUUCUGAA	2992
D-2483	768-788	AAUAGCAGACUUGUCCGAC	101	AGUCGGAACAAGUCUGCUAUU	3003
D-2181	794-816	CAGAUUGCUUACUCAGACAC	115	AGUGUCUGAGUAAGCAAUCUGUG	2916
D-2194	796-816	CAGAUUGCUUACUCAGACAC	115	AGUGUCUGAGUAAGCAAUCUG	2924
D-2175	892-914	CUUCAGGCCCAUAUUGUAA	142	AUUACAUAUUGGGCCUGAAGUG	2910
D-2188	894-914	CUUCAGGCCCAUAUUGUAA	142	AUUACAUAUUGGGCCUGAAG	2918
D-2223	1110-1130	UGGAAAAUACCACUCUUUG	152	ACAAAGAGUGGUGAUUUUCCA	2937
D-2464	1108-1130	UGGAAAAUACCACUCUUUG	152	ACAAAGAGUGGUGAUUUUCCAUA	2994
D-2226	1255-1275	GACAACACUUGAAGCAUGGU	168	AACCAUGCUUCAAGUGUUGUC	2940
D-2488	1346-1366	GUGUCUCAAUGCUUCAUGU	175	AACAUUGAAGCAUUGAGACAC	3008
D-2219	1350-1370	CUCAAUGCUUCAUUGUCCCA	178	AUGGGACAUUGAAGCAUUGAG	2933
D-2176	1350-1372	CAAUGCUUCAUUGUCCAGU	179	AACUGGGACAUUGAAGCAUUGUG	2911
D-2182; D-2389; D-2391; D-2401; D-2402; D-2403	1350-1372	CAAUGCUUCAUUGUCCAGU	179	AACUGGGACAUUGAAGCAUUGAG	2917
D-2189; D-2384; D-2385;	1352-1372	CAAUGCUUCAUUGUCCAGU	179	AACUGGGACAUUGAAGCAUUG	2919

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D-2399					
D-2221	1355-1375	UGCUCUCAAUGUCCCAGUGCA	181	UUGCACUGGGACAUUGAAGCA	2935
D-2225	1438-1458	ACAGGAUUCUGAAAACUCCC	186	AGGGAGUUUUCAGAAUCCUGU	2939
D-2222	1794-1814	UCAGACAGCAUUGGAUUUCC	215	AGGAAAUCCAAUGCUGUCUGA	2936
D-2224	1796-1816	AGACAGCAUUGGAUUUCCUA	217	UUAGGAAAUCCAAUGCUGUCU	2938
D-2220	2014-2034	UUGUUUAAAACCCAUAUCU	245	UAGAUUUUGGGUUUUAAACAA	2934
D-2461	2012-2034	UUGUUUAAAACCCAUAUCU	245	UAGAUUUUGGGUUUUAAACAACU	2991
D-2180	2055-2077	CUAAGAUCUGAUGAAGUAUA	247	AUAUACUUCAUCAAGAUUUAGUG	2915
D-2193	2057-2077	CUAAGAUCUGAUGAAGUAUA	247	AUAUACUUCAUCAAGAUUUAG	2923
D-2463	2055-2077	CUAAGAUCUGAUGAAGUAUA	247	AUAUACUUCAUCAAGAUUUAGAG	2993
D-2472	2057-2077	AAGAUCUGAUGAAGUAUAUU	249	AUAUACUUCAUCAAGAUUUAG	2923
D-2178	2109-2131	GGAAGUUGACUAAACUUGAA	258	UUUCAAGUUUAGUCAACUCCUG	2913
D-2191	2111-2131	GGAAGUUGACUAAACUUGAA	258	UUUCAAGUUUAGUCAACUCC	2921
D-2486	2082-2102	UAUUGCCAUUUUGUCCUUUG	268	UCAAGGACAAAUGGCAUA	3006
D-2109	2113-2133	AAGUUGACUAAACUUGAAAA	270	UUUUUCAAGUUUAGUCAACUUUU	2906
D-2485	1253-1273	AUGACAACACUUGAAGCAUG	301	ACAUGCUUCAAGUGUUGUCAU	3005
D-2254	985-1005	GUGAUGGCUUGUCCAGAUG	369	ACAUCUGGAACAAGCCAUCAC	2952
D-2437	1211-1231	AUGUCCUGGAAUAUAGAUG	387	ACAUCUAAUAUCCAGGACAU	2982
D-2255	1212-1232	UGUCCUGGAAUAUAGAUGC	388	AGCAUCUAAUAUCCAGGACA	2953
D-2256	1213-1233	GUCCUGGAAUAUAGAUGCC	389	AGGCAUCUAAUAUCCAGGAC	2954
D-2258	1214-1234	UCCUGGAAUAUAGAUGCCU	390	AAGGCAUCUAAUAUCCAGGA	2956
D-2241; D-2482	1215-1233	CCUGGAAUAUAGAUGCCUU	391	AGGCAUCUAAUAUCCAGGUU	2949
D-2243	1216-1234	CUGGAAUAUAGAUGCCUUU	392	AAGGCAUCUAAUAUCCAGUU	2951
D-2466	1939-1959	AGAAGAAAAGUGAUUCAGUG	398	UCACUGAAUCACUUUUCUUCU	2996
D-2469	1937-1959	AGAAGAAAAGUGAUUCAGUG	398	UCACUGAAUCACUUUUCUUCUCC	2999
D-2487	2050-2070	UAUAACUCUAGAUCUGAUG	405	UCAUCAGAUCUUGAGUUUAUA	3007
D-2465	2052-2072	UAACUCUAGAUCUGAUGAA	407	AUUAUCAGAUCUUGAGUUUA	2995
D-2468	2050-2072	UAACUCUAGAUCUGAUGAA	407	AUUAUCAGAUCUUGAGUUUAUA	2998
D-2257	2054-2074	ACUCUAAGAUCUGAUGAAGU	409	UACUUAUCAGAUCUUGAGU	2955
D-2431	1219-1239	GAAUAUAGAUGCCUUUUAA	527	UUUAAAAGGCAUCUAAUAUUC	2976
D-2436	1227-1247	GAUGCCUUUUAAAAUUGUUC	528	AGAACAUUUUUAAAAGGCAUC	2981
D-2430	1314-1334	GAUUUUCACAUUUUUCGUCU	535	AAGACGAAAAAUGUGAAAAUC	2975
D-2467	1312-1334	GAUUUUCACAUUUUUCGUCU	535	AAGACGAAAAAUGUGAAAAUCAC	2997
D-2434	1385-1405	AAAUUAAGUCUCAAUAACUU	557	UAAGUUAUUGAGACUAUAUUU	2979
D-2484	1455-1475	CCCCGUUUAAACUGAUUAUGG	583	UCCAUAUACAGUUAACGGGG	3004
D-2435	1506-1526	UACCAAGAGCGCAGACUUGC	597	UGCAAGUCUGCGCUCUUGGUA	2980
D-2480	1504-1526	UACCAAGAGCGCAGACUUGC	597	UGCAAGUCUGCGCUCUUGGUAGA	3002
D-2432	1997-2017	AGGAAAGCAUAUGUCAGUUG	657	ACAACUGACAUAGCUUUCCU	2977
D-2433	2086-2106	GCCAUUUUGUCCUUUGAUUA	669	AUAAUCAAGGACAAAUGGC	2978
D-2158; D-2387; D-2390; D-2400	1354-1372	AUGCUUCAUGUCCCAGUUU	2804	AACUGGGACAUUGAAGCAUUU	2907
D-2386; D-2392	1352-1372	AUGCUUCAUGUCCCAGUUU	2804	AACUGGGACAUUGAAGCAUUG	2919

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D-2159	1096-1114	GAACGAAAGUUAUAUGGAAU	2805	UUCCAUAUAACUUUCGUUCUU	2908
D-2479	1094-1114	GAACGAAAGUUAUAUGGAAU	2805	UUCCAUAUAACUUUCGUUCUG	2920
D-2160	798-816	GAUUGCUUACUCAGACACUU	2806	AGUGUCUGAGUAAGCAAUCUU	2909
D-2195	1352-1370	CAAUGCUUCAAUGUCCCAUU	2807	AUGGGACAUUGAAGCAUUGUU	2925
D-2196	2016-2034	GUUUAAAACCCAAUAUCUAAU	2808	UAGAUUUUGGGUUUUAAACUU	2926
D-2197	1357-1375	CUUCAAUGUCCAGUGCAAU	2809	UUGCACUGGGACAUUGAAGUU	2927
D-2198	1796-1814	AGACAGCAUUGGAUUUCCUU	2810	AGGAAAUCCAAUGCUGUCUUU	2928
D-2199	1112-1130	GAAAAUACCCACUCUUUGUU	2811	ACAAAGAGUGGUGAUUUUCUU	2929
D-2475	1110-1130	GAAAAUACCCACUCUUUGUU	2811	ACAAAGAGUGGUGAUUUUCCA	2937
D-2200	1798-1816	ACAGCAUUGGAUUUCCUAAU	2812	UUAGGAAAUCCAAUGCUGUUU	2930
D-2201	1440-1458	AGGAUUCUGAAAACUCCUU	2813	AGGGAGUUUUCAGAAUCCUUU	2931
D-2202	1257-1275	CAACACUUGAAGCAUGGUUU	2814	AACCAUGCUUCAAGUGUUGUU	2932
D-2233	2014-2034	CUGUUUAAAACCCAAUAUCU	2815	UAGAUUUUGGGUUUUAAACAGUU	2941
D-2234	1355-1375	CGCUUCAAUGUCCAGUGCA	2816	UUGCACUGGGACAUUGAAGCGUU	2942
D-2235	1794-1814	CCAGACAGCAUUGGAUUUCC	2817	AGGAAAUCCAAUGCUGUCUGGUU	2943
D-2236	1110-1130	CGGAAAAUACCCACUCUUUG	2818	ACAAAGAGUGGUGAUUUUCCGUU	2944
D-2237	1796-1816	GGACAGCAUUGGAUUUCCUA	2819	UUAGGAAAUCCAAUGCUGUCCUU	2945
D-2238	1438-1458	GCAGGAUUCUGAAAACUCCC	2820	AGGGAGUUUUCAGAAUCCUGCUU	2946
D-2239	987-1005	GAUGGCUUGUCCAGAUUUU	2821	ACAUCUGGAACAAGCCAUCUU	2947
D-2240	1214-1232	UCCUGGAAUAUUAGAUGCUU	2822	AGCAUCUAAUAUCCAGGAUU	2948
D-2242	2056-2074	UCUAAGAUCUGAUGAAGUAU	2823	UACUUCAUCAGAUUUAGAUU	2950
D-2259	1214-1234	CCCUGGAAUAUUAGAUGCCU	2824	AAGGCAUCUAAUAUCCAGGGUU	2957
D-2260; D-2454; D-2455; D-2456	2054-2074	GCUCUAAGAUCUGAUGAAGU	2825	UACUUCAUCAGAUUUAGAGCUU	2958
D-2261	1212-1232	CGUCCUGGAAUAUUAGAUGC	2826	AGCAUCUAAUAUCCAGGACGUU	2959
D-2262	2052-2072	CAACUCUAAGAUCUGAUGAA	2827	AUUCAUCAGAUUUAGAGUUGUU	2960
D-2263	1939-1959	GGAAGAAAAGUGAUUCAGUG	2828	UCACUGAAUCACUUUUUCUCCUU	2961
D-2268	1213-1233	GUCCAGGAAUAUUAGAUGCC	2829	AGGCAUCUAAUAUCCUGGACUU	2962
D-2269	1213-1233	GUGCUGGAAUAUUAGAUGCC	2830	AGGCAUCUAAUAUCCAGCACUU	2963
D-2270	1214-1234	UCCUCGAAUAUUAGAUGCCU	2831	AAGGCAUCUAAUAUUCGAGGAUU	2964
D-2271	1214-1234	UCGUGGAAUAUUAGAUGCCU	2832	AAGGCAUCUAAUAUCCACGAUU	2965
D-2272	2054-2074	ACACUAAGAUCUGAUGAAGU	2833	UACUUCAUCAGAUUUAGUGUUU	2966
D-2273	2054-2074	AGUCUAAGAUCUGAUGAAGU	2834	UACUUCAUCAGAUUUAGACUUU	2967
D-2274	1796-1816	AGUCAGCAUUGGAUUUCCUA	2835	UUAGGAAAUCCAAUGCUGACUUU	2968
D-2275	1796-1816	ACACAGCAUUGGAUUUCCUA	2836	UUAGGAAAUCCAAUGCUGUGUUU	2969
D-2359; D-2364; D-2369	986-1006	UGAUGGCUUGUCCAGAUUC	2837	UGCAUCUGGAACAAGCCAUAUU	2970
D-2360; D-2365; D-2370	987-1007	GAUGGCUUGUCCAGAUUGCA	2838	AUGCAUCUGGAACAAGCCAUCUU	2971
D-2361; D-2366; D-2371	1793-1813	CUCAGACAGCAUUGGAUUUC	2839	AGAAAUCCAAUGCUGUCUGAGUU	2972

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2362; D-2367; D-2372	2085-2105	UGCCAUUUUGUCCUUUGAUU	2840	UAAUCAAGGACAAAAUGGCAUU	2973
D-2363 D-2368 D-2373	2087-2107	CCAUUUUGUCCUUUGAUU	2841	UAUAAUCAAGGACAAAAUGGUU	2974
D-2446	1316-1334	UUUUCACAUUUUUCGUCUUU	2842	AAGACGAAAAAUGUGAAAAUU	2983
D-2476	1314-1334	UUUUCACAUUUUUCGUCUUU	2842	AAGACGAAAAAUGUGAAAAUC	2975
D-2473	2054-2072	ACUCUAAGAUCUGAUGAAUU	2843	AUUCAUCAGAUUUAGAGUUU	3000
D-2477	2052-2072	ACUCUAAGAUCUGAUGAAUU	2843	AUUCAUCAGAUUUAGAGUUA	2995
D-2474	1941-1959	AAGAAAAGUGAUUCAGUGAU	2844	UCACUGAAUCACUUUUUUUU	3001
D-2478	1939-1959	AAGAAAAGUGAUUCAGUGAU	2844	UCACUGAAUCACUUUUUUUU	2996
D-2447	1221-1239	AUAUUAGAUGCCUUUUAAU	2845	UUUAAAAGGCAUCUAAUUAUU	2984
D-2448	1999-2017	GAAAGCAUAUGUCAGUUGUU	2846	ACAACUGACAUUGCUUUUUU	2985
D-2449	2088-2106	CAUUUUGUCCUUUGAUUAUU	2847	AUAAUCAAGGACAAAAUGUU	2986
D-2450	1387-1405	AUAUAGUCUCAAUACUUUU	2848	UAAGUUUUUGAGACUAAUUUU	2979
D-2451	1508-1526	CCAAGAGCGCAGACUUGCAU	2849	UGCAAGUCUGCGCUCUUGGUU	2987
D-2481	1506-1526	CCAAGAGCGCAGACUUGCAU	2849	UGCAAGUCUGCGCUCUUGGUA	2980
D-2452	1229-1247	UGCCUUUUAAAAUGUUCUU	2850	AGAACAUUUUAAAAAGGCAUU	2988
D-2453	1213-1231	GUCCUGGAAUAUAGAUGUU	2851	ACAUCUAAUAUUCAGGACUU	2989
D-2457	2056-2074	CCUAAGAUCUGAUGAAGUUA	2852	UACUUCAUCAGAUUUAGGUU	2990
D-2458; D-2459; D-2460	2056-2074	CCUAAGAUCUGAUGAAGUUA	2852	UACUUCAUCAGAUUUAGGUU	2990
D-2495	768-788	UAGCAGACUUGUUCGACUU	2853	AGUCGGAACAAGUCUGCUAUU	3003
D-2496	1455-1475	CCGUUUAAACUGAUUAUGGAU	2854	UCCAUAUACAGUUAACGGUU	3009
D-2497	1253-1273	GACAACACUUGAAGCAUGUU	2855	ACAUGCUUCAAGUGUUGUCUU	3010
D-2498	2082-2102	UUGCCAUUUUGUCCUUUGAU	2856	UCAAAGGACAAAAUGGCAUU	3011
D-2499	2050-2070	UAACUCUAGAUCUGAUGAU	2857	UCAUCAGAUUUAGAGUUAUU	3012
D-2500	1346-1366	GUCUCAUUGCUUCAAUGUUU	2858	AACAUUGAAGCAUUGAGACUU	3013
D-2514	985-1005	GUGAUGGCUUGUUCGGAUG	2859	ACAUCGGAACAAGCCAUCAC	3014
D-2515	985-1005	GUGAUGGCUUGUUGCAGAUG	2860	ACAUCUGCAACAAGCCAUCAC	3015
D-2516	1092-1114	CAGAACGAAAGUUAUGUGGA	2861	UCCACAUAAUUUUCGUUCUGAA	3016
D-2517	1092-1114	CAGAACGAAAGUUGUAUGGA	2862	UCCAUACAACUUUUCGUUCUGAA	3017
D-2518	1210-1230	UAUGUCCUGGAAUAUAAGAU	2863	AAUCUUAUAUUCAGGACAUUU	3018
D-2519	1210-1230	UAUGUCCUGGAAUGUUAGAU	2864	AAUCUAAUAUUCAGGACAUUU	3019
D-2520	1211-1231	AUGUCCUGGAAUAUUGGAUG	2865	ACAUCCAAUAUUCAGGACAUUU	3020
D-2521	1211-1231	AUGUCCUGGAAUAUAGAU	2866	ACAUCUAAUAUUCAGGACAUUU	3021
D-2522	1212-1232	UGUCCUGGAAUAUAAAUGC	2867	AGCAUUUAAUAUUCAGGACAUU	3022
D-2523	1212-1232	UGUCCUGGAAUAUAGAUGC	2868	AGCAUCUUAUAUUCAGGACAUU	3023
D-2524	1215-1233	CCUGGAAUAUAGGUGCCUU	2869	AGGCACCUAAUAUUCAGGUU	3024
D-2529	1215-1235	CCUGGAAUAUAGGUGCCUU	2869	AAAGGCACCUAAUAUUCAGGUU	3029
D-2525	1215-1233	CCUGGAAUAUUGGAUGCCUU	2870	AGGCAUCCAAUAUUCAGGUU	3025
D-2526	1214-1234	UCCUGGAAUAUAGAAGCCU	2871	AAGGCUUCUAAUAUUCAGGA	3026
D-2527	1214-1234	UCCUGGAAUAUAAAUGCCU	2872	AAGGCAUUUAAUAUUCAGGA	3027
D-2528	1215-1235	CCUGGAAUAUAGAUACCUU	2873	AAAGGUAUCUAAUAUUCAGGUU	3028

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D-2530	1216-1236	CUGGAUUAUAGAUGGCUUU	2874	AAAAGCCAUCUAAUUAUCCAGUU	3030
D-2531	1216-1236	CUGGAUUAUAGAAGCCUUU	2875	AAAAGGCUUCUAAUUAUCCAGUU	3031
D-2532	1219-1239	GAAUUAUAGAUGCCUUAUAA	2876	UUUAAUAGGCAUCUAAUUAUUCUU	3032
D-2533	1219-1239	GAAUUAUAGAUGCGUUUUAA	2877	UUUAAAACGCAUCUAAUUAUUCUU	3033
D-2534	1227-1247	GAUGCCUUUUAAAAAGUUC	2878	AGAACUUUUUUAAAAGGCAUCUU	3034
D-2535	1227-1247	GAUGCCUUUUAAAGAUGUUC	2879	AGAACAUCUUUUAAAAGGCAUCUU	3035
D-2536	1314-1334	GAUUUUCACAUUUUUGGUCU	2880	AAGACCAAAAAUGUGAAAAUCUU	3036
D-2537	1314-1334	GAUUUUCACAUUUAUCGUCU	2881	AAGACGAUAAAUGUGAAAAUCUU	3037
D-2538	1350-1370	CUCAAUGCUUCAAUGACCCA	2882	AUGGGUCAUUGAAGCAUUGAGUU	3038
D-2539	1350-1370	CUCAAUGCUUCAAAGUCCCA	2883	AUGGGACUUUGAAGCAUUGAGUU	3039
D-2540	1352-1372	CAAUGCUUCAUGUCGAGU	2884	AACUGCGACAUUGAAGCAUUG	3040
D-2541	1352-1372	CAAUGCUUCAUGACCCAGU	2885	AACUGGGUCAUUGAAGCAUUG	3041
D-2542	1385-1405	AAAUUAUGUCUCAAUGACUU	2886	UAAGUCAUUGAGACUAUUAUUUUU	3042
D-2543	1385-1405	AAAUUAUGUCUAGUAAACUU	2887	UAAGUUACUGAGACUAUUAUUUUU	3043
D-2544	1438-1458	GCAGGAUUCUGAAAAGUCCC	2888	AGGGACUUUUUCAGAAUCCUGCUU	3044
D-2545	1438-1458	GCAGGAUUCUGAAGACUCCC	2889	AGGGAGUCUUUCAGAAUCCUGCUU	3045
D-2546	1506-1526	UACCAAGAGCGCAGAGUUGC	2890	UGCAACUCUGCGCUCUUGGUUUU	3046
D-2547	1506-1526	UACCAAGAGCGCAAACUUGC	2891	UGCAAGUUUGCGCUCUUGGUUUU	3047
D-2548	1997-2017	AGGAAAGCAUUAUGUCGUUG	2892	ACAACCGACAUUAUGCUUUCCUUU	3048
D-2549	1997-2017	AGGAAAGCAUUAUGACGUUG	2893	ACAACUGUCAUUAUGCUUUCCUUU	3049
D-2550	2016-2034	GUUUAAAACCCAAAUCUUAU	2894	UAGAUUUUGGGUUUUAAACUU	3050
D-2551	2016-2034	GUUUAAAACCCGAUAUCUUAU	2895	UAGAUUAUCGGGUUUUAAACUU	3051
D-2552	2039-2059	UUAACUGAUUGUAUAGCUCU	2896	UAGAGCUAUACAACAGUUAUUU	3052
D-2553	2039-2059	UUAACUGAUUGUAAAACUCU	2897	UAGAGUUUUACAACAGUUAUUU	3053
D-2554	2052-2072	UAACUCUAGAUCUGGUGAA	2898	AUUCACCAGAUUUUAGAGUUA	3054
D-2555	2052-2072	UAACUCUAGAUCAGAUAGAA	2899	AUUCAUUCUGAUUUUAGAGUUA	3055
D-2556	2054-2074	ACUCUAAGAUCUGAUAAAGU	2900	UACUUUAUCAGAUUUUAGAGUUU	3056
D-2557	2054-2074	ACUCUAAGAUCUGGUGAAGU	2901	UACUUCACCAGAUUUUAGAGUUU	3057
D-2558	2082-2102	UAUUGCCAUUUUGUCGUUUG	2902	UCAAACGACAAAUGGCAUAUUU	3058
D-2559	2082-2102	UAUUGCCAUUUUGACCUUUG	2903	UCAAAGGUCAAAAUGGCAUAUUU	3059
D-2560	2086-2106	GCCAUUUUGUCCUUUAUUUA	2904	AUAAUUAAAAGGACAAAUGGCUU	3060
D-2561	2086-2106	GCCAUUUUGUCCUAUGAUUA	2905	AUAAUCAUAGGACAAAUGGCUU	3061

Table 2. Modified *mARC1* siRNA sequences

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1000	[GalNAc3]sgagcaaGfcAfCfUfAfuauggaaus{invAb}	1340	usUfsccauAfuaguGfcUfugcucsgsu	2072
D-1001	[GalNAc3]sagaaguUfcUfCfGfGfcaaaugaus{invAb}	1341	usCfsauuuGfccgaGfaAfcuucsgsu	2073
D-1002	[GalNAc3]sgagcaaGfcUfGfAfAfuauggaaus{invAb}	1342	usUfsccaaAfuucaGfcUfugcucsgsu	2074
D-1003	[GalNAc3]sagaaguUfcAfGfCfGfcuaauggaus{invAb}	1343	usCfsauuaGfcgcuGfaAfcuucsgsu	2075
D-1004	gsasaggaCfGfAfCfUfGfcucugaus{invAb}	1344	asAfsuCfaGfagcagCfGfUfccuucsu	2076
D-1005	asgsagcGfAfCfUfGfCfGfcuugaus{invAb}	1345	asCfsaAfuCfagcagCfGfUgucucsu	2077
D-1006	gsasagcGfAfCfUfGfCfGfcuugaus{invAb}	1346	asCfscAfaUfcagagCfGfGfcuucsu	2078
D-1007	ascsgcacUfGfCfUfGfGfcuugccs{invAb}	1347	asGfsgCfCfauagagCfGfGfcuucsu	2079
D-1008	csugscucUfGfAfUfGfGfcggaas{invAb}	1348	asUfscCfGfGfcgcauAfaGfagcagcu	2080

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Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1115	gsasuugcUfuAfCfUfCfagacaccas{invAb}	1455	asUfsgGfuGfucugaguAfaGfcaaususu	2187
D-1116	asusugcuUfaCfUfCfAfgacaccags{invAb}	1456	asCfsuGfgUfgucugagUfaAfgcaaususu	2188
D-1117	gscsuuacUfcAfGfAfCfaccagcccs{invAb}	1457	usGfsgGfcUfggugucuGfaGfuaagcsusu	2189
D-1118	ususacucAfgAfCfAfCfagcccaus{invAb}	1458	asAfsuGfgGfcugugucuGfuGfagaaususu	2190
D-1119	csgsgaucUfcAfCfUfCfaggcuas{invAb}	1459	asUfsaGfcCfuggaguuGfaGfaucgsusu	2191
D-1120	gsgsauucCfaAfCfUfCfaggcuags{invAb}	1460	usCfsuAfgCfaggaguuUfgAfgauccsusu	2192
D-1121	gsasucucAfaCfUfCfaggcuagags{invAb}	1461	asUfscUfaGfccuggagUfuGfagauccsusu	2193
D-1122	asuscucaAfcUfCfAfggcuagags{invAb}	1462	usCfsuGfuAfgccuggaGfuUfgagaususu	2194
D-1123	asasuccAfgGfCfUfAfgagaaags{invAb}	1463	usUfsuGfuUfcucugCfuGfgaguuusu	2195
D-1124	asgsaagaAfaGfUfUfAfaagcaaccs{invAb}	1464	usGfsgUfuGfucuuuacUfuUfcuucsusu	2196
D-1125	gsasagaaAfgUfUfAfaagcaaccas{invAb}	1465	usUfsgGfuUfgcuuuuacUfuUfcuucsusu	2197
D-1126	asasgaaaGfuUfAfaAfgcaaccaas{invAb}	1466	asUfsuGfgUfgcuuuuacUfuUfcuucsusu	2198
D-1127	asgsaaagUfuAfaAfaGfcaaccaacs{invAb}	1467	asGfsuUfgGfuugcuuuAfaGfuucsusu	2199
D-1128	gsasaaguUfaAfaAfaGfcaaccaacs{invAb}	1468	asAfsuUfuGfuugcuuuUfaAfcuucsusu	2200
D-1129	asasaguuAfaAfaAfaGfcaaccaacs{invAb}	1469	asAfsaGfuUfgguugcuUfuAfcuucsusu	2201
D-1130	asasguuaAfaGfCfAfaAfaaccaacs{invAb}	1470	usGfsaAfgUfgguugcuUfuUfaaccaacsusu	2202
D-1131	asgsuuuaAfgCfAfaAfaaccaacs{invAb}	1471	asUfsgAfaGfuugcuUfuUfaaccaacsusu	2203
D-1132	gsusuaaaGfcAfaAfaAfaaccaacs{invAb}	1472	asCfsuGfaAfguugcuUfuUfaaccaacsusu	2204
D-1133	asasagcaAfcCfAfaAfaAfaaccaacs{invAb}	1473	asGfsgCfcUfgaaguuGfuUfgcuucsusu	2205
D-1134	asgsaacCfaAfcUfUfCfaggcccas{invAb}	1474	usUfsgGfgCfcugaagUfgGfuugcsusu	2206
D-1135	csasaccaAfcUfUfCfAfggccaacs{invAb}	1475	usAfsuUfgGfgccugaaGfuUfgguugsusu	2207
D-1136	asascaaCfuUfCfAfaGfccaacs{invAb}	1476	asUfsaUfuGfgccugaAfgUfgguugsusu	2208
D-1137	cscsaacuUfcAfaGfCfccaacs{invAb}	1477	asAfsaUfaUfggcccGfaAfguugsusu	2209
D-1138	csasacuUfcAfaGfCfccaacs{invAb}	1478	asCfsaAfuAfuugggcUfgAfguugsusu	2210
D-1139	ascsuuaGfgCfCfAfaAfaAfaaccaacs{invAb}	1479	usUfsaCfaAfaAfaAfaAfaaccaacs{invAb}	2211
D-1140	csusucagGfcCfCfAfaAfaAfaaccaacs{invAb}	1480	asUfsuAfaAfaAfaAfaAfaaccaacs{invAb}	2212
D-1141	ususcaggCfcCfAfaAfaAfaAfaaccaacs{invAb}	1481	asAfsaUfaAfaAfaAfaAfaaccaacs{invAb}	2213
D-1142	uscsaggCfcCfAfaAfaAfaAfaaccaacs{invAb}	1482	asAfsaUfuAfaAfaAfaAfaaccaacs{invAb}	2214
D-1143	asgsagccAfaAfaAfaAfaAfaaccaacs{invAb}	1483	usGfsaAfaAfaAfaAfaAfaaccaacs{invAb}	2215
D-1144	gsgsccaAfaAfaAfaAfaAfaaccaacs{invAb}	1484	asUfsgAfaAfaAfaAfaAfaaccaacs{invAb}	2216
D-1145	gsasugagCfuUfCfUfUfAfaAfaaccaacs{invAb}	1485	asUfscAfcAfaAfaAfaAfaaccaacs{invAb}	2217
D-1146	asusagagCfuUfCfUfUfAfaAfaaccaacs{invAb}	1486	asGfsuAfaAfaAfaAfaAfaaccaacs{invAb}	2218
D-1147	asusaaggAfaAfaAfaAfaAfaaccaacs{invAb}	1487	asAfsaAfaAfaAfaAfaAfaaccaacs{invAb}	2219
D-1148	usasuggaAfaAfaAfaAfaAfaaccaacs{invAb}	1488	asAfsaGfaAfaAfaAfaAfaaccaacs{invAb}	2220
D-1149	asusggaaAfaAfaAfaAfaAfaaccaacs{invAb}	1489	asAfsaAfaAfaAfaAfaAfaaccaacs{invAb}	2221
D-1150	usgsaaaAfuCfAfaAfaAfaAfaaccaacs{invAb}	1490	asCfsaAfaAfaAfaAfaAfaaccaacs{invAb}	2222
D-1151	csusggaaAfaCfCfAfaAfaAfaaccaacs{invAb}	1491	asAfsuGfgUfcccuggUfuUfuccagsusu	2223
D-1152	gsgsaaaCfcCfAfaAfaAfaAfaaccaacs{invAb}	1492	usUfsgAfuGfguccugGfuUfuuccsusu	2224
D-1153	gsasaaacCfcAfaAfaAfaAfaaccaacs{invAb}	1493	usUfsuGfaUfgguccuGfgGfuuuucsusu	2225
D-1154	cscsaggGfaCfCfAfaAfaAfaaccaacs{invAb}	1494	asCfscAfcUfuugaggUfcCfuccggsusu	2226
D-1155	cscsaggGfaCfCfAfaAfaAfaaccaacs{invAb}	1495	usCfscCfaCfuugaugGfuCfuccggsusu	2227
D-1156	gsgsgaccAfuCfAfaAfaAfaAfaaccaacs{invAb}	1496	asUfscUfcCfaccuuUfuGfgucccsusu	2228
D-1157	gsgsgagaCfcCfUfGfUfGfuccgcs{invAb}	1497	asGfscAfgGfuacacagGfgUfucccsusu	2229
D-1158	gsusaccuGfcUfGfGfGfaccgaaas{invAb}	1498	asAfsuUfaCfuggcccaGfcAfgguacsusu	2230
D-1159	usgscuggGfcCfAfaAfaAfaAfaaccaacs{invAb}	1499	asUfsuGfcAfaAfaAfaAfaaccaacs{invAb}	2231
D-1160	asasauguUfcUfCfAfaAfaAfaaccaacs{invAb}	1500	usUfsgUfcAfaAfaAfaAfaaccaacs{invAb}	2232
D-1161	asasuguUfcUfCfAfaAfaAfaaccaacs{invAb}	1501	asUfsuGfuCfaAfaAfaAfaaccaacs{invAb}	2233
D-1162	asasaugAfaCfAfaAfaAfaAfaaccaacs{invAb}	1502	usGfscUfuCfaaguguGfuCfaAfaAfaaccaacs{invAb}	2234
D-1163	asasaugaCfaAfaAfaAfaAfaaccaacs{invAb}	1503	asUfsgCfuUfcaaguguUfgUfcauuususu	2235
D-1164	asasugacAfaCfAfaAfaAfaAfaaccaacs{invAb}	1504	asAfsuGfcUfcaaguguUfuGfucauuususu	2236
D-1165	usgsacaaCfaCfUfUfGfagcauggs{invAb}	1505	asCfscAfuGfcuugaagUfgUfugucasusu	2237
D-1166	gsascaacAfcUfUfGfAfaAfaAfaaccaacs{invAb}	1506	asAfsaCfaUfgcuucaGfuGfuugcsusu	2238
D-1167	ascsaacaCfuUfGfAfaAfaAfaaccaacs{invAb}	1507	asCfsaCfaAfgcuucaAfgUfguugsusu	2239

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Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1221	gsasuccuUfgCfCfAfUfuucccucas{invAb}	1561	asUfsgAfgGfggaauaggCfaAfggaucsusu	2293
D-1222	cscsuugcCfaUfUfCfCfccucagcus{invAb}	1562	usAfsGfCfuGfaggggaaUfgGfcaagsusu	2294
D-1223	csusugccAfuUfCfCfCfCucagcuas{invAb}	1563	usUfsaGfcUfgaggggaAfuGfcaagsusu	2295
D-1224	gscscuuCfcCfCfUfCfagcuuagcs{invAb}	1564	usCfsaUfuAfgcugaggGfgAfauggcsusu	2296
D-1225	csasuuccCfUfCfAfGfCuaaagacs{invAb}	1565	asGfsuCfaUfuagcugaGfgGfgaugsusu	2297
D-1226	ascsggagUfgCfUfCfCfuucccags{invAb}	1566	asCfsuGfgAfgaaggagCfaCfuccgususu	2298
D-1227	gsasaaacCfuUfUfAfAfagggggaas{invAb}	1567	usUfsuCfcCfccuuuaaAfgGfuuuucsusu	2299
D-1228	csasuuaugUfCfAfGfUfUfguuuaaas{invAb}	1568	asUfsuUfuAfaacaacuGfaCfaaugsusu	2300
D-1229	uscsguuGfuUfUfAfAfAfaaccau{invAb}	1569	usAfsuUfgGfguuuaaAfcAfacugususu	2301
D-1230	asgsuuguUfuUfAfAfAfcccauau{invAb}	1570	asAfsuAfuUfggguuuuAfaAfaacususu	2302
D-1231	asasggacGfcAfCfUfGfCucugauus{invAb}	1571	asAfsaUfcAfgagcaguGfcGfuccuususu	2303
D-1232	csasagccCfcGfGfCfuagcuuuus{invAb}	1572	asAfsaAfaGfcuagcccGfgGfgcuugususu	2304
D-1233	cscscggGfCfUfAfGfCfuuuuagaa{invAb}	1573	asUfsuUfcAfaaagcuAfcCfcggggsusu	2305
D-1234	gsascugaGfgUfGfAfCfCfuucaggas{invAb}	1574	usUfscCfuGfaaggucaCfcUfcagucsusu	2306
D-1235	usasuuuaUfuUfUfCfCfaaagauus{invAb}	1575	asAfsGfAfuCfuagggaaCfuUfaaauasusu	2307
D-1236	ususuuccAfuAfGfAfUfcuggauc{invAb}	1576	asAfsGfAfuCfcagaucaAfuGfgaaaasusu	2308
D-1237	ususcucaGfaCfAfGfCfaauggauus{invAb}	1577	asAfsaUfcCfaaagcugCfuUfgagaasusu	2309
D-1238	ususuccuAfaAfGfGfUfgcucaggas{invAb}	1578	asUfscCfuGfagcaccuUfuAfggaaasusu	2310
D-1239	cscsuggaUfcCfUfUfGfccauuccs{invAb}	1579	asGfsgGfaAfggcaagGfaUfccaggususu	2311
D-1240	uscscuugCfcAfUfUfCfccucagcs{invAb}	1580	asGfscUfgAfggggaaUfgCfaaggasusu	2312
D-1241	cscsaauccCfcUfUfCfAfgcuuag{invAb}	1581	asUfscAfuUfagcugagGfgGfaaugsusu	2313
D-1242	asasaaccUfuUfAfAfAfagggggaas{invAb}	1582	usUfsuUfcCfccuuuaAfaGfguuuususu	2314
D-1243	usuguuuAfaAfAfCfCfaaauauc{invAb}	1583	usAfsGfAfuAfuuggguuUfuAfaaasusu	2315
D-1244	csuscuuaGfaUfCfUfGfauagaauas{invAb}	1584	asUfsaCfuUfcaucagaUfcUfuagagsusu	2316
D-1245	csusaagaUfcUfGfAfUfGfaagauuas{invAb}	1585	asUfsaUfaCfuauucaGfaUfcuagususu	2317
D-1246	usasagauCfuGfAfUfGfagauauas{invAb}	1586	asAfsuAfuAfcuucacAfgAfcuuaasusu	2318
D-1247	asasgaucUfgAfUfGfAfgauauuas{invAb}	1587	asAfsaUfaUfauucaCfaGfaucucususu	2319
D-1248	gsasugaaGfuAfUfAfUfuuuuuuas{invAb}	1588	asAfsaUfaAfaaaauAfcUfucaucususu	2320
D-1249	ususuuauUfgCfCfAfUfuuuuguccs{invAb}	1589	asAfsGfAfaaaauaggCfaAfaaaasusu	2321
D-1250	ususuuauGfcAfUfUfuuguccuus{invAb}	1590	asAfsaGfgAfaaaagGfcAfaaaasusu	2322
D-1251	ususauugCfcAfUfUfUfuguccuus{invAb}	1591	asAfsaAfgGfacaauaGfgCfaaauasusu	2323
D-1252	asusugccAfuUfUfUfGfuccuuugas{invAb}	1592	asUfscAfaAfggacaaAfuGfgcaasusu	2324
D-1253	asusauugGfgAfAfGfUfugacuaaas{invAb}	1593	asUfsuUfaGfucaacuUfcCfaaauasusu	2325
D-1254	usgsaggaaGfuUfGfAfCfaaauugs{invAb}	1594	usCfsaAfgUfuuaagcaAfcUfuccasusu	2326
D-1255	gsgsgaagUfuGfAfCfUfaaauugas{invAb}	1595	usUfscAfaGfuuuagucAfaCfuucccsusu	2327
D-1256	gsgsaaguUfgAfCfUfAfaauugaas{invAb}	1596	usUfsuCfaAfguuuaguCfaAfcuuccsusu	2328
D-1257	ascugugAfaUfAfAfAfuggaagcus{invAb}	1597	usAfsGfCfuUfccuuuaUfuCfagagususu	2329
D-1258	usgsaauaAfaUfGfGfAfgcuuac{invAb}	1598	asAfsaGfuAfgcuucaUfuUfaucuasusu	2330
D-1259	usasaaugGfaAfGfCfUfacuuaagcs{invAb}	1599	asGfsuCfaAfaagucUfcCfaauuasusu	2331
D-1260	asasauggAfaGfCfUfAfcuuuagcus{invAb}	1600	usAfsGfUfcAfaagugCfuUfcfaauuasusu	2332
D-1261	asasgcuAfuUfUfGfAfcuaguuus{invAb}	1601	usGfsaAfaCfuagucuaAfgUfagcuususu	2333
D-1262	asgscuacUfuUfGfAfCfuaguuucas{invAb}	1602	asUfsgAfaAfcuagucAfaGfuagcususu	2334
D-1263	gsgsagugCfuCfCfUfUfuccaguu{invAb}	1603	asAfsaCfuGfgagaaggAfgCfaccususu	2335
D-1264	asascuuUfaAfAfGfGfggaaaggs{invAb}	1604	asCfsuUfuUfccccuuUfaAfaagguususu	2336
D-1265	ascscuuUfaAfAfGfGfggaaaggs{invAb}	1605	usCfscUfuUfuccccuuUfuAfaagguususu	2337
D-1266	usasuuugCfaUfUfUfUfguccuuus{invAb}	1606	usCfsaAfaGfgacaaaUfgGfcaauasusu	2338
D-1267	gsasaguuGfaCfUfAfAfacuugaas{invAb}	1607	usUfsuUfcAfaaguuagUfcAfacuucsusu	2339
D-1268	asasguugAfcUfAfAfAfcuugaaas{invAb}	1608	usUfsuUfuCfaaguuuaGfuCfaaauasusu	2340
D-1269	gscsuacuUfuGfAfCfUfaguuucags{invAb}	1609	usCfsuGfaAfaagucAfaAfguagcsusu	2341
D-1270	usgsacucUfcAfGfUfGfagccuacs{invAb}	1610	usGfsuAfgGfugcacUfaGfagucasusu	2342
D-1271	ascsgcccAfcCfAfCfAfaaagcag{invAb}	1611	asAfsCfUfgCfaauuugGfuGfggcgususu	2343
D-1272	cscscaguGfgAfUfAfAfcagcuucs{invAb}	1612	asGfsaAfgCfugguuauCfcAfcugggususu	2344
D-1273	csasucaaAfuAfGfCfAfgacuuguus{invAb}	1613	asAfsaCfaAfgucugcuAfuUfugaugsusu	2345

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1274	uscasaaAfgCfAfGfAfcuuguuccs(invAb)	1614	asGfsgAfaCfaagucugCfuAfuuuugasusu	2346
D-1275	csasggcuAfgAfGfAfAfgaaaguuas(invAb)	1615	usUfsaAfcUfuuccuucCfuAfgccugsusu	2347
D-1276	asgsdcuaGfaGfAfGfAfaaaguuas(invAb)	1616	usUfsuAfaCfuuuuucUfcUfagccususu	2348
D-1277	ascscacUfuCfAfGfGfccccauaus(invAb)	1617	asAfsuAfuUfgggccugAfaGfuuggususu	2349
D-1278	gsasgcuCfuUfAfUfUfggugacgus(invAb)	1618	asAfsCfuCfaccaaAfaGfagcucsusu	2350
D-1279	csusucuuAfuUfGfGfUfgacguggas(invAb)	1619	usUfscCfaCfugacaccaAfuAfaagaasusu	2351
D-1280	uscuuuuUfgGfUfGfAfcguggaacs(invAb)	1620	asGfsuUfcCfagucacCfaAfaagagasusu	2352
D-1281	asusugguGfaCfGfUfGfagacugaas(invAb)	1621	usUfsuCfaGfuuccacgUfcAfaaacsusu	2353
D-1282	csusuguuCfcAfGfAfUfGcauuuuaas(invAb)	1622	usUfsaAfaAfugcauucGfGfacaasusu	2354
D-1283	usgsuuccAfgAfuUfGfCfauuuuuacs(invAb)	1623	asGfsuUfaAfaauucauCfuGfgaacasusu	2355
D-1284	csusggaaAfcAfCfUfGfagaguuas(invAb)	1624	asUfsaAfcUfuccagugGfuUfuccagsusu	2356
D-1285	usgsaaaCfaCfUfGfAfagaguuuas(invAb)	1625	asAfsuAfaCfuuuacUfgUfuuccasusu	2357
D-1286	asasagauUfaUfCfGfCfcagugugas(invAb)	1626	asUfscAfcAfcugcgAfaAfcucuususu	2358
D-1287	asgsaguuAfcCfGfCfcagugagacs(invAb)	1627	asGfsuCfaCfagucggCfuAfaucucusus	2359
D-1288	gsusuuuuUfgGfAfAfaucaccacs(invAb)	1628	asGfsuGfgUfgauuuuucCfaUfaaacsusu	2360
D-1289	gsusgcuGfaAfaAfCfcaggagacs(invAb)	1629	asGfsuCfcCfuggguuUfcCfagcacsusu	2361
D-1290	usgsucggAfaAfaCfCfcaggagacs(invAb)	1630	usGfsgUfcCfcuggguuUfcCfcagcasusu	2362
D-1291	gsusuggaAfaAfcCfCfcaggagaccs(invAb)	1631	asUfsgGfuCfcuggguuUfuUfccagcsusu	2363
D-1292	asasaaccCfaGfGfGfAfcacuaaas(invAb)	1632	asUfsuUfgAfguguccUfgGfuuuuususu	2364
D-1293	asasaccAfgGfGfAfcacuaaags(invAb)	1633	asCfsuUfuGfauguccCfuGfguuususu	2365
D-1294	asascccaGfgGfAfCfCfaucuaaags(invAb)	1634	asAfsCfuUfgauggucCfcUfgggususu	2366
D-1295	ascsccagGfgAfcCfCfAfucaagugs(invAb)	1635	asCfsaCfuUfugagucCfcCfugggususu	2367
D-1296	gsusgggaGfaCfcCfUfugugaccus(invAb)	1636	asAfsGfuAfcacaggUfcUfccacsusu	2368
D-1297	gsusgggCfcAfcUfUfAfauggaacs(invAb)	1637	asGfsuUfcCfcauuucGfgCfccagcsusu	2369
D-1298	csasaaaaUfgAfcAfcAfcacuaaas(invAb)	1638	asUfsuCfaAfgugugCfuUfuuuugsusu	2370
D-1299	asusgacaAfcAfcUfUfAfaagcaugs(invAb)	1639	asCfsaUfgCfucaaguGfuUfgucaususu	2371
D-1300	ascsuugaAfgCfAfuUfguguuuacs(invAb)	1640	asUfsgAfaAfcacagCfuUfcaagususu	2372
D-1301	asasauuuGfuGfAfUfUfuacuuuacs(invAb)	1641	asAfsaUfgUfgaaaaucCfaAfaauususu	2373
D-1302	asasugcuUfcAfaUfUfguccagugs(invAb)	1642	asCfsaCfuGfggacauuGfaAfgcauususu	2374
D-1303	asasaugaCfaAfcAfcAfcaggaucuu(invAb)	1643	asAfsGfaUfcugucUfgUfcauuususu	2375
D-1304	ususaugAfaUfAfGfUfucuuucucs(invAb)	1644	asGfsaGfaAfaagacuUfuCfcauuaasusu	2376
D-1305	usasuggaAfuAfcGfUfUfucuuucucs(invAb)	1645	asGfsgAfaAfaagacuAfuUfcauuaasusu	2377
D-1306	gsasauagUfuCfUfUfUfuccugcucs(invAb)	1646	asAfsGfaGfgagaaAfaCfuauuucusus	2378
D-1307	asasuagUfcUfUfUfUfuccugcuus(invAb)	1647	asAfsaGfcAfgagaaaGfaAfuauuususu	2379
D-1308	usgsaucCfuGfUfCfAfcuaccacucs(invAb)	1648	asAfsGfuGfuagugacAfgGfagcasusu	2380
D-1309	gscauuccUfgUfCfAfcuaccacucs(invAb)	1649	asGfsaGfuGfuagugaCfaGfagucgsusu	2381
D-1310	cscsgggCfaGfCfUfUfuuaaagugs(invAb)	1650	asCfsaUfuUfcaaaagCfaGfcccggsusu	2382
D-1311	csgsggcUfGfCfUfUfugaaaagugs(invAb)	1651	asCfsaUfuUfcaaaagCfuAfgcccggsusu	2383
D-1312	asasagcuGfaGfGfUfGfaccuucags(invAb)	1652	asCfsuGfaAfggucaccUfcAfgucuuususu	2384
D-1313	asgsugaCfcUfUfCfAfggaagcacs(invAb)	1653	asGfsuGfcUfuccugaaGfgUfaccususu	2385
D-1314	cscsaugAfuCfUfGfGfauccggccs(invAb)	1654	asGfsgCfcAfgaaccagAfuCfuauuggsusu	2386
D-1315	usgsaguuUfcCfUfAfAfaaggugcucs(invAb)	1655	usGfsaGfcAfcuuuagGfaAfauccasusu	2387
D-1316	gsasuuucCfuAfaAfGfGfugcucags(invAb)	1656	asCfsuGfaGfcacuuuAfgGfaaaacsusu	2388
D-1317	uscscuaaAfgGfUfGfCfucaggaggs(invAb)	1657	usCfscUfcCfugagcacCfuUfuaggasusu	2389
D-1318	usgsaggAfcCfCfUfGfgauccuugs(invAb)	1658	asAfsaGfgAfuaccaggGfuCfuccasusu	2390
D-1319	gsasaggAfcCfCfUfGfgauccuugs(invAb)	1659	asCfsaAfgGfauccaggGfgUfuccususu	2391
D-1320	gsasggacCfcCfUfGfGfauccuugcs(invAb)	1660	asGfscAfaGfgauccagGfgGfuccususu	2392
D-1321	csgsgaguGfcUfCfCfUfucuccagugs(invAb)	1661	asAfsCfuUfgGfagaaggaGfcAfcuccgsusu	2393
D-1322	asgsaaggAfcCfCfAfcfugcucugacs(invAb)	1662	asUfscAfgAfgcagugCfuCfucucusus	2394
D-1323	csuscugaUfuGfGfCfCfcgaagggs(invAb)	1663	asCfscCfuUfccgggCfaUfcagagsusu	2395
D-1324	uscsgauUfgGfCfCfGfagagggs(invAb)	1664	asAfsCfcUfuccgggCfaAfuacagasusu	2396
D-1325	csusgaaUfgGfCfCfGfagagggs(invAb)	1665	asAfsaCfcCfuuccgggCfaAfuacagasusu	2397
D-1326	gsasccaaAfgGfCfCfGfaccuuccs(invAb)	1666	asGfsgAfaGfgugcgCfuUfuggccsusu	2398

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1327	cscsucgcGfgAfGfAfGccagccas{invAb}	1667	asUfsgGfcUfggcuucuCfcGfcgaggsusu	2399
D-1328	gsasgaaGfcCfAfGfCfcaugggcs{invAb}	1668	asCfsgCfcCfauggcugGfcUfucccsusu	2400
D-1329	gsasgaagCfcAfGfCfcaugggcs{invAb}	1669	asGfscGfcCfcauggcugGfcUfucccsusu	2401
D-1330	gsasucaaCfcAfGfCfAfgggaacacs{invAb}	1670	asUfsgUfuUfcccuccuGfgUfugaucsusu	2402
D-1331	ascsgcuCfcCfAfGfGfagaccucgs{invAb}	1671	asCfsgAfgGfuuccugCfcAfgcaggsusu	2403
D-1332	uscsgccaGfgAfAfCfCfucgaccggs{invAb}	1672	asCfscAfgGfcgagguCfcUfgcgcsusu	2404
D-1333	gscscaggAfaCfCfUfCfcccugucs{invAb}	1673	asGfsaCfcAfggagcagUfuCfucgcsusu	2405
D-1334	gsasaccuCfcCfCfAfGfuccugaus{invAb}	1674	asAfsuCfaGfgaccaggCfcAfgguucsusu	2406
D-1335	asusggugAfcAfCfCfCfugacucucs{invAb}	1675	usGfsaGfaGfucagguGfuCfaccasusu	2407
D-1336	usgsugacCfaCfCfUfGfucucucas{invAb}	1676	asUfsgAfgAfgucaggUfgUfcaccasusu	2408
D-1337	gsascaccCfuGfAfCfUfucagugcs{invAb}	1677	usGfscAfcUfgagagucAfgGfgugcsusu	2409
D-1338	ascsgcuCfcUfCfUfCfagucagcs{invAb}	1678	asGfscUfgCfagagagaGfuCfagggusu	2410
D-1339	cscsgcccAfgUfGfGfAfaaacagcs{invAb}	1679	asGfscUfgGfuuaaccaCfuGfgcggsusu	2411
D-1340	cscsgccuGfgUfGfCfAfcuucgagcs{invAb}	1680	asGfscUfcGfaagugcaCfcAfgcggsusu	2412
D-1341	csgsgcuGfuGfCfAfcuucgagcs{invAb}	1681	asGfsgCfuCfagagugAfcCfagcggsusu	2413
D-1342	gscscuggUfgCfAfCfUfucgagccus{invAb}	1682	asAfsGfCfCfagagugCfaCfcaggsusu	2414
D-1343	cscsugguGfcAfCfUfUfCfagccucgs{invAb}	1683	usGfsaGfgCfucgaaguGfcAfcaggsusu	2415
D-1344	csusggugCfaCfUfUfCfagccucacs{invAb}	1684	asUfsgAfgGfcucgaaguUfgCfaccaggsusu	2416
D-1345	usgsugcAfcUfUfCfCfagccucacs{invAb}	1685	usGfsuGfaGfgcucgaGfuGfcaccasusu	2417
D-1346	gsugsucaCfuUfCfGfAfgccucacacs{invAb}	1686	asUfsgUfgAfggucgaAfgUfgcaccsusu	2418
D-1347	gsusgcacUfuCfGfAfgccucacacs{invAb}	1687	asAfsuGfuGfagcugCfaGfugcaccsusu	2419
D-1348	usgsacacUfcGfAfCfCfucacacacs{invAb}	1688	asCfsaUfgUfgagcugGfaAfgugcasusu	2420
D-1349	gscsacuuCfcAfcCfCfucacacacs{invAb}	1689	asGfscAfuGfugagcugCfcAfgugcsusu	2421
D-1350	csasucuuGfaGfCfCfUfCfagccucgs{invAb}	1690	usCfsgCfaUfgugagcUfcGfaaggsusu	2422
D-1351	ascsuucGfGfCfCfUfCfagccucacs{invAb}	1691	asUfscGfcAfuugagcCfuCfagaggsusu	2423
D-1352	csusucgaGfcUfCfCfAfcagccucacs{invAb}	1692	asGfsuCfcCfagugagGfcUfcaggsusu	2424
D-1353	ususcgagCfuUfCfAfcfagccucacs{invAb}	1693	asGfsgUfcGfcaugugaAfgCfucaggsusu	2425
D-1354	uscsgagCfuCfAfCfAfcfagccucacs{invAb}	1694	usCfsgGfuCfagcugAfgGfcucaggsusu	2426
D-1355	csgsagccUfcAfCfAfcfagccucacs{invAb}	1695	asUfscGfgUfcgcauguGfaGfgcucgsusu	2427
D-1356	gscscucaCfaUfGfCfCfagccucacs{invAb}	1696	asGfsuCfuCfagcugCfaUfgaggsusu	2428
D-1357	csusugauCfcUfUfUfCfagccucacs{invAb}	1697	asAfsCfCfCfagcagGfaAfucaaggsusu	2429
D-1358	csusggcgGfaUfCfUfCfaacuccaggs{invAb}	1698	asCfsuGfgAfguaggaUfcCfagccaggsusu	2430
D-1359	usgsccgAfuCfUfCfAfcuucaggs{invAb}	1699	asCfscUfgGfagugagAfuCfagccaggsusu	2431
D-1360	gscsagugUfcUfAfuUfGfagcaggs{invAb}	1700	asAfsuCfcUfcgcauaGfCfagccaggsusu	2432
D-1361	gsasugucUfaUfGfCfAfgaggaucs{invAb}	1701	asGfsaAfuCfcucugcaUfaGfacaucsusu	2433
D-1362	usgsucuaUfgCfAfGfAfggaucucs{invAb}	1702	asAfsaGfaAfuucucugCfaUfagacacsusu	2434
D-1363	gsuscuauGfcAfGfAfggaucucs{invAb}	1703	asCfsaAfgAfaucucuGfcAfuagacacsusu	2435
D-1364	uscscuagCfaGfAfGfGfaucucaggs{invAb}	1704	asCfscAfaGfaauccugUfgCfaucaggsusu	2436
D-1365	csusagcAfgAfGfGfaucucaggs{invAb}	1705	usCfscCfaAfgaauccuGfuGfauaggsusu	2437
D-1366	gsugsugauGfgCfuUfUfGfuuccaggs{invAb}	1706	asAfsuCfuGfgaacaagCfcAfuaccsusu	2438
D-1367	gsusgagGfcUfUfGfUfuccaggs{invAb}	1707	asCfsaUfcUfggaacaGfcCfauccsusu	2439
D-1368	usgsccuGfuUfCfCfAfgagcaucs{invAb}	1708	asAfsaUfgCfauccagAfcAfgaccsusu	2440
D-1369	csasuuaaAfaCfCfAfcfagggaccs{invAb}	1709	asGfsgUfcCfagcugUfuAfaaaggsusu	2441
D-1370	usuuuaaCfcAfCfAfcfagggaccs{invAb}	1710	asUfsgGfgUfcccugGfuUfuuaaaggsusu	2442
D-1371	usuuuaaCfaCfAfGfUfggaccaggs{invAb}	1711	usCfsuGfgGfuccagUfgGfuuaaaggsusu	2443
D-1372	csascacUfcUfUfUfGfgcaggaucs{invAb}	1712	asAfsuAfcUfgcccaaaGfaGfuggsusu	2444
D-1373	ascscacuCfuUfUfGfGfagcaggaucs{invAb}	1713	asAfsaUfaCfugcccaaAfgAfguggsusu	2445
D-1374	csusuuggGfcAfGfUfAfuuuugucs{invAb}	1714	asGfscAfcAfaaaauGfcCfaaaggsusu	2446
D-1375	usuuuggCfaGfUfAfuuuugucs{invAb}	1715	asAfsGfCfaaaauuUfgCfcaaggsusu	2447
D-1376	usuuuggAfgUfAfuUfUfugucggs{invAb}	1716	asCfsaGfcAfaaaauCfuGfccaaggsusu	2448
D-1377	usgsagcaGfuAfuUfUfugucggs{invAb}	1717	usCfscAfgCfaaaauAfcUfgcccasusu	2449
D-1378	gsagcaguAfuUfUfUfugucggaacs{invAb}	1718	usUfsuCfcAfgcacaauAfuAfcugccsusu	2450
D-1379	usasuuuGfuGfCfUfGfgaaacacs{invAb}	1719	usGfsgGfuUfuuccagCfcAfaaauaggsusu	2451

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Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1433	uscsggggUfuGfCfCfGfcgucgggcs{invAb}	1773	asGfscCfcAfgcgccgAfaCfcccgasusu	2505
D-1434	gsgsuugCfGfCfCfUfgggccugcs{invAb}	1774	asUfscAfgGfcccagcCfGfcaaccsusu	2506
D-1435	gscscgCfUfGfGfCfCfGfcgucggcs{invAb}	1775	asGfscGfGfUfcaggccAfgCfGcgcsusu	2507
D-1436	gscscgCfGfCfCfUfGfaccgucgcs{invAb}	1776	asAfcCfGfCfGgucaggCfcCfagcgcsusu	2508
D-1437	usgsgccUfGfCfCfGfCfGgucggcs{invAb}	1777	asCfsgCfcAfcgCgguCfaGfgcccasusu	2509
D-1438	gsgsgccUfGfCfCfGfCfGgucggcs{invAb}	1778	asGfscGfcCfaccgCgUfCfGgcccusu	2510
D-1439	gsasgggAfaCfAfUfGfuuacugcs{invAb}	1779	asGfscAfgUfaaccaUfuUfcccucsu	2511
D-1440	gsgsaacAfuGfGfUfGfGgucgcs{invAb}	1780	asCfsgAfgCfaguaccAfuGfuuccsusu	2512
D-1441	gsasaacUfGfUfUfAfcugucgcs{invAb}	1781	asGfscGfaGfcagaaCfaUfguuucsu	2513
D-1442	asasacUfGfUfUfAfcugucgcs{invAb}	1782	usGfsgCfGfAfgcagaaCfcAfuguususu	2514
D-1443	asascaUfGfUfAfcUfGfGgucgcs{invAb}	1783	asUfsgGfcGfagcagaaAfcCfaguususu	2515
D-1444	ascsaugUfUfAfcUfGfGgucgcs{invAb}	1784	asCfsuGfGfGfagcagaaAfcCfaguususu	2516
D-1445	gsusuacuGfCfUfCfGfCfaggaaccs{invAb}	1785	asGfsgUfuCfGgCgGfCfAfgaaacsusu	2517
D-1446	ususcUfGfCfCfUfGfGgucgcs{invAb}	1786	usCfsaCfcAfcgCgagUfCfAfggaacsusu	2518
D-1447	ascscugCfUfGfUfGfGgucgcs{invAb}	1787	asAfgGfGfUfGgacaaUfCfGfagcagusu	2519
D-1448	gsusgCfCfUfAfcAfaaaaggacs{invAb}	1788	asGfsuCfcUfuuguaGfGfCfGgacusu	2520
D-1449	usgscagCfUfAfcAfaaaaggacs{invAb}	1789	asGfsgUfcUfuuguaGfGfCfGgacusu	2521
D-1450	csasgCfUfAfcAfaaaaggacs{invAb}	1790	asUfscGfGfUfGgacaaUfGfGgacusu	2522
D-1451	asgscCfUfAfcAfaaaaggacs{invAb}	1791	asGfsuAfgGfGgacaaUfGfGgacusu	2523
D-1452	gscscUfAfcAfaaaaggacs{invAb}	1792	usAfgUfAfgGgacaaUfGfGgacusu	2524
D-1453	csusuacCfAfaaaaggacs{invAb}	1793	asUfscGfGfUfGgacaaUfGfGgacusu	2525
D-1454	csusacCfAfaaaaggacs{invAb}	1794	asGfsuAfgUfGgacaaUfGfGgacusu	2526
D-1455	csasaaaGfGfCfUfGfGgacaaUfGfGgacusu	1795	asGfscAfgUfGgacaaUfGfGgacusu	2527
D-1456	asgsgacCfUfUfGfGgacaaUfGfGgacusu	1796	usGfscUfAfgGgacaaUfGfGgacusu	2528
D-1457	gsgsaccUfUfAfcUfGfGgacaaUfGfGgacusu	1797	usUfsgAfuAfggacaaUfGfGgacusu	2529
D-1458	ascscUfUfAfcUfGfGgacaaUfGfGgacusu	1798	usUfscUfGfGgacaaUfGfGgacusu	2530
D-1459	usascUfUfAfcUfGfGgacaaUfGfGgacusu	1799	asCfsgUfuUfGgacaaUfGfGgacusu	2531
D-1460	csusacUfCfUfAfaaaaggacs{invAb}	1800	asGfsgCfGfUfuuguaGfGfCfGgacusu	2532
D-1461	gscscUfUfAfaaaaggacs{invAb}	1801	asUfsgGfUfGgacaaUfGfGgacusu	2533
D-1462	ascscUfUfAfaaaaggacs{invAb}	1802	asUfscGfUfGgacaaUfGfGgacusu	2534
D-1463	csasaaaUfGfCfUfGfGgacaaUfGfGgacusu	1803	asAfcUfUfGfGgacaaUfGfGgacusu	2535
D-1464	csasaaUfGfCfUfGfGgacaaUfGfGgacusu	1804	usGfscAfcUfGgacaaUfGfGgacusu	2536
D-1465	asusgCfUfCfAfaaaaggacs{invAb}	1805	asUfscUfGfGgacaaUfGfGgacusu	2537
D-1466	asgsugCfAfaaaaggacs{invAb}	1806	usGfscAfcUfGgacaaUfGfGgacusu	2538
D-1467	ascsaUfGfCfAfaaaaggacs{invAb}	1807	asGfscCfGfGgacaaUfGfGgacusu	2539
D-1468	csasagUfGfCfAfaaaaggacs{invAb}	1808	asGfsgCfcGfGgacaaUfGfGgacusu	2540
D-1469	usgscagUfGfCfAfaaaaggacs{invAb}	1809	asUfscCfGfGgacaaUfGfGgacusu	2541
D-1470	asgsagUfCfCfGfCfGgacaaUfGfGgacusu	1810	usAfsuCfCfGgacaaUfGfGgacusu	2542
D-1471	gsasugCfCfGfCfGgacaaUfGfGgacusu	1811	asUfscUfCfGgacaaUfGfGgacusu	2543
D-1472	usgsagaUfAfaaaaggacs{invAb}	1812	asGfsuCfcUfGgacaaUfGfGgacusu	2544
D-1473	uscscUfAfgUfCfAfaaaaggacs{invAb}	1813	asGfsuAfgGfGgacaaUfGfGgacusu	2545
D-1474	csusgaUfCfAfaaaaggacs{invAb}	1814	asCfsgGfUfGgacaaUfGfGgacusu	2546
D-1475	gsasagUfCfAfaaaaggacs{invAb}	1815	asGfsgCfGfUfGgacaaUfGfGgacusu	2547
D-1476	cscsucUfUfGfCfAfaaaaggacs{invAb}	1816	asCfsgUfCfGgacaaUfGfGgacusu	2548
D-1477	csuscUfUfGfCfAfaaaaggacs{invAb}	1817	asAfcUfCfGgacaaUfGfGgacusu	2549
D-1478	uscscUfUfGfCfAfaaaaggacs{invAb}	1818	asGfsaCfGfGgacaaUfGfGgacusu	2550
D-1479	csascaUfGfCfAfaaaaggacs{invAb}	1819	asGfsgAfcGfGgacaaUfGfGgacusu	2551
D-1480	ascsaUfGfCfAfaaaaggacs{invAb}	1820	asAfgGfAfgGgacaaUfGfGgacusu	2552
D-1481	usgscagCfGfAfaaaaggacs{invAb}	1821	asAfsuGfAfgGgacaaUfGfGgacusu	2553
D-1482	gscsgacCfGfAfaaaaggacs{invAb}	1822	usGfsaUfGfGgacaaUfGfGgacusu	2554
D-1483	cscsgagCfUfCfCfUfGfGgacaaUfGfGgacusu	1823	usAfsuUfUfGfGgacaaUfGfGgacusu	2555
D-1484	csasagCfUfCfCfUfGfGgacaaUfGfGgacusu	1824	asUfscUfUfGfGgacaaUfGfGgacusu	2556
D-1485	asgsagCfUfCfCfUfGfGgacaaUfGfGgacusu	1825	usGfscUfUfGfGgacaaUfGfGgacusu	2557

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1486	uscscucaUfcAfAfUfagcagac{invAb}	1826	asAfsGfUfcUfgcuuuuGfaUfgaggasusu	2558
D-1487	csuscaucAfaAfUfAfGfcagacuugs{invAb}	1827	asCfsaAfgUfcugcuauUfuGfaugagsusu	2559
D-1488	csasgacaCfcAfGfCfcfcauucuugs{invAb}	1828	usCfsaAfgAfaugggcuGfgUfgucgususu	2560
D-1489	asgsacacCfaGfCfCfcfcauucuugs{invAb}	1829	asUfscAfaGfaaugggcuGfgUfugucususu	2561
D-1490	gsascaccAfgCfCfCfAfuucuugaus{invAb}	1830	asAfsuCfaAfgaugggCfuGfgugucususu	2562
D-1491	csasgcccAfuUfCfUfUfgauccuuus{invAb}	1831	asAfsaAfgGfaucagaAfuGfggucgususu	2563
D-1492	cscsauucUfuGfAfUfCfuuucugus{invAb}	1832	asUfscAfgAfauggaAfaGfaauggsusu	2564
D-1493	gsasagagGfaUfUfCfUfugggauugs{invAb}	1833	asUfscAfuCfcaagaaUfcCfucugcsusu	2565
D-1494	asusucuuGfgGfAfUfGfagcuucuu{invAb}	1834	usAfsaGfaAfgcucaucCfcAfagaasusu	2566
D-1495	csusugggAfuGfAfGfCfuucuuuu{invAb}	1835	asAfsaUfaAfgaagcAfuCfcaagsusu	2567
D-1496	gssgaugAfgCfUfUfCfuuuuugus{invAb}	1836	asAfsCfaAfaaagaagCfuCfaucacsusu	2568
D-1497	gsgsaugaGfUfUfCfUfuuuuugus{invAb}	1837	usCfsaCfAfaaagaGfcUfcaucacsusu	2569
D-1498	gsusggaaCfuGfAfAfAfgggugaus{invAb}	1838	asAfsuCfaCfccccuUfUfuccacsusu	2570
D-1499	usgsaacUfgAfaAfAfgggugaus{invAb}	1839	asCfsaUfcAfccuuuuCfaGfuuccasusu	2571
D-1500	gsasacugAfaAfGfGfgugaugcs{invAb}	1840	asGfscCfaUfcacccuuUfcCfaguucususu	2572
D-1501	csusgaaaAfgGfGfUfGfauggcuugs{invAb}	1841	asCfsaAfgCfcaucaccCfuUfuucagsusu	2573
D-1502	usgsaaaaGfgUfGfAfggcuugus{invAb}	1842	asAfsCfaGfcaucacCfcUfuuccasusu	2574
D-1503	gsasaaagGfgUfGfAfUfaggcuugus{invAb}	1843	asAfsaCfaAfgccaucaCfcUfuucacsusu	2575
D-1504	asasaaggGfuGfAfUfGfgcuugucs{invAb}	1844	asGfsaAfcAfgccaucaAfcCfuuucususu	2576
D-1505	gsusggacCfcAfGfAfCfaccggugus{invAb}	1845	asAfsCfCfaggugucUfgGfuccacsusu	2577
D-1506	usgsagacCfaGfAfCfAfcggugucs{invAb}	1846	usGfsaCfaCfaggugucUfgGfuccasusu	2578
D-1507	gsasagccAfgAfCfAfcfagugucas{invAb}	1847	asUfsgAfcAfcggugucUfuGfggucacsusu	2579
D-1508	ascscagAfcAfCfCfGfgugucaugs{invAb}	1848	usCfsaUfgAfcaggugUfuCfugggususu	2580
D-1509	cscsagacAfcCfGfUfGfaucaugs{invAb}	1849	asCfsuCfaUfgacaccGfuGfucggsusu	2581
D-1510	csasccggUfgUfCfAfUfgagcaggas{invAb}	1850	usUfscCfuGfcaucaGfaCfaggugususu	2582
D-1511	gsuscaugAfgCfAfGfGfaaggaaacs{invAb}	1851	asGfsgUfuCfuuuccGfuCfaugacsusu	2583
D-1512	asusgagCfGfAfAfGfagaaaccgus{invAb}	1852	asAfsGfGfuuuccuUfcGfcaucasusu	2584
D-1513	asgsaagGfaAfCfCfGfaggaaacs{invAb}	1853	usGfsuUfuCfagcggUfcCfuuccasusu	2585
D-1514	gsgsaaggAfaCfCfGfaggaaacs{invAb}	1854	asUfsgUfuUfccagcgUfuCfuuccasusu	2586
D-1515	gsasaggaAfcCfCfUfaggaaacs{invAb}	1855	asGfsuGfuUfccagcgGfuUfccuacsusu	2587
D-1516	csusgggcCfaGfUfAfUfgggaaacs{invAb}	1856	asGfsgUfuCfcauuacUfgGfccagsusu	2588
D-1517	gsusggccaGfuAfaUfUfggaaaccgus{invAb}	1857	usAfsCfGfUfuccauUfcUfggcccusu	2589
D-1518	gsusccagUfaAfUfGfGfagaaaccgus{invAb}	1858	asUfsaCfGfuuuccaUfaCfuggccsusu	2590
D-1519	gsccsaguAfaUfGfGfGfagaaaccgus{invAb}	1859	asAfsuAfcGfuuuccaUfuAfcuggccsusu	2591
D-1520	cscsaguaAfuGfGfGfAfcgguuugs{invAb}	1860	asCfsaUfaCfagguuuccAfuUfacuggsusu	2592
D-1521	csasguuaUfgGfGfAfcgguuugs{invAb}	1861	asAfsCfuAfcgguuccCfaUfuacgususu	2593
D-1522	asgsuaauGfgGfAfAfcgguuugs{invAb}	1862	asGfsaCfaUfcgguuccCfaUfuacgususu	2594
D-1523	usgsaggaaCfcGfUfAfUfguccggas{invAb}	1863	usUfscCfaGfgacaucaGfgUfuuccasusu	2595
D-1524	gsusaaaccGfuAfuGfUfccuggaas{invAb}	1864	usAfsuUfcCfaggacauAfcGfuuccsusu	2596
D-1525	gsasauauUfaGfAfUfGfccuuuuas{invAb}	1865	usUfsuAfaAfgggcaucUfaAfaauccsusu	2597
D-1526	gsasugccUfuUfUfAfAfaaaguucs{invAb}	1866	asGfsaAfcAfuuuuuuAfaGfgcaucususu	2598
D-1527	gsusuucaGfaAfcUfUfgagaccuc{invAb}	1867	usAfsGfGfucucaguUfcUfgaaacsusu	2599
D-1528	uscagaaCfuGfAfGfAfcuucacas{invAb}	1868	asUfsgUfaGfaggucCfUfucugasusu	2600
D-1529	ascugagAfcCfUfCfUfacaauuucs{invAb}	1869	asGfsaAfaAfuagagGfuCfucagususu	2601
D-1530	csusgagaCfcUfCfUfAfaauuuc{invAb}	1870	asAfsGfAfaAfaugaGfgUfcucagususu	2602
D-1531	usgsagacCfuCfUfAfcfaauuuc{invAb}	1871	asAfsaGfaAfaaaguagAfgGfucucasusu	2603
D-1532	usgsauuuUfcAfcAfUfuuuucgucs{invAb}	1872	asGfsaCfGfAfaaaguGfaAfaucasusu	2604
D-1533	gsasuuuuCfaCfAfUfUfuucguc{invAb}	1873	asAfsGfAfaaauuUfgAfaaacsusu	2605
D-1534	asusuuucAfcAfUfUfuucguc{invAb}	1874	asAfsaGfaCfgaauuuGfuGfaaauususu	2606
D-1535	ususucacAfuUfUfUfUfgucuuu{invAb}	1875	asAfsaAfaGfagcauuAfuGfugaasusu	2607
D-1536	ususcacaUfuUfUfUfUfgucuuu{invAb}	1876	asCfsaAfaAfgagcauuAfuGfugaasusu	2608
D-1537	uscscacuUfuUfUfUfUfgucuuu{invAb}	1877	usCfscAfaAfgagcauuAfuGfugaasusu	2609
D-1538	ascsauuuUfuCfGfUfCfuuuugacs{invAb}	1878	asGfsuCfCfaaagacGfaAfaaugsusu	2610

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Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-1645	uscscuccuCfaGfCfUfAfaugacggas{invAb}	1985	asUfscCfGfUfcuuagcUfgAfggggasusu	2717
D-1646	uscsgacuaAfaUfGfAfCfGgagugcus{invAb}	1986	asAfsGfCfaCfuccgucaUfuAfgcugasusu	2718
D-1647	gsasaaaaGfuUfCfUfGfaauucugus{invAb}	1987	asAfsCfGfAfaauucagaAfcUfuuuucsusu	2719
D-1648	asgsuucuGfaAfUfUfCfuguggaggs{invAb}	1988	usCfscUfCfCfagacauUfcAfgaacususu	2720
D-1649	asgsugauUfuCfAfGfAfuagacuacs{invAb}	1989	asGfsuAfgUfcuauucgAfaAfuacacususu	2721
D-1650	asusuucaGfaUfAfGfAfcuacugaas{invAb}	1990	usUfsuCfaGfuagucuaUfcUfgaaususu	2722
D-1651	csasgauaGfaCfUfAfCfGfaaaacccs{invAb}	1991	asGfsgUfuUfucaguagUfcUfaucugsusu	2723
D-1652	usasgacuAfcUfGfAfAfaacuuuuaas{invAb}	1992	usUfsaAfaGfguuuuaGfAfgucuasusu	2724
D-1653	asgsacuaCfuGfAfAfaacuuuuaas{invAb}	1993	usUfsuAfaAfggguuuuaAfgUfagucususu	2725
D-1654	asasggaaAfgCfAfUfAfugucaguus{invAb}	1994	asAfsaCfuGfacaauagCfuUfuccuususu	2726
D-1655	asgsaaaaGfcAfUfAfUfugucaguus{invAb}	1995	asCfsaAfcUfgacauuGfcUfuuccususu	2727
D-1656	gsgsaaagCfaUfAfUfGfucaguugus{invAb}	1996	asAfsCfAfaCfagacauUfgCfuuuccsusu	2728
D-1657	asasagcaUfaUfGfUfCfaguuuuus{invAb}	1997	usAfsaAfcAfacugacaUfaUfgcuuususu	2729
D-1658	asasgcauAfuGfUfCfAfguuuuuuaas{invAb}	1998	usUfsaAfaCfaacugacAfuAfgucuuusu	2730
D-1659	asgscauaUfgUfCfAfguuuuuuaas{invAb}	1999	usUfsuAfaAfaacugacCfaUfagucususu	2731
D-1660	usasaaacCfcAfAfUfAfucuaauuuus{invAb}	2000	asAfsaAfaUfagauuuGfgGfuuuuasusu	2732
D-1661	asascccaAfuAfuUfCfUfauuuuuuaas{invAb}	2001	usUfsaAfaAfaauagauAfuUfggguuusu	2733
D-1662	ususaacuGfaUfUfGfUfaaaacucuc{invAb}	2002	usAfsGfAfgUfuuaacaUfcAfguuuasusu	2734
D-1663	usasacugAfuUfGfUfAfaaacucuaas{invAb}	2003	usUfsaGfaGfuuaacaAfaCfaguuaasusu	2735
D-1664	ascsugauUfgUfAfUfAfacucuaags{invAb}	2004	usCfsuUfaGfaguuaaCfaAfuucagususu	2736
D-1665	csusgaaUGfaUfAfAfcucuaaags{invAb}	2005	asUfscUfuAfgaguuuAfcAfaucagsusu	2737
D-1666	gsasuuguAfuAfcUfUfcuaagauacs{invAb}	2006	asGfsaUfcUfagaguUfuAfaaacsusu	2738
D-1667	gscscuuUfuGfUfCfCfuugauuuaas{invAb}	2007	asUfsaAfuCfaaaggacAfaAfauggcsusu	2739
D-1668	usgsuccuUfuGfAfUfUfaauuugggs{invAb}	2008	usCfscCfaAfaauaauAfaAfggacacusu	2740
D-2000	[GalNAc3]saggcccAfaUfAfUfUfguaauuucs{invAb}	2009	usGfsaaauUfacaauaUfuGfgccususu	2741
D-2001	[GalNAc3]scagaacGfaAfAfGfUfuuauggas{invAb}	2010	usUfscacuAfaaauuUfcGfuucugsusu	2742
D-2002	[GalNAc3]suuccagAfuGfCfAfUfuuaaccas{invAb}	2011	asUfsgguuAfaaauGfAfuucgacacusu	2743
D-2003	[GalNAc3]sugcauuUfuAfAfCfCfaguggas{invAb}	2012	asUfscacUfgugguuAfaAfaugcasusu	2744
D-2004	[GalNAc3]scagugGfaUfAfAfCfagcuucs{invAb}	2013	asGfsgaagCfugguuUfcCfagucgusu	2745
D-2005	[GalNAc3]sgcuggaAfaCfAfCfUfgaagaguus{invAb}	2014	usAfsacucUfucagugUfuUfccagcsusu	2746
D-2006	[GalNAc3]sgaaacaCfuGfAfAfGfaguuaucgs{invAb}	2015	asCfsgauaAfcuucUfcUfguuucsusu	2747
D-2007	[GalNAc3]saacacuGfaAfGfAfGfuuaucgccs{invAb}	2016	usGfsgcgaUfaacucUfcAfguguuusu	2748
D-2008	[GalNAc3]scccgauUfaAfCfUfGfuuauggas{invAb}	2017	usUfscacuAfaaagUfuAfaacgggsusu	2749
D-2009	[GalNAc3]saaauGaCfaAfCfAfCfuugaagcas{invAb}	2018	asUfsgcuuAfaaguuUfgUfcauuusu	2750
D-2010	[GalNAc3]scacuGfaGfCfAfUfgguuuucs{invAb}	2019	usGfsaaacAfcaugUfuCfaagugsusu	2751
D-2011	[GalNAc3]sgauuuGfgAfAfUfAfguucuuucs{invAb}	2020	asGfsaaagAfaaauUfcAfaaacsusu	2752
D-2012	[GalNAc3]sauuagGfaAfUfAfGfuucuuuc{invAb}	2021	asAfsGaaaGfaacuuUfcCfaaauusu	2753
D-2013	[GalNAc3]sugguguCfuCfAfUfGfucuaaas{invAb}	2022	asAfsuugaAfgcauUfgAfcaccasusu	2754
D-2014	[GalNAc3]sgacaagAfcAfGfGfAfuucugaaas{invAb}	2023	usUfsuuaGfaaauUfcUfuucugsusu	2755
D-2015	[GalNAc3]scuuuagUfcAfGfUfUfguuuaaas{invAb}	2024	asUfsuuuaAfaacuuGfaCfaaugsusu	2756
D-2016	[GalNAc3]saguuguUfuAfAfAfAfcacuaaas{invAb}	2025	asAfsuuuGfgguuuAfaAfaacacusu	2757
D-2017	[GalNAc3]suuguuuAfaAfAfCfCfaaauuc{invAb}	2026	usAfsGauaUfugguuUfuAfaaacsusu	2758
D-2018	[GalNAc3]sgaugaaGfuAfUfUfuuuuuuuaas{invAb}	2027	asAfsauaaAfaaauUfcUfcaucusu	2759
D-2019	[GalNAc3]suuuuuUfgCfCfAfUfuuuuguccs{invAb}	2028	asAfsGgacAfaauggCfaAfaaaasusu	2760
D-2020	[GalNAc3]sauuuccAfuUfUfUfGfucuuugas{invAb}	2029	asUfscaaaGfgacaaAfuGfgcauususu	2761
D-2021	[GalNAc3]sauuuugGfgAfAfGfUfugacuaaas{invAb}	2030	asUfsuuagUfcaacuUfcCfaaauusu	2762
D-2022	[GalNAc3]sggaaguUfgAfcUfAfaacuugaas{invAb}	2031	usUfsucaGfuuuaguCfaAfcuucscusu	2763
D-2023	[GalNAc3]sacugugAfaUfAfAfUfggaagcus{invAb}	2032	usAfsGcuCfcauuuUfuCfagucusu	2764
D-2024	[GalNAc3]scagauuGfcUfUfAfCfucagacacs{invAb}	2033	asGfsugucUfgaguuGfcAfaucgusu	2765
D-2025	[GalNAc3]scugaagAfgUfUfUfUfgccagugs{invAb}	2034	asCfsacugCfcauuuUfcUfuucgusu	2766
D-2026	[GalNAc3]saccuuCfaGfAfAfCfagaaguuas{invAb}	2035	asUfsaacuUfucguucUfgAfgggususu	2767
D-2027	[GalNAc3]sgugaccCfuUfCfAfGfaacgaags{invAb}	2036	asCfsuuucGfuucugaAfgGfgucacusu	2768
D-2028	[GalNAc3]sucagaaCfGfAfAfGfuuauggs{invAb}	2037	usCfscauAfaacuuCfUfucugusu	2769

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2029	[GalINAc3]suucuuuUfuGfGfUfGfagcuggaas{invAb}	2038	asUfsuccaCfugcaccAfaUfaagaasusu	2770
D-2030	[GalINAc3]saguuuuAfuGfGfAfAfaaaccas{invAb}	2039	asUfsggugAfuuuuuccAfuAfaaacususu	2771
D-2031	[GalINAc3]scccuucAfgAfAfCfGfaaaguuaas{invAb}	2040	usAfsuaacUfuucguUfcGfaaggsusu	2772
D-2032	[GalINAc3]sccuucGfaAfCfGfAfaaguuaas{invAb}	2041	asUfsauaaCfuucguUfcUfgaaggsusu	2773
D-2033	[GalINAc3]scuucagAfaCfGfAfAfauguuaas{invAb}	2042	asAfsuaaaCfuucguUfcUfgaaggsusu	2774
D-2034	[GalINAc3]scaacuuCfaGfGfCfCfaaauuugs{invAb}	2043	asCfsaauaUfuggccUfgAfaguugsusu	2775
D-2035	[GalINAc3]sggaacAfcUfGfAfAfgaguuaacs{invAb}	2044	asGfsauaaCfucucaGfuGfuuuccsusu	2776
D-2036	[GalINAc3]sacuucaGfgCfCfAfAfaauuugas{invAb}	2045	usUfsacaaUfaauugggCfcUfgaaggsusu	2777
D-2037	[GalINAc3]saaguuuAfaGfCfAfAfcaacuucs{invAb}	2046	usGfsaaguUfgguugCfuUfaacuususu	2778
D-2038	[GalINAc3]scuucagGfcCfCfAfAfaauuugaas{invAb}	2047	asUfsuacaAfaauuggGfcCfugaagsusu	2779
D-2039	[GalINAc3]sgaccagAfuUfGfCfUfuacucagas{invAb}	2048	asUfscugaGfuaagcaAfuCfuggucsusu	2780
D-2040	[GalINAc3]sacugauUfaUfGfGfAfauguuacs{invAb}	2049	asAfsaacUfaauccaUfaAfucagususu	2781
D-2041	[GalINAc3]saaauaggAfaAfAfUfCfaccacucus{invAb}	2050	asAfsaguGfgugauUfuCfcauauususu	2782
D-2042	[GalINAc3]scaaugCfuCfAfAfUfucccagusc{invAb}	2051	asAfsaugGfacaugAfaGfcauugcsusu	2783
D-2043	[GalINAc3]sugucagAfaUfGfCfCfagucgac{invAb}	2052	usUfsgcacUfgggcaUfuGfagagcsusu	2784
D-2044	[GalINAc3]saaugacAfaGfAfCfAfggaucucs{invAb}	2053	usCfsagaaUfccugCfuUfGfucuuususu	2785
D-2045	[GalINAc3]scuaagaUfcUfGfAfUfgaaguuaas{invAb}	2054	asUfsauacUfucacuaGfaUfcuaggsusu	2786
D-2046	[GalINAc3]scuggugUfcUfCfAfAfugcucaas{invAb}	2055	asUfsagaaGfcauugaGfaCfaccagsusu	2787
D-2047	[GalINAc3]sugucucAfaUfGfCfUfucaauugcs{invAb}	2056	asGfsacauUfgaagcaUfuGfagacagusu	2788
D-2048	[GalINAc3]suuuuccAfuAfGfAfUfcuggaucusc{invAb}	2057	asAfsaucCfagaucaAfuGfgaaaasusu	2789
D-2049	[GalINAc3]sugugacCfcUfUfCfAfgaacgaaas{invAb}	2058	asUfsuucgUfucugaaGfgGfucacagusu	2790
D-2050	[GalINAc3]scaguguGfaCfCfCfUfucagaacgs{invAb}	2059	usCfsguucUfgaagggUfcAfcacugcsusu	2791
D-2051	[GalINAc3]scaccccAfaAfUfAfUfggcuggaas{invAb}	2060	asUfsuccaGfcauauUfuGfgggugcsusu	2792
D-2052	[GalINAc3]scucaauGfcUfUfCfAfauguccas{invAb}	2061	asUfsgggaCfaauugaGfcAfuagagsusu	2793
D-2053	[GalINAc3]sacaggaUfuCfUfGfAfaaacuccs{invAb}	2062	asGfsggagUfuucagAfaUfcuugcsusu	2794
D-2054	[GalINAc3]sggaucUfuGfCfCfAfuuccuccs{invAb}	2063	usGfsagggGfaauaggAfaGfgauccsusu	2795
D-2055	[GalINAc3]scugcagAfuAfUfUfAfauuuccas{invAb}	2064	asUfsggaaAfaauaaUfuCfugcagsusu	2796
D-2056	[GalINAc3]saagauCfuGfAfUfGfAfauguuaas{invAb}	2065	asAfsauaaCfuucacUfaGfauucsusu	2797
D-2057	[GalINAc3]saaugacAfgAfCfUfUfuguccgacs{invAb}	2066	asGfscuggAfaaaguCfuGfcauauususu	2798
D-2058	[GalINAc3]sgacaacAfcUfUfGfAfaugaugus{invAb}	2067	asAfscauGfcaucaaGfuGfuugcsusu	2799
D-2059	[GalINAc3]sucagacAfgCfAfUfUfggaauuacs{invAb}	2068	asGfsgaaaUfccauugCfuGfucugcsusu	2800
D-2060	[GalINAc3]suggaaaAfuCfAfCfCfaccuucgs{invAb}	2069	asCfsaagAfguggugAfuUfuuccasusu	2801
D-2061	[GalINAc3]sagacagCfaUfUfGfAfauuuccas{invAb}	2070	usUfsaggaAfauccaaUfgCfugucsusu	2802
D-2062	[GalINAc3]scugauuAfuGfGfAfAfauguuacs{invAb}	2071	asAfsagaaCfuauuccAfuAfaucagsusu	2803
D-2063	[GalINAc3]sguauuGfcUfGfGfAfaauuagac{invAb}	3062	asUfscuaaUfaauccaGfgAfaucacsusu	3321
D-2064	[GalINAc3]saggcuaGfaGfAfGfAfaaguuaas{invAb}	3063	usUfsuaacUfuucucUfcUfagccsusu	3322
D-2065	[GalINAc3]suguaaAfcUfCfUfAfaugacugac{invAb}	3064	asUfscagaUfcuugaGfuUfaucacsusu	3323
D-2066	[GalINAc3]sccgauGfuCfCfUfGfgaauuacs{invAb}	3065	asUfsaauaUfccaggAfaUfucgcsusu	3324
D-2067	[GalINAc3]scaaaaaUfgAfCfAfAfcacuugaas{invAb}	3066	asUfsucaaGfuguuGfuUfuuuugsusu	3325
D-2068	[GalINAc3]suacugaAfaAfCfCfUfuuaaagggs{invAb}	3067	asCfscuuUfaaagguUfuUfcagucsusu	3326
D-2069	[GalINAc3]sacuaaGfaAfAfCfCuuuaags{invAb}	3068	asCfsuuuaAfgguuuUfcAfguagcsusu	3327
D-2070	[GalINAc3]sagaagaAfaAfGfUfGfauucagusc{invAb}	3069	usCfsacugAfaucacUfuUfcuucsusu	3328
D-2071	[GalINAc3]suuuggCfaGfUfAfUfuuuugucsc{invAb}	3070	asAfsagacAfaaaucUfgCfcaasusu	3329
D-2072	[GalINAc3]suacaaGfaGfCfGfCfagacugcs{invAb}	3071	usGfscagUfcugcgUfcUfugguasusu	3330
D-2073	[GalINAc3]scggcuAfgCfUfUfUfugaauggs{invAb}	3072	asCfscuuUfcaaaagCfuAfgcccsusu	3331
D-2074	[GalINAc3]scuggaaAfcAfCfUfGfaagguuas{invAb}	3073	asUfsaacUfuucaguGfuUfuccagsusu	3332
D-2075	[GalINAc3]sauguccCfaGfUfGfCfaaaaguas{invAb}	3074	usUfsacuuUfuugcacUfgGfgacacusu	3333
D-2076	[GalINAc3]scuggaaUfaUfUfAfGfagccuuus{invAb}	3075	asAfsaaggCfaucuaaUfaUfuccagsusu	3334
D-2077	[GalINAc3]sccuggAfuAfUfUfAfgaugccuuc{invAb}	3076	asAfsaggCfucuaaUfuUfuccagsusu	3335
D-2078	[GalINAc3]succuggAfaUfAfUfUfagauccusc{invAb}	3077	asAfsaggCfucuaaUfuUfuccagsusu	3336
D-2079	[GalINAc3]sacucuaAfgAfUfCfUfagauagusc{invAb}	3078	usAfsuucAfuacagUfuUfagagcsusu	3337
D-2080	[GalINAc3]sguccugGfaAfUfUfUfagauccsc{invAb}	3079	asGfsgcaUfuaauUfcCfaggacsusu	3338
D-2081	[GalINAc3]suguccGfgAfAfUfAfaugaugcs{invAb}	3080	asGfscuacUfaauuUfcAfggacacusu	3339

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2082	[GalNac3]suaacucUfaAfGfAfUfcgugaas{invAb}	3081	asUfsucauCfagaucUfaGfaguuasusu	3340
D-2083	[GalNac3]sgugaugGfcUfUfGfUfuccagaugs{invAb}	3082	asCfsaucuGfgaacaGfcCfaucacsusu	3341
D-2084	[GalNac3]sgucuaUGfcAfGfAfGfgauucuuGs{invAb}	3083	asCfsaagaAfuccucUfGfAfuaagacsusu	3342
D-2085	[GalNac3]saccucAfcUfCfUfCfagucagcs{invAb}	3084	asGfscugCfCfaggagaGfUfCfagggususu	3343
D-2086	[GalNac3]sagccuaCfaCfAfAfAfggaccuacs{invAb}	3085	asGfsuaggUfccuuugUfgUfaggcususu	3344
D-2087	[GalNac3]saccaagAfgCfGfCfAfgacuugcas{invAb}	3086	asUfsgcaaGfucucgcCfuCfuuggususu	3345
D-2088	[GalNac3]sgaaggAfcCfGfCfUfGfgaaacacs{invAb}	3087	asGfsuguUfCagcgGfUfCcuucsusu	3346
D-2089	[GalNac3]suuccuUfuUfCfUfUfcaagccs{invAb}	3088	asGfsgcuUGfagaagaAfaAfgggaasusu	3347
D-2090	[GalNac3]scugucAfcUfAfCfCfacuuguas{invAb}	3089	asUfsaacGfagguaGfUfGfacaggsusu	3348
D-2091	[GalNac3]scgcgcUfuGfUfCfCfucccgcs{invAb}	3090	asCfsgcgGfagggacAfaAfgcgcsusu	3349
D-2092	[GalNac3]sgaaacaUfgGfUfUfAfcugcugcs{invAb}	3091	asGfscgagCfaguacCfaUfguuucsusu	3350
D-2093	[GalNac3]scuuuguCfcUfCfCfUfcgcgaas{invAb}	3092	asAfsuugCfGcaggagGfGfcaaggsusu	3351
D-2094	[GalNac3]sgcauaaAfgAfCfUfGfaggugaccs{invAb}	3093	asGfsgucaCfcucaguCfuUfuaugcsusu	3352
D-2095	[GalNac3]suuugucCfuCfCfUfCfGcgcauacs{invAb}	3094	asGfsauugCfGcgaggAfgGfcaaaasusu	3353
D-2096	[GalNac3]sgaaaagGfgUfGfAfUfggcuuguus{invAb}	3095	asAfsacaGfccauCaCfcCfuuuucsusu	3354
D-2097	[GalNac3]saaaagGfUGfAfUfGfgcuuguus{invAb}	3096	asGfsaacAfGCCaUCfCfcuuuusu	3355
D-2098	[GalNac3]scuacugCfcUfAfUfCfaaaacgcs{invAb}	3097	asGfsgcuUfuuguaGfGfCfaguagsusu	3356
D-2099	[GalNac3]scucaucAfaAfUfAfGfcagacuugs{invAb}	3098	asCfsaaguCfugcuauUfuGfauaggsusu	3357
D-2100	[GalNac3]sagacacCfaGfCfCfCfauucugas{invAb}	3099	asUfscagAfaugggCfGfugucusu	3358
D-2101	[GalNac3]scagcccAfuUfCfUfUfgaucuuus{invAb}	3100	asAfsaaggAfucaagaAfuGfggcugsusu	3359
D-2102	[GalNac3]sgcagagGfaUfUfCfUfGfggaugas{invAb}	3101	asUfscacCfcaagaaUfCfCucugcsusu	3360
D-2103	[GalNac3]scuaaagGfUGfCfUfCfaggagaus{invAb}	3102	asAfsuccCfGcagacAfCfcuuuagsusu	3361
D-2104	[GalNac3]saaagcaUfaUfGfUfCfaguuguus{invAb}	3103	usAfsaacaAfcugacaUfaUfGcuuuusu	3362
D-2105	[GalNac3]suuaacuGfaUfUfGfUfauaacucus{invAb}	3104	usAfsagauUfauacaaUfcAfguuasusu	3363
D-2106	[GalNac3]suaacugAfuUfGfUfAfuuaacucuas{invAb}	3105	usUfsagagUfuuaacaAfuCfaguuasusu	3364
D-2107	[GalNac3]sugaaaaCfuCfCfCfGfuuuuacuc{invAb}	3106	asAfsguuAfacggggAfgUfuuucasusu	3365
D-2108	[GalNac3]sgaugccUfuUfUfAfAfaaauguus{invAb}	3107	asGfsaacaUfuuuuaaAfaGfgcaucusu	3366
D-2109	[GalNac3]saaguagAfcUfAfaAfAfgauagaaas{invAb}	3108	usUfsuuccAfaguuuaGfCfcaucusu	3367
D-2110	[GalNac3]scacaaaGfgAfCfCfUfacuacugcs{invAb}	3109	asGfscaguAfguaggCfcUfuuggususu	3368
D-2111	[GalNac3]sgauuuuCfaCfaUfUfuuucgucuc{invAb}	3110	asAfsagacAfaaaugUfgAfaaaucusu	3369
D-2112	[GalNac3]sccauucUfuGfAfUfCfuuucugas{invAb}	3111	asUfscagaAfggaucAfaGfaauggsusu	3370
D-2113	[GalNac3]sgaaauaUfaGfAfUfGfccuuuuaas{invAb}	3112	usUfsuaaaAfggcaucUfaAfuauucsusu	3371
D-2114	[GalNac3]saaggaaAfgCfAfUfAfugucaguus{invAb}	3113	asAfsacugAfcuaugCfuUfuccuusu	3372
D-2115	[GalNac3]saggaaaGfcAfUfAfUfugacuugs{invAb}	3114	asCfsaacUfcauuauGfUfuccuusu	3373
D-2116	[GalNac3]sccccguUfAfAfCfUfaguuauggs{invAb}	3115	usCfscauaAfcuaguuAfaAfcggggusu	3374
D-2117	[GalNac3]sggaaagCfaUfAfUfGfucaguugus{invAb}	3116	asAfscaacUfgacauUfgCfuuuccusu	3375
D-2118	[GalNac3]sgccauuUfuGfUfCfCfuugauuas{invAb}	3117	asUfsaaucAfaaggacAfaAfauggcsusu	3376
D-2119	[GalNac3]saugacaAfcAfCfUfUfgaagcaugs{invAb}	3118	asCfsaugCfucaaguGfuUfgucaususu	3377
D-2120	[GalNac3]scuccugCfuUfCfUfCfguuuuacs{invAb}	3119	asGfsauaaAfcggagaAfgCfaggagsusu	3378
D-2121	[GalNac3]scagacuUfgCfAfUfCfcugucacuc{invAb}	3120	usAfsuguAfaggagCfaAfgucugusu	3379
D-2122	[GalNac3]sgagggaAfaCfAfUfGfuuuacugcs{invAb}	3121	asGfscaguAfaccagUfUfCccucusu	3380
D-2123	[GalNac3]suggcauAfaAfGfAfCfugaggugas{invAb}	3122	asUfscaccUfcagucuUfuAfugccasusu	3381
D-2124	[GalNac3]succuagAfaUfGfUfGfuuaugccs{invAb}	3123	asGfsgcaaUfaacacaUfuCfuaggasusu	3382
D-2125	[GalNac3]suggaaaCfaCfUfGfAfagaguuaus{invAb}	3124	asAfsuaacUfcuucagUfgUfuuccasusu	3383
D-2130	[GalNac3]suggauuUfcCfUfAfAfggugucuc{invAb}	3125	usGfsagcaCfcuuuagGfaAfuaccasusu	3384
D-2131	[GalNac3]sgaggagAfaGfAfAfAfgaguauucs{invAb}	3126	usGfsaauAfcuuuucUfCfuuccucusu	3385
D-2134	[GalNac3]saccuacUfaCfUfGfGfcuaaacaas{invAb}	3127	usUfsuugaUfaggagUfaGfuaggususu	3386
D-2135	[GalNac3]suacuacUfgCfCfUfAfucaaaaacs{invAb}	3128	asCfsguuUfgauaggCfaGfuaguasusu	3387

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2141	[GalNAc3]saaagugAfuUfCfAfGfugauuucas{invAb}	3134	asUfsgaaaUfcacugaAfuCfacuususu	3393
D-2142	[GalNAc3]suaugucCfuGfGfAfuaauugaas{invAb}	3135	asAfsucuaAfuauuccAfgGfacauasusu	3394
D-2143	[GalNAc3]saaacuCfuAfAfGfAfucugaugas{invAb}	3136	usUfscaucAfgaucuuAfgAfguuasusu	3395
D-2144	[GalNAc3]scuuguuCfAfGfAfUfgcauuuuaas{invAb}	3137	usUfsaaaaUfgcaucuGfGfacaagsusu	3396
D-2145	[GalNAc3]suaauugCfaUfUfUfUfguccuuugs{invAb}	3138	usCfsaaagGfacaaaaUfgGfcauauasusu	3397
D-2146	[GalNAc3]sugauuuUfCfAfAfUfuuuucgucs{invAb}	3139	asGfsacgaAfaaauGfAfaauucasusu	3398
D-2147	[GalNAc3]scaagagCfGfAfAfAfcuugcaucs{invAb}	3140	asGfsaugcAfgucugCfGfCfucugsusu	3399
D-2148	[GalNAc3]scagauaGfaCfUfAfCfugaaaaacs{invAb}	3141	asGfsuuuuUfcaguuGfUfauucgsusu	3400
D-2149	[GalNAc3]suaauugAfaUfAfGfUfucuuucucs{invAb}	3142	asGfsagaaAfgaacuaUfUfcauauasusu	3401
D-2150	[GalNAc3]scaugguGfuUfUfCfAfAgaacugags{invAb}	3143	usCfsucagUfucugaaAfcAfcaugsusu	3402
D-2151	[GalNAc3]sgaagaaAfaGfUfGfAfuucagugas{invAb}	3144	asUfscacuGfaaucacUfuUfucucgsusu	3403
D-2152	[GalNAc3]sgucccaGfuGfCfAfAfaaguaaas{invAb}	3145	asUfsuuacUfuuuugCfCfUfgggacsusu	3404
D-2153	[GalNAc3]sacugauUfgUfAfUfAfacucuaags{invAb}	3146	usCfsuuagAfguuuaaCfaAfcugususu	3405
D-2154	[GalNAc3]saccguaUfgUfCfCfUfggaauuugs{invAb}	3147	usAfsauauUfccaggaCfaUfaccgususu	3406
D-2155	[GalNAc3]succcgUfuUfAfAfCfugauuugs{invAb}	3148	asCfsauaaUfcaguuAfaCfggggasusu	3407
D-2156	[GalNAc3]sauauugUfCfAfAfuaacuuaags{invAb}	3149	asCfsuaagUfuauugaGfaCfuaauasusu	3408
D-2157	[GalNAc3]succagUfgCfAfAfAfaaguaaags{invAb}	3150	usCfsuuuaCfuuuuugCfaCfugggasusu	3409
D-2158	[GalNAc3]saugcuCfaUfUfGfUfccaguuus{invAb}	3151	asAfsucggGfacauugAfaGfcaususu	3410
D-2159	[GalNAc3]sgaacgaAfaGfUfUfAfuauuggaas{invAb}	3152	usUfscacuAfuuaacuUfCfGfuucgsusu	3411
D-2160	[GalNAc3]sgauugcUfuAfCfUfCfagacacuus{invAb}	3153	asGfsugucUfgaguuAfaAfaucgsusu	3412
D-2161	[GalNAc3]scuucagGfcCfCfAfAfuauuguaas{invAb}	2047	asUfsuAfcAfuauuugGfCfCfauugsusu	2212
D-2162	[GalNAc3]scaaugcUfuCfAfAfUfguccagus{invAb}	2051	asAfsUfgGfgacuuAfaGfcauugsusu	2249
D-2163	[GalNAc3]scagaacGfaAfAfGfUfuauuggas{invAb}	2010	usUfscCfaUfaaaacuUfCfGfuucgsusu	2168
D-2164	[GalNAc3]sggaaguUfgAfCfUfAfaacuugaas{invAb}	2031	usUfsuCfaAfguuuagUfCfaAfcuucgsusu	2328
D-2165	[GalNAc3]scagugGfaUfAfAfCfcagcuuacs{invAb}	2013	asGfsgAfaGfcuguuUfCfCfucgsusu	2116
D-2166	[GalNAc3]scuaagaUfCfUfGfAfUfgaaguuas{invAb}	2054	asUfsaUfaCfuucauGfaUfcuuaugsusu	2317
D-2167	[GalNAc3]scagaauGfcUfUfAfCfucagacacs{invAb}	2033	asGfsuGfuCfugaguuAfaGfcaucgsusu	2185
D-2168	[GalNAc3]scuucaggCfCfAfAfUfuuguaas{invAb}	3154	asUfsuacaAfuauuGfGfCfcugaagsusu	3413
D-2169	[GalNAc3]scaaugcuCfaUfUfGfUfccagus{invAb}	3155	asAfsucggGfacauUfgAfgacauugsusu	3414
D-2170	[GalNAc3]scagaacgaAfaGfUfUfAfuauuggas{invAb}	3156	usUfscacuAfuuaacuUfUfCfGfuucgsusu	3415
D-2171	[GalNAc3]sggaaguUfgAfCfUfAfAfAfcuugaas{invAb}	3157	usUfsucaaGfuuuuGfuCfaacuucgsusu	3416
D-2172	[GalNAc3]scaguggaUfaAfCfAfAfcuucacs{invAb}	3158	asGfsgaagCfugguUfaUfccacuggsusu	3417
D-2173	[GalNAc3]scuaagauCfGfAfAfAfaaguuas{invAb}	3159	asUfsauacUfucacuCfaGfaucuuugsusu	3418
D-2174	[GalNAc3]scagauugCfUfCfUfCfagacacs{invAb}	3160	asGfsugucUfgaguAfaGfcauucgsusu	3419
D-2175	[GalNAc3]scuucagGfcCfCfAfAfuauuguaas{invAb}	2047	asUfsuacaAfuauuggGfCfCfugasasgsu	3420
D-2176	[GalNAc3]scaaugcUfuCfAfAfUfguccagus{invAb}	2051	asAfsucggGfacauugAfaGfcausugsusu	3421
D-2177	[GalNAc3]scagaacGfaAfAfGfUfuauuggas{invAb}	2010	usUfscacuAfuuaacuUfCfGfuucsgsusg	3422
D-2178	[GalNAc3]sggaaguUfgAfCfUfAfaacuugaas{invAb}	2031	usUfsucaaGfuuuuagUfCfaAfcuucscsusg	3423
D-2179	[GalNAc3]scagugGfaUfAfAfCfcagcuuacs{invAb}	2013	asGfsgaagCfugguuUfCfCfucsgsusg	3424
D-2180	[GalNAc3]scuaagaUfCfUfGfAfUfgaaguuas{invAb}	2054	asUfsauacUfucacuGfaUfcuuaugsusu	3425
D-2181	[GalNAc3]scagauGfcUfUfAfCfucagacacs{invAb}	2033	asGfsugucUfgaguuAfaAfaucsgsusg	3426
D-2182	[GalNAc3]scaaugcUfuCfAfAfUfguccagus{invAb}	2051	asAfsucggGfacauugAfaGfcauugsasg	3427
D-2183	[GalNAc3]scaaugcUfuCfaAfuguccagus{invAb}	3161	asAfsucgggacauUfgAfaGfcauugsusu	3428
D-2184	[GalNAc3]scaaugcUfuCfAfAfUfguccagus{invAb}	2051	asAfsUfgGfcauugAfaGfcauugsusu	3429
D-2185	[GalNAc3]scaaugcUfuCfAfAfUfguccagus{invAb}	2051	asAfsucgGfGfcauugAfaGfcauugsusu	3430
D-2186	[GalNAc3]scaaugcUfuCfAfAfUfguccagus{invAb}	2051	asAfsucggGfcauUfgAfaGfcauugsusu	3431
D-2187	[GalNAc3]scaaugcUfuCfAfAfUfguccagus{invAb}	2051	asAfsUfgGfGfcauugAfaGfcauugsusu	3432
D-2188	[GalNAc3]scuucagGfcCfCfAfAfuauuguaas{invAb}	2047	asUfsuacaAfuauuggGfCfCfugasasg	3433
D-2189	[GalNAc3]scaaugcUfuCfAfAfUfguccagus{invAb}	2051	asAfsucggGfcauugAfaGfcausugsu	3434
D-2190	[GalNAc3]scagaacGfaAfAfGfUfuauuggas{invAb}	2010	usUfscacuAfuuaacuUfCfGfuucsgsu	3435
D-2191	[GalNAc3]sggaaguUfgAfCfUfAfaacuugaas{invAb}	2031	usUfsucaaGfuuuuagUfCfaAfcuucsc	3436
D-2192	[GalNAc3]scagugGfaUfAfAfCfcagcuuacs{invAb}	2013	asGfsgaagCfugguuUfCfCfucsgsg	3437
D-2193	[GalNAc3]scuaagaUfCfUfGfAfUfgaaguuas{invAb}	2054	asUfsauacUfucacuGfaUfcuuaasg	3438

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2194	[GalNac3]scagauuGfcUfUfAfCfucagacacs{invAb}	2033	asGfsugucUfgaguuaGfcAfaucsusg	3439
D-2195	[GalNac3]scaaugcUfuCfAfAfUfgucccauus{invAb}	3162	asUfsgggaCfaauGaaGfcAfuugsusu	3440
D-2196	[GalNac3]sguuuuAfaCfCfCfAfaaucauus{invAb}	3163	usAfsghaaUfuggguUfuAfaacsusu	3441
D-2197	[GalNac3]scuucaaUfgUfCfCfCfagugcauus{invAb}	3164	usUfsgcacUfgggacaUfuGfaagsusu	3442
D-2198	[GalNac3]sagacagCfaUfUfGfGfauuuccuus{invAb}	3165	asGfsgaaaUfccaugCfuGfucususu	3443
D-2199	[GalNac3]sgaaaaCfaCfCfAfCfucuuuguus{invAb}	3166	asCfsaaagAfgugguAfuUfuucsusu	3444
D-2200	[GalNac3]sacagcaUfuGfGfAfUfuuccuaa{invAb}	3167	usUfsaggaAfauccaaUfgCfugususu	3445
D-2201	[GalNac3]saggauuCfuGfAfAfafacuccuus{invAb}	3168	asGfsggagUfuuccagAfaUfccususu	3446
D-2202	[GalNac3]scaaacUfuGfAfAfGfcaugguus{invAb}	3169	asAfsccauGfcucaaGfuGfugususu	3447
D-2203	[GalNac3]scucaaUfUfCfAfAfUfgucccs{invAb}	3170	asUfsgggaCfaauGfAfaGfcauagagsusu	3448
D-2204	[GalNac3]suuuuuAfaCfCfCfAfaaucauus{invAb}	3171	usAfsghaaUfugggUfuUfuaaacaasusu	3449
D-2205	[GalNac3]sugcucaaUfgUfCfCfCfagugcas{invAb}	3172	usUfsgcacUfgggcaCfaUfugaagcasusu	3450
D-2206	[GalNac3]sucagacagCfaUfUfGfGfauuuccs{invAb}	3173	asGfsgaaaUfccaUfgCfugucugasusu	3451
D-2207	[GalNac3]suggaaaaCfaCfCfAfCfucuuugs{invAb}	3174	asCfsaaagAfguggUfgAfuuuuccasusu	3452
D-2208	[GalNac3]sagacagcaUfuGfGfAfUfuuccuas{invAb}	3175	usUfsaggaAfauccAfaUfgcugucususu	3453
D-2209	[GalNac3]sacaggauuCfuGfAfAfafacuccs{invAb}	3176	asGfsggagUfuuuCfAfauccugususu	3454
D-2210	[GalNac3]sgacaacacUfuGfAfAfGfcauggus{invAb}	3177	asAfsccauGfcuucAfaGfuguugucsusu	3455
D-2211	[GalNac3]scucaaUfUfCfAfafagucccs{invAb}	2061	asUfsgGfGfAfaauGaaGfcAfuugagsusu	2248
D-2212	[GalNac3]suuguuuAfaAfAfCfCfcaauaucus{invAb}	2026	usAfsghaaUfuuggguUfuAfaacaasusu	2315
D-2213	[GalNac3]sugcuucAfaUfGfUfCfCfagugcas{invAb}	2052	usUfsgCfaCfugggacaUfuGfaagcasusu	2251
D-2214	[GalNac3]sagacagCfGfAfUfUfggauuuccs{invAb}	2068	asGfsgAfaAfucaugCfuGfucugagasusu	2285
D-2215	[GalNac3]suggaaaAfuCfAfCfCfcauucuuugs{invAb}	2069	asCfsaAfaGfagugguAfuUfuuccasusu	2222
D-2216	[GalNac3]sagacagCfaUfUfGfGfauuuccuas{invAb}	2070	usUfsaGfGfAfaauccaaUfgCfugucususu	2287
D-2217	[GalNac3]sacaggaUfuCfUfGfAfaaacuccs{invAb}	2062	asGfsgGfGfUfuuuucagAfaUfccugususu	2256
D-2218	[GalNac3]sgacaacAfUfUfGfAfagcauggus{invAb}	2067	asAfsccauGfucuaaGfuGfuugucsusu	2238
D-2219	[GalNac3]scucaaUfUfCfAfafagucccs{invAb}	2061	asUfsgggaCfaauGaaGfcAfuugsasg	3456
D-2220	[GalNac3]suuguuuAfaAfAfCfCfcauauucus{invAb}	2026	usAfsghaaUfuggguUfuAfaacsasa	3457
D-2221	[GalNac3]sugcuucAfaUfGfUfCfCfagugcas{invAb}	2052	usUfsgcacUfgggacaUfuGfaagscsa	3458
D-2222	[GalNac3]sucagacAfgCfAfUfUfggauuuccs{invAb}	2068	asGfsgaaaUfccaugCfuGfucugsusa	3459
D-2223	[GalNac3]suggaaaAfuCfAfCfCfcauucuuugs{invAb}	2069	asCfsaaagAfgugguAfuUfuuccscsa	3460
D-2224	[GalNac3]sagacagCfaUfUfGfGfauuuccuas{invAb}	2070	usUfsaggaAfauccaaUfgCfugucscsu	3461
D-2225	[GalNac3]sacaggaUfuCfUfGfAfaaacuccs{invAb}	2062	asGfsggagUfuuuucagAfaUfccusgsu	3462
D-2226	[GalNac3]sgacaacAfUfUfGfAfagcauggus{invAb}	2067	asAfsccauGfcucaaGfuGfuugucsusu	3463
D-2227	[GalNac3]sucagaaCfGfAfAfGfGfaauuauugs{invAb}	2037	usCfscAfuAfaaacuuuGfuUfucugagasusu	2167
D-2228	[GalNac3]suuccagAfuGfCfAfUfuuuuaccas{invAb}	2011	asUfsgGfuUfaaaugAfuCfuggaasusu	2133
D-2229	[GalNac3]scuuucaGfaAfCfGfAfaaguuaas{invAb}	2041	asUfsaUfaAfcuuucguUfCfugaagsusu	2164
D-2230	[GalNac3]scuucagAfaCfGfAfAfaguuauaas{invAb}	2042	asAfsuAfaAfaucuuucUfuCfugaagsusu	2165
D-2231	[GalNac3]scaacuUfaGfGfCfcaauuugs{invAb}	2043	asCfsaAfuAfuuggggCfUfgAfaugususu	2210
D-2232	[GalNac3]sacuucaGfgCfCfCfAfaauuugas{invAb}	2045	usUfsaCfaAfaauugggCfCfUfgaagususu	2211
D-2233	[GalNac3]scuguuuAfaAfAfCfCfcauauucus{invAb}	3178	usAfsghaaUfuggguUfuAfaacagasusu	3464
D-2234	[GalNac3]scgcuucAfaUfGfUfCfCfagugcas{invAb}	3179	usUfsgcacUfgggacaUfuGfaagcsusu	3465
D-2235	[GalNac3]sccagacAfgCfAfUfUfggauuuccs{invAb}	3180	asGfsgaaaUfccaugCfuGfucuggsusu	3466
D-2236	[GalNac3]scggaaaAfuCfAfCfCfcauucuuugs{invAb}	3181	asCfsaaagAfgugguAfuUfuuccgsusu	3467
D-2237	[GalNac3]sggacagCfaUfUfGfGfauuuccuas{invAb}	3182	usUfsaggaAfauccaaUfgCfugucscsu	3468
D-2238	[GalNac3]sgcaggaUfuCfUfGfAfaaacuccs{invAb}	3183	asGfsggagUfuuuucagAfaUfccugcsusu	3469
D-2239	[GalNac3]sgauggcUfuGfUfUfCfcaugaugus{invAb}	3184	asCfsaucuGfgaacaaGfcCfaucsusu	3470
D-2240	[GalNac3]succuggAfaUfAfUfUfagauccuus{invAb}	3185	asGfscaucUfaauuuCfCfaggsusu	3471
D-2241	[GalNac3]scuggaAfuAfUfUfUfagauccuus{invAb}	3076	asGfsgcauUfaauuuUfcCfaggsusu	3472
D-2242	[GalNac3]sucuaagAfuCfUfGfAfaugaauas{invAb}	3186	usAfsccauCfucagauCfuUfagagasusu	3473
D-2243	[GalNac3]scuggaaUfaUfUfUfUfagauccuus{invAb}	3075	asAfsggcaUfcauuuUfuCfcagsusu	3474
D-2244	[GalNac3]sgugauggcUfuGfUfUfCfcaugcs{invAb}	3187	asCfsaucuGfgaacAfaGfcaucacsusu	3475
D-2245	[GalNac3]suguccuggAfaUfAfUfUfagauccs{invAb}	3188	asGfscaucUfaauUfuCfcaggacacusu	3476
D-2246	[GalNac3]suguccuggAfaUfUfUfUfagauccs{invAb}	3189	asGfsgcauUfaauUfuUfccaggacsusu	3477

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2247	[GalNac3]sacucuaagAfuCfUfGfAfugaagus(invAb)	3190	usAfsuucAfucagAfuCfuuaagagususu	3478
D-2248	[GalNac3]succuggaaUfaUfUfAfGfaguccus(invAb)	3191	asAfsggcaUfcuaaUfaUfuccagagusu	3479
D-2249	[GalNac3]sgugaugGfcUfUfGfUfuccagaus(invAb)	3082	asCfsaUfcUfggaacaaGfcCfaucacsusu	2439
D-2250	[GalNac3]suguccuGfgAfAfUfAfuaagagcs(invAb)	3080	asGfscAfuCfuuaauuuCfcAfggacagusu	2458
D-2251	[GalNac3]sguccugGfAfUfUfUfagaugccs(invAb)	3079	asGfsgCfaUfcuaauuuUfcCfaggacsusu	2459
D-2252	[GalNac3]sacucuaAfgAfUfCfUfagaagus(invAb)	3078	usAfsCfUfCfuaagauCfuUfagagagusu	2479
D-2253	[GalNac3]succuggAfaUfAfUfUfagaugccs(invAb)	3077	asAfsGfCfAfucuaauUfUfCfaggagusu	2460
D-2254	[GalNac3]sguccuGfCfUfUfGfUfuccagaus(invAb)	3082	asCfsaucUfgaacaUfcCfauacsasc	3480
D-2255	[GalNac3]suguccuGfgAfAfUfAfuaagagcs(invAb)	3080	asGfscacuUfaauuuCfcAfggacscsa	3481
D-2256	[GalNac3]sguccugGfAfUfAfUfagaugccs(invAb)	3079	asGfsgcaUfuaauuuUfcCfaggagasc	3482
D-2257	[GalNac3]sacucuaAfgAfUfCfUfagaagus(invAb)	3078	usAfsuucAfucagauCfuUfagaggsu	3483
D-2258	[GalNac3]succuggAfaUfAfUfUfagaugccs(invAb)	3077	asAfsggcaUfcuaauUfUfCfagggsa	3484
D-2259	[GalNac3]sccuggAfaUfAfUfUfagaugccs(invAb)	3192	asAfsggcaUfcuaauUfUfCfagggsusu	3485
D-2260	[GalNac3]sgucuaAfgAfUfCfUfagaagus(invAb)	3193	usAfsuucAfucagauCfuUfagagcsusu	3486
D-2261	[GalNac3]sguccuGfgAfAfUfAfuaagagcs(invAb)	3194	asGfscacuUfaauuuCfcAfggagcsusu	3487
D-2262	[GalNac3]scaacucUfaAfgAfUfCfugaugaas(invAb)	3195	asUfsuacuCfagaucuUfaGfaguugsusu	3488
D-2263	[GalNac3]sggaagaAfaAfgUfGfauuacagcs(invAb)	3196	usCfsacugAfaucacuUfUfCfucacsusu	3489
D-2264	[GalNac3]s(invAb)guccugGfAfUfUfUfagaugcs(invAb)	3197	asGfsgcaUfuaauUfCfCfaggacsusu	3338
D-2265	[GalNac3]s(invAb)uccuggAfaUfAfUfUfagaugccs(invAb)	3198	asAfsggcaUfcuaauUfUfCfaggagusu	3336
D-2266	[GalNac3]s(invAb)acucuaAfgAfUfCfUfagaaggs(invAb)	3199	usAfsuucAfucagauCfuUfagagagusu	3337
D-2267	[GalNac3]s(invAb)agacagCfaUfUfGfGfauuuccsas(invAb)	3200	usUfsaggaAfaucuaUfgCfugucgusu	2802
D-2268	[GalNac3]sguccagGfAfUfUfUfagaugccs(invAb)	3201	asGfsgcaUfuaauUfCfCfaggacsusu	3490
D-2269	[GalNac3]sgucugGfAfUfUfUfagaugccs(invAb)	3202	asGfsgcaUfuaauUfCfCfagcacsusu	3491
D-2270	[GalNac3]succugAfaUfAfUfUfagaugccs(invAb)	3203	asAfsggcaUfcuaauUfUfCfaggagusu	3492
D-2271	[GalNac3]succuggAfaUfAfUfUfagaugccs(invAb)	3204	asAfsggcaUfcuaauUfUfCfagagusu	3493
D-2272	[GalNac3]sacacuaAfgAfUfCfUfagaagus(invAb)	3205	usAfsuucAfucagauCfuUfagugagusu	3494
D-2273	[GalNac3]sagucuaAfgAfUfCfUfagaagagcs(invAb)	3206	usAfsuucAfucagauCfuUfagagagusu	3495
D-2274	[GalNac3]sagucagCfaUfUfGfGfauuuccuas(invAb)	3207	usUfsaggaAfaucuaUfgCfugagagusu	3496
D-2275	[GalNac3]sacacagCfaUfUfGfGfauuuccuas(invAb)	3208	usUfsaggaAfaucuaUfgCfugagagusu	3497
D-2276	[GalNac3]s(invAb)guccuggAfaUfUfUfAfgagcs(invAb)	3209	asGfsgcaUfuaauUfCfCfaggacsusu	3338
D-2277	[GalNac3]s(invAb)guccugGfAfUfUfUfagaugcs(invAb)	3210	asGfsgcaUfuaauUfCfCfaggacsusu	3338
D-2278	[GalNac3]s(invAb)guccugGfAfUfUfUfagaugcs(invAb)	3211	asGfsgcaUfuaauUfUfCfaggagcsusu	3477
D-2279	[GalNac3]s(invAb)guccuggAfaUfUfUfAfgagcs(invAb)	3209	asGfsgcaUfuaauUfUfCfaggagcsusu	3477
D-2280	[GalNac3]s(invAb)guccugGfAfUfUfUfagaugcs(invAb)	3210	asGfsgcaUfuaauUfUfCfaggagcsusu	3477
D-2281	[GalNac3]s(invAb)guccugGfAfUfUfUfagaugcs(invAb)	3211	asGfsgcaUfuaauUfCfCfaggagcsusu	3498
D-2282	[GalNac3]s(invAb)guccuggAfaUfUfUfAfgagcs(invAb)	3209	asGfsgcaUfuaauUfCfCfaggagcsusu	3498
D-2283	[GalNac3]s(invAb)guccugGfAfUfUfUfagaugcs(invAb)	3210	asGfsgcaUfuaauUfCfCfaggagcsusu	3498
D-2284	[GalNac3]s(invAb)guccugGfAfUfUfUfagaugcs(invAb)	3211	asGfsgcaUfuaauUfCfCfaggagcsusu	3499
D-2285	[GalNac3]s(invAb)guccuggAfaUfUfUfAfgagcs(invAb)	3209	asGfsgcaUfuaauUfCfCfaggagcsusu	3499
D-2286	[GalNac3]s(invAb)guccugGfAfUfUfUfagaugcs(invAb)	3210	asGfsgcaUfuaauUfCfCfaggagcsusu	3499
D-2287	[GalNac3]s(invAb)guccugGfAfUfUfUfagaugcs(invAb)	3211	asGfsgcaUfuaauUfUfCfaggagcsusu	3500
D-2288	[GalNac3]s(invAb)guccuggAfaUfUfUfAfgagcs(invAb)	3209	asGfsgcaUfuaauUfUfCfaggagcsusu	3500
D-2289	[GalNac3]s(invAb)guccugGfAfUfUfUfagaugcs(invAb)	3210	asGfsgcaUfuaauUfUfCfaggagcsusu	3500
D-2291	[GalNac3]scaaugCfUfCfAfUfaguccagag(invAb)	3161	asAfsucggGfacauUfAfgcauugsusu	2783
D-2292	[GalNac3]scaaugCfUfCfAfUfaguccagag(invAb)	2051	asAfsucggGfacauUfAfgcauugsusu	3414
D-2293	[GalNac3]scaaugCfUfCfAfUfaguccagag(invAb)	3161	asAfsucggGfacauUfAfgcauugsusu	3414
D-2294	[GalNac3]scaaugCfUfCfAfUfaguccagag(invAb)	2051	asAfsucggGfacauUfAfgcauugsusu	3428
D-2295	[GalNac3]scaaugcuCfAfUfGfUfcccagag(invAb)	3155	asAfsucggGfacauUfAfgcauugsusu	3428
D-2296	[GalNac3]scaaugcuCfAfUfGfUfcccagag(invAb)	3155	asAfsucgGfGfacauUfAfgcauugsusu	3430
D-2297	[GalNac3]scaaugCfUfCfAfUfaguccagag(invAb)	3161	asAfsucgGfGfacauUfAfgcauugsusu	3430
D-2298	[GalNac3]scaaugcuCfAfUfGfUfcccagag(invAb)	3155	asAfsucggGfacauUfAfgcauugsusu	3431
D-2299	[GalNac3]scaaugCfUfCfAfUfaguccagag(invAb)	3161	asAfsucggGfacauUfAfgcauugsusu	3431
D-2301	[GalNac3]sauguccUfgGfAfUfUfauuagagcs(invAb)	3212	asCfsaucUfuaauUfCfGfagagagusu	3501

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2302	[GalNAC3]suauaacUfcUfAfAfGfaucugaugs{invAb}	3213	usCfsaucaGfaucuuuGfaGfuuuuasusu	3502
D-2303	[GalNAC3]suaagauCfuGfAfUfGfaaguuauus{invAb}	3214	asAfsuauaCfuucauAfgAfucuuasusu	3503
D-2304	[GalNAC3]sggugucUfcAfAfUfGfcuucuaugs{invAb}	3215	asCfsauugAfagcauuGfaGfacaccsusu	3504
D-2305	[GalNAC3]sgugucuCfaAfUfGfcfuucuaugs{invAb}	3216	asAfscauuGfaagcauUfgAfgacacsusu	3505
D-2306	[GalNAC3]succuaaUfgCfUfCfaauguccs{invAb}	3217	usGfsggacAfuugaagCfaUfagagasusu	3506
D-2307	[GalNAC3]saaugcuUfcAfAfUfGfuuccagugs{invAb}	3218	asCfsacugGfgacauuGfaAfgcauususu	3507
D-2308	[GalNAC3]saugcuuCfaAfUfGfuccagugcs{invAb}	3219	usGfscacuGfggacauUfgAfgcaususu	3508
D-2309	[GalNAC3]succugGfaUfaUfugaugccs{invAb}	3220	asAfsggcaUfcuaauUfcCfcaggasusu	3336
D-2310	[GalNAC3]sacucuaAfgAfUfCfugaugaugs{invAb}	3221	usAfscaucAfucagauCfuUfagagasusu	3337
D-2311	[GalNAC3]sguccugGfaAfUfAfuugaugccs{invAb}	3222	asGfsgcauCfuuaauUfcCfaggacsusu	3338
D-2312	[GalNAC3]suguccuGfgAfaUfaugaugcs{invAb}	3223	asGfscacuUfaauuuCfcAfggacacusu	3339
D-2313	[GalNAC3]suaacucUfaAfgAfucugaugaas{invAb}	3224	asUfsucauCfagauCfuGfaguuasusu	3340
D-2314	[GalNAC3]succuggaaUfaUfUfAfGfaugccs{invAb}	3191	asAfsggcaUfcuaauUfcCfcaggasusu	3336
D-2315	[GalNAC3]sacucuaagAfuCfUfGfAfugaagus{invAb}	3190	usAfscaucAfucagauCfuUfagagasusu	3337
D-2316	[GalNAC3]sguccugGfaAfUfUfAfgaugccs{invAb}	3189	asGfsgcauCfuuaauUfcCfaggacsusu	3338
D-2317	[GalNAC3]suguccugAfaUfAfUfUfagugcs{invAb}	3188	asGfscacuUfaauuuCfcAfggacacusu	3339
D-2318	[GalNAC3]suaacucuaAfgAfUfCfUfugaugaas{invAb}	3225	asUfsucauCfagauCfuGfaguuasusu	3340
D-2319	[GalNAC3]succugGfaUfaUfugaugccs{invAb}	3220	asAfsggcaUfcuaaUfaUfuccaggasusu	3479
D-2320	[GalNAC3]sacucuaAfgAfUfCfugaugaugs{invAb}	3221	usAfscaucAfucagAfuCfuugaugasusu	3478
D-2321	[GalNAC3]sguccugGfaAfUfAfuugaugccs{invAb}	3222	asGfsgcauCfuuaaUfuUfccaggacsusu	3477
D-2322	[GalNAC3]suguccuGfgAfaUfaugaugcs{invAb}	3223	asGfscacuUfaauuUfuCfcaggacsusu	3476
D-2323	[GalNAC3]suaacucUfaAfgAfucugaugaas{invAb}	3224	asUfsucauCfagauCfuUfagaguuasusu	3509
D-2324	[GalNAC3]succugGfaUfaUfUfagugccs{invAb}	3077	asAfsggcaucuaaUfaUfCfcaggasusu	3510
D-2325	[GalNAC3]sacucuaAfgAfUfCfUfugaugaugs{invAb}	3078	usAfscaucacagAfuCfuUfagagasusu	3511
D-2326	[GalNAC3]sguccugGfaAfUfAfuugaugccs{invAb}	3079	asGfsgcaucuaaUfuUfcCfaggacsusu	3512
D-2327	[GalNAC3]suguccuGfgAfaUfAfuugaugcs{invAb}	3080	asGfscacuuaaUfuCfcAfggacacusu	3513
D-2328	[GalNAC3]suaacucUfaAfgAfUfCfugaugaas{invAb}	3081	asUfsucaucagauCfuUfaGfaguuasusu	3514
D-2329	[GalNAC3]succugGfaUfaUfUfagugccs{invAb}	3077	asAfsggcaUfcuaaUfaUfuccaggasusu	3479
D-2330	[GalNAC3]sacucuaAfgAfUfCfUfugaugaugs{invAb}	3078	usAfscaucAfucagAfuCfuugaugasusu	3478
D-2331	[GalNAC3]sguccugGfaAfUfAfuugaugccs{invAb}	3079	asGfsgcauCfuuaaUfuUfccaggacsusu	3477
D-2332	[GalNAC3]suguccuGfgAfaUfAfuugaugcs{invAb}	3080	asGfscacuUfaauuUfuCfcaggacsusu	3476
D-2333	[GalNAC3]suaacucUfaAfgAfUfCfugaugaas{invAb}	3081	asUfsucauCfagauCfuUfagaguuasusu	3509
D-2334	[GalNAC3]succuggaaUfaUfUfAfGfagccs{invAb}	3191	asAfsggcaucuaaUfaUfCfcaggasusu	3510
D-2335	[GalNAC3]sacucuaagAfuCfUfGfAfugaagus{invAb}	3190	usAfscaucacagAfuCfuUfagagasusu	3511
D-2336	[GalNAC3]sguccugGfaAfUfUfAfgaugccs{invAb}	3189	asGfsgcaucuaaUfuUfcCfaggacsusu	3512
D-2337	[GalNAC3]suguccugAfaUfAfUfUfagugcs{invAb}	3188	asGfscacuuaaUfuCfcAfggacacusu	3513
D-2338	[GalNAC3]suaacucuaAfgAfUfCfUfugaugaas{invAb}	3225	asUfsucaucagauCfuUfaGfaguuasusu	3514
D-2339	[GalNAC3]succuggaaUfaUfUfAfGfaugccs{invAb}	3191	asAfsggcaUfcuaaUfaUfCfcaggasusu	3515
D-2340	[GalNAC3]sacucuaagAfuCfUfGfAfugaagus{invAb}	3190	usAfscaucAfucagAfuCfuUfagagasusu	3516
D-2341	[GalNAC3]sguccugGfaAfUfUfAfgaugccs{invAb}	3189	asGfsgcauCfuuaaUfuUfcCfaggacsusu	3500
D-2342	[GalNAC3]suguccugAfaUfAfUfUfagugcs{invAb}	3188	asGfscacuUfaauuUfuCfcAfggacacusu	3517
D-2343	[GalNAC3]suaacucuaAfgAfUfCfUfugaugaas{invAb}	3225	asUfsucauCfagauCfuUfaGfaguuasusu	3518
D-2344	[GalNAC3]succugGfaUfaUfugaugccs{invAb}	3220	asAfsggcaUfcuaaUfuCfcaggasusu	3519
D-2345	[GalNAC3]sacucuaAfgAfUfCfugaugaugs{invAb}	3221	usAfscaucAfucagauCfuUfagagasusu	3520
D-2346	[GalNAC3]sguccugGfaAfUfAfuugaugccs{invAb}	3222	asGfsgcaUfcuaauUfuCfcaggacsusu	3499
D-2347	[GalNAC3]suguccuGfgAfaUfaugaugcs{invAb}	3223	asGfscacuUfaauuuCfcAfggacacusu	3521
D-2348	[GalNAC3]suaacucUfaAfgAfucugaugaas{invAb}	3224	asUfsucaUfCfagauCfuGfaguuasusu	3522
D-2349	[GalNAC3]succuggaaUfaUfUfAfGfaugccs{invAb}	3191	asAfsggcaUfcuaaUfuCfcaggasusu	3519
D-2350	[GalNAC3]sacucuaagAfuCfUfGfAfugaagus{invAb}	3190	usAfscaucAfucagauCfuUfagagasusu	3520
D-2351	[GalNAC3]sguccugGfaAfUfUfAfgaugccs{invAb}	3189	asGfsgcaUfcuaauUfuCfcaggacsusu	3499
D-2352	[GalNAC3]suguccugAfaUfAfUfUfagugcs{invAb}	3188	asGfscacuUfaauuuCfcAfggacacusu	3521
D-2353	[GalNAC3]suaacucuaAfgAfUfCfUfugaugaas{invAb}	3225	asUfsucaUfCfagauCfuGfaguuasusu	3522
D-2354	[GalNAC3]succugGfaUfaUfugaugccs{invAb}	3220	asAfsggcaUfcuaaUfuUfCfcaggasusu	3515

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2355	[GalINAc3]sacucuaAfgAfuCfugaugaagus(invAb)	3221	usAfsucuAfuCagAfuCfuUfagagususu	3516
D-2356	[GalINAc3]sguccugGfaAfuAfuuaugccs(invAb)	3222	asGfsgcauCfuuaaUfuUfcCfaggacsusu	3500
D-2357	[GalINAc3]suguccuGfgAfaUfaauagaugcs(invAb)	3223	asGfscacuUfaauaUfuCfcAfggacacusu	3517
D-2358	[GalINAc3]suaacucUfaAfgAfuCugaugaas(invAb)	3224	asUfsucauCfagauCfuUfaGfaguuasusu	3518
D-2359	[GalINAc3]sugauggCfuUfGfUfUfccagaugcs(invAb)	3226	usGfscaucUfggaacaAfgCfcaucasusu	3523
D-2360	[GalINAc3]sgauggcUfuGfUfUfcCagaugcas(invAb)	3227	asUfsgcauCfuggaacAfaGfccaucsusu	3524
D-2361	[GalINAc3]scucagaCfaGfCfAfUfuggauuucs(invAb)	3228	asGfsaaauCfcaaugCfuUfcugagsusu	3525
D-2362	[GalINAc3]sgccauUfuUfGfUfCfuugaauus(invAb)	3229	usAfsaucaAfaaggacaAfaCfcaucasusu	3526
D-2363	[GalINAc3]sccauuuUfgUfCfUfuugaauus(invAb)	3230	usAfsuaauCfaaaggacAfaAfauggsusu	3527
D-2364	[GalINAc3]sugauggcuUfgUfUfCfCagaugcs(invAb)	3231	usGfscaucUfggaaCfaAfgccaucasusu	3528
D-2365	[GalINAc3]sgauggcuUfuUfCfCfAfgaugcas(invAb)	3232	asUfsgcauCfuggaAfcAfgccaucasusu	3529
D-2366	[GalINAc3]scucagacaGfCfAfUfGfgauuucs(invAb)	3233	asGfsaaauCfcauGfcUfgucugagsusu	3530
D-2367	[GalINAc3]sugccauuuUfgUfCfUfuugaauus(invAb)	3234	usAfsaucaAfaaggacAfaAfauggcasusu	3531
D-2368	[GalINAc3]sccauuuUfgCfUfUfUfgauuucs(invAb)	3235	usAfsuaauCfaaagGfaCfaaauugsusu	3532
D-2369	[GalINAc3]sugauggCfuUfGfUfUfccagaugcs(invAb)	3226	usGfscAfuCfuggaacaAfgCfcaucasusu	3533
D-2370	[GalINAc3]sgauggcUfuGfUfUfCfCagaugcas(invAb)	3227	asUfsgCfaUfcuggaacAfaGfccaucsusu	3534
D-2371	[GalINAc3]scucagaCfaGfCfAfUfuggauuucs(invAb)	3228	asGfsaAfaUfccaaugCfuUfcugagsusu	3535
D-2372	[GalINAc3]sugccauUfuUfGfUfCfuugaauus(invAb)	3229	usAfsaUfcAfaaggacaAfaUfuggcasusu	3536
D-2373	[GalINAc3]sccauuuUfgUfCfUfuugaauuucs(invAb)	3230	usAfsuAfaUfcaaggacAfaAfauggsusu	3537
D-2374	[GalINAc3]sgsaaaaUfaCfAfUfUfuucgucuc(invAb)	3236	asAfsagacAfaaaugUfgAfaaaucsuu	3369
D-2375	[GalINAc3]sgauuuucaCfaUfUfUfUfucgucuc(invAb)	3237	asAfsagacAfaaaUfgUfgaaucsuu	3538
D-2376	[GalINAc3]sgaaauuaGfaUfGfCfCfuuuuacs(invAb)	3238	usUfsuaaaAfggcaUfcUfaauuucsuu	3539
D-2377	[GalINAc3]saggaagCfaUfUfGfUfcaguuus(invAb)	3239	asCfsaacuGfacauAfuGfuuuucsuu	3540
D-2378	[GalINAc3]sgccauuuUfuUfGfUfUfugauuacs(invAb)	3240	asUfsaaucAfaaggAfcAfaauggcsusu	3541
D-2379	[GalINAc3]sgauuuuUfaCfAfUfUfuucgucuc(invAb)	3110	asAfsagCfCfaaaugUfgAfaaaucsuu	2605
D-2380	[GalINAc3]sgaaauuUfaGfAfUfUfuccuuuacs(invAb)	3112	usUfsuAfaAfaaggcauCfaAfaauucsuu	2597
D-2381	[GalINAc3]saggaagCfaUfUfUfUfugcaguuus(invAb)	3114	asCfsaAfcUfgacauuGfcUfuuccsuu	2727
D-2382	[GalINAc3]sgccauuUfuGfUfCfCfuugaauuacs(invAb)	3117	asUfsaAfuCfaaaggacAfaAfauggcsusu	2739
D-2383	[GalINAc3]sgsasuuuUfaCfAfUfUfuucgucuc(invAb)	3241	asAfsagacAfaaaugUfgAfaaaucsuu	3369
D-2384	[GalINAc3]scaaugcuUfaUfGfUfUfccaguuus(invAb)	3155	asAfsucggGfacauuGfaGfcausug	3434
D-2385	[GalINAc3]scaaugcUfuCfAfUfUfucccaguuus(invAb)	2051	asAfsucgGfGfacauuGfaGfcausug	3542
D-2386	[GalINAc3]saugcuUfaUfUfUfUfccaguuuacs(invAb)	3151	asAfsucggGfacauuGfaGfcausug	3434
D-2387	[GalINAc3]saugcuUfaUfUfUfUfccaguuuacs(invAb)	3151	asAfsucgGfGfacauuGfaGfcaususu	3543
D-2388	[GalINAc3]scaaugcuUfaUfUfUfUfccaguuus(invAb)	3155	asAfsucggGfacauuGfaGfcauugsusu	2783
D-2389	[GalINAc3]scaaugcuUfaUfUfUfUfccaguuus(invAb)	3155	asAfsucggGfacauuGfaGfcauugsasg	3427
D-2390	[GalINAc3]saugcUfuCfAfUfUfucccaguuuacs(invAb)	3242	asAfsucggGfacauuGfaGfcaususu	3410
D-2391	[GalINAc3]scaaugcUfuCfAfUfUfucccaguuus(invAb)	2051	asAfsucgGfGfacauuGfaGfcauugsasg	3544
D-2392	[GalINAc3]saugcUfuCfAfUfUfucccaguuuacs(invAb)	3242	asAfsucggGfacauuGfaGfcausug	3434
D-2393	[GalINAc3]succugGfaUfaUfuagaugccs(invAb)	3220	asAfsggcaucuaaUfaUfuCfaggasusu	3510
D-2394	[GalINAc3]sacucuaAfgAfuCfugaugaagus(invAb)	3221	usAfsucuAfuCagAfuCfuUfagagususu	3511
D-2395	[GalINAc3]sguccugGfaAfuAfuuaugccs(invAb)	3222	asGfsgcaucuaaUfuUfcCfaggacsusu	3512
D-2396	[GalINAc3]suguccuGfgAfaUfaauagaugcs(invAb)	3223	asGfscaucuaaUfuCfcAfggacacusu	3513
D-2397	[GalINAc3]suaacucUfaAfgAfuCugaugaas(invAb)	3224	asUfsucaucagauCfuUfaGfaguuasusu	3514
D-2399	[GalINAc3]scaaugcUfuCfAfUfUfucccaguuus(invAb)	2051	asAfsucggGfacauUfgAfaGfcausug	3545
D-2400	[GalINAc3]saugcuUfaUfUfUfUfccaguuuacs(invAb)	3151	asAfsucggGfacauUfgAfaGfcaususu	3546
D-2401	[GalINAc3]scaaugcUfuCfAfUfUfUfucccaguuus(invAb)	2051	asAfsucggGfacauUfgAfaGfcauugsasg	3547
D-2402	[GalINAc3]scaaugcuUfaUfUfUfUfccaguuus(invAb)	3155	asAfsucgGfGfacauuGfaGfcauugsasg	3544
D-2403	[GalINAc3]scaaugcuUfaUfUfUfUfccaguuus(invAb)	3155	asAfsucggGfacauUfgAfaGfcauugsasg	3547
D-2430	[GalINAc3]sgauuuuUfaCfAfUfUfuucgucuc(invAb)	3110	asAfsagacAfaaaugUfgAfaaausc	3548
D-2431	[GalINAc3]sgaaauuUfaGfAfUfGfuuuuaacs(invAb)	3112	usUfsuaaaAfggcauCfaAfaaususc	3549
D-2432	[GalINAc3]saggaagCfaUfUfUfUfucaguuus(invAb)	3114	asCfsaacuGfacauuGfcUfuucscsu	3550
D-2433	[GalINAc3]sgccauuUfuGfUfCfCfuugaauuacs(invAb)	3117	asUfsaaucAfaaggacAfaAfaugsgsc	3551
D-2434	[GalINAc3]saaauuAfgUfCfUfCfaaaacuuus(invAb)	3129	usAfsaguuAfuugagaCfuAfaaususu	3552

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Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2488	[GalNAc3]sgugucuCfaAfUfGfCfuucaugus{invAb}	3216	asAfscauuGfaagcauUfgAfgacsasc	3590
D-2489	[GalNAc3]saauagcAfgAfCfUfUfguuccgacs{invAb}	2066	asGfsuCfGfGfaacaaguCfuGfcuaususu	2171
D-2490	[GalNAc3]sccccguUfuAfAfCfUfgauuaggs{invAb}	3115	usCfscAfuAfaucaguuAfaAfcggggsusu	2653
D-2491	[GalNAc3]saugacaAfcAfCfUfUfgaagcaugs{invAb}	3118	asCfsaUfgCfuucaaguGfuUfgucaususu	2371
D-2492	[GalNAc3]suauugcCfaUfUfUfUfguccuuugs{invAb}	3138	usCfsaAfaGfgacaaaaUfgGfcauasusu	2338
D-2493	[GalNAc3]suauaacUfcUfAfAfGfauccugaus{invAb}	3213	usCfsaUfcAfgaucuaaGfaGfuuaususu	2475
D-2494	[GalNAc3]sgugucuCfaAfUfGfCfuucaugus{invAb}	3216	asAfscaUfuUfgaagcauUfgAfgacacsusu	2245
D-2495	[GalNAc3]suagcagAfcUfUfGfUfuccgacus{invAb}	3262	asGfsucggAfacaaguCfuAfaacgggsusu	3585
D-2496	[GalNAc3]sccguuuAfaCfUfGfAfuuauggasus{invAb}	3263	usCfscauaAfucaguuAfaAfcgggsusu	3591
D-2497	[GalNAc3]sgacaacAfcUfUfGfAfgcaugus{invAb}	3264	asCfsaugcUfucaguGfuUfgucsusu	3592
D-2498	[GalNAc3]suugccaUfuUfUfGfUfuccuuugasus{invAb}	3265	usCfsaaagGfacaauUfgGfcaasusu	3593
D-2499	[GalNAc3]suaacucUfaAfGfAfUfcugaugasus{invAb}	3266	usCfsaucaGfaucuaaGfaGfuuasusu	3594
D-2500	[GalNAc3]sgucucaAfuGfCfUfUfcaauugus{invAb}	3267	asAfscauuGfaagcauUfgAfgacsusu	3595
D-2501	[GalNAc3]saauagcagAfcUfUfGfUfuccgacs{invAb}	3268	asGfsucggAfacaagGfuCfugcuauususu	3596
D-2502	[GalNAc3]sccccguuuAfaCfUfGfAfuuauggs{invAb}	3269	usCfscauaAfucagUfuAfaAfcggggsusu	3597
D-2503	[GalNAc3]saugacaacAfcUfUfGfAfgcaugs{invAb}	3270	asCfsaugcUfucaaGfuGfuugucaususu	3598
D-2504	[GalNAc3]suauugccaUfuUfUfGfUfuccuuugs{invAb}	3271	usCfsaaagGfacaAfaUfggcaauasusu	3599
D-2505	[GalNAc3]suauaacucUfaAfGfAfUfcugaus{invAb}	3272	usCfsaucaGfaucUfaGfaguauasusu	3600
D-2506	[GalNAc3]sgugucuAfuGfCfUfUfcaaugus{invAb}	3273	asAfscauuGfaagcAfuUfgagacacsusu	3601
D-2507	[GalNAc3]saauagcagAfcUfUfGfUfuccgacs{invAb}	3268	asGfsucggAfacaagGfuCfuGfcuaususu	3602
D-2508	[GalNAc3]sccccguuuAfaCfUfGfAfuuauggs{invAb}	3269	usCfscauaAfucagUfuAfaAfcggggsusu	3603
D-2509	[GalNAc3]saugacaacAfcUfUfGfAfgcaugs{invAb}	3270	asCfsaugcUfucaaGfuGfuUfgucaususu	3604
D-2510	[GalNAc3]suauugccaUfuUfUfGfUfuccuuugs{invAb}	3271	usCfsaaagGfacaAfaUfgGfcauasusu	3605
D-2511	[GalNAc3]suauaacucUfaAfGfAfUfcugaus{invAb}	3272	usCfsaucaGfaucUfaGfaGfuuaususu	3606
D-2512	[GalNAc3]sgugucuAfuGfCfUfUfcaaugus{invAb}	3273	asAfscauuGfaagcAfuUfgAfgacacsusu	3607
D-2514	gsusgaugGfcUfUfGfUfuccggaugs{invAb}	3274	asCfsauccGfgaacaGfcCfaucsasc	3608
D-2515	gsusgaugGfcUfUfGfUfugcagaugs{invAb}	3275	asCfsaucuGfcaacaGfcCfaucsasc	3609
D-2516	csasgaacGfaAfAfGfUfuauugga{invAb}	3276	usUfscacAfuaacuuUfcGfuucugsasa	3610
D-2517	csasgaacGfaAfAfGfUfugaugga{invAb}	3277	usUfscacAfuaacuuUfcGfuucugsasa	3611
D-2518	usasugucCfuGfGfAfAfuaaagaugs{invAb}	3278	asAfsucuuAfuaauuccAfgGfacaasusu	3612
D-2519	usasugucCfuGfGfAfAfugaagaugs{invAb}	3279	asAfsucuaAfcauuccAfgGfacaasusu	3613
D-2520	asusguccUfgGfAfAfUfauuggaugs{invAb}	3280	asCfsauccAfauauucCfaGfgacaasusu	3614
D-2521	asusguccUfgGfAfAfUfauaagaugs{invAb}	3281	asCfsaucuAfuaauucCfaGfgacaasusu	3615
D-2522	usgsuccuGfgAfAfUfAfuaaagaugs{invAb}	3282	asGfscauuUfaauuuCfaAfggacacusu	3616
D-2523	usgsuccuGfgAfAfUfAfuaaagaugs{invAb}	3283	asGfscaucUfuaauuUfcAfggacacusu	3617
D-2524	cscsuggaAfuAfUfUfAfggugccuus{invAb}	3284	asGfsgcacCfuauuuUfcCfaggsusu	3618
D-2525	cscsuggaAfuAfUfUfGfagugccuus{invAb}	3285	asGfsgcauCfcauuUfcCfaggsusu	3619
D-2526	uscscuggAfuAfUfUfUfagaagccus{invAb}	3286	asAfsggcuUfcauaUfuCfcagsgsa	3620
D-2527	uscscuggAfuAfUfUfUfafaagccus{invAb}	3287	asAfsggcuUfuaauUfuCfcagsgsa	3621
D-2528	cscsuggaAfuAfUfUfAfgauaccuus{invAb}	3288	asAfsagguAfucuaUfuUfccaggsusu	3622
D-2529	cscsuggaAfuAfUfUfAfggugccuus{invAb}	3284	asAfsagguAfccuaUfuUfccaggsusu	3623
D-2530	csusggaaUfaUfUfAfGfauugccuus{invAb}	3289	asAfsaagcCfaucuaUfaUfuccagsusu	3624
D-2531	csusggaaUfaUfUfAfGfagccuus{invAb}	3290	asAfsaaggCfuucuaUfaUfuccagsusu	3625
D-2532	gsasauuuUfaGfAfUfGfccaauuaa{invAb}	3291	usUfsauuuAfggcaucUfaAfuaucusu	3626
D-2533	gsasauuuUfaGfAfUfGfccaauuaa{invAb}	3292	usUfsauuuAfcgcaucUfaAfuaucusu	3627
D-2534	gsasugccUfuUfUfAfAfaaaaguc{invAb}	3293	asGfsaacuUfuuuuuAfaGfgcaucusu	3628
D-2535	gsasugccUfuUfUfAfAfaaguc{invAb}	3294	asGfsaacaUfuuuuAfaGfgcaucusu	3629
D-2536	gsasuuuuCfaCfAfUfUfuugguc{invAb}	3295	asAfsagccAfaaaugUfgAfaaaucusu	3630
D-2537	gsasuuuuCfaCfAfUfUfuuguc{invAb}	3296	asAfsagccAfaaaugUfgAfaaaucusu	3631
D-2538	csuscauuGfcUfUfCfAfaugacca{invAb}	3297	asUfsgggcCfauugaaGfcAfuugagsusu	3632
D-2539	csuscauuGfcUfUfCfAfaugacca{invAb}	3298	asUfsgggcCfauugaaGfcAfuugagsusu	3633
D-2540	csasaugcUfaCfAfUfUfgucgag{invAb}	3299	asAfsucgGfacaUfgAfaGfcausug	3634
D-2541	csasaugcUfuCfAfUfUfgaccag{invAb}	3300	asAfsucgGfacaUfgAfaGfcausug	3635

Duplex No.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-2542	asasauauAfgUfCfUfCfaaagacuus{invAb}	3301	usAfsagucAfuugagaCfuAfuauuususu	3636
D-2543	asasauauAfgUfCfUfCfaguacuus{invAb}	3302	usAfsaguuAfcugagaCfuAfuauuususu	3637
D-2544	gscsaggaUfuCfUfGfAfaagucccs{invAb}	3303	asGfsggacUfuuuacagAfaUfccugcsusu	3638
D-2545	gscsaggaUfuCfUfGfAfaagucccs{invAb}	3304	asGfsggagUfcuucagAfaUfccugcsusu	3639
D-2546	usasccaaGfaGfCfGfCfagaguugs{invAb}	3305	usGfscacUfcugcgUfcUfugguasusu	3640
D-2547	usasccaaGfaGfCfGfCfaaacuugs{invAb}	3306	usGfscagUfuugcgUfcUfugguasusu	3641
D-2548	asgsaaaaGfCfUfAfuUfgucguugs{invAb}	3307	asCfsaacGfacaauGfCfuuccususu	3642
D-2549	asgsaaaaGfCfUfAfuUfgacaguugs{invAb}	3308	asCfsaacUfucuuGfCfuuccususu	3643
D-2550	gsusuuuaAfaCfCfAfaaacuua{invAb}	3309	usAfsgauUfugguuUfuAfaacsusu	3644
D-2551	gsusuuuaAfaCfCfGfauaucua{invAb}	3310	usAfsgauUfugguuUfuAfaacsusu	3645
D-2552	ususaacuGfaUfUfGfUfauagcucus{invAb}	3311	usAfsagcUfauacaaUfcAfguuasusu	3646
D-2553	ususaacuGfaUfUfGfUfaaacucus{invAb}	3312	usAfsagauUfuuaaaUfcAfguuasusu	3647
D-2554	usasacucUfaAfgAfUfcugugaa{invAb}	3313	asUfsucacCfagauUfaGfagususa	3648
D-2555	usasacucUfaAfgAfUfcagugaa{invAb}	3314	asUfsucaUfcagauUfaGfagususa	3649
D-2556	ascscuaAfgAfUfCfUfgauaag{invAb}	3315	usAfsuuUfucagUfcUfagagususu	3650
D-2557	ascscuaAfgAfUfCfUfgugaag{invAb}	3316	usAfsuuUfcagUfcUfagagususu	3651
D-2558	usasuuccaUfuUfUfGfUfcguugs{invAb}	3317	usCfsaacGfacaAfaUfgGfcauusu	3652
D-2559	usasuuccaUfuUfUfGfUfcguugs{invAb}	3318	usCfsaacGfacaAfaUfgGfcauusu	3653
D-2560	gscscuuUfuUfUfCfUfuuaaua{invAb}	3319	asUfsuuAfaaggacAfaAfauggcsusu	3654
D-2561	gscscuuUfuUfUfCfUfuuaaua{invAb}	3320	asUfsaacAfaaggacAfaAfauggcsusu	3655

Example 3. In Vitro Evaluation of mARC1 siRNA Molecules in a Cell-Based Assay

[0214] The mARC1 siRNA molecules having different sequences prioritized from the bioinformatics analyses described in Example 2 were screened for efficacy in reducing human mARC1 mRNA using an RNA FISH (fluorescence *in situ* hybridization) assay. Hep3B cells (purchased from ATCC) 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). The mARC1 siRNA molecules were tested in a 10-point dose response format, 3-fold dilutions, ranging from 500 nM to 25 pM (run 1), 25 nM to 1 pM (run 2), or 100 nM to 5 pM (run 3), final concentrations. 1 μ L of the test siRNA molecule or phosphate-buffered saline (PBS) vehicle and 4 μ L of base 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 base EMEM without supplements (0.035 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 Hep3B 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. 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 (Thermo Fisher Scientific) 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). 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 normalized values against the total siRNA concentrations were plotted and the data were fit to a four-parameter sigmoidal model using Genedata Screener data analysis software (Genedata) to obtain IC₅₀ and maximum activity values. If the data could not be fit to the model, an IC₅₀ value was not calculated and only a maximum activity value was reported.

[0215] The mARC1 siRNA molecules were initially screened in a first run at ten different concentrations ranging from 500 nM to 25 pM. siRNA molecules exhibiting significant activity in the first run were screened in second and third runs at ten different concentrations over narrower concentration ranges (run 2: 25 nM to 1 pM; run 3: 100 nM to 5 pM). The results of the assays for all three runs are shown in Table 3 below.

Table 3. In vitro inhibition of human mARC1 mRNA in Hep3B cells

Duplex No.	Run 1 (500 nM to 25 pM)		Run 2 (25 nM to 1 pM)		Run 3 (100 nM to 5 pM)	
	IC50 [M]	Max Activity	IC50 [M]	Max Activity	IC50 [M]	Max Activity
D-1092	1.64E-10	-96.0	1.60E-09	-93.0	2.43E-09	-96.5
D-1093	1.03E-10	-89.5	1.19E-09	-90.9	9.30E-10	-95.8
D-1139	3.44E-10	-87.1	2.43E-09	-93.7	2.35E-09	-90.6
D-1061	3.44E-11	-89.0	9.04E-10	-90.5	1.79E-09	-93.0
D-1138	1.13E-10	-89.9	2.19E-09	-87.9	1.60E-09	-92.4
D-1095	1.27E-10	-86.9	1.34E-09	-86.5	1.28E-09	-92.4
D-1191	—	-93.5	1.06E-09	-91.7	8.45E-10	-86.4
D-1180	1.52E-10	-86.2	1.41E-09	-88.3	2.15E-09	-89.6
D-1090	1.26E-10	-88.1	1.42E-09	-87.6	2.10E-09	-89.5
D-1062	3.36E-11	-88.5	1.15E-09	-87.9	1.01E-09	-89.0
D-1177	5.02E-11	-81.0	1.43E-09	-90.2	2.33E-09	-86.5
D-1083	6.31E-10	-87.8	1.88E-09	-84.8	1.19E-09	-91.8
D-1245	1.04E-10	-83.9	4.46E-10	-87.6	2.19E-09	-88.5
D-1067	—	-79.8	1.41E-09	-85.5	9.69E-10	-90.3
D-1143	—	-92.8	1.49E-09	-85.2	2.41E-09	-90.3
D-1170	1.87E-10	-86.4	1.21E-09	-86.0	9.50E-10	-89.1
D-1044	4.69E-11	-81.3	1.45E-09	-89.4	1.03E-09	-85.6
D-1096	7.11E-11	-91.0	5.60E-10	-82.5	8.71E-10	-91.8
D-1113	1.15E-10	-85.9	1.56E-09	-87.1	1.39E-09	-85.5
D-1086	2.40E-10	-83.5	2.26E-09	-84.0	2.28E-09	-88.5
D-1256	—	-88.9	6.08E-10	-87.1	8.37E-10	-85.2
D-1189	1.50E-10	-84.7	1.36E-09	-85.4	2.08E-09	-86.7
D-1091	9.38E-11	-88.8	2.12E-09	-87.8	1.42E-09	-84.2
D-1174	1.50E-10	-84.1	1.57E-09	-85.5	2.53E-09	-86.5
D-1185	3.25E-11	-86.6	4.67E-10	-82.6	2.18E-09	-88.6
D-1066	4.91E-11	-80.3	1.33E-09	-86.7	1.21E-09	-84.3
D-1171	—	-83.8	1.10E-09	-88.0	1.01E-09	-83.0
D-1140	3.09E-10	-87.8	2.64E-09	-86.5	2.97E-09	-84.0
D-1130	1.76E-10	-77.0	2.94E-09	-88.9	2.36E-09	-81.5
D-1068	4.98E-11	-80.1	1.40E-09	-82.9	1.08E-09	-87.5
D-1243	—	-90.2	6.70E-10	-84.9	8.36E-10	-85.4
D-1074	6.75E-11	-76.5	1.01E-09	-85.8	1.41E-09	-83.7
D-1150	1.78E-10	-87.5	1.21E-09	-84.3	2.11E-09	-84.7
D-1249	2.48E-11	-85.1	1.03E-09	-84.2	2.11E-09	-84.5
D-1111	6.71E-11	-87.3	1.10E-09	-85.4	1.52E-09	-82.9
D-1230	3.95E-11	-83.7	9.01E-10	-84.7	1.20E-09	-83.5
D-1087	2.03E-10	-83.3	1.75E-09	-85.3	1.76E-09	-82.9
D-1099	4.39E-11	-79.6	1.82E-09	-84.8	1.16E-09	-82.9
D-1190	1.47E-10	-82.9	1.15E-09	-84.8	2.01E-09	-82.8

Duplex No.	Run 1 (500 nM to 25 pM)		Run 2 (25 nM to 1 pM)		Run 3 (100 nM to 5 pM)	
	IC50 [M]	Max Activity	IC50 [M]	Max Activity	IC50 [M]	Max Activity
D-1236	2.72E-10	-85.2	1.20E-09	-85.3	2.14E-09	-82.2
D-1184	1.62E-10	-81.3	2.24E-09	-81.8	2.43E-09	-85.6
D-1228	—	-83.3	5.73E-10	-78.9	5.66E-10	-87.3
D-1220	5.60E-10	-86.0	2.05E-09	-80.8	9.99E-10	-85.1
D-1204	4.99E-11	-79.7	1.84E-09	-78.9	2.51E-09	-87.0
D-1179	7.45E-11	-81.8	1.64E-09	-86.5	1.26E-09	-78.1
D-1147	3.64E-10	-85.0	8.60E-10	-89.7	2.85E-09	-73.8
D-1097	3.39E-10	-86.6	2.97E-09	-85.2	3.27E-09	-78.0
D-1194	1.31E-10	-78.9	1.40E-09	-71.2	2.49E-09	-86.3
D-1054	1.63E-10	-66.3	1.89E-09	-85.2	4.36E-09	-71.2
D-1176	4.61E-11	-74.7	1.34E-09	-67.1	1.55E-09	-85.1
D-1215	1.08E-10	-85.0	1.53E-09	-84.5	2.35E-09	-82.4
D-1166	8.24E-11	-84.0	1.94E-09	-84.2	2.39E-09	-82.4
D-1213	4.13E-11	-73.9	5.89E-10	-84.3	1.23E-09	-82.1
D-1187	1.55E-10	-87.9	2.30E-09	-82.7	2.25E-09	-83.3
D-1210	—	—	2.12E-09	-82.4	1.93E-09	-83.5
D-1209	1.10E-10	-78.7	1.81E-09	-82.3	1.84E-09	-83.0
D-1246	5.28E-11	-77.0	5.07E-10	-84.1	2.19E-09	-80.4
D-1257	—	-82.1	9.40E-10	-80.7	2.03E-09	-83.4
D-1020	1.18E-10	-78.3	2.53E-09	-84.8	1.79E-09	-78.9
D-1168	3.87E-11	-84.5	1.32E-09	-82.0	8.52E-10	-81.5
D-1241	2.42E-10	-81.0	1.92E-09	-81.2	2.63E-09	-81.9
D-1255	2.93E-11	-80.7	1.27E-09	-80.4	1.24E-09	-82.5
D-1181	2.85E-10	-85.0	1.30E-09	-78.1	1.69E-09	-84.6
D-1252	—	-81.6	8.95E-10	-78.4	2.22E-09	-84.3
D-1172	9.64E-11	-78.7	1.51E-09	-83.3	1.04E-09	-79.2
D-1175	6.64E-11	-76.8	1.28E-09	-80.9	2.21E-09	-81.5
D-1235	2.60E-10	-83.0	1.66E-09	-81.3	2.63E-09	-80.8
D-1229	1.30E-10	-82.5	6.74E-10	-84.3	1.29E-09	-77.9
D-1070	—	-80.2	1.32E-09	-81.7	1.48E-09	-79.9
D-1203	9.51E-11	-80.8	1.73E-09	-82.0	2.51E-09	-78.4
D-1183	1.14E-10	-76.4	9.71E-10	-81.9	2.10E-09	-78.3
D-1050	5.15E-11	-87.0	1.30E-09	-83.6	1.22E-09	-76.7
D-1167	2.87E-11	-76.6	5.21E-10	-79.4	1.14E-09	-80.8
D-1164	3.14E-10	-87.8	1.75E-09	-81.6	2.49E-09	-78.4
D-1237	9.94E-10	-78.1	1.88E-09	-80.7	2.19E-09	-79.0
D-1247	2.30E-11	-78.7	8.40E-10	-77.1	2.03E-09	-82.3
D-1075	1.17E-10	-73.8	1.90E-09	-84.5	1.00E-09	-74.9
D-1211	6.67E-11	-72.9	1.52E-09	-75.0	3.10E-09	-84.0
D-1248	3.22E-11	-83.3	8.91E-10	-80.6	1.37E-09	-77.8
D-1250	5.19E-11	-77.3	6.63E-10	-77.5	2.30E-09	-80.8

Duplex No.	Run 1 (500 nM to 25 pM)		Run 2 (25 nM to 1 pM)		Run 3 (100 nM to 5 pM)	
	IC50 [M]	Max Activity	IC50 [M]	Max Activity	IC50 [M]	Max Activity
D-1069	8.02E-11	-78.9	1.81E-09	-78.2	2.22E-09	-80.1
D-1253	—	-81.2	4.63E-10	-77.9	2.21E-09	-80.3
D-1056	6.68E-11	-76.7	2.02E-09	-78.4	1.48E-09	-79.6
D-1079	8.81E-11	-66.6	1.23E-09	-78.5	1.70E-09	-79.2
D-1162	6.89E-11	-77.8	2.08E-09	-83.7	2.24E-09	-73.5
D-1045	7.98E-11	-71.8	2.14E-09	-78.6	1.63E-09	-78.5
D-1173	1.41E-10	-84.6	1.70E-09	-77.0	2.35E-09	-80.0
D-1182	6.61E-11	-90.2	3.09E-09	-81.5	2.92E-09	-75.4
D-1146	1.18E-10	-77.7	3.39E-09	-77.3	3.03E-09	-79.2
D-1244	7.71E-11	-74.6	8.53E-10	-78.7	2.23E-09	-77.8
D-1186	1.07E-10	-71.3	1.03E-09	-77.5	2.35E-09	-78.9
D-1258	1.60E-10	-76.9	1.42E-09	-77.4	2.26E-09	-78.7
D-1043	8.57E-10	-81.2	3.33E-09	-71.8	9.87E-09	-83.9
D-1163	3.85E-11	-87.7	1.85E-10	-80.1	2.11E-09	-75.4
D-1206	1.35E-10	-78.8	1.62E-09	-77.8	1.91E-09	-77.5
D-1089	2.34E-10	-84.6	2.27E-09	-81.6	2.51E-09	-73.7
D-1207	2.94E-11	-74.0	1.54E-09	-77.6	1.40E-09	-77.6
D-1202	3.74E-11	-67.6	1.31E-09	-77.0	1.47E-09	-78.3
D-1221	1.77E-10	-84.4	2.08E-09	-79.4	3.46E-09	-75.7
D-1212	6.59E-11	-77.9	2.20E-09	-77.9	2.18E-09	-77.0
D-1188	2.07E-10	-84.5	1.62E-09	-70.6	1.57E-09	-83.7
D-1037	3.48E-10	-80.6	2.28E-09	-76.3	2.12E-09	-77.5
D-1251	3.53E-11	-78.2	6.32E-10	-77.3	2.00E-09	-76.0
D-1148	9.64E-11	-86.5	1.80E-09	-76.0	1.41E-09	-77.0
D-1214	4.88E-11	-71.7	1.72E-09	-75.4	6.69E-10	-77.6
D-1046	2.18E-10	-70.4	3.35E-09	-84.0	4.63E-09	-68.4
D-1051	1.12E-10	-72.4	1.53E-09	-78.6	1.05E-09	-73.6
D-1112	6.34E-11	-67.5	1.80E-09	-77.6	2.24E-09	-74.7
D-1114	7.18E-11	-75.2	1.66E-09	-75.0	2.27E-09	-77.1
D-1149	2.18E-10	-76.5	1.86E-09	-80.9	2.15E-09	-71.0
D-1119	8.91E-11	-73.1	3.58E-09	-78.6	5.56E-09	-73.4
D-1126	1.04E-10	-82.6	2.07E-09	-70.7	2.02E-09	-81.1
D-1254	6.11E-11	-81.4	1.45E-09	-73.5	2.37E-09	-78.2
D-1219	5.51E-11	-72.2	1.85E-09	-77.9	2.36E-09	-73.8
D-1134	2.91E-10	-75.9	1.69E-09	-77.5	2.11E-09	-73.4
D-1023	1.49E-10	-86.2	2.22E-09	-74.7	2.97E-09	-76.1
D-1201	9.75E-11	-69.6	2.02E-09	-71.0	2.77E-09	-79.0
D-1059	—	-66.9	2.32E-09	-77.5	1.80E-09	-72.2
D-1195	—	—	1.48E-09	-71.7	5.53E-10	-77.5
D-1160	1.39E-10	-78.9	5.70E-10	-66.1	1.70E-09	-82.5
D-1141	4.31E-10	-81.0	4.03E-09	-74.1	3.60E-09	-73.9

Duplex No.	Run 1 (500 nM to 25 pM)		Run 2 (25 nM to 1 pM)		Run 3 (100 nM to 5 pM)	
	IC50 [M]	Max Activity	IC50 [M]	Max Activity	IC50 [M]	Max Activity
D-1137	1.93E-10	-81.6	3.29E-09	-65.3	6.20E-09	-82.5
D-1260	6.31E-11	-69.6	1.51E-09	-74.8	5.40E-09	-72.4
D-1073	—	-77.7	1.78E-09	-75.5	1.90E-09	-71.6
D-1178	4.29E-10	-73.4	4.35E-09	-67.2	8.66E-09	-79.1
D-1157	3.87E-10	-74.0	—	-70.6	7.10E-09	-75.3
D-1047	1.26E-10	-74.5	2.58E-09	-76.4	2.69E-09	-69.0
D-1161	5.65E-11	-76.8	1.10E-09	-61.9	2.17E-09	-83.5
D-1098	4.18E-10	-86.1	—	-68.2	3.05E-09	-75.3
D-1081	7.18E-11	-67.3	2.33E-09	-73.4	2.35E-09	-69.6
D-1240	8.69E-10	-72.9	1.68E-09	-69.4	1.86E-09	-73.2
D-1259	2.52E-11	-70.1	7.91E-10	-73.1	7.64E-10	-69.3
D-1120	3.48E-10	-83.6	2.24E-09	-71.1	2.52E-09	-69.3
D-1104	9.89E-11	-64.0	2.73E-09	-69.8	2.86E-09	-70.5
D-1225	—	-68.8	1.17E-09	-65.3	2.11E-09	-74.4
D-1052	3.31E-11	-70.1	1.64E-09	-69.5	9.63E-10	-70.2
D-1072	—	-75.6	2.14E-09	-71.8	1.53E-09	-67.7
D-1082	1.54E-10	-70.1	2.11E-09	-72.4	2.47E-09	-67.2
D-1224	9.53E-11	-80.0	2.19E-09	-67.3	2.87E-09	-70.3
D-1032	1.35E-10	-89.8	3.18E-09	-73.1	2.64E-09	-64.3
D-1017	1.16E-10	-69.3	2.49E-09	-69.6	1.90E-09	-66.5
D-1208	1.46E-10	-67.5	2.45E-09	-64.3	3.96E-09	-71.7
D-1048	2.86E-10	-67.2	3.12E-09	-70.4	2.60E-09	-65.6
D-1080	1.19E-10	-55.0	3.84E-09	-75.4	1.82E-09	-59.2
D-1102	4.22E-11	-64.6	2.07E-09	-70.8	1.97E-09	-63.8
D-1076	1.18E-10	-57.7	2.38E-09	-62.5	2.29E-09	-71.5
D-1055	—	-47.6	2.89E-09	-64.5	5.23E-09	-69.2
D-1216	1.83E-10	-70.6	4.14E-09	-67.1	3.59E-09	-66.2
D-1193	1.79E-10	-82.0	1.40E-09	-60.6	4.45E-09	-72.5
D-1217	2.58E-10	-67.5	3.12E-09	-60.9	4.77E-09	-71.1
D-1200	1.40E-10	-70.4	3.63E-09	-64.5	4.11E-09	-67.1
D-1058	1.46E-10	-52.8	2.63E-09	-65.4	1.94E-09	-65.7
D-1084	1.13E-10	-75.6	1.98E-09	-71.5	2.19E-09	-59.4
D-1118	3.51E-10	-75.1	2.94E-09	-65.1	6.26E-09	-65.0
D-1136	1.63E-10	-65.7	3.06E-09	-65.6	3.20E-09	-63.3
D-1116	3.67E-10	-76.6	3.95E-09	-58.9	3.33E-09	-69.4
D-1169	1.79E-10	-72.8	1.99E-09	-53.5	4.33E-09	-74.5
D-1065	1.57E-10	-60.6	1.91E-09	-64.1	2.14E-09	-63.5
D-1063	2.80E-11	-65.2	1.38E-09	-63.2	1.26E-09	-63.1
D-1034	1.45E-10	-68.7	1.87E-09	-62.6	1.70E-09	-60.7
D-1218	2.05E-10	-62.9	2.21E-09	-58.8	2.67E-09	-63.7
D-1154	1.84E-10	-69.2	2.55E-09	-55.5	3.44E-09	-66.0

Duplex No.	Run 1 (500 nM to 25 pM)		Run 2 (25 nM to 1 pM)		Run 3 (100 nM to 5 pM)	
	IC50 [M]	Max Activity	IC50 [M]	Max Activity	IC50 [M]	Max Activity
D-1049	3.04E-10	-70.7	2.10E-09	-69.9	2.53E-09	-51.4
D-1088	5.85E-10	-73.7	3.65E-09	-58.6	3.15E-09	-62.6
D-1199	3.95E-10	-73.2	2.70E-09	-55.1	4.45E-09	-64.4
D-1165	2.02E-10	-72.7	—	-52.5	4.14E-09	-66.5
D-1028	1.82E-09	-84.0	5.79E-09	-51.0	1.80E-08	-64.3
D-1078	1.53E-10	-55.4	1.97E-09	-54.0	4.95E-09	-60.8
D-1222	1.82E-10	-59.9	2.33E-09	-60.4	2.18E-09	-54.4
D-1131	6.25E-10	-75.0	5.53E-09	-56.9	5.17E-09	-57.8
D-1027	6.87E-11	-66.4	1.94E-09	-51.6	2.22E-09	-63.1
D-1151	1.39E-10	-59.0	2.21E-09	-52.8	1.89E-09	-61.2
D-1135	2.33E-10	-61.2	4.03E-09	-56.0	5.09E-09	-56.9
D-1038	—	-35.4	3.59E-09	-73.4	7.37E-09	-36.7
D-1196	1.37E-10	-57.4	3.05E-09	-49.5	3.84E-09	-58.0
D-1223	1.38E-10	-63.6	2.96E-09	-54.8	2.75E-09	-44.6
D-1100	8.61E-11	-46.0	2.94E-09	-54.5	1.94E-09	-43.5
D-1197	1.96E-10	-53.9	3.68E-09	-49.1	5.22E-09	-46.9
D-1205	2.98E-10	-67.1	2.83E-09	-50.0	4.84E-09	-43.7
D-1192	—	-84.6	> 25E-9	-5.1	2.17E-09	-82.6
D-1024	8.25E-10	-71.0	3.63E-09	-52.2	> 100E-9	-34.5
D-1231	2.40E-09	-74.7	6.04E-09	-37.4	1.15E-08	-45.5
D-1031	9.42E-11	-43.6	—	-38.0	6.12E-09	-41.0
D-1103	6.03E-11	-67.1	> 25E-9	-2.0	1.77E-09	-60.0
D-1132	2.93E-10	-79.2	> 25E-9	-2.4	2.87E-09	-50.1
D-1025	—	-27.8	> 25E-9	-21.9	> 100E-9	-20.8
D-1004	> 500E-9	-5.3	—	—	—	—
D-1005	> 500E-9	-8.5	—	—	—	—
D-1006	> 500E-9	17.0	—	—	—	—
D-1007	> 500E-9	38.0	—	—	—	—
D-1008	> 500E-9	4.8	—	—	—	—
D-1009	> 500E-9	-2.1	—	—	—	—
D-1010	> 500E-9	9.8	—	—	—	—
D-1011	> 500E-9	-6.4	—	—	—	—
D-1012	> 500E-9	39.7	—	—	—	—
D-1013	> 500E-9	37.7	—	—	—	—
D-1014	> 500E-9	-23.4	—	—	—	—
D-1015	3.51E-10	-57.4	—	—	—	—
D-1016	2.06E-10	-51.2	—	—	—	—
D-1018	> 500E-9	1.9	—	—	—	—
D-1019	2.61E-10	-36.5	—	—	—	—
D-1021	1.86E-10	-39.0	—	—	—	—
D-1022	2.63E-09	-47.8	—	—	—	—

Duplex No.	Run 1 (500 nM to 25 pM)		Run 2 (25 nM to 1 pM)		Run 3 (100 nM to 5 pM)	
	IC50 [M]	Max Activity	IC50 [M]	Max Activity	IC50 [M]	Max Activity
D-1026	> 500E-9	21.9	—	—	—	—
D-1029	2.61E-10	-57.4	—	—	—	—
D-1030	2.66E-10	-55.4	—	—	—	—
D-1033	> 500E-9	37.1	—	—	—	—
D-1035	7.68E-10	-57.2	—	—	—	—
D-1036	5.91E-10	-55.7	—	—	—	—
D-1039	> 500E-9	-18.2	—	—	—	—
D-1040	> 500E-9	-14.3	—	—	—	—
D-1041	> 500E-9	-18.8	—	—	—	—
D-1042	3.74E-10	-45.5	—	—	—	—
D-1053	> 500E-9	-17.6	—	—	—	—
D-1057	> 500E-9	-5.1	—	—	—	—
D-1060	> 500E-9	-3.6	—	—	—	—
D-1064	> 500E-9	22.6	—	—	—	—
D-1071	> 500E-9	-6.8	—	—	—	—
D-1077	> 500E-9	-4.7	—	—	—	—
D-1085	> 500E-9	-0.4	—	—	—	—
D-1094	3.76E-10	-66.8	—	—	—	—
D-1101	> 500E-9	-3.5	—	—	—	—
D-1105	> 500E-9	-10.8	—	—	—	—
D-1106	4.64E-10	-53.1	—	—	—	—
D-1107	> 500E-9	-0.1	—	—	—	—
D-1108	> 500E-9	-7.8	—	—	—	—
D-1109	7.32E-10	-36.0	—	—	—	—
D-1110	> 500E-9	1.0	—	—	—	—
D-1115	> 500E-9	-5.2	—	—	—	—
D-1117	2.06E-10	-41.7	—	—	—	—
D-1121	2.62E-09	-54.1	—	—	—	—
D-1122	3.22E-10	-65.9	—	—	—	—
D-1123	> 500E-9	16.9	—	—	—	—
D-1124	4.33E-10	-56.1	—	—	—	—
D-1128	3.74E-10	-51.3	—	—	—	—
D-1129	> 500E-9	-24.9	—	—	—	—
D-1133	6.33E-10	-39.4	—	—	—	—
D-1142	4.80E-10	-65.9	—	—	—	—
D-1144	> 500E-9	6.1	—	—	—	—
D-1145	> 500E-9	2.0	—	—	—	—
D-1152	7.09E-10	-44.4	—	—	—	—
D-1153	8.57E-08	-48.1	—	—	—	—
D-1155	1.48E-10	-32.2	—	—	—	—
D-1156	> 500E-9	-8.3	—	—	—	—

Duplex No.	Run 1 (500 nM to 25 pM)		Run 2 (25 nM to 1 pM)		Run 3 (100 nM to 5 pM)	
	IC50 [M]	Max Activity	IC50 [M]	Max Activity	IC50 [M]	Max Activity
D-1158	1.94E-09	-35.0	—	—	—	—
D-1159	7.15E-10	-67.2	—	—	—	—
D-1198	3.37E-10	-69.0	—	—	—	—
D-1226	> 500E-9	-2.5	—	—	—	—
D-1227	> 500E-9	3.4	—	—	—	—
D-1232	8.99E-10	-61.4	—	—	—	—
D-1233	1.19E-09	-68.5	—	—	—	—
D-1234	5.48E-10	-65.1	—	—	—	—
D-1238	1.51E-09	-45.6	—	—	—	—
D-1239	6.25E-10	-67.1	—	—	—	—
D-1242	6.22E-10	-63.4	—	—	—	—
D-1261	> 500E-9	-19.1	—	—	—	—
D-1262	> 500E-9	-21.5	—	—	—	—

[0216] Of the initial 257 mARC1 siRNA molecules evaluated in the RNA FISH assay, 74 molecules exhibited an average of 80% or greater knockdown of human mARC1 mRNA and had IC50 values at least in the single-digit nanomolar range in assay runs 2 and 3. In particular, 32 molecules (duplex nos. D-1092; D-1093; D-1139; D-1061; D-1138; D-1095; D-1191; D-1180; D-1090; D-1062; D-1177; D-1083; D-1245; D-1067; D-1143; D-1170; D-1044; D-1096; D-1113; D-1086; D-1256; D-1189; D-1091; D-1174; D-1185; D-1066; D-1171; D-1140; D-1130; D-1068; D-1243; D-1074) reduced human mARC1 mRNA by at least 85% in one or both assay runs 2 and 3.

[0217] In a second series of experiments, additional mARC1 siRNA molecules were evaluated in the RNA FISH assay at ten different concentrations ranging from 100 nM to 5 pM, and IC50 and maximum activity values were calculated as described above. The results of the assays from this second series of experiments are shown in Table 4 below. Assays were repeated for a subset of molecules. For such molecules, the IC50 and maximum activity values for both runs are shown.

Table 4. In vitro inhibition of human mARC1 mRNA by select mARC1 siRNA molecules in Hep3B cells

Duplex No.	IC50 [M]	Max Activity	Duplex No.	IC50 [M]	Max Activity
D-1061	663E-12	-99.13	D-1267 – run 1	3.4E-9	-80.64
D-1093	720E-12	-90.29	D-1267 – run 2	1.33E-09	-83.64
D-1139	1.72E-09	-97.32	D-1268 – run 1	1.23E-9	-88.75
D-1220	3.26E-9	-97.17	D-1268 – run 2	3.98E-10	-89.45
D-1245	93.3E-12	-88.21	D-1269	> 100E-9	-32.26
D-1263	3.9E-9	-74.11	D-1270	1.38E-9	-56.38
D-1264	1.4E-9	-79.53	D-1271	> 100E-9	-26.78
D-1265	2.68E-9	-77.10	D-1272 – run 1	941E-12	-84.38
D-1266 – run 1	541E-12	-85.44	D-1272 – run 2	1.36E-09	-89.35
D-1266 – run 2	1.61E-10	-93.80	D-1273 – run 1	1.22E-9	-85.29
D-1274 – run 1	638E-12	-86.28	D-1273 – run 2	1.17E-09	-90.43
D-1274 – run 2	8.95E-10	-89.55	D-1281 – run 1	2.58E-9	-86.39
D-1275	428E-12	-79.99	D-1281 – run 2	1.43E-09	-88.37
D-1276 – run 1	1.54E-9	-92.38	D-1282 – run 1	638E-12	-87.53
D-1276 – run 2	1.59E-09	-88.32	D-1282 – run 2	5.56E-10	-95.34
D-1277	2E-9	-79.86	D-1283 – run 1	1.97E-9	-80.62
D-1278 – run 1	1.21E-9	-81.71	D-1283 – run 2	1.90E-09	-81.20
D-1278 – run 2	1.55E-09	-84.13	D-1284 – run 1	1.94E-9	-91.35
D-1279	323E-12	-76.50	D-1284 – run 2	3.09E-09	-91.61
D-1280	> 100E-9	1.94	D-1285 – run 1	1E-9	-88.21
D-1286 – run 1	2.04E-9	-89.49	D-1285 – run 2	1.54E-09	-86.72
D-1286 – run 2	2.42E-09	-94.63	D-1293	—	-56.99
D-1287 – run 1	1.31E-9	-82.87	D-1294	2.72E-9	-40.67
D-1287 – run 2	1.11E-09	-83.35	D-1295 – run 1	3.86E-9	-81.47
D-1288 – run 1	3.58E-9	-88.81	D-1295 – run 2	4.77E-09	-79.64
D-1288 – run 2	3.36E-09	-90.32	D-1296 – run 1	1.29E-9	-87.96
D-1289	2.17E-9	-73.71	D-1296 – run 2	1.97E-09	-89.76
D-1290	29.3E-9	-50.69	D-1297	> 100E-9	0.97
D-1291	2.37E-9	-62.67	D-1298 – run 1	636E-12	-94.52
D-1292 – run 1	6.56E-9	-81.82	D-1298 – run 2	4.99E-10	-94.67

Duplex No.	IC50 [M]	Max Activity	Duplex No.	IC50 [M]	Max Activity
D-1292 – run 2	5.35E-09	-75.91	D-1299 – run 1	293E-12	-86.71
D-1300	2.7E-9	-79.68	D-1299 – run 2	6.23E-10	-90.92
D-1301	> 100E-9	-46.76	D-1308 – run 1	1.61E-9	-83.41
D-1302	2.15E-9	-80.01	D-1308 – run 2	1.28E-09	-85.58
D-1303 – run 1	1.44E-9	-85.61	D-1309	405E-12	-78.77
D-1303 – run 2	1.05E-09	-88.46	D-1310 – run 1	1.83E-9	-89.68
D-1304 – run 1	490E-12	-85.23	D-1310 – run 2	1.91E-09	-95.65
D-1304 – run 2	6.56E-10	-88.62	D-1311 – run 1	1.05E-9	-90.99
D-1305	802E-12	-79.34	D-1311 – run 2	8.00E-10	-87.63
D-1306	2.4E-9	-77.95	D-1312 – run 1	2.26E-9	-87.43
D-1307	2.43E-9	-77.80	D-1312 – run 2	1.65E-09	-82.70
D-1314	768E-12	-76.88	D-1313	1.85E-9	-78.77
D-1315 – run 1	2.2E-9	-88.75	D-1322 – run 1	> 100E-9	-6.77
D-1315 – run 2	2.49E-09	-83.37	D-1322 – run 2	> 100E-9	-1.46
D-1316	3.66E-9	-71.22	D-1323	> 100E-9	2.99
D-1317	3.03E-9	-69.28	D-1324	> 100E-9	-6.04
D-1318	8.65E-9	-59.48	D-1325	> 100E-9	15.82
D-1319 – run 1	6.1E-9	-82.28	D-1326 – run 1	> 100E-9	-16.18
D-1319 – run 2	3.94E-09	-79.12	D-1326 – run 2	> 100E-9	-6.29
D-1320	4.95E-9	-70.44	D-1327	6.21E-9	-56.80
D-1321 – run 1	2.21E-9	-84.41	D-1328	> 100E-9	-40.40
D-1321 – run 2	1.74E-09	-79.23	D-1329	> 100E-9	-39.95
D-1330 – run 1	7.48E-9	-82.11	D-1335 – run 1	1.15E-9	-87.64
D-1330 – run 2	7.14E-09	-78.69	D-1335 – run 2	9.61E-10	-86.06
D-1331 – run 1	3.59E-9	-65.41	D-1336 – run 1	2.62E-9	-85.53
D-1331 – run 2	4.38E-9	-65.82	D-1336 – run 2	1.58E-09	-80.06
D-1332 – run 1	> 100E-9	-11.88	D-1337	4.88E-9	-68.99
D-1332 – run 2	> 100E-9	-8.78	D-1338 – run 1	2.16E-9	-95.31
D-1333 – run 1	5.73E-9	-60.02	D-1338 – run 2	2.44E-09	-95.49
D-1333 – run 2	20.5E-9	-72.67	D-1339	5.6E-9	-77.24
D-1334 – run 1	5.96E-9	-86.77	D-1340	3.77E-9	-67.14
D-1334 – run 2	5.74E-9	-70.29	D-1341 – run 1	1.27E-9	-82.33

Duplex No.	IC50 [M]	Max Activity	Duplex No.	IC50 [M]	Max Activity
D-1334 – run 3	6.24E-09	-79.62	D-1341 – run 2	1.22E-09	-85.14
D-1342	3.79E-9	-79.64	D-1351 – run 1	2.49E-9	-83.34
D-1343	7.69E-9	-76.38	D-1351 – run 2	2.06E-09	-84.99
D-1344	4.7E-9	-80.14	D-1352	2.29E-9	-78.03
D-1345	> 100E-9	-33.98	D-1353	2.4E-9	-51.04
D-1346	1.8E-9	-67.30	D-1354	1.99E-9	-69.59
D-1347	3.71E-9	-72.82	D-1355	3.05E-9	-60.02
D-1348	21.7E-9	-58.27	D-1356	5.45E-9	-41.04
D-1349	1.7E-9	-78.63	D-1357	2.85E-9	-57.34
D-1350 – run 1	438E-12	-86.65	D-1358 – run 1	967E-12	-82.23
D-1350 – run 2	4.23E-10	-82.90	D-1358 – run 2	1.17E-09	-90.43
D-1359	2.03E-9	-70.00	D-1366	4.75E-9	-76.16
D-1360 – run 1	3.62E-9	-87.34	D-1367 – run 1	2.26E-9	-93.08
D-1360 – run 2	3.10E-09	-83.45	D-1367 – run 2	1.98E-09	-93.44
D-1361	632E-12	-76.77	D-1368 – run 1	2.82E-9	-83.59
D-1362	2.58E-9	-76.67	D-1368 – run 2	1.12E-09	-88.39
D-1363 – run 1	1.29E-9	-91.72	D-1369	2.11E-9	-75.09
D-1363 – run 2	2.30E-09	-91.91	D-1370	1.96E-9	-79.61
D-1364 – run 1	1.11E-9	-87.19	D-1371 – run 1	1.19E-9	-84.84
D-1364 – run 2	1.14E-09	-91.01	D-1371 – run 2	1.14E-09	-86.39
D-1365 – run 1	1.42E-9	-85.38	D-1372	1.38E-9	-69.85
D-1365 – run 2	1.80E-09	-88.72	D-1373	2.62E-9	-68.36
D-1374	2.83E-9	-78.50	D-1380 – run 1	2.43E-9	-81.50
D-1375 – run 1	754E-12	-91.87	D-1380 – run 2	2.13E-09	-84.97
D-1375 – run 2	8.44E-10	-89.51	D-1381 – run 1	202E-12	-89.58
D-1376 – run 1	2.47E-9	-85.68	D-1381 – run 2	3.79E-10	-89.29
D-1376 – run 2	2.26E-09	-85.67	D-1382 – run 1	429E-12	-97.54
D-1377 – run 1	1.24E-9	-83.02	D-1382 – run 2	2.17E-10	-90.44
D-1377 – run 2	1.45E-09	-88.30	D-1383 – run 1	939E-12	-92.11
D-1378	4.05E-9	-53.31	D-1383 – run 2	7.75E-10	-90.60
D-1379 – run 1	2.45E-9	-85.07	D-1384 – run 1	29.6E-9	-81.72
D-1379 – run 2	1.58E-09	-87.92	D-1384 – run 2	1.62E-10	-93.78

Duplex No.	IC50 [M]	Max Activity	Duplex No.	IC50 [M]	Max Activity
D-1385 – run 1	470E-12	-84.34	D-1390 – run 1	587E-12	-101.09
D-1385 – run 2	1.96E-10	-85.42	D-1390 – run 2	2.46E-10	-93.89
D-1386 – run 1	508E-12	-93.47	D-1391 – run 1	206E-12	-86.03
D-1386 – run 2	3.20E-10	-93.01	D-1391 – run 2	1.91E-10	-89.58
D-1387 – run 1	564E-12	-93.18	D-1392 – run 1	602E-12	-87.07
D-1387 – run 2	3.07E-10	-90.08	D-1392 – run 2	8.32E-10	-83.70
D-1388 – run 1	632E-12	-92.58	D-1393 – run 1	1.28E-9	-80.15
D-1388 – run 2	7.64E-10	-95.22	D-1393 – run 2	8.95E-10	-74.95
D-1389 – run 1	227E-12	-94.67	D-1394 – run 1	1.72E-9	-80.33
D-1389 – run 2	3.90E-10	-95.16	D-1394 – run 2	1.05E-09	-80.33
D-1395 – run 1	746E-12	-88.44	D-1400 – run 1	1.17E-9	-93.27
D-1395 – run 2	5.06E-10	-77.24	D-1400 – run 2	6.99E-10	-86.44
D-1396 – run 1	784E-12	-92.23	D-1401 – run 1	753E-12	-92.66
D-1396 – run 2	9.88E-10	-86.55	D-1401 – run 2	6.27E-10	-85.65
D-1397 – run 1	551E-12	-86.58	D-1402 – run 1	411E-12	-90.34
D-1397 – run 2	5.51E-10	-84.90	D-1402 – run 2	1.29E-10	-91.80
D-1398 – run 1	489E-12	-80.69	D-1403 – run 1	771E-12	-88.84
D-1398 – run 2	2.09E-10	-86.47	D-1403 – run 2	4.78E-10	-86.79
D-1399 – run 1	369E-12	-86.49	D-1404 – run 1	421E-12	-86.45
D-1399 – run 2	1.34E-10	-93.52	D-1404 – run 2	4.48E-10	-93.17
D-1405 – run 1	187E-12	-91.82	D-1412	> 100E-9	-20.63
D-1405 – run 2	2.50E-10	-95.68	D-1413 – run 1	5.18E-9	-81.68
D-1406 – run 1	282E-12	-88.00	D-1413 – run 2	3.13E-09	-76.27
D-1406 – run 2	1.25E-10	-91.00	D-1414	2.02E-9	-63.97
D-1407 – run 1	403E-12	-91.27	D-1415	3.84E-9	-56.01
D-1407 – run 2	2.01E-10	-82.75	D-1416 – run 1	1.94E-9	-94.76
D-1408	> 100E-9	19.37	D-1416 – run 2	1.47E-09	-85.86
D-1409	> 100E-9	44.69	D-1417	5.26E-9	-50.98
D-1410	> 100E-9	-16.05	D-1418	5.94E-9	-63.89
D-1411	> 100E-9	10.66	D-1419	> 100E-9	-19.86
D-1420 – run 1	2.68E-9	-94.55	D-1428	> 100E-9	4.40
D-1420 – run 2	1.24E-09	-86.57	D-1429	> 100E-9	-9.19

Duplex No.	IC50 [M]	Max Activity	Duplex No.	IC50 [M]	Max Activity
D-1421 – run 1	5.7E-9	-89.95	D-1430	> 100E-9	2.73
D-1421 – run 2	6.19E-09	-84.56	D-1431	> 100E-9	-19.92
D-1422	25.5E-9	-53.28	D-1432	> 100E-9	-2.75
D-1423	31.8E-9	-62.33	D-1433	> 100E-9	-12.03
D-1424	> 100E-9	-30.24	D-1434	4.58E-9	-53.99
D-1425	> 100E-9	19.38	D-1435	> 100E-9	2.85
D-1426	> 100E-9	1.22	D-1436	> 100E-9	-21.73
D-1427	> 100E-9	-8.72	D-1437	9.37E-9	-53.74
D-1438	> 33.3E-9	-33.44	D-1445	7.92E-9	-71.51
D-1439 – run 1	3.21E-9	-88.80	D-1446	> 100E-9	-28.05
D-1439 – run 2	2.07E-09	-86.97	D-1447 – run 1	4.6E-9	-81.98
D-1440	15.8E-9	-53.11	D-1447 – run 2	1.92E-09	-74.90
D-1441 – run 1	860E-12	-93.62	D-1448	754E-12	-75.31
D-1441 – run 2	1.41E-09	-92.60	D-1449	1.61E-9	-73.73
D-1442	15.3E-9	-60.48	D-1450	1.91E-9	-78.64
D-1443	4.55E-9	-61.60	D-1451 – run 1	1.41E-9	-92.19
D-1444 – run 1	3.64E-9	-80.44	D-1451 – run 2	1.61E-09	-88.76
D-1444 – run 2	1.88E-09	-75.71	D-1452 – run 1	477E-12	-84.31
D-1453	1.64E-9	-77.22	D-1452 – run 2	5.50E-10	-81.90
D-1454 – run 1	1.39E-9	-87.14	D-1459 – run 1	845E-12	-85.31
D-1454 – run 2	2.24E-09	-87.40	D-1459 – run 2	1.24E-09	-93.61
D-1455 – run 1	341E-12	-86.11	D-1460 – run 1	702E-12	-88.96
D-1455 – run 2	2.42E-10	-95.21	D-1460 – run 2	9.15E-10	-89.53
D-1456 – run 1	2.03E-9	-86.90	D-1461	1.49E-9	-71.01
D-1456 – run 2	1.41E-09	-84.06	D-1462	7.37E-9	-66.33
D-1457	1.92E-9	-78.57	D-1463	> 100E-9	-17.28
D-1458 – run 1	6.71E-9	-86.68	D-1464	7.58E-9	-61.74
D-1458 – run 2	2.24E-09	-94.33	D-1465	5.16E-9	-75.36
D-1466	> 100E-9	-17.33	D-1475	9.72E-9	-59.40
D-1467	10.9E-9	-56.04	D-1476	1.08E-9	-54.33
D-1468	3.78E-9	-61.93	D-1477	2.27E-9	-55.97
D-1469 – run 1	953E-12	-81.14	D-1478	1.15E-9	-54.86

Duplex No.	IC50 [M]	Max Activity	Duplex No.	IC50 [M]	Max Activity
D-1469 – run 2	1.59E-09	-83.63	D-1479	1.33E-9	-44.54
D-1470	19.6E-9	-41.41	D-1480 – run 1	2.03E-9	-85.44
D-1471	46.7E-9	-37.18	D-1480 – run 2	8.61E-10	-88.52
D-1472	4.45E-9	-50.43	D-1481 – run 1	1.57E-9	-80.97
D-1473	2.17E-9	-78.87	D-1481 – run 2	1.33E-09	-90.57
D-1474	8.29E-9	-61.78	D-1482	6.26E-9	-53.31
D-1483	10.8E-9	-73.64	D-1489 – run 1	2.49E-9	-92.70
D-1484	1.63E-9	-80.04	D-1489 – run 2	2.02E-09	-100.75
D-1485 – run 1	614E-12	-86.35	D-1490	7.08E-9	-77.03
D-1485 – run 2	7.55E-10	-90.60	D-1491 – run 1	1.31E-9	-95.30
D-1486 – run 1	2.44E-9	-81.67	D-1491 – run 2	9.32E-10	-92.84
D-1486 – run 2	5.61E-10	-85.95	D-1492 – run 1	470E-12	-88.29
D-1487 – run 1	3.14E-9	-92.01	D-1492 – run 2	6.96E-10	-91.86
D-1487 – run 2	4.26E-10	-90.53	D-1493 – run 1	2.72E-9	-89.31
D-1488 – run 1	4.58E-9	-82.33	D-1493 – run 2	2.25E-09	-89.06
D-1488 – run 2	2.65E-09	-80.98	D-1494	2.08E-9	-79.36
D-1495	3.7E-9	-63.78	D-1502	12.3E-9	-60.25
D-1496 – run 1	2.26E-9	-82.93	D-1503 – run 1	1.35E-9	-94.10
D-1496 – run 2	6.17E-10	-86.34	D-1503 – run 2	8.46E-10	-88.39
D-1497 – run 1	3.09E-9	-83.24	D-1504 – run 1	2.62E-9	-92.42
D-1497 – run 2	1.20E-09	-89.93	D-1504 – run 2	2.39E-09	-84.78
D-1498	958E-12	-79.10	D-1505	12.1E-9	-44.23
D-1499 – run 1	434E-12	-82.58	D-1506 – run 1	2.33E-9	-82.44
D-1499 – run 2	7.85E-10	-86.02	D-1506 – run 2	2.43E-09	-74.70
D-1500	2.94E-9	-64.87	D-1507 – run 1	7.22E-9	-85.49
D-1501	3.79E-9	-67.10	D-1507 – run 2	3.07E-09	-78.73
D-1508	9.61E-9	-69.25	D-1516	4.11E-9	-72.86
D-1509 – run 1	1.84E-9	-87.02	D-1517	1.86E-9	-70.15
D-1509 – run 2	1.54E-09	-90.33	D-1518	5.19E-9	-80.44
D-1510 – run 1	2E-9	-84.70	D-1519 – run 1	3.16E-9	-87.18
D-1510 – run 2	1.33E-09	-74.09	D-1519 – run 2	1.85E-09	-81.61
D-1511	4.91E-9	-70.77	D-1520	2.61E-9	-75.37

Duplex No.	IC50 [M]	Max Activity	Duplex No.	IC50 [M]	Max Activity
D-1512	13.7E-9	-50.81	D-1521	8.95E-9	-71.81
D-1513	10.4E-9	-61.35	D-1522	1.05E-9	-77.55
D-1514	8.52E-9	-58.65	D-1523	5.61E-9	-56.61
D-1515 – run 1	3.02E-9	-94.07	D-1524	8.18E-9	-70.51
D-1515 – run 2	2.11E-09	-88.32	D-1525 – run 1	187E-12	-85.31
D-1526 – run 1	724E-12	-88.90	D-1525 – run 2	3.09E-10	-89.32
D-1526 – run 2	1.09E-10	-93.08	D-1533 – run 1	160E-12	-87.58
D-1527	969E-12	-79.47	D-1533 – run 2	1.77E-10	-89.17
D-1528 – run 1	476E-12	-81.98	D-1534	4.12E-9	-77.89
D-1528 – run 2	5.16E-10	-86.43	D-1535 – run 1	3.91E-9	-81.08
D-1529	275E-12	-80.46	D-1535 – run 2	2.53E-09	-83.97
D-1530	603E-12	-79.76	D-1536 – run 1	1.17E-9	-85.54
D-1531 – run 1	465E-12	-81.21	D-1536 – run 2	5.45E-10	-84.54
D-1531 – run 2	4.26E-10	-86.14	D-1537	5.53E-9	-72.51
D-1532 – run 1	234E-12	-82.79	D-1538	869E-12	-74.09
D-1532 – run 2	2.09E-10	-88.87	D-1539	6.85E-9	-74.08
D-1540 – run 1	2.09E-9	-83.12	D-1548	27.6E-9	-37.78
D-1540 – run 2	1.27E-09	-88.11	D-1549 – run 1	1.04E-9	-93.06
D-1541	932E-12	-76.06	D-1549 – run 2	8.95E-10	-88.71
D-1542 – run 1	3.16E-9	-81.16	D-1550	652E-12	-79.25
D-1542 – run 2	1.48E-09	-83.09	D-1551 – run 1	500E-12	-86.59
D-1543	8.54E-9	-79.76	D-1551 – run 2	5.64E-10	-84.20
D-1544	8.28E-9	-73.28	D-1552 – run 1	228E-12	-81.86
D-1545	1.7E-9	-75.05	D-1552 – run 2	3.22E-10	-89.73
D-1546	1.45E-9	-79.08	D-1553 – run 1	931E-12	-80.68
D-1547	22.3E-9	-69.31	D-1553 – run 2	8.28E-10	-89.65
D-1554	1.27E-9	-78.63	D-1560	456E-12	-74.69
D-1555 – run 1	663E-12	-88.13	D-1561 – run 1	2.39E-9	-83.41
D-1555 – run 2	4.61E-10	-90.35	D-1561 – run 2	3.83E-9	-80.47
D-1556 – run 1	165E-12	-83.51	D-1561 – run 3	2.15E-09	-83.36
D-1556 – run 2	2.53E-10	-87.06	D-1562 – run 1	1.1E-9	-72.98
D-1557 – run 1	440E-12	-87.71	D-1562 – run 2	1.26E-9	-74.09

Duplex No.	IC50 [M]	Max Activity	Duplex No.	IC50 [M]	Max Activity
D-1557 – run 2	2.50E-10	-85.00	D-1563 – run 1	898E-12	-78.70
D-1558 – run 1	762E-12	-81.35	D-1563 – run 2	1.07E-9	-76.14
D-1558 – run 2	2.60E-10	-80.18	D-1564 – run 1	906E-12	-85.03
D-1559 – run 1	668E-12	-87.94	D-1564 – run 2	1.75E-9	-76.80
D-1559 – run 2	5.42E-10	-86.43	D-1564 – run 3	1.01E-09	-81.88
D-1565 – run 1	467E-12	-79.91	D-1570 – run 1	925E-12	-78.14
D-1565 – run 2	1.27E-9	-78.07	D-1570 – run 2	992E-12	-76.81
D-1566 – run 1	1.5E-9	-80.84	D-1571 – run 1	779E-12	-80.29
D-1566 – run 2	4.17E-9	-85.05	D-1571 – run 2	2.7E-9	-80.52
D-1566 – run 3	8.64E-10	-84.74	D-1571 – run 3	8.27E-10	-84.74
D-1567 – run 1	3.71E-9	-75.99	D-1572	820E-12	-76.58
D-1567 – run 2	2.34E-9	-72.76	D-1573 – run 1	1.52E-9	-79.66
D-1568	7.49E-9	-49.04	D-1573 – run 2	3.19E-9	-79.88
D-1569 – run 1	2.74E-9	-78.08	D-1574 – run 1	4.19E-9	-60.81
D-1569 – run 2	3.13E-9	-74.70	D-1574 – run 2	> 100E-9	-15.89
D-1575 – run 1	1.59E-9	-76.35	D-1579 – run 1	515E-12	-84.80
D-1575 – run 2	2.88E-9	-71.95	D-1579 – run 2	207E-12	-79.57
D-1576 – run 1	1.07E-9	-90.18	D-1579 – run 3	2.98E-09	-83.77
D-1576 – run 2	1.37E-09	-94.66	D-1580 – run 1	233E-12	-83.48
D-1577 – run 1	1.3E-9	-83.26	D-1580 – run 2	3.19E-10	-90.62
D-1577 – run 2	1.52E-9	-80.99	D-1581 – run 1	376E-12	-89.56
D-1577 – run 3	1.14E-09	-85.26	D-1581 – run 2	164E-12	-84.43
D-1578 – run 1	1.34E-9	-84.03	D-1581 – run 3	4.10E-10	-88.78
D-1578 – run 2	571E-12	-77.18	D-1582 – run 1	1.25E-9	-77.75
D-1578 – run 3	6.20E-10	-79.39	D-1582 – run 2	1.38E-9	-73.23
D-1583 – run 1	3.97E-9	-79.12	D-1589	1.89E-9	-79.52
D-1583 – run 2	2.2E-9	-78.20	D-1590 – run 1	1.56E-9	-86.60
D-1584 – run 1	377E-12	-84.12	D-1590 – run 2	9.85E-10	-86.66
D-1584 – run 2	5.41E-10	-86.04	D-1591	1.01E-9	-78.77
D-1585 – run 1	854E-12	-83.31	D-1592	1.67E-9	-78.16
D-1585 – run 2	1.15E-09	-89.54	D-1593	3.47E-9	-58.82
D-1586	1.24E-9	-76.28	D-1594	2.08E-9	-71.26

Duplex No.	IC50 [M]	Max Activity	Duplex No.	IC50 [M]	Max Activity
D-1587 – run 1	1.04E-9	-87.24	D-1595 – run 1	531E-12	-92.76
D-1587 – run 2	1.22E-09	-90.08	D-1595 – run 2	4.46E-10	-93.09
D-1588 – run 1	1.24E-9	-82.16	D-1596 – run 1	655E-12	-95.03
D-1588 – run 2	2.00E-09	-84.12	D-1596 – run 2	6.71E-10	-88.34
D-1597 – run 1	566E-12	-87.01	D-1603 – run 1	868E-12	-84.49
D-1597 – run 2	9.25E-10	-86.25	D-1603 – run 2	1.25E-09	-89.46
D-1598 – run 1	1.07E-9	-81.80	D-1604 – run 1	1.03E-9	-85.81
D-1598 – run 2	1.18E-09	-77.57	D-1604 – run 2	8.37E-10	-82.91
D-1599 – run 1	844E-12	-85.25	D-1605 – run 1	831E-12	-87.43
D-1599 – run 2	7.40E-10	-79.77	D-1605 – run 2	7.85E-10	-84.90
D-1600	1.34E-9	-65.29	D-1606 – run 1	617E-12	-91.60
D-1601	646E-12	-71.11	D-1606 – run 2	9.69E-10	-83.11
D-1602 – run 1	668E-12	-88.45	D-1607 – run 1	549E-12	-85.52
D-1602 – run 2	8.97E-10	-91.07	D-1607 – run 2	7.47E-10	-77.90
D-1608	1.35E-9	-75.97	D-1614 – run 1	803E-12	-80.05
D-1609 – run 1	1.54E-9	-81.34	D-1614 – run 2	6.78E-10	-86.26
D-1609 – run 2	1.63E-09	-77.49	D-1615	2.12E-9	-67.39
D-1610 – run 1	2.58E-9	-84.25	D-1616	38.3E-9	-57.61
D-1610 – run 2	2.56E-09	-80.89	D-1617	4.8E-9	-57.99
D-1611 – run 1	865E-12	-89.50	D-1618 – run 1	1.18E-9	-85.32
D-1611 – run 2	6.04E-10	-86.80	D-1618 – run 2	2.42E-09	-85.91
D-1612	1.89E-9	-77.95	D-1619	> 100E-9	2.12
D-1613 – run 1	1.29E-9	-84.46	D-1620	—	-47.40
D-1613 – run 2	1.44E-09	-80.67	D-1621	> 100E-9	1.40
D-1622	1.37E-9	-79.11	D-1630 – run 1	1.67E-9	-83.08
D-1623	3.43E-9	-66.62	D-1630 – run 2	2.29E-09	-83.88
D-1624 – run 1	6.9E-9	-85.54	D-1631 – run 1	1.42E-9	-87.66
D-1624 – run 2	3.15E-09	-84.79	D-1631 – run 2	1.12E-09	-86.08
D-1625	2.07E-9	-79.25	D-1632 – run 1	1.3E-9	-88.34
D-1626 – run 1	2.14E-9	-98.64	D-1632 – run 2	8.33E-10	-85.76
D-1626 – run 2	2.02E-09	-87.31	D-1633 – run 1	1.79E-9	-90.59
D-1627	6E-9	-67.49	D-1633 – run 2	1.66E-09	-82.90

Duplex No.	IC50 [M]	Max Activity	Duplex No.	IC50 [M]	Max Activity
D-1628	> 100E-9	3.55	D-1634 – run 1	837E-12	-82.47
D-1629 – run 1	1.13E-9	-87.48	D-1634 – run 2	7.69E-10	-84.53
D-1629 – run 2	1.43E-09	-81.66	D-1635 – run 1	1.04E-9	-88.75
D-1636	964E-12	-69.05	D-1635 – run 2	1.58E-09	-93.88
D-1637	2.36E-9	-75.45	D-1646	517E-12	-80.04
D-1638 – run 1	583E-12	-82.46	D-1647	319E-12	-73.09
D-1638 – run 2	7.20E-10	-85.90	D-1648 – run 1	1.57E-9	-81.70
D-1639	411E-12	-68.37	D-1648 – run 2	1.30E-09	-84.65
D-1640	788E-12	-79.76	D-1649	275E-12	-79.59
D-1641	1.85E-9	-69.30	D-1650	1.63E-9	-80.12
D-1642	2.52E-9	-75.03	D-1651 – run 1	415E-12	-83.10
D-1643	3.97E-9	-73.66	D-1651 – run 2	3.97E-10	-90.33
D-1644	886E-12	-67.60	D-1652 – run 1	445E-12	-81.69
D-1645	822E-12	-70.30	D-1652 – run 2	1.61E-10	-86.02
D-1653	197E-12	-79.25	D-1663 – run 1	144E-12	-87.88
D-1654 – run 1	279E-12	-85.62	D-1663 – run 2	1.92E-10	-91.58
D-1654 – run 2	3.82E-10	-89.31	D-1664 – run 1	155E-12	-81.73
D-1655 – run 1	380E-12	-88.31	D-1664 – run 2	2.87E-10	-89.13
D-1655 – run 2	3.35E-10	-96.53	D-1665 – run 1	164E-12	-81.33
D-1656 – run 1	200E-12	-87.91	D-1665 – run 2	2.62E-10	-87.08
D-1656 – run 2	1.86E-10	-85.63	D-1666 – run 1	484E-12	-84.08
D-1657 – run 1	144E-12	-85.58	D-1666 – run 2	2.86E-10	-82.03
D-1657 – run 2	3.53E-10	-88.57	D-1667 – run 1	408E-12	-85.17
D-1658	197E-12	-80.34	D-1667 – run 2	2.66E-10	-87.72
D-1659	255E-12	-80.45	D-1668 – run 1	650E-12	-83.77
D-1660	597E-12	-78.68	D-1668 – run 2	2.74E-10	-86.81
D-1661	219E-12	-78.29			
D-1662 – run 1	369E-12	-89.73			
D-1662 – run 2	2.84E-10	-96.38			

[0218] Of the additional 406 mARC1 siRNA molecules targeting different regions of the human mARC1 transcript, 128 molecules produced a reduction of human mARC1 mRNA in Hep3B

cells of 85% or greater. Forty-six molecules (duplex nos. D-1061; D-1093; D-1220; D-1276; D-1284; D-1298; D-1310; D-1311; D-1338; D-1363; D-1367; D-1375; D-1381; D-1382; D-1383; D-1386; D-1387; D-1388; D-1389; D-1390; D-1396; D-1400; D-1401; D-1402; D-1405; D-1407; D-1416; D-1420; D-1421; D-1441; D-1451; D-1487; D-1489; D-1491; D-1503; D-1504; D-1515; D-1549; D-1576; D-1581; D-1595; D-1596; D-1606; D-1626; D-1633; and D-1662) reduced human mARC1 mRNA by at least 90% with the majority of the molecules having IC50 values below 1 nM.

Example 4. In Vivo Efficacy of siRNA Molecules in AAV Human mARC1 Mouse Model

[0219] To assess the efficacy of the mARC1 siRNA molecules *in vivo*, the sense strand in each siRNA molecule was conjugated to the trivalent GalNAc moiety shown in Formula VII by the methods described in Example 2 and the mARC1 siRNA molecules were administered to mice expressing the human *MARC1* gene. 10-12-week-old C57BL/6 mice (The Jackson Laboratory) were fed standard chow (Harlan, 2020× Teklad global soy protein-free extruded rodent diet). Mice were intraperitoneally (i.p.) injected with an adeno-associated virus (AAV) encoding the human *MARC1* gene (AAV-hmARC1) at a dose of 1×10^{11} genome copies (GC) per animal. One week following AAV-hmARC1 injection, mice received a single subcutaneous (s.c.) injection of buffer or the mARC1 siRNA molecule at a dose of 0.5 mg/kg, 1 mg/kg, or 3 mg/kg body weight in buffer (n=3 each group). Animals were fasted and harvested four weeks following siRNA administration for further analysis. Liver total RNA from harvested animals was processed for qPCR analysis and serum parameters were measured by clinical analyzer (AU400 Chemistry Analyzer, Olympus). A percentage change in human mARC1 mRNA in liver for each animal was calculated relative to human mARC1 mRNA liver levels in control animals which expressed human mARC1 mRNA and received the buffer only injection (i.e. AAV-hmARC1 only animals).

[0220] The top performing mARC1 siRNA molecules from the *in vitro* activity assays described in Example 3 were evaluated for *in vivo* efficacy in this model. mARC1 siRNA molecules that exhibited significant *in vivo* knockdown activity were further evaluated in SAR studies to further improve *in vivo* potency and durability by altering chemical modification patterns. Results of 18 separate studies in the AAV-hmARC1 mouse model with different mARC1 siRNA molecules are shown in Tables 5-22 below. Data are expressed as average percent change from control at

week 5 of study (4 weeks after siRNA injection) for each treatment group (n = 3 animals/group). If a mARC1 siRNA molecule has the same trigger family designation as another mARC1 siRNA molecule, then the two molecules have the same core sequence (i.e. target the same region of the mARC1 transcript) but differ in chemical modification pattern.

Table 5. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 1

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2000	1	T918	-58	D-2032	1	T1110	6.8
D-2001	1	T1114	-71.6	D-2033	1	T1111	8.4
D-2002	1	T1016	-50.6	D-2034	1	T911	-14.1
D-2003	1	T1023	-51.5	D-2035	1	T1079	-25
D-2004	1	T704	-67.4	D-2036	1	T913	-23.6
D-2005	1	T1076	-43.3	D-2038	1	T914	-67.2
D-2008	1	T1476	-45.3	D-2040	1	T1484	-54.7
D-2011	1	T1487	-54.2	D-2042	1	T1372	-76.6
D-2013	1	T1364	-17.3	D-2044	1	T1449	-62.6
D-2022	1	T2131	-67.6	D-2045	1	T2077	-69.2
D-2024	1	T816	-72.8	D-2046	1	T1363	-39.7
D-2026	1	T1108	-10.5	D-2047	1	T1367	-58.4
D-2028	1	T1113	-4.8	D-2049	1	T1104	-26
D-2031	1	T1109	-27.8	D-2050	1	T1101	-42.4

Table 6. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 2

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2006	1	T1080	-60.12	D-2048	1	T1780	-48.24
D-2015	1	T2024	-59.3	D-2051	1	T1670	-61.04
D-2016	1	T2032	-63.1	D-2052	1	T1370	-89.53
D-2017	1	T2034	-70.1	D-2053	1	T1458	-81.49
D-2019	1	T2099	-43.07	D-2054	1	T1878	-36.34
D-2025	1	T1086	-53.07	D-2055	1	T1767	-66.47
D-2027	1	T1105	-22.88	D-2057	1	T788	-69.06

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2029	1	T976	-42.62	D-2058	1	T1275	-84.33
D-2030	1	T1123	-28.6	D-2059	1	T1814	-78.71
D-2037	1	T898	-18.98	D-2060	1	T1130	-74.14
D-2039	1	T813	-69.93	D-2061	1	T1816	-75.23
D-2041	1	T1127	-21.84	D-2062	1	T1485	-58.27
D-2043	1	T1375	-72.11				

Table 7. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 3

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2063	1	T1229	-69.57	D-2075	1	T1382	-52.85
D-2064	1	T885	-26.21	D-2076	1	T1236	-86.21
D-2065	1	T2068	-73.42	D-2077	1	T1235	-87.22
D-2066	1	T1227	-54.74	D-2078	1	T1234	-91.7
D-2067	1	T1268	-27.15	D-2079	1	T2074	-85.91
D-2068	1	T1992	-56.89	D-2080	1	T1233	-88.99
D-2069	1	T1990	-17.92	D-2081	1	T1232	-89.64
D-2070	1	T1959	-72.22	D-2082	1	T2072	-74.89
D-2071	1	T1146	-55.69	D-2083	1	T1005	-78.85
D-2072	1	T1526	-81.87	D-2084	1	T948	-45.28
D-2073	1	T1717	-57.1	D-2085	1	T573	-34.79
D-2074	1	T1077	-25.26	D-2101	1	T836	-57

Table 8. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 4

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2042	1	T1372	-72.75	D-2097	1	T999	-11.78
D-2086	1	T590	-18.09	D-2098	1	T609	-44.23
D-2087	1	T1527	-51.27	D-2099	1	T781	-60.5

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2088	1	T1067	-23.35	D-2100	1	T830	-41.23
D-2089	1	T1696	-40.51	D-2102	1	T954	-61.93
D-2090	1	T1548	-51.00	D-2103	1	T1833	-35.41
D-2091	1	T235	-20.06	D-2104	1	T2020	-36.31
D-2092	1	T508	-5.28	D-2105	1	T2059	-70.02
D-2093	1	T239	-11.41	D-2106	1	T2060	-64.34
D-2094	1	T1736	-50.26	D-2107	1	T1467	-37.67
D-2095	1	T240	13.33	D-2108	1	T1247	-79.83
D-2096	1	T998	-7.13	D-2109	1	T2133	-31.79

Table 9. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 5

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2042	1	T1372	-75.98	D-2110	1	T596	-67.89
D-2052	3	T1370	-91.31	D-2111	1	T1334	-88.01
D-2052	1	T1370	-79.79	D-2112	1	T840	-57.49
D-2052	0.5	T1370	-51.84	D-2113	1	T1239	-76.41
D-2053	3	T1458	-91.83	D-2114	1	T2016	-59.91
D-2053	1	T1458	-85.54	D-2115	1	T2017	-80.5
D-2053	0.5	T1458	-30.4	D-2116	1	T1475	-71.84
D-2058	3	T1275	-85.79	D-2117	1	T2018	-59.18
D-2058	1	T1275	-74.59	D-2118	1	T2106	-82.04
D-2058	0.5	T1275	-52.58	D-2119	1	T1273	-70.63
D-2059	1	T1814	-71.24	D-2120	1	T1506	-53.72
D-2061	1	T1816	-67.34	D-2121	1	T1537	-67.99

Table 10. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 6

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2042	1	T1372	-70.56	D-2137	1	T2073	-28.29
D-2078	3	T1234	-95.31	D-2138	1	T1089	-42.53
D-2078	1	T1234	-81.28	D-2139	1	T1716	-60.34
D-2078	0.5	T1234	-78.05	D-2140	1	T1124	-46.49
D-2079	3	T2074	-87.42	D-2141	1	T1965	-51.64
D-2079	1	T2074	-71.78	D-2142	1	T1230	-73.09
D-2079	0.5	T2074	-68.17	D-2143	1	T2071	-47.83
D-2080	1	T1233	-87.66	D-2144	1	T1012	-17.18
D-2081	3	T1232	-96.49	D-2145	1	T2102	-73.86
D-2081	1	T1232	-85.71	D-2158	1	T1372	-80.83
D-2081	0.5	T1232	-70.37	D-2169	1	T1372	-71.01
D-2083	1	T1005	-64.01	D-2182	1	T1372	-80.03
D-2134	1	T604	15.84	D-2185	1	T1372	-76.36
D-2135	1	T607	-47.29	D-2189	1	T1372	-82.41
D-2136	1	T1405	-76.24				

Table 11. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 7

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2042	1	T1372	-70.27	D-2210	1	T1275	-40.33
D-2161	1	T914	-29.66	D-2211	1	T1370	-80.39
D-2162	1	T1372	-53.65	D-2212	1	T2034	-66.09
D-2163	1	T1114	-60.02	D-2213	1	T1375	-72.26
D-2166	1	T2077	-9.73	D-2214	1	T1814	-66.69
D-2167	1	T816	-9.79	D-2215	1	T1130	-24.86
D-2183	1	T1372	-64.17	D-2216	1	T1816	-44.88
D-2184	1	T1372	-68.3	D-2217	1	T1458	-53.44
D-2186	1	T1372	-73.66	D-2218	1	T1275	-67.9
D-2187	1	T1372	-65.74	D-2222	1	T1814	-61.29
D-2201	1	T1458	-46.02	D-2223	1	T1130	-71.27
D-2206	1	T1814	-32.35	D-2224	1	T1816	-41.34
D-2207	1	T1130	-24.97	D-2225	1	T1458	-82.05
D-2208	1	T1816	24.09	D-2226	1	T1275	-66.42

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2209	1	T1458	-71.78				

Table 12. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 8

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2081	1	T1232	-89	D-2250	0.5	T1232	-68.42
D-2081	1	T1232	-84.81	D-2251	0.5	T1233	-61.68
D-2081	0.5	T1232	-81.83	D-2252	0.5	T2074	-73.55
D-2239	0.5	T1005	-43.57	D-2253	0.5	T1234	-75.93
D-2240	0.5	T1232	-70.09	D-2254	0.5	T1005	-72.84
D-2241	0.5	T1233	-91.21	D-2255	0.5	T1232	-85.73
D-2242	0.5	T2074	-72.33	D-2256	0.5	T1233	-73.31
D-2243	0.5	T1234	-82.12	D-2257	0.5	T2074	-57.42
D-2244	0.5	T1005	-61.6	D-2258	0.5	T1234	-86.98
D-2245	0.5	T1232	-70.32	D-2259	0.5	T1234	-76.42
D-2246	0.5	T1233	-82.34	D-2260	0.5	T2074	-72.66
D-2247	0.5	T2074	-71.57	D-2261	0.5	T1232	-78.9
D-2248	0.5	T1234	-78.58	D-2262	0.5	T2072	-43.95
D-2249	0.5	T1005	-33.8				

Table 13. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 9

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2042	1	T1372	-70.46	D-2265	0.5	T1234	-70
D-2081	0.5	T1232	-73.32	D-2266	0.5	T2074	-47.47
D-2168	1	T914	-25.57	D-2268	0.5	T1233	-63.89
D-2170	1	T1114	-59.16*	D-2269	0.5	T1233	-58.41
D-2173	1	T2077	-29.63	D-2270	0.5	T1234	-53.36
D-2190	1	T1114	-1.89	D-2271	0.5	T1234	-57.52

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2193	1	T2077	-52.59*	D-2272	0.5	T2074	-65.81
D-2204	1	T2034	-37.36	D-2273	0.5	T2074	-62.06
D-2220	1	T2034	-65.89	D-2301	1	T1231	-81.85
D-2227	1	T1113	-39.03	D-2302	1	T2070	-72.03
D-2229	1	T1110	-67.96	D-2303	1	T2078	-54.08
D-2232	1	T913	-63.89	D-2304	1	T1365	-67.08
D-2233	1	T2034	-62.85	D-2305	1	T1366	-71.92
D-2236	1	T1130	-61.02	D-2306	1	T1369	-64.17
D-2264	0.5	T1233	-63.96				

*averages include one outlier; if outlier removed, average % change would be -79.41% (D-2170) and -70.68% (D-2193).

Table 14. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 10

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2042	1	T1372	-74.85	D-2345	0.5	T2074	-66.64
D-2081	0.5	T1232	-79.33	D-2346	0.5	T1233	-71.49
D-2307	1	T1373	-57.28	D-2347	0.5	T1232	-67.88
D-2308	1	T1374	-54.28	D-2348	0.5	T2072	-29.7
D-2309	0.5	T1234	-68.23	D-2349	0.5	T1234	-63.39
D-2310	0.5	T2074	-49.9	D-2350	0.5	T2074	-53.12
D-2311	0.5	T1233	-71.87	D-2351	0.5	T1233	-67.77
D-2312	0.5	T1232	-56.57	D-2352	0.5	T1232	-36.82
D-2313	0.5	T2072	-46.01	D-2353	0.5	T2072	-37.66
D-2314	0.5	T1234	-72.33	D-2393	0.5	T1234	-47.75
D-2315	0.5	T2074	-61.11	D-2394	0.5	T2074	-65.84
D-2316	0.5	T1233	-80.59	D-2395	0.5	T1233	-70.01
D-2317	0.5	T1232	-79.12	D-2396	0.5	T1232	-54.78
D-2318	0.5	T2072	-60.72	D-2397	0.5	T2072	-28.06
D-2344	0.5	T1234	-79.85				

Table 15. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 11

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2081	0.5	T1232	-79.43	D-2333	0.5	T2072	-28.56
D-2319	0.5	T1234	-63.31	D-2334	0.5	T1234	-69.42
D-2320	0.5	T2074	-61.86	D-2335	0.5	T2074	-40.1
D-2321	0.5	T1233	-75.48	D-2336	0.5	T1233	-59.06
D-2322	0.5	T1232	-59.65	D-2337	0.5	T1232	-53.38
D-2323	0.5	T2072	-34.97	D-2338	0.5	T2072	-56.97
D-2324	0.5	T1234	-72.96	D-2339	0.5	T1234	-72.93
D-2325	0.5	T2074	-66.78	D-2340	0.5	T2074	-46.96
D-2326	0.5	T1233	-66.35	D-2341	0.5	T1233	-83.39
D-2327	0.5	T1232	-55.48	D-2342	0.5	T1232	-64.03
D-2328	0.5	T2072	-32.95	D-2354	0.5	T1234	-66.85
D-2329	0.5	T1234	-79.94	D-2355	0.5	T2074	-49.63
D-2330	0.5	T2074	-35.52	D-2356	0.5	T1233	-80.84
D-2331	0.5	T1233	-55.59	D-2357	0.5	T1232	-76.56
D-2332	0.5	T1232	-77.85				

Table 16. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 12

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2042	1	T1372	-78.96	D-2384	1	T1372	-87.07
D-2080	0.5	T1233	-76.6	D-2385	1	T1372	-86.66
D-2081	0.5	T1232	-80.5	D-2386	1	T1372	-82.75
D-2241	0.5	T1233	-79.44	D-2387	1	T1372	-85.64
D-2258	0.5	T1234	-79.5	D-2388	1	T1372	-85.26
D-2374	1	T1334	-76.39	D-2389	1	T1372	-82.12
D-2375	1	T1334	-84.32	D-2390	1	T1372	-78.41
D-2376	1	T1239	-77.92	D-2391	1	T1372	-88.62
D-2377	1	T2017	-68.11	D-2392	1	T1372	-79.8
D-2378	1	T2106	-73.92	D-2399	1	T1372	-90.61
D-2379	1	T1334	-81.46	D-2400	1	T1372	-82.94
D-2380	1	T1239	-60.94	D-2401	1	T1372	-92.12
D-2381	1	T2017	-73.06	D-2402	1	T1372	-73.56
D-2382	1	T2106	-72.66	D-2403	1	T1372	-89.72

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2383	1	T1334	-85.19				

Table 17. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 13

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2042	1	T1372	-72.06	D-2225	0.5	T1458	-65.93
D-2045	1	T2077	-70.1	D-2228	1	T1016	-81.59
D-2053	0.5	T1458	-43.98	D-2230	1	T1111	-28.82
D-2079	0.5	T2074	-74.22	D-2231	1	T911	-41.89
D-2079	0.5	T2074	-67.06	D-2237	1	T1816	-50.64
D-2081	0.5	T1232	-75.85	D-2238	1	T1458	-80.45
D-2158	0.5	T1372	-77.49	D-2242	0.5	T2074	-69.91
D-2159	1	T1114	-73.23	D-2247	0.5	T2074	-59.81
D-2170	1	T1114	-69.02	D-2252	0.5	T2074	-63.16
D-2182	0.5	T1372	-80.47	D-2254	0.5	T1005	-34.25
D-2188	1	T914	-78.98	D-2260	0.5	T2074	-71.08
D-2189	0.5	T1372	-76.83	D-2267	1	T1816	-21.42
D-2193	1	T2077	-69.63	D-2343	0.5	T2072	-37.41
D-2196	1	T2034	-87.29	D-2358	0.5	T2072	-36.05
D-2200	1	T1816	-69.25				

Table 18. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 14

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2081	0.5	T1232	-76.37	D-2439	0.5	T1526	-64.23
D-2108	0.5	T1247	-75.82	D-2440	0.5	T1247	-78.51
D-2111	0.5	T1334	-78.2	D-2441	0.5	T1231	-72.52
D-2113	0.5	T1239	-69.06	D-2442	0.5	T1405	-9.8
D-2115	0.5	T2017	-69.6	D-2443	0.5	T1526	-48.33

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2118	0.5	T2106	-66.06	D-2444	0.5	T1247	-62.49
D-2430	0.5	T1334	-72.94	D-2445	0.5	T1231	-56.81
D-2431	0.5	T1239	-66.56	D-2446	0.5	T1334	-68.94
D-2432	0.5	T2017	-76.11	D-2447	0.5	T1239	-56.33
D-2433	0.5	T2106	-67.19	D-2448	0.5	T2017	-67.27
D-2434	0.5	T1405	-24.95	D-2449	0.5	T2106	-75.69
D-2435	0.5	T1526	-68.17	D-2450	0.5	T1405	-45.34
D-2436	0.5	T1247	-69.01	D-2451	0.5	T1526	-64.83
D-2437	0.5	T1231	-75.43	D-2453	0.5	T1231	-65.09
D-2438	0.5	T1405	-35.85				

Table 19. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 15

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2081	0.5	T1232	-78.97	D-2467	0.5	T1334	-75.26
D-2199	0.5	T1130	-59.09	D-2468	0.5	T2072	-60.05
D-2454	0.5	T2074	-65.23	D-2469	0.5	T1959	-44.15
D-2455	0.5	T2074	-67.42	D-2470	0.5	T2072	-51.87
D-2456	0.5	T2074	-61.94	D-2471	0.5	T1959	-34.89
D-2457	0.5	T2074	-65.7	D-2472	0.5	T2077	-43.85
D-2458	0.5	T2074	-46.41	D-2473	0.5	T2072	-60.33
D-2459	0.5	T2074	-50.02	D-2474	0.5	T1959	-38.56
D-2460	0.5	T2074	-60.38	D-2475	0.5	T1130	-38.23
D-2461	0.5	T2034	-58.32	D-2476	0.5	T1334	-65.84
D-2462	0.5	T1114	-77.64	D-2477	0.5	T2072	-45.84
D-2463	0.5	T2077	-70.9	D-2478	0.5	T1959	-50.33
D-2464	0.5	T1130	-58.04	D-2479	0.5	T1114	-62.99
D-2465	0.5	T2072	-65.15	D-2480	0.5	T1526	-79.32
D-2466	0.5	T1959	-55.27				

Table 20. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 16

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2078	0.5	T1234	-80.46	D-2255	3	T1232	-95.38
D-2080	0.5	T1233	-78.74	D-2255	1	T1232	-84.2
D-2081	0.5	T1232	-71.47	D-2255	0.5	T1232	-76.6
D-2082	0.5	T2072	-63.84	D-2258	3	T1234	-96.65
D-2105	0.5	T2059	-62.69	D-2258	1	T1234	-89.16
D-2136	0.5	T1405	-32.32	D-2258	0.5	T1234	-79.98
D-2241	3	T1233	-96.62	D-2301	0.5	T1231	-87.12
D-2241	1	T1233	-92.47	D-2316	0.5	T1233	-76.86
D-2241	0.5	T1233	-84.8	D-2317	0.5	T1232	-66.58
D-2243	3	T1234	-97.39	D-2318	0.5	T2072	-54.2
D-2243	1	T1234	-94.88	D-2341	0.5	T1233	-90.21
D-2243	0.5	T1234	-83.38	D-2344	0.5	T1234	-72.37
D-2246	3	T1233	-95.55	D-2481	0.5	T1526	-78.98
D-2246	1	T1233	-92.55	D-2072	0.5	T1526	-71.36
D-2246	0.5	T1233	-81.55				

Table 21. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 17

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2057	0.5	T788	-36.45	D-2391	0.5	T1372	-69.13
D-2060	0.5	T1130	-49.77	D-2399	0.5	T1372	-75.08
D-2081	0.5	T1232	-78.72	D-2399	1	T1372	-78.92
D-2188	0.5	T914	-41.93	D-2399	3	T1372	-95.3
D-2196	3	T2034	-94.08	D-2401	0.5	T1372	-56.74
D-2196	1	T2034	-78.27	D-2401	1	T1372	-84.24
D-2196	0.5	T2034	-67.92	D-2401	3	T1372	-91.75
D-2225	3	T1458	-91.32	D-2403	0.5	T1372	-58.73
D-2225	1	T1458	-79.05	D-2462	3	T1114	-86.71
D-2225	0.5	T1458	-57.61	D-2462	1	T1114	-55.52
D-2238	0.5	T1458	-74.65	D-2462	0.5	T1114	-35.15
D-2260	3	T2074	-91.09	D-2465	3	T2072	-91.63
D-2260	1	T2074	-74.13	D-2465	1	T2072	-67.47
D-2260	0.5	T2074	-56.43	D-2465	0.5	T2072	-62.5

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2384	0.5	T1372	-76.06				

Table 22. In vivo inhibition of human mARC1 mRNA in AAV-hmARC1 mice – Study 18

Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA	Treatment (duplex no.)	Dose (mg/kg)	Trigger Family Designation	Avg. % Change in human mARC1 mRNA
D-2081	0.5	T1232	-80.49	D-2497	0.5	T1273	-59.29
D-2483	0.5	T788	-19.16	D-2498	0.5	T2102	-21.14
D-2484	0.5	T1475	-48.32	D-2499	0.5	T2070	-15.52
D-2485	0.5	T1273	-34.62	D-2500	0.5	T1366	-35.23
D-2486	0.5	T2102	-50.34	D-2501	0.5	T788	-23.95
D-2487	0.5	T2070	-44.11	D-2502	0.5	T1475	-53.81
D-2488	0.5	T1366	-55.46	D-2503	0.5	T1273	-52.52
D-2489	0.5	T788	-15.04	D-2504	0.5	T2102	-66.42
D-2490	0.5	T1475	-71.42	D-2505	0.5	T2070	-37.75
D-2491	0.5	T1273	-47.55	D-2506	0.5	T1366	-62.14
D-2492	0.5	T2102	-59.06	D-2507	0.5	T788	-45.32
D-2493	0.5	T2070	-51.01	D-2509	0.5	T1273	-15.16
D-2494	0.5	T1366	-65.43	D-2510	0.5	T2102	-80.41
D-2495	0.5	T788	-46.33	D-2511	0.5	T2070	-65.62
D-2496	0.5	T1475	-35.85	D-2512	0.5	T1366	-68.19

[0221] Two mARC1 siRNA molecules, which exhibited significant silencing activity in early *in vivo* studies (duplex nos. D-2042 and D-2081), were used as benchmark compounds in later *in vivo* studies. Seventy mARC1 siRNA molecules produced a 75% or greater reduction of human mARC1 mRNA in the AAV-hmARC1 mice at four weeks following a single s.c. injection at a dose of 1 mg/kg. Some of the tested mARC1 siRNA molecules, including D-2081, D-2241, D-2255, and D-2258, were particularly potent as evidenced by an 85% or greater reduction of human mARC1 mRNA at four weeks with just a single s.c. injection of 0.5 mg/kg. In addition, mARC1 siRNA molecules targeting certain regions of the human mARC1 transcript were observed to produce greater reductions of human mARC1 mRNA *in vivo* as compared to

mARC1 siRNA molecules targeting other regions of the transcript. For example, mARC1 siRNA molecules with antisense strands having a sequence complementary to a region of the human mARC1 transcript (SEQ ID NO: 1) between nucleotides 1205 to 1250, nucleotides 1345 to 1375, or nucleotides 2039 to 2078 exhibited significant knockdown activity four weeks after a single s.c. injection at 1 mg/kg (Table 23). Table 23 summarizes the average percent change in human mARC1 mRNA liver levels from the studies described above for siRNA molecules having the same chemical modification pattern and targeting the human transcript at the indicated nucleotide range. mARC1 siRNA molecules targeting the human transcript between nucleotides 1211 to 1236 were especially efficacious as administration of a single s.c. dose of 1 mg/kg of such siRNA molecules reduced human mARC1 mRNA levels by greater than 80% for at least four weeks following dosing.

Table 23. Summary of in vivo efficacy for mARC1 siRNA molecules targeting specific transcript regions

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Antisense sequence (unmodified)	Antisense sequence (modified)	Avg. % change in human mARC1 mRNA at 4 weeks (1 mg/kg)
<i>Human MARC1 transcript region 1</i>				
D-2066	1207-1227	AUAAUAUUC CAGGACAUACGGUU (SEQ ID NO: 1053)	asUfsaauaUfuccaggAfcAfuacggsusu (SEQ ID NO: 3324)	-54.74
D-2063	1209-1229	AUCUAAUAUUC CAGGACAUACUU (SEQ ID NO: 1054)	asUfscuaaUfauuccaGfgAfcuacsusu (SEQ ID NO: 3321)	-69.57
D-2142	1210-1230	AAUCUAAUAUUC CAGGACAUAAU (SEQ ID NO: 1055)	asAfsucuaAfuauuccAfgGfcauasusu (SEQ ID NO: 3394)	-73.09
D-2301	1211-1231	ACAUCUAAUAUUC CAGGACAUUU (SEQ ID NO: 1055)	asCfsaucuAfaauuucCfaGfgacaususu (SEQ ID NO: 3501)	-81.85
D-2081	1212-1232	AGCAUCUAAUAUUC CAGGACAUU (SEQ ID NO: 1057)	asGfscaucUfaauuuCfcAfggacasusu (SEQ ID NO: 3339)	-87.30 ¹
D-2080	1213-1233	AGGCAUCUAAUAUUC CAGGACUU (SEQ ID NO: 1058)	asGfsgcauCfuaauuUfcCfaggacsusu (SEQ ID NO: 3338)	-88.32 ²
D-2078	1214-1234	AAGGCAUCUAAUAUUC CAGGAUU (SEQ ID NO: 1059)	asAfsaggcUfcuaauUfuCfcaggasusu (SEQ ID NO: 3336)	-86.49 ²
D-2077	1215-1235	AAAGGCAUCUAAUAUUC CAGGUU (SEQ ID NO: 1060)	asAfsaggcAfucuaauAfuUfccaggsusu (SEQ ID NO: 3335)	-87.22
D-2076	1216-1236	AAAAGGCAUCUAAUAUUC CAGUU (SEQ ID NO: 1061)	asAfsaaggCfaucuaaUfaUfuccagsusu (SEQ ID NO: 3334)	-86.21

Duplex No.	Target site within human <i>MARCI</i> transcript (SEQ ID NO: 1)	Antisense sequence (unmodified)	Antisense sequence (modified)	Avg. % change in human <i>mARC1</i> mRNA at 4 weeks (1 mg/kg)
D-2113	1219-1239	UUUAAAAGGCAUCUAAUUAUUCUU (SEQ ID NO: 1196)	usUfsuaaaAfggcaucUfaAfuauucsusu (SEQ ID NO: 3371)	-76.41
D-2108	1227-1247	AGAACAUUUUUAAAAGGCAUCUU (SEQ ID NO: 1197)	asGfsaacaUfuuuuaaAfaGfgcaucsusu (SEQ ID NO: 3366)	-79.83
D-2067	1248-1268	AUUCAAGUGUUGUCAUUUUUGUU (SEQ ID NO: 969)	asUfsucaaaGfuguuguCfaUfuuuugsusu (SEQ ID NO: 3325)	-27.15
Human <i>MARCI</i> transcript region 2				
D-2013	1344-1364	AAUUGAAGCAUUGAGACACCAUU (SEQ ID NO: 842)	asAfsuugaAfgcauugAfgAfcaccasusu (SEQ ID NO: 2754)	-17.3
D-2304	1345-1365	ACAUUGAAGCAUUGAGACACCUU (SEQ ID NO: 843)	asCfsauugAfgcauuGfaGfacaccsusu (SEQ ID NO: 3504)	-67.08
D-2305	1346-1366	AACAUUGAAGCAUUGAGACACUU (SEQ ID NO: 844)	asAfscauuGfaagcauUfgAfgacacsusu (SEQ ID NO: 3505)	-71.92
D-2047	1347-1367	AGACAUUGAAGCAUUGAGACAUU (SEQ ID NO: 845)	asGfsacauUfgaagcaUfuGfagacacsusu (SEQ ID NO: 2788)	-58.4
D-2306	1349-1369	UGGGACAUUGAAGCAUUGAGAUU (SEQ ID NO: 846)	usGfsggacAfuugaagCfaUfugagasusu (SEQ ID NO: 3506)	-64.17
D-2052	1350-1370	AUGGGACAUUGAAGCAUUGAGUU (SEQ ID NO: 847)	asUfsgggaCfaugaaGfcAfuugagsusu (SEQ ID NO: 2793)	-84.66 ³
D-2042	1352-1372	AACUGGGACAUUGAAGCAUUGUU (SEQ ID NO: 848)	asAfsucggGfacauugAfaGfcauugsusu (SEQ ID NO: 2783)	-73.61 ⁴
D-2307	1353-1373	ACACUGGGACAUUGAAGCAUUUU (SEQ ID NO: 973)	asCfsacugGfgacauuGfaAfgcauususu (SEQ ID NO: 3507)	-57.28
D-2308	1354-1374	UGCACUGGGACAUUGAAGCAUUU (SEQ ID NO: 849)	usGfscacuGfggacauUfgAfgacacsusu (SEQ ID NO: 3508)	-54.28
D-2043	1355-1375	UUGCACUGGGACAUUGAAGCAUU (SEQ ID NO: 850)	usUfsgcacUfgggacaUfuGfaagcasusu (SEQ ID NO: 2784)	-72.11
D-2075	1362-1382	UUACUUUUUGCACUGGGACAUUU (SEQ ID NO: 1220)	usUfsacuuUfuugcacUfgGfgacacsusu (SEQ ID NO: 3333)	-52.85
Human <i>MARCI</i> transcript region 3				
D-2017	2014-2034	UAGAUUUUGGUGUUUAAACAAUU (SEQ ID NO: 914)	usAfsgauaUfuggguuUfuAfaacaasusu (SEQ ID NO: 2758)	-70.1
D-2105	2039-2059	UAGAGUUAUACAAUCAGUUAUU (SEQ ID NO: 1333)	usAfsagauUfaucuaUfcAfguuasusu (SEQ ID NO: 3363)	-70.02
D-2106	2040-2060	UUAGAGUUAUACAAUCAGUUAUU (SEQ ID NO: 1334)	usUfsagagUfuauacaAfuCfaguuasusu (SEQ ID NO: 3364)	-64.34
D-2065	2048-2068	AUCAGAUCUUAGAGUUAUACAUU (SEQ ID NO: 1073)	asUfscagaUfcuugaGfuUfaucacsusu (SEQ ID NO: 3323)	-73.42
D-2302	2050-2070	UCAUCAGAUCUUAGAGUUAUAAU (SEQ ID NO: 1074)	usCfsaucaGfaucuaGfaGfuuaasusu (SEQ ID NO: 3502)	-72.03
D-2143	2051-2071	UUCAUCAGAUCUUAGAGUUAUUU (SEQ ID NO: 1075)	usUfscaucAfgaucuuAfgAfguuasusu (SEQ ID NO: 3395)	-47.83
D-2082	2052-2072	AUUCAUCAGAUCUUAGAGUUAUU (SEQ ID NO: 1075)	asUfsucauUfagacuUfaGfaguuasusu (SEQ ID NO: 3340)	-74.89

Duplex No.	Target site within human <i>MARC1</i> transcript (SEQ ID NO: 1)	Antisense sequence (unmodified)	Antisense sequence (modified)	Avg. % change in human <i>mARC1</i> mRNA at 4 weeks (1 mg/kg)
D-2137	2053-2073	ACUUCAUCAGAUCUUAGAGUUUU (SEQ ID NO: 1077)	asCfsuucUfcagauCfuAfgaguususu (SEQ ID NO: 3389)	-28.29
D-2079	2054-2074	UACUUCAUCAGAUCUUAGAGUUU (SEQ ID NO: 1078)	usAfsuucAfucagauCfuUfagagususu (SEQ ID NO: 3337)	-78.84 ²
D-2045	2057-2077	AUAUACUUCAUCAGAUCUUAGUU (SEQ ID NO: 916)	asUfsauacUfucaucaGfaUfcuuagsusu (SEQ ID NO: 2786)	-69.65 ⁵
D-2303	2058-2078	AAUAUACUUCAUCAGAUCUUUUU (SEQ ID NO: 917)	asAfsuauaCfuucaucAfgAfucuuasusu (SEQ ID NO: 3503)	-54.08
D-2019	2079-2099	AAGGACAAA AUGGCAAUAAA AUU (SEQ ID NO: 920)	asAfsaggacAfaaauggCfaAfuaaaasusu (SEQ ID NO: 2760)	-43.07

¹ Average from 1 mg/kg dose groups in studies 3, 6, and 8 (Tables 7, 10, and 12, respectively)

² Average from 1 mg/kg dose groups in studies 3 and 6 (Tables 7 and 10, respectively)

³ Average from 1 mg/kg dose groups in studies 2 and 5 (Tables 6 and 9, respectively)

⁴ Average from 1 mg/kg dose groups in studies 1, 4, 5, 6, 7, 9, 10, 12, and 13 (Tables 5, 8, 9, 10, 11, 13, 14, 16 and 17, respectively)

⁵ Average from 1 mg/kg dose groups in studies 1 and 13 (Tables 5 and 17, respectively)

Example 5. Efficacy of *mARC1* siRNA in treatment of NASH in a mouse model

[0222] To determine whether inhibition of *mARC1* expression may be therapeutic for fatty liver diseases, mice on a 0.2% cholesterol diet (TD190883 diet) were administered an siRNA molecule targeting the mouse *Marc1* gene or a control siRNA molecule. The TD190883 diet contains 0.2% cholesterol, 20% fructose, 12% sucrose, and 22% hydrogenated vegetable oil (HVO). Similar diets have been shown to induce features of NAFLD and NASH in mice placed on the diet over several weeks (*see, e.g., Zhong et al., Digestion, Vol. 101:522–535, 2020 and Kroh et al., Gastroenterol Res Pract. Vol. 2020:7347068, 2020, doi:10.1155/2020/7347068*).

[0223] 6-week-old male c57BL/6 mice (Charles River Laboratories) were fed standard chow (Harlan, 2020× Teklad global soy protein-free extruded rodent diet) or 0.2% cholesterol diet (TD190883, Envigo). Mice on the 0.2% cholesterol diet received, by subcutaneous injection, buffer alone (phosphate-buffered saline), *mARC1*-targeted siRNA (duplex no. D-1000), or a control siRNA (duplex no. D-1002) at 3 mg/kg body weight in 0.2 ml buffer once every two weeks for 24 weeks. The siRNA molecules were synthesized and conjugated to a trivalent GalNAc moiety (structure shown in Formula VII) as described in Example 2. The structure of each of the siRNA molecules is provided in Tables 1 and 2. Animals were fasted and harvested

on week 24 for further analysis. Liver total RNA from harvested animals was processed for qPCR analysis and serum parameters were measured by clinical analyzer (AU400 Chemistry Analyzer, Olympus). mRNA levels were first normalized to 18S ribosomal RNA levels in each liver sample, and then compared to the expression levels in the chow control group. Data were presented as relative fold over expression in the chow control group. Liver tissues were homogenized and extracted by isopropanol for total cholesterol and total triglyceride measurement (ThermoFisher, Infinity cholesterol and Infinity triglyceride). All animal housing conditions and research protocols were approved by the Amgen Institutional Animal Care and Use Committee (IACUC). Mice were housed in a specified-pathogen free, AAALAC, Intl-accredited facility in ventilated microisolators. Procedures and housing rooms were positively pressured and regulated on a 12:12 dark: light cycle. All animals received reverse-osmosis purified water ad libitum via an automatic watering system.

[0224] Liver expression of both mARC1 and mARC2 was reduced in mice fed the 0.2% cholesterol diet. mARC1 expression, but not mARC2 expression, was further reduced in animals treated with the mARC1-targeted siRNA (Figures 5A and 5B). As expected, mice on the 0.2% cholesterol diet had increased serum levels of liver enzymes (AST and ALT), cholesterol, LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) over the course of the study (Figures 6A-6E). Treatment with the mARC1-targeted siRNA reduced the diet-induced increases in serum cholesterol, LDL-C and HDL-C (Figures 6C-6E). The mARC1 siRNA treatment also showed a trend in reducing diet-induced serum levels of liver enzymes (Figures 6A-6B). Animals on the 0.2% cholesterol diet had increased body and liver weight after 24 weeks (Figures 7A and 7B). Triglyceride and cholesterol levels in the liver were also increased in animals on the 0.2% cholesterol diet at 24 weeks (Figures 7C and 7D). mARC1 siRNA treatment did not significantly reduce the diet-induced increases in body weight, liver weight, liver triglyceride levels or liver cholesterol levels (Figures 7A-7D).

[0225] In sum, the results of this study show that inhibition of mARC1 liver expression with a mARC1-targeted siRNA molecule reduces serum cholesterol, LDL-C, HDL-C, and liver enzymes in a mouse model of NASH, suggesting that mARC1 siRNA molecules may be a novel therapeutic approach for treating this disease and other fatty liver disorders.

Example 6. Impact of mismatches on potency of mARC1 siRNA molecules

[0226] To assess the effect of base pair mismatches on the potency of mARC1 siRNA molecules, analogs of a subset of the most potent siRNA molecules were synthesized to have a different nucleotide at positions 6 or 8 from the 5' end of the antisense strand such that a base pair mismatch was created at that position when the antisense strand hybridized to its target region of the mARC1 mRNA transcript. However, in each analog, the sequence of the sense strand was designed to be fully complementary to the sequence of the antisense strand so no mismatches were created between the sense and antisense strands in the siRNA duplex. The unmodified and modified sequences for each of the mismatch analogs (duplex nos. D-2514 to D-2561) and the parental siRNA molecules (duplex nos. D-2052, D-2072, D-2076, D-2077, D-2079, D-2081, D-2105, D-2108, D-2111, D-2113, D-2115, D-2118, D-2142, D-2136, D-2189, D-2196, D-2238, D-2241, D-2254, D-2258, D-2301, D-2462, D-2465, and D-2510) are provided in Tables 1 and 2, respectively. The efficacy of the mismatch analogs and the parental siRNA molecules in reducing human mARC1 mRNA levels was evaluated in Hep3B cells using the *in vitro* RNA FISH assay described in Example 3 above. Ten different concentrations of each of the siRNA molecules ranging from 100 nM to 5 pM were tested, and IC₅₀ and maximum activity values were calculated from the dose response curves as described in Example 3. The results of these assays are shown in Table 24 below.

Table 24. In vitro efficacy of mARC1 siRNA mismatch analogs in Hep3B cells

Duplex No.	Target site within human MARC1 transcript (SEQ ID NO: 1)	Mismatch Position from 5' end of antisense strand	IC ₅₀ [M]	Max Activity
D-2254	985-1005	none	4.17E-09	-83.59
D-2514	985-1005	6	—	-74.91
D-2515	985-1005	8	2.97E-08	-78.35
D-2462	1092-1114	none	6.9E-10	-93.14
D-2516	1092-1114	6	2.00E-08	-79.30
D-2517	1092-1114	8	1.54E-09	-87.85
D-2142	1210-1230	none	6.82E-10	-90.23
D-2518	1210-1230	6	3.34E-09	-82.58
D-2519	1210-1230	8	4.63E-09	-85.78
D-2301	1211-1231	none	3.3E-10	-84.34

Duplex No.	Target site within human MARC1 transcript (SEQ ID NO: 1)	Mismatch Position from 5' end of antisense strand	IC50 [M]	Max Activity
D-2520	1211-1231	6	7.59E-09	-79.51
D-2521	1211-1231	8	1.49E-08	-70.30
D-2081	1212-1232	none	5.88E-10	-86.84
D-2522	1212-1232	6	2.91E-09	-85.61
D-2523	1212-1232	8	2.33E-09	-89.43
D-2241	1215-1233	none	1.26E-09	-86.29
D-2524	1215-1233	6	2.51E-08	-82.90
D-2525	1215-1233	8	5.49E-09	-85.28
D-2258	1214-1234	none	7.55E-10	-81.90
D-2526	1214-1234	6	3.37E-09	-86.17
D-2527	1214-1234	8	2.24E-08	-73.80
D-2077	1215-1235	none	4.42E-10	-87.32
D-2528	1215-1235	6	5.33E-09	-86.59
D-2529	1215-1235	8	5.6E-09	-86.43
D-2076	1216-1236	none	5.41E-10	-89.64
D-2530	1216-1236	6	1.79E-08	-82.25
D-2531	1216-1236	8	2.52E-09	-82.91
D-2113	1219-1239	none	5.86E-10	-86.53
D-2532	1219-1239	6	1.10E-08	-82.08
D-2533	1219-1239	8	6.44E-09	-76.61
D-2108	1227-1247	none	1.44E-09	-85.90
D-2534	1227-1247	6	4.7E-09	-78.40
D-2535	1227-1247	8	3.69E-09	-85.20
D-2111	1314-1334	none	2.78E-10	-88.86
D-2536	1314-1334	6	—	-31.51
D-2537	1314-1334	8	4.7E-09	-83.69
D-2052	1350-1370	none	5.75E-10	-80.89
D-2538	1350-1370	6	1.49E-08	-75.03
D-2539	1350-1370	8	2.19E-09	-81.35
D-2189	1352-1372	none	1.49E-09	-85.52
D-2540	1352-1372	6	—	-76.77
D-2541	1352-1372	8	4.1E-09	-88.64
D-2136	1385-1405	none	9.11E-10	-84.91
D-2542	1385-1405	6	—	-16.91
D-2543	1385-1405	8	3.21E-08	-70.17
D-2238	1438-1458	none	7.37E-10	-77.36
D-2544	1438-1458	6	1.12E-08	-61.11

Duplex No.	Target site within human MARC1 transcript (SEQ ID NO: 1)	Mismatch Position from 5' end of antisense strand	IC50 [M]	Max Activity
D-2545	1438-1458	8	7.51E-09	-82.10
D-2072	1506-1526	none	8.57E-10	-87.83
D-2546	1506-1526	6	8.49E-09	-83.30
D-2547	1506-1526	8	2.68E-09	-87.92
D-2115	1997-2017	none	5.67E-10	-82.42
D-2548	1997-2017	6	8.32E-09	-84.98
D-2549	1997-2017	8	2.82E-09	-83.58
D-2196	2016-2034	none	1.38E-09	-82.91
D-2550	2016-2034	6	1.85E-08	-78.12
D-2551	2016-2034	8	—	-75.52
D-2105	2039-2059	none	7.52E-10	-89.10
D-2552	2039-2059	6	1.45E-08	-83.79
D-2553	2039-2059	8	4.00E-09	-82.31
D-2465	2052-2072	none	5.98E-10	-84.77
D-2554	2052-2072	6	6.74E-09	-77.83
D-2555	2052-2072	8	2.05E-09	-86.44
D-2079	2054-2074	none	4.03E-10	-85.54
D-2556	2054-2074	6	2.74E-09	-71.14
D-2557	2054-2074	8	3.57E-09	-84.85
D-2510	2082-2102	none	4.08E-10	-81.51
D-2558	2082-2102	6	2.35E-08	-62.54
D-2559	2082-2102	8	1.61E-09	-84.40
D-2118	2086-2106	none	4.64E-10	-82.20
D-2560	2086-2106	6	9.57E-09	-75.61
D-2561	2086-2106	8	7.37E-09	-83.48

[0227] For the majority of the molecules, the mismatches at positions 6 and 8, which are located within the seed region of the antisense strand, did not significantly affect the maximum knockdown activity or the potency of the siRNA molecules as compared to the parental molecules in which the antisense strand was fully complementary to the target mARC1 mRNA sequence. These results are somewhat surprising as the seed region of the antisense strand (i.e. nucleotides 2 to 8 from the 5' end) is believed to be important for on-target efficacy.

Example 7. In Vivo Efficacy of mARC1 siRNA Molecules in Non-Human Primates

[0228] Efficacy and pharmacokinetic profile of three different mARC1 siRNA molecules (duplex nos. D-2241, D-2081, or D-2258) were evaluated in cynomolgus monkeys. Each of the three different mARC1 siRNA molecules had antisense strand sequences that cross-reacted with the cynomolgus monkey (*Macaca fascicularis*) *MARC1* gene. Female treatment-naïve cynomolgus macaque monkeys, ages 22 to 48 months, of Mauritius origin were sourced from Charles River Laboratories, Inc. Research Model Services (Houston, TX). Animals (n = 3 per treatment group) were administered a single 3 mg/kg subcutaneous (s.c.) injection into the scapular and mid-dorsal region of GalNAc-conjugated mARC1 siRNA molecule, either duplex no. D-2241, D-2081, or D-2258, formulated in 1X phosphate buffered saline. Serum was prepared from whole blood collected at the following time points post-dose: 0.083, 0.25, 1, 2, 4, 24, 28, 96, 168, 264, 336, 456, 528, 576, 720, 864, and 1056 hours. Surgical liver biopsies (approximately 100 mg tissue per left and right liver lobe) were collected under anesthesia at pre-treatment (either days -13 or -7) and days 14 and 30 post-dose. Day 44 post-dose liver samples were collected at necropsy.

Serum and Liver Pharmacokinetics

[0229] To determine the serum and liver pharmacokinetic profiles of each of the GalNAc-conjugated mARC1 siRNA molecules, serum and liver samples collected at different time points following treatment with a single 3 mg/kg s.c. dose of the mARC1 siRNA molecules were analyzed for each of the mARC1 siRNA molecules (antisense and sense strands) using a plate-based oligonucleotide electro-chemiluminescent (POE) immunoassay similar to that described in Thayer *et al.*, Sci. Rep., Vol. 10(1): 10425, 2020. Oligonucleotide capture (biotin) and detection (digoxigenin) probes were custom synthesized from Qiagen Inc. (Hilden, Germany), the sequences for which are listed in Table 25 below. Liver samples were homogenized in lysis buffer containing 50 mM Tris HCl, 100 mM NaCl, 0.1% Triton X100, and Roche protease inhibitor cocktail (11836170001) to a final concentration of 200 mg/mL. For the bioanalysis, GalNAc-mARC1 siRNA standards were spiked into serum or liver homogenate over a concentration range of 0.13 to 2500 ng/mL. Standards and biological samples were then diluted 1:10 in a 96 well PCR plate to a final volume of 50 µL. Oligonucleotide capture and detection probes were prepared in a hybridization buffer consisting of 60 mM Na₂PO₄ (pH 7.0, dibasic), 1

M NaCl, 5 mM EDTA, and 0.02% Tween 20. Probes were combined and added to the PCR plate at a final concentration of 10 nM bringing the total sample volume to 100 μ L per well. Hybridization was performed using a thermal cycler under the following conditions: 90°C for 5 minutes, 40°C for 30 minutes, and a final hold at 12°C. After hybridization, 45 μ L of samples were transferred to a Meso Scale Diagnostics, LLC MSD Gold 96-well Streptavidin SECTOR plate (L15SA) and incubated at room temperature for 30 minutes while shaking. The plates were washed with SerCare Life Sciences 1X KPL immunoassay wash solution (5150-0011). After washing, plates were incubated for 1 hour with 50 μ L of 0.5 μ g/mL ruthenium labeled anti-digoxigenin antibody diluted in ThermoFisher Scientific SuperBlock T20 TBS Blocking Buffer (37536). A final wash was performed prior to the addition of Meso Scale Diagnostics, LLC 1X MSD Read Buffer T (R92TC; 150 μ L) and read on a Meso Scale Diagnostics, LLC Meso Sector S 600 instrument. Serum and liver concentrations of the mARC1 siRNA molecules were interpolated from a standard curve using a 4-parameter logistic model and a weighting factor of 1/Y² in Watson LIMS bioanalytical software version 7.5 (ThermoFisher Scientific). Liver concentrations were converted from units of ng/mL to ng/mg by dividing by 200 mg/mL. Serum pharmacokinetic parameters from 0.083 to 24 hours post-dose were determined using noncompartmental analysis in Phoenix WinNonlin software version 8.3.2.116 (Pharsight).

Table 25. POE immunoassay capture and detection probes

Duplex No.	Strand	Sequence (5'→3') ¹	SEQ ID NO:
D-2241	Antisense	/5Biosg/ACCTGGAATA	3659
D-2241	Antisense	TTAGATGCCT/3Dig_N/	3660
D-2241	Sense	/5Biosg/AAGGCATCTA	3661
D-2241	Sense	ATATTCCAGG/3Dig_N/	3662
D-2081	Antisense	/5Biosg/ATGTCCTGGAA	3663
D-2081	Antisense	TATTAGATGCT/3Dig_N/	3664
D-2081	Sense	/5Biosg/GCATCTAATA	3665
D-2081	Sense	TTCCAGGACA/3Dig_N/	3666
D-2258	Antisense	/5Biosg/CCTGGGAATAT	3667
D-2258	Antisense	TAGATGCCTT/3Dig_N/	3668
D-2258	Sense	/5Biosg/AGGCATCTAA	3669

Duplex No.	Strand	Sequence (5'→3') ¹	SEQ ID NO:
D-2258	Sense	T <u>A</u> T <u>T</u> C <u>C</u> A <u>G</u> G <u>A</u> /3Dig_N/	3670

¹Underlined base = locked nucleic acid modification; /5Biosg/ = biotin conjugation via a six-carbon linker; /3Dig_N/ = digoxigenin conjugation via a N-hydroxysuccinimide ester.

[0230] Serum concentration-time profiles for antisense and sense strand concentrations for each of the three different mARC1 siRNA molecules are shown in Figures 8A-8F. The mean maximum observed antisense strand concentration ($C_{\max}$) in serum was 511, 496, and 321 ng/mL for D-2241, D-2258, and D-2081, respectively, at 2.0 to 4.0 hours post-dose as summarized in Table 26. The mean area under the concentration time curve from the start of dose administration to 24 hours post-dose ($AUC_{0-24 \text{ hour}}$) for serum antisense strands was 6399, 5040, and 4137 h*ng/mL for D-2258, D-2241, and D-2081, respectively. The ratio of the serum concentrations of the sense strand to antisense strand for duplex no. D-2258 indicates a potential instability of the duplex with strand separation possibly occurring at the site of injection or in systemic circulation. siRNA liver concentrations for antisense and sense strands on days 14, 30 and 44 post-dose are reported in Table 27. Day 14 liver antisense strand concentrations were greatest for duplex no. D-2081 followed by D-2241 and then D-2258. Consistent with the serum pharmacokinetic profile, the ratio of the liver concentrations of the sense and antisense strands for duplex no. D-2258 indicates strand separation.

Table 26. Antisense strand serum pharmacokinetic parameters with a single 3 mg/kg s.c. dose of mARC1 siRNA molecules in cynomolgus macaque monkeys

Pharmacokinetic Parameter ¹	GalNAc-conjugated mARC1 siRNA Treatment (duplex no.)		
	D-2241	D-2081	D-2258
$T_{\max}$ (h)	2.0	4.0	4.0
$C_{\max}$ (ng/mL)	511	321	496
$AUC_{0-24 \text{ hour}}$ (h*ng/mL)	5040	4137	6399

¹ $T_{\max}$ = the time after dosing at which the maximum observed concentration was observed; $C_{\max}$ = the maximum observed concentration measured after dosing; $AUC_{0-24 \text{ hour}}$ = the area under the concentration versus time curve using the linear trapezoidal method from the start of dose administration to 24 hours post-dose. N = 3 animals per treatment group.

Table 27. Antisense and sense strand liver concentrations with a single 3 mg/kg s.c. dose of mARC1 siRNA molecules in cynomolgus macaque monkeys

	GalNAc-conjugated mARC1 siRNA Treatment (duplex no.)					
	D-2241 (Mean $\pm$ SD; ng/mg)		D-2081 (Mean $\pm$ SD; ng/mg)		D-2258 (Mean $\pm$ SD; ng/mg)	
	Antisense	Sense	Antisense	Sense	Antisense	Sense
Day 14 Post-Dose	28 $\pm$ 11	29 $\pm$ 6.7	39 $\pm$ 10	20 $\pm$ 3.5	14 $\pm$ 1.1	42 $\pm$ 3.7
Day 30 Post-Dose	11 $\pm$ 4.5	12 $\pm$ 1.7	4.3 $\pm$ 0.37	11 $\pm$ 1.9	7.4 $\pm$ 0.60	29 $\pm$ 1.4
Day 44 Post-Dose	5.9 $\pm$ 3.0	0.69 $\pm$ 0.29	2.4 $\pm$ 0.33	5.1 $\pm$ 0.95	5.1 $\pm$ 0.57	16 $\pm$ 3.6

SD = standard deviation

Liver mARC1 mRNA Silencing

[0231] The three GalNAc-conjugated mARC1 siRNA molecules (duplex nos. D-2241, D-2081, and D-2258) were evaluated for efficacy in knocking down mARC1 mRNA levels in the liver of cynomolgus macaque monkeys following a 3 mg/kg s.c. dose. RNA was purified from snap frozen liver using the ThermoFisher Scientific MagMAX-96 Total RNA Isolation Kit (AM1830) of which sample integrity (260/280 ratio) and RNA concentrations were determined with a ThermoFisher Scientific NanoDrop 2000 Spectrophotometer (ND-2000). One step reverse transcription-polymerase chain reaction (RT-PCR) was performed using ThermoFisher Scientific's TaqMan™ RNA-to-CT 1-Step Kit (4392938). Reactions were assembled into a 96 well PCR plate by mixing 50 ng of RNA template with 2X TaqMan RT-PCR Mix, 40X TaqMan RT Enzyme Mix, 20X mARC1 primer-probe (IDT, forward primer 5'-TTCAGGATGCGATGTCTATGC-3' (SEQ ID NO: 3671), reverse primer 5'-TGCCCAAAGAGTGGTGATTT-3' (SEQ ID NO: 3672), probe 5'-/56-FAM/AGCCGCTGG (SEQ ID NO: 3673)/ZEN/AAACACTGAAGAGTT (SEQ ID NO: 3674)/3IABkFQ/-3'), and 20X glyceraldehyde-3-phosphate dehydrogenase primer-probe (GAPDH; ThermoFisher Scientific, Mf04392546_g1 VIC-MGB). RT-PCR was performed using the ThermoFisher Scientific QuantStudio 7 Flex Real-Time PCR System (4485701) under the following conditions: 48°C for 30 minutes, and 90°C for 10 minutes followed by 40 cycles of 90°C for 15 seconds and 60°C for 1 minute. mRNA expression for

each sample was normalized by taking a ratio of the concentration of the gene of interest (mARC1) over the concentration of the housekeeping gene (GAPDH). Percent (%) of mARC1 mRNA expression post-siRNA dose (days 14, 30, and 44) was then calculated relative to the pre-treatment (days -13 or -7) time point for each animal replicate per treatment group, which was expressed as % remaining of pre-treatment. Percent (%) silencing of mARC1 mRNA transcript was ultimately calculated by subtracting the % remaining of pre-treatment value from 100%. Both mRNA % remaining of pre-treatment and % silencing values are summarized below in Table 28. Duplex no. D-2241 was the most potent GalNAc-conjugated mARC1 siRNA molecule tested, reducing cynomolgus mARC1 liver mRNA to < 20% remaining of pre-treatment (> 80% silencing) on days 14, 30, and 44 following a single subcutaneous injection.

Table 28. Cynomolgus macaque liver mARC1 mRNA silencing with a single 3 mg/kg s.c. dose of GalNAc-conjugated mARC siRNA molecules

	GalNAc-conjugated mARC1 siRNA Treatment (duplex no.)	D-2241			D-2081			D-2258		
	Animal Replicate	1	2	3	1	2	3	1	2	3
Day 14 Post-Dose	% Remaining of Pre-treatment	ND (0)	0.67	0.57	29	22	14	20	38	1.0
	% Silencing	100	99	99	71	78	86	80	62	99
	% Silencing; Mean $\pm$ SD	99 $\pm$ 0.58			78 $\pm$ 7.5			80 $\pm$ 19		
Day 30 Post-Dose	% Remaining of Pre-treatment	3.7	23	22	36	52	21	37	40	57
	% Silencing	96	77	78	64	48	79	63	60	43
	% Silencing; Mean $\pm$ SD	84 $\pm$ 11			64 $\pm$ 16			55 $\pm$ 11		
Day 44 Post-Dose	% Remaining of Pre-treatment	0.20	23	21	47	41	8.8	30	30	28
	% Silencing	100	78	79	53	59	91	70	70	72
	% Silencing; Mean $\pm$ SD	86 $\pm$ 12			68 $\pm$ 21			71 $\pm$ 1.0		

	Mean $\pm$ SD			
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ND = not detected; SC = subcutaneous; SD = standard deviation; Samples in which mARC1 mRNA expression was below the limit of assay detection were denoted as "ND" (not detected) and set to zero.

Liver mARC1 Protein Silencing

[0232] Efficacy of the three GalNAc-conjugated mARC1 siRNA molecules (duplex nos. D-2241, D-2081, and D-2258) in knocking down mARC1 protein levels in the liver of cynomolgus macaque following a 3 mg/kg s.c. dose was also assessed. Snap frozen liver tissue was homogenized at 200 mg/mL in Boston Bioproduct NP-40 Lysis Buffer (BP-119) containing ThermoFisher Scientific Protease Inhibitor Tablets (A32963). Homogenates were then spun down at 10,000 x g under 4°C for 10 minutes and supernatants were transferred to a 2 mL 96 deep-well plate. Supernatants were treated with 1% trifluoroacetic acid in methanol while incubating for 15 minutes at room temperature and shaking at 1400 rpm. Precipitated proteins were pelleted for 15 minutes at 4,000 rpm from which the supernatants were aspirated and the pellets were washed twice with methanol. Resulting proteins were reduced and denatured in a solution containing 10 mM tris(2-carboxyethyl)phosphine (ThermoFisher Scientific, 77720) and 8 M urea for 30 minutes at 37°C. Iodoacetamide (20 mM; ThermoFisher Scientific, A39271) was then added to the samples in 20 mM ammonium bicarbonate buffer and incubated for 30 minutes at room temperature. Tryptic digestion was performed overnight at 37°C with the addition of 30 µg trypsin (ThermoFisher Scientific, A90058) and 10 pmol of the stable isotopically labeled (SIL) peptide (ThermoFisher Scientific custom peptide; SPLFGQYFVLENPGTIK (SEQ ID NO: 3675)). The digestion reaction was terminated with 20% formic acid and the samples were prepared for solid phase extraction (SPE) desalting (Waters Corporation, 186008052). Prior to loading samples, the SPE plate was conditioned with methanol and washed once with 1% acetonitrile. Samples were added to the conditioned SPE plate and analytes were eluted using 70% acetonitrile. Eluates were resuspended in 10 mM ammonium formate at pH 10 and injected onto an Agilent 1260 Infinity Bio-inert Analytical-scale Fraction Collector (G5664A). The fractionated samples (11th fraction) were resuspended in 0.1% formic acid solution for analysis on a ThermoFisher Scientific Ultimate 3000 ultra-high performance liquid chromatography (LC) system coupled to an Orbitrap Lumos mass spectrometer (MS). The LC method was performed as follows: trapping at 3% acetonitrile/water, 8 µL/minute and analytical gradient at 3.0 to 36% acetonitrile/water over 1.0

to 12.1 minutes, 350 nL/minute, with a column temperature at 45°C. A parallel reaction monitoring experiment was performed on the Orbitrap Fusion Lumos instrument monitoring light- and heavy-labeled peptides SPLFGQYFVLENPGTIK (SEQ ID NO: 3675) at m/z = 955.5066 and SPLFGQYFVLENPGTIK (SEQ ID NO: 3675) at m/z = 959.5137, respectively. Data was then imported into Skyline 21.1 software (Pino LK et al. The Skyline ecosystem: Informatics for quantitative mass spectrometry proteomics. Mass Spectrom Rev. 2020 May;39(3):229-244. doi: 10.1002/mas.21540. Epub 2017 Jul 9.), where the SPLFGQYFVLENPGTIK (SEQ ID NO: 3675) peptide peak area from each sample was normalized to the peak area of the spiked-in SIL peptide SPLFGQYFVLENPGTIK (SEQ ID NO: 3675). The measurement of GAPDH housekeeping protein was performed using the same starting tissue homogenate and precipitated with ice-cold acetone followed by mixing at 1250 rpm for 10 minutes and centrifugation at 3220 x g for 15 minutes. The supernatants were aspirated and protein pellets were washed with methanol, dissolved in 50 mM ammonium bicarbonate buffer containing 10 µg trypsin, and digested overnight at 37°C with mixing at 1000 rpm. The digestion reaction was terminated with 20% formic acid and injected for LC-MS/MS analysis monitoring the GAPDH peptide: LISWYDNEFGYSNR (SEQ ID NO: 3676) at 588.61 and 743.35 m/z . The GAPDH peptide peak area was integrated using SCIEX Analyst software. Protein expression for each sample was normalized by taking a ratio of the concentration of the protein of interest (mARC1) as determined relative to the SIL peptide over the concentration of the housekeeping protein (GAPDH). Percent (%) of mARC1 protein expression post-siRNA dose (days 14, 30, and 44) was then calculated relative to the pre-treatment (days -13 or -7) time point for each animal replicate per treatment group, which was expressed as % remaining of pre-treatment. Percent (%) silencing of mARC1 protein expression was ultimately calculated by subtracting the % remaining of pre-treatment value from 100%. Both protein % remaining of pre-treatment and % silencing values are summarized in Table 29. Duplex no. D-2081 showed the greatest reduction in cynomolgus mARC1 liver protein expression on day 14 post-dose with $89 \pm 0.71\%$ silencing following a single subcutaneous injection. On day 30 post-dose, duplex nos. D-2081 and D-2241 decreased protein expression to $< 20\%$ remaining of pre-treatment with $82 \pm 7.8\%$ and $87 \pm 11\%$ silencing, respectively, which was maintained or increased through day 44 post-dose.

Table 29. Cynomolgus macaque liver mARC1 protein silencing with a single 3 mg/kg s.c. dose of GalNAc-conjugated mARC siRNA molecules

	GalNAc-conjugated mARC1 siRNA Treatment (duplex no.)	D-2241			D-2081			D-2258		
	Animal Replicate	1	2	3	1	2	3	1	2	3
Day 14 Post-Dose	% Remaining of Pre-treatment	34	35	22	ND (0)	11	12	56	68	25
	% Silencing	66	65	78	N/A	89	88	44	32	75
	% Silencing; Mean $\pm$ SD	70 $\pm$ 7.2			89 $\pm$ 0.71			50 $\pm$ 22		
Day 30 Post-Dose	% Remaining of Pre-treatment	0.99	14	22	ND (0)	24	13	39	54	3.6
	% Silencing	99	86	78	N/A	76	87	61	46	96
	% Silencing; Mean $\pm$ SD	87 $\pm$ 11			82 $\pm$ 7.8			68 $\pm$ 26		
Day 44 Post-Dose	% Remaining of Pre-treatment	10	16	ND (0)	ND (0)	9	12	44	52	14
	% Silencing	90	84	N/A	N/A	91	88	56	48	86
	% Silencing; Mean $\pm$ SD	86 $\pm$ 4.2			90 $\pm$ 2.1			64 $\pm$ 20		

N/A = not applicable; ND = not detected; SC = subcutaneous; SD = standard deviation; Samples in which mARC1 protein expression was below the limit of assay detection were denoted as "ND" (not detected) and set to zero.

[0233] All publications, patents, and patent applications discussed and cited herein are hereby incorporated by reference in their entireties. It is understood that the disclosed invention is not limited to the particular methodology, protocols and materials described as these can vary. It is also understood that the terminology used herein is for the purposes of describing particular embodiments only and is not intended to limit the scope of the appended claims.

[0234] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed:

1. An RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having a sequence that is substantially complementary to a mARC1 mRNA sequence, and wherein said region comprises at least 15 contiguous nucleotides from an antisense sequence listed in Table 1 or Table 2.
2. The RNAi construct of claim 1, 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.
3. The RNAi construct of claim 2, wherein the duplex region is about 17 to about 24 base pairs in length.
4. The RNAi construct of claim 2, wherein the duplex region is about 19 to about 21 base pairs in length.
5. The RNAi construct of any one of claims 1 to 4, wherein the sense strand and the antisense strand are each independently about 19 to about 30 nucleotides in length.
6. The RNAi construct of claim 5, wherein the sense strand and the antisense strand are each independently about 19 to about 23 nucleotides in length.
7. The RNAi construct of any one of claims 1 to 6, wherein the RNAi construct comprises one or two blunt ends.
8. The RNAi construct of any one of claims 1 to 6, wherein the RNAi construct comprises one or two nucleotide overhangs of 1 to 4 unpaired nucleotides.

9. The RNAi construct of claim 8, wherein the nucleotide overhang has 2 unpaired nucleotides.
10. The RNAi construct of claim 8 or 9, 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.
11. The RNAi construct of any one of claims 1 to 10, wherein the RNAi construct comprises at least one modified nucleotide.
12. The RNAi construct of claim 11, wherein the modified nucleotide is a 2'-modified nucleotide.
13. The RNAi construct of claim 11, wherein the modified nucleotide is a 2'-fluoro modified nucleotide, a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, 2'-O-alkyl modified nucleotide, a 2'-O-allyl modified nucleotide, a bicyclic nucleic acid (BNA), a deoxyribonucleotide, or combinations thereof.
14. The RNAi construct of claim 11, wherein all of the nucleotides in the sense and antisense strands are modified nucleotides.
15. The RNAi construct of claim 14, wherein the modified nucleotides are 2'-O-methyl modified nucleotides, 2'-fluoro modified nucleotides, or combinations thereof.
16. The RNAi construct of any one of claims 1 to 15, 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.
17. The RNAi construct of claim 16, wherein the abasic nucleotide is linked to the adjacent nucleotide through a 3'-3' internucleotide linkage or a 5'-5' internucleotide linkage.

18. The RNAi construct of any one of claims 1 to 17, wherein the sense strand, the antisense strand, or both the sense and antisense strands comprise one or more phosphorothioate internucleotide linkages.
19. The RNAi construct of claim 18, wherein the antisense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends.
20. The RNAi construct of claim 18 or 19, wherein the sense strand comprises a single phosphorothioate internucleotide linkage between the terminal nucleotides at the 3' end.
21. The RNAi construct of claim 18 or 19, wherein the sense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at the 3' end.
22. The RNAi construct of any one of claims 1 to 21, wherein the antisense strand comprises or consists of a sequence selected from the antisense sequences listed in Table 1 or Table 2.
23. The RNAi construct of any one of claims 1 to 22, wherein the antisense strand comprises or consists of a sequence selected from SEQ ID NO: 715; SEQ ID NO: 732; SEQ ID NO: 733; SEQ ID NO: 738; SEQ ID NO: 754; SEQ ID NO: 761; SEQ ID NO: 763; SEQ ID NO: 764; SEQ ID NO: 766; SEQ ID NO: 809; SEQ ID NO: 810; SEQ ID NO: 814; SEQ ID NO: 841; SEQ ID NO: 848; SEQ ID NO: 851; SEQ ID NO: 862; SEQ ID NO: 916; SEQ ID NO: 1057; SEQ ID NO: 1078; SEQ ID NO: 2919; SEQ ID NO: 2926; SEQ ID NO: 2946; SEQ ID NO: 2949; SEQ ID NO: 2953; and SEQ ID NO: 2956.
24. The RNAi construct of any one of claims 1 to 23, wherein the sense strand comprises or consists of a sequence selected from the sense sequences listed in Table 1 or Table 2.
25. The RNAi construct of claim 24, wherein the sense strand comprises or consists of a sequence selected from SEQ ID NO: 46; SEQ ID NO: 63; SEQ ID NO: 64; SEQ ID NO: 69;

SEQ ID NO: 85; SEQ ID NO: 92; SEQ ID NO: 94; SEQ ID NO: 95; SEQ ID NO: 97; SEQ ID NO: 140; SEQ ID NO: 141; SEQ ID NO: 145; SEQ ID NO: 172; SEQ ID NO: 179; SEQ ID NO: 182; SEQ ID NO: 193; SEQ ID NO: 247; SEQ ID NO: 388; SEQ ID NO: 390; SEQ ID NO: 391; SEQ ID NO: 409; SEQ ID NO: 2808; and SEQ ID NO: 2820.

26. The RNAi construct of any one of claims 1 to 25, wherein:

(i) the sense strand comprises or consists of the sequence of SEQ ID NO: 46 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 715;

(ii) the sense strand comprises or consists of the sequence of SEQ ID NO: 63 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 732;

(iii) the sense strand comprises or consists of the sequence of SEQ ID NO: 64 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 733;

(iv) the sense strand comprises or consists of the sequence of SEQ ID NO: 69 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 738;

(v) the sense strand comprises or consists of the sequence of SEQ ID NO: 85 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 754;

(vi) the sense strand comprises or consists of the sequence of SEQ ID NO: 92 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 761;

(vii) the sense strand comprises or consists of the sequence of SEQ ID NO: 94 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 763;

(viii) the sense strand comprises or consists of the sequence of SEQ ID NO: 95 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 764;

(ix) the sense strand comprises or consists of the sequence of SEQ ID NO: 97 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 766;

(x) the sense strand comprises or consists of the sequence of SEQ ID NO: 140 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 809;

(xi) the sense strand comprises or consists of the sequence of SEQ ID NO: 141 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 810;

(xii) the sense strand comprises or consists of the sequence of SEQ ID NO: 145 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 814;

(xiii) the sense strand comprises or consists of the sequence of SEQ ID NO: 172 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 841;

(xiv) the sense strand comprises or consists of the sequence of SEQ ID NO: 179 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 848;

(xv) the sense strand comprises or consists of the sequence of SEQ ID NO: 182 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 851;

(xvi) the sense strand comprises or consists of the sequence of SEQ ID NO: 193 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 862; or

(xvii) the sense strand comprises or consists of the sequence of SEQ ID NO: 247 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 916.

27. The RNAi construct of any one of claims 1 to 25, wherein:

(i) the sense strand comprises or consists of the sequence of SEQ ID NO: 409 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 1078;

(ii) the sense strand comprises or consists of the sequence of SEQ ID NO: 388 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 1057;

(iii) the sense strand comprises or consists of the sequence of SEQ ID NO: 2808 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 2926;

(iv) the sense strand comprises or consists of the sequence of SEQ ID NO: 2820 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 2946;

(v) the sense strand comprises or consists of the sequence of SEQ ID NO: 391 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 2949;

(vi) the sense strand comprises or consists of the sequence of SEQ ID NO: 390 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 2956;

(vii) the sense strand comprises or consists of the sequence of SEQ ID NO: 179 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 2919;

(viii) the sense strand comprises or consists of the sequence of SEQ ID NO: 388 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 2953; or

(ix) the sense strand comprises or consists of the sequence of SEQ ID NO: 388 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 1057.

28. The RNAi construct of claim 27, wherein:

(i) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3078 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3337;

(ii) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3080 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3339;

(iii) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3163 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3441;

(iv) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3183 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3469;

(v) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3076 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3472;

(vi) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3077 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3484;

(vii) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 2051 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3545;

(viii) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3080 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3481;

(ix) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3188 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3339;

(x) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3080 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3476; or

(xi) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3223 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3517.

29. The RNAi construct of any one of claims 1 to 28, wherein the RNAi construct is any one of the duplex compounds listed in Tables 1-24.

30. The RNAi construct of claim 29, wherein the RNAi construct is D-2078, D-2079, D-2081, D-2182, D-2196, D-2238, D-2241, D-2243, D-2246, D-2255, D-2258, D-2301, D-2316, D-2317, D-2329, D-2332, D-2341, D-2344, D-2356, D-2357, D-2399, or D-2510.

31. The RNAi construct of claim 30, wherein the RNAi construct is D-2079, D-2081, D-2196, D-2238, D-2241, D-2255, D-2258, D-2317, D-2332, D-2357, or D-2399.

32. An RNAi construct for inhibiting expression of a human *MARCI* gene in a cell, said RNAi construct comprising a sense strand and an antisense strand that hybridize to form a duplex region of about 15 to about 30 base pairs in length, and wherein the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1205 to 1250 of SEQ ID NO: 1.

33. The RNAi construct of claim 32, wherein the region of the antisense strand comprises a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1209 to 1239 of SEQ ID NO: 1.

34. The RNAi construct of claim 32 or 33, wherein the region of the antisense strand comprises a sequence of CAUCUAAUAUCCAG (SEQ ID NO: 3656).

35. The RNAi construct of claim 32, wherein the RNAi construct is D-2063, D-2066, D-2076, D-2077, D-2078, D-2080, D-2081, D-2108, D-2113, D-2142, D-2240, D-2241, D-2243, D-2245, D-2246, D-2248, D-2250, D-2251, D-2253, D-2255, D-2256, D-2258, D-2259, D-2261, D-2264, D-2265, D-2268, D-2269, D-2270, D-2271, D-2301, D-2309, D-2311, D-2312, D-2314,

D-2316, D-2317, D-2319, D-2321, D-2322, D-2324, D-2326, D-2327, D-2329, D-2331, D-2332, D-2334, D-2336, D-2337, D-2339, D-2341, D-2342, D-2344, D-2346, D-2347, D-2349, D-2351, D-2352, D-2354, D-2356, D-2357, D-2376, D-2380, D-2393, D-2395, D-2396, D-2431, D-2436, D-2437, D-2440, D-2441, D-2444, D-2445, D-2447, D-2453, D-2518, D-2519, D-2520, D-2521, D-2522, D-2523, D-2524, D-2525, D-2526, D-2527, D-2528, D-2529, D-2530, D-2531, D-2532, D-2533, D-2534, or D-2535.

36. The RNAi construct of claim 35, wherein the RNAi construct is D-2063, D-2066, D-2076, D-2077, D-2078, D-2080, D-2081, D-2108, D-2113, D-2142, or D-2301.

37. An RNAi construct for inhibiting expression of a human *MARCI* gene in a cell, said RNAi construct comprising a sense strand and an antisense strand that hybridize to form a duplex region of about 15 to about 30 base pairs in length, and wherein the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1345 to 1375 of SEQ ID NO: 1.

38. The RNAi construct of claim 37, wherein the region of the antisense strand comprises a sequence of UGGGACAUUGAAGCA (SEQ ID NO: 3657).

39. The RNAi construct of claim 37, wherein the RNAi construct is D-2042, D-2043, D-2047, D-2052, D-2158, D-2162, D-2169, D-2182, D-2183, D-2184, D-2185, D-2186, D-2187, D-2189, D-2211, D-2213, D-2304, D-2305, D-2306, D-2307, D-2308, D-2384, D-2384, D-2385, D-2386, D-2387, D-2388, D-2389, D-2390, D-2391, D-2392, D-2399, D-2400, D-2401, D-2402, D-2403, D-2488, D-2494, D-2500, D-2506, D-2512, D-2538, D-2539, D-2540, or D-2541.

40. The RNAi construct of claim 39, wherein the RNAi construct is D-2042, D-2043, D-2047, D-2052, D-2304, D-2305, D-2306, D-2307, or D-2308.

41. An RNAi construct for inhibiting expression of a human *MARCI* gene in a cell, said RNAi construct comprising a sense strand and an antisense strand that hybridize to form a duplex region of about 15 to about 30 base pairs in length, and wherein the antisense strand

comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 2039 to 2078 of SEQ ID NO: 1.

42. The RNAi construct of claim 41, wherein the region of the antisense strand comprises a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 2048 to 2074 of SEQ ID NO: 1.

43. The RNAi construct of claim 41 or 42, wherein the region of the antisense strand comprises a sequence of AUCAGAUCUUAGAGU (SEQ ID NO: 3658).

44. The RNAi construct of claim 41, wherein the RNAi construct is D-2045, D-2065, D-2079, D-2082, D-2105, D-2106, D-2137, D-2143, D-2166, D-2173, D-2193, D-2242, D-2247, D-2252, D-2257, D-2260, D-2262, D-2266, D-2272, D-2273, D-2302, D-2303, D-2310, D-2313, D-2315, D-2318, D-2320, D-2323, D-2325, D-2328, D-2330, D-2333, D-2335, D-2338, D-2340, D-2343, D-2345, D-2348, D-2350, D-2353, D-2355, D-2358, D-2394, D-2397, D-2454, D-2455, D-2456, D-2457, D-2458, D-2459, D-2460, D-2463, D-2465, D-2465, D-2468, D-2470, D-2472, D-2473, D-2477, D-2487, D-2493, D-2499, D-2505, D-2511, D-2552, D-2553, D-2554, D-2555, D-2556, or D-2557.

45. The RNAi construct of claim 44, wherein the RNAi construct is D-2045, D-2065, D-2079, D-2082, D-2105, D-2106, D-2137, D-2143, D-2302, or D-2303.

46. The RNAi construct of any one of claims 32 to 45, wherein the duplex region is about 19 to about 21 base pairs in length.

47. The RNAi construct of any one of claims 32 to 46, wherein the sense strand and the antisense strand are each independently about 19 to about 30 nucleotides in length.

48. The RNAi construct of claim 47, wherein the sense strand and the antisense strand are each independently about 19 to about 23 nucleotides in length.

49. The RNAi construct of any one of claims 32 to 48, wherein the RNAi construct comprises one or two blunt ends.
50. The RNAi construct of any one of claims 32 to 48, wherein the RNAi construct comprises one or two nucleotide overhangs of 1 to 4 unpaired nucleotides.
51. The RNAi construct of claim 50, wherein the nucleotide overhang has 2 unpaired nucleotides.
52. The RNAi construct of claim 50 or 51, 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.
53. The RNAi construct of any one of claims 32 to 52, wherein the RNAi construct comprises at least one modified nucleotide.
54. The RNAi construct of claim 53, wherein the modified nucleotide is a 2'-modified nucleotide.
55. The RNAi construct of claim 54, wherein the modified nucleotide is a 2'-fluoro modified nucleotide, a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, 2'-O-alkyl modified nucleotide, a 2'-O-allyl modified nucleotide, a BNA, a deoxyribonucleotide, or combinations thereof.
56. The RNAi construct of claim 53, wherein all of the nucleotides in the sense and antisense strands are modified nucleotides.
57. The RNAi construct of claim 56, wherein the modified nucleotides are 2'-O-methyl modified nucleotides, 2'-fluoro modified nucleotides, or combinations thereof.

58. The RNAi construct of any one of claims 32 to 57, 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.
59. The RNAi construct of claim 58, wherein the abasic nucleotide is linked to the adjacent nucleotide through a 3'-3' internucleotide linkage or a 5'-5' internucleotide linkage.
60. The RNAi construct of any one of claims 32 to 59, wherein the sense strand, the antisense strand, or both the sense and antisense strands comprise one or more phosphorothioate internucleotide linkages.
61. The RNAi construct of claim 60, wherein the antisense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends.
62. The RNAi construct of claim 60 or 61, wherein the sense strand comprises a single phosphorothioate internucleotide linkage between the terminal nucleotides at the 3' end.
63. The RNAi construct of claim 60 or 61, wherein the sense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at the 3' end.
64. The RNAi construct of any one of claims 1 to 63, wherein the RNAi construct further comprises a ligand.
65. The RNAi construct of claim 64, 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.
66. The RNAi construct of claim 64, wherein the ligand comprises galactose, galactosamine, or N-acetyl-galactosamine.

67. The RNAi construct of claim 66, wherein the ligand comprises a multivalent galactose moiety or multivalent N-acetyl-galactosamine moiety.
68. The RNAi construct of claim 67, wherein the multivalent galactose moiety or multivalent N-acetyl-galactosamine moiety is trivalent or tetravalent.
69. The RNAi construct of any one of claims 64 to 68, wherein the ligand is covalently attached to the sense strand optionally through a linker.
70. The RNAi construct of claim 69, wherein the ligand is covalently attached to the 5' end of the sense strand.
71. A pharmaceutical composition comprising the RNAi construct of any one of claims 1 to 70 and a pharmaceutically acceptable carrier or excipient.
72. A method for reducing the expression of mARC1 protein in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 70 or the pharmaceutical composition of claim 71.
73. The method of claim 72, wherein the expression level of mARC1 in hepatocytes is reduced in the patient following administration of the RNAi construct or pharmaceutical composition as compared to the mARC1 expression level in a patient not receiving the RNAi construct or pharmaceutical composition.
74. The method of claim 72, wherein the patient is diagnosed with or at risk for cardiovascular disease, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, or cirrhosis.
75. A method for reducing serum cholesterol in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 70 or the pharmaceutical composition of claim 71.

76. The method of claim 75, wherein the serum cholesterol is non-HDL cholesterol or LDL cholesterol.
77. A method for treating, preventing, or reducing the risk of developing fatty liver disease in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 70 or the pharmaceutical composition of claim 71.
78. The method of claim 77, wherein the fatty liver disease is nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.
79. The method of claim 77 or 78, wherein the patient is diagnosed with type 2 diabetes, a metabolic disorder, or is obese.
80. The method of claim 77 or 78, wherein the patient has elevated levels of non-HDL cholesterol or triglycerides.
81. A method for treating, preventing, or reducing liver fibrosis in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 70 or the pharmaceutical composition of claim 71.
82. The method of claim 81, wherein administration of the RNAi construct or pharmaceutical composition to the patient prevents or delays cirrhosis.
83. The method of claim 81 or 82, wherein the patient is diagnosed with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.
84. The method of any one of claims 72 to 83, wherein the RNAi construct or pharmaceutical composition is administered to the patient via a parenteral route of administration.
85. The method of claim 84, wherein the parenteral route of administration is intravenous or subcutaneous.

86. An RNAi construct of any one of claims 1 to 70 for use in a method for reducing serum cholesterol in a patient in need thereof.
87. The RNAi construct of claim 86, wherein the serum cholesterol is non-HDL cholesterol or LDL cholesterol.
88. An RNAi construct of any one of claims 1 to 70 for use in a method for treating, preventing, or reducing the risk of developing fatty liver disease in a patient in need thereof.
89. The RNAi construct of claim 88, wherein the fatty liver disease is nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.
90. An RNAi construct of any one of claims 1 to 70 for use in a method for treating, preventing, or reducing liver fibrosis in a patient in need thereof.
91. The RNAi construct of claim 90, wherein the patient is diagnosed with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.
92. Use of an RNAi construct of any one of claims 1 to 70 in the preparation of a medicament for reducing serum cholesterol in a patient in need thereof.
93. The use of claim 92, wherein the serum cholesterol is non-HDL cholesterol or LDL cholesterol.
94. Use of an RNAi construct of any one of claims 1 to 70 in the preparation of a medicament for treating, preventing, or reducing the risk of developing fatty liver disease in a patient in need thereof.
95. The use of claim 94, wherein the fatty liver disease is nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.

96. Use of an RNAi construct of any one of claims 1 to 70 in the preparation of a medicament for treating, preventing, or reducing liver fibrosis in a patient in need thereof.

97. The use of claim 96, wherein the patient is diagnosed with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.