

COMPOSITIONS AND METHODS FOR INHIBITING MITOCHONDRIA AMIDOXIME REDUCING COMPONENT 1 (MARC1) EXPRESSION

BACKGROUND OF INVENTION

The liver plays a critical role in the metabolism of lipids. Abnormalities in normal hepatic lipid metabolism are associated with the development of various liver diseases or disorders such as, non-alcoholic fatty liver disease (NAFLD), its subsequent progression to non-alcoholic steatohepatitis (NASH) and potentially other advanced liver abnormalities.

NAFLD is one of the most common liver diseases, with increasing prevalence worldwide (Loomba R., & Sanyal A.J. (2013) NAT REV GASTROENTEROL HEPATOL 10(11):686-90). NAFLD is characterized by a spectrum of clinical and pathological severity ranging from simple steatosis to nonalcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, hepatocellular carcinoma (HCC) and liver failure (Bessone F, et al., (2019) CELL MOL LIFE SCI 76(1):99-128). NAFLD is characterized as the presence of fat in the liver in the absence of significant alcohol consumption and other causes of fat in the liver such as medications, starvation, and viral disease (Chalasani, N., et al., (2012) HEPATOLOGY (Baltimore, Md.), 55(6), 2005–23). Additionally, as the disease progresses into NASH, patients also have an increased risk of developing extra-hepatic complications, particularly cardiovascular diseases (CVD), which are among the most common causes of death in this patient population. The abnormalities in hepatic lipid metabolism that lead to NAFLD also drive the progression of atherogenic dyslipidemia, where elevated plasma triglycerides (TG), cholesterol and lipoprotein particles infiltrate the arterial wall and subsequently develop atherosclerotic plaques (Loomba R & Sanyal AJ (2013) NAT REV GASTROENTEROL HEPATOL 10(11):686-90). Thus, there remains an unmet need for the development and use of therapeutics for treatment of NAFLD.

SUMMARY OF DISCLOSURE

The current invention is based in part on the discovery of oligonucleotides (*e.g.*, RNAi oligonucleotides) that reduce *MARC1* (Mitochondrial Amidoxime Reducing Component 1) expression in the liver. Specifically, target sequences within *MARC1* mRNA were identified and oligonucleotides that bind to these target sequences and inhibit *MARC1* mRNA expression were generated. As demonstrated herein, the oligonucleotides inhibited human and non-human primate (NHP) *MARC1* expression in the liver.

In an aspect, the invention provides an RNAi oligonucleotide for reducing MARC1 expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a MARC1 mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the MARC1 mRNA target sequence.

In some embodiments of the RNAi oligonucleotide, (i) the sense strand is 15 to 50 or 18 to 36 nucleotides in length, optionally 36 nucleotides in length; optionally (ii) the antisense strand is 15 to 30 nucleotides in length, optionally 22 nucleotides in length; and optionally (iii) the duplex region is at least 19 nucleotides or at least 20 nucleotides in length.

In some embodiments of the RNAi oligonucleotide, the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein (i) S1 is complementary to S2, optionally wherein S1 and S2 are each 1-10 nucleotides in length and have the same length, optionally wherein S1 and S2 are each 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, further optionally wherein S1 and S2 are 6 nucleotides in length; and (ii) L forms a loop between S1 and S2 of 3-5 nucleotides in length, optionally wherein L is a triloop or a tetraloop, optionally wherein the tetraloop comprises the sequence 5'-GAAA-3', optionally wherein the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 1681).

In some embodiments of the RNAi oligonucleotide, the antisense strand comprises an overhang sequence of one or more nucleotides in length at the 3' terminus, optionally wherein the overhang comprises purine nucleotides, optionally wherein the overhang sequence is 2 nucleotides in length, optionally wherein the overhang is selected from AA, GG, AG, and GA, optionally wherein the overhang is GG.

In some embodiments of the RNAi oligonucleotide, at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands, optionally wherein:

(a) each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide or lipid; (b) the stem loop comprises one or more targeting ligands conjugated to one or more nucleotides of the stem loop; (c) the one or more targeting ligands is conjugated to one or more nucleotides of the loop, optionally wherein the loop comprises 4 nucleotides numbered 1-4 from 5' to 3', wherein nucleotides at positions 2, 3, and 4 each comprise one or more targeting ligands, wherein the targeting ligands are the same or different; (d) each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety, optionally wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety; and/or (e) up to 4 nucleotides of L of the stem-

loop are each conjugated to a monovalent GalNAc moiety. In some embodiments of the RNAi oligonucleotide, the targeting ligand comprises at least one GalNAc moiety and targets human liver cells (e.g., human hepatocytes).

In some embodiments of the RNAi oligonucleotide, the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;

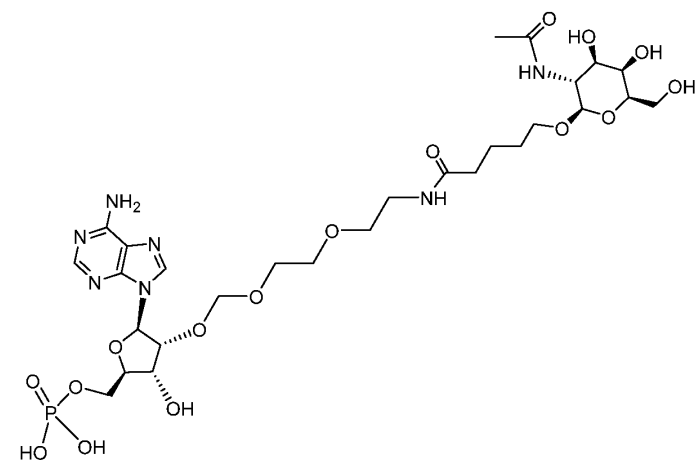
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively.

In some embodiments of the RNAi oligonucleotide, the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1609 and 1645, respectively;
- (b) SEQ ID NOs: 1610 and 1646, respectively;
- (c) SEQ ID NOs: 1611 and 1647, respectively;
- (d) SEQ ID NOs: 1612 and 1648, respectively;
- (e) SEQ ID NOs: 1613 and 1649, respectively;
- (f) SEQ ID NOs: 1614 and 1650, respectively;
- (g) SEQ ID NOs: 1615 and 1651, respectively;
- (h) SEQ ID NOs: 1616 and 1652, respectively;
- (i) SEQ ID NOs: 1617 and 1653, respectively;
- (j) SEQ ID NOs: 1618 and 1654, respectively;
- (k) SEQ ID NOs: 1619 and 1655, respectively;
- (l) SEQ ID NOs: 1620 and 1656, respectively;
- (m) SEQ ID NOs: 1621 and 1657, respectively;
- (n) SEQ ID NOs: 1622 and 1658, respectively;
- (o) SEQ ID NOs: 1623 and 1659, respectively;
- (p) SEQ ID NOs: 1624 and 1660, respectively;
- (q) SEQ ID NOs: 1625 and 1661, respectively;
- (r) SEQ ID NOs: 1626 and 1662, respectively;
- (s) SEQ ID NOs: 1627 and 1663, respectively;
- (t) SEQ ID NOs: 1628 and 1664, respectively;
- (u) SEQ ID NOs: 1628 and 1665, respectively;
- (v) SEQ ID NOs: 1630 and 1666, respectively;
- (w) SEQ ID NOs: 1631 and 1667, respectively;
- (x) SEQ ID NOs: 1632 and 1668, respectively;
- (y) SEQ ID NOs: 1633 and 1669, respectively;
- (z) SEQ ID NOs: 1634 and 1670, respectively;
- (aa) SEQ ID NOs: 1635 and 1671, respectively;

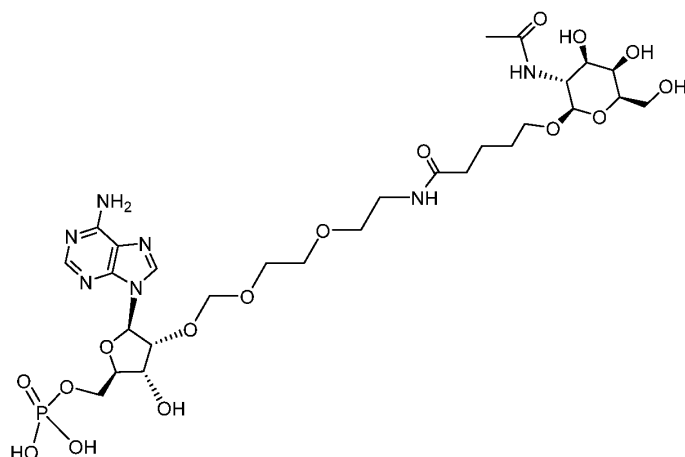
- (bb) SEQ ID NOs: 1636 and 1672, respectively;
- (cc) SEQ ID NOs: 1637 and 1673, respectively;
- (dd) SEQ ID NOs: 1638 and 1674, respectively;
- (ee) SEQ ID NOs: 1639 and 1675, respectively;
- (ff) SEQ ID NOs: 1640 and 1676, respectively;
- (gg) SEQ ID NOs: 1641 and 1677, respectively; and,
- (hh) SEQ ID NOs: 1642 and 1678, respectively.

In an embodiment a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of MARC1 is provided, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a MARC1 RNA transcript, wherein the sense strand comprises the sequence and all of the modifications of 5'-mGs-mG-mC-mU-mA-mG-mA-fG-fA-fA-fG-mA-mA-mA-mG-mU-mU-mA-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1615), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fUs-fA-fA-mC-fU-mU-mU-fC-mU-mU-mC-fU-mC-mU-mA-mG-mC-mCs-mGs-mG-3' (SEQ ID NO: 1651), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU= 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =

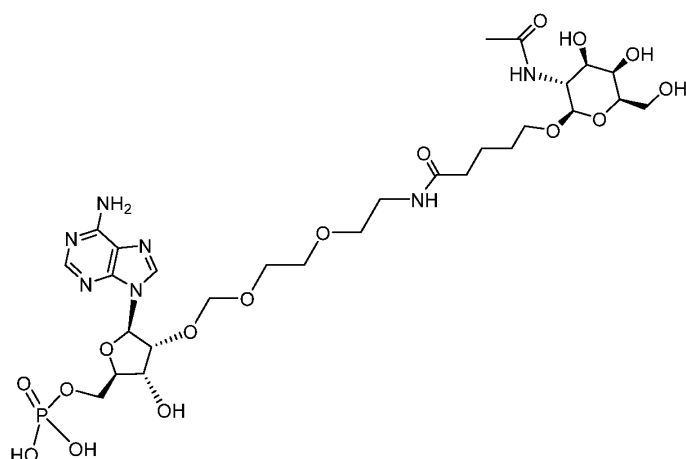


In an embodiment a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of MARC1 is provided, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a MARC1 RNA transcript, wherein the sense strand comprises the sequence and all of the modifications of 5'-mAs-mG-mA-mA-mC-mG-mA-fA-fA-fG-fU-mU-mA-mU-mA-mU-mG-mG-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-

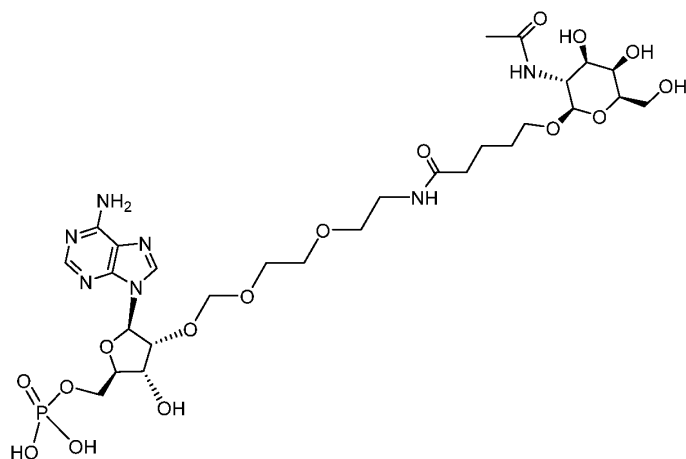
mG-mC-mU-mG-mC-3' (SEQ ID NO: 1632), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fCs-fC-fA-mU-fA-mU-mA-fA-mC-mU-mU-fU-mC-mG-mU-mU-mC-mUs-mGs-mG-3' (SEQ ID NO: 1668), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



In an embodiment a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of MARC1 is provided, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a MARC1 RNA transcript, wherein the sense strand comprises the sequence and all of the modifications of 5'-mAs-mA-mG-mU-mU-mG-mA-fC-fU-fA-fA-mA-mC-mU-mU-mG-mA-mA-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1640), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fUs-fU-fC-mA-fA-mG-mU-fU-mU-mA-mG-fU-mC-mA-mA-mC-mU-mUs-mGs-mG-3' (SEQ ID NO: 1676), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



In an embodiment a double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of *MARC1* is provided, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a *MARC1* RNA transcript, wherein the sense strand comprises the sequence and all of the modifications of 5'-mUs-mG-mU-mG-mA-mA-mU-fA-fA-fA-fU-mG-mG-mA-mA-mG-mC-mU-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1625), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fAs-fG-fC-mU-fU-mC-mC-fA-mU-mU-mU-fA-mU-mU-mC-mA-mC-mAs-mGs-mG-3' (SEQ ID NO: 1661), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



Without being bound by theory, the oligonucleotides described herein are useful for treating a disease, disorder or condition where the *MARC1* enzyme plays a causal role.

In an aspect, the invention provides a pharmaceutical composition comprising the RNAi oligonucleotide described herein and a pharmaceutically acceptable carrier, delivery agent or excipient.

In an aspect, the invention provides a kit comprising the RNAi described herein, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with MARC1 expression, optionally for the treatment of NAFLD, NASH, or alcoholic steatohepatitis (ASH).

In an aspect, the invention provides a use of the RNAi oligonucleotide described herein, in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with MARC1 expression, optionally for the treatment of a disease or condition associated with MARC1 expression in hepatocytes, optionally for the treatment of NAFLD, NASH, or ASH. optionally for use in combination with a second composition or therapeutic agent.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 provides a graph depicting the percent (%) of human *MARC1* mRNA remaining in Huh7 cells endogenously expressing human MARC1, also referred to as MTARC1, after 24-hours treatment with 1 nM of DsiRNA targeting various regions of the *MARC1* gene. 384 DsiRNAs were designed and screened. Two primer pairs were used to measure *MARC1* (SEQ ID NOs: 1684-1687), and expression was normalized between samples using the HPRT housekeeping gene (SEQ ID NOs: 1688 and 1689).

FIG. 2 provides a graph depicting the percent (%) of human *MARC1* mRNA remaining in the liver of mice exogenously expressing human *MARC1* (hydrodynamic injection model) after treatment with GalNAc-conjugated *MARC1* oligonucleotides. Mice were dosed subcutaneously with 2 mg/kg of the indicated GalNAc-*MARC1* oligonucleotides formulated in phosphate buffered saline (PBS). Three days post-dose mice were hydrodynamically injected (HDI) with a DNA plasmid encoding human *MARC1*. The level of human *MARC1* mRNA was determined from livers collected after 18 hours. Arrows indicate oligonucleotides selected for validation.

FIG. 3 provides a graph depicting the percent (%) of human *MARC1* mRNA remaining in the liver of mice exogenously expressing human *MARC1* (hydrodynamic injection model) after treatment with human GalNAc-conjugated *MARC1* oligonucleotides selected for validation based on the results in **FIG. 2**. Mice were dosed subcutaneously with 2 mg/kg of the indicated GalNAc-*MARC1* oligonucleotides formulated in PBS. Three days

post-dose mice were HDI with a DNA plasmid encoding *MARCI*. The level of human *MARCI* mRNA was determined from livers collected 18 hours later.

FIG. 4 provides a graph depicting the dose response of GalNAc-conjugated *MARCI* oligonucleotides selected for NHP studies. The percent (%) of human *MARCI* mRNA remaining in the liver of mice exogenously expressing human *MARCI* (hydrodynamic injection model) after treatment with human GalNAc-conjugated *MARCI* oligonucleotides at three doses (0.1 mg/kg, 0.3 mg/kg, and 1 mg/kg) was measured. Three days post-dose mice were HDI with a DNA plasmid encoding *MARCI*. The level of human *MARCI* mRNA was determined from livers collected 18 hours later.

FIG. 5 and **FIG. 6** provide graphs depicting the level of liver triglycerides (TG) and total cholesterol (TC) in samples collected on day 56 from mice fed a DIO-NASH diet or Lean Chow diet and treated with 8 weekly doses of the indicated GalNAc-conjugated *MARCI* oligonucleotides (3 mg/kg) or control GLP-1 peptide (Jesper Lau et al. *J. Med. Chem.* (2015); **58**, 7370-80, compound **22**) (GLP-1 '22') (10 nmol/kg) relative to mice treated with PBS. Relative (**FIG. 5**) and total (**FIG. 6**) TG and TC levels were compared to DIO-NASH vehicle control. ***= $p < 0.001$, *= $p < 0.05$.

FIG. 7 provides a graph depicting NAFLD activity score in samples from mice fed a DIO-NASH diet or Lean Chow diet and treated with 8 weekly doses of the indicated GalNAc-conjugated *MARCI* oligonucleotides (3 mg/kg) or GLP-1 '22' (10 nmol/kg) as control relative to mice treated with PBS. The score was calculated based on the NAFLD score at the end of the study.

FIG. 8 provides a graph depicting the Steatosis Score in samples from mice fed a DIO-NASH diet or Lean Chow diet and treated with 8 weekly doses of the indicated GalNAc-conjugated *MARCI* oligonucleotides (3 mg/kg) or GLP-1 '22' (10 nmol/kg) relative to mice treated with PBS. The score was calculated based on the Steatosis score at the end of the study.

FIGs. 9A and **9B** provide graphs quantifying the steatosis fraction (*i.e.* the percent (%) of liver steatosis in a given area) (**FIG. 9A**) and the percent (%) hepatocytes with lipid droplets (**FIG. 9B**) from mice fed a DIO-NASH diet or Lean Chow diet and treated with 8 weekly doses of the indicated GalNAc-conjugated *MARCI* oligonucleotides, (10 nmol/kg) (3 mg/kg), or PBS. ***= $p < 0.001$ (relative to DIO-NASH vehicle treatment).

FIG. 10 provides a graph depicting α -SMA levels in liver samples from mice fed a DIO-NASH diet and treated with the indicated GalNAc-conjugated *MARCI* oligonucleotides, (10 nmol/kg) PBS, or fed a Lean-Chow diet. ***= $p < 0.001$, *= $p < 0.05$ (relative to DIO-NASH vehicle treatment).

FIG. 11 provides a schematic depicting the dosing and specimen collection schedules for non-human primate (NHP) studies using GalNAc-conjugated *MARCI* oligonucleotides.

FIG. 12 is a schematic of an exemplary nicked tetraloop oligonucleotide structure.

DETAILED DESCRIPTION

MARCI (Mitochondrial Amidoxime Reducing Component 1, Molybdenum Cofactor Sulfurase C-terminal Domain-Containing Protein 1, Moco Sulfurase C-Terminal Domain Containing Protein 1, MOSC1, MOSC Domain-Containing Protein 1, MTARC1) is a protein which catalyzes the reduction of N-oxygenated molecules in various metabolic processes. While the biological function and mechanisms of MARC1 have yet to be elucidated, a common missense variant has been identified in *MARCI* that protects subjects against cirrhosis. Carriers of this variant also have lower blood cholesterol levels and reduced liver fat, indicating *MARCI* may be an effective therapeutic target for NAFLD, NASH and ASH. It should be understood that the genetic polymorphisms in *MARCI* impact expression and/or functionality of MARC1 across all bodily tissues from birth, with MARC1 being expressed widely and at various levels in different organs. As described herein, oligonucleotides targeting *MARCI* specifically in hepatocytes not only inhibit MARC1 expression *in vitro* and *in vivo*, but also provide a therapeutic effect in a mouse model of NASH. Specifically, reduction of *MARCI* expression reduced the number of hepatocytes with liver droplets and the steatosis fraction. Additionally, *MARCI* inhibition reduced several regulators of hepatic fibrosis in the NASH model. These various improved disease outcomes demonstrate the therapeutic efficacy of *MARCI* inhibition, specifically in hepatocytes.

Taken together, and without being bound by theory, antagonism/inhibition of MARC1, specifically in hepatocytes (*e.g.*, *via MARCI*-targeted RNAi oligonucleotides), may decrease the risk and severity of NAFLD, NASH, and alcoholic steatohepatitis (ASH). This approach may be best managed by a specific and targeted reduction of the *MARCI* expression in the liver while other organs, tissues or cells expressing *MARCI* are left essentially unaffected. In this sense the current invention may provide an improved modality of treatment given its specific targeting of mRNA production in the liver.

According to some aspects, the current invention provides oligonucleotides (*e.g.*, RNAi oligonucleotides) that reduce *MARCI* expression in the liver. In some embodiments, the oligonucleotides provided herein are designed to treat diseases associated with *MARCI* expression in the liver. In some respects, the current invention provides methods of treating a

disease associated with overall *MARCI* expression by reducing *MARCI* expression in specific cells (*e.g.*, hepatocytes) or organs (*e.g.*, liver).

Oligonucleotide Inhibitors of *MARCI* Expression

***MARCI* Target Sequences**

In some embodiments, an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) is targeted to a target sequence comprising a *MARCI* mRNA. In some embodiments, an oligonucleotide described herein is targeted to a target sequence within a *MARCI* mRNA sequence. In some embodiments, the oligonucleotide described herein corresponds to a target sequence within a *MARCI* mRNA sequence. In some embodiments, the oligonucleotide, or a portion, fragment, or strand thereof (*e.g.*, an antisense strand or a guide strand of a double-stranded (ds) RNAi oligonucleotide) binds or anneals to a target sequence comprising *MARCI* mRNA, thereby inhibiting *MARCI* expression.

In some embodiments, the oligonucleotide is targeted to a *MARCI* target sequence for the purpose of inhibiting *MARCI* expression *in vivo*. In some embodiments, the amount or extent of inhibition of *MARCI* expression by an oligonucleotide targeted to a *MARCI* target sequence correlates with the potency of the oligonucleotide. In some embodiments, the amount or extent of inhibition of *MARCI* expression by an oligonucleotide targeted to a *MARCI* target sequence correlates with the amount or extent of therapeutic benefit in a subject or patient having a disease, disorder or condition associated with *MARCI* expression treated with the oligonucleotide.

Through examination of the nucleotide sequence of mRNAs encoding *MARCI*, including mRNAs of multiple different species (*e.g.*, human, cynomolgus monkey, and mouse; *see, e.g.*, Example 2) and as a result of *in vitro* and *in vivo* testing (*see, e.g.*, Examples 2-5), it has been discovered that certain nucleotide sequences of *MARCI* mRNA are more amenable than others to oligonucleotide-based inhibition and are thus useful as target sequences for the oligonucleotides herein. In some embodiments, a sense strand of an oligonucleotide (*e.g.*, an RNAi oligonucleotide) described herein comprises a *MARCI* target sequence. In some embodiments, a portion or region of the sense strand of an oligonucleotide described herein (*e.g.*, an RNAi oligonucleotide) comprises a *MARCI* target sequence. In some embodiments, a *MARCI* target sequence comprises, or consists of, a sequence of any one of SEQ ID NOs: 1-384. In some embodiments, a *MARCI* target sequence comprises, or consists of, the sequence set forth in SEQ ID NO: 234, 298, 356, or 376.

MARCI Targeting Sequences

In some embodiments, the oligonucleotides herein (*e.g.*, RNAi oligonucleotides) have regions of complementarity to *MARCI* mRNA (*e.g.*, within a target sequence of *MARCI* mRNA) for purposes of targeting the *MARCI* mRNA in cells and inhibiting and/or reducing *MARCI* expression. In some embodiments, the oligonucleotides herein comprise a *MARCI* targeting sequence (*e.g.*, an antisense strand or a guide strand of a dsRNAi oligonucleotide) having a region of complementarity that binds or anneals to a *MARCI* target sequence by complementary (Watson-Crick) base pairing. The targeting sequence or region of complementarity is generally of a suitable length and base content to enable binding or annealing of the oligonucleotide (or a strand thereof) to a *MARCI* mRNA for purposes of inhibiting and/or reducing *MARCI* expression. In some embodiments, the targeting sequence or region of complementarity is at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, at least about 25, at least about 26, at least about 27, at least about 28, at least about 29, or at least about 30 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is about 12 to about 30 (*e.g.*, 12 to 30, 12 to 22, 15 to 25, 17 to 21, 18 to 27, 19 to 27, or 15 to 30) nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 18 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 19 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 20 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 21 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 22 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 23 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 24 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 1-384, and the targeting sequence or region of complementarity is 18 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 1-384, and the targeting sequence or region of complementarity is 19 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a

sequence of any one of SEQ ID NOs: 769-1152, and the targeting sequence or region of complementarity is 20 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 769-1152, and the targeting sequence or region of complementarity is 21 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 769-1152, and the targeting sequence or region of complementarity is 22 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 769-1152, and the targeting sequence or region of complementarity is 23 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 769-1152 and the targeting sequence or region of complementarity is 24 nucleotides in length.

In some embodiments, an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) comprises a targeting sequence or a region of complementarity (*e.g.*, an antisense strand or a guide strand of a double-stranded oligonucleotide) that is fully complementary to a *MARCI* target sequence. In some embodiments, the targeting sequence or region of complementarity is partially complementary to a *MARCI* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to a *MARCI* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to a *MARCI* target sequence.

In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to a sequence of any one of SEQ ID NOs: 1-384. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to the sequence set forth in SEQ ID NOs: 234, 298, 356, or 376. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to a sequence of any one of SEQ ID NOs: 1-384. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to the sequence set forth in SEQ ID NOs: 234, 298, 356, or 376.

In some embodiments, an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides within a *MARCI* mRNA, wherein the contiguous sequence

of nucleotides is about 12 to about 30 nucleotides in length (*e.g.*, 12 to 30, 12 to 28, 12 to 26, 12 to 24, 12 to 20, 12 to 18, 12 to 16, 14 to 22, 16 to 20, 18 to 20, or 18 to 19 nucleotides in length). In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides within a *MARCI* mRNA, wherein the contiguous sequence of nucleotides is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides within a *MARCI* mRNA, wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides within a *MARCI* mRNA, wherein the contiguous sequence of nucleotides is 20 nucleotides in length.

In some embodiments, an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 1-384, optionally wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 234, 298, 356, or 376, wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 769-1152, wherein the contiguous sequence of nucleotides is 20 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 1002, 1066, 1124, and 1144, wherein the contiguous sequence of nucleotides is 20 nucleotides in length.

In some embodiments, a targeting sequence or region of complementarity of an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 1-384 and spans the entire length of an antisense strand. In some embodiments, a targeting sequence or region of complementarity of the oligonucleotide is complementary to a contiguous sequence of nucleotides of SEQ ID NOs: 1-384 and spans a portion of the entire length of an antisense strand. In some embodiments, an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) comprises a region of complementarity (*e.g.*, on an antisense strand of a dsRNA) that is at least partially (*e.g.*, fully) complementary

to a contiguous stretch of nucleotides spanning nucleotides 1-19 or 1-20 of a sequence as set forth in any one of SEQ ID NOs: 769-1152.

In some embodiments, an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) comprises a targeting sequence or region of complementarity having one or more base pair (bp) mismatches with the corresponding *MARCI* target sequence. In some embodiments, the targeting sequence or region of complementarity may have up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding *MARCI* target sequence provided that the ability of the targeting sequence or region of complementarity to bind or anneal to the *MARCI* mRNA under appropriate hybridization conditions and/or the ability of the oligonucleotide to inhibit *MARCI* expression is maintained. Alternatively, the targeting sequence or region of complementarity may have no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding *MARCI* target sequence provided that the ability of the targeting sequence or region of complementarity to bind or anneal to the *MARCI* mRNA under appropriate hybridization conditions and/or the ability of the oligonucleotide to inhibit *MARCI* expression is maintained. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 1 mismatch with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 2 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 3 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 4 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 5 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having more than one mismatch (*e.g.*, 2, 3, 4, 5, or more mismatches) with the corresponding target sequence, wherein at least 2 (*e.g.*, all) of the mismatches are positioned consecutively (*e.g.*, 2, 3, 4, 5, or more mismatches in a row), or wherein the mismatches are interspersed throughout the targeting sequence or region of complementarity. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having more than one mismatch (*e.g.*, 2, 3, 4, 5, or more mismatches) with the corresponding target sequence, wherein at least 2 (*e.g.*, all) of the mismatches are positioned consecutively (*e.g.*, 2, 3, 4, 5, or more mismatches in a row), or wherein at least one or more

non-mismatched base pair is located between the mismatches, or a combination thereof. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 1-384, wherein the targeting sequence or region of complementarity may have up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding *MARCI* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 1-384, wherein the targeting sequence or region of complementarity may have no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding *MARCI* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 234, 298, 356, or 376, wherein the targeting sequence or region of complementarity may have up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding *MARCI* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 234, 298, 356, or 376, wherein the targeting sequence or region of complementarity may have no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding *MARCI* target sequence.

Types of Oligonucleotides

A variety of oligonucleotide types and/or structures are useful for targeting *MARCI* in the methods herein including, but not limited to, RNAi oligonucleotides, antisense oligonucleotides (ASOs), miRNAs, *etc.* Any of the oligonucleotide types described herein or elsewhere are contemplated for use as a framework to incorporate a *MARCI* targeting sequence herein for the purposes of inhibiting *MARCI* expression.

In some embodiments, the oligonucleotides herein inhibit *MARCI* expression by engaging with RNA interference (RNAi) pathways upstream or downstream of Dicer involvement. For example, RNAi oligonucleotides have been developed with each strand having sizes of about 19-25 nucleotides with at least one 3'-overhang of 1 to 5 nucleotides (*see, e.g.*, US Patent No. 8,372,968). Longer oligonucleotides also have been developed that are processed by Dicer to generate active RNAi products (*see, e.g.*, US Patent No. 8,883,996). Further work produced extended dsRNAs where at least one end of at least one strand is

extended beyond a duplex targeting region, including structures where one of the strands includes a thermodynamically stabilizing tetraloop structure (*see, e.g.*, US Patent Nos. 8,513,207 and 8,927,705, as well as Intl. Patent Application Publication No. WO 2010/033225). Such structures may include single-stranded (ss) extensions (on one or both sides of the molecule) as well as double-stranded (ds) extensions.

In some embodiments, the oligonucleotides herein engage with the RNAi pathway downstream of the involvement of Dicer (*e.g.*, Dicer cleavage). In some embodiments, the oligonucleotides described herein are Dicer substrates. In some embodiments, upon endogenous Dicer processing, double-stranded nucleic acids of 19-23 nucleotides in length capable of reducing *MARCI* expression are produced. In some embodiments, the oligonucleotide has an overhang (*e.g.*, of 1, 2, or 3 nucleotides in length) in the 3' end of the antisense strand. In some embodiments, the oligonucleotide (*e.g.*, siRNA) comprises a 21-nucleotide guide strand that is antisense to a target RNA and a complementary passenger strand, in which both strands anneal to form a 19-bp duplex and 2 nucleotide overhangs at either or both 3' ends. Longer oligonucleotide designs also are available including oligonucleotides having a guide strand of 23 nucleotides and a passenger strand of 21 nucleotides, where there is a blunt end on the right side of the molecule (3' end of passenger strand/5' end of guide strand) and a two nucleotide 3'-guide strand overhang on the left side of the molecule (5' end of the passenger strand/3' end of the guide strand). In such molecules, there is a 21 bp duplex region. *See, e.g.*, US Patent Nos. 9,012,138; 9,012,621; and 9,193,753.

In some embodiments, the oligonucleotides herein comprise sense and antisense strands that are both in the range of about 17 to 36 (*e.g.*, 17 to 36, 20 to 25, or 21-23) nucleotides in length. In some embodiments, the oligonucleotides described herein comprise an antisense strand of 19-30 nucleotides in length and a sense strand of 19-50 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand. In some embodiments, an oligonucleotide herein comprises a sense and antisense strand that are both in the range of about 19-22 nucleotides in length. In some embodiments, the sense and antisense strands are of equal length. In some embodiments, an oligonucleotide comprises sense and antisense strands, such that there is a 3'-overhang on either the sense strand or the antisense strand, or both the sense and antisense strand. In some embodiments, for oligonucleotides that have sense and antisense strands that are both in the range of about 21-23 nucleotides in length, a 3'-overhang on the sense, antisense, or both sense and antisense strands is 1 or 2 nucleotides in length. In some embodiments, the oligonucleotide has a guide strand of 22 nucleotides and

a passenger strand of 20 nucleotides, where there is a blunt end on the right side of the molecule (3' end of passenger strand/5' end of guide strand) and a 2 nucleotide 3'-guide strand overhang on the left side of the molecule (5' end of the passenger strand/3' end of the guide strand). In such molecules, there is a 20 bp duplex region.

Other oligonucleotide designs for use with the compositions and methods herein include: 16-mer siRNAs (*see, e.g.*, NUCLEIC ACIDS IN CHEMISTRY AND BIOLOGY, Blackburn (ed.), ROYAL SOCIETY OF CHEMISTRY, 2006), shRNAs (*e.g.*, having 19 bp or shorter stems; *see, e.g.*, Moore *et al.* (2010) METHODS MOL. BIOL. 629:141-158), blunt siRNAs (*e.g.*, of 19 bps in length; *see, e.g.*, Kraynack & Baker (2006) RNA 12:163-176), asymmetrical siRNAs (aiRNA; *see, e.g.*, Sun *et al.* (2008) NAT. BIOTECHNOL. 26:1379-82), asymmetric shorter-duplex siRNA (*see, e.g.*, Chang *et al.* (2009) MOL. THER. 17:725-32), fork siRNAs (*see, e.g.*, Hohjoh (2004) FEBS LETT. 557:193-98), ss siRNAs (Elsner (2012) NAT. BIOTECHNOL. 30:1063), dumbbell-shaped circular siRNAs (*see, e.g.*, Abe *et al.* (2007) J. AM. CHEM. SOC. 129:15108-09), and small internally segmented interfering RNA (siRNA; *see, e.g.*, Bramsen *et al.* (2007) NUCLEIC ACIDS RES. 35:5886-97). Further non-limiting examples of an oligonucleotide structures that may be used in some embodiments to reduce or inhibit the expression of *MARCI* are microRNA (miRNA), short hairpin RNA (shRNA) and short siRNA (*see, e.g.*, Hamilton *et al.* (2002) EMBO J. 21:4671-79; *see also*, US Patent Application Publication No. 2009/0099115).

Still, in some embodiments, an oligonucleotide for reducing or inhibiting *MARCI* expression herein is single-stranded (ss). Such structures may include but are not limited to single-stranded RNAi molecules. Recent efforts have demonstrated the activity of ss RNAi molecules (*see, e.g.*, Matsui *et al.* (2016) MOL. THER. 24:946-55). However, in some embodiments, oligonucleotides herein are antisense oligonucleotides (ASOs). An antisense oligonucleotide is a single-stranded oligonucleotide that has a nucleobase sequence which, when written in the 5' to 3' direction, comprises the reverse complement of a targeted segment of a particular nucleic acid and is suitably modified (*e.g.*, as a gapmer) to induce RNaseH-mediated cleavage of its target RNA in cells or (*e.g.*, as a mixmer) so as to inhibit translation of the target mRNA in cells. ASOs for use herein may be modified in any suitable manner known in the art including, for example, as shown in US Patent No. 9,567,587 (including, *e.g.*, length, sugar moieties of the nucleobase (pyrimidine, purine), and alterations of the heterocyclic portion of the nucleobase). Further, ASOs have been used for decades to reduce expression of specific target genes (*see, e.g.*, Bennett *et al.* (2017) ANNU. REV. PHARMACOL. 57:81-105).

In some embodiments, the antisense oligonucleotide shares a region of complementarity with *MARCI* mRNA. In some embodiments, the antisense oligonucleotide targets various areas of the human MARC1 gene identified as NM_001251935.1. In some embodiments, the antisense oligonucleotide is 15-50 nucleotides in length. In some embodiments, the antisense oligonucleotide is 15-25 nucleotides in length. In some embodiments, the antisense oligonucleotide is 22 nucleotides in length. In some embodiments, the antisense oligonucleotide is complementary to any one of SEQ ID NOs: 1-384. In some embodiments, the antisense oligonucleotide is at least 15 contiguous nucleotides in length. In some embodiments, the antisense oligonucleotide is at least 19 contiguous nucleotides in length. In some embodiments, the antisense oligonucleotide is at least 20 contiguous nucleotides in length. In some embodiments, the antisense oligonucleotide differs by 1, 2, or 3 nucleotides from the target sequence.

Double-Stranded Oligonucleotides

In some aspects, the current invention provides double-stranded (ds) RNAi oligonucleotides for targeting *MARCI* mRNA and inhibiting *MARCI* expression (*e.g.*, via the RNAi pathway) comprising a sense strand (also referred to herein as a passenger strand) and an antisense strand (also referred to herein as a guide strand). In some embodiments, the sense strand and antisense strand are separate strands and are not covalently linked. In some embodiments, the sense strand and antisense strand are covalently linked. In some embodiments, the sense strand and antisense strand form a duplex region, wherein the sense strand and antisense strand, or a portion thereof, binds with one another in a complementary fashion (*e.g.*, by Watson-Crick base pairing).

In some embodiments, the sense strand has a first region (R1) and a second region (R2), wherein R2 comprises a first subregion (S1), a tetraloop or triloop (L), and a second subregion (S2), wherein L is located between S1 and S2, and wherein S1 and S2 form a second duplex (D2). D2 may have various length. In some embodiments, D2 is about 1-6 bp in length. In some embodiments, D2 is 2-6, 3-6, 4-6, 5-6, 1-5, 2-5, 3-5, or 4-5 bp in length. In some embodiments, D2 is 1, 2, 3, 4, 5, or 6 bp in length. In some embodiments, D2 is 6 bp in length. In some embodiments, R1 of the sense strand and the antisense strand form a first duplex (D1). In some embodiments, D1 is at least about 15 (*e.g.*, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 21) nucleotides in length. In some embodiments, D1 is in the range of about 12 to 30 nucleotides in length (*e.g.*, 12 to 30, 12 to 27, 15 to 22, 18 to 22, 18 to 25, 18 to 27, 18 to 30, or 21 to 30 nucleotides in length). In some embodiments, D1 is at

least 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 20, at least 25, or at least 30 nucleotides in length). In some embodiments, D1 is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, D1 is 20 nucleotides in length. In some embodiments, D1 comprising sense strand and antisense strand does not span the entire length of the sense strand and/or antisense strand. In some embodiments, D1 comprising the sense strand and antisense strand spans the entire length of either the sense strand or antisense strand or both. In certain embodiments, D1 comprising the sense strand and antisense strand spans the entire length of both the sense strand and the antisense strand.

In some embodiments, an oligonucleotide provided herein comprises a sense strand having a sequence of any one of SEQ ID NOs: 769-1152 and an antisense strand comprising a complementary sequence selected from SEQ ID NOs: 1153-1536. In some embodiments, an oligonucleotide provided herein comprises a sense strand having a sequence of any one of SEQ ID NOs: 1-384 and an antisense strand comprising a complementary sequence selected from SEQ ID NOs: 385-768.

In some embodiments, an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) comprises a sense strand having a sequence of any one of SEQ ID NOs: 1537-1570 and an antisense strand comprising a complementary sequence selected from SEQ ID NOs: 1573-1606 as is arranged in **Tables 4** and **6**.

In some embodiments, an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) comprises a sense strand and an antisense strand comprising nucleotide sequences selected from:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;

- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively.

In some embodiments, an oligonucleotide provided herein (e.g., an RNAi oligonucleotide) comprises a sense strand and an antisense strand comprising nucleotide sequences selected from:

- (a) SEQ ID NOs: 1543 and 1579, respectively;
- (b) SEQ ID NOs: 1560 and 1596, respectively;
- (c) SEQ ID NOs: 1568 and 1604, respectively; and,
- (d) SEQ ID NOs: 1553 and 1589, respectively.

In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 1543 and the antisense strand comprises the sequence of SEQ ID NO: 1579.

In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 1560 and the antisense strand comprises the sequence of SEQ ID NO: 1596.

In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 1568 and the antisense strand comprises the sequence of SEQ ID NO: 1604.

In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 1553 and the antisense strand comprises the sequence of SEQ ID NO: 1589.

It should be appreciated that, in some embodiments, sequences presented in the Sequence Listing may be referred to in describing the structure of an oligonucleotide (e.g., a dsRNAi oligonucleotide) or other nucleic acid. In such embodiments, the actual oligonucleotide or other nucleic acid may have one or more alternative nucleotides (e.g., an RNA counterpart of a DNA nucleotide or a DNA counterpart of an RNA nucleotide) and/or one or more modified nucleotides and/or one or more modified internucleotide linkages and/or one or more other modification when compared with the specified sequence while retaining essentially same or similar complementary properties as the specified sequence.

In some embodiments, an oligonucleotide herein (e.g., an RNAi oligonucleotide) comprises a 25-nucleotide sense strand and a 27-nucleotide antisense strand that when acted upon by a Dicer enzyme results in an antisense strand that is incorporated into the mature RISC. In some embodiments, the 25-nucleotide sense strand comprises a sequence selected from SEQ ID NOs: 769-1152. In some embodiments, the 27-nucleotide antisense strand comprises a sequence selected from SEQ ID NOs: 1153-1536. In some embodiments, the sense strand of the oligonucleotide is longer than 27 nucleotides (e.g., 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides). In some embodiments, the sense strand of the oligonucleotide is longer than 25 nucleotides (e.g., 26, 27, 28, 29 or 30 nucleotides). In some embodiments, the sense strand of the oligonucleotide comprises a nucleotide sequence selected from SEQ ID NOs: 1537-1570, wherein the nucleotide sequence is longer than 27 nucleotides (e.g., 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides). In some embodiments, the sense strand of the oligonucleotide comprises a nucleotide sequence selected from SEQ ID NOs: 1537-1570, wherein the nucleotide sequence is longer than 25 nucleotides (e.g., 26, 27, 28, 29, or 30 nucleotides).

In some embodiments, oligonucleotides herein (e.g., RNAi oligonucleotides) have one 5' end that is thermodynamically less stable when compared to the other 5' end. In some embodiments, an asymmetric oligonucleotide is provided that includes a blunt end at the 3' end of a sense strand and a 3'-overhang at the 3' end of an antisense strand. In some embodiments, the 3'-overhang on the antisense strand is about 1-8 nucleotides in length (e.g., 1, 2, 3, 4, 5, 6, 7, or 8 nucleotides in length). In some embodiments, the oligonucleotide has an overhang

comprising two (2) nucleotides on the 3' end of the antisense (guide) strand. However, other overhangs are possible. In some embodiments, an overhang is a 3'-overhang comprising a length of between 1 and 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5, or 6 nucleotides. However, in some embodiments, the overhang is a 5'-overhang comprising a length of between 1 and 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5, or 6 nucleotides. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 1-384, and a 5'-overhang comprising a length of between 1 and 6 nucleotides. In some embodiments, the oligonucleotide comprises a sense strand comprising a nucleotide sequence selected from SEQ ID NOs: 1537-1570, wherein the oligonucleotide comprises a 5'-overhang comprising a length of between 1 and 6 nucleotides. In some embodiments, the oligonucleotide comprises an antisense strand comprising a nucleotide sequence selected from SEQ ID NOs: 1573-1606, wherein the oligonucleotide comprises a 5'-overhang comprising a length of between 1 and 6 nucleotides. In some embodiments, the oligonucleotide comprises a sense strand comprising a nucleotide sequence selected from SEQ ID NOs: 1537-1570 and antisense strand comprising a nucleotide sequence selected from SEQ ID NOs: 1573-1606, wherein the oligonucleotide comprises a 5'-overhang comprising a length of between 1 and 6 nucleotides.

In some embodiments, two (2) terminal nucleotides on the 3' end of an antisense strand are modified. In some embodiments, the two (2) terminal nucleotides on the 3' end of the antisense strand are complementary with the target mRNA (e.g., *MARC1* mRNA). In some embodiments, the two (2) terminal nucleotides on the 3' end of the antisense strand are not complementary with the target mRNA. In some embodiments, the two (2) terminal nucleotides on the 3' end of the antisense strand of an oligonucleotide herein are unpaired. In some embodiments, the two (2) terminal nucleotides on the 3' end of the antisense strand of an oligonucleotide herein comprise an unpaired GG. In some embodiments, the two (2) terminal nucleotides on the 3' end of an antisense strand of an oligonucleotide herein are not complementary to the target mRNA. In some embodiments, two (2) terminal nucleotides on each 3' end of an oligonucleotide are GG. In some embodiments, one or both of the two (2) terminal GG nucleotides on each 3' end of an oligonucleotide herein is not complementary with the target mRNA. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides

of any one of SEQ ID NOs: 1-384, wherein the two (2) terminal nucleotides on the 3' end of the antisense strand of the oligonucleotide herein comprises an unpaired GG. In some embodiments, the oligonucleotide comprises an antisense strand comprising a nucleotide sequence selected from SEQ ID NOs: 385-768, wherein the two (2) terminal nucleotides on the 3' end of the antisense strand of the oligonucleotide comprises an unpaired GG. In some embodiments, the oligonucleotide comprises a sense strand comprising a nucleotide sequence selected from SEQ ID NOs: 1537-1570 and antisense strand comprising a nucleotide sequence selected from SEQ ID NOs: 1573-1606, wherein the two (2) terminal nucleotides on the 3' end of the antisense strand of the oligonucleotide comprises an unpaired GG.

In some embodiments, there is one or more (*e.g.*, 1, 2, 3, 4, or 5) mismatch(s) between a sense and antisense strand comprising an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide). If there is more than one mismatch between a sense and antisense strand, they may be positioned consecutively (*e.g.*, 2, 3 or more in a row), or interspersed throughout the region of complementarity. In some embodiments, the 3' end of the sense strand comprises one or more mismatches. In some embodiments, two (2) mismatches are incorporated at the 3' end of the sense strand. In some embodiments, base mismatches, or destabilization of segments at the 3' end of the sense strand of an oligonucleotide herein improves or increases the potency of the oligonucleotide. In some embodiments, the sense and antisense strands of an oligonucleotide herein comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;

- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively,

wherein there is one or more (*e.g.*, 1, 2, 3, 4, or 5) mismatch(s) between the sense and antisense strands.

In some embodiments, an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) comprises a sense strand and an antisense strand comprising nucleotide sequences selected from:

- (a) SEQ ID NOs: 1543 and 1579, respectively;
- (b) SEQ ID NOs: 1560 and 1596, respectively;
- (c) SEQ ID NOs: 1568 and 1604, respectively; and,
- (d) SEQ ID NOs: 1553 and 1589, respectively,

wherein there is one or more (*e.g.*, 1, 2, 3, 4, or 5) mismatch(s) between the sense and antisense strands.

Antisense Strands

In some embodiments, an antisense strand of an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) is referred to as a “guide strand”. For example, an antisense strand that

engages with RNA-induced silencing complex (RISC) and binds to an *Argonaute* protein such as Ago2, or engages with or binds to one or more similar factors, and directs silencing of a target gene, as the antisense strand is referred to as a guide strand. In some embodiments, a sense strand comprising a region of complementary to a guide strand is referred to herein as a “passenger strand.”

In some embodiments, an oligonucleotide herein (e.g., an RNAi oligonucleotide) comprises an antisense strand of up to about 50 nucleotides in length (e.g., up to 50, up to 40, up to 35, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17, or up to 12 nucleotides in length). In some embodiments, an oligonucleotide comprises an antisense strand of at least about 12 nucleotides in length (e.g., at least 12, at least 15, at least 19, at least 21, at least 22, at least 25, at least 27, at least 30, at least 35, or at least 38 nucleotides in length). In some embodiments, an oligonucleotide comprises an antisense strand in a range of about 12 to about 40 (e.g., 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to 36, 15 to 32, 15 to 28, 17 to 22, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40, or 32 to 40) nucleotides in length. In some embodiments, an oligonucleotide comprises antisense strand of 15 to 30 nucleotides in length. In some embodiments, an antisense strand of any one of the oligonucleotides disclosed herein is of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides in length. In some embodiments, an oligonucleotide comprises an antisense strand of 22 nucleotides in length.

In some embodiments, an oligonucleotide disclosed herein (e.g., an RNAi oligonucleotide) for targeting *MARCI* comprises an antisense strand comprising or consisting of a sequence as set forth in any one of SEQ ID NOs: 1153-1536. In some embodiments, an oligonucleotide herein comprises an antisense strand comprising at least about 12 (e.g., at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1153-1536. In some embodiments, an oligonucleotide disclosed herein for targeting *MARCI* comprises an antisense strand comprising or consisting of a sequence as set forth in any one of SEQ ID NOs: 1573-1606. In some embodiments, an oligonucleotide herein comprises an antisense strand comprising at least about 12 (e.g., at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1573-1606. In some embodiments, an oligonucleotide disclosed herein for targeting *MARCI* comprises an antisense strand comprising or consisting of a sequence as set forth in any one of SEQ ID NOs: 1579, 1596, 1604, and 1589. In some embodiments, an

oligonucleotide herein comprises an antisense strand comprising at least about 12 (*e.g.*, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1579, 1596, 1604, and 1589.

In some embodiments, an oligonucleotide herein comprises an antisense strand comprising a nucleotide sequence selected from SEQ ID NOs: 385-768. In some embodiments, an oligonucleotide herein comprises an antisense strand comprising a nucleotide sequence selected from SEQ ID NOs: 618, 682, 740, and 760.

Sense Strands

In some embodiments, an oligonucleotide disclosed herein (*e.g.*, an RNAi oligonucleotide) for targeting *MARCI* mRNA and inhibiting *MARCI* expression comprises a sense strand sequence as set forth in any one of SEQ ID NOs: 1-384. In some embodiments, an oligonucleotide disclosed herein (*e.g.*, an RNAi oligonucleotide) for targeting *MARCI* mRNA and inhibiting *MARCI* expression comprises a sense strand sequence as set forth in any one of SEQ ID NOs: 769-1152. In some embodiments, an oligonucleotide herein has a sense strand comprised of at least about 12 (*e.g.*, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 769-1152. In some embodiments, an oligonucleotide herein has a sense strand comprised of at least about 12 (*e.g.*, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, or at least 19) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1-384. In some embodiments, an oligonucleotide disclosed herein for targeting *MARCI* mRNA and inhibiting *MARCI* expression comprises a sense strand sequence as set forth in any one of SEQ ID NOs: 1537-1570. In some embodiments, an oligonucleotide herein has a sense strand comprised of least about 12 (*e.g.*, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1537-1570. In some embodiments, an oligonucleotide disclosed herein for targeting *MARCI* mRNA and inhibiting *MARCI* expression comprises a sense strand sequence as set forth in any one of SEQ ID NOs: 1543, 1560, 1568, and 1553. In some embodiments, an oligonucleotide herein has a sense strand that comprise at least about 12 (*e.g.*, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1543, 1560, 1568, or 1553. In some embodiments, an oligonucleotide

disclosed herein for targeting *MARCI* mRNA and inhibiting *MARCI* expression comprises a sense strand sequence as set forth in any one of SEQ ID NOs: 234, 298, 356, and 376. In some embodiments, an oligonucleotide herein has a sense strand that comprise at least about 12 (*e.g.*, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, or at least 19) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 234, 298, 356, and 376.

In some embodiments, an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) comprises a sense strand (or passenger strand) of up to about 50 nucleotides in length (*e.g.*, up to 50, up to 40, up to 36, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17, or up to 12 nucleotides in length). In some embodiments, an oligonucleotide herein comprises a sense strand of at least about 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 19, at least 21, at least 25, at least 27, at least 30, at least 36 or at least 38 nucleotides in length). In some embodiments, an oligonucleotide herein comprises a sense strand in a range of about 12 to about 50 (*e.g.*, 12 to 50, 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to 36, 15 to 32, 15 to 28, 17 to 21, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40, or 32 to 40) nucleotides in length. In some embodiments, an oligonucleotide herein comprises a sense strand of 15 to 50 nucleotides in length. In some embodiments, an oligonucleotide herein comprises a sense strand of 18 to 36 nucleotides in length. In some embodiments, an oligonucleotide herein comprises a sense strand of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides in length. In some embodiments, an oligonucleotide herein comprises a sense strand of 36 nucleotides in length.

In some embodiments, an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) comprises a sense strand comprising a stem-loop structure at the 3' end of the sense strand. In some embodiments, the stem-loop is formed by intrastrand base pairing. In some embodiments, a sense strand comprises a stem-loop structure at its 5' end. In some embodiments, the stem of the stem-loop comprises a duplex of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 2 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 3 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 4 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 5 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 6 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 7 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 8 nucleotides in length. In some embodiments, the stem of the stem-loop comprises

a duplex of 9 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 10 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 11 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 12 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 13 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 14 nucleotides in length.

In some embodiments, a stem-loop provides the oligonucleotide protection against degradation (*e.g.*, enzymatic degradation), facilitates or improves targeting and/or delivery to a target cell, tissue, or organ (*e.g.*, the liver), or both. For example, in some embodiments, the loop of a stem-loop is comprised of nucleotides comprising one or more modifications that facilitate, improve, or increase targeting to a target mRNA (*e.g.*, a *MARCI* mRNA), inhibition of target gene expression (*e.g.*, *MARCI* expression), and/or delivery, uptake, and/or penetrance into a target cell, tissue, or organ (*e.g.*, the liver), or a combination thereof. In some embodiments, the stem-loop itself or modification(s) to the stem-loop do not affect or do not substantially affect the inherent gene expression inhibition activity of the oligonucleotide, but facilitates, improves, or increases stability (*e.g.*, provides protection against degradation) and/or delivery, uptake, and/or penetrance of the oligonucleotide to a target cell, tissue, or organ (*e.g.*, the liver). In certain embodiments, an oligonucleotide herein comprises a sense strand comprising (*e.g.*, at its 3' end) a stem-loop set forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a single-stranded loop of linked nucleotides between S1 and S2 of up to about 10 nucleotides in length (*e.g.*, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length). In some embodiments, the loop (L) is 3 nucleotides in length. In some embodiments, the loop (L) is 4 nucleotides in length. In some embodiments, the loop (L) is 5 nucleotides in length. In some embodiments, the loop (L) is 6 nucleotides in length. In some embodiments, the loop (L) is 7 nucleotides in length. In some embodiments, the loop (L) is 8 nucleotides in length. In some embodiments, the loop (L) is 9 nucleotides in length. In some embodiments, the loop (L) is 10 nucleotides in length.

In some embodiments, the tetraloop comprises the sequence 5'-GAAA-3'. In some embodiments, the stem loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 1681).

In some embodiments, an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) comprises a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 1-384, and the oligonucleotide comprises a sense strand comprising (*e.g.*, at its 3' end) a stem-loop set

forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a single-stranded loop between S1 and S2 of up to about 10 nucleotides in length (*e.g.*, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length). In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementary that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 1-384, and the oligonucleotide comprises a sense strand comprising (*e.g.*, at its 3' end) a stem-loop set forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a single-stranded loop between S1 and S2 of 4 nucleotides in length.

In some embodiments, a loop (L) of a stem-loop having the structure S1-L-S2 as described herein is a triloop. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementary that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 1-384 and a triloop. In some embodiments, the triloop comprises ribonucleotides, deoxyribonucleotides, modified nucleotides, ligands (*e.g.*, delivery ligands), and combinations thereof.

In some embodiments, a loop (L) of a stem-loop having the structure S1-L-S2 as described above is a tetraloop as describe in US Patent No. 10,131,912, incorporated herein by reference. In some embodiments, an oligonucleotide herein comprises a targeting sequence or a region of complementary that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 1-384 and a tetraloop. In some embodiments, the tetraloop comprises ribonucleotides, deoxyribonucleotides, modified nucleotides, ligands (*e.g.*, delivery ligands), and combinations thereof.

Duplex Length

In some embodiments, a duplex formed between a sense and antisense strand is at least 12 (*e.g.*, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 21) nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is in the range of 12-30 nucleotides in length (*e.g.*, 12 to 30, 12 to 27, 12 to 22, 15 to 25, 18 to 30, 18 to 22, 18 to 25, 18 to 27, 18 to 30, 19 to 30, or 21 to 30 nucleotides in length). In some embodiments, a duplex formed between a sense and antisense strand is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 12 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 13 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 14 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense

strand is 15 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 16 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 17 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 18 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 19 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 20 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 21 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 22 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 23 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 24 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 25 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 26 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 27 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 28 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 29 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 30 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand does not span the entire length of the sense strand and/or antisense strand. In some embodiments, a duplex between a sense and antisense strand spans the entire length of either the sense or antisense strands. In some embodiments, a duplex between a sense and antisense strand spans the entire length of both the sense strand and the antisense strand. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;

- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively;

wherein a duplex formed between a sense and antisense strand is in the range of 12-30 nucleotides in length (*e.g.*, 12 to 30, 12 to 27, 12 to 22, 15 to 25, 18 to 30, 18 to 22, 18 to 25, 18 to 27, 18 to 30, 19 to 30, or 21 to 30 nucleotides in length)

In some embodiments, a duplex between a sense and antisense strand spans the entire length of both the sense strand and the antisense strand. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1543 and 1579, respectively;
- (b) SEQ ID NOs: 1560 and 1596, respectively;
- (c) SEQ ID NOs: 1568 and 1604, respectively; and,

(d) SEQ ID NOs: 1553 and 1589, respectively, wherein a duplex formed between a sense and antisense strand is in the range of 12-30 nucleotides in length (e.g., 12 to 30, 12 to 27, 12 to 22, 15 to 25, 18 to 30, 18 to 22, 18 to 25, 18 to 27, 18 to 30, 19 to 30, or 21 to 30 nucleotides in length)

Oligonucleotide Termini

In some embodiments, an oligonucleotide disclosed herein (e.g., an RNAi oligonucleotide) comprises a sense strand and an antisense strand, wherein the termini of either or both strands comprise a blunt end. In some embodiments, an oligonucleotide herein comprises sense and antisense strands that are separate strands which form an asymmetric duplex region having an overhang at the 3' terminus of the antisense strand. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the termini of either or both strands comprise an overhang comprising one or more nucleotides. In some embodiments, the one or more nucleotides comprising the overhang are unpaired nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the 3' termini of the sense strand and the 5' termini of the antisense strand comprise a blunt end. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the 5' termini of the sense strand and the 3' termini of the antisense strand comprise a blunt end.

In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the 3' terminus of either or both strands comprise a 3'-overhang comprising one or more nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the sense strand comprises a 3'-overhang comprising one or more nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the antisense strand comprises a 3'-overhang comprising one or more nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein both the sense strand and the antisense strand comprises a 3'-overhang comprising one or more nucleotides.

In some embodiments, the 3'-overhang is about one (1) to twenty (20) nucleotides in length (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or about 20 nucleotides in length). In some embodiments, the 3'-overhang is about one (1) to nineteen (19), one (1) to eighteen (18), one (1) to seventeen (17), one (1) to sixteen (16), one (1) to fifteen (15), one (1) to fourteen (14), one (1) to thirteen (13), one (1) to twelve (12), one (1) to eleven (11), one (1) to ten (10), one (1) to nine (9), one (1) to eight (8), one (1) to seven (7), one (1)

to six (6), one (1) to five (5), one (1) to four (4), one (1) to three (3), or about one (1) to two (2) nucleotides in length. In some embodiments, the 3'-overhang is (1) nucleotide in length. In some embodiments, the 3'-overhang is two (2) nucleotides in length. In some embodiments, the 3'-overhang is three (3) nucleotides in length. In some embodiments, the 3'-overhang is four (4) nucleotides in length. In some embodiments, the 3'-overhang is five (5) nucleotides in length. In some embodiments, the 3'-overhang is six (6) nucleotides in length. In some embodiments, the 3'-overhang is seven (7) nucleotides in length. In some embodiments, the 3'-overhang is eight (8) nucleotides in length. In some embodiments, the 3'-overhang is nine (9) nucleotides in length. In some embodiments, the 3'-overhang is ten (10) nucleotides in length. In some embodiments, the 3'-overhang is eleven (11) nucleotides in length. In some embodiments, the 3'-overhang is twelve (12) nucleotides in length. In some embodiments, the 3'-overhang is thirteen (13) nucleotides in length. In some embodiments, the 3'-overhang is fourteen (14) nucleotides in length. In some embodiments, the 3'-overhang is fifteen (15) nucleotides in length. In some embodiments, the 3'-overhang is sixteen (16) nucleotides in length. In some embodiments, the 3'-overhang is seventeen (17) nucleotides in length. In some embodiments, the 3'-overhang is eighteen (18) nucleotides in length. In some embodiments, the 3'-overhang is nineteen (19) nucleotides in length. In some embodiments, the 3'-overhang is twenty (20) nucleotides in length.

In some embodiments, an oligonucleotide disclosed herein (e.g., an RNAi oligonucleotide) comprises a sense strand and an antisense strand, wherein the antisense strand comprises a 3'-overhang, wherein the sense and antisense strands of the oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;

- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively,

and wherein the antisense strand comprises a 3'-overhang about one (1) to twenty (20) nucleotides in length (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or about 20 nucleotides in length), optionally wherein the 3'-overhang is two (2) nucleotides in length.

In some embodiments, an oligonucleotide disclosed herein (*e.g.*, an RNAi oligonucleotide) comprises a sense strand and an antisense strand, wherein the antisense strand comprises a 3'-overhang, wherein the sense and antisense strands of the oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1543 and 1579, respectively;
- (b) SEQ ID NOs: 1560 and 1596, respectively;
- (c) SEQ ID NOs: 1568 and 1604, respectively; and,
- (d) SEQ ID NOs: 1553 and 1589, respectively,

and wherein the antisense strand comprises a 3'-overhang about one (1) to twenty (20) nucleotides in length (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or about 20 nucleotides in length), optionally wherein the 3'-overhang is two (2) nucleotides in length.

In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the 5' terminus of either or both strands comprise a 5'-overhang comprising one or more nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the sense strand comprises a 5'-overhang comprising one or more nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the antisense strand comprises a 5'-overhang comprising one or more nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein both the sense strand and the antisense strand comprises a 5'-overhang comprising one or more nucleotides.

In some embodiments, the 5'-overhang is about one (1) to twenty (20) nucleotides in length (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or about 20 nucleotides in length). In some embodiments, the 5'-overhang is about one (1) to nineteen (19), one (1) to eighteen (18), one (1) to seventeen (17), one (1) to sixteen (16), one (1) to fifteen (15), one (1) to fourteen (14), one (1) to thirteen (13), one (1) to twelve (12), one (1) to eleven (11), one (1) to ten (10), one (1) to nine (9), one (1) to eight (8), one (1) to seven (7), one (1) to six (6), one (1) to five (5), one (1) to four (4), one (1) to three (3), or about one (1) to two (2) nucleotides in length. In some embodiments, the 5'-overhang is (1) nucleotide in length. In some embodiments, the 5'-overhang is two (2) nucleotides in length. In some embodiments, the 5'-overhang is three (3) nucleotides in length. In some embodiments, the 5'-overhang is four (4) nucleotides in length. In some embodiments, the 5'-overhang is five (5) nucleotides in length. In some embodiments, the 5'-overhang is six (6) nucleotides in length. In some embodiments, the 5'-overhang is seven (7) nucleotides in length. In some embodiments, the 5'-overhang is eight (8) nucleotides in length. In some embodiments, the 5'-overhang is nine (9) nucleotides in length. In some embodiments, the 5'-overhang is ten (10) nucleotides in length. In some embodiments, the 5'-overhang is eleven (11) nucleotides in length. In some embodiments, the 5'-overhang is twelve (12) nucleotides in length. In some embodiments, the 5'-overhang is thirteen (13) nucleotides in length. In some embodiments, the 5'-overhang is fourteen (14) nucleotides in length. In some embodiments, the 5'-overhang is fifteen (15) nucleotides in length. In some embodiments, the 5'-overhang is sixteen (16) nucleotides in length. In some embodiments, the 5'-overhang is seventeen (17) nucleotides in length. In some

embodiments, the 5'-overhang is eighteen (18) nucleotides in length. In some embodiments, the 5'-overhang is nineteen (19) nucleotides in length. In some embodiments, the 5'-overhang is twenty (20) nucleotides in length.

In some embodiments, an oligonucleotide disclosed herein (e.g., an RNAi oligonucleotide) comprises a sense strand and an antisense strand, wherein the antisense strand comprises a 5'-overhang, wherein the sense and antisense strands of the oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;

- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively;

and wherein the antisense strand comprises a 5'-overhang about one (1) to twenty (20) nucleotides in length (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or about 20 nucleotides in length), optionally wherein the 5'-overhang is two (2) nucleotides in length.

In some embodiments, an oligonucleotide disclosed herein (e.g., an RNAi oligonucleotide) comprises a sense strand and an antisense strand, wherein the antisense strand comprises a 5'-overhang, wherein the sense and antisense strands of the oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1543 and 1579, respectively;
- (b) SEQ ID NOs: 1560 and 1596, respectively;
- (c) SEQ ID NOs: 1568 and 1604, respectively; and,
- (d) SEQ ID NOs: 1553 and 1589, respectively;

and wherein the antisense strand comprises a 5'-overhang about one (1) to twenty (20) nucleotides in length (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or about 20 nucleotides in length), optionally wherein the 5'-overhang is two (2) nucleotides in length.

In some embodiments, one or more (e.g., 2, 3, 4, 5, or more) nucleotides comprising the 3' terminus or 5' terminus of a sense and/or antisense strand are modified. For example, in some embodiments, one or two terminal nucleotides of the 3' terminus of the antisense strand are modified. In some embodiments, the last nucleotide at the 3' terminus of an antisense strand is modified, such that it comprises 2' modification, or it comprises, a 2'-O-methoxyethyl. In some embodiments, the last one or two terminal nucleotides at the 3' terminus of an antisense strand are complementary with the target. In some embodiments, the last one or two nucleotides at the 3' terminus of the antisense strand are not complementary with the target.

In some embodiments, an oligonucleotide disclosed herein (e.g., an RNAi oligonucleotide) comprises a sense strand and an antisense strand, wherein the 3' terminus of the sense strand comprises a step-loop described herein and the 3' terminus of the antisense

strand comprises a 3'-overhang described herein. In some embodiments, an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) comprises a sense strand and an antisense strand that form a nicked tetraloop structure described herein, wherein the 3' terminus of the sense strand comprises a stem-loop, wherein the loop is a tetraloop described herein, and wherein the 3' terminus of the antisense strand comprises a 3'-overhang described herein. In some embodiments, the 3'-overhang is two (2) nucleotides in length. In some embodiments, the two (2) nucleotides comprising the 3'-overhang both comprise guanine (G) nucleobases. Typically, one or both of the nucleotides comprising the 3'-overhang of the antisense strand are not complementary with the target mRNA. An exemplary nicked tetraloop structure is provided in **FIG. 12**. In some embodiments, an oligonucleotide described herein comprises the nicked tetraloop structure shown in **FIG. 12**.

Oligonucleotide Modifications

In some embodiments, an oligonucleotide described herein (*e.g.*, an RNAi oligonucleotide) comprises a modification. Oligonucleotides (*e.g.*, RNAi oligonucleotides) may be modified in various ways to improve or control specificity, stability, delivery, bioavailability, resistance from nuclease degradation, immunogenicity, base-pairing properties, RNA distribution and cellular uptake and other features relevant to therapeutic or research use.

In some embodiments, the modification is a modified sugar. In some embodiments, the modification is a 5'-terminal phosphate group. In some embodiments, the modification is a modified internucleotide linkage. In some embodiments, the modification is a modified base. In some embodiments, an oligonucleotide described herein can comprise any one of the modifications described herein or any combination thereof. For example, in some embodiments, an oligonucleotide described herein comprises at least one modified sugar, a 5'-terminal phosphate group, at least one modified internucleotide linkage, and at least one modified base. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;

- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively;

wherein the oligonucleotide comprises at least one modified sugar, a 5'-terminal phosphate group, at least one modified internucleotide linkage, and at least one modified base.

In some embodiments, an oligonucleotide described herein comprises at least one modified sugar, a 5'-terminal phosphate group, at least one modified internucleotide linkage, and at least one modified base. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1543 and 1579, respectively;
- (b) SEQ ID NOs: 1560 and 1596, respectively;
- (c) SEQ ID NOs: 1568 and 1604, respectively; and,
- (d) SEQ ID NOs: 1553 and 1589, respectively,

wherein the oligonucleotide comprises at least one modified sugar, a 5'-terminal phosphate group, at least one modified internucleotide linkage, and at least one modified base.

The number of modifications on an oligonucleotide (*e.g.*, an RNAi oligonucleotide) and the position of those nucleotide modifications may influence the properties of an oligonucleotide. For example, oligonucleotides may be delivered *in vivo* by conjugating them to or encompassing them in a lipid nanoparticle (LNP) or similar carrier. However, when an oligonucleotide is not protected by an LNP or similar carrier, it may be advantageous for at least some of the nucleotides to be modified. Accordingly, in some embodiments, all or substantially all the nucleotides of an oligonucleotide are modified. In some embodiments, more than half of the nucleotides are modified. In some embodiments, less than half of the nucleotides are modified. In some embodiments, the sugar moiety of all nucleotides comprising the oligonucleotide is modified at the 2' position. The modifications may be reversible or irreversible. In some embodiments, an oligonucleotide as disclosed herein has a number and type of modified nucleotides sufficient to cause the desired characteristics (*e.g.*, protection from enzymatic degradation, capacity to target a desired cell after *in vivo* administration, and/or thermodynamic stability).

Sugar Modifications

In some embodiments, an oligonucleotide described herein (*e.g.*, an RNAi oligonucleotide) comprises a modified sugar. In some embodiments, a modified sugar (also referred herein to a sugar analog) includes a modified deoxyribose or ribose moiety in which, for example, one or more modifications occur at the 2', 3', 4', and/or 5' carbon position of the sugar. In some embodiments, a modified sugar may also include non-natural alternative carbon structures such as those present in locked nucleic acids ("LNA"; *see, e.g.*, Koshkin *et al.* (1998) TETRAHEDON 54:3607-30), unlocked nucleic acids ("UNA"; *see, e.g.*, Snead *et al.* (2013) MOL. THER-NUCL. ACIDS 2:e103) and bridged nucleic acids ("BNA"; *see, e.g.*, Imanishi & Obika (2002) CHEM COMMUN. (CAMB) 21:1653-59).

In some embodiments, a nucleotide modification in a sugar comprises a 2'-modification. In some embodiments, a 2'-modification may be 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-fluoro (2'-F), 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-

O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), or 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA). In some embodiments, the modification is 2'-F, 2'-OMe, or 2'-MOE. In some embodiments, a modification in a sugar comprises a modification of the sugar ring, which may comprise modification of one or more carbons of the sugar ring. For example, a modification of a sugar of a nucleotide may comprise a 2'-oxygen of a sugar is linked to a 1'-carbon or 4'-carbon of the sugar, or a 2'-oxygen is linked to the 1'-carbon or 4'-carbon *via* an ethylene or methylene bridge. In some embodiments, a modified nucleotide has an acyclic sugar that lacks a 2'-carbon to 3'-carbon bond. In some embodiments, a modified nucleotide has a thiol group, *e.g.*, in the 4' position of the sugar.

In some embodiments, an oligonucleotide (*e.g.*, an RNAi oligonucleotide) described herein comprises at least about 1 modified nucleotide (*e.g.*, at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, or more). In some embodiments, the sense strand of the oligonucleotide comprises at least about 1 modified nucleotide (*e.g.*, at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, or more). In some embodiments, the antisense strand of the oligonucleotide comprises at least about 1 modified nucleotide (*e.g.*, at least 1, at least 5, at least 10, at least 15, at least 20, or more).

In some embodiments, all the nucleotides of the sense strand of the oligonucleotide are modified. In some embodiments, all the nucleotides of the antisense strand of the oligonucleotide are modified. In some embodiments, all the nucleotides of the oligonucleotide (*i.e.*, both the sense strand and the antisense strand) are modified. In some embodiments, the modified nucleotide comprises a 2'-modification (*e.g.*, a 2'-F or 2'-OMe, 2'-MOE, and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid).

In some embodiments, the current invention provides oligonucleotides having different modification patterns. In some embodiments, an oligonucleotide herein comprises a sense strand having a modification pattern as set forth in the Examples and Sequence Listing and an antisense strand having a modification pattern as set forth in the Examples and Sequence Listing.

In some embodiments, an oligonucleotide disclosed herein (*e.g.*, an RNAi oligonucleotide) comprises an antisense strand having nucleotides that are modified with 2'-F. In some embodiments, an oligonucleotide herein comprises an antisense strand comprising nucleotides that are modified with 2'-F and 2'-OMe. In some embodiments, an oligonucleotide disclosed herein comprises a sense strand having nucleotides that are modified with 2'-F. In

some embodiments, an oligonucleotide disclosed herein comprises a sense strand comprises nucleotides that are modified with 2'-F and 2'-OMe.

In some embodiments, an oligonucleotide described herein comprises a sense strand with about 10-15%, 10%, 11%, 12%, 13%, 14%, or 15% of the nucleotides of the sense strand comprising a 2'-fluoro modification. In some embodiments, about 11% of the nucleotides of the sense strand comprise a 2'-fluoro modification. In some embodiments, an oligonucleotide described herein comprises an antisense strand with about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, or 35% of the nucleotides of the antisense strand comprising a 2'-fluoro modification. In some embodiments, about 32% of the nucleotides of the antisense strand comprise a 2'-fluoro modification. In some embodiments, the oligonucleotide has about 15-25%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, or 25% of its nucleotides comprising a 2'-fluoro modification. In some embodiments, about 19% of the nucleotides in the dsRNAi oligonucleotide comprise a 2'-fluoro modification.

In some embodiments, one or more of positions 8, 9, 10, or 11 of the sense strand is modified with a 2'-F group. In some embodiments, one or more of positions 3, 8, 9, 10, 12, 13, and 17 of the sense strand is modified with a 2'-F group. In some embodiments, one or more of positions 2, 3, 4, 5, 7, 10, and 14 of the antisense strand is modified with a 2'-F group. In some embodiments, one or more of positions 2, 3, 4, 5, 7, 8, 10, 14, 16, and 19 is modified with a 2'-F group. In some embodiments, the sugar moiety at each of nucleotides at positions 1-7 and 12-20 in the sense strand is modified with a 2'-OMe. In some embodiments, the sugar moiety at each of nucleotides at positions 1-7, 12-27, and 31-36 in the sense strand is modified with a 2'-OMe. In some embodiments, the sugar moiety at each of nucleotides at positions 6, 9, 11-13, 15, 17, 18, and 20-22 in the sense strand is modified with a 2'-OMe.

In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;

- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively;

wherein one or more of positions 8, 9, 10 or 11 of the sense strand is modified with a 2'-F group.

In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1543 and 1579, respectively;
- (b) SEQ ID NOs: 1560 and 1596, respectively;
- (c) SEQ ID NOs: 1568 and 1604, respectively; and,
- (d) SEQ ID NOs: 1553 and 1589, respectively;

wherein one or more of positions 8, 9, 10, or 11 of the sense strand is modified with a 2'-F group.

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 5, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 1, 2, 5, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 4, 5, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 1, 2, 3, 5, 7, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 3, 4, 5, 7, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group

consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 1, 2, 3, 5, 10, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 3, 4, 5, 10, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 3, 5, 7, 10, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 3, 4, 5, 7, 10, and 14 of the antisense strand modified with 2'-F and the sugar moiety of each of the remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid (2'-FANA).

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety of each of the nucleotides at positions 2, 3, 4, 5, 7, 8, 10, 14, 16, and, 19 of the antisense strand modified with 2'-F and the sugar moiety of each of the

remaining nucleotides of the antisense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid (2'-FANA).

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, or position 22 modified with 2'-F.

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, or position 22 modified with 2'-OMe.

In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, or position 22 modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid (2'-FANA).

In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 8-11 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 3, 8, 9, 10, 12, 13 and 17 modified with 2'-F. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 1-7 and 12-17, or 12-20 modified with 2'OMe. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 1-7, 12-27, and 31-36 modified with 2'OMe. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety of each of the nucleotides at positions 1-7 and 12-17, or 12-20 of the sense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-

fluoro- β -d-arabinonucleic acid (2'-FANA). In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 1-2, 4-7, 11, 14-16, and 18-20 modified with 2'OMe. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety of each of the nucleotides at positions 1-2, 4-7, 11, 14-16, and 18-20 of the sense strand modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid (2'-FANA).

In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, position 22, position 23, position 24, position 25, position 26, position 27, position 28, position 29, position 30, position 31, position 32, position 33, position 34, position 35, or position 36 modified with 2'-F.

In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, position 22, position 23, position 24, position 25, position 26, position 27, position 28, position 29, position 30, position 31, position 32, position 33, position 34, position 35, or position 36 modified with 2'-OMe.

In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, position 22, position 23, position 24, position 25, position 26, position 27, position 28, position 29, position 30, position 31, position 32, position 33, position 34, position 35, or position 36 modified with a modification selected from the group consisting of 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid (2'-FANA).

5'-Terminal Phosphate

In some embodiments, an oligonucleotide described herein (e.g., an RNAi oligonucleotide) comprises a sense strand and an antisense strand, wherein the antisense strand comprises a 5'-terminal phosphate. In some embodiments, 5'-terminal phosphate groups of an RNAi oligonucleotide enhance the interaction with Ago2. However, oligonucleotides comprising a 5'-phosphate group may be susceptible to degradation *via* phosphatases or other enzymes, which can limit their performance and/or bioavailability *in vivo*. In some embodiments, an oligonucleotide herein includes analogs of 5'-phosphates that are resistant to such degradation. In some embodiments, the phosphate analog is oxymethyl phosphonate, vinylphosphonate or malonylphosphonate, or a combination thereof. In certain embodiments, the 5' terminus of an oligonucleotide strand is attached to chemical moiety that mimics the electrostatic and steric properties of a natural 5'-phosphate group ("phosphate mimic"). In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;

- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively;

wherein the oligonucleotide comprises a 5'-terminal phosphate, optionally a 5'-terminal phosphate analog.

In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotides sequences selected from the group consisting of:

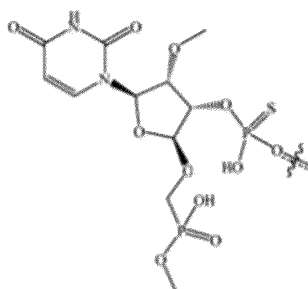
- (a) SEQ ID NOs: 1543 and 1579, respectively;
- (b) SEQ ID NOs: 1560 and 1596, respectively;
- (c) SEQ ID NOs: 1568 and 1604, respectively; and,
- (d) SEQ ID NOs: 1553 and 1589, respectively;

wherein the oligonucleotide comprises a 5'-terminal phosphate, optionally a 5'-terminal phosphate analog.

In some embodiments, an oligonucleotide herein (e.g., an RNAi oligonucleotide) has a phosphate analog at a 4'-carbon position of the sugar (referred to as a "4'-phosphate analog"). *See, e.g.*, Intl. Patent Application Publication No. WO 2018/045317. In some embodiments, an oligonucleotide herein comprises a 4'-phosphate analog at a 5'-terminal nucleotide. In some embodiments, a phosphate analog is an oxymethyl phosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (e.g., at its 4'-carbon) or analog thereof. In other embodiments, a 4'-phosphate analog is a thiomethyl phosphonate or an aminomethyl phosphonate, in which the sulfur atom of the thiomethyl group or the nitrogen atom of the amino methyl group is bound to the 4'-carbon of the sugar moiety or analog thereof. In certain embodiments, a 4'-phosphate analog is an oxymethyl phosphonate. In some embodiments, an oxymethyl phosphonate is represented by the formula $-O-CH_2-PO(OH)_2$, $-O-CH_2-PO(OR)_2$,

or -O-CH₂-PO(OH)(R), in which R is independently selected from -H, -CH₃, an alkyl group, -CH₂CH₂CN, -CH₂OCOC(CH₃)₃, -CH₂OCH₂CH₂Si(CH₃)₃ or a protecting group. In certain embodiments, the alkyl group is CH₂CH₃. More typically, R is independently selected from -H, -CH₃ or -CH₂CH₃. In some embodiment, R is -CH₃. In some embodiments, the 4'-phosphate analog is 5'-methoxyphosphonate-4'-oxy.

In some embodiments, an oligonucleotide provided herein comprises an antisense strand comprising a 4'-phosphate analog at the 5'-terminal nucleotide, wherein 5'-terminal nucleotide comprises the following structure:



5'-methoxyphosphonate-4'-oxy-2'-O-methyluridine phosphorothioate [MePhosphonate-4OmUs].

Modified Internucleotide Linkage

In some embodiments, an oligonucleotide provided herein (e.g., a RNAi oligonucleotide) comprises a modified internucleotide linkage. In some embodiments, phosphate modifications or substitutions result in an oligonucleotide that comprises at least about 1 (e.g., at least 1, at least 2, at least 3, or at least 5) modified internucleotide linkage. In some embodiments, any one of the oligonucleotides disclosed herein comprises about 1 to about 10 (e.g., 1 to 10, 2 to 8, 4 to 6, 3 to 10, 5 to 10, 1 to 5, 1 to 3, or 1 to 2) modified internucleotide linkages. In some embodiments, any one of the oligonucleotides disclosed herein comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 modified internucleotide linkages.

A modified internucleotide linkage may be a phosphorodithioate linkage, a phosphorothioate linkage, a phosphotriester linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a phosphoramidite linkage, a phosphonate linkage or a boranophosphate linkage. In some embodiments, at least one modified internucleotide linkage of any one of the oligonucleotides as disclosed herein is a phosphorothioate linkage.

In some embodiments, an oligonucleotide provided herein (*e.g.*, a RNAi oligonucleotide) has a phosphorothioate linkage between one or more of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand. In some embodiments, the oligonucleotide described herein has a phosphorothioate linkage between each of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;

- (y) SEQ ID NOs: 1561 and 1597, respectively;
 - (z) SEQ ID NOs: 1562 and 1598, respectively;
 - (aa) SEQ ID NOs: 1563 and 1599, respectively;
 - (bb) SEQ ID NOs: 1564 and 1600, respectively;
 - (cc) SEQ ID NOs: 1565 and 1601, respectively;
 - (dd) SEQ ID NOs: 1566 and 1602, respectively;
 - (ee) SEQ ID NOs: 1567 and 1603, respectively;
 - (ff) SEQ ID NOs: 1568 and 1604, respectively;
 - (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
 - (hh) SEQ ID NOs: 1570 and 1606, respectively,
- wherein the oligonucleotide comprises a modified internucleotide linkage.

In some embodiments, the oligonucleotide described herein has a phosphorothioate linkage between each of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1543 and 1579, respectively;
 - (b) SEQ ID NOs: 1560 and 1596, respectively;
 - (c) SEQ ID NOs: 1568 and 1604, respectively; and,
 - (d) SEQ ID NOs: 1553 and 1589, respectively,
- wherein the oligonucleotide comprises a modified internucleotide linkage.

Base Modifications

In some embodiments, an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotides) comprises one or more modified nucleobases. In some embodiments, modified nucleobases (also referred to herein as base analogs) are linked at the 1' position of a nucleotide sugar moiety. In certain embodiments, a modified nucleobase is a nitrogenous base. In some embodiments, a modified nucleobase does not contain nitrogen atom. *See, e.g.*, US Patent Application Publication No. 2008/0274462. In some embodiments, a modified nucleotide comprises a universal base. In some embodiments, a modified nucleotide does not contain a nucleobase (abasic). In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;

- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively;

wherein the oligonucleotide comprises one or more modified nucleobases.

In some embodiments, a modified nucleotide comprises a universal base. In some embodiments, a modified nucleotide does not contain a nucleobase (abasic). In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1543 and 1579, respectively;
- (b) SEQ ID NOs: 1560 and 1596, respectively;
- (c) SEQ ID NOs: 1568 and 1604, respectively; and,
- (d) SEQ ID NOs: 1553 and 1589, respectively,

wherein the oligonucleotide comprises one or more modified nucleobases.

In some embodiments, a universal base is a heterocyclic moiety located at the 1' position of a nucleotide sugar moiety in a modified nucleotide, or the equivalent position in a nucleotide sugar moiety substitution, that, when present in a duplex, can be positioned opposite more than one type of base without substantially altering structure of the duplex. In some embodiments, compared to a reference single-stranded nucleic acid (*e.g.*, oligonucleotide) that is fully complementary to a target nucleic acid (*e.g.*, a *MARCI* mRNA), a single-stranded nucleic acid containing a universal base forms a duplex with the target nucleic acid that has a lower T_m than a duplex formed with the complementary nucleic acid. In some embodiments, when compared to a reference single-stranded nucleic acid in which the universal base has been replaced with a base to generate a single mismatch, the single-stranded nucleic acid containing the universal base forms a duplex with the target nucleic acid that has a higher T_m than a duplex formed with the nucleic acid comprising the mismatched base.

Non-limiting examples of universal-binding nucleotides include, but are not limited to, inosine, 1- β -D-ribofuranosyl-5-nitroindole and/or 1- β -D-ribofuranosyl-3-nitropyrrole (*see*, US Patent Application Publication No. 2007/0254362; Van Aerschot *et al.* (1995) NUCLEIC ACIDS RES. 23:4363-4370; Loakes *et al.* (1995) NUCLEIC ACIDS RES. 23:2361-66; and Loakes & Brown (1994) NUCLEIC ACIDS RES. 22:4039-43).

Targeting Ligands

In some embodiments, it is desirable to target an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) to one or more cells or cell type, tissues, organs, or anatomical regions or compartments. Such a strategy may help to avoid undesirable effects to the organism treated and/or to avoid undue loss of the oligonucleotide to cells, tissues, organs, or anatomical regions or compartments that would not benefit from the oligonucleotide or its effects (*e.g.*, inhibition or reduction of *MARCI* expression). Accordingly, in some embodiments,

oligonucleotides disclosed herein (*e.g.*, RNAi oligonucleotides) are modified to facilitate targeting and/or delivery to particular cells or cell types, tissues, organs, or anatomical regions or compartments (*e.g.*, to facilitate delivery of the oligonucleotide to the liver). In some embodiments, an oligonucleotide comprises at least one nucleotide (*e.g.*, 1, 2, 3, 4, 5, 6, or more nucleotides) conjugated to one or more targeting ligand(s). In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;

- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively;

wherein the oligonucleotide comprises a targeting ligand conjugated to at least one nucleotide.

In some embodiments, an oligonucleotide comprises at least one nucleotide (*e.g.*, 1, 2, 3, 4, 5, 6, or more nucleotides) conjugated to one or more targeting ligand(s). In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1543 and 1579, respectively;
- (b) SEQ ID NOs: 1560 and 1596, respectively;
- (c) SEQ ID NOs: 1568 and 1604, respectively; and,
- (d) SEQ ID NOs: 1553 and 1589, respectively;

wherein the oligonucleotide comprises a targeting ligand conjugated to at least one nucleotide.

In some embodiments, the targeting ligand comprises a carbohydrate, amino sugar, cholesterol, peptide, polypeptide, protein, or part of a protein (*e.g.*, an antibody or antibody fragment), or lipid. In certain embodiments, the targeting ligand is a carbohydrate comprising at least one GalNAc moiety.

In some embodiments, 1 or more (*e.g.*, 1, 2, 3, 4, 5, or 6) nucleotides of an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) are each conjugated to a separate targeting ligand (*e.g.*, a GalNAc moiety). In some embodiments, 2 to 4 nucleotides of an oligonucleotide are each conjugated to a separate targeting ligand. In some embodiments, targeting ligands are conjugated to 2 to 4 nucleotides at either ends of the sense or antisense strand (*e.g.*, targeting ligands are conjugated to a 2 to 4 nucleotide overhang or extension on the 5' or 3' terminus of the sense or antisense strand) such that the targeting ligands resemble bristles of a toothbrush, and the oligonucleotide resembles a toothbrush. For example, an oligonucleotide may comprise a stem-loop at either the 5' or 3' terminus of the sense strand and 1, 2, 3, or 4 nucleotides of the loop of the stem may be individually conjugated to a targeting ligand. In some embodiments, an oligonucleotide provided by the current invention (*e.g.*, a RNAi oligonucleotide) comprises a stem-loop at the 3' terminus of the sense strand, wherein the loop of the stem-loop comprises a triloop or a tetraloop, and wherein the 3 or 4 nucleotides

comprising the triloop or tetraloop, respectively, are individually conjugated to a targeting ligand. In some embodiments, an oligonucleotide provided by the current invention (*e.g.*, a RNAi oligonucleotide) comprises a stem-loop at the 3' terminus of the sense strand, wherein the loop of the stem-loop comprises a tetraloop, and wherein 3 nucleotides of the tetraloop are individually conjugated to a targeting ligand.

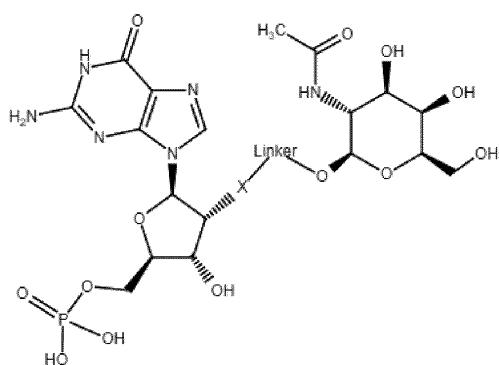
GalNAc is a high affinity carbohydrate ligand for the asialoglycoprotein receptor (ASGPR), which is primarily expressed on the surface of hepatocyte cells and has a major role in binding, internalizing and subsequent clearing circulating glycoproteins that contain terminal galactose or GalNAc residues (asialoglycoproteins). Conjugation (either indirect or direct) of GalNAc moieties to oligonucleotides of the instant disclosure can be used to target these oligonucleotides to the ASGPR expressed on cells. In some embodiments, an oligonucleotide of the instant disclosure (*e.g.*, an RNAi oligonucleotide) is conjugated to at least one or more GalNAc moieties, wherein the GalNAc moieties target the oligonucleotide to an ASGPR expressed on human liver cells (*e.g.*, human hepatocytes). In some embodiments, the GalNAc moiety target the oligonucleotide to the liver.

In some embodiments, an oligonucleotide of the instant disclosure (*e.g.*, an RNAi oligonucleotide) is conjugated directly or indirectly to a monovalent GalNAc moiety. In some embodiments, the oligonucleotide is conjugated directly or indirectly to more than one monovalent GalNAc (*i.e.*, is conjugated to 2, 3 or 4 monovalent GalNAc moieties and is typically conjugated to 3 or 4 monovalent GalNAc moieties). In some embodiments, an oligonucleotide is conjugated to one or more bivalent GalNAc, trivalent GalNAc or tetravalent GalNAc moieties. In some embodiments, a bivalent, trivalent or tetravalent GalNAc moiety is conjugated to an oligonucleotide *via* a branched linker. In some embodiments, a monovalent GalNAc moiety is conjugated to a first nucleotide and a bivalent, trivalent, or tetravalent GalNAc moiety is conjugated to a second nucleotide *via* a branched linker.

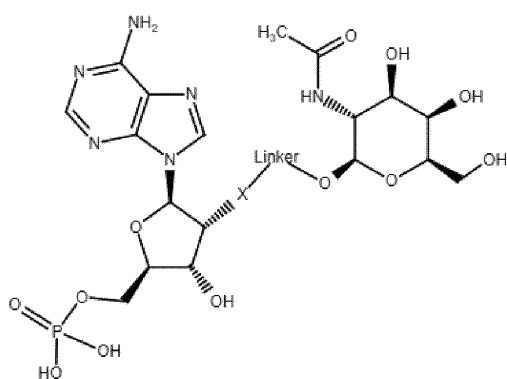
In some embodiments, one (1) or more (*e.g.*, 1, 2, 3, 4, 5, or 6) nucleotides of an oligonucleotide described herein (*e.g.*, an RNAi oligonucleotide) are each conjugated to a GalNAc moiety. In some embodiments, two (2) to four (4) nucleotides of a tetraloop are each conjugated to a separate GalNAc moiety. In some embodiments, one (1) to three (3) nucleotides of a triloop are each conjugated to a separate GalNAc moiety. In some embodiments, targeting ligands are conjugated to two (2) to four (4) nucleotides at either ends of the sense or antisense strand (*e.g.*, ligands are conjugated to a two (2) to four (4) nucleotide overhang or extension on the 5' or 3' terminus of the sense or antisense strand) such that the GalNAc moieties resemble bristles of a toothbrush and the oligonucleotide resembles a toothbrush. In some embodiments,

GalNAc moieties are conjugated to a nucleotide of the sense strand. For example, three (3) or four (4) GalNAc moieties can be conjugated to nucleotides in the tetraloop of the sense strand where each GalNAc moiety is conjugated to one (1) nucleotide.

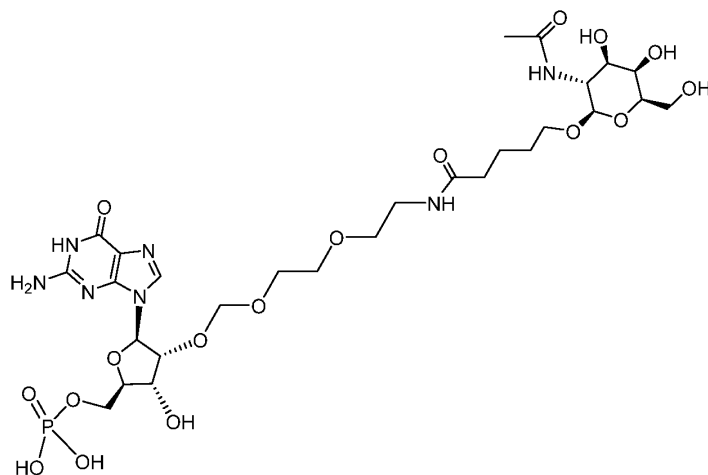
In some embodiments, an oligonucleotide described herein (e.g., an RNAi oligonucleotide) comprises a tetraloop, wherein the tetraloop (L) is any combination of adenine (A) and guanine (G) nucleotides. In some embodiments, the tetraloop (L) comprises a monovalent GalNAc moiety attached to any one or more guanine (G) nucleotides of the tetraloop *via* any linker described herein, as depicted below (X = heteroatom):



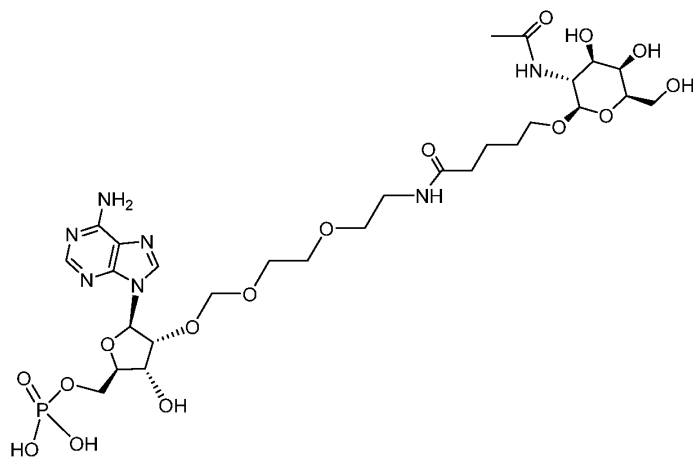
In some embodiments, the tetraloop (L) has a monovalent GalNAc attached to any one or more adenine nucleotides of the tetraloop *via* any linker described herein, as depicted below (X = heteroatom):



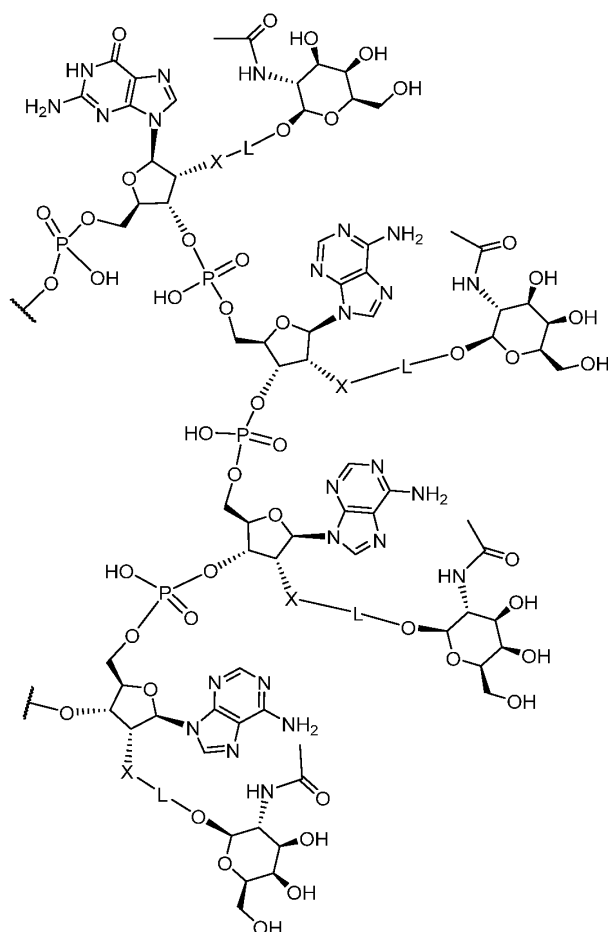
In some embodiments, an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) comprises a monovalent GalNAc moiety attached to a guanine (G) nucleotide referred to as [ademG-GalNAc] or 2'-aminodiethoxymethanol-Guanine-GalNAc, as depicted below:



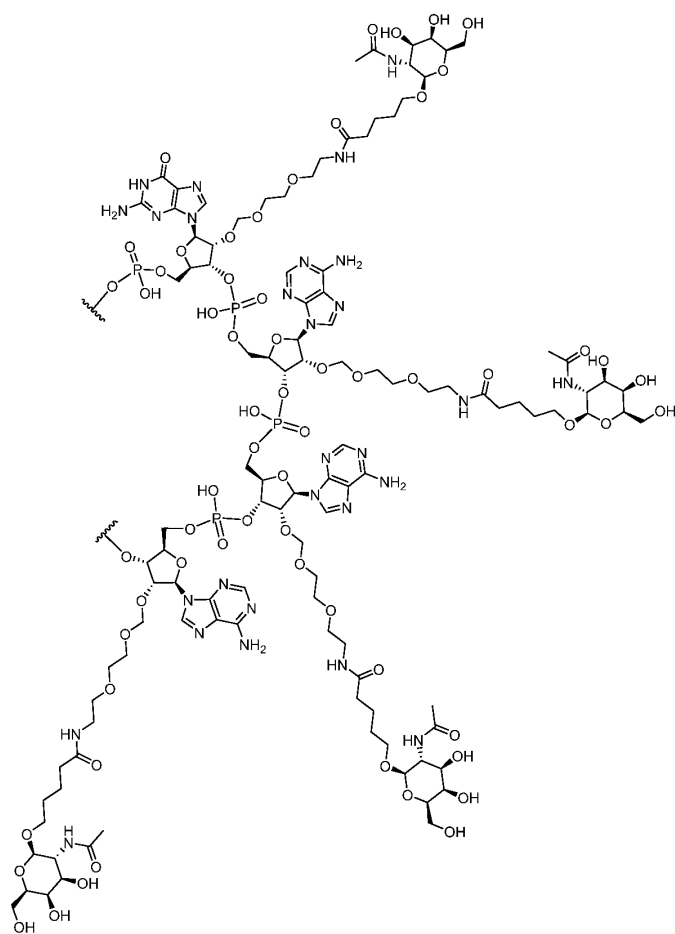
In some embodiments, an oligonucleotide herein comprises a monovalent GalNAc moiety attached to an adenine nucleotide, referred to as [ademA-GalNAc] or 2'-aminodiethoxymethanol-Adenine-GalNAc, as depicted below:



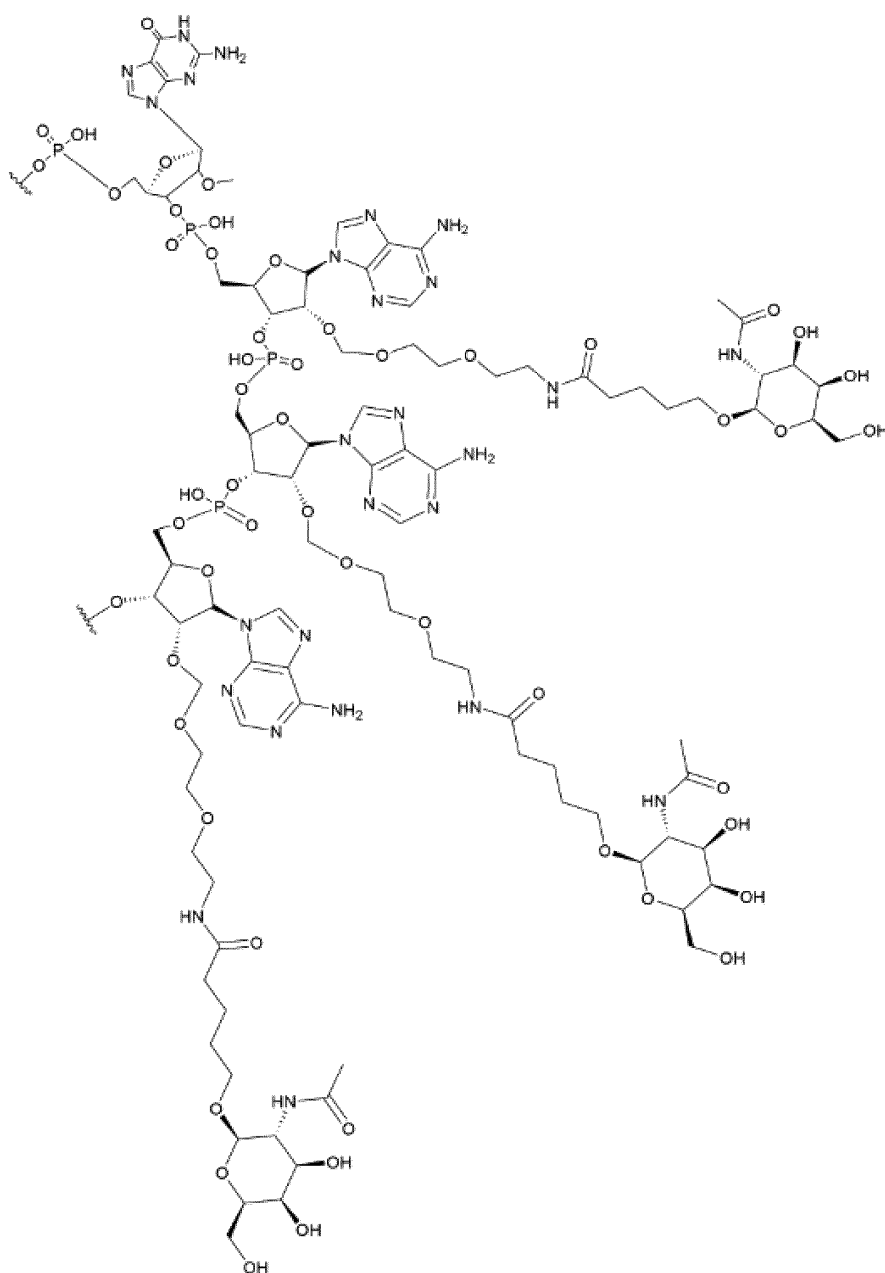
An example of such conjugation is shown below for a loop comprising from 5' to 3' the nucleotide sequence GAAA (L = linker, X = heteroatom). Such a loop may be present, for example, at positions 27-30 of a sense strand provided herein. In the chemical formula, $\frac{3}{2}$ is used to describe an attachment point to the oligonucleotide strand.



Appropriate methods or chemistry (*e.g.*, click chemistry) can be used to link a targeting ligand to a nucleotide. In some embodiments, a targeting ligand is conjugated to a nucleotide comprising an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) using a click linker. In some embodiments, an acetal-based linker is used to conjugate a targeting ligand to a nucleotide of any one of the oligonucleotides described herein. Acetal-based linkers are disclosed, for example, in Intl. Patent Application Publication No. WO2016/100401. In some embodiments, the linker is a labile linker. However, in other embodiments, the linker is stable. An example is shown below for a loop comprising from 5' to 3' the nucleotides GAAA, in which GalNAc moieties are attached to nucleotides of the loop using an acetal linker. Such a loop may be present, for example, at positions 27-30 of the any one of the sense strands. In the chemical formula,  is an attachment point to the oligonucleotide strand.



or



As mentioned, various appropriate methods or chemistry synthetic techniques (*e.g.*, click chemistry) can be used to link a targeting ligand to a nucleotide. In some embodiments, a targeting ligand is conjugated to a nucleotide using a click linker. In some embodiments, an acetal-based linker is used to conjugate a targeting ligand to a nucleotide of any one of the oligonucleotides described herein. Acetal-based linkers are disclosed, for example, in Intl.

Patent Application Publication No. WO 2016/100401. In some embodiments, the linker is a labile linker. However, in other embodiments, the linker is a stable linker.

In some embodiments, a duplex extension (*e.g.*, of up to 3, 4, 5, or 6 bp in length) is provided between a targeting ligand (*e.g.*, a GalNAc moiety) and the oligonucleotide. In some embodiments, the oligonucleotides herein (*e.g.*, RNAi oligonucleotides) do not have a GalNAc conjugated thereto.

In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;

- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively,

wherein the oligonucleotide comprises at least one GalNAc moiety conjugated to a nucleotide.

In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotides sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1543 and 1579, respectively;
- (b) SEQ ID NOs: 1560 and 1596, respectively;
- (c) SEQ ID NOs: 1568 and 1604, respectively; and,
- (d) SEQ ID NOs: 1553 and 1589, respectively,

wherein the oligonucleotide comprises at least one GalNAc moiety conjugated to a nucleotide.

Exemplary Oligonucleotides for Reducing MARC1 Expression

In some embodiments, the *MARC1*-targeting dsRNAi oligonucleotide for reducing *MARC1* expression provided by the current invention comprise a sense strand and an antisense strand, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the antisense strand comprises a region of complementarity to a *MARC1* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is at least 15 contiguous nucleotides in length. In some embodiments, the 5'-terminal nucleotide of the antisense strand comprises 5'-methoxyphosphonate-4'-oxy-2'-O-methyluridine [MePhosphonate-4O-mU], as described herein. In some embodiments, the 5'-terminal nucleotide of the antisense strand comprises a phosphorothioate linkage. In some embodiments, the antisense strand and the sense strand comprise one or more 2'-fluoro (2'-F) and 2'-O-methyl (2'-OMe) modified nucleotides and at least one phosphorothioate linkage. In some embodiments, the antisense strand comprises four (4) phosphorothioate linkages and the sense strand comprises one (1) phosphorothioate linkage. In some embodiments, the antisense strand comprises five (5) phosphorothioate linkages and the sense strand comprises one (1) phosphorothioate linkage.

In some embodiments, an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) comprises a sense strand having a sequence of any one of SEQ ID NOs: 769-1152 and an antisense strand comprising a complementary sequence selected from SEQ ID NOs: 1153-1536.

In some embodiments, an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) comprises a sense strand having a sequence of any one of SEQ ID NOs: 1537-1570 and an antisense strand comprising a complementary sequence selected from SEQ ID NOs: 1573-1606.

In some embodiments, an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) comprises a sense strand having a sequence of any one of SEQ ID NOs: 1609-1642 and an antisense strand comprising a complementary sequence selected from SEQ ID NOs: 1645-1678.

In some embodiments, an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) for reducing *MARCI* expression comprises:

a sense strand comprising a 2'-F modified nucleotide at positions 8-11, a 2'-OMe modified nucleotide at positions 1-7, 12-27, and 31-36, a GalNAc-conjugated nucleotide at position 28, 29, and 30; and a phosphorothioate linkage between positions 1 and 2;

an antisense strand comprising a 2'-F modified nucleotide at positions 2, 3, 4, 5, 7, 10 and 14, a 2'-OMe at positions 1, 6, 8, 9, 11-13, and 15-22, a phosphorothioate linkage between positions 1 and 2, positions 2 and 3, positions 3 and 4, positions 20 and 21, and positions 21 and 22, and a 5'-terminal nucleotide at position 1 comprising a 4'-phosphate analog, optionally wherein the 5'-terminal nucleotide comprises 5'-methoxyphosphonate-4'-oxy-2'-O-methyluridine [MePhosphonate-4O-mU]; wherein positions 1-20 of the antisense strand form a duplex region with positions 1-20 of the sense strand, wherein positions 21-36 of the sense strand form a stem-loop, wherein positions 27-30 form the loop of the stem-loop, optionally wherein positions 27-30 comprise a tetraloop, wherein positions 21 and 22 of the antisense strand comprise an overhang, and wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;

- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively;

In some embodiments, the *MARCI*-targeting dsRNAi oligonucleotides for reducing *MARCI* expression comprise:

a sense strand comprising a 2'-F modified nucleotide at positions 8-11, a 2'-OMe modified nucleotide at positions 1-7, 12-27, and 31-36, a GalNAc-conjugated nucleotide at position 28, 29 and 30; and a phosphorothioate linkage between positions 1 and 2;

an antisense strand comprising a 2'-F modified nucleotide at positions 2, 3, 4, 5, 7, 10, and 14, a 2'-OMe at positions 1, 6, 8, 9, 11-13, and 15-22, a phosphorothioate linkage between positions 1 and 2, positions 2 and 3, positions 3 and 4, positions 20 and 21, and positions 21 and 22, and a 5'-terminal nucleotide at position 1 comprising a 4'-phosphate analog, optionally wherein the 5'-terminal nucleotide comprises 5'-methoxyphosphonate-4'-oxy-2'-O-methyluridine [MePhosphonate-4O-mU]; wherein positions 1-20 of the antisense strand form a duplex region with positions 1-20 of the sense strand, wherein positions 21-36 of the sense strand form a stem-loop, wherein positions 27-30 form the loop of the stem-loop, optionally wherein positions 27-30 comprise a tetraloop, wherein positions 21 and 22 of the antisense strand comprise an overhang, and wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1543 and 1579, respectively;
- (b) SEQ ID NOs: 1560 and 1596, respectively;
- (c) SEQ ID NOs: 1568 and 1604, respectively; and,
- (d) SEQ ID NOs: 1553 and 1589, respectively.

In some embodiments, a *MARCI*-targeting oligonucleotide for reducing *MARCI* expression provided by the current invention comprises a sense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1543 and an antisense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1579. In some embodiments, a *MARCI*-targeting oligonucleotide for reducing *MARCI* expression provided by the current invention comprises a sense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1560 and an antisense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1596. In some embodiments, a *MARCI*-targeting oligonucleotide for reducing *MARCI* expression provided by the current invention comprises a sense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1568 and an antisense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1604. In some embodiments, a *MARCI*-targeting oligonucleotide for reducing *MARCI* expression provided by the current invention comprises a sense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1553 and an antisense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1589.

In some embodiments, a *MARCI*-targeting dsRNAi oligonucleotide for reducing *MARCI* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARCI* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 618; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of

complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 682; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 740; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 760; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 618; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a

loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 682; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 740; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 760; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 618; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 234, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 682; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 298, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 740; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 356, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 760; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 376, wherein the antisense and sense strands are

separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 618; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 234, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 682; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 298, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 740; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 356, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and

sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, a MARC1-targeting dsRNAi oligonucleotide for reducing *MARC1* expression comprises (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is set forth in SEQ ID NO: 760; and (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand and a stem-loop at the 3' terminus, wherein the region of complementarity to the antisense strand is set forth in SEQ ID NO: 376, wherein the stem-loop is set forth as S1-L-S2, wherein S1 is complementary to S2 and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

In some embodiments, the current invention provides an oligonucleotide (e.g., an RNAi oligonucleotide) for reducing *MARC1* expression, wherein the oligonucleotide comprises a sense strand and an antisense strand according to:

Sense Strand: 5'-mX-S-mX-mX-mX-mX-mX-mX-fX-fX-fX-fX-mX-mX-mX-mX-mX-mX-mX-mX-mX-mX-mX-mX-mX-mX-mX-mX-mX-mX-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mX-mX-mX-mX-mX-mX-3';

hybridized to:

Antisense Strand: 5'-[MePhosphonate-4O-mX]-S-fX-S-fX-S-fX-fX-mX-fX-mX-mX-fX-mX-mX-mX-fX-mX-mX-mX-mX-mX-mX-mX-S-mX-S-mX-3';

wherein mX = 2'-O-methyl modified nucleotide, fX = 2'-fluoro modified nucleotide, -S- = phosphorothioate linkage, - = phosphodiester linkage, [MePhosphonate-4O-mX] = 5'-methoxyphosphonate-4-oxy modified nucleotide, and ademA-GalNAc = GalNAc attached to an adenine nucleotide.

In some embodiments, the current invention provides an oligonucleotide (e.g., an RNAi oligonucleotide) for reducing *MARC1* expression, wherein the oligonucleotide comprises a sense strand and an antisense strand comprising nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1609 and 1645, respectively;
- (b) SEQ ID NOs: 1610 and 1646, respectively;
- (c) SEQ ID NOs: 1611 and 1647, respectively;
- (d) SEQ ID NOs: 1612 and 1648, respectively;

- (e) SEQ ID NOs: 1613 and 1649, respectively;
- (f) SEQ ID NOs: 1614 and 1650, respectively;
- (g) SEQ ID NOs: 1615 and 1651, respectively;
- (h) SEQ ID NOs: 1616 and 1652, respectively;
- (i) SEQ ID NOs: 1617 and 1653, respectively;
- (j) SEQ ID NOs: 1618 and 1654, respectively;
- (k) SEQ ID NOs: 1619 and 1655, respectively;
- (l) SEQ ID NOs: 1620 and 1656, respectively;
- (m) SEQ ID NOs: 1621 and 1657, respectively;
- (n) SEQ ID NOs: 1622 and 1658, respectively;
- (o) SEQ ID NOs: 1623 and 1659, respectively;
- (p) SEQ ID NOs: 1624 and 1660, respectively;
- (q) SEQ ID NOs: 1625 and 1661, respectively;
- (r) SEQ ID NOs: 1626 and 1662, respectively;
- (s) SEQ ID NOs: 1627 and 1663, respectively;
- (t) SEQ ID NOs: 1628 and 1664, respectively;
- (u) SEQ ID NOs: 1628 and 1665, respectively;
- (v) SEQ ID NOs: 1630 and 1666, respectively;
- (w) SEQ ID NOs: 1631 and 1667, respectively;
- (x) SEQ ID NOs: 1632 and 1668, respectively;
- (y) SEQ ID NOs: 1633 and 1669, respectively;
- (z) SEQ ID NOs: 1634 and 1670, respectively;
- (aa) SEQ ID NOs: 1635 and 1671, respectively;
- (bb) SEQ ID NOs: 1636 and 1672, respectively;
- (cc) SEQ ID NOs: 1637 and 1673, respectively;
- (dd) SEQ ID NOs: 1638 and 1674, respectively;
- (ee) SEQ ID NOs: 1639 and 1675, respectively;
- (ff) SEQ ID NOs: 1640 and 1676, respectively;
- (gg) SEQ ID NOs: 1641 and 1677, respectively; and,
- (hh) SEQ ID NOs: 1642 and 1678, respectively;

In some embodiments, a *MARCI*-targeting oligonucleotide for reducing *MARCI* expression provided by the current invention comprises a sense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1615 and an antisense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1651. In some embodiments, a *MARCI*-

targeting oligonucleotide for reducing *MARCI* expression provided by the current invention comprises a sense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1632 and an antisense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1668. In some embodiments, a *MARCI*-targeting oligonucleotide for reducing *MARCI* expression provided by the current invention comprises a sense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1640 and an antisense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1676. In some embodiments, a *MARCI*-targeting oligonucleotide for reducing *MARCI* expression provided by the current invention comprises a sense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1625 and an antisense strand comprising the nucleotide sequence as set forth in SEQ ID NO: 1661.

Formulations

Various formulations (e.g., pharmaceutical formulations) have been developed for oligonucleotide use. For example, oligonucleotides (e.g., RNAi oligonucleotides) can be delivered to a subject or a cellular environment using a formulation that minimizes degradation, facilitates delivery and/or uptake, or provides another beneficial property to the oligonucleotides in the formulation. In some embodiments, provided herein are compositions comprising oligonucleotides (e.g., RNAi oligonucleotides) reduce the expression of *MARCI*. Such compositions can be suitably formulated such that when administered to a subject, either into the immediate environment of a target cell or systemically, a sufficient portion of the oligonucleotides enter the cell to reduce *MARCI* expression. Any variety of suitable oligonucleotide formulations can be used to deliver oligonucleotides for the reduction of *MARCI* as disclosed herein. In some embodiments, an oligonucleotide is formulated in buffer solutions such as PBS solutions, liposomes, micellar structures, and capsids. Any of the oligonucleotides described herein may be provided not only as nucleic acids, but also in the form of a pharmaceutically acceptable salt.

Formulations of oligonucleotides with cationic lipids can be used to facilitate transfection of the oligonucleotides into cells. For example, cationic lipids, such as lipofectin, cationic glycerol derivatives, and polycationic molecules (e.g., polylysine), can be used. Suitable lipids include Oligofectamine, Lipofectamine (Life Technologies), NC388 (Ribozyme Pharmaceuticals, Inc., Boulder, Colo.), or FuGene 6 (Roche) all of which can be used according to the manufacturer's instructions.

Accordingly, in some embodiments, a formulation comprises a lipid nanoparticle. In some embodiments, an excipient comprises a liposome, a lipid, a lipid complex, a microsphere,

a microparticle, a nanosphere or a nanoparticle, or may be otherwise formulated for administration to the cells, tissues, organs, or body of a subject in need thereof (*see, e.g., Remington: THE SCIENCE AND PRACTICE OF PHARMACY*, 22nd edition, Pharmaceutical Press, 2013).

In some embodiments, the formulations herein comprise an excipient. In some embodiments, an excipient confers to a composition improved stability, improved absorption, improved solubility and/or therapeutic enhancement of the active ingredient. In some embodiments, an excipient is a buffering agent (*e.g.,* sodium citrate, sodium phosphate, a tris base, or sodium hydroxide) or a vehicle (*e.g.,* a buffered solution, petrolatum, dimethyl sulfoxide, or mineral oil). In some embodiments, an oligonucleotide is lyophilized for extending its shelf-life and then made into a solution before use (*e.g.,* administration to a subject). Accordingly, an excipient in a composition comprising any one of the oligonucleotides described herein may be a lyoprotectant (*e.g.,* mannitol, lactose, polyethylene glycol or polyvinylpyrrolidone) or a collapse temperature modifier (*e.g.,* dextran, Ficoll™ or gelatin).

In some embodiments, a pharmaceutical composition is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral (*e.g.,* intravenous, intramuscular, intraperitoneal, intradermal, subcutaneous), oral (*e.g.,* inhalation), transdermal (*e.g.,* topical), transmucosal and rectal administration.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or PBS. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.,* glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Sterile injectable solutions can be prepared by incorporating the oligonucleotides in a required amount in a selected solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization.

In some embodiments, a composition may contain at least about 0.1% of the therapeutic agent (*e.g.,* a RNAi oligonucleotide for reducing *MARCI* expression) or more, although the percentage of the active ingredient(s) may be between about 1% to about 80% or more of the weight or volume of the total composition. Factors such as solubility, bioavailability, biological

half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

Methods of Use

Reducing MARC1 Expression

In some embodiments, the current invention provides methods for contacting or delivering to a cell or population of cells an effective amount of oligonucleotides provided herein (e.g., RNAi oligonucleotides) to reduce *MARC1* expression. In some embodiments, a reduction of *MARC1* expression is determined by measuring a reduction in the amount or level of *MARC1* mRNA, MARC1 protein, or MARC1 activity in a cell. The methods include those described herein and known to one of ordinary skill in the art.

Methods provided herein are useful in any appropriate cell type. In some embodiments, a cell is any cell that expresses *MARC1* mRNA (e.g., hepatocytes). In some embodiments, the cell is a primary cell obtained from a subject. In some embodiments, the primary cell has undergone a limited number of passages such that the cell substantially maintains its natural phenotypic properties. In some embodiments, a cell to which the oligonucleotide is delivered is *ex vivo* or *in vitro* (i.e., can be delivered to a cell in culture or to an organism in which the cell resides).

In some embodiments, the oligonucleotides herein (e.g., RNAi oligonucleotides) are delivered to a cell or population of cells using a nucleic acid delivery method known in the art including, but not limited to, injection of a solution containing the oligonucleotides, bombardment by particles covered by the oligonucleotides, exposing the cell or population of cells to a solution containing the oligonucleotides, or electroporation of cell membranes in the presence of the oligonucleotides. Other methods known in the art for delivering oligonucleotides to cells may be used, such as lipid-mediated carrier transport, chemical-mediated transport, and cationic liposome transfection such as calcium phosphate, and others.

In some embodiments, reduction of *MARC1* expression is determined by an assay or technique that evaluates one or more molecules, properties, or characteristics of a cell or population of cells associated with *MARC1* expression, or by an assay or technique that evaluates molecules that are directly indicative of *MARC1* expression in a cell or population of cells (e.g., *MARC1* mRNA or MARC1 protein). In some embodiments, the extent to which an oligonucleotide provided herein reduces *MARC1* expression is evaluated by comparing *MARC1* expression in a cell or population of cells contacted with the oligonucleotide to an

appropriate control (*e.g.*, an appropriate cell or population of cells not contacted with the oligonucleotide or contacted with a control oligonucleotide). In some embodiments, a control amount or level of *MARCI* expression in a control cell or population of cells is predetermined, such that the control amount or level need not be measured in every instance the assay or technique is performed. The predetermined level or value can take a variety of forms. In some embodiments, a predetermined level or value can be single cut-off value, such as a median or mean.

In some embodiments, contacting or delivering an oligonucleotide described herein (*e.g.*, an RNAi oligonucleotide) to a cell or a population of cells results in a reduction in *MARCI* expression in a cell or population of cells not contacted with the oligonucleotide or contacted with a control oligonucleotide. In some embodiments, the reduction in *MARCI* expression is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40% or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower relative to a control amount or level of *MARCI* expression. In some embodiments, the control amount or level of *MARCI* expression is an amount or level of *MARCI* mRNA and/or MARC1 protein in a cell or population of cells that has not been contacted with an oligonucleotide herein. In some embodiments, the effect of delivery of an oligonucleotide herein to a cell or population of cells according to a method herein is assessed after any finite period or amount of time (*e.g.*, minutes, hours, days, weeks, months). For example, in some embodiments, *MARCI* expression is determined in a cell or population of cells at least about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 24 hours; or at least about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 21 days, about 28 days, about 35 days, about 42 days, about 49 days, about 56 days, about 63 days, about 70 days, about 77 days, or about 84 days or more after contacting or delivering the oligonucleotide to the cell or population of cells. In some embodiments, *MARCI* expression is determined in a cell or population of cells at least about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, or about 6 months or more after contacting or delivering the oligonucleotide to the cell or population of cells.

In some embodiments, an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide) is delivered in the form of a transgene that is engineered to express in a cell the oligonucleotide or strands comprising the oligonucleotide (*e.g.*, its sense and antisense

strands). In some embodiments, an oligonucleotide herein is delivered using a transgene engineered to express any oligonucleotide disclosed herein. Transgenes may be delivered using viral vectors (*e.g.*, adenovirus, retrovirus, vaccinia virus, poxvirus, adeno-associated virus, or herpes simplex virus) or non-viral vectors (*e.g.*, plasmids or synthetic mRNAs). In some embodiments, transgenes can be injected directly to a subject.

Treatment Methods

The current invention provides oligonucleotides (*e.g.*, RNAi oligonucleotides) for use as a medicament, in particular for use in a method for the treatment of diseases, disorders, and conditions associated with expression of *MARCI*. The current invention also provides oligonucleotides for use, or adaptable for use, to treat a subject (*e.g.*, a human having a disease, disorder or condition associated with *MARCI* expression) that would benefit from reducing *MARCI* expression. In some respects, the current invention provides oligonucleotides for use, or adapted for use, to treat a subject having a disease, disorder or condition associated with expression of *MARCI*. The current invention also provides oligonucleotides for use, or adaptable for use, in the manufacture of a medicament or pharmaceutical composition for treating a disease, disorder or condition associated with *MARCI* expression. In some embodiments, the oligonucleotides for use, or adaptable for use, target *MARCI* mRNA and reduce *MARCI* expression (*e.g.*, *via* the RNAi pathway). In some embodiments, the oligonucleotides for use, or adaptable for use, target *MARCI* mRNA and reduce the amount or level of *MARCI* mRNA, MARC1 protein and/or *MARCI* activity.

In addition, in some embodiments of the methods herein, a subject having a disease, disorder, or condition associated with *MARCI* expression or is predisposed to the same is selected for treatment with an oligonucleotide provided herein (*e.g.*, an RNAi oligonucleotide). In some embodiments, the method comprises selecting an individual having a marker (*e.g.*, a biomarker) for a disease, disorder, or condition associated with *MARCI* expression or predisposed to the same, such as, but not limited to, *MARCI* mRNA, MARC1 protein, or a combination thereof. Likewise, and as detailed below, some embodiments of the methods provided by the current invention include steps such as measuring or obtaining a baseline value for a marker of *MARCI* expression (*e.g.*, *MARCI* mRNA), and then comparing such obtained value to one or more other baseline values or values obtained after the subject is administered the oligonucleotide to assess the effectiveness of treatment.

The current invention also provides methods of treating a subject having, suspected of having, or at risk of developing a disease, disorder or condition associated with *MARCI*

expression with an oligonucleotide provided herein. In some aspects, the current invention provides methods of treating or attenuating the onset or progression of a disease, disorder or condition associated with *MARCI* expression using the oligonucleotides herein. In other aspects, the current invention provides methods to achieve one or more therapeutic benefits in a subject having a disease, disorder, or condition associated with *MARCI* expression using the oligonucleotides provided herein. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of any one or more of the oligonucleotides provided herein. In some embodiments, treatment comprises reducing *MARCI* expression. In some embodiments, the subject is treated therapeutically. In some embodiments, the subject is treated prophylactically.

In some embodiments of the methods herein, one or more oligonucleotides herein (e.g., RNAi oligonucleotides), or a pharmaceutical composition comprising one or more oligonucleotides, is administered to a subject having a disease, disorder or condition associated with *MARCI* expression such that *MARCI* expression is reduced in the subject, thereby treating the subject. In some embodiments, an amount or level of *MARCI* mRNA is reduced in the subject. In some embodiments, an amount or level of MARC1 protein is reduced in the subject. In some embodiments, an amount or level of *MARCI* activity is reduced in the subject.

In some embodiments of the methods herein, an oligonucleotide provided herein (e.g., an RNAi oligonucleotide), or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *MARCI* such that *MARCI* expression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to *MARCI* expression prior to administration of one or more oligonucleotides or pharmaceutical composition. In some embodiments, *MARCI* expression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to *MARCI* expression in a subject (e.g., a reference or control subject) not receiving the oligonucleotide or oligonucleotides or pharmaceutical composition or receiving a control oligonucleotide or oligonucleotides, pharmaceutical composition or treatment.

In some embodiments of the methods herein, an oligonucleotide or oligonucleotides herein (e.g., RNAi oligonucleotides), or a pharmaceutical composition comprising the oligonucleotide or oligonucleotides, is administered to a subject having a disease, disorder or

condition associated with *MARCI* expression such that an amount or level of *MARCI* mRNA is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to the amount or level of *MARCI* mRNA prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of *MARCI* mRNA is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of *MARCI* mRNA in a subject (e.g., a reference or control subject) not receiving the oligonucleotide or oligonucleotides or pharmaceutical composition or receiving a control oligonucleotide or oligonucleotides, pharmaceutical composition or treatment.

In some embodiments of the methods herein, an oligonucleotide or oligonucleotides herein, or a pharmaceutical composition comprising the oligonucleotide or oligonucleotides, is administered to a subject having a disease, disorder or condition associated with *MARCI* expression such that an amount or level of MARC1 protein is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to the amount or level of MARC1 protein prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of MARC1 protein is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of MARC1 protein in a subject (e.g., a reference or control subject) not receiving the oligonucleotide or oligonucleotides or pharmaceutical composition or receiving a control oligonucleotide, oligonucleotides or pharmaceutical composition or treatment.

In some embodiments of the methods herein, an oligonucleotide or oligonucleotides (e.g., RNAi oligonucleotides) herein, or a pharmaceutical composition comprising the oligonucleotide or oligonucleotides, is administered to a subject having a disease, disorder or condition associated with *MARCI* such that an amount or level of *MARCI* gene activity/expression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to the amount or level of *MARCI* activity prior to administration of the oligonucleotide or

pharmaceutical composition. In some embodiments, an amount or level of *MARCI* activity is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of *MARCI* activity in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

Suitable methods for determining *MARCI* expression, the amount or level of *MARCI* mRNA, MARC1 protein, *MARCI* activity, or a biomarker related to or affected by modulation of *MARCI* expression (*e.g.*, a plasma biomarker), in the subject, or in a sample from the subject, are known in the art. Further, the Examples set forth herein illustrate methods for determining *MARCI* expression.

In some embodiments, *MARCI* expression, the amount or level of *MARCI* mRNA, MARC1 protein, *MARCI* activity, or a biomarker related to or affected by modulation of *MARCI* expression, or any combination thereof, is reduced in a cell (*e.g.*, a hepatocyte), a population or a group of cells (*e.g.*, an organoid), an organ (*e.g.*, liver), blood or a fraction thereof (*e.g.*, plasma), a tissue (*e.g.*, liver tissue), a sample (*e.g.*, a liver biopsy sample), or any other appropriate biological material obtained or isolated from the subject. In some embodiments, *MARCI* expression, the amount or level of *MARCI* mRNA, MARC1 protein, *MARCI* activity, or a biomarker related to or affected by modulation of *MARCI* expression, or any combination thereof, is reduced in more than one type of cell (*e.g.*, a hepatocyte and one or more other type(s) of cell), more than one groups of cells, more than one organ (*e.g.*, liver and one or more other organ(s)), more than one fraction of blood (*e.g.*, plasma and one or more other blood fraction(s)), more than one type of tissue (*e.g.*, liver tissue and one or more other type(s) of tissue), or more than one type of sample (*e.g.*, a liver biopsy sample and one or more other type(s) of biopsy sample).

Because of their high specificity, the oligonucleotides provided herein (*e.g.*, dsRNAi oligonucleotides) specifically target mRNA of target genes (*e.g.*, *MARCI* mRNA) of cells and tissue(s), or organs(s) (*e.g.*, in the liver). In preventing disease, the target gene may be one which is required for initiation or maintenance of the disease or which has been identified as being associated with a higher risk of contracting the disease. In treating disease, the oligonucleotide can be brought into contact with the cells, tissue(s), or organ(s) (*e.g.*, liver) exhibiting or responsible for mediating the disease. For example, an oligonucleotide (*e.g.*, an RNAi oligonucleotide) substantially identical to all or part of a wild-type (*i.e.*, native) or

mutated gene associated with a disorder or condition associated with *MARCI* expression may be brought into contact with or introduced into a cell or tissue type of interest such as a hepatocyte or other liver cell.

Examples of a disease, disorder or condition associated with *MARCI* expression include, but are not limited to non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), or metabolic syndrome. In some embodiments, the disease is NAFLD. In some embodiments, the disease is NASH. In some embodiments, the disease is ASH.

In some embodiments, an amount or level of liver steatosis is reduced in a subject. In some embodiments, an amount or level of liver fibrosis is reduced in a subject. In some embodiments, an amount or level of cholesterol is reduced in a subject. In some embodiments, an amount or level of triglyceride is reduced in a subject. In some embodiments, an amount or level of alanine aminotransferase is reduced in a subject. In some embodiments, an amount or level of aspartate aminotransferase is reduced in a subject. In some embodiments, any combination of the following is reduced or altered in the subject: *MARCI* expression, an amount or level of *MARCI* mRNA, an amount or level of MARC1 protein, an amount or level of *MARCI* activity, an amount or level of TG, an amount or level of cholesterol and/or the ratio of total cholesterol to HDL cholesterol, an amount or level of liver steatosis, an amount or level of liver fibrosis, an amount or level of alanine aminotransferase, and an amount or level of aspartate aminotransferase.

In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *MARCI* expression such that an amount or level of liver fibrosis is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to the amount or level of liver fibrosis prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of liver fibrosis is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of liver fibrosis in a subject (e.g., a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

In some embodiments of the methods herein, an oligonucleotide herein, or a

pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *MARCI* expression such that an amount or level of liver steatosis is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to the amount or level of liver steatosis prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of liver steatosis is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of liver steatosis in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *MARCI* expression such that an amount or level of alanine aminotransferase is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to the amount or level of alanine aminotransferase prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of alanine aminotransferase is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of alanine aminotransferase in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *MARCI* expression such that an amount or level of aspartate aminotransferase is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to the amount or level of aspartate aminotransferase prior to administration of the

oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of aspartate aminotransferase is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of aspartate aminotransferase in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *MARCI* expression such that an amount or level of triglyceride is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to the amount or level of triglyceride prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of triglyceride is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of triglyceride in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with *MARCI* expression such that an amount or level of cholesterol (*e.g.*, total cholesterol, LDL cholesterol, and/or HDL cholesterol) is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to the amount or level of cholesterol prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of cholesterol is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of cholesterol in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

In some embodiments, the target gene may be a target gene from any mammal, such as a human target. Any target gene may be silenced according to the method described herein.

Methods described herein typically involve administering to a subject an effective amount of an oligonucleotide herein (*e.g.*, a RNAi oligonucleotide), that is, an amount that produces or generates a desirable therapeutic result. A therapeutically acceptable amount may be an amount that therapeutically treats a disease or disorder. The appropriate dosage for any one subject will depend on certain factors, including the subject's size, body surface area, age, the composition to be administered, the active ingredient(s) in the composition, time and route of administration, general health, and other drugs being administered concurrently.

In some embodiments, a subject is administered any one of the compositions herein (*e.g.*, a composition comprising an RNAi oligonucleotide described herein) either enterally (*e.g.*, orally, by gastric feeding tube, by duodenal feeding tube, *via* gastrostomy or rectally), parenterally (*e.g.*, subcutaneous injection, intravenous injection or infusion, intra-arterial injection or infusion, intraosseous infusion, intramuscular injection, intracerebral injection, intracerebroventricular injection, intrathecal), topically (*e.g.*, epicutaneous, inhalational, *via* eye drops, or through a mucous membrane), or by direct injection into a target organ (*e.g.*, the liver of a subject). Typically, oligonucleotides herein are administered intravenously or subcutaneously.

In some embodiments, an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide), or a pharmaceutical composition comprising the oligonucleotide, is administered alone or in combination. In some embodiments, the oligonucleotides herein are administered in combination concurrently, sequentially (in any order), or intermittently. For example, two oligonucleotides may be co-administered concurrently. Alternatively, one oligonucleotide may be administered and followed any amount of time later (*e.g.*, one hour, one day, one week or one month) by the administration of a second oligonucleotide.

In some embodiments, the subject to be treated is a human or non-human primate or other mammalian subject. Other exemplary subjects include domesticated animals such as dogs and cats; livestock such as horses, cattle, pigs, sheep, goats, and chickens; and animals such as mice, rats, guinea pigs, and hamsters.

Kits

In some embodiments, the current invention provides a kit comprising an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide), and instructions for use. In some embodiments, the kit comprises an oligonucleotide herein, and a package insert containing

instructions for use of the kit and/or any component thereof. In some embodiments, the kit comprises, in a suitable container, an oligonucleotide herein, one or more controls, and various buffers, reagents, enzymes and other standard ingredients well known in the art. In some embodiments, the container comprises at least one vial, well, test tube, flask, bottle, syringe, or other container means, into which the oligonucleotide is placed, and in some instances, suitably aliquoted. In some embodiments where an additional component is provided, the kit contains additional containers into which this component is placed. The kits can also include a means for containing the oligonucleotide and any other reagent in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which the desired vials are retained. Containers and/or kits can include labeling with instructions for use and/or warnings.

In some embodiments, a kit comprises an oligonucleotide herein (e.g., an RNAi oligonucleotide), and a pharmaceutically acceptable carrier, or a pharmaceutical composition comprising the oligonucleotide and instructions for treating or delaying progression of a disease, disorder or condition associated with *MARCI* expression in a subject in need thereof.

Definitions

As used herein, the term “antisense oligonucleotide” encompasses a nucleic acid-based molecule which has a sequence complementary to all or part of the target mRNA, in particular seed sequence thereby capable of forming a duplex with a mRNA. Thus, the term “antisense oligonucleotide”, as used herein, may be referred to as “complementary nucleic acid-based inhibitor”.

As used herein, “approximately” or “about,” as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

As used herein, “administer,” “administering,” “administration” and the like refers to providing a substance (e.g., an oligonucleotide) to a subject in a manner that is pharmacologically useful (e.g., to treat a disease, disorder, or condition in the subject).

As used herein, “attenuate,” “attenuating,” “attenuation” and the like refers to reducing or effectively halting. As a non-limiting example, one or more of the treatments herein may reduce or effectively halt the onset or progression of NAFLD or NASH in a subject. This

attenuation may be exemplified by, for example, a decrease in one or more aspects (*e.g.*, symptoms, tissue characteristics, and cellular, inflammatory, or immunological activity, *etc.*) of NAFLD, NASH, or ASH, no detectable progression (worsening) of one or more aspects of fatty liver disease, or no detectable aspects of NAFLD, NASH, or ASH) in a subject when they might otherwise be expected.

As used herein, “complementary” refers to a structural relationship between two nucleotides (*e.g.*, on two opposing nucleic acids or on opposing regions of a single nucleic acid strand) that permits the two nucleotides to form base pairs with one another. For example, a purine nucleotide of one nucleic acid that is complementary to a pyrimidine nucleotide of an opposing nucleic acid may base pair together by forming hydrogen bonds with one another. In some embodiments, complementary nucleotides can base pair in the Watson-Crick manner or in any other manner that allows for the formation of stable duplexes. In some embodiments, two nucleic acids may have regions of multiple nucleotides that are complementary with each other to form regions of complementarity, as described herein.

As used herein, “deoxyribonucleotide” refers to a nucleotide having a hydrogen in place of a hydroxyl at the 2' position of its pentose sugar when compared with a ribonucleotide. A modified deoxyribonucleotide is a deoxyribonucleotide having one or more modifications or substitutions of atoms other than at the 2' position, including modifications or substitutions in or of the sugar, phosphate group or base.

As used herein, “double-stranded oligonucleotide” or “ds oligonucleotide” refers to an oligonucleotide that is substantially in a duplex form. In some embodiments, the complementary base-pairing of duplex region(s) of a double-stranded oligonucleotide is formed between antiparallel sequences of nucleotides of covalently separate nucleic acid strands. In some embodiments, complementary base-pairing of duplex region(s) of a double-stranded oligonucleotide is formed between antiparallel sequences of nucleotides of nucleic acid strands that are covalently linked. In some embodiments, complementary base-pairing of duplex region(s) of a double-stranded oligonucleotide is formed from single nucleic acid strand that is folded (*e.g.*, *via* a hairpin) to provide complementary antiparallel sequences of nucleotides that base pair together. In some embodiments, a double-stranded oligonucleotide comprises two covalently separate nucleic acid strands that are fully duplexed with one another. However, in some embodiments, a double-stranded oligonucleotide comprises two covalently separate nucleic acid strands that are partially duplexed (*e.g.*, having overhangs at one or both ends). In some embodiments, a double-stranded oligonucleotide comprises antiparallel

sequence of nucleotides that are partially complementary, and thus, may have one or more mismatches, which may include internal mismatches or end mismatches.

As used herein, “duplex” in reference to nucleic acids (*e.g.*, oligonucleotides), refers to a structure formed through complementary base pairing of two antiparallel sequences of nucleotides.

As used herein, “excipient” refers to a non-therapeutic agent that may be included in a composition, for example, to provide or contribute to a desired consistency or stabilizing effect.

As used herein, “hepatocyte” or “hepatocytes” refers to cells of the parenchymal tissues of the liver. These cells make up about 70%-85% of the liver's mass and manufacture serum albumin, FBN and the prothrombin group of clotting factors (except for Factors 3 and 4). Markers for hepatocyte lineage cells include, but are not limited to, transthyretin (Ttr), glutamine synthetase (Glul), hepatocyte nuclear factor 1a (Hnf1a) and hepatocyte nuclear factor 4a (Hnf4a). Markers for mature hepatocytes may include, but are not limited to, cytochrome P450 (Cyp3a11), fumarylacetoacetate hydrolase (Fah), glucose 6-phosphate (G6p), albumin (Alb) and OC2-2F8. *See, e.g.*, Huch *et al.* (2013) NATURE 494:247-50.

As used herein, a “hepatotoxic agent” refers to a chemical compound, virus or other substance that is itself toxic to the liver or can be processed to form a metabolite that is toxic to the liver. Hepatotoxic agents may include, but are not limited to, carbon tetrachloride (CCl₄), acetaminophen (paracetamol), vinyl chloride, arsenic, chloroform, nonsteroidal anti-inflammatory drugs (such as aspirin and phenylbutazone).

As used herein, the term “*MARCI*” refers to Mitochondrial Amidoxime Reducing Component 1. MARC1 is a protein which catalyzes the reduction of molecules. “*MARCI*” may also refer to the gene which encodes the protein.

As used herein, “labile linker” refers to a linker that can be cleaved (*e.g.*, by acidic pH). A “stable linker” refers to a linker that cannot be cleaved.

As used herein, “liver inflammation” or “hepatitis” refers to a physical condition in which the liver becomes swollen, dysfunctional and/or painful, especially as a result of injury or infection, as may be caused by exposure to a hepatotoxic agent. Symptoms may include jaundice (yellowing of the skin or eyes), fatigue, weakness, nausea, vomiting, appetite reduction and weight loss. Liver inflammation, if left untreated, may progress to fibrosis, cirrhosis, liver failure or liver cancer.

As used herein, “liver fibrosis” “Liver Fibrosis” or “fibrosis of the liver” refers to an excessive accumulation in the liver of extracellular matrix proteins, which could include collagens (I, III, and IV), FBN, undulin, elastin, laminin, hyaluronan and proteoglycans

resulting from inflammation and liver cell death. Liver fibrosis, if left untreated, may progress to cirrhosis, liver failure or liver cancer.

As used herein, “loop” refers to an unpaired region of a nucleic acid (*e.g.*, oligonucleotide) that is flanked by two antiparallel regions of the nucleic acid that are sufficiently complementary to one another, such that under appropriate hybridization conditions (*e.g.*, in a phosphate buffer, in a cell), the two antiparallel regions, which flank the unpaired region, hybridize to form a duplex (referred to as a “stem”).

As used herein, “modified internucleotide linkage” refers to an internucleotide linkage having one or more chemical modifications when compared with a reference internucleotide linkage comprising a phosphodiester bond. In some embodiments, a modified nucleotide is a non-naturally occurring linkage. Typically, a modified internucleotide linkage confers one or more desirable properties to a nucleic acid in which the modified internucleotide linkage is present. For example, a modified internucleotide linkage may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, *etc.*

As used herein, “modified nucleotide” refers to a nucleotide having one or more chemical modifications when compared with a corresponding reference nucleotide selected from: adenine ribonucleotide, guanine ribonucleotide, cytosine ribonucleotide, uracil ribonucleotide, adenine deoxyribonucleotide, guanine deoxyribonucleotide, cytosine deoxyribonucleotide and thymidine deoxyribonucleotide. In some embodiments, a modified nucleotide is a non-naturally occurring nucleotide. In some embodiments, a modified nucleotide has one or more chemical modification in its sugar, nucleobase and/or phosphate group. In some embodiments, a modified nucleotide has one or more chemical moieties conjugated to a corresponding reference nucleotide. Typically, a modified nucleotide confers one or more desirable properties to a nucleic acid in which the modified nucleotide is present. For example, a modified nucleotide may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, *etc.*

As used herein, “nicked tetraloop structure” refers to a structure of a RNAi oligonucleotide that is characterized by separate sense (passenger) and antisense (guide) strands, in which the sense strand has a region of complementarity with the antisense strand, and in which at least one of the strands, generally the sense strand, has a tetraloop configured to stabilize an adjacent stem region formed within the at least one strand.

As used herein, “oligonucleotide” refers to a short nucleic acid (*e.g.*, less than about 100 nucleotides in length). An oligonucleotide may be single-stranded (ss) or ds. An

oligonucleotide may or may not have duplex regions. As a set of non-limiting examples, an oligonucleotide may be, but is not limited to, a small interfering RNA (siRNA), microRNA (miRNA), short hairpin RNA (shRNA), dicer substrate interfering RNA (DsiRNA), antisense oligonucleotide, short siRNA or ss siRNA. In some embodiments, a double-stranded (dsRNA) is an RNAi oligonucleotide.

As used herein, “overhang” refers to terminal non-base pairing nucleotide(s) resulting from one strand or region extending beyond the terminus of a complementary strand with which the one strand or region forms a duplex. In some embodiments, an overhang comprises one or more unpaired nucleotides extending from a duplex region at the 5' terminus or 3' terminus of an oligonucleotide. In certain embodiments, the overhang is a 3'- or 5'-overhang on the antisense strand or sense strand of an oligonucleotide.

As used herein, “phosphate analog” refers to a chemical moiety that mimics the electrostatic and/or steric properties of a phosphate group. In some embodiments, the phosphate analog mimics the electrostatic and/or steric properties of a phosphate group in biologic systems. In some embodiments, a phosphate analog is positioned at the 5'-terminal nucleotide of an oligonucleotide in place of a 5'-phosphate, which is often susceptible to enzymatic removal. In some embodiments, a 5'-phosphate analog contains a phosphatase-resistant linkage. Examples of phosphate analogs include, but are not limited to, 5'-phosphonates, such as 5'-methylene phosphonate (5'-MP) and 5'-(E)-vinylphosphonate (5'-VP). In some embodiments, an oligonucleotide has a phosphate analog at a 4'-carbon position of the sugar (referred to as a “4'-phosphate analog”) at a 5'-terminal nucleotide. An example of a 4'-phosphate analog is oxymethyl phosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (*e.g.*, at its 4'-carbon) or analog thereof. *See, e.g.*, US Patent Publication No. 2019-0177729. Other modifications have been developed for the 5' end of oligonucleotides (*see, e.g.*, Intl. Patent Application No. WO 2011/133871; US Patent No. 8,927,513; and Prakash *et al.* (2015) NUCLEIC ACIDS RES. 43:2993-3011).

As used herein, “reduced expression” of a gene (*e.g.*, *MARCI*) refers to a decrease in the amount or level of RNA transcript (*e.g.*, *MARCI* mRNA) or protein encoded by the gene and/or a decrease in the amount or level of activity of the gene in a cell, a population of cells, a sample, or a subject, when compared to an appropriate reference (*e.g.*, a reference cell, population of cells, sample or subject). For example, the act of contacting a cell with an oligonucleotide herein (*e.g.*, an oligonucleotide comprising an antisense strand having a nucleotide sequence that is complementary to a nucleotide sequence comprising *MARCI* mRNA) may result in a decrease in the amount or level of *MARCI* mRNA, protein and/or

activity (*e.g.*, *via* degradation of *MARCI* mRNA by the RNAi pathway) when compared to a cell that is not treated with the oligonucleotide. Similarly, and as used herein, “reducing expression” refers to an act that results in reduced expression of a gene (*e.g.*, *MARCI*).

As used herein, “reduction of *MARCI* expression” refers to a decrease in the amount or level of *MARCI* mRNA, *MARCI* protein and/or *MARCI* activity in a cell, a population of cells, a sample or a subject when compared to an appropriate reference (*e.g.*, a reference cell, population of cells, sample, or subject).

As used herein, “region of complementarity” refers to a sequence of nucleotides of a nucleic acid (*e.g.*, an oligonucleotide) that is sufficiently complementary to an antiparallel sequence of nucleotides to permit hybridization between the two sequences of nucleotides under appropriate hybridization conditions (*e.g.*, in a phosphate buffer, in a cell, *etc.*). In some embodiments, an oligonucleotide herein comprises a targeting sequence having a region of complementarity to a mRNA target sequence.

As used herein, “ribonucleotide” refers to a nucleotide having a ribose as its pentose sugar, which contains a hydroxyl group at its 2' position. A modified ribonucleotide is a ribonucleotide having one or more modifications or substitutions of atoms other than at the 2' position, including modifications or substitutions in or of the ribose, phosphate group or base.

As used herein, “RNAi oligonucleotide” refers to either (a) a double-stranded oligonucleotide having a sense strand (passenger) and antisense strand (guide), in which the antisense strand or part of the antisense strand is used by the *Argonaute 2* (Ago2) endonuclease in the cleavage of a target mRNA (*e.g.*, *MARCI* mRNA) or (b) a single-stranded oligonucleotide having a single antisense strand, where that antisense strand (or part of that antisense strand) is used by the Ago2 endonuclease in the cleavage of a target mRNA (*e.g.*, *MARCI* mRNA).

As used herein, “strand” refers to a single, contiguous sequence of nucleotides linked together through internucleotide linkages (*e.g.*, phosphodiester linkages or phosphorothioate linkages). In some embodiments, a strand has two free ends (*e.g.*, a 5' end and a 3' end).

As used herein, “subject” means any mammal, including mice, rabbits, and humans. In one embodiment, the subject is a human or NHP. Moreover, “individual” or “patient” may be used interchangeably with “subject.”

As used herein, “synthetic” refers to a nucleic acid or other molecule that is artificially synthesized (*e.g.*, using a machine (*e.g.*, a solid-state nucleic acid synthesizer)) or that is otherwise not derived from a natural source (*e.g.*, a cell or organism) that normally produces the molecule.

As used herein, “targeting ligand” refers to a molecule (*e.g.*, a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid) that selectively binds to a cognate molecule (*e.g.*, a receptor) of a tissue or cell of interest and that is conjugatable to another substance for purposes of targeting the other substance to the tissue or cell of interest. For example, in some embodiments, a targeting ligand may be conjugated to an oligonucleotide for purposes of targeting the oligonucleotide to a specific tissue or cell of interest. In some embodiments, a targeting ligand selectively binds to a cell surface receptor. Accordingly, in some embodiments, a targeting ligand when conjugated to an oligonucleotide facilitates delivery of the oligonucleotide into a particular cell through selective binding to a receptor expressed on the surface of the cell and endosomal internalization by the cell of the complex comprising the oligonucleotide, targeting ligand and receptor. In some embodiments, a targeting ligand is conjugated to an oligonucleotide *via* a linker that is cleaved following or during cellular internalization such that the oligonucleotide is released from the targeting ligand in the cell. In some embodiments, the targeting ligand comprises at least one GalNAc moiety and targets the liver and human liver cells (*e.g.*, human hepatocytes).

As used herein, “tetraloop” refers to a loop that increases stability of an adjacent duplex formed by hybridization of flanking sequences of nucleotides. The increase in stability is detectable as an increase in melting temperature (T_m) of an adjacent stem duplex that is higher than the T_m of the adjacent stem duplex expected, on average, from a set of loops of comparable length consisting of randomly selected sequences of nucleotides. For example, a tetraloop can confer a T_m of at least about 50°C, at least about 55°C, at least about 56°C, at least about 58°C, at least about 60°C, at least about 65°C, or at least about 75°C in 10 mM Na_2HPO_4 to a hairpin comprising a duplex of at least 2 base pairs (bp) in length. In some embodiments, a tetraloop can confer a T_m of at least about 50°C, at least about 55°C, at least about 56°C, at least about 58°C, at least about 60°C, at least about 65°C, or at least about 75°C in 10 mM NaH_2PO_4 to a hairpin comprising a duplex of at least 2 base pairs (bp) in length. In some embodiments, a tetraloop may stabilize a bp in an adjacent stem duplex by stacking interactions. In addition, interactions among the nucleotides in a tetraloop include, but are not limited to, non-Watson-Crick base pairing, stacking interactions, hydrogen bonding and contact interactions (Cheong *et al.* (1990) NATURE 346:680-82; Heus & Pardi (1991) SCIENCE 253:191-94). In some embodiments, a tetraloop comprises or consists of 3 to 6 nucleotides and is typically 4 to 5 nucleotides. In certain embodiments, a tetraloop comprises or consists of 3, 4, 5, or 6 nucleotides, which may or may not be modified (*e.g.*, which may or may not be conjugated to a targeting moiety). In one embodiment, a tetraloop consists of 4 nucleotides. Any nucleotide

may be used in the tetraloop and standard IUPAC-IUB symbols for such nucleotides may be used as described in Cornish-Bowden (1985) NUCLEIC ACIDS RES. 13:3021-30. For example, the letter “N” may be used to mean that any base may be in that position, the letter “R” may be used to show that A (adenine) or G (guanine) may be in that position, and “B” may be used to show that C (cytosine), G (guanine), or T (thymine) may be in that position. Examples of tetraloops include the UUCG family of tetraloops (*e.g.*, UUCG), the GNRA family of tetraloops (*e.g.*, GAAA), and the CUUG tetraloop (Woese *et al.* (1990) PROC. NATL. ACAD. SCI. USA 87:8467-71; Antao *et al.* (1991) NUCLEIC ACIDS RES. 19:5901-05). Examples of DNA tetraloops include the d(GNNA) family of tetraloops (*e.g.*, d(GTTA), the d(GNRA)) family of tetraloops, the d(GNAB) family of tetraloops, the d(CNNG) family of tetraloops, and the d(TNCG) family of tetraloops (*e.g.*, d(TTCG)). *See, e.g.*, Nakano *et al.* (2002) BIOCHEM. 41:14281-92; Shinji *et al.* (2000) NIPPON KAGAKKAI KOEN YOKOSHU 78:731. In some embodiments, the tetraloop is contained within a nicked tetraloop structure.

As used herein, “treat” or “treating” refers to the act of providing care to a subject in need thereof, for example, by administering a therapeutic agent (*e.g.*, an oligonucleotide herein) to the subject, for purposes of improving the health and/or well-being of the subject with respect to an existing condition (*e.g.*, a disease, disorder) or to prevent or decrease the likelihood of the occurrence of a condition. In some embodiments, treatment involves reducing the frequency or severity of at least one sign, symptom or contributing factor of a condition (*e.g.*, disease, disorder) experienced by a subject.

EXAMPLES

While the current invention has been described with reference to the specific embodiments set forth in the following Examples, it should be understood by those skilled in the art that various changes may be made, and equivalents may be substituted without departing from the true spirit and scope of the current invention. Further, the following Examples are offered by way of illustration and are not intended to limit the scope of the current invention in any manner. In addition, modifications may be made to adapt to a situation, material, composition of matter, process, process step or steps, to the objective, spirit, and scope of the current invention. All such modifications are intended to be within the scope of the current invention. Standard techniques well known in the art or the techniques specifically described below were utilized.

Example 1: Preparation of Double-Stranded RNAi Oligonucleotides*Oligonucleotide Synthesis and Purification*

The double-stranded RNAi (dsRNA) oligonucleotides described in the foregoing Examples were chemically synthesized using methods described herein. Generally, dsRNAi oligonucleotides were synthesized using solid phase oligonucleotide synthesis methods as described for 19-23mer siRNAs (*see, e.g.,* Scaringe *et al.* (1990) *Nucleic Acids Res.* 18:5433-5441 and Usman *et al.* (1987) *J. Am. Chem. Soc.* 109:7845-7845; *see also*, US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,008,400; 6,111,086; 6,117,657; 6,353,098; 6,362,323; 6,437,117; and 6,469,158) in addition to using known phosphoramidite synthesis (*see, e.g.* Hughes and Ellington (2017) *Cold Spring Harb Perspect Biol.* 9(1):a023812; Beaucage S.L., Caruthers M.H. Studies on Nucleotide Chemistry V: Deoxynucleoside Phosphoramidites—A New Class of Key Intermediates for Deoxypolynucleotide Synthesis. *Tetrahedron Lett.* (1981);22:1859–1862. doi: 10.1016/S0040-4039(01)90461-7). dsRNAi oligonucleotides having a 19mer core sequence were formatted into constructs having a 25mer sense strand and a 27mer antisense strand to allow for processing by the RNAi machinery. The 19mer core sequence is complementary to a region in the *MARCI* mRNA.

Individual RNA strands were synthesized and HPLC purified according to standard methods (Integrated DNA Technologies; Coralville, IA). For example, RNA oligonucleotides were synthesized using solid phase phosphoramidite chemistry, deprotected and desalted on NAP-5 columns (Amersham Pharmacia Biotech; Piscataway, NJ) using standard techniques (Damha & Olgivie (1993) *Methods Mol. Biol.* 20:81-114; Wincott *et al.* (1995) *Nucleic Acids Res.* 23:2677-2684). The oligomers were purified using ion-exchange high performance liquid chromatography (IE-HPLC) on an Amersham Source 15Q column (1.0 cm×25 cm; Amersham Pharmacia Biotech) using a 15 min. step-linear gradient. The gradient varied from 90:10 Buffers A:B to 52:48 Buffers A:B, where Buffer A is 100 mM Tris pH 8.5 and Buffer B is 100 mM Tris pH 8.5, 1 M NaCl. Samples were monitored at 260 nm and peaks corresponding to the full-length oligonucleotide species were collected, pooled, desalted on NAP-5 columns, and lyophilized. Single strand RNA oligomers were stored lyophilized or in nuclease-free water at –80°C.

The purity of each oligomer was determined by capillary electrophoresis (CE) on a Beckman PACE 5000 (Beckman Coulter, Inc.; Fullerton, CA). The CE capillaries have a 100 µm inner diameter and contain ssDNA 100R Gel (Beckman-Coulter). Typically, about 0.6 nmole of oligonucleotide was injected into a capillary, run in an electric field of 444 V/cm and was detected by UV absorbance at 260 nm. Denaturing Tris-Borate-7 M-urea running buffer

was purchased from Beckman-Coulter. Oligoribonucleotides were obtained that were at least 90% pure as assessed by CE for use in experiments described below. Compound identity was verified by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectroscopy on a Voyager DE™ Biospectrometry WorkStation (Applied Biosystems; Foster City, CA) following the manufacturer's recommended protocol. Relative molecular masses of all oligomers were obtained, often within 0.2% of expected molecular mass.

Preparation of Duplexes

Single strand RNA oligomers were resuspended (e.g., at 100 μ M concentration) in duplex buffer consisting of 100 mM potassium acetate, 30 mM HEPES, pH 7.5. Complementary sense and antisense strands were mixed in equal molar amounts to yield a final solution of, for example, 50 μ M duplex. Samples were heated to 100°C for 5 min. in RNA buffer (Integrated DNA Technologies (IDT)) and were allowed to cool to room temperature before use. The dsRNA oligonucleotides were stored at –20°C.

Example 2: Generation of *MARCI*-Targeting Double-Stranded RNAi Oligonucleotides

*Identification of *MARCI* mRNA Target Sequences*

MARCI is an enzyme involved in catalyzing N-oxygenated molecules. To generate RNAi oligonucleotide inhibitors of *MARCI* expression, a computer-based algorithm was used to computationally identify *MARCI* mRNA target sequences suitable for assaying inhibition of *MARCI* expression by the RNAi pathway. The algorithm provided RNAi oligonucleotide guide (antisense) strand sequences each having a region of complementarity to a suitable *MARCI* target sequence of human *MARCI* mRNA (e.g., SEQ ID NO: 1692; **Table 1**). Some of the guide strand sequences identified by the algorithm were also complementary to the corresponding *MARCI* target sequence of monkey *MARCI* mRNA (SEQ ID NO: 1693 **Table 1**). *MARCI* RNAi oligonucleotides comprising a region of complementarity to homologous *MARCI* mRNA target sequences with nucleotide sequence similarity are predicted to have the ability to target homologous *MARCI* mRNAs.

Table 1: Sequences of Human and Monkey *MARCI* mRNA

Species	Ref Seq #	SEQ ID NO
Human (Hs)	NM_022746.4	1692
Cynomolgus monkey (Mf)	XM_005540898.2	1693

RNAi oligonucleotides (formatted as DsiRNA oligonucleotides) were generated as described in **Example 1** for evaluation *in vitro*. Each DsiRNA was generated with the same modification pattern, and each with a unique guide strand having a region of complementarity to a *MARCI* target sequence identified by SEQ ID NOs: 1-384. Modifications for the sense and anti-sense DsiRNA included the following (*X* = any nucleotide; *m* = 2'-O-methyl modified nucleotide; *r* = ribosyl modified nucleotide):

Sense Strand:

rXmXrXmXrXrXrXrXrXrXrXmXrXmXrXrXrXrXrXrXXX

Anti-sense Strand:

mXmXmXmXrXrXrXrXrXrXmXrXmXrXrXrXrXrXrXrXrXrXmXrXmXmXmX

In Vitro Cell-Based Assays

The ability of each of the modified DsiRNA in **Table 2** to reduce *MARCI* mRNA was measured using *in vitro* cell-based assays. Briefly, human hepatocyte (Huh7) cells expressing endogenous human *MARCI* gene were transfected with each of the DsiRNAs listed in **Table 2** at 1 nM in separate wells of a multi-well cell-culture plate. Cells were maintained for 24 hours following transfection with the modified DsiRNA, and then the amount of remaining *MARCI* mRNA from the transfected cells was determined using TAQMAN®-based qPCR assays. Two qPCR assays, a 3' assay (Forward- (SEQ ID NO: 1684), Reverse- (SEQ ID NO: 1685), Probe- /56-FAM/AAAGG TGC T/Zen/CAGGAGGATGGTTGT/3IABkFQ (SEQ ID NO: 1694)) and a 5' assay (Forward- (SEQ ID NO: 1686), Reverse- (SEQ ID NO: 1687), Probe- /56-FAM/TCAAAACGC/ZEN/CCACCACAAATGCA/3IABkFQ (SEQ ID NO: 1695)) were used to determine *MARCI* mRNA levels as measured using PCR probes conjugated to 6-carboxy-fluorescein (FAM) and normalized to the HPRT housekeeping gene (Forward- (SEQ ID NO: 1688), Reverse- (SEQ ID NO: 1689); Probe- 5HEX /ATGGTCAAG/ZEN/ GTCGCAAGCTTGCTGGT/31ABkFQ/ -3'(SEQ ID NO: 1696). Each primer pair was assayed for % remaining RNA as shown in **Table 2 and FIG. 1**. DsiRNAs resulting in less than or equal to 10% *MARCI* mRNA remaining in DsiRNA-transfected cells when compared to mock-transfected cells were considered DsiRNA "hits". The Huh7 cell-based assay evaluating the ability of the DsiRNAs listed in **Table 2** to inhibit *MARCI* expression identified several candidate DsiRNAs.

Taken together, these results show that DsiRNAs designed to target human *MARCI* mRNA inhibit *MARCI* expression in cells, as determined by a reduced amount of *MARCI*

mRNA in DsiRNA-transfected cells relative to control cells. These results demonstrate that the nucleotide sequences comprising the DsiRNA are useful for generating RNAi oligonucleotides to inhibit *MARC1* expression. Further, these results demonstrate that multiple *MARC1* mRNA target sequences are suitable for the RNAi-mediated inhibition of *MARC1* expression.

Table 2. Analysis of *MARC1* mRNA in Huh7 cells

SED ID NO (Sense Strand)	SED ID NO (Anti-sense Strand)	DsiRNA name	MARC1-5' Assay		MARC1-3' Assay	
			% remain- ing	SEM	% remain- ing	SEM
769	1153	MARC1-231	25.8	2.4	35.7	2.8
770	1154	MARC1-233	40.3	3.3	39.9	4.9
771	1155	MARC1-234	17.7	2.8	19.6	2.5
772	1156	MARC1-235	25.0	3.7	25.4	3.0
773	1157	MARC1-236	23.8	6.4	34.8	6.9
774	1158	MARC1-237	35.1	5.8	40.1	6.0
775	1159	MARC1-238	30.6	4.2	39.1	4.7
776	1160	MARC1-239	21.6	3.4	33.0	5.5
777	1161	MARC1-240	9.2	1.1	16.5	1.6
778	1162	MARC1-241	29.0	3.3	36.5	2.6
779	1163	MARC1-242	60.8	2.4	68.1	3.7
780	1164	MARC1-243	27.9	3.6	37.4	4.6
781	1165	MARC1-244	35.4	3.4	43.5	3.8
782	1166	MARC1-245	72.0	5.2	89.6	6.7
783	1167	MARC1-247	21.0	2.3	29.5	2.5
784	1168	MARC1-248	22.0	2.9	32.3	5.4
785	1169	MARC1-249	16.6	1.5	22.3	1.6
786	1170	MARC1-253	29.3	3.5	30.1	3.0
787	1171	MARC1-255	28.6	1.4	32.8	1.6
788	1172	MARC1-318	64.7	3.6	71.7	5.6
789	1173	MARC1-319	84.5	5.0	91.8	5.8
790	1174	MARC1-320	42.4	3.0	59.7	5.5
791	1175	MARC1-321	29.6	2.2	42.0	3.2
792	1176	MARC1-323	16.2	1.2	26.0	2.3
793	1177	MARC1-324	3.7	0.5	6.3	0.9
794	1178	MARC1-325	24.6	7.4	29.9	8.8
795	1179	MARC1-326	10.7	2.1	14.1	2.9
796	1180	MARC1-327	10.8	0.6	16.0	2.0

797	1181	MARC1-328	11.9	0.9	13.3	0.9
798	1182	MARC1-329	13.4	0.9	16.2	1.8
799	1183	MARC1-330	10.3	1.1	13.6	1.3
800	1184	MARC1-331	11.5	1.1	12.3	1.2
801	1185	MARC1-332	29.2	1.9	34.4	4.7
802	1186	MARC1-334	52.6	4.1	64.5	5.8
803	1187	MARC1-335	21.5	1.5	26.2	2.4
804	1188	MARC1-337	31.2	3.6	32.9	4.4
805	1189	MARC1-338	35.4	2.5	36.8	2.5
806	1190	MARC1-339	35.1	5.1	41.7	5.6
807	1191	MARC1-340	33.2	2.7	36.1	3.4
808	1192	MARC1-341	17.8	1.2	20.4	1.9
809	1193	MARC1-342	11.4	4.4	22.1	7.6
810	1194	MARC1-343	30.6	2.1	34.5	3.2
811	1195	MARC1-345	43.3	2.9	38.8	2.8
812	1196	MARC1-346	19.1	2.5	22.9	3.4
813	1197	MARC1-347	91.0	7.7	83.7	8.8
814	1198	MARC1-348	35.8	3.2	37.9	3.7
815	1199	MARC1-349	29.9	1.7	29.9	2.9
816	1200	MARC1-350	40.5	6.7	30.4	6.3
817	1201	MARC1-351	20.2	2.2	29.7	3.3
818	1202	MARC1-352	35.5	3.8	44.5	4.1
819	1203	MARC1-353	43.8	6.8	42.7	7.4
820	1204	MARC1-354	54.9	6.1	58.6	6.2
821	1205	MARC1-356	76.2	9.1	59.2	5.3
822	1206	MARC1-357	26.0	4.0	28.5	3.6
823	1207	MARC1-358	50.5	7.7	40.2	6.0
824	1208	MARC1-359	68.7	7.5	53.4	6.2
825	1209	MARC1-360	22.5	1.4	34.6	2.5
826	1210	MARC1-361	63.0	7.1	72.8	6.5
827	1211	MARC1-362	61.4	5.9	63.8	5.8
828	1212	MARC1-365	70.5	4.1	66.5	4.2
829	1213	MARC1-376	90.8	6.8	70.2	7.2
830	1214	MARC1-379	95.1	7.6	82.4	7.8
831	1215	MARC1-384	44.8	5.2	36.5	3.6
832	1216	MARC1-385	62.4	5.2	46.9	5.1
833	1217	MARC1-388	29.0	3.1	32.2	3.2
834	1218	MARC1-390	43.1	1.7	48.7	2.6

835	1219	MARC1-391	29.9	3.7	33.2	3.7
836	1220	MARC1-393	36.6	1.4	35.8	1.8
837	1221	MARC1-395	68.6	4.1	68.0	4.3
838	1222	MARC1-405	19.2	2.1	24.1	2.8
839	1223	MARC1-409	29.7	3.0	33.9	3.6
840	1224	MARC1-411	50.4	3.7	46.1	3.8
841	1225	MARC1-412	31.4	2.2	35.9	2.6
842	1226	MARC1-413	16.1	1.8	21.8	3.1
843	1227	MARC1-414	28.1	3.5	25.8	2.9
844	1228	MARC1-415	19.8	4.5	30.4	6.5
845	1229	MARC1-416	16.9	2.2	20.4	1.8
846	1230	MARC1-417	34.4	3.6	36.6	3.3
847	1231	MARC1-418	46.9	5.0	45.2	4.8
848	1232	MARC1-419	24.8	3.3	27.0	3.1
849	1233	MARC1-420	68.4	6.5	77.6	9.1
850	1234	MARC1-421	14.6	1.0	25.2	2.2
851	1235	MARC1-422	25.9	1.5	27.7	1.4
852	1236	MARC1-423	15.5	1.0	18.3	1.6
853	1237	MARC1-424	32.2	3.1	31.1	5.0
854	1238	MARC1-425	42.7	3.7	41.5	4.4
855	1239	MARC1-426	33.6	2.5	38.2	3.7
856	1240	MARC1-427	20.1	1.3	28.6	2.4
857	1241	MARC1-428	46.5	8.1	69.6	11.3
858	1242	MARC1-429	17.4	1.8	33.6	3.5
859	1243	MARC1-430	29.1	3.2	42.1	5.0
860	1244	MARC1-431	23.1	2.7	40.8	3.5
861	1245	MARC1-433	12.5	0.7	20.2	1.7
862	1246	MARC1-434	16.0	1.3	24.7	1.8
863	1247	MARC1-435	18.7	2.0	26.8	2.5
864	1248	MARC1-436	42.1	3.7	62.6	5.9
865	1249	MARC1-437	20.1	2.2	42.8	9.0
866	1250	MARC1-438	35.8	3.4	36.0	3.6
867	1251	MARC1-439	21.0	2.6	26.4	3.0
868	1252	MARC1-440	38.0	11.5	104.7	29.2
869	1253	MARC1-441	18.7	1.7	23.7	2.0
870	1254	MARC1-445	30.1	3.4	36.6	3.4
871	1255	MARC1-446	14.2	2.8	25.0	3.9
872	1256	MARC1-447	25.4	6.7	35.9	8.2

873	1257	MARC1-448	26.9	5.3	27.5	4.5
874	1258	MARC1-449	22.4	3.3	26.9	4.4
875	1259	MARC1-450	21.1	1.3	22.8	1.7
876	1260	MARC1-451	30.6	1.5	33.4	1.9
877	1261	MARC1-452	78.5	9.6	85.6	16.8
878	1262	MARC1-453	44.4	2.3	49.4	3.2
879	1263	MARC1-454	29.1	2.7	43.3	3.5
880	1264	MARC1-456	19.7	2.3	24.6	2.7
881	1265	MARC1-457	14.6	1.5	25.1	2.3
882	1266	MARC1-458	18.1	1.2	25.1	3.3
883	1267	MARC1-459	29.4	1.7	35.1	3.3
884	1268	MARC1-460	30.5	1.5	34.0	3.2
885	1269	MARC1-462	33.2	3.3	38.2	3.9
886	1270	MARC1-468	49.0	4.2	61.9	7.9
887	1271	MARC1-469	24.5	1.6	28.9	2.9
888	1272	MARC1-470	32.1	3.3	35.5	4.3
889	1273	MARC1-471	39.8	1.7	48.7	2.4
890	1274	MARC1-473	27.1	1.9	32.1	2.6
891	1275	MARC1-475	78.8	2.8	70.6	2.3
892	1276	MARC1-476	108.2	7.7	107.7	8.6
893	1277	MARC1-482	36.1	2.3	39.0	3.2
894	1278	MARC1-483	28.8	1.7	43.0	2.5
895	1279	MARC1-484	33.9	3.0	44.0	5.3
896	1280	MARC1-552	44.8	3.3	70.4	7.3
897	1281	MARC1-553	17.9	1.0	32.0	1.8
898	1282	MARC1-554	21.9	2.2	31.8	2.0
899	1283	MARC1-555	28.6	2.1	40.5	3.6
900	1284	MARC1-556	18.5	0.8	27.8	1.6
901	1285	MARC1-557	25.3	2.0	31.6	2.7
902	1286	MARC1-558	43.5	2.7	66.1	5.3
903	1287	MARC1-559	41.0	2.6	47.0	3.2
904	1288	MARC1-560	21.3	1.5	37.7	3.1
905	1289	MARC1-561	19.8	1.5	26.1	2.1
906	1290	MARC1-562	78.6	4.6	85.6	8.3
907	1291	MARC1-563	61.7	3.3	73.4	4.2
908	1292	MARC1-564	31.4	2.3	37.6	3.3
909	1293	MARC1-565	56.3	3.7	60.5	4.8
910	1294	MARC1-566	41.7	5.4	53.1	5.8

911	1295	MARC1-567	68.1	5.1	76.5	6.7
912	1296	MARC1-568	46.7	3.5	67.5	5.8
913	1297	MARC1-589	23.4	2.2	35.4	2.6
914	1298	MARC1-591	14.9	1.1	21.5	2.9
915	1299	MARC1-592	21.8	3.2	24.8	4.2
916	1300	MARC1-593	71.2	7.2	96.1	12.4
917	1301	MARC1-597	43.2	2.6	53.7	5.2
918	1302	MARC1-600	24.1	5.7	29.1	5.7
919	1303	MARC1-612	22.6	2.0	26.3	2.4
920	1304	MARC1-614	34.2	4.1	48.3	7.2
921	1305	MARC1-617	59.0	6.1	75.3	8.1
922	1306	MARC1-618	22.8	1.4	37.6	3.0
923	1307	MARC1-620	28.9	1.8	39.9	3.2
924	1308	MARC1-621	32.0	4.6	34.8	4.0
925	1309	MARC1-622	14.6	1.0	23.4	1.6
926	1310	MARC1-623	28.6	2.1	36.3	2.8
927	1311	MARC1-624	30.6	2.6	36.4	3.1
928	1312	MARC1-625	38.3	4.8	39.0	5.4
929	1313	MARC1-626	21.1	2.6	25.5	2.9
930	1314	MARC1-627	14.5	1.3	17.9	1.7
931	1315	MARC1-628	39.6	3.9	43.3	3.8
932	1316	MARC1-629	54.1	3.6	52.5	2.9
933	1317	MARC1-630	25.9	3.4	35.6	4.1
934	1318	MARC1-631	19.8	1.2	29.5	2.4
935	1319	MARC1-632	17.7	2.1	22.3	2.1
936	1320	MARC1-633	16.9	1.0	20.2	1.9
937	1321	MARC1-634	21.4	1.2	39.9	4.1
938	1322	MARC1-635	23.2	1.9	26.1	2.9
939	1323	MARC1-636	45.3	1.6	38.1	1.9
940	1324	MARC1-637	53.9	6.0	54.5	9.8
941	1325	MARC1-638	15.2	0.9	21.9	1.6
942	1326	MARC1-639	17.7	1.3	23.9	2.9
943	1327	MARC1-640	29.5	3.6	36.9	4.2
944	1328	MARC1-641	22.8	2.4	45.1	7.5
945	1329	MARC1-642	19.2	1.9	47.2	5.3
946	1330	MARC1-643	19.4	1.1	27.6	2.8
947	1331	MARC1-644	24.2	1.7	30.0	4.5
948	1332	MARC1-645	37.6	2.3	44.5	3.2

949	1333	MARC1-646	41.5	2.5	43.1	4.1
950	1334	MARC1-647	46.5	4.2	49.6	5.2
951	1335	MARC1-648	19.0	1.6	27.0	3.6
952	1336	MARC1-649	35.7	5.0	39.8	5.7
953	1337	MARC1-650	72.2	6.8	84.2	5.8
954	1338	MARC1-651	71.7	4.7	70.7	6.9
955	1339	MARC1-652	57.0	2.1	62.3	8.8
956	1340	MARC1-653	18.2	1.4	20.7	2.4
957	1341	MARC1-654	17.9	1.0	19.5	1.5
958	1342	MARC1-655	71.5	7.0	71.2	9.3
959	1343	MARC1-656	41.9	3.6	44.1	4.4
960	1344	MARC1-657	18.2	2.8	21.7	3.1
961	1345	MARC1-658	30.2	2.1	45.9	2.7
962	1346	MARC1-659	47.1	14.7	51.8	11.1
963	1347	MARC1-660	17.7	1.7	23.6	2.0
964	1348	MARC1-661	13.0	1.4	20.4	2.5
965	1349	MARC1-662	25.5	2.4	30.9	2.6
966	1350	MARC1-663	34.3	3.5	36.3	3.4
967	1351	MARC1-664	37.1	4.4	41.9	4.1
968	1352	MARC1-665	22.5	2.2	37.8	3.6
969	1353	MARC1-666	17.8	1.9	32.6	4.5
970	1354	MARC1-667	27.4	5.0	32.6	7.3
971	1355	MARC1-668	45.6	3.0	58.0	2.8
972	1356	MARC1-669	33.1	2.4	42.1	2.8
973	1357	MARC1-670	26.3	2.7	29.7	2.6
974	1358	MARC1-671	62.9	3.4	66.9	6.9
975	1359	MARC1-672	60.3	3.5	70.9	5.1
976	1360	MARC1-673	38.8	4.0	56.7	8.1
977	1361	MARC1-674	21.4	1.5	37.8	2.9
978	1362	MARC1-675	47.6	3.7	51.1	4.0
979	1363	MARC1-676	53.9	4.1	54.2	4.9
980	1364	MARC1-677	44.5	8.6	69.6	17.2
981	1365	MARC1-678	38.1	3.8	37.7	4.3
982	1366	MARC1-679	50.7	3.6	49.1	6.0
983	1367	MARC1-680	27.5	1.8	29.5	2.0
984	1368	MARC1-681	24.9	2.1	32.7	2.0
985	1369	MARC1-682	51.4	2.4	55.4	2.2
986	1370	MARC1-683	28.0	1.7	26.9	2.5

987	1371	MARC1-684	23.8	2.1	23.8	3.0
988	1372	MARC1-685	72.2	13.5	81.3	15.1
989	1373	MARC1-686	18.8	1.2	20.5	3.4
990	1374	MARC1-687	18.0	1.8	22.3	3.1
991	1375	MARC1-691	21.8	2.3	23.6	2.6
992	1376	MARC1-692	25.7	2.9	25.4	2.7
993	1377	MARC1-724	49.0	2.8	74.6	10.5
994	1378	MARC1-726	36.6	3.5	37.6	4.1
995	1379	MARC1-728	38.9	3.1	40.0	4.2
996	1380	MARC1-729	31.8	3.4	36.0	4.8
997	1381	MARC1-730	62.3	3.1	60.0	7.8
998	1382	MARC1-731	66.0	6.6	66.1	6.8
999	1383	MARC1-733	33.8	4.4	28.0	3.7
1000	1384	MARC1-734	17.7	2.0	25.8	3.4
1001	1385	MARC1-735	9.5	1.4	16.7	2.2
1002	1386	MARC1-736	12.0	2.1	13.5	1.7
1003	1387	MARC1-737	17.0	1.0	18.8	1.2
1004	1388	MARC1-738	25.6	4.5	24.0	4.0
1005	1389	MARC1-739	19.1	2.2	16.2	1.3
1006	1390	MARC1-740	31.5	3.5	30.1	3.5
1007	1391	MARC1-741	36.4	2.7	29.1	2.6
1008	1392	MARC1-742	32.9	5.4	29.7	4.7
1009	1393	MARC1-743	45.3	5.5	59.2	5.0
1010	1394	MARC1-744	25.4	2.6	34.7	2.7
1011	1395	MARC1-745	23.2	2.7	27.8	4.6
1012	1396	MARC1-746	121.1	19.5	153.6	26.6
1013	1397	MARC1-747	29.4	3.2	33.1	3.4
1014	1398	MARC1-748	26.9	4.1	30.0	4.9
1015	1399	MARC1-750	33.3	6.4	36.3	6.3
1016	1400	MARC1-751	35.1	5.3	42.0	8.0
1017	1401	MARC1-752	22.9	2.6	27.1	5.4
1018	1402	MARC1-753	41.3	2.5	42.9	2.8
1019	1403	MARC1-754	84.7	7.7	57.0	5.7
1020	1404	MARC1-755	22.1	1.5	31.3	6.5
1021	1405	MARC1-756	46.6	2.1	46.2	2.5
1022	1406	MARC1-758	36.5	5.4	43.8	5.8
1023	1407	MARC1-759	57.6	10.7	73.2	15.8
1024	1408	MARC1-760	33.0	6.1	41.1	10.1

1025	1409	MARC1-761	16.1	1.8	19.6	2.7
1026	1410	MARC1-762	16.3	1.0	20.3	1.8
1027	1411	MARC1-763	22.9	1.5	25.1	2.3
1028	1412	MARC1-764	43.1	1.7	49.5	3.2
1029	1413	MARC1-765	57.2	5.0	50.2	4.5
1030	1414	MARC1-766	30.2	2.1	35.3	3.8
1031	1415	MARC1-767	84.0	12.8	83.7	19.5
1032	1416	MARC1-768	20.9	3.5	22.9	4.2
1033	1417	MARC1-769	21.0	3.8	29.6	3.4
1034	1418	MARC1-770	24.1	1.3	29.9	1.6
1035	1419	MARC1-771	40.2	2.9	35.8	2.7
1036	1420	MARC1-772	80.6	29.6	123.8	45.0
1037	1421	MARC1-773	37.5	2.6	39.5	4.7
1038	1422	MARC1-774	19.5	1.4	24.3	2.2
1039	1423	MARC1-775	18.6	1.5	22.5	2.7
1040	1424	MARC1-776	32.4	4.4	39.9	5.9
1041	1425	MARC1-777	28.7	1.9	33.7	2.4
1042	1426	MARC1-778	18.7	1.5	25.3	2.3
1043	1427	MARC1-779	24.6	3.0	41.9	7.7
1044	1428	MARC1-780	22.5	4.3	32.3	7.0
1045	1429	MARC1-781	25.8	2.3	25.7	2.2
1046	1430	MARC1-782	19.4	3.9	30.7	7.7
1047	1431	MARC1-783	23.2	3.9	27.1	4.5
1048	1432	MARC1-784	19.6	2.9	27.1	4.3
1049	1433	MARC1-785	15.2	0.9	19.1	1.8
1050	1434	MARC1-786	41.3	3.9	44.4	6.4
1051	1435	MARC1-787	25.2	3.3	27.4	3.8
1052	1436	MARC1-788	12.7	1.2	18.7	1.4
1053	1437	MARC1-789	15.2	1.6	21.0	2.2
1054	1438	MARC1-790	20.3	2.3	25.1	3.1
1055	1439	MARC1-791	29.7	2.4	32.2	2.5
1056	1440	MARC1-792	36.7	4.8	43.2	5.9
1057	1441	MARC1-863	11.8	1.8	18.6	1.8
1058	1442	MARC1-929	37.4	6.8	42.9	8.0
1059	1443	MARC1-930	54.5	6.6	60.7	10.4
1060	1444	MARC1-934	55.3	8.2	78.8	12.0
1061	1445	MARC1-955	37.2	4.9	41.5	5.7
1062	1446	MARC1-959	17.8	1.8	22.1	1.7

1063	1447	MARC1-960	25.2	2.5	29.9	5.9
1064	1448	MARC1-963	32.1	4.3	34.8	6.4
1065	1449	MARC1-964	20.0	2.3	23.0	2.9
1066	1450	MARC1-965	15.2	1.2	21.0	1.0
1067	1451	MARC1-966	19.9	0.9	22.2	1.7
1068	1452	MARC1-967	18.4	2.7	25.0	7.0
1069	1453	MARC1-969	19.9	1.4	23.5	1.6
1070	1454	MARC1-970	28.1	1.6	30.7	3.8
1071	1455	MARC1-971	24.2	1.6	26.3	2.4
1072	1456	MARC1-1107	24.2	3.9	24.7	4.7
1073	1457	MARC1-1113	49.9	4.3	56.3	6.4
1074	1458	MARC1-1118	18.2	1.6	21.9	2.1
1075	1459	MARC1-1123	25.7	2.5	28.3	1.2
1076	1460	MARC1-1126	21.1	7.6	27.2	10.2
1077	1461	MARC1-1127	29.6	2.4	29.6	2.6
1078	1462	MARC1-1128	23.9	1.0	27.8	2.0
1079	1463	MARC1-1129	27.1	4.1	33.3	5.0
1080	1464	MARC1-1130	34.3	5.3	32.6	4.9
1081	1465	MARC1-1132	24.3	2.6	19.2	4.1
1082	1466	MARC1-1133	26.2	3.1	31.0	3.6
1083	1467	MARC1-1134	21.3	1.6	21.9	1.5
1084	1468	MARC1-1135	36.3	7.5	36.5	10.8
1085	1469	MARC1-1139	25.3	2.3	25.3	1.6
1086	1470	MARC1-1144	49.8	7.4	48.3	9.1
1087	1471	MARC1-1165	38.9	6.7	35.7	6.2
1088	1472	MARC1-1167	90.1	7.0	61.4	9.1
1089	1473	MARC1-1173	32.7	2.4	35.8	6.1
1090	1474	MARC1-1177	14.9	1.2	20.4	2.1

1091	1475	MARC1-1179	11.6	0.7	13.4	1.5
1092	1476	MARC1-1329	24.9	1.8	26.6	2.3
1093	1477	MARC1-1330	23.4	1.7	23.5	1.8
1094	1478	MARC1-1332	33.9	5.1	32.9	5.5
1095	1479	MARC1-1333	48.9	6.1	50.8	6.9
1096	1480	MARC1-1334	34.7	7.0	31.1	6.8
1097	1481	MARC1-1335	16.8	1.5	19.2	2.4
1098	1482	MARC1-1620	18.9	2.7	18.1	3.0
1099	1483	MARC1-1622	22.1	1.5	21.2	1.5
1100	1484	MARC1-1660	29.6	6.1	23.2	4.1
1101	1485	MARC1-1663	39.1	3.9	33.8	5.5
1102	1486	MARC1-1664	26.5	3.4	23.2	3.3
1103	1487	MARC1-1812	30.7	2.6	26.3	2.9
1104	1488	MARC1-1816	41.2	10.1	27.3	7.3
1105	1489	MARC1-1868	21.0	4.7	27.9	5.8
1106	1490	MARC1-1869	25.7	3.6	28.5	5.6
1107	1491	MARC1-1876	20.4	1.9	15.6	1.9
1108	1492	MARC1-1877	33.1	1.6	20.1	3.9
1109	1493	MARC1-1878	24.1	1.3	17.3	2.1
1110	1494	MARC1-1879	27.4	4.3	18.8	3.3
1111	1495	MARC1-1882	29.8	3.3	17.4	3.2
1112	1496	MARC1-1883	34.8	6.8	13.0	3.3
1113	1497	MARC1-1884	22.6	2.0	20.6	4.7
1114	1498	MARC1-1885	20.2	1.9	13.8	2.0

1115	1499	MARC1-1886	28.6	3.2	25.6	4.0
1116	1500	MARC1-1935	25.6	1.8	23.2	1.4
1117	1501	MARC1-1936	38.8	3.3	17.0	2.8
1118	1502	MARC1-1937	25.4	3.0	15.9	4.2
1119	1503	MARC1-1939	60.6	6.1	25.1	4.1
1120	1504	MARC1-1941	36.9	7.7	27.4	9.8
1121	1505	MARC1-1953	22.0	2.9	35.2	10.0
1122	1506	MARC1-1955	20.3	1.6	24.9	2.4
1123	1507	MARC1-1981	24.8	1.4	24.5	2.3
1124	1508	MARC1-1983	26.7	2.2	19.2	6.6
1125	1509	MARC1-1985	41.5	2.2	16.4	2.5
1126	1510	MARC1-1986	22.6	1.8	15.0	2.8
1127	1511	MARC1-1988	35.6	4.6	63.9	24.7
1128	1512	MARC1-1989	39.6	4.4	26.2	4.3
1129	1513	MARC1-1990	25.8	1.9	18.8	2.2
1130	1514	MARC1-1995	27.8	1.2	22.9	2.5
1131	1515	MARC1-1996	36.0	2.3	19.7	2.0
1132	1516	MARC1-1998	108.0	16.4	51.0	8.5
1133	1517	MARC1-1999	57.4	4.9	74.3	12.0
1134	1518	MARC1-2000	34.4	2.3	17.8	3.5
1135	1519	MARC1-2001	53.6	7.9	17.9	3.0
1136	1520	MARC1-2002	68.0	17.7	11.3	3.4
1137	1521	MARC1-2005	27.4	5.7	34.1	12.2
1138	1522	MARC1-2006	25.2	1.8	23.8	2.6

1139	1523	MARC1-2010	63.5	7.7	33.0	4.5
1140	1524	MARC1-2011	21.8	2.0	22.0	4.9
1141	1525	MARC1-2012	19.1	1.2	9.9	1.0
1142	1526	MARC1-2013	34.8	5.6	10.7	2.1
1143	1527	MARC1-2015	93.3	24.0	23.5	6.8
1144	1528	MARC1-2016	57.0	11.1	12.6	2.9
1145	1529	MARC1-2017	24.8	1.2	25.3	2.0
1146	1530	MARC1-2018	34.4	4.1	29.9	5.6
1147	1531	MARC1-2019	25.5	2.6	22.4	2.5
1148	1532	MARC1-2020	25.7	2.6	27.9	7.9
1149	1533	MARC1-2022	18.5	1.5	18.4	2.6
1150	1534	MARC1-2023	34.1	2.4	14.6	1.2
1151	1535	MARC1-2025	137.2	22.1	24.1	4.8
1152	1536	MARC1-2027	158.4	33.6	39.5	9.7

Example 3: RNAi Oligonucleotide Inhibition of MARC1 *In Vivo*

The *in vitro* screening assay in **Example 2** validated the ability of *MARC1*-targeting oligonucleotides to knock-down target mRNA. To confirm the ability of the RNAi oligonucleotides to knockdown *MARC1 in vivo*, an HDI mouse model was used. A subset of the DsiRNAs identified in **Example 2** were used to generate corresponding double-stranded RNAi oligonucleotides comprising a nicked tetraloop GalNAc-conjugated structure (referred to herein as “GalNAc-conjugated *MARC1* oligonucleotides” or “GalNAc-*MARC1* oligonucleotides”) having a 36-mer passenger strand and a 22-mer guide strand (**Table 4**). Further, the nucleotide sequences comprising the passenger strand and guide strand have a distinct pattern of modified nucleotides and phosphorothioate linkages (sense strand SEQ ID Nos: 1609-1642; antisense SEQ ID Nos: 1645-1678). Three of the nucleotides comprising the tetraloop were each conjugated to a GalNAc moiety (CAS#14131-60-3). The modification pattern of each strand is illustrated below:

Sense Strand: 5'-mX-S-mX-mX-mX-mX-mX-fX-fX-fX[-mX-]₁₆-[ademX-GalNAc]-[ademX-GalNAc]-[ademX-GalNAc]-mX-mX-mX-mX-mX-mX-3'.

Hybridized to:

Antisense Strand: 5'-[MePhosphonate-4O-mX]-S-fX-S-fX-S-fX-fX-mX-fX-mX-mX-fX-mX-mX-mX-mX-mX-mX-S-mX-S-mX-3'.

Or, represented as:

Sense Strand:

[mXs][mX][mX][mX][mX][mX][mX][fX][fX][fX][mX][mX][mX]
[mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][ademA-
GalNAc][ademA-GalNAc][ademA-GalNAc][mX][mX][mX][mX][mX][mX]

Hybridized to:

Antisense Strand: [MePhosphonate-4O-mXs][fXs][fXs][fX][fX][mX][fX][mX]

[mX][fX][mX][mX][mX][fX][mX][mX][mX][mX][mXs][mXs][mX]

(Modification key: **Table 3**).

Symbol	Modification/linkage
Key 1	
mX	2'-O-methyl modified nucleotide
fX	2'-fluoro modified nucleotide
-S-	phosphorothioate linkage
-	phosphodiester linkage
[MePhosphonate-4O-mX]	5'-methoxyphosphonate-4'-oxy modified nucleotide
ademA-GalNAc	GalNAc attached to an adenine nucleotide
Key 2	
[mXs]	2'-O-methyl modified nucleotide with a phosphorothioate linkage to the neighboring nucleotide
[fXs]	2'-fluoro modified nucleotide with a phosphorothioate linkage to the neighboring nucleotide
[mX]	2'-O-methyl modified nucleotide with phosphodiester linkages to neighboring nucleotides
[fX]	2'-fluoro modified nucleotide with phosphodiester linkages to neighboring nucleotides

Oligonucleotides in **Table 4** were evaluated in mice engineered to transiently express human *MARCI* mRNA in hepatocytes of the mouse liver. Briefly, 6-8-week-old female CD-1 mice (n = 4-5) were subcutaneously administered the indicated GalNAc-conjugated *MARCI* oligonucleotides at a dose of 2 mg/kg formulated in PBS. A control group of mice (n = 5) were administered only PBS. Three days later (72 hours), the mice were HDI with a DNA plasmid encoding the full human *MARCI* gene (SEQ ID NO: 1682) (25 µg) under control of a ubiquitous cytomegalovirus (CMV) promoter sequence. One day after introduction of the DNA plasmid, liver samples from HDI mice were collected. Total RNA derived from these HDI mice were subjected to qRT-PCR analysis to determine *MARCI* mRNA levels as described in **Example 2**. mRNA levels were measured for human mRNA. The values were normalized for transfection efficiency using the NeoR gene included on the DNA plasmid.

Table 4. GalNAc-Conjugated *MARCI* RNAi Oligonucleotides for HDI screen

	Unmodified Sense Strand (SEQ ID NO)	Unmodified Antisense strand (SEQ ID NO)	Modified Sense Strand (SEQ ID NO)	Modified Antisense strand (SEQ ID NO)
MARC1-0324	1537	1573	1609	1645
MARC1-0326	1538	1574	1610	1646
MARC1-0327	1539	1575	1611	1647
MARC1-0330	1540	1576	1612	1648
MARC1-0331	1541	1577	1613	1649
MARC1-0735	1542	1578	1614	1650
MARC1-0736	1543	1579	1615	1651
MARC1-0788	1544	1580	1616	1652
MARC1-0863	1545	1581	1617	1653
MARC1-1179	1546	1582	1618	1654
MARC1-2012	1547	1583	1619	1655
MARC1-2013	1548	1584	1620	1656
MARC1-0661	1549	1585	1621	1657
MARC1-1869	1550	1586	1622	1658
MARC1-1876	1551	1587	1623	1659
MARC1-1886	1552	1588	1624	1660
MARC1-2016	1553	1589	1625	1661
MARC1-0413	1554	1590	1626	1662
MARC1-0416	1555	1591	1627	1663
MARC1-0622	1556	1592	1628	1664
MARC1-0638	1557	1593	1629	1665
MARC1-0657	1558	1594	1630	1666
MARC1-0660	1559	1595	1631	1667
MARC1-0965	1560	1596	1632	1668
MARC1-0966	1561	1597	1633	1669
MARC1-0967	1562	1598	1634	1670
MARC1-0969	1563	1599	1635	1671

MARC1-1177	1564	1600	1636	1672
MARC1-1884	1565	1601	1637	1673
MARC1-1885	1566	1602	1638	1674
MARC1-1955	1567	1603	1639	1675
MARC1-1983	1568	1604	1640	1676
MARC1-1986	1569	1605	1641	1677
MARC1-2011	1570	1606	1642	1678

The results in **FIG. 2** demonstrate that GalNAc-conjugated *MARC1* oligonucleotides designed to target human *MARC1* mRNA inhibited human *MARC1* mRNA expression in HDI mice, as determined by a reduction in the amount of human *MARC1* mRNA expression in liver samples from HDI mice treated with GalNAc-conjugated *MARC1* oligonucleotides relative to control HDI mice treated with only PBS.

A subset of the GalNAc-conjugated *MARC1* oligonucleotides tested in **FIG. 2** were further validated in repeat assays as shown in **FIG. 3** using oligonucleotides selected from **Table 4**. The assays verified knock-down efficiency of each GalNAc-conjugated *MARC1* oligonucleotide, and four oligonucleotides were selected for further analysis.

Specifically, dosing studies were carried out using four GalNAc-conjugated *MARC1* oligonucleotides (MARC1-0736, MARC1-965, MARC1-1983, and MARC1-2016). Mice were HDI as described above and treated with 0.1 mg/kg, 0.3 mg/kg, or 1 mg/kg of oligonucleotide. Livers were collected after one day, and *MARC1* expression was measured to determine a potent dose (**FIG. 4**). All GalNAc-conjugated *MARC1* oligonucleotides were able to reduce *MARC1* expression at a 1 mg/kg dose. Overall, the HDI studies identified several potential GalNAc-conjugated *MARC1* oligonucleotides for inhibiting *MARC1* expression in liver.

Example 4: RNAi Oligonucleotide Inhibition of MARC1 in DIO-NASH Disease Model

To investigate the therapeutic effect of GalNAc-conjugated *MARC1* oligonucleotides on liver diseases such as NAFLD and NASH, the diet-induced obese (DIO)-NASH model was used (Kristiansen, M., *et al.* 2016. *WJH.* 8(16): 673-684). The model exhibits histopathology and clinical endpoints similar to NASH and is initiated through a diet high in fat, fructose, and cholesterol. Two mice specific surrogate GalNAc-conjugated *MARC1* oligonucleotides with different levels of knockdown (**Table 5B**) were tested in this murine model of NASH. Mice were fed Lean Chow (11% fat, 24% protein, and 65% carbohydrate; Altromin 1324, Brogaarden, Denmark), or a NASH diet consisting of 40% fat, 22% fructose and 2% cholesterol (D09100310, Research Diets) for 36 weeks (DIO-NASH). Prior to

treatment with oligonucleotides and the GLP-1 receptor agonist mice were randomized into chow control, PBS control, GLP-1 '22', MARC1-1113 (SEQ ID NOs: 1643 and 1679), and MARC1-1575 (SEQ ID NOs: 1644 and 1680) treatment groups by their fibrosis state as determined by *Coll1a1*, *i.e.*, collagen, levels (data not shown). Weekly concurrent, subcutaneous dosing was initiated on week 36 and mice were treated with 3 mg/kg of MARC1-1113, 3 mg/kg of MARC1-1575, 10 nmol/kg of GLP-1 '22', or PBS control ("DIO-NASH vehicle") for 8 weeks. The GLP-1 receptor agonist (GLP-1 '22') is a long acting GLP-1 receptor agonist and used as a benchmark in these studies. Injections were given on days 0, 7, 14, 21, 28, 35, 42, and 49 after initiation of the study (*i.e.* week 36 on DIO-NASH or Lean Chow diet). The DIO-NASH vehicle control, MARC1-1113, and MARC1-1575 mice increased their relative body weight at similar pace throughout the duration of the study (Table 5A). As expected, the Lean-Chow showed a slower rate of body weight gain, while GLP-1 '22' controls showed a reduction in relative body weight to the start of the study.

Table 5A provides the body weight of mice throughout treatment with GalNAc-conjugated *MARC1* oligonucleotides targeting mouse *MARC1* or a long acting GLP-1 receptor agonist (GLP-1 '22') used as positive control for disease regression in a diet induced obesity (DIO) - NASH model. Weights are relative to starting weight. Mice were fed a DIO-NASH (AMLN diet) or Lean-Chow diet.

Body Weight (%)										
Study Day	Lean-Chow		DIO-NASH Vehicle		MARC1-1113		MARC1-1575		GLP-1 '22'	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
-4	101.02	0.48	99.86	0.56	99.13	0.33	100.18	0.39	99.91	0.50
-3	100.79	0.53	99.95	0.50	98.73	0.28	100.20	0.37	99.39	0.49
-2	100.75	0.38	99.74	0.41	98.96	0.37	99.75	0.32	99.16	0.45
-1	100.52	0.31	99.74	0.25	99.10	0.25	99.74	0.31	99.33	0.33
0	100.00	0.00	100.00	0.00	100.00	0.00	100.00	0.00	100.00	0.00
1	99.46	0.50	100.13	0.30	99.28	0.24	99.72	0.33	98.23	0.35
2	99.66	0.34	100.10	0.30	99.42	0.25	99.72	0.47	96.88	0.39
3	99.77	0.44	100.81	0.37	99.61	0.28	100.59	0.37	95.46	0.47
4	100.11	0.41	101.09	0.42	100.34	0.25	101.18	0.47	92.30	0.64
5	100.38	0.61	100.99	0.40	100.04	0.39	100.80	0.52	89.71	0.69
6	100.87	0.58	101.24	0.48	99.92	0.49	101.04	0.56	86.62	0.84

7	101.37	0.55	101.86	0.56	100.52	0.54	101.65	0.56	86.13	1.09
8	101.31	0.55	101.82	0.55	101.14	0.40	102.28	0.56	84.75	1.50 —
9	101.10	0.70	102.34	0.71	101.90	0.51	102.28	0.63	83.78	1.76 —
10	101.60	0.73	102.75	0.61	102.57	0.56	103.09	0.63	84.31	1.65 —
11	101.63	0.88	102.88	0.68	102.74	0.57	103.45	0.76	84.25	1.54 —
12	101.50	0.82	102.71	0.67	102.47	0.51	103.01	0.81	83.92	1.51 —
13	101.30	0.79	102.66	0.61	102.45	0.66	101.92	0.60	83.88	1.27 —
14	101.38	0.69	103.13	0.68	102.37	0.54	104.19	0.85	83.46	1.35 —
15	100.75	0.79	102.89	0.64	102.52	0.72	103.85	0.83	83.39	1.37 —
16	101.63	1.18	102.47	0.67	102.34	0.70	103.58	0.86	83.39	1.26 —
17	102.92	0.88	103.49	0.65	102.98	0.66	104.44	0.85	82.71	1.31 —
18	103.67	1.08	103.61	0.66	102.97	0.76	104.75	0.85	82.51	1.41 —
19	103.62	0.94	103.69	0.64	103.10	0.68	104.75	0.88	82.12	1.45 —
20	102.89	0.73	103.65	0.63	103.29	0.82	105.00	0.89	81.96	1.20 —
21	102.36	0.95	103.73	0.73	103.76	0.86	105.52	0.89	82.52	1.02 —
22	101.94	0.96	104.69	0.56	103.86	0.82	105.45	0.79	82.74	1.03 —
23	102.50	0.93	104.39	0.58	103.61	0.80	105.32	0.71	83.14	1.02 —
24	103.73	1.07	104.71	0.85	104.19	0.73	106.05	0.82	82.30	1.05 —
25	102.48	0.75	103.46	0.72	103.92	0.73	106.28	0.69	82.66	1.02 —
26	101.93	0.95	103.08	0.79	103.56	0.76	105.30	0.74	82.37	0.98 —
27	102.19	0.80	102.52	0.79	102.83	0.62	104.33	0.87	81.69	0.94 —
28	101.51	0.74	103.28	0.77	102.98	0.66	104.89	0.90	82.04	0.86 —
29	101.95	0.76	103.24	0.75	103.38	0.82	104.34	0.96	82.26	0.94 —
30	102.50	0.75	103.89	0.78	104.13	0.81	105.52	0.96	82.09	0.93 —
31	102.80	0.65	103.38	0.73	103.80	0.90	105.25	0.84	81.99	0.96 —
32	102.83	0.59	104.30	0.84	104.40	0.77	105.67	0.88	82.49	0.89 —
33	102.03	0.80	104.44	0.94	104.52	0.71	105.65	0.97	82.35	0.85 —
34	102.69	0.89	104.26	0.91	104.13	0.76	105.25	1.02	81.87	0.83 —
35	102.08	0.93	104.79	0.92	104.93	0.75	105.20	0.82	82.25	0.87 —
36	102.37	0.75	105.56	0.96	106.31	0.73	107.05	0.78	83.11	0.85 —
37	102.12	1.02	105.43	0.91	106.24	0.84	106.24	0.91	81.99	0.86 —
38	101.59	0.67	105.11	0.96	106.36	0.80	106.94	0.78	82.54	0.92 —

39	102.70	0.68	105.38	0.94	106.37	0.81	107.12	0.90	82.73	1.06
40	101.56	0.87	105.64	1.09	106.83	0.88	107.44	0.79	82.70	1.05
41	101.72	0.78	105.93	1.17	106.36	0.96	107.19	0.75	82.86	0.89
42	101.61	1.01	106.56	1.14	106.20	0.95	106.85	0.84	82.14	0.97
43	101.40	1.05	107.48	1.12	107.12	0.90	108.24	0.87	82.88	0.93
44	102.44	0.89	107.39	1.11	106.59	0.81	107.73	0.88	82.56	1.01
45	102.32	0.90	106.94	1.07	106.76	0.86	107.73	1.04	82.44	1.16
46	101.98	1.22	106.96	1.26	107.00	0.91	107.79	0.99	82.91	1.14
47	102.43	1.09	107.36	1.33	107.18	0.98	108.15	0.98	82.76	1.12
48	102.28	0.77	107.51	1.32	107.36	0.88	108.50	1.07	83.12	1.18
49	103.32	1.02	107.94	1.14	107.82	0.94	108.40	1.09	82.35	1.05
50	102.74	0.95	108.53	1.14	108.70	0.74	107.63	1.09	82.91	1.09
51	103.84	1.11	108.51	1.39	108.46	0.92	108.05	0.96	83.41	1.01
52	103.49	1.27	108.86	1.28	109.03	0.79	108.28	0.88	83.14	1.03
53	102.83	0.89	109.09	1.30	109.06	0.72	108.15	1.06	83.33	1.10
54	101.77	1.30	108.67	1.32	108.76	0.77	108.41	1.11	82.31	1.24
55	102.81	0.95	109.63	1.23	109.77	0.70	109.05	1.19	83.46	1.26
56	103.33	0.95	109.84	1.31	110.04	0.83	109.29	1.04	83.57	1.23

After week 8 of dosing, plasma was collected and analyzed for plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglyceride (TG), and total cholesterol (TC). The model performed as expected, as measured by the GLP-1 '22' control reducing ALT, AST, and TC levels. Treatment of DIO-NASH mice with the GalNAc-conjugated *MARCI* oligonucleotides did not change the plasma ALT, AST, TG, or TC levels compared to PBS treated DIO-NASH mice (data not shown). Liver tissue was collected at week 8, weighed and processed for analysis. As expected, liver weight was lower in both Lean Chow mice and DIO-NASH mice treated with GLP-1 '22' at termination of the study compared to the NASH vehicle group. However, there was no observed difference in liver weight in the DIO-NASH mice treated with vehicle control or the GalNAc-conjugated *MARCI* oligonucleotides (data not shown). In the liver, TG levels were reduced in both MARC1-1113 and MARC1-1575 treated mice compared to DIO-NASH vehicle control (**FIGs. 5 and 6**). Further, NAFLD activity was measured. The NAFLD activity score is used to measure changes in disease features concurrent with treatment for NAFLD and is

measured by staining liver samples and using clinical criteria outlined in Kleiner *et al.* (Kleiner *et al.* 2005. *Hepatology*. 41: 1313-1321) to determine the score. The MARC1-1113 oligonucleotide demonstrated an improved NAFLD score in the DIO-NASH model (**FIG. 7**). Similarly, treatment with the MARC1-1113 oligonucleotide reduced steatosis (calculated as a percentage of hepatocytes with lipid droplets) in the animals (**FIG. 8**), but no reduction was observed for hepatocellular ballooning or lobular inflammation (data not shown) as determined by histopathological analysis as described in Kleiner *et al.* Reduced steatosis fraction (*i.e.* measured area fraction of steatosis in a histology sample) and hepatocytes with liver droplets is observed in MARC1-1113 treated mice, as determined by quantification of histopathological analysis using methods described in Kleiner *et al.* (**FIGs. 9A and 9B**). Inflammation and fibrosis do not appear to be changed with treatment as there was no observed difference in the number of inflammatory cells, inflammatory foci, CD45, CD11b, fibrosis, periportal fibrosis, sinusoidal fibrosis, or Col1a among treatment groups (data not shown). However, the stellate cell activation marker α -SMA, an early indicator of hepatic fibrosis was reduced by MARC1-1113 treatment demonstrating that although a reduction in overall fibrosis was not observed, treatment with MARC1-1113 reduced fibrosis development (**FIG. 10**). Finally, qPCR was performed on a panel of genes related to MARC1 expression, steatosis, cholesterol metabolism, fibrosis, phosphatidylcholine, and potential biomarkers (**Table 5B**). Reduced expression was observed for several steatosis relevant genes: *Fasn*, *Acaca*, *AcacB*, and *ApoB*, following MARC1-1113 treatment. Additionally, a reduction in several early regulators of fibrosis and potential biomarker genes were also reduced following MARC1-1113 treatment including: *Col1a1*, *Tgfb*, *Timp1*, *Mmp9*, *Mmp2*, and *Fabp1*. These findings demonstrate that MARC1 inhibition reduces genes that regulate steatosis and fibrosis development.

In conclusion, the DIO-NASH study demonstrates the therapeutic effect of hepatic MARC1 inhibition using GalNAc-conjugated *MARC1* oligonucleotides.

Table 5B: Summary of Gene Expression in MARC1 treated DIO-NASH Mice

		Mean % mRNA Remaining (Relative to DIO-NASH Vehicle)				
	Gene	Lean-Chow	DIO-NASH Vehicle	MARC1-1113	MARC1-1575	GLP-1 '22'
Target-Related Genes	<i>Marc1</i>	140.38	100.00	10.61	30.60	114.18
	<i>Marc2</i>	131.34	100.00	86.09	114.58	117.14

	<i>Nr1h3</i>	108.41	100.00	92.01	118.46	111.44
	<i>Nr1h2</i>	108.56	100.00	94.98	124.83	114.30
	<i>Fmo3</i>	311.16	100.00	119.93	172.15	251.50
	<i>Dgat2</i>	145.27	100.00	92.25	127.87	120.47
Steatosis-Related Genes	<i>Fasn</i>	172.84	100.00	67.93	132.57	173.23
	<i>Cidec</i>	3.45	100.00	92.15	138.33	65.26
	<i>Acc1</i> (<i>AcacA</i>)	107.88	100.00	92.85	138.20	117.28
	<i>Acc2</i> (<i>AcacB</i>)	158.79	100.00	59.13	102.16	144.66
	<i>Sdc1</i>	115.80	100.00	99.88	119.66	118.81
	<i>ApoB</i>	88.84	100.00	78.57	97.86	97.60
Cholesterol Metabolism-Related Genes	<i>Abca1</i>	83.94	100.00	99.39	130.12	110.81
	<i>Abcg5</i>	28.58	100.00	90.89	96.52	95.70
	<i>Hmgcr</i>	562.47	100.00	84.95	146.22	157.49
Phosphatidylcholine Hypothesis	<i>Pemt</i>	160.40	100.00	86.47	115.15	115.73
Early Regulators of Fibrosis Genes	<i>Colla1</i>	9.02	100.00	57.83	142.74	58.97
	<i>Tgfb1</i>	59.54	100.00	84.72	120.06	85.16
	<i>Timp1</i>	3.02	100.00	49.32	136.88	48.32
	<i>Mmp9</i>	104.95	100.00	68.95	99.70	99.41
	<i>Mmp2</i>	20.57	100.00	81.04	174.74	124.65
Biomarker Genes	<i>p1a2gl2b</i>	120.28	100.00	92.93	124.68	102.55
	<i>Cpm</i>	136.88	100.00	122.37	140.68	125.86
	<i>Fabp1</i>	128.78	100.00	82.50	176.75	216.97
	<i>Smpd1</i>	107.65	100.00	95.05	121.59	115.48
	<i>Cyp7a1</i>	75.08	100.00	126.34	120.64	121.09

Example 5 RNAi Oligonucleotide Inhibition of MARC1 Expression and Studies in NHP

Effective GalNAc-conjugated *MARC1* oligonucleotides identified in the HDI mouse studies were assayed for targeting efficiency in NHP. Specifically, GalNAc-conjugated *MARC1* oligonucleotides listed in **Table 6** were evaluated in non-naïve cynomolgus monkeys (*Macaca fascicularis*). In this study, the monkeys were grouped so that their mean body weights (about 2.5 kg) were comparable between the control and experimental groups. Each cohort contained all male subjects. The GalNAc-conjugated *MARC1* oligonucleotides were administered subcutaneously at a dose of either 1 mg/kg or 4 mg/kg on study days 0, 28, 54, and 86. As depicted in the study scheme in **FIG. 11**, blood samples were collected two weeks prior to dosing (Day -14), on the dosing date (Day 1) and days 15, 29, 57, and 113 after dosing. Ultrasound-guided core needle liver biopsies were collected on Study Days -13,

27, 55, and 111. At each time point, total RNA derived from the liver biopsy samples was subjected to qRT-PCR analysis to measure *MARC1* mRNA in oligonucleotide-treated monkeys relative to those treated with a comparable volume of PBS. To normalize the data, the measurements were made relative to the reference gene, *PPIB*. The following SYBR assays purchased from IDT were used to evaluate *MARC1* gene expression: Forward- SEQ ID NO: 1690, Reverse- SEQ ID NO: 1691. The following TaqMan qPCR probe purchased from ThermoFisher Scientific, was used to evaluate *PPIB* gene expression: Rh02802984_m1. Treating NHPs with the GalNAc-conjugated *MARC1* oligonucleotides listed in **Table 6** inhibited *MARC1* expression in the liver, as determined by a reduced amount of *MARC1* mRNA in liver samples from oligonucleotide-treated NHPs relative to NHPs treated with PBS (**Table 7**).

Table 6. Single-dose GalNAc-conjugated-MARC1 Oligonucleotides for NHP Study

Name	Sense strand (SEQ ID NO)	Anti-sense strand (SEQ ID NO)
MARC1-0736	1615	1651
MARC1-0965	1632	1668
MARC1-1983	1640	1676
MARC1-2016	1625	1661

Table 7 provides the percent (%) of NHP *MARC1* mRNA remaining after treatment with GalNAc-conjugated *MARC1* oligonucleotides. NHP were treated with four doses of the indicated oligonucleotides at 1 mg/kg or 4 mg/kg according to the dosing scheme shown in **FIG. 11**. The percent (%) of mRNA remaining in liver was determined in livers collected on the indicated days (0, 28, 56, and 112). No difference was observed in weight among treatment groups.

Table 7. *MARC1* mRNA in liver samples from oligonucleotide-treated NHPs

Percent (%) <i>MARC1</i> mRNA (normalized to pre-dose & time matched PBS)					
		Study Day			
		0	28	56	112
PBS	Mean	100	100.0	100.0	100.0
	SEM	0	17.7	17.2	16.2

1mg/kg MARC1-0736	Mean	100	74.6	34.8	48.6
	SEM	0	17.0	6.4	5.9
4mg/kg MARC1-0736	Mean	100	38.1	18.3	35.3
	SEM	0	6.9	6.2	8.6
1mg/kg MARC1-0965	Mean	100	80.5	32.2	41.1
	SEM	0	15.0	12.1	14.2
4mg/kg MARC1-0965	Mean	100	57.7	23.3	39.5
	SEM	0	9.4	4.6	6.7
1mg/kg MARC1-1983	Mean	100	81.0	70.6	93.6
	SEM	0	12.6	11.0	8.4
4mg/kg MARC1-1983	Mean	100	49.8	34.5	68.8
	SEM	0	6.2	6.3	8.7
1mg/kg MARC1-2016	Mean	100	83.9	71.9	120.3
	SEM	0	9.4	17.4	23.5
4mg/kg MARC1-2016	Mean	100	62.0	56.1	71.1
	SEM	0	14.7	15.4	16.8

Gene expression related to phosphatidylcholine metabolism (*DGAT1*, *DGAT2*, *MTTP*, *APOB*, *CHKA*, *CHKB*, *PCYT1A*, *CEPT1*, *PEMT*, *PCYT2*, *ETNK*, *FMO3*, *ACC2*, *FASN*, and *FABP*) was measured on days 27, 55, and 111 and showed no changes between PBS and GalNAc-conjugated *MARC1* oligonucleotide treated NHPs (data not shown). Circulating lipids were measured on days 14, 29, 57, and 113 and there was no difference observed in TG, Cholesterol, LDLc, HDLc, or ApoB100 between PBS and GalNAc-conjugated *MARC1* oligonucleotide treated NHPs (data not shown). Similarly, no difference was observed in liver enzymes including alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), or gamma-glutamyl transferase (GGT) (data not shown).

Taken together, these results show that GalNAc-conjugated *MARC1* oligonucleotides designed to target human *MARC1* mRNA inhibit *MARC1* expression *in vivo* in the liver (as determined by the reduction in amount of hepatic *MARC1* mRNA).

Example 6 - Effect of reducing *MARC1* mRNA on lipid accumulation in vitro

The effect on lipid accumulation through the reduction of *MARC1* mRNA was assessed *in vitro* using primary human hepatocytes (PHH).

Briefly, PHH expressing endogenous human *MARC1* gene were cultured for 27 days using long-term maintenance media (Xiang et al, Science 364, 399-402, 2019). A total of 7 PHH donors were used across 25 individual experiments.

On day 7 PHH were transfected with 30 nM Dharmacon ON-TARGET plus Human

MARCI siRNA (L-019358-02-0010) or non-targeting siRNA (D-001810-10-20). On day 24 cells were treated with 0 or 800 μ M of a BSA conjugated Free Fatty Acids (FFA) mixture comprised of Oleic Acid, Linoleic Acid, Alpha Linoleic Acid and Palmitic Acid. On day 27 cells were harvested for mRNA or fixed with 4% formaldehyde.

Expression levels of *MARCI* (TaqMan™ Gene Expression Assays #4331182, Hs00224227_m1) and a housekeeping gene, *TBP* (Hs00427620_m1), were determined by qRT-PCR. *MARCI* siRNA reduced *MARCI* mRNA with an average of 18% and 14% *MARCI* mRNA remaining after 0 and 800 μ M FFA treatment, respectively, compared to non-targeting siRNA (**Table 8**).

Fixed cells were stained using Nile Red to quantify lipid accumulation (Diaz et al, Micron 39, 819-824, 2008). The Nile Red ratio was calculated as the neutral lipid fluorescence (540-15 nm/600-20 nm) divided by the phospholipid fluorescence (540-15 nm/640-20 nm). To normalize data across experiments non-targeting siRNA values were set to 0% for 0 μ M FFA and 100% for 800 μ M FFA treatment using the following equation: % of lipid accumulation = $((\text{Nile Red Ratio}_x - \text{Nile Red Ratio}_{\text{non-targeting 0 } \mu\text{M FFA}}) / (\text{Nile Red Ratio}_{\text{non-targeting 800 } \mu\text{M FFA}} - \text{Nile Red Ratio}_{\text{non-targeting 0 } \mu\text{M FFA}})) \times 100$.

In **Table 8**, lipid accumulation and *MARCI* RNA shown % remaining in 7 PHH donors across 25 independent experiments following transfection with *MARCI* siRNA and treatment with either 0 or 800 μ M FFA. Non-targeting control values at 0 μ M were set to 0% and at 800 μ M were set to 100%. Two-way ANOVA analysis demonstrated significant Fat and siRNA main effects. ** $p < 0.01$ compared to non-targeting siRNA within fat treatment by Sidak's multiple comparison test. n/a = unable to obtain values due to unsuccessful isolation of RNA.

MARCI siRNA significantly ($p < 0.01$) reduced lipid accumulation by 27% and 35% at 0 and 800 μ M FFA, respectively, compared to non-targeting siRNA (**Table 8**). It was concluded that the knockdown of *MARCI* significantly lowered both basal and FFA-induced lipid accumulation in cultured PHH.

Table 8: Effects of *MARCI* siRNA on lipid accumulation and mRNA in PHH.

Donor	Experiment	<i>MARCI</i>			
		0 μ M FFA		800 μ M FFA	
		% lipid Accumulation	% remaining (RNA)	% lipid Accumulation	% remaining (RNA)
Donor A	1	-19	8	29	4
Donor A	2	-3	5	53	5

Donor B	1	-21	n/a	68	n/a
Donor C	1	19	17	125	17
Donor C	2	-140	7	-39	6
Donor C	3	-65	9	34	8
Donor C	4	-125	7	36	4
Donor C	5	-53	11	77	9
Donor C	6	-24	88	68	17
Donor D	1	2	6	98	5
Donor D	2	-16	14	86	14
Donor E	1	-13	9	41	10
Donor E	2	-17	28	45	4
Donor E	3	-72	9	21	8
Donor E	4	-26	10	56	8
Donor E	5	-3	8	53	10
Donor E	6	-36	8	25	7
Donor F	1	-2	12	107	13
Donor F	2	-81	33	-25	31
Donor F	3	10	17	152	15
Donor F	4	4	28	110	29
Donor F	5	1	29	121	55
Donor F	6	-2	27	102	25
Donor G	1	-11	17	92	16
Donor G	2	11	23	99	17
Average		-27**	18	65**	14

SEQUENCE LISTING

Name	Strand	Sequence	SEQ ID NO
MTARC1-231	19 mer Sense Strand	GCGCAGCUCUGGAUCUACC	1
MTARC1-233	19 mer Sense Strand	GCAGCUCUGGAUCUACCCU	2
MTARC1-234	19 mer Sense Strand	CAGCUCUGGAUCUACCCUG	3
MTARC1-235	19 mer Sense Strand	AGCUCUGGAUCUACCCUGU	4
MTARC1-236	19 mer Sense Strand	GCUCUGGAUCUACCCUGUG	5
MTARC1-237	19 mer Sense Strand	CUCUGGAUCUACCCUGUGA	6
MTARC1-238	19 mer Sense Strand	UCUGGAUCUACCCUGUGAA	7
MTARC1-239	19 mer Sense Strand	CUGGAUCUACCCUGUGAAA	8
MTARC1-240	19 mer Sense Strand	UGGAUCUACCCUGUGAAAU	9
MTARC1-241	19 mer Sense Strand	GGAUCUACCCUGUGAAAUC	10
MTARC1-242	19 mer Sense Strand	GAUCUACCCUGUGAAAUCC	11
MTARC1-243	19 mer Sense Strand	AUCUACCCUGUGAAAUCCU	12
MTARC1-244	19 mer Sense Strand	UCUACCCUGUGAAAUCCUG	13
MTARC1-245	19 mer Sense Strand	CUACCCUGUGAAAUCCUGC	14
MTARC1-247	19 mer Sense Strand	ACCCUGUGAAAUCCUGCAA	15
MTARC1-248	19 mer Sense Strand	CCCUGUGAAAUCCUGCAAG	16
MTARC1-249	19 mer Sense Strand	CCUGUGAAAUCCUGCAAGG	17

MTARC1-253	19 mer Sense Strand	UGAAAUCCUGCAAGGGGGU	18
MTARC1-255	19 mer Sense Strand	AAAUCCUGCAAGGGGGUGC	19
MTARC1-318	19 mer Sense Strand	AACCUGCGGGACAGGUUUU	20
MTARC1-319	19 mer Sense Strand	ACCUGCGGGACAGGUUUUG	21
MTARC1-320	19 mer Sense Strand	CCUGCGGGACAGGUUUUGG	22
MTARC1-321	19 mer Sense Strand	CUGCGGGACAGGUUUUGGC	23
MTARC1-323	19 mer Sense Strand	GCGGGACAGGUUUUGGCUU	24
MTARC1-324	19 mer Sense Strand	CGGGACAGGUUUUGGCUUG	25
MTARC1-325	19 mer Sense Strand	GGGACAGGUUUUGGCUUGU	26
MTARC1-326	19 mer Sense Strand	GGACAGGUUUUGGCUUGUG	27
MTARC1-327	19 mer Sense Strand	GACAGGUUUUGGCUUGUGA	28
MTARC1-328	19 mer Sense Strand	ACAGGUUUUGGCUUGUGAU	29
MTARC1-329	19 mer Sense Strand	CAGGUUUUGGCUUGUGAUC	30
MTARC1-330	19 mer Sense Strand	AGGUUUUGGCUUGUGAUCA	31
MTARC1-331	19 mer Sense Strand	GGUUUUUGGCUUGUGAUCAA	32
MTARC1-332	19 mer Sense Strand	GUUUUUGGCUUGUGAUCAAC	33
MTARC1-334	19 mer Sense Strand	UUUGGCUUGUGAUCAACCA	34
MTARC1-335	19 mer Sense Strand	UUGGCUUGUGAUCAACCAG	35
MTARC1-337	19 mer Sense Strand	GGCUUGUGAUCAACCAGGA	36
MTARC1-338	19 mer Sense Strand	GCUUGUGAUCAACCAGGAG	37
MTARC1-339	19 mer Sense Strand	CUUGUGAUCAACCAGGAGG	38
MTARC1-340	19 mer Sense Strand	UUGUGAUCAACCAGGAGGG	39
MTARC1-341	19 mer Sense Strand	UGUGAUCAACCAGGAGGGA	40
MTARC1-342	19 mer Sense Strand	GUGAUCAACCAGGAGGGAA	41
MTARC1-343	19 mer Sense Strand	UGAUCAACCAGGAGGGAAA	42
MTARC1-345	19 mer Sense Strand	AUCAACCAGGAGGGAAACA	43
MTARC1-346	19 mer Sense Strand	UCAACCAGGAGGGAAACAU	44
MTARC1-347	19 mer Sense Strand	CAACCAGGAGGGAAACAUG	45
MTARC1-348	19 mer Sense Strand	AACCAGGAGGGAAACAUGG	46
MTARC1-349	19 mer Sense Strand	ACCAGGAGGGAAACAUGGU	47
MTARC1-350	19 mer Sense Strand	CCAGGAGGGAAACAUGGUU	48
MTARC1-351	19 mer Sense Strand	CAGGAGGGAAACAUGGUUA	49
MTARC1-352	19 mer Sense Strand	AGGAGGGAAACAUGGUUAC	50
MTARC1-353	19 mer Sense Strand	GGAGGGAAACAUGGUUACU	51
MTARC1-354	19 mer Sense Strand	GAGGAAACAUGGUUACUG	52
MTARC1-356	19 mer Sense Strand	GGAACAUGGUUACUGCU	53
MTARC1-357	19 mer Sense Strand	GGAAACAUGGUUACUGCUC	54
MTARC1-358	19 mer Sense Strand	GAAACAUGGUUACUGCUCG	55
MTARC1-359	19 mer Sense Strand	AAACAUGGUUACUGCUCGC	56
MTARC1-360	19 mer Sense Strand	AACAUGGUUACUGCUCGCC	57
MTARC1-361	19 mer Sense Strand	ACAUGGUUACUGCUCGCCA	58
MTARC1-362	19 mer Sense Strand	CAUGGUUACUGCUCGCCAG	59
MTARC1-365	19 mer Sense Strand	GGUUACUGCUCGCCAGGAA	60
MTARC1-376	19 mer Sense Strand	GCCAGGAACCUCGCCUGGU	61
MTARC1-379	19 mer Sense Strand	AGGAACCUCGCCUGGUCCU	62
MTARC1-384	19 mer Sense Strand	CCUCGCCUGGUCCUGAUUU	63
MTARC1-385	19 mer Sense Strand	CUCGCCUGGUCCUGAUUUC	64
MTARC1-388	19 mer Sense Strand	GCCUGGUCCUGAUUUCCCU	65
MTARC1-390	19 mer Sense Strand	CUGGUCCUGAUUUCCUGA	66
MTARC1-391	19 mer Sense Strand	UGGUCCUGAUUUCCUGAC	67
MTARC1-393	19 mer Sense Strand	GUCCUGAUUUCCUGACCU	68
MTARC1-395	19 mer Sense Strand	CCUGAUUUCCUGACCGUC	69
MTARC1-405	19 mer Sense Strand	CUGACCUGCGAUGGUGACA	70

MTARC1-409	19 mer Sense Strand	CCUGCGAUGGUGACACCCU	71
MTARC1-411	19 mer Sense Strand	UGCGAUGGUGACACCCUGA	72
MTARC1-412	19 mer Sense Strand	GCGAUGGUGACACCCUGAC	73
MTARC1-413	19 mer Sense Strand	CGAUGGUGACACCCUGACU	74
MTARC1-414	19 mer Sense Strand	GAUGGUGACACCCUGACUC	75
MTARC1-415	19 mer Sense Strand	AUGGUGACACCCUGACUCU	76
MTARC1-416	19 mer Sense Strand	UGGUGACACCCUGACUCUC	77
MTARC1-417	19 mer Sense Strand	GGUGACACCCUGACUCUCA	78
MTARC1-418	19 mer Sense Strand	GUGACACCCUGACUCUCAG	79
MTARC1-419	19 mer Sense Strand	UGACACCCUGACUCUCAGU	80
MTARC1-420	19 mer Sense Strand	GACACCCUGACUCUCAGUG	81
MTARC1-421	19 mer Sense Strand	ACACCCUGACUCUCAGUGC	82
MTARC1-422	19 mer Sense Strand	CACCCUGACUCUCAGUGCA	83
MTARC1-423	19 mer Sense Strand	ACCCUGACUCUCAGUGCAG	84
MTARC1-424	19 mer Sense Strand	CCCUGACUCUCAGUGCAGC	85
MTARC1-425	19 mer Sense Strand	CCUGACUCUCAGUGCAGCC	86
MTARC1-426	19 mer Sense Strand	CUGACUCUCAGUGCAGCCU	87
MTARC1-427	19 mer Sense Strand	UGACUCUCAGUGCAGCCUA	88
MTARC1-428	19 mer Sense Strand	GACUCUCAGUGCAGCCUAC	89
MTARC1-429	19 mer Sense Strand	ACUCUCAGUGCAGCCUACA	90
MTARC1-430	19 mer Sense Strand	CUCUCAGUGCAGCCUACAC	91
MTARC1-431	19 mer Sense Strand	UCUCAGUGCAGCCUACACA	92
MTARC1-433	19 mer Sense Strand	UCAGUGCAGCCUACACAAA	93
MTARC1-434	19 mer Sense Strand	CAGUGCAGCCUACACAAAG	94
MTARC1-435	19 mer Sense Strand	AGUGCAGCCUACACAAAGG	95
MTARC1-436	19 mer Sense Strand	GUGCAGCCUACACAAAGGA	96
MTARC1-437	19 mer Sense Strand	UGCAGCCUACACAAAGGAC	97
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MTARC1-448	19 mer Sense Strand	CAAAGGACCUACUACUGCC	105
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MTARC1-450	19 mer Sense Strand	AAGGACCUACUACUGCCUA	107
MTARC1-451	19 mer Sense Strand	AGGACCUACUACUGCCUAU	108
MTARC1-452	19 mer Sense Strand	GGACCUACUACUGCCUAUC	109
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MTARC1-462	19 mer Sense Strand	CUGCCUAUCAAAACGCCCA	117
MTARC1-468	19 mer Sense Strand	AUCAAAACGCCCACCACAA	118
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MTARC1-473	19 mer Sense Strand	AACGCCCACCACAAUGCA	122
MTARC1-475	19 mer Sense Strand	CGCCCACCACAAUGCAGU	123

MTARC1-476	19 mer Sense Strand	GCCCACCACAAAUGCAGUG	124
MTARC1-482	19 mer Sense Strand	CACAAAUGCAGUGCACAAG	125
MTARC1-483	19 mer Sense Strand	ACAAAUGCAGUGCACAAGU	126
MTARC1-484	19 mer Sense Strand	CAAAUGCAGUGCACAAGUG	127
MTARC1-552	19 mer Sense Strand	GCCCAGUGGAUAACCAGCU	128
MTARC1-553	19 mer Sense Strand	CCCAGUGGAUAACCAGCUU	129
MTARC1-554	19 mer Sense Strand	CCAGUGGAUAACCAGCUUC	130
MTARC1-555	19 mer Sense Strand	CAGUGGAUAACCAGCUUCC	131
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MTARC1-562	19 mer Sense Strand	UAACCAGCUUCCUGAAGUC	138
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MTARC1-564	19 mer Sense Strand	ACCAGCUUCCUGAAGUCAC	140
MTARC1-565	19 mer Sense Strand	CCAGCUUCCUGAAGUCACA	141
MTARC1-566	19 mer Sense Strand	CAGCUUCCUGAAGUCACAG	142
MTARC1-567	19 mer Sense Strand	AGCUUCCUGAAGUCACAGC	143
MTARC1-568	19 mer Sense Strand	GCUUCCUGAAGUCACAGCC	144
MTARC1-589	19 mer Sense Strand	ACCGCCUGGUGCACUUCGA	145
MTARC1-591	19 mer Sense Strand	CGCCUGGUGCACUUCGAGC	146
MTARC1-592	19 mer Sense Strand	GCCUGGUGCACUUCGAGCC	147
MTARC1-593	19 mer Sense Strand	CCUGGUGCACUUCGAGCCU	148
MTARC1-597	19 mer Sense Strand	GUGCACUUCGAGCCUCACA	149
MTARC1-600	19 mer Sense Strand	CACUUCGAGCCUCACAUGC	150
MTARC1-612	19 mer Sense Strand	CACAUGCGACCGAGACGUC	151
MTARC1-614	19 mer Sense Strand	CAUGCGACCGAGACGUCCU	152
MTARC1-617	19 mer Sense Strand	GCGACCGAGACGUCCUCAU	153
MTARC1-618	19 mer Sense Strand	CGACCGAGACGUCCUCAUC	154
MTARC1-620	19 mer Sense Strand	ACCGAGACGUCCUCAUCAA	155
MTARC1-621	19 mer Sense Strand	CCGAGACGUCCUCAUCAAA	156
MTARC1-622	19 mer Sense Strand	CGAGACGUCCUCAUCAAU	157
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MTARC1-627	19 mer Sense Strand	CGUCCUCAUCAAUAGCAG	162
MTARC1-628	19 mer Sense Strand	GUCCUCAUCAAUAGCAGA	163
MTARC1-629	19 mer Sense Strand	UCCUCAUCAAUAGCAGAC	164
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MTARC1-633	19 mer Sense Strand	CAUCAAUAGCAGACUUGU	168
MTARC1-634	19 mer Sense Strand	AUCAAUAGCAGACUUGUU	169
MTARC1-635	19 mer Sense Strand	UCAAUAGCAGACUUGUUC	170
MTARC1-636	19 mer Sense Strand	CAAAUAGCAGACUUGUCC	171
MTARC1-637	19 mer Sense Strand	AAAUAGCAGACUUGUCCG	172
MTARC1-638	19 mer Sense Strand	AAUAGCAGACUUGUCCGA	173
MTARC1-639	19 mer Sense Strand	AUAGCAGACUUGUCCGAC	174
MTARC1-640	19 mer Sense Strand	UAGCAGACUUGUCCGACC	175
MTARC1-641	19 mer Sense Strand	AGCAGACUUGUCCGACCC	176

MTARC1-642	19 mer Sense Strand	GCAGACUUGUUCCGACCCA	177
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MTARC1-644	19 mer Sense Strand	AGACUUGUUCCGACCCAAG	179
MTARC1-645	19 mer Sense Strand	GACUUGUUCCGACCCAAGG	180
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MTARC1-648	19 mer Sense Strand	UUGUUCCGACCCAAGGACC	183
MTARC1-649	19 mer Sense Strand	UGUUCCGACCCAAGGACCA	184
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MTARC1-652	19 mer Sense Strand	UCCGACCCAAGGACCAGAU	187
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MTARC1-665	19 mer Sense Strand	CCAGAUUGCUUACUCAGAC	200
MTARC1-666	19 mer Sense Strand	CAGAUUGCUUACUCAGACA	201
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MTARC1-678	19 mer Sense Strand	UCAGACACCAGCCCAUUCU	213
MTARC1-679	19 mer Sense Strand	CAGACACCAGCCCAUUCUU	214
MTARC1-680	19 mer Sense Strand	AGACACCAGCCCAUUCUUG	215
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MTARC1-683	19 mer Sense Strand	CACCAGCCCAUUCUUGAUC	218
MTARC1-684	19 mer Sense Strand	ACCAGCCCAUUCUUGAUCC	219
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MTARC1-686	19 mer Sense Strand	CAGCCCAUUCUUGAUCCUU	221
MTARC1-687	19 mer Sense Strand	AGCCCAUUCUUGAUCCUUU	222
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MTARC1-692	19 mer Sense Strand	AUUCUUGAUCCUUUCUGAG	224
MTARC1-724	19 mer Sense Strand	AUCUCAACUCCAGGCUAGA	225
MTARC1-726	19 mer Sense Strand	CUCAACUCCAGGCUAGAGA	226
MTARC1-728	19 mer Sense Strand	CAACUCCAGGCUAGAGAAG	227
MTARC1-729	19 mer Sense Strand	AACUCCAGGCUAGAGAAGA	228
MTARC1-730	19 mer Sense Strand	ACUCCAGGCUAGAGAAGAA	229

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MTARC1-733	19 mer Sense Strand	CCAGGCUAGAGAAGAAAGU	231
MTARC1-734	19 mer Sense Strand	CAGGCUAGAGAAGAAAGUU	232
MTARC1-735	19 mer Sense Strand	AGGCUAGAGAAGAAAGUUA	233
MTARC1-736	19 mer Sense Strand	GGCUAGAGAAGAAAGUAAA	234
MTARC1-737	19 mer Sense Strand	GCUAGAGAAGAAAGUAAAA	235
MTARC1-738	19 mer Sense Strand	CUAGAGAAGAAAGUAAAAG	236
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MTARC1-743	19 mer Sense Strand	GAAGAAAGUAAAAGCAACC	241
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MTARC1-759	19 mer Sense Strand	ACCAACUUCAGGCCCAAUA	255
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MTARC1-761	19 mer Sense Strand	CAACUUCAGGCCCAAUAUU	257
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MTARC1-763	19 mer Sense Strand	ACUUCAGGCCCAAUAUUGU	259
MTARC1-764	19 mer Sense Strand	CUUCAGGCCCAAUAUUGUA	260
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MTARC1-779	19 mer Sense Strand	UGUAAUUUCAGGAUGCGAU	275
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MTARC1-781	19 mer Sense Strand	UAAUUUCAGGAUGCGAUGU	277
MTARC1-782	19 mer Sense Strand	AAUUUCAGGAUGCGAUGUC	278
MTARC1-783	19 mer Sense Strand	AUUUCAGGAUGCGAUGUCU	279
MTARC1-784	19 mer Sense Strand	UUUCAGGAUGCGAUGUCUA	280
MTARC1-785	19 mer Sense Strand	UUCAGGAUGCGAUGUCUAU	281
MTARC1-786	19 mer Sense Strand	UCAGGAUGCGAUGUCUAUG	282

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MTARC1-788	19 mer Sense Strand	AGGAUGCGAUGUCUAUGCA	284
MTARC1-789	19 mer Sense Strand	GGAUGCGAUGUCUAUGCAG	285
MTARC1-790	19 mer Sense Strand	GAUGCGAUGUCUAUGCAGA	286
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MTARC1-792	19 mer Sense Strand	UGCGAUGUCUAUGCAGAGG	288
MTARC1-863	19 mer Sense Strand	UUGUCCAGAUGCAUUUUA	289
MTARC1-929	19 mer Sense Strand	GGAAACACUGAAGAGUUUA	290
MTARC1-930	19 mer Sense Strand	GAAACACUGAAGAGUUAUC	291
MTARC1-934	19 mer Sense Strand	CACUGAAGAGUUAUCGCCA	292
MTARC1-955	19 mer Sense Strand	GUGACCCUUCAGAACGAAA	293
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MTARC1-1165	19 mer Sense Strand	ACAUUUUCUUUAAAUUUGU	319
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MTARC1-1173	19 mer Sense Strand	UUUAAAUUUGUGAUUUUCA	321
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MTARC1-1664	19 mer Sense Strand	UCAGACAGCAUUGGAUUUC	334
MTARC1-1812	19 mer Sense Strand	AGAAAAGUGAUUCAGUGAU	335

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MTARC1-1868	19 mer Sense Strand	GGAAAGCAUAUGUCAGUUG	337
MTARC1-1869	19 mer Sense Strand	GAAAGCAUAUGUCAGUUGU	338
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MTARC1-1883	19 mer Sense Strand	GUUGUUUAAAACCCAAUAU	344
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MTARC1-1935	19 mer Sense Strand	UGAUGAAGUAUAUUUUUUA	348
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MTARC1-1953	19 mer Sense Strand	AUUGCCAUUUUGUCCUUG	353
MTARC1-1955	19 mer Sense Strand	UGCCAUUUUGUCCUUGAU	354
MTARC1-1981	19 mer Sense Strand	GGAAGUUGACUAAACUUGA	355
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MTARC1-2017	19 mer Sense Strand	GUGAAUAAAUGGAAGCUAC	377
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MTARC1-2027	19 mer Sense Strand	GGAAGCUACUUUGACUAGU	384
MTARC1-231	19 mer Anti-sense Strand	GGUAGAUCAGAGCUGCGC	385
MTARC1-233	19 mer Anti-sense Strand	AGGGUAGAUCAGAGCUGC	386
MTARC1-234	19 mer Anti-sense Strand	CAGGGUAGAUCAGAGCUG	387
MTARC1-235	19 mer Anti-sense Strand	ACAGGGUAGAUCAGAGCU	388

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MTARC1-356	19 mer Anti-sense Strand	AGCAGUAACCAUGUUUCCC	437
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MTARC1-358	19 mer Anti-sense Strand	CGAGCAGUAACCAUGUUUC	439
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MTARC1-360	19 mer Anti-sense Strand	GGCGAGCAGUAACCAUGUU	441

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MTARC1-362	19 mer Anti-sense Strand	CUGGCGAGCAGUAACCAUG	443
MTARC1-365	19 mer Anti-sense Strand	UUCCUGGCGAGCAGUAACC	444
MTARC1-376	19 mer Anti-sense Strand	ACCAGGCGAGGUUCCUGGC	445
MTARC1-379	19 mer Anti-sense Strand	AGGACCAGGCGAGGUUCCU	446
MTARC1-384	19 mer Anti-sense Strand	AAAUCAGGACCAGGCGAGG	447
MTARC1-385	19 mer Anti-sense Strand	GAAAUCAGGACCAGGCGAG	448
MTARC1-388	19 mer Anti-sense Strand	AGGGAAAUCAGGACCAGGC	449
MTARC1-390	19 mer Anti-sense Strand	UCAGGGAAAUCAGGACCAG	450
MTARC1-391	19 mer Anti-sense Strand	GUCAGGGAAAUCAGGACCA	451
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MTARC1-419	19 mer Anti-sense Strand	ACUGAGAGUCAGGGUGUCA	464
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MTARC1-423	19 mer Anti-sense Strand	CUGCACUGAGAGUCAGGGU	468
MTARC1-424	19 mer Anti-sense Strand	GCUGCACUGAGAGUCAGGG	469
MTARC1-425	19 mer Anti-sense Strand	GGCUGCACUGAGAGUCAGG	470
MTARC1-426	19 mer Anti-sense Strand	AGGCUGCACUGAGAGUCAG	471
MTARC1-427	19 mer Anti-sense Strand	UAGGCUGCACUGAGAGUCA	472
MTARC1-428	19 mer Anti-sense Strand	GUAGGCUGCACUGAGAGUC	473
MTARC1-429	19 mer Anti-sense Strand	UGUAGGCUGCACUGAGAGU	474
MTARC1-430	19 mer Anti-sense Strand	GUGUAGGCUGCACUGAGAG	475
MTARC1-431	19 mer Anti-sense Strand	UGUGUAGGCUGCACUGAGA	476
MTARC1-433	19 mer Anti-sense Strand	UUUGUGUAGGCUGCACUGA	477
MTARC1-434	19 mer Anti-sense Strand	CUUUGUGUAGGCUGCACUG	478
MTARC1-435	19 mer Anti-sense Strand	CCUUUGUGUAGGCUGCACU	479
MTARC1-436	19 mer Anti-sense Strand	UCCUUUGUGUAGGCUGCAC	480
MTARC1-437	19 mer Anti-sense Strand	GUCCUUUGUGUAGGCUGCA	481
MTARC1-438	19 mer Anti-sense Strand	GGUCCUUUGUGUAGGCUGC	482
MTARC1-439	19 mer Anti-sense Strand	AGGUCCUUUGUGUAGGCUG	483
MTARC1-440	19 mer Anti-sense Strand	UAGGUCCUUUGUGUAGGCU	484
MTARC1-441	19 mer Anti-sense Strand	GUAGGUCCUUUGUGUAGGC	485
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MTARC1-446	19 mer Anti-sense Strand	CAGUAGUAGGUCCUUUGUG	487
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MTARC1-448	19 mer Anti-sense Strand	GGCAGUAGUAGGUCCUUUG	489
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MTARC1-450	19 mer Anti-sense Strand	UAGGCAGUAGUAGGUCCUU	491
MTARC1-451	19 mer Anti-sense Strand	AUAGGCAGUAGUAGGUCCU	492
MTARC1-452	19 mer Anti-sense Strand	GAUAGGCAGUAGUAGGUCC	493
MTARC1-453	19 mer Anti-sense Strand	UGAUAGGCAGUAGUAGGUC	494

MTARC1-454	19 mer Anti-sense Strand	UUGAUAGGCAGUAGUAGGU	495
MTARC1-456	19 mer Anti-sense Strand	UUUUGAUAGGCAGUAGUAG	496
MTARC1-457	19 mer Anti-sense Strand	GUUUUGAUAGGCAGUAGUA	497
MTARC1-458	19 mer Anti-sense Strand	CGUUUUGAUAGGCAGUAGU	498
MTARC1-459	19 mer Anti-sense Strand	GCGUUUUGAUAGGCAGUAG	499
MTARC1-460	19 mer Anti-sense Strand	GGCGUUUUGAUAGGCAGUA	500
MTARC1-462	19 mer Anti-sense Strand	UGGGCGUUUUGAUAGGCAG	501
MTARC1-468	19 mer Anti-sense Strand	UUGUGGUGGGCGUUUUGAU	502
MTARC1-469	19 mer Anti-sense Strand	UUUGUGGUGGGCGUUUUGA	503
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MTARC1-471	19 mer Anti-sense Strand	CAUUUGUGGUGGGCGUUUU	505
MTARC1-473	19 mer Anti-sense Strand	UGCAUUUGUGGUGGGCGUU	506
MTARC1-475	19 mer Anti-sense Strand	ACUGCAUUUGUGGUGGGCG	507
MTARC1-476	19 mer Anti-sense Strand	CACUGCAUUUGUGGUGGGC	508
MTARC1-482	19 mer Anti-sense Strand	CUUGUGCACUGCAUUUGUG	509
MTARC1-483	19 mer Anti-sense Strand	ACUUGUGCACUGCAUUUGU	510
MTARC1-484	19 mer Anti-sense Strand	CACUUGUGCACUGCAUUUG	511
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MTARC1-553	19 mer Anti-sense Strand	AAGCUGGUUAUCCACUGGG	513
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MTARC1-564	19 mer Anti-sense Strand	GUGACUUCAGGAAGCUGGU	524
MTARC1-565	19 mer Anti-sense Strand	UGUGACUUCAGGAAGCUGG	525
MTARC1-566	19 mer Anti-sense Strand	CUGUGACUUCAGGAAGCUG	526
MTARC1-567	19 mer Anti-sense Strand	GCUGUGACUUCAGGAAGCU	527
MTARC1-568	19 mer Anti-sense Strand	GGCUGUGACUUCAGGAAGC	528
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MTARC1-597	19 mer Anti-sense Strand	UGUGAGGCUCGAAGUGCAC	533
MTARC1-600	19 mer Anti-sense Strand	GCAUGUGAGGCUCGAAGUG	534
MTARC1-612	19 mer Anti-sense Strand	GACGUCUCGGUCGCAUGUG	535
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MTARC1-617	19 mer Anti-sense Strand	AUGAGGACGUCUCGGUCGC	537
MTARC1-618	19 mer Anti-sense Strand	GAUGAGGACGUCUCGGUCG	538
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MTARC1-621	19 mer Anti-sense Strand	UUUGAUGAGGACGUCUCGG	540
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MTARC1-623	19 mer Anti-sense Strand	UAUUUGAUGAGGACGUCUC	542
MTARC1-624	19 mer Anti-sense Strand	CUAUUUUGAUGAGGACGUCU	543
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MTARC1-626	19 mer Anti-sense Strand	UGCUAUUUGAUGAGGACGU	545
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MTARC1-628	19 mer Anti-sense Strand	UCUGCUAUUUUGAUGAGGAC	547

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MTARC1-645	19 mer Anti-sense Strand	CCUUGGGUCGGAACAAGUC	564
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MTARC1-657	19 mer Anti-sense Strand	AAGCAAUCUGGUCCUUGGG	576
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MTARC1-662	19 mer Anti-sense Strand	UGAGUAAGCAAUCUGGUCC	581
MTARC1-663	19 mer Anti-sense Strand	CUGAGUAAGCAAUCUGGUC	582
MTARC1-664	19 mer Anti-sense Strand	UCUGAGUAAGCAAUCUGGU	583
MTARC1-665	19 mer Anti-sense Strand	GUCUGAGUAAGCAAUCUGG	584
MTARC1-666	19 mer Anti-sense Strand	UGUCUGAGUAAGCAAUCUG	585
MTARC1-667	19 mer Anti-sense Strand	GUGUCUGAGUAAGCAAUCU	586
MTARC1-668	19 mer Anti-sense Strand	GGUGUCUGAGUAAGCAAUC	587
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MTARC1-671	19 mer Anti-sense Strand	GCUGGUGUCUGAGUAAGCA	590
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MTARC1-676	19 mer Anti-sense Strand	AAUGGGCUGGUGUCUGAGU	595
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MTARC1-724	19 mer Anti-sense Strand	UCUAGCCUGGAGUUGAGAU	609
MTARC1-726	19 mer Anti-sense Strand	UCUCUAGCCUGGAGUUGAG	610
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MTARC1-731	19 mer Anti-sense Strand	UUUCUUCUCUAGCCUGGAG	614
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MTARC1-734	19 mer Anti-sense Strand	AACUUUCUUCUCUAGCCUG	616
MTARC1-735	19 mer Anti-sense Strand	UAAUUUCUUCUCUAGCCU	617
MTARC1-736	19 mer Anti-sense Strand	UUAACUUUCUUCUCUAGCC	618
MTARC1-737	19 mer Anti-sense Strand	UUUAACUUUCUUCUCUAGC	619
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MTARC1-741	19 mer Anti-sense Strand	UUGCUIUAACUUUCUUCUC	623
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MTARC1-764	19 mer Anti-sense Strand	UACAAUAUUGGGCCUGAAG	644
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MTARC1-766	19 mer Anti-sense Strand	AUUACAAUAUUGGGCCUGA	646
MTARC1-767	19 mer Anti-sense Strand	AAUUACAAUAUUGGGCCUG	647
MTARC1-768	19 mer Anti-sense Strand	AAAUUACAAUAUUGGGCCU	648
MTARC1-769	19 mer Anti-sense Strand	GAAAUUACAAUAUUGGGCC	649
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MTARC1-784	19 mer Anti-sense Strand	UAGACAUCGCAUCCUGAAA	664
MTARC1-785	19 mer Anti-sense Strand	AUAGACAUCGCAUCCUGAA	665
MTARC1-786	19 mer Anti-sense Strand	CAUAGACAUCGCAUCCUGA	666
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MTARC1-789	19 mer Anti-sense Strand	CUGCAUAGACAUCGCAUCC	669
MTARC1-790	19 mer Anti-sense Strand	UCUGCAUAGACAUCGCAUC	670
MTARC1-791	19 mer Anti-sense Strand	CUCUGCAUAGACAUCGCAU	671
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MTARC1-863	19 mer Anti-sense Strand	UAAAAUGCAUCUGGAACAA	673
MTARC1-929	19 mer Anti-sense Strand	AUAACUCUUCAGUGUUUCC	674
MTARC1-930	19 mer Anti-sense Strand	GAUAACUCUUCAGUGUUUC	675
MTARC1-934	19 mer Anti-sense Strand	UGGCGAUAACUCUUCAGUG	676
MTARC1-955	19 mer Anti-sense Strand	UUUCGUUCUGAAGGGUCAC	677
MTARC1-959	19 mer Anti-sense Strand	UAACUUUCGUUCUGAAGGG	678
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MTARC1-971	19 mer Anti-sense Strand	UGAUUUCCAUAUAACUUU	687
MTARC1-1107	19 mer Anti-sense Strand	CAUUUUUGAGAACAUUUUU	688
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MTARC1-1118	19 mer Anti-sense Strand	UCAAGUGUUGUCAUUUUUG	690
MTARC1-1123	19 mer Anti-sense Strand	AUGCUUCAAGUGUUGUCAU	691
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MTARC1-1128	19 mer Anti-sense Strand	ACACCAUGCUUCAAGUGUU	694
MTARC1-1129	19 mer Anti-sense Strand	AACACCAUGCUUCAAGUGU	695
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MTARC1-1132	19 mer Anti-sense Strand	UGAAACACCAUGCUUCAAG	697
MTARC1-1133	19 mer Anti-sense Strand	CUGAAACACCAUGCUUCA	698
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MTARC1-1139	19 mer Anti-sense Strand	UCAGUUCUGAAACACCAUG	701
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MTARC1-1167	19 mer Anti-sense Strand	UCACAAAUUUAAAGAAAAU	704
MTARC1-1173	19 mer Anti-sense Strand	UGAAAAUCACAAAUUUAAA	705
MTARC1-1177	19 mer Anti-sense Strand	AAUGUGAAAAUCACAAAUU	706

MTARC1-1179	19 mer Anti-sense Strand	AAAAUGUGAAAAUCACAAA	707
MTARC1-1329	19 mer Anti-sense Strand	AUUCCAUAUUCAGUUAAC	708
MTARC1-1330	19 mer Anti-sense Strand	UAUUCCAUAUUCAGUUA	709
MTARC1-1332	19 mer Anti-sense Strand	ACUAUCCAUAUUCAGUUA	710
MTARC1-1333	19 mer Anti-sense Strand	AACUAUCCAUAUUCAGUU	711
MTARC1-1334	19 mer Anti-sense Strand	GAACUAUCCAUAUUCAGU	712
MTARC1-1335	19 mer Anti-sense Strand	AGAACUAUCCAUAUUCAG	713
MTARC1-1620	19 mer Anti-sense Strand	UAUGGAAAAUUAUUCUG	714
MTARC1-1622	19 mer Anti-sense Strand	UCUAUGGAAAAUUAUUC	715
MTARC1-1660	19 mer Anti-sense Strand	UCCAAUGCUGUCUGAGAAG	716
MTARC1-1663	19 mer Anti-sense Strand	AAAUCCAUGCUGUCUGAG	717
MTARC1-1664	19 mer Anti-sense Strand	GAAAUCCAUGCUGUCUGA	718
MTARC1-1812	19 mer Anti-sense Strand	AUCACUGAAUCACUUUUCU	719
MTARC1-1816	19 mer Anti-sense Strand	UGAAAUACUGAAUCACUU	720
MTARC1-1868	19 mer Anti-sense Strand	CAACUGACAUUUGCUUCC	721
MTARC1-1869	19 mer Anti-sense Strand	ACAACUGACAUUUGCUUUC	722
MTARC1-1876	19 mer Anti-sense Strand	GUUUUAAACAACUGACAU	723
MTARC1-1877	19 mer Anti-sense Strand	GGUUUAAACAACUGACAU	724
MTARC1-1878	19 mer Anti-sense Strand	GGGUUUUAAACAACUGACA	725
MTARC1-1879	19 mer Anti-sense Strand	UGGGUUUAAACAACUGAC	726
MTARC1-1882	19 mer Anti-sense Strand	UAUUGGUUUUAAACAACU	727
MTARC1-1883	19 mer Anti-sense Strand	AUAUUGGUUUUAAACAAC	728
MTARC1-1884	19 mer Anti-sense Strand	GAUAUUGGUUUUAAACAA	729
MTARC1-1885	19 mer Anti-sense Strand	AGAUUUGGUUUUAAACA	730
MTARC1-1886	19 mer Anti-sense Strand	UAGAUUUGGUUUUAAAC	731
MTARC1-1935	19 mer Anti-sense Strand	UAAAAAUUACUUCAUCA	732
MTARC1-1936	19 mer Anti-sense Strand	AUAAAAAUUACUUCAUUC	733
MTARC1-1937	19 mer Anti-sense Strand	AAUAAAAAUUACUUCAU	734
MTARC1-1939	19 mer Anti-sense Strand	GCAAUAAAAAUUACUUC	735
MTARC1-1941	19 mer Anti-sense Strand	UGGCAAUAAAAAUUACU	736
MTARC1-1953	19 mer Anti-sense Strand	CAAAGGACAAAUGGCAU	737
MTARC1-1955	19 mer Anti-sense Strand	AUCAAAGGACAAAUGGCA	738
MTARC1-1981	19 mer Anti-sense Strand	UCAAGUUUAGUCAACUCC	739
MTARC1-1983	19 mer Anti-sense Strand	UUUCAAGUUUAGUCAACU	740
MTARC1-1985	19 mer Anti-sense Strand	UUUUUCAAGUUUAGUCAAC	741
MTARC1-1986	19 mer Anti-sense Strand	AUUUUUCAAGUUUAGUCA	742
MTARC1-1988	19 mer Anti-sense Strand	ACAUUUUUCAGUUUAGUC	743
MTARC1-1989	19 mer Anti-sense Strand	AACAUUUUUCAGUUUAGU	744
MTARC1-1990	19 mer Anti-sense Strand	AAACAUUUUUCAGUUUAG	745
MTARC1-1995	19 mer Anti-sense Strand	UUUAAAAACAUUUUUCAAG	746
MTARC1-1996	19 mer Anti-sense Strand	UUUUAAAAACAUUUUUCA	747
MTARC1-1998	19 mer Anti-sense Strand	AGUUUUAAAAACAUUUUUC	748
MTARC1-1999	19 mer Anti-sense Strand	CAGUUUUAAAAACAUUUUU	749
MTARC1-2000	19 mer Anti-sense Strand	ACAGUUUUAAAAACAUUUU	750
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MTARC1-2005	19 mer Anti-sense Strand	UAUUCACAGUUUUAAAAAC	753
MTARC1-2006	19 mer Anti-sense Strand	UUAUUCACAGUUUUAAAAA	754
MTARC1-2010	19 mer Anti-sense Strand	CCAUUUAUUCACAGUUUUA	755
MTARC1-2011	19 mer Anti-sense Strand	UCCAUUUAUUCACAGUUUU	756
MTARC1-2012	19 mer Anti-sense Strand	UUCCAUUUAUUCACAGUUU	757
MTARC1-2013	19 mer Anti-sense Strand	CUUCCAUUUAUUCACAGUU	758
MTARC1-2015	19 mer Anti-sense Strand	AGCUUCCAUUUAUUCACAG	759

MTARC1-2016	19 mer Anti-sense Strand	UAGCUUCCAUUUAUUCACA	760
MTARC1-2017	19 mer Anti-sense Strand	GUAGCUUCCAUUUAUUCAC	761
MTARC1-2018	19 mer Anti-sense Strand	AGUAGCUUCCAUUUAUUCA	762
MTARC1-2019	19 mer Anti-sense Strand	AAGUAGCUUCCAUUUAUUC	763
MTARC1-2020	19 mer Anti-sense Strand	AAAGUAGCUUCCAUUUAUU	764
MTARC1-2022	19 mer Anti-sense Strand	UCAAAGUAGCUUCCAUUUA	765
MTARC1-2023	19 mer Anti-sense Strand	GUCAAAGUAGCUUCCAUUU	766
MTARC1-2025	19 mer Anti-sense Strand	UAGUCAAGUAGCUUCCA	767
MTARC1-2027	19 mer Anti-sense Strand	ACUAGUCAAGUAGCUUCC	768
MTARC1-231	25 mer Sense Strand	GCGCAGCUCUGGAUCUACCAUGUGA	769
MTARC1-233	25 mer Sense Strand	GCAGCUCUGGAUCUACCCUAGUAAA	770
MTARC1-234	25 mer Sense Strand	CAGCUCUGGAUCUACCCUGAGAAAU	771
MTARC1-235	25 mer Sense Strand	AGCUCUGGAUCUACCCUGUAAAAUC	772
MTARC1-236	25 mer Sense Strand	GCUCUGGAUCUACCCUGUGAAAUCC	773
MTARC1-237	25 mer Sense Strand	CUCUGGAUCUACCCUGUGAAAUCCU	774
MTARC1-238	25 mer Sense Strand	UCUGGAUCUACCCUGUGAAAUCCUG	775
MTARC1-239	25 mer Sense Strand	CUGGAUCUACCCUGUGAAAUCCUGC	776
MTARC1-240	25 mer Sense Strand	UGGAUCUACCCUGUGAAAUACUGCA	777
MTARC1-241	25 mer Sense Strand	GGAUCUACCCUGUGAAAUCAUGCAA	778
MTARC1-242	25 mer Sense Strand	GAUCUACCCUGUGAAAUCCAGCAAG	779
MTARC1-243	25 mer Sense Strand	AUCUACCCUGUGAAAUCCUACAAGG	780
MTARC1-244	25 mer Sense Strand	UCUACCCUGUGAAAUCCUGAAAGGG	781
MTARC1-245	25 mer Sense Strand	CUACCCUGUGAAAUCCUGCAAGGGG	782
MTARC1-247	25 mer Sense Strand	ACCCUGUGAAAUCCUGCAAAGGGGU	783
MTARC1-248	25 mer Sense Strand	CCCUGUGAAAUCCUGCAAGAGGGUG	784
MTARC1-249	25 mer Sense Strand	CCUGUGAAAUCCUGCAAGGAGGUGC	785
MTARC1-253	25 mer Sense Strand	UGAAAUCCUGCAAGGGGGUACCGGU	786
MTARC1-255	25 mer Sense Strand	AAAUCCUGCAAGGGGGUGCAGGUGA	787
MTARC1-318	25 mer Sense Strand	AACCUGCGGGACAGGUUUUAGCUUG	788
MTARC1-319	25 mer Sense Strand	ACCUGCGGGACAGGUUUUGACUUGU	789
MTARC1-320	25 mer Sense Strand	CCUGCGGGACAGGUUUUGGAUUGUG	790
MTARC1-321	25 mer Sense Strand	CUGCGGGACAGGUUUUGGCAUGUGA	791
MTARC1-323	25 mer Sense Strand	GCGGGACAGGUUUUGGCUUAUGAUC	792
MTARC1-324	25 mer Sense Strand	CGGGACAGGUUUUGGCUUGAGAUA	793
MTARC1-325	25 mer Sense Strand	GGGACAGGUUUUGGCUUGUAAUCAA	794
MTARC1-326	25 mer Sense Strand	GGACAGGUUUUGGCUUGUGAUCAAC	795
MTARC1-327	25 mer Sense Strand	GACAGGUUUUGGCUUGUGAACAACC	796
MTARC1-328	25 mer Sense Strand	ACAGGUUUUGGCUUGUGAUAAACCA	797
MTARC1-329	25 mer Sense Strand	CAGGUUUUGGCUUGUGAUCAACCAG	798
MTARC1-330	25 mer Sense Strand	AGGUUUUGGCUUGUGAUCAACCAGG	799
MTARC1-331	25 mer Sense Strand	GGUUUUUGGCUUGUGAUCAAAACAGGA	800
MTARC1-332	25 mer Sense Strand	GUUUUUGGCUUGUGAUCAACAAGGAG	801
MTARC1-334	25 mer Sense Strand	UUUGGCUUGUGAUCAACCAAGAGGG	802
MTARC1-335	25 mer Sense Strand	UUGGCUUGUGAUCAACCAGAAGGGA	803
MTARC1-337	25 mer Sense Strand	GGCUUGUGAUCAACCAGGAAGGAAA	804
MTARC1-338	25 mer Sense Strand	GCUUGUGAUCAACCAGGAGAGAAAC	805
MTARC1-339	25 mer Sense Strand	CUUGUGAUCAACCAGGAGGAAAACA	806
MTARC1-340	25 mer Sense Strand	UUGUGAUCAACCAGGAGGGAAACAU	807
MTARC1-341	25 mer Sense Strand	UGUGAUCAACCAGGAGGGAAACAUG	808
MTARC1-342	25 mer Sense Strand	GUGAUCAACCAGGAGGGAAACAUGG	809
MTARC1-343	25 mer Sense Strand	UGAUCAACCAGGAGGGAAAAAUGGU	810
MTARC1-345	25 mer Sense Strand	AUCAACCAGGAGGGAAACAAGGUUA	811
MTARC1-346	25 mer Sense Strand	UCAACCAGGAGGGAAACAAGUUAC	812

MTARC1-347	25 mer Sense Strand	CAACCAGGAGGGGAAACAUGAUUACU	813
MTARC1-348	25 mer Sense Strand	AACCAGGAGGGGAAACAUGGAUACUG	814
MTARC1-349	25 mer Sense Strand	ACCAGGAGGGGAAACAUGGUUACUGC	815
MTARC1-350	25 mer Sense Strand	CCAGGAGGGGAAACAUGGUUACUGCU	816
MTARC1-351	25 mer Sense Strand	CAGGAGGGGAAACAUGGUUAAUGCUC	817
MTARC1-352	25 mer Sense Strand	AGGAGGGGAAACAUGGUUACAGCUCG	818
MTARC1-353	25 mer Sense Strand	GGAGGGGAAACAUGGUUACUACUCGC	819
MTARC1-354	25 mer Sense Strand	GAGGGAAACAUGGUUACUGAUCGCC	820
MTARC1-356	25 mer Sense Strand	GGGAAACAUGGUUACUGCUAGCCAG	821
MTARC1-357	25 mer Sense Strand	GGAACAUGGUUACUGCUCACCAGG	822
MTARC1-358	25 mer Sense Strand	GAAACAUGGUUACUGCUCGACAGGA	823
MTARC1-359	25 mer Sense Strand	AAACAUGGUUACUGCUCGCAAGGAA	824
MTARC1-360	25 mer Sense Strand	AACAUGGUUACUGCUCGCCAGGAAC	825
MTARC1-361	25 mer Sense Strand	ACAUGGUUACUGCUCGCCAAGAACC	826
MTARC1-362	25 mer Sense Strand	CAUGGUUACUGCUCGCCAGAAACCU	827
MTARC1-365	25 mer Sense Strand	GGUUACUGCUCGCCAGGAAACUCGC	828
MTARC1-376	25 mer Sense Strand	GCCAGGAACCUCGCCUGGUACUGAU	829
MTARC1-379	25 mer Sense Strand	AGGAACCUCGCCUGGUCCUAAUUC	830
MTARC1-384	25 mer Sense Strand	CCUCGCCUGGUCCUGAUUUACCUGA	831
MTARC1-385	25 mer Sense Strand	CUCGCCUGGUCCUGAUUUCACUGAC	832
MTARC1-388	25 mer Sense Strand	GCCUGGUCCUGAUUUCCCUAACUG	833
MTARC1-390	25 mer Sense Strand	CUGGUCCUGAUUUCCCUAACUGCG	834
MTARC1-391	25 mer Sense Strand	UGGUCCUGAUUUCCCUGACAUGCGA	835
MTARC1-393	25 mer Sense Strand	GUCCUGAUUUCCCUGACCUACGAUG	836
MTARC1-395	25 mer Sense Strand	CCUGAUUUCCCUGACCUCAAUGGU	837
MTARC1-405	25 mer Sense Strand	CUGACCUGCGAUGGUGACAACCUGA	838
MTARC1-409	25 mer Sense Strand	CCUGCGAUGGUGACACCCUAAUCUCU	839
MTARC1-411	25 mer Sense Strand	UGCGAUGGUGACACCCUGAAUCUCA	840
MTARC1-412	25 mer Sense Strand	GCGAUGGUGACACCCUGACACUCAG	841
MTARC1-413	25 mer Sense Strand	CGAUGGUGACACCCUGACUAUCAGU	842
MTARC1-414	25 mer Sense Strand	GAUGGUGACACCCUGACUCACAGUG	843
MTARC1-415	25 mer Sense Strand	AUGGUGACACCCUGACUCUAAGUGC	844
MTARC1-416	25 mer Sense Strand	UGGUGACACCCUGACUCUCAGUGCA	845
MTARC1-417	25 mer Sense Strand	GGUGACACCCUGACUCUCAAUGCAG	846
MTARC1-418	25 mer Sense Strand	GUGACACCCUGACUCUCAGAGCAGC	847
MTARC1-419	25 mer Sense Strand	UGACACCCUGACUCUCAGUAGGCC	848
MTARC1-420	25 mer Sense Strand	GACACCCUGACUCUCAGUGAAGCCU	849
MTARC1-421	25 mer Sense Strand	ACACCCUGACUCUCAGUGCAGCCUA	850
MTARC1-422	25 mer Sense Strand	CACCCUGACUCUCAGUGCAACCUAC	851
MTARC1-423	25 mer Sense Strand	ACCCUGACUCUCAGUGCAGACUACA	852
MTARC1-424	25 mer Sense Strand	CCCUGACUCUCAGUGCAGCAUACAC	853
MTARC1-425	25 mer Sense Strand	CCUGACUCUCAGUGCAGCCAACACA	854
MTARC1-426	25 mer Sense Strand	CUGACUCUCAGUGCAGCCUACACAA	855
MTARC1-427	25 mer Sense Strand	UGACUCUCAGUGCAGCCUAAACAAA	856
MTARC1-428	25 mer Sense Strand	GACUCUCAGUGCAGCCUACACAAAG	857
MTARC1-429	25 mer Sense Strand	ACUCUCAGUGCAGCCUACAAAAAGG	858
MTARC1-430	25 mer Sense Strand	CUCUCAGUGCAGCCUACACAAAGGA	859
MTARC1-431	25 mer Sense Strand	UCUCAGUGCAGCCUACACAAAGGAC	860
MTARC1-433	25 mer Sense Strand	UCAGUGCAGCCUACACAAAGACCU	861
MTARC1-434	25 mer Sense Strand	CAGUGCAGCCUACACAAAGAACCUA	862
MTARC1-435	25 mer Sense Strand	AGUGCAGCCUACACAAAGGACCUAC	863
MTARC1-436	25 mer Sense Strand	GUGCAGCCUACACAAAGGAACUACU	864
MTARC1-437	25 mer Sense Strand	UGCAGCCUACACAAAGGACAUAUA	865

MTARC1-438	25 mer Sense Strand	GCAGCCUACACAAAGGACCAACUAC	866
MTARC1-439	25 mer Sense Strand	CAGCCUACACAAAGGACCUACUACU	867
MTARC1-440	25 mer Sense Strand	AGCCUACACAAAGGACCUAAUACUG	868
MTARC1-441	25 mer Sense Strand	GCCUACACAAAGGACCUACAACUGC	869
MTARC1-445	25 mer Sense Strand	ACACAAAGGACCUACUACUACCUAU	870
MTARC1-446	25 mer Sense Strand	CACAAAGGACCUACUACUGACUAUC	871
MTARC1-447	25 mer Sense Strand	ACAAAGGACCUACUACUGCAUAUCA	872
MTARC1-448	25 mer Sense Strand	CAAAGGACCUACUACUGCCAAUCAA	873
MTARC1-449	25 mer Sense Strand	AAAGGACCUACUACUGCCUACUAAA	874
MTARC1-450	25 mer Sense Strand	AAGGACCUACUACUGCCUAAACAAA	875
MTARC1-451	25 mer Sense Strand	AGGACCUACUACUGCCUAAAAAAC	876
MTARC1-452	25 mer Sense Strand	GGACCUACUACUGCCUAAAAACG	877
MTARC1-453	25 mer Sense Strand	GACCUACUACUGCCUAAAAACGC	878
MTARC1-454	25 mer Sense Strand	ACCUACUACUGCCUAAAAACGCC	879
MTARC1-456	25 mer Sense Strand	CUACUACUGCCUAAAAAGCCCA	880
MTARC1-457	25 mer Sense Strand	UACUACUGCCUAAAAACCCAC	881
MTARC1-458	25 mer Sense Strand	ACUACUGCCUAAAAACGACCACC	882
MTARC1-459	25 mer Sense Strand	CUACUGCCUAAAAACGCACACCA	883
MTARC1-460	25 mer Sense Strand	UACUGCCUAAAAACGCCAACAC	884
MTARC1-462	25 mer Sense Strand	CUGCCUAAAAACGCCAACACAA	885
MTARC1-468	25 mer Sense Strand	AUCAAACGCCACCACAAAUGCAG	886
MTARC1-469	25 mer Sense Strand	UCAAACGCCACCACAAAAGCAGU	887
MTARC1-470	25 mer Sense Strand	CAAACGCCACCACAAAUACAGUG	888
MTARC1-471	25 mer Sense Strand	AAAACGCCACCACAAUGAAGUGC	889
MTARC1-473	25 mer Sense Strand	AACGCCACCACAAUGCAAUGCAC	890
MTARC1-475	25 mer Sense Strand	CGCCCACCACAAUGCAGUACACAA	891
MTARC1-476	25 mer Sense Strand	GCCCACCACAAUGCAGUGAACAAAG	892
MTARC1-482	25 mer Sense Strand	CACAAUGCAGUGCACAAGAGCAGA	893
MTARC1-483	25 mer Sense Strand	ACAAUGCAGUGCACAAGUACAGAG	894
MTARC1-484	25 mer Sense Strand	CAAUGCAGUGCACAAGUGAAGAGU	895
MTARC1-552	25 mer Sense Strand	GCCCAGUGGAUAACCAGCUACCUGA	896
MTARC1-553	25 mer Sense Strand	CCCAGUGGAUAACCAGCUUACUGAA	897
MTARC1-554	25 mer Sense Strand	CCAGUGGAUAACCAGCUUCAUGAAG	898
MTARC1-555	25 mer Sense Strand	CAGUGGAUAACCAGCUUCCAGAAGU	899
MTARC1-556	25 mer Sense Strand	AGUGGAUAACCAGCUUCCUAAAGUC	900
MTARC1-557	25 mer Sense Strand	GUGGAUAACCAGCUUCCUGAAGUCA	901
MTARC1-558	25 mer Sense Strand	UGGAUAACCAGCUUCCUGAAGUCAC	902
MTARC1-559	25 mer Sense Strand	GGAUAACCAGCUUCCUGAAAUCACA	903
MTARC1-560	25 mer Sense Strand	GAUAACCAGCUUCCUGAAGACACAG	904
MTARC1-561	25 mer Sense Strand	AUAACCAGCUUCCUGAAGUACAGC	905
MTARC1-562	25 mer Sense Strand	UAACCAGCUUCCUGAAGUCACAGCC	906
MTARC1-563	25 mer Sense Strand	AACCAGCUUCCUGAAGUCAAGCCC	907
MTARC1-564	25 mer Sense Strand	ACCAGCUUCCUGAAGUCACAGCCCU	908
MTARC1-565	25 mer Sense Strand	CCAGCUUCCUGAAGUCACAACCCUA	909
MTARC1-566	25 mer Sense Strand	CAGCUUCCUGAAGUCACAGACCUAC	910
MTARC1-567	25 mer Sense Strand	AGCUUCCUGAAGUCACAGCACUACC	911
MTARC1-568	25 mer Sense Strand	GCUUCCUGAAGUCACAGCCAUACCG	912
MTARC1-589	25 mer Sense Strand	ACCGCCUGGUGCACUUCGAACCUCA	913
MTARC1-591	25 mer Sense Strand	CGCCUGGUGCACUUCGAGCAUCACA	914
MTARC1-592	25 mer Sense Strand	GCCUGGUGCACUUCGAGCCACACAU	915
MTARC1-593	25 mer Sense Strand	CCUGGUGCACUUCGAGCCUACAUG	916
MTARC1-597	25 mer Sense Strand	GUGCACUUCGAGCCUCACAAGCGAC	917
MTARC1-600	25 mer Sense Strand	CACUUCGAGCCUCACAUGCAACCGA	918

MTARC1-612	25 mer Sense Strand	CACAUGCGACCGAGACGUCAUCAUC	919
MTARC1-614	25 mer Sense Strand	CAUGCGACCGAGACGUCCUAAUCAA	920
MTARC1-617	25 mer Sense Strand	GCGACCGAGACGUCCUCAUAAAAUA	921
MTARC1-618	25 mer Sense Strand	CGACCGAGACGUCCUCAUAAAUAG	922
MTARC1-620	25 mer Sense Strand	ACCGAGACGUCCUCAUAAAUAGCA	923
MTARC1-621	25 mer Sense Strand	CCGAGACGUCCUCAUAAAAAGCAG	924
MTARC1-622	25 mer Sense Strand	CGAGACGUCCUCAUAAAUAGCAGA	925
MTARC1-623	25 mer Sense Strand	GAGACGUCCUCAUAAAUAACAGAC	926
MTARC1-624	25 mer Sense Strand	AGACGUCCUCAUAAAUAGAAGACU	927
MTARC1-625	25 mer Sense Strand	GACGUCCUCAUAAAUAGCAGACUU	928
MTARC1-626	25 mer Sense Strand	ACGUCCUCAUAAAUAGCAAACUUG	929
MTARC1-627	25 mer Sense Strand	CGUCCUCAUAAAUAGCAGACUUGU	930
MTARC1-628	25 mer Sense Strand	GUCCUCAUAAAUAGCAGAAUUGUU	931
MTARC1-629	25 mer Sense Strand	UCCUCAUAAAUAGCAGACAUGUUC	932
MTARC1-630	25 mer Sense Strand	CCUCAUAAAUAGCAGACUAGUUC	933
MTARC1-631	25 mer Sense Strand	CUCAUAAAUAGCAGACUUAUUCG	934
MTARC1-632	25 mer Sense Strand	UCAUAAAUAGCAGACUUGAUCCGA	935
MTARC1-633	25 mer Sense Strand	CAUAAAUAGCAGACUUGUACCGAC	936
MTARC1-634	25 mer Sense Strand	AUAAAUAGCAGACUUGUACGACC	937
MTARC1-635	25 mer Sense Strand	UCAAUAGCAGACUUGUUCAGACCC	938
MTARC1-636	25 mer Sense Strand	CAAAUAGCAGACUUGUCCAACCCA	939
MTARC1-637	25 mer Sense Strand	AAAUAGCAGACUUGUCCGACCCAA	940
MTARC1-638	25 mer Sense Strand	AAUAGCAGACUUGUCCGAACCAAG	941
MTARC1-639	25 mer Sense Strand	AUAGCAGACUUGUCCGACACAAGG	942
MTARC1-640	25 mer Sense Strand	UAGCAGACUUGUCCGACCAAAGGA	943
MTARC1-641	25 mer Sense Strand	AGCAGACUUGUCCGACCCAAGGAC	944
MTARC1-642	25 mer Sense Strand	GCAGACUUGUCCGACCCAAGGACC	945
MTARC1-643	25 mer Sense Strand	CAGACUUGUCCGACCCAAGACCA	946
MTARC1-644	25 mer Sense Strand	AGACUUGUCCGACCCAAGAACAG	947
MTARC1-645	25 mer Sense Strand	GACUUGUCCGACCCAAGGACCAGA	948
MTARC1-646	25 mer Sense Strand	ACUUGUCCGACCCAAGGAACAGAU	949
MTARC1-647	25 mer Sense Strand	CUUGUCCGACCCAAGGACAAGAUU	950
MTARC1-648	25 mer Sense Strand	UUGUCCGACCCAAGGACCAGAUUG	951
MTARC1-649	25 mer Sense Strand	UGUCCGACCCAAGGACCAAAUUGC	952
MTARC1-650	25 mer Sense Strand	GUUCCGACCCAAGGACCAGAUUGCU	953
MTARC1-651	25 mer Sense Strand	UCCGACCCAAGGACCAGAAUGCUU	954
MTARC1-652	25 mer Sense Strand	UCCGACCCAAGGACCAGAUAGCUUA	955
MTARC1-653	25 mer Sense Strand	CCGACCCAAGGACCAGAUUACUUA	956
MTARC1-654	25 mer Sense Strand	CGACCCAAGGACCAGAUUGAUUACU	957
MTARC1-655	25 mer Sense Strand	GACCCAAGGACCAGAUUGCAUACUC	958
MTARC1-656	25 mer Sense Strand	ACCCAAGGACCAGAUUGCUAACUCA	959
MTARC1-657	25 mer Sense Strand	CCCAAGGACCAGAUUGCUUACUCAG	960
MTARC1-658	25 mer Sense Strand	CCAAGGACCAGAUUGCUUAAUCAGA	961
MTARC1-659	25 mer Sense Strand	CAAGGACCAGAUUGCUUACACAGAC	962
MTARC1-660	25 mer Sense Strand	AAGGACCAGAUUGCUUACUAAAGACA	963
MTARC1-661	25 mer Sense Strand	AGGACCAGAUUGCUUACUCAGACAC	964
MTARC1-662	25 mer Sense Strand	GGACCAGAUUGCUUACUCAACACC	965
MTARC1-663	25 mer Sense Strand	GACCAGAUUGCUUACUCAGACACCA	966
MTARC1-664	25 mer Sense Strand	ACCAGAUUGCUUACUCAGAAACCAG	967
MTARC1-665	25 mer Sense Strand	CCAGAUUGCUUACUCAGACACCAGC	968
MTARC1-666	25 mer Sense Strand	CAGAUUGCUUACUCAGACAACAGCC	969
MTARC1-667	25 mer Sense Strand	AGAUUGCUUACUCAGACACAAGCCC	970
MTARC1-668	25 mer Sense Strand	GAUUGCUUACUCAGACACCAGCCCA	971

MTARC1-669	25 mer Sense Strand	AUUGCUUACUCAGACACCAACCCAU	972
MTARC1-670	25 mer Sense Strand	UUGCUUACUCAGACACCAGACCAU	973
MTARC1-671	25 mer Sense Strand	UGC UUACUCAGACACCAGCACAUUC	974
MTARC1-672	25 mer Sense Strand	GCUUACUCAGACACCAGCCAAUUCU	975
MTARC1-673	25 mer Sense Strand	CUUACUCAGACACCAGCCCAUUCU	976
MTARC1-674	25 mer Sense Strand	UUACUCAGACACCAGCCCAUUCUUG	977
MTARC1-675	25 mer Sense Strand	UACUCAGACACCAGCCCAUACUUGA	978
MTARC1-676	25 mer Sense Strand	ACUCAGACACCAGCCCAUUAUUGAU	979
MTARC1-677	25 mer Sense Strand	CUCAGACACCAGCCCAUUCUAGAUC	980
MTARC1-678	25 mer Sense Strand	UCAGACACCAGCCCAUUCUAGAUCC	981
MTARC1-679	25 mer Sense Strand	CAGACACCAGCCCAUUCUUAUCCU	982
MTARC1-680	25 mer Sense Strand	AGACACCAGCCCAUUCUUGAUCCU	983
MTARC1-681	25 mer Sense Strand	GACACCAGCCCAUUCUUGAACCUU	984
MTARC1-682	25 mer Sense Strand	ACACCAGCCCAUUCUUGAUACUUC	985
MTARC1-683	25 mer Sense Strand	CACCAGCCCAUUCUUGAUCAUUCU	986
MTARC1-684	25 mer Sense Strand	ACCAGCCCAUUCUUGAUCCAUCUG	987
MTARC1-685	25 mer Sense Strand	CCAGCCCAUUCUUGAUCCUACUGA	988
MTARC1-686	25 mer Sense Strand	CAGCCCAUUCUUGAUCCUACUGAG	989
MTARC1-687	25 mer Sense Strand	AGCCCAUUCUUGAUCCUUAUGAGG	990
MTARC1-691	25 mer Sense Strand	CAUUCUUGAUCCUUCUGAAGCGUC	991
MTARC1-692	25 mer Sense Strand	AUUCUUGAUCCUUCUGAGACGUCG	992
MTARC1-724	25 mer Sense Strand	AUCUCAACUCCAGGCUAGAAAAGAA	993
MTARC1-726	25 mer Sense Strand	CUCAACUCCAGGCUAGAGAAGAAAG	994
MTARC1-728	25 mer Sense Strand	CAACUCCAGGCUAGAGAAGAAAGUU	995
MTARC1-729	25 mer Sense Strand	AACUCCAGGCUAGAGAAGAAAGUUA	996
MTARC1-730	25 mer Sense Strand	ACUCCAGGCUAGAGAAGAAAGUAAA	997
MTARC1-731	25 mer Sense Strand	CUCCAGGCUAGAGAAGAAAAUAAA	998
MTARC1-733	25 mer Sense Strand	CCAGGCUAGAGAAGAAAGUAAAAGC	999
MTARC1-734	25 mer Sense Strand	CAGGCUAGAGAAGAAAGUAAAAGCA	1000
MTARC1-735	25 mer Sense Strand	AGGCUAGAGAAGAAAGUAAAAGCAA	1001
MTARC1-736	25 mer Sense Strand	GGCUAGAGAAGAAAGUAAAAGCAAC	1002
MTARC1-737	25 mer Sense Strand	GCUAGAGAAGAAAGUAAAACAACC	1003
MTARC1-738	25 mer Sense Strand	CUAGAGAAGAAAGUAAAAGAAACCA	1004
MTARC1-739	25 mer Sense Strand	UAGAGAAGAAAGUAAAAGCAACCAA	1005
MTARC1-740	25 mer Sense Strand	AGAGAAGAAAGUAAAAGCAACCAAC	1006
MTARC1-741	25 mer Sense Strand	GAGAAGAAAGUAAAAGCAAAACACU	1007
MTARC1-742	25 mer Sense Strand	AGAAGAAAGUAAAAGCAACAAACUU	1008
MTARC1-743	25 mer Sense Strand	GAAGAAAGUAAAAGCAACCAACUUC	1009
MTARC1-744	25 mer Sense Strand	AAGAAAGUAAAAGCAACCAACUUCA	1010
MTARC1-745	25 mer Sense Strand	AGAAAGUAAAAGCAACCAAAUUCAG	1011
MTARC1-746	25 mer Sense Strand	GAAAGUAAAAGCAACCAACUUCAGG	1012
MTARC1-747	25 mer Sense Strand	AAAGUAAAAGCAACCAACUACAGGC	1013
MTARC1-748	25 mer Sense Strand	AAGUAAAAGCAACCAACUUAAGGCC	1014
MTARC1-750	25 mer Sense Strand	GUUAAAAGCAACCAACUUCAGCCCA	1015
MTARC1-751	25 mer Sense Strand	UUAAGCAACCAACUUCAGACCCAA	1016
MTARC1-752	25 mer Sense Strand	UAAAGCAACCAACUUCAGGACCAAU	1017
MTARC1-753	25 mer Sense Strand	AAAGCAACCAACUUCAGGCACAAUA	1018
MTARC1-754	25 mer Sense Strand	AAGCAACCAACUUCAGGCCAAAUUA	1019
MTARC1-755	25 mer Sense Strand	AGCAACCAACUUCAGGCCCAUAUUA	1020
MTARC1-756	25 mer Sense Strand	GCAACCAACUUCAGGCCCAUAUUG	1021
MTARC1-758	25 mer Sense Strand	AACCAACUUCAGGCCCAUAUUGUA	1022
MTARC1-759	25 mer Sense Strand	ACCAACUUCAGGCCCAUUAUUGUAA	1023
MTARC1-760	25 mer Sense Strand	CCAACUUCAGGCCCAUAUAGUAAU	1024

MTARC1-761	25 mer Sense Strand	CAACUUCAGGCCCAUAUUAUAAUU	1025
MTARC1-762	25 mer Sense Strand	AACUUCAGGCCCAUAUUGAAAUUU	1026
MTARC1-763	25 mer Sense Strand	ACUUCAGGCCCAUAUUGUAAAUUC	1027
MTARC1-764	25 mer Sense Strand	CUUCAGGCCCAUAUUGUAAAUUCA	1028
MTARC1-765	25 mer Sense Strand	UUCAGGCCCAUAUUGUAAAUUCAG	1029
MTARC1-766	25 mer Sense Strand	UCAGGCCCAUAUUGUAAAUUCAGG	1030
MTARC1-767	25 mer Sense Strand	CAGGCCCAUAUUGUAAAUUCAGGA	1031
MTARC1-768	25 mer Sense Strand	AGGCCCAUAUUGUAAAUUAGGAU	1032
MTARC1-769	25 mer Sense Strand	GGCCCAUAUUGUAAAUUCAGGAUG	1033
MTARC1-770	25 mer Sense Strand	GCCCAUAUUGUAAAUUUCAGGAUGC	1034
MTARC1-771	25 mer Sense Strand	CCCAUAUUGUAAAUUUCAGGAUGCG	1035
MTARC1-772	25 mer Sense Strand	CCAAUAUUGUAAAUUUCAGGAUGCGA	1036
MTARC1-773	25 mer Sense Strand	CAUAUUGUAAAUUUCAGGAAGCGAU	1037
MTARC1-774	25 mer Sense Strand	AAUAUUGUAAAUUUCAGGAUACGAUG	1038
MTARC1-775	25 mer Sense Strand	AUAUUGUAAAUUUCAGGAUGAGAUGU	1039
MTARC1-776	25 mer Sense Strand	UAUUGUAAAUUUCAGGAUGCAAUGUC	1040
MTARC1-777	25 mer Sense Strand	AUUGUAAAUUUCAGGAUGCGAUGUCU	1041
MTARC1-778	25 mer Sense Strand	UUGUAAAUUUCAGGAUGCGAAGUCUA	1042
MTARC1-779	25 mer Sense Strand	UGUAAAUUUCAGGAUGCGAUUAUCUAU	1043
MTARC1-780	25 mer Sense Strand	GUAUUUUCAGGAUGCGAUGACUAUG	1044
MTARC1-781	25 mer Sense Strand	UAAUUUUCAGGAUGCGAUGUAUAUGC	1045
MTARC1-782	25 mer Sense Strand	AAUUUUCAGGAUGCGAUGUCAUAUGCA	1046
MTARC1-783	25 mer Sense Strand	AUUUUCAGGAUGCGAUGUCUAUGCAG	1047
MTARC1-784	25 mer Sense Strand	UUUCAGGAUGCGAUGUCUAAGCAGA	1048
MTARC1-785	25 mer Sense Strand	UUCAGGAUGCGAUGUCUAUACAGAG	1049
MTARC1-786	25 mer Sense Strand	UCAGGAUGCGAUGUCUAUGAAGAGG	1050
MTARC1-787	25 mer Sense Strand	CAGGAUGCGAUGUCUAUGCAGAGGA	1051
MTARC1-788	25 mer Sense Strand	AGGAUGCGAUGUCUAUGCAAAGGAU	1052
MTARC1-789	25 mer Sense Strand	GGAUGCGAUGUCUAUGCAGAGGAUU	1053
MTARC1-790	25 mer Sense Strand	GAUGCGAUGUCUAUGCAGAAGAUUC	1054
MTARC1-791	25 mer Sense Strand	AUGCGAUGUCUAUGCAGAGAAUUCU	1055
MTARC1-792	25 mer Sense Strand	UGCGAUGUCUAUGCAGAGGAAACAC	1056
MTARC1-863	25 mer Sense Strand	UUGUCCAGAUGCAUUUUAACCACA	1057
MTARC1-929	25 mer Sense Strand	GGAAACACUGAAGAGUUAUAGCCAG	1058
MTARC1-930	25 mer Sense Strand	GAAACACUGAAGAGUUAUACCCAGU	1059
MTARC1-934	25 mer Sense Strand	CUGAAGAGUUAUCGCCAAUGUGA	1060
MTARC1-955	25 mer Sense Strand	GUGACCCUUCAGAACGAAAAUUAUA	1061
MTARC1-959	25 mer Sense Strand	CCCUUCAGAACGAAAGUUAUUAUGGA	1062
MTARC1-960	25 mer Sense Strand	CCUUCAGAACGAAAGUUAUUAUGGAA	1063
MTARC1-963	25 mer Sense Strand	UCAGAACGAAAGUUAUUAUGAAAAAU	1064
MTARC1-964	25 mer Sense Strand	CAGAACGAAAGUUAUUAUGGAAAAUC	1065
MTARC1-965	25 mer Sense Strand	AGAACGAAAGUUAUUAUGGAAAAUCA	1066
MTARC1-966	25 mer Sense Strand	GAACGAAAGUUAUUAUGGAAAAUCAC	1067
MTARC1-967	25 mer Sense Strand	AACGAAAGUUAUUAUGGAAAAUCACC	1068
MTARC1-969	25 mer Sense Strand	CGAAAGUUAUUAUGGAAAAUAACCAC	1069
MTARC1-970	25 mer Sense Strand	GAAAGUUAUUAUGGAAAAUCACCACU	1070
MTARC1-971	25 mer Sense Strand	AAAGUUAUUAUGGAAAAUCAACACUC	1071
MTARC1-1107	25 mer Sense Strand	AAAAAUGUUCUAAAAAUGACAACA	1072
MTARC1-1113	25 mer Sense Strand	GUUCUAAAAAUGACAACAAUUGAA	1073
MTARC1-1118	25 mer Sense Strand	CAAAAAUGACAACACUUGAAGCAUG	1074
MTARC1-1123	25 mer Sense Strand	AUGACAACACUUGAAGCAUAGUGUU	1075
MTARC1-1126	25 mer Sense Strand	ACAACACUUGAAGCAUGGUAAUUCU	1076
MTARC1-1127	25 mer Sense Strand	CAACACUUGAAGCAUGGUGAUUCAG	1077

MTARC1-1128	25 mer Sense Strand	AACACUUGAAGCAUGGUGUAUCAGA	1078
MTARC1-1129	25 mer Sense Strand	ACACUUGAAGCAUGGUGUUACAGAA	1079
MTARC1-1130	25 mer Sense Strand	CACUUGAAGCAUGGUGUUUAGAAC	1080
MTARC1-1132	25 mer Sense Strand	CUUGAAGCAUGGUGUUUCAAACUG	1081
MTARC1-1133	25 mer Sense Strand	UUGAAGCAUGGUGUUUCAGAACUGA	1082
MTARC1-1134	25 mer Sense Strand	UGAAGCAUGGUGUUUCAGAACUGAG	1083
MTARC1-1135	25 mer Sense Strand	GAAGCAUGGUGUUUCAGAAUUGAGA	1084
MTARC1-1139	25 mer Sense Strand	CAUGGUGUUUCAGAACUGAAACCUC	1085
MTARC1-1144	25 mer Sense Strand	UGUUUCAGAACUGAGACCUAUACAU	1086
MTARC1-1165	25 mer Sense Strand	ACAUUUUCUUUAAAUUUGUAAUUUU	1087
MTARC1-1167	25 mer Sense Strand	AUUUUCUUUAAAUUUGUGAAUUUCA	1088
MTARC1-1173	25 mer Sense Strand	UUUAAAUUUGUGAUUUUCAAUUUUU	1089
MTARC1-1177	25 mer Sense Strand	AAUUUGUGAUUUUCACAUUUAUUCGU	1090
MTARC1-1179	25 mer Sense Strand	UUUGUGAUUUUCACAUUUUACGUCU	1091
MTARC1-1329	25 mer Sense Strand	GUUUAAACUGAUUAUGGAAUAGUUCU	1092
MTARC1-1330	25 mer Sense Strand	UUUAAACUGAUUAUGGAAUAAUUCUU	1093
MTARC1-1332	25 mer Sense Strand	UAAACUGAUUAUGGAAUAGUACUUUC	1094
MTARC1-1333	25 mer Sense Strand	AACUGAUUAUGGAAUAGUUAUUUCU	1095
MTARC1-1334	25 mer Sense Strand	ACUGAUUAUGGAAUAGUUCAUUCUC	1096
MTARC1-1335	25 mer Sense Strand	CUGAUUAUGGAAUAGUUCUAUCUCC	1097
MTARC1-1620	25 mer Sense Strand	CAGAUUUUUUUUCCAUAAAUCUG	1098
MTARC1-1622	25 mer Sense Strand	GAUUAUUUUUUUCCAUAGAACUGGA	1099
MTARC1-1660	25 mer Sense Strand	CUUCUCAGACAGCAUUGGAAUUCU	1100
MTARC1-1663	25 mer Sense Strand	CUCAGACAGCAUUGGAUUUACUAAA	1101
MTARC1-1664	25 mer Sense Strand	UCAGACAGCAUUGGAUUUCAUAAAG	1102
MTARC1-1812	25 mer Sense Strand	AGAAAAGUGAUUCAGUGAUUUCAGA	1103
MTARC1-1816	25 mer Sense Strand	AAGUGAUUCAGUGAUUUCAAUAGA	1104
MTARC1-1868	25 mer Sense Strand	GGAAAGCAUAUGUCAGUUGAUUAAA	1105
MTARC1-1869	25 mer Sense Strand	GAAAGCAUAUGUCAGUUGAUUAAA	1106
MTARC1-1876	25 mer Sense Strand	UAUGUCAGUUGUUUAAAACACAAUA	1107
MTARC1-1877	25 mer Sense Strand	AUGUCAGUUGUUUAAAACCAAUAU	1108
MTARC1-1878	25 mer Sense Strand	UGUCAGUUGUUUAAAACCCAAUAUC	1109
MTARC1-1879	25 mer Sense Strand	GUCAGUUGUUUAAAACCCAAUAUCU	1110
MTARC1-1882	25 mer Sense Strand	AGUUGUUUAAAACCCAAUAACUAU	1111
MTARC1-1883	25 mer Sense Strand	GUUGUUUAAAACCCAAUAUAUAUUU	1112
MTARC1-1884	25 mer Sense Strand	UUGUUUAAAACCCAAUAUCAUUUUU	1113
MTARC1-1885	25 mer Sense Strand	UGUUUAAAACCCAAUAUCUAUUUUU	1114
MTARC1-1886	25 mer Sense Strand	GUUUAAAACCCAAUAUCUAAUUUUU	1115
MTARC1-1935	25 mer Sense Strand	UGAUGAAGUAUAUUUUUUAAUGCCA	1116
MTARC1-1936	25 mer Sense Strand	GAUGAAGUAUAUUUUUUUAUAGCCAU	1117
MTARC1-1937	25 mer Sense Strand	AUGAAGUAUAUUUUUUUAUACCAUU	1118
MTARC1-1939	25 mer Sense Strand	GAAGUAUAUUUUUUUAUUGCAAUUUU	1119
MTARC1-1941	25 mer Sense Strand	AGUAUAUUUUUUUAUUGCCAAUUUGU	1120
MTARC1-1953	25 mer Sense Strand	AUUGCCAUUUUGUCCUUUGAUUAUA	1121
MTARC1-1955	25 mer Sense Strand	UGCCAUUUUGUCCUUUGAUAAUAUU	1122
MTARC1-1981	25 mer Sense Strand	GGAAGUUGACUAAACUUGAAAAAUG	1123
MTARC1-1983	25 mer Sense Strand	AAGUUGACUAAACUUGAAAAAUGUU	1124
MTARC1-1985	25 mer Sense Strand	GUUGACUAAACUUGAAAAAAGUUUU	1125
MTARC1-1986	25 mer Sense Strand	UUGACUAAACUUGAAAAAUUUUUU	1126
MTARC1-1988	25 mer Sense Strand	GACUAAACUUGAAAAAUGUAUUUAA	1127
MTARC1-1989	25 mer Sense Strand	ACUAAACUUGAAAAAUGUUAUUAAA	1128
MTARC1-1990	25 mer Sense Strand	CUAAACUUGAAAAAUGUUUAUUAAA	1129
MTARC1-1995	25 mer Sense Strand	CUUGAAAAAUGUUUUUAAAACUGUG	1130

MTARC1-1996	25 mer Sense Strand	UUGAAAAAUGUUUUUAAAAAUGUGA	1131
MTARC1-1998	25 mer Sense Strand	GAAAAAUGUUUUUAAAAACUAUGAAU	1132
MTARC1-1999	25 mer Sense Strand	AAAAAUGUUUUUAAAAACUGAGAAUA	1133
MTARC1-2000	25 mer Sense Strand	AAAAUGUUUUUAAAAACUGUAAAUAA	1134
MTARC1-2001	25 mer Sense Strand	AAUGUUUUUAAAAACUGUGAAUAAA	1135
MTARC1-2002	25 mer Sense Strand	AAUGUUUUUAAAAACUGUGAAUAAA	1136
MTARC1-2005	25 mer Sense Strand	GUUUUUAAAAACUGUGAAUAAAUGGA	1137
MTARC1-2006	25 mer Sense Strand	UUUUUAAAAACUGUGAAUAAAUGGAA	1138
MTARC1-2010	25 mer Sense Strand	UAAAACUGUGAAUAAAUGGAAGCUA	1139
MTARC1-2011	25 mer Sense Strand	AAAACUGUGAAUAAAUGGAAGCUAC	1140
MTARC1-2012	25 mer Sense Strand	AAACUGUGAAUAAAUGGAAGCUACU	1141
MTARC1-2013	25 mer Sense Strand	AACUGUGAAUAAAUGGAAGAUACUU	1142
MTARC1-2015	25 mer Sense Strand	CUGUGAAUAAAUGGAAGCUACUUUG	1143
MTARC1-2016	25 mer Sense Strand	UGUGAAUAAAUGGAAGCUAAUUUGA	1144
MTARC1-2017	25 mer Sense Strand	GUGAAUAAAUGGAAGCUACAUUGAC	1145
MTARC1-2018	25 mer Sense Strand	UGAAUAAAUGGAAGCUACUAUGACU	1146
MTARC1-2019	25 mer Sense Strand	GAAUAAAUGGAAGCUACUUAGACUA	1147
MTARC1-2020	25 mer Sense Strand	AAUAAAUGGAAGCUACUUUAACUAG	1148
MTARC1-2022	25 mer Sense Strand	UAAAUGGAAGCUACUUUGAAUAGUU	1149
MTARC1-2023	25 mer Sense Strand	AAAUGGAAGCUACUUUGACAAGUUU	1150
MTARC1-2025	25 mer Sense Strand	AUGGAAGCUACUUUGACUAAUUUCA	1151
MTARC1-2027	25 mer Sense Strand	GGAAGCUACUUUGACUAGUAUCAGA	1152
MTARC1-231	27 mer Anti-sense Strand	UCACAUGGUAGAUCAGAGCUGCG CCA	1153
MTARC1-233	27 mer Anti-sense Strand	UUUCAUAGGGUAGAUCAGAGCUG CGC	1154
MTARC1-234	27 mer Anti-sense Strand	AUUUCUCAGGGUAGAUCAGAGCU GCG	1155
MTARC1-235	27 mer Anti-sense Strand	GAUUUUACAGGGUAGAUCAGAGC UGC	1156
MTARC1-236	27 mer Anti-sense Strand	GGAUUUCACAGGGUAGAUCAGAG CUG	1157
MTARC1-237	27 mer Anti-sense Strand	AGGAUUUCACAGGGUAGAUCAGAG GCU	1158
MTARC1-238	27 mer Anti-sense Strand	CAGGAUUUCACAGGGUAGAUCAG AGC	1159
MTARC1-239	27 mer Anti-sense Strand	GCAGGUUUUCACAGGGUAGAUCCA GAG	1160
MTARC1-240	27 mer Anti-sense Strand	UGCAGUAUUUCACAGGGUAGAUCC AGA	1161
MTARC1-241	27 mer Anti-sense Strand	UUGCAUGAUUUUCACAGGGUAGAU CAG	1162
MTARC1-242	27 mer Anti-sense Strand	CUUGCUGGAUUUCACAGGGUAGAU CCA	1163
MTARC1-243	27 mer Anti-sense Strand	CCUUGUAGGAUUUCACAGGGUAGA UCC	1164
MTARC1-244	27 mer Anti-sense Strand	CCCUUUCAGGAUUUCACAGGGUAG AUC	1165
MTARC1-245	27 mer Anti-sense Strand	CCCCUUGCAGGAUUUCACAGGGUA GAU	1166
MTARC1-247	27 mer Anti-sense Strand	ACCCCUUUGCAGGAUUUCACAGGG UAG	1167

MTARC1-248	27 mer Anti-sense Strand	CACCCUCUUGCAGGAUUUCACAGG GUA	1168
MTARC1-249	27 mer Anti-sense Strand	GCACCUCCUUGCAGGAUUUCACAG GGU	1169
MTARC1-253	27 mer Anti-sense Strand	ACCGGUACCCCUUGCAGGAUUUC ACA	1170
MTARC1-255	27 mer Anti-sense Strand	UCACCUGCACCCCUUGCAGGAUU UCA	1171
MTARC1-318	27 mer Anti-sense Strand	CAAGCUAAAACCUGUCCCGCAGGU UGC	1172
MTARC1-319	27 mer Anti-sense Strand	ACAAGUCAAAAACCUGUCCCGCAGG UUG	1173
MTARC1-320	27 mer Anti-sense Strand	CACAAUCCAAAACCUGUCCCGCAG GUU	1174
MTARC1-321	27 mer Anti-sense Strand	UCACAUGCCAAAACCUGUCCCGCA GGU	1175
MTARC1-323	27 mer Anti-sense Strand	GAUCAUAAGCCAAAACCUGUCCCG CAG	1176
MTARC1-324	27 mer Anti-sense Strand	UGAUCUCAAGCCAAAACCUGUCCCG GCA	1177
MTARC1-325	27 mer Anti-sense Strand	UUGAUUACAAGCCAAAACCUGUCC CGC	1178
MTARC1-326	27 mer Anti-sense Strand	GUUGAUCACAAGCCAAAACCUGUC CCG	1179
MTARC1-327	27 mer Anti-sense Strand	GGUUGUUCACAAGCCAAAACCUGU CCC	1180
MTARC1-328	27 mer Anti-sense Strand	UGGUUUUAUCACAAGCCAAAACCUG UCC	1181
MTARC1-329	27 mer Anti-sense Strand	CUGGUUGAUCACAAGCCAAAACCU GUC	1182
MTARC1-330	27 mer Anti-sense Strand	CCUGGUUGAUCACAAGCCAAAACC UGU	1183
MTARC1-331	27 mer Anti-sense Strand	UCCUGUUUGAUCACAAGCCAAAAC CUG	1184
MTARC1-332	27 mer Anti-sense Strand	CUCCUUGUUGAUCACAAGCCAAA CCU	1185
MTARC1-334	27 mer Anti-sense Strand	CCCUCUUGGUUGAUCACAAGCCAA AAC	1186
MTARC1-335	27 mer Anti-sense Strand	UCCCUUCUGGUUGAUCACAAGCCA AAA	1187
MTARC1-337	27 mer Anti-sense Strand	UUCCUUCUGGUUGAUCACAAGC CAA	1188
MTARC1-338	27 mer Anti-sense Strand	GUUUCUCUCCUGGUUGAUCACAAG CCA	1189
MTARC1-339	27 mer Anti-sense Strand	UGUUUCCUCCUGGUUGAUCACAA GCC	1190
MTARC1-340	27 mer Anti-sense Strand	AUGUUUCCUCCUGGUUGAUCACA AGC	1191
MTARC1-341	27 mer Anti-sense Strand	CAUGUUUCCUCCUGGUUGAUCAC AAG	1192
MTARC1-342	27 mer Anti-sense Strand	CCAUGUUUCCUCCUGGUUGAUC CAA	1193
MTARC1-343	27 mer Anti-sense Strand	ACCAUUUUUCCUCCUGGUUGAUC ACA	1194

MTARC1-345	27 mer Anti-sense Strand	UAACCUUGUUUCCCUCCUGGUUGA UCA	1195
MTARC1-346	27 mer Anti-sense Strand	GUAACUAUGUUUCCCUCCUGGUUG AUC	1196
MTARC1-347	27 mer Anti-sense Strand	AGUAAUCAUGUUUCCCUCCUGGUU GAU	1197
MTARC1-348	27 mer Anti-sense Strand	CAGUAUCCAUGUUUCCCUCCUGGU UGA	1198
MTARC1-349	27 mer Anti-sense Strand	GCAGUUACCAUGUUUCCCUCCUGG UUG	1199
MTARC1-350	27 mer Anti-sense Strand	AGCAGUAACCAUGUUUCCCUCCUG GUU	1200
MTARC1-351	27 mer Anti-sense Strand	GAGCAUUAACCAUGUUUCCCUCCU GGU	1201
MTARC1-352	27 mer Anti-sense Strand	CGAGCUGUAACCAUGUUUCCCUCC UGG	1202
MTARC1-353	27 mer Anti-sense Strand	GCGAGUAGUAACCAUGUUUCCCUCC CUG	1203
MTARC1-354	27 mer Anti-sense Strand	GGCGAUCAGUAACCAUGUUUCCCU CCU	1204
MTARC1-356	27 mer Anti-sense Strand	CUGGCUAGCAGUAACCAUGUUUCC CUC	1205
MTARC1-357	27 mer Anti-sense Strand	CCUGGUGAGCAGUAACCAUGUUUC CCU	1206
MTARC1-358	27 mer Anti-sense Strand	UCCUGUCGAGCAGUAACCAUGUUU CCC	1207
MTARC1-359	27 mer Anti-sense Strand	UUCCUUGCGAGCAGUAACCAUGUU UCC	1208
MTARC1-360	27 mer Anti-sense Strand	GUUCCUGGCGAGCAGUAACCAUGU UUC	1209
MTARC1-361	27 mer Anti-sense Strand	GGUUCUUGGCGAGCAGUAACCAUG UUU	1210
MTARC1-362	27 mer Anti-sense Strand	AGGUUUCUGGCGAGCAGUAACCAU GUU	1211
MTARC1-365	27 mer Anti-sense Strand	GCGAGUUUCCUGGCGAGCAGUAAC CAU	1212
MTARC1-376	27 mer Anti-sense Strand	AUCAGUACCAGGCGAGGUUCCUGG CGA	1213
MTARC1-379	27 mer Anti-sense Strand	GAAAUUAGGACCAGGCGAGGUUCC UGG	1214
MTARC1-384	27 mer Anti-sense Strand	UCAGGUAAAUCAGGACCAGGCGAG GUU	1215
MTARC1-385	27 mer Anti-sense Strand	GUCAGUGAAAUCAGGACCAGGCGA GGU	1216
MTARC1-388	27 mer Anti-sense Strand	CAGGUUAGGGAAAUCAGGACCAGG CGA	1217
MTARC1-390	27 mer Anti-sense Strand	CGCAGUUCAGGGAAAUCAGGACCA GGC	1218
MTARC1-391	27 mer Anti-sense Strand	UCGCAUGUCAGGGAAAUCAGGACC AGG	1219
MTARC1-393	27 mer Anti-sense Strand	CAUCGUAGGUCAGGGAAAUCAGGA CCA	1220
MTARC1-395	27 mer Anti-sense Strand	ACCAUUGCAGGUCAGGGAAAUCAG GAC	1221

MTARC1-405	27 mer Anti-sense Strand	UCAGGUUGUCACCAUCGCAGGUCA GGG	1222
MTARC1-409	27 mer Anti-sense Strand	AGAGUUAGGGUGUCACCAUCGCAG GUC	1223
MTARC1-411	27 mer Anti-sense Strand	UGAGAUUCAGGGUGUCACCAUCGC AGG	1224
MTARC1-412	27 mer Anti-sense Strand	CUGAGUGUCAGGGUGUCACCAUCG CAG	1225
MTARC1-413	27 mer Anti-sense Strand	ACUGAUAGUCAGGGUGUCACCAUC GCA	1226
MTARC1-414	27 mer Anti-sense Strand	CACUGUGAGUCAGGGUGUCACCAU CGC	1227
MTARC1-415	27 mer Anti-sense Strand	GCACUUAGAGUCAGGGUGUCACCA UCG	1228
MTARC1-416	27 mer Anti-sense Strand	UGCACUGAGAGUCAGGGUGUCACC AUC	1229
MTARC1-417	27 mer Anti-sense Strand	CUGCAUUGAGAGUCAGGGUGUCAC CAU	1230
MTARC1-418	27 mer Anti-sense Strand	GCUGCUCUGAGAGUCAGGGUGUCA CCA	1231
MTARC1-419	27 mer Anti-sense Strand	GGCUGUACUGAGAGUCAGGGUGUC ACC	1232
MTARC1-420	27 mer Anti-sense Strand	AGGCUUCACUGAGAGUCAGGGUGU CAC	1233
MTARC1-421	27 mer Anti-sense Strand	UAGGCUGCACUGAGAGUCAGGGUG UCA	1234
MTARC1-422	27 mer Anti-sense Strand	GUAGGUUGCACUGAGAGUCAGGGU GUC	1235
MTARC1-423	27 mer Anti-sense Strand	UGUAGUCUGCACUGAGAGUCAGGG UGU	1236
MTARC1-424	27 mer Anti-sense Strand	GUGUAUGCUGCACUGAGAGUCAGG GUG	1237
MTARC1-425	27 mer Anti-sense Strand	UGUGUUGGCUGCACUGAGAGUCAG GGU	1238
MTARC1-426	27 mer Anti-sense Strand	UUGUGUAGGCUGCACUGAGAGUCA GGG	1239
MTARC1-427	27 mer Anti-sense Strand	UUUGUUUAGGCUGCACUGAGAGUC AGG	1240
MTARC1-428	27 mer Anti-sense Strand	CUUUGUGUAGGCUGCACUGAGAGU CAG	1241
MTARC1-429	27 mer Anti-sense Strand	CCUUUUUGUAGGCUGCACUGAGAG UCA	1242
MTARC1-430	27 mer Anti-sense Strand	UCCUUUGUGUAGGCUGCACUGAGA GUC	1243
MTARC1-431	27 mer Anti-sense Strand	GUCCUUUGUGUAGGCUGCACUGAG AGU	1244
MTARC1-433	27 mer Anti-sense Strand	AGGUCUUUUGUGUAGGCUGCACUG AGA	1245
MTARC1-434	27 mer Anti-sense Strand	UAGGUUCUUUGUGUAGGCUGCACU GAG	1246
MTARC1-435	27 mer Anti-sense Strand	GUAGGUCCUUUGUGUAGGCUGCAC UGA	1247
MTARC1-436	27 mer Anti-sense Strand	AGUAGUCCUUUGUGUAGGCUGCA CUG	1248

MTARC1-437	27 mer Anti-sense Strand	UAGUAUGUCCUUUGUGUAGGCUGC ACU	1249
MTARC1-438	27 mer Anti-sense Strand	GUAGUUGGUCCUUUGUGUAGGCUG CAC	1250
MTARC1-439	27 mer Anti-sense Strand	AGUAGUAGGUCCUUUGUGUAGGC GCA	1251
MTARC1-440	27 mer Anti-sense Strand	CAGUAUUAGGUCCUUUGUGUAGGC UGC	1252
MTARC1-441	27 mer Anti-sense Strand	GCAGUUGUAGGUCCUUUGUGUAGG CUG	1253
MTARC1-445	27 mer Anti-sense Strand	AUAGGUAGUAGUAGGUCCUUUGUG UAG	1254
MTARC1-446	27 mer Anti-sense Strand	GAUAGUCAGUAGUAGGUCCUUUGU GUA	1255
MTARC1-447	27 mer Anti-sense Strand	UGAUUAGCAGUAGUAGGUCCUUUG UGU	1256
MTARC1-448	27 mer Anti-sense Strand	UUGAUUGGCAGUAGUAGGUCCUUU GUG	1257
MTARC1-449	27 mer Anti-sense Strand	UUUGAUAGGCAGUAGUAGGUCCUU UGU	1258
MTARC1-450	27 mer Anti-sense Strand	UUUGUAGGCAGUAGUAGGUCCU UUG	1259
MTARC1-451	27 mer Anti-sense Strand	GUUUUUUAGGCAGUAGUAGGUCC UUU	1260
MTARC1-452	27 mer Anti-sense Strand	CGUUUUUAGGCAGUAGUAGGUC CUU	1261
MTARC1-453	27 mer Anti-sense Strand	GCGUUUUAGGCAGUAGUAGGU CCU	1262
MTARC1-454	27 mer Anti-sense Strand	GGCGUUUUAGGCAGUAGUAGG UCC	1263
MTARC1-456	27 mer Anti-sense Strand	UGGGCUUUUAGGCAGUAGUA GGU	1264
MTARC1-457	27 mer Anti-sense Strand	GUGGGUGUUUAGGCAGUAGU AGG	1265
MTARC1-458	27 mer Anti-sense Strand	GGUGGUCGUUUAGGCAGUAG UAG	1266
MTARC1-459	27 mer Anti-sense Strand	UGGUGUGCGUUUAGGCAGUA GUA	1267
MTARC1-460	27 mer Anti-sense Strand	GUGGUUGGCGUUUAGGCAGU AGU	1268
MTARC1-462	27 mer Anti-sense Strand	UUGUGUUGGGCGUUUAGGCAG GUA	1269
MTARC1-468	27 mer Anti-sense Strand	CUGCAUUUGUGGUGGGCGUUUGA UAG	1270
MTARC1-469	27 mer Anti-sense Strand	ACUGCUUUUGUGGUGGGCGUUUG AUA	1271
MTARC1-470	27 mer Anti-sense Strand	CACUGUAUUUGUGGUGGGCGUUU GAU	1272
MTARC1-471	27 mer Anti-sense Strand	GCACUUCUUUGUGGUGGGCGUUU UGA	1273
MTARC1-473	27 mer Anti-sense Strand	GUGCAUUGCAUUUGUGGUGGGCGU UUU	1274
MTARC1-475	27 mer Anti-sense Strand	UUGUGUACUGCAUUUGUGGUGGGC GUU	1275

MTARC1-476	27 mer Anti-sense Strand	CUUGUUCACUGCAUUUGUGGUGGG CGU	1276
MTARC1-482	27 mer Anti-sense Strand	UCUGCUCUUGUGCACUGCAUUUGU GGU	1277
MTARC1-483	27 mer Anti-sense Strand	CUCUGUACUUGUGCACUGCAUUUG UGG	1278
MTARC1-484	27 mer Anti-sense Strand	ACUCUUCACUUGUGCACUGCAUUU GUG	1279
MTARC1-552	27 mer Anti-sense Strand	UCAGGUAGCUGGUUAUCCACUGGG CGG	1280
MTARC1-553	27 mer Anti-sense Strand	UUCAGUAAGCUGGUUAUCCACUGG GCG	1281
MTARC1-554	27 mer Anti-sense Strand	CUUCAUGAAGCUGGUUAUCCACUG GGC	1282
MTARC1-555	27 mer Anti-sense Strand	ACUUCUGGAAGCUGGUUAUCCACU GGG	1283
MTARC1-556	27 mer Anti-sense Strand	GACUUUAGGAAGCUGGUUAUCCAC UGG	1284
MTARC1-557	27 mer Anti-sense Strand	UGACUUCAGGAAGCUGGUUAUCCA CUG	1285
MTARC1-558	27 mer Anti-sense Strand	GUGACUUCAGGAAGCUGGUUAUCC ACU	1286
MTARC1-559	27 mer Anti-sense Strand	UGUGAUUUCAGGAAGCUGGUUAUC CAC	1287
MTARC1-560	27 mer Anti-sense Strand	CUGUGUCUUCAGGAAGCUGGUUAU CCA	1288
MTARC1-561	27 mer Anti-sense Strand	GCUGUUACUUCAGGAAGCUGGUUA UCC	1289
MTARC1-562	27 mer Anti-sense Strand	GGCUGUGACUUCAGGAAGCUGGUU AUC	1290
MTARC1-563	27 mer Anti-sense Strand	GGGCUUUGACUUCAGGAAGCUGGU UAU	1291
MTARC1-564	27 mer Anti-sense Strand	AGGGCUGUGACUUCAGGAAGCUGG UUA	1292
MTARC1-565	27 mer Anti-sense Strand	UAGGGUUGUGACUUCAGGAAGCUG GUU	1293
MTARC1-566	27 mer Anti-sense Strand	GUAGGUCUGUGACUUCAGGAAGCU GGU	1294
MTARC1-567	27 mer Anti-sense Strand	GGUAGUGCUGUGACUUCAGGAAGC UGG	1295
MTARC1-568	27 mer Anti-sense Strand	CGGUAUGGCUGUGACUUCAGGAAG CUG	1296
MTARC1-589	27 mer Anti-sense Strand	UGAGGUUCGAAGUGCACCAGGCGG UAG	1297
MTARC1-591	27 mer Anti-sense Strand	UGUGAUGCUCGAAGUGCACCAGGC GGU	1298
MTARC1-592	27 mer Anti-sense Strand	AUGUGUGGCUCGAAGUGCACCAGG CGG	1299
MTARC1-593	27 mer Anti-sense Strand	CAUGUUAGGCUCGAAGUGCACCAG GCG	1300
MTARC1-597	27 mer Anti-sense Strand	GUCGCUUGUGAGGCUCGAAGUGCA CCA	1301
MTARC1-600	27 mer Anti-sense Strand	UCGGUUGCAUGUGAGGCUCGAAGU GCA	1302

MTARC1-612	27 mer Anti-sense Strand	GAUGAUGACGUCUCGGUCGCAUGU GAG	1303
MTARC1-614	27 mer Anti-sense Strand	UUGAUUAGGACGUCUCGGUCGCAU GUG	1304
MTARC1-617	27 mer Anti-sense Strand	UAUUUUAUGAGGACGUCUCGGUCG CAU	1305
MTARC1-618	27 mer Anti-sense Strand	CUAUUUGAUGAGGACGUCUCGGUC GCA	1306
MTARC1-620	27 mer Anti-sense Strand	UGCUAUUUGAUGAGGACGUCUCGG UCG	1307
MTARC1-621	27 mer Anti-sense Strand	CUGCUUUUUGAUGAGGACGUCUCG GUC	1308
MTARC1-622	27 mer Anti-sense Strand	UCUGCUAUUUGAUGAGGACGUCUC GGU	1309
MTARC1-623	27 mer Anti-sense Strand	GUCUGUUAUUUGAUGAGGACGUCU CGG	1310
MTARC1-624	27 mer Anti-sense Strand	AGUCUUCUAUUUGAUGAGGACGUC UCG	1311
MTARC1-625	27 mer Anti-sense Strand	AAGUCUGCUAUUUGAUGAGGACGU CUC	1312
MTARC1-626	27 mer Anti-sense Strand	CAAGUUUGCUAUUUGAUGAGGACG UCU	1313
MTARC1-627	27 mer Anti-sense Strand	ACAAGUCUGCUAUUUGAUGAGGAC GUC	1314
MTARC1-628	27 mer Anti-sense Strand	AACAAUUCUGCUAUUUGAUGAGGA CGU	1315
MTARC1-629	27 mer Anti-sense Strand	GAACAUGUCUGCUAUUUGAUGAGG ACG	1316
MTARC1-630	27 mer Anti-sense Strand	GGAACUAGUCUGCUAUUUGAUGAG GAC	1317
MTARC1-631	27 mer Anti-sense Strand	CGGAUAAGUCUGCUAUUUGAUGA GGA	1318
MTARC1-632	27 mer Anti-sense Strand	UCGGAUCAAGUCUGCUAUUUGAUG AGG	1319
MTARC1-633	27 mer Anti-sense Strand	GUCGGUACAAGUCUGCUAUUUGAU GAG	1320
MTARC1-634	27 mer Anti-sense Strand	GGUCGUAACAAGUCUGCUAUUUGA UGA	1321
MTARC1-635	27 mer Anti-sense Strand	GGGUCUGAACAAGUCUGCUAUUUG AUG	1322
MTARC1-636	27 mer Anti-sense Strand	UGGGUUGGAACAAGUCUGCUAUUU GAU	1323
MTARC1-637	27 mer Anti-sense Strand	UUGGGUCGGAACAAGUCUGCUAUU UGA	1324
MTARC1-638	27 mer Anti-sense Strand	CUUGGUUCGGAACAAGUCUGCUAU UUG	1325
MTARC1-639	27 mer Anti-sense Strand	CCUUGUGUCGGAACAAGUCUGCUA UUU	1326
MTARC1-640	27 mer Anti-sense Strand	UCCUUUGGUCGGAACAAGUCUGCU AUU	1327
MTARC1-641	27 mer Anti-sense Strand	GUCCUUGGUCGGAACAAGUCUGC UAU	1328
MTARC1-642	27 mer Anti-sense Strand	GGUCCUUGGGUCGGAACAAGUCUG CUA	1329

MTARC1-643	27 mer Anti-sense Strand	UGGUCUUUGGGUCGGAACAAGUCU GCU	1330
MTARC1-644	27 mer Anti-sense Strand	CUGGUUCUUGGGUCGGAACAAGUC UGC	1331
MTARC1-645	27 mer Anti-sense Strand	UCUGGUCCUUGGGUCGGAACAAGU CUG	1332
MTARC1-646	27 mer Anti-sense Strand	AUCUGUCCUUGGGUCGGAACAAG UCU	1333
MTARC1-647	27 mer Anti-sense Strand	AAUCUUGUCCUUGGGUCGGAACAA GUC	1334
MTARC1-648	27 mer Anti-sense Strand	CAAUCUGGUCCUUGGGUCGGAACA AGU	1335
MTARC1-649	27 mer Anti-sense Strand	GCAAUUUGGUCCUUGGGUCGGAAC AAG	1336
MTARC1-650	27 mer Anti-sense Strand	AGCAAUCUGGUCCUUGGGUCGGA CAA	1337
MTARC1-651	27 mer Anti-sense Strand	AAGCAUUCUGGUCCUUGGGUCGGA ACA	1338
MTARC1-652	27 mer Anti-sense Strand	UAAGCUAUCUGGUCCUUGGGUCGG AAC	1339
MTARC1-653	27 mer Anti-sense Strand	GUAAGUAAUCUGGUCCUUGGGUCG GAA	1340
MTARC1-654	27 mer Anti-sense Strand	AGUAAUCAUCUGGUCCUUGGGUC GGA	1341
MTARC1-655	27 mer Anti-sense Strand	GAGUAUGCAAUCUGGUCCUUGGGU CGG	1342
MTARC1-656	27 mer Anti-sense Strand	UGAGUUAGCAAUCUGGUCCUUGGG UCG	1343
MTARC1-657	27 mer Anti-sense Strand	CUGAGUAAGCAAUCUGGUCCUUGG GUC	1344
MTARC1-658	27 mer Anti-sense Strand	UCUGAUUAAGCAAUCUGGUCCUUG GGU	1345
MTARC1-659	27 mer Anti-sense Strand	GUCUGUGUAAGCAAUCUGGUCCU GGG	1346
MTARC1-660	27 mer Anti-sense Strand	UGUCUUAGUAAGCAAUCUGGUCCU UGG	1347
MTARC1-661	27 mer Anti-sense Strand	GUGUCUGAGUAAGCAAUCUGGUCC UUG	1348
MTARC1-662	27 mer Anti-sense Strand	GGUGUUUGAGUAAGCAAUCUGGUC CUU	1349
MTARC1-663	27 mer Anti-sense Strand	UGGUGUCUGAGUAAGCAAUCUGGU CCU	1350
MTARC1-664	27 mer Anti-sense Strand	CUGGUUUCUGAGUAAGCAAUCUGG UCC	1351
MTARC1-665	27 mer Anti-sense Strand	GCUGGUGUCUGAGUAAGCAAUCUG GUC	1352
MTARC1-666	27 mer Anti-sense Strand	GGCUGUUGUCUGAGUAAGCAAUCU GGU	1353
MTARC1-667	27 mer Anti-sense Strand	GGGCUUGUGUCUGAGUAAGCAAUC UGG	1354
MTARC1-668	27 mer Anti-sense Strand	UGGGCUGGUGUCUGAGUAAGCAAU CUG	1355
MTARC1-669	27 mer Anti-sense Strand	AUGGGUUGGUGUCUGAGUAAGCAA UCU	1356

MTARC1-670	27 mer Anti-sense Strand	AAUGGUCUGGUGUCUGAGUAAGCA AUC	1357
MTARC1-671	27 mer Anti-sense Strand	GAAUGUGCUGGUGUCUGAGUAAGC AAU	1358
MTARC1-672	27 mer Anti-sense Strand	AGAAUUGGCUGGUGUCUGAGUAAG CAA	1359
MTARC1-673	27 mer Anti-sense Strand	AAGAAUGGGCUGGUGUCUGAGUAA GCA	1360
MTARC1-674	27 mer Anti-sense Strand	CAAGAUUGGGCUGGUGUCUGAGUA AGC	1361
MTARC1-675	27 mer Anti-sense Strand	UCAAGUAUGGGCUGGUGUCUGAGU AAG	1362
MTARC1-676	27 mer Anti-sense Strand	AUCAAAUUGGGCUGGUGUCUGAG UAA	1363
MTARC1-677	27 mer Anti-sense Strand	GAUCAAGAAUGGGCUGGUGUCUGA GUA	1364
MTARC1-678	27 mer Anti-sense Strand	GGAUCUAGAAUGGGCUGGUGUCUG AGU	1365
MTARC1-679	27 mer Anti-sense Strand	AGGAUUAAGAAUGGGCUGGUGUCU GAG	1366
MTARC1-680	27 mer Anti-sense Strand	AAGGAUCAAGAAUGGGCUGGUGUC UGA	1367
MTARC1-681	27 mer Anti-sense Strand	AAAGGUUCAAGAAUGGGCUGGUGU CUG	1368
MTARC1-682	27 mer Anti-sense Strand	GAAAGUAUCAAGAAUGGGCUGGUG UCU	1369
MTARC1-683	27 mer Anti-sense Strand	AGAAAUGAUCAAGAAUGGGCUGGU GUC	1370
MTARC1-684	27 mer Anti-sense Strand	CAGAAUGGAUCAAGAAUGGGCUGG UGU	1371
MTARC1-685	27 mer Anti-sense Strand	UCAGAUAGGAUCAAGAAUGGGCUG GUG	1372
MTARC1-686	27 mer Anti-sense Strand	CUCAGUAAGGAUCAAGAAUGGGCU GGU	1373
MTARC1-687	27 mer Anti-sense Strand	CCUCAUAAAGGAUCAAGAAUGGGC UGG	1374
MTARC1-691	27 mer Anti-sense Strand	GACGCUUCAGAAAGGAUCAAGAAU GGG	1375
MTARC1-692	27 mer Anti-sense Strand	CGACGUCUCAGAAAGGAUCAAGAA UGG	1376
MTARC1-724	27 mer Anti-sense Strand	UUCUUUUCUAGCCUGGAGUUGAGA UCC	1377
MTARC1-726	27 mer Anti-sense Strand	CUUUCUUCUCUAGCCUGGAGUUGA GAU	1378
MTARC1-728	27 mer Anti-sense Strand	AACUUUCUUCUCUAGCCUGGAGUU GAG	1379
MTARC1-729	27 mer Anti-sense Strand	UAACUUUCUUCUCUAGCCUGGAGU UGA	1380
MTARC1-730	27 mer Anti-sense Strand	UUAACUUUCUUCUCUAGCCUGGAG UUG	1381
MTARC1-731	27 mer Anti-sense Strand	UUUAAUUUUCUUCUCUAGCCUGGA GUU	1382
MTARC1-733	27 mer Anti-sense Strand	GCUUUUACUUUCUUCUCUAGCCUG GAG	1383

MTARC1-734	27 mer Anti-sense Strand	UGC U U U A A C U U U C U U C U C U A G C C U G G A	1384
MTARC1-735	27 mer Anti-sense Strand	U U G C U U U A A C U U U C U U C U C U A G C C U G G	1385
MTARC1-736	27 mer Anti-sense Strand	G U U G C U U U A A C U U U C U U C U C U A G C C U G	1386
MTARC1-737	27 mer Anti-sense Strand	G G U U G U U U U A A C U U U C U U C U C U A G C C U	1387
MTARC1-738	27 mer Anti-sense Strand	U G G U U U C U U U A A C U U U C U U C U C U A G C C	1388
MTARC1-739	27 mer Anti-sense Strand	U U G G U U G C U U U A A C U U U C U U C U C U A G C	1389
MTARC1-740	27 mer Anti-sense Strand	G U U G G U U G C U U U A A C U U U C U U C U C U A G	1390
MTARC1-741	27 mer Anti-sense Strand	A G U U G U U U G C U U U A A C U U U C U U C U C U A	1391
MTARC1-742	27 mer Anti-sense Strand	A A G U U U G U U G C U U U A A C U U U C U U C U C U	1392
MTARC1-743	27 mer Anti-sense Strand	G A A G U U G G U U G C U U U A A C U U U C U U C U C	1393
MTARC1-744	27 mer Anti-sense Strand	U G A A G U U G G U U G C U U U A A C U U U C U U C U	1394
MTARC1-745	27 mer Anti-sense Strand	C U G A A U U U G G U U G C U U U A A C U U U C U U C	1395
MTARC1-746	27 mer Anti-sense Strand	C C U G A U G U U G G U U G C U U U A A C U U U C U U	1396
MTARC1-747	27 mer Anti-sense Strand	G C C U G U A G U U G G U U G C U U U A A C U U C U C U	1397
MTARC1-748	27 mer Anti-sense Strand	G G C C U U A A G U U G G U U G C U U U A A C U U C U C	1398
MTARC1-750	27 mer Anti-sense Strand	U G G G C U U G A A G U U G G U U G C U U U A A C U U	1399
MTARC1-751	27 mer Anti-sense Strand	U U G G G U C U G A A G U U G G U U G C U U U A A C U	1400
MTARC1-752	27 mer Anti-sense Strand	A U U G G U C C U G A A G U U G G U U G C U U U A A C	1401
MTARC1-753	27 mer Anti-sense Strand	U A U U G U G C C U G A A G U U G G U U G C U U U A A	1402
MTARC1-754	27 mer Anti-sense Strand	A U A U U U G G C C U G A A G U U G G U U G C U U U A	1403
MTARC1-755	27 mer Anti-sense Strand	A A U A U U G G G C C U G A A G U U G G U U G C U U U	1404
MTARC1-756	27 mer Anti-sense Strand	C A A U A U U G G G C C U G A A G U U G G U U G C U U	1405
MTARC1-758	27 mer Anti-sense Strand	U A C A A U A U U G G G C C U G A A G U U G G U U G C	1406
MTARC1-759	27 mer Anti-sense Strand	U U A C A U A U U G G G C C U G A A G U U G G U U G	1407
MTARC1-760	27 mer Anti-sense Strand	A U U A C U A U A U U G G G C C U G A A G U U G G U U	1408
MTARC1-761	27 mer Anti-sense Strand	A A U U A U A A U A U U G G G C C U G A A G U U G G U	1409
MTARC1-762	27 mer Anti-sense Strand	A A A U U U C A A U A U U G G G C C U G A A G U U G G	1410

MTARC1-763	27 mer Anti-sense Strand	GAAAUUACAAUAUUGGGCCUGAAG UUG	1411
MTARC1-764	27 mer Anti-sense Strand	UGAAAUUACAAUAUUGGGCCUGAA GUU	1412
MTARC1-765	27 mer Anti-sense Strand	CUGAAUUUACAAUAUUGGGCCUGA AGU	1413
MTARC1-766	27 mer Anti-sense Strand	CCUGAUUUACAAUAUUGGGCCUG AAG	1414
MTARC1-767	27 mer Anti-sense Strand	UCCUGUAAUUACAAUAUUGGGCCU GAA	1415
MTARC1-768	27 mer Anti-sense Strand	AUCCUUAUUUACAAUAUUGGGCC UGA	1416
MTARC1-769	27 mer Anti-sense Strand	CAUCCUGAAAUUACAAUAUUGGGC CUG	1417
MTARC1-770	27 mer Anti-sense Strand	GCAUCUUGAAAUUACAAUAUUGGG CCU	1418
MTARC1-771	27 mer Anti-sense Strand	CGCAUUCUGAAAUUACAAUAUUGG GCC	1419
MTARC1-772	27 mer Anti-sense Strand	UCGCAUCCUGAAAUUACAAUAUUG GGC	1420
MTARC1-773	27 mer Anti-sense Strand	AUCGCUCCUGAAAUUACAAUAUUG GGG	1421
MTARC1-774	27 mer Anti-sense Strand	CAUCGUAUCCUGAAAUUACAAUAU UGG	1422
MTARC1-775	27 mer Anti-sense Strand	ACAUCUCAUCCUGAAAUUACAAUA UUG	1423
MTARC1-776	27 mer Anti-sense Strand	GACAUUGCAUCCUGAAAUUACAAU AUU	1424
MTARC1-777	27 mer Anti-sense Strand	AGACAUCCUGCAUCCUGAAAUUACAA UAU	1425
MTARC1-778	27 mer Anti-sense Strand	UAGACUUCGCAUCCUGAAAUUACA AUA	1426
MTARC1-779	27 mer Anti-sense Strand	AUAGAUUAGCAUCCUGAAAUUAC AAU	1427
MTARC1-780	27 mer Anti-sense Strand	CAUAGUCAUCCUGCAUCCUGAAAUUA CAA	1428
MTARC1-781	27 mer Anti-sense Strand	GCAUAUACAUCGCAUCCUGAAAUU ACA	1429
MTARC1-782	27 mer Anti-sense Strand	UGCAUUGACAUCGCAUCCUGAAAU UAC	1430
MTARC1-783	27 mer Anti-sense Strand	CUGCAUAGACAUCGCAUCCUGAAA UUA	1431
MTARC1-784	27 mer Anti-sense Strand	UCUGCUUAGACAUCGCAUCCUGAA AUU	1432
MTARC1-785	27 mer Anti-sense Strand	CUCUGUAUAGACAUCGCAUCCUGA AAU	1433
MTARC1-786	27 mer Anti-sense Strand	CCUCUUCAUAGACAUCGCAUCCUG AAA	1434
MTARC1-787	27 mer Anti-sense Strand	UCCUCUGCAUAGACAUCGCAUCCU GAA	1435
MTARC1-788	27 mer Anti-sense Strand	AUCCUUUGCAUAGACAUCGCAUCC UGA	1436
MTARC1-789	27 mer Anti-sense Strand	AAUCCUCUGCAUAGACAUCGCAUC CUG	1437

MTARC1-790	27 mer Anti-sense Strand	GAAUCUUCUGCAUAGACAUCGCAU CCU	1438
MTARC1-791	27 mer Anti-sense Strand	AGAAUUCUCUGCAUAGACAUCGCA UCC	1439
MTARC1-792	27 mer Anti-sense Strand	GUGUUUCCUCUGCAUAGACAUCGC AUC	1440
MTARC1-863	27 mer Anti-sense Strand	UGUGGUUAAAAUGCAUCUGGAACA AGC	1441
MTARC1-929	27 mer Anti-sense Strand	CUGGCUAUAACUCUUCAGUGUUUC CAG	1442
MTARC1-930	27 mer Anti-sense Strand	ACUGGUGAUAACUCUUCAGUGUUU CCA	1443
MTARC1-934	27 mer Anti-sense Strand	UCACAUUGGCGAUAACUCUUCAGU GUU	1444
MTARC1-955	27 mer Anti-sense Strand	UAUAAUUUUCGUUCUGAAGGGUCA CAC	1445
MTARC1-959	27 mer Anti-sense Strand	UCCAUUUAAACUUUCGUUCUGAAGG GUC	1446
MTARC1-960	27 mer Anti-sense Strand	UCCAUUAUAACUUUCGUUCUGAAG GGU	1447
MTARC1-963	27 mer Anti-sense Strand	AUUUUUCAUAUAACUUUCGUUCUG AAG	1448
MTARC1-964	27 mer Anti-sense Strand	GAUUUUCCAUAUAACUUUCGUUCU GAA	1449
MTARC1-965	27 mer Anti-sense Strand	UGAUUUUCCAUAUAACUUUCGUUC UGA	1450
MTARC1-966	27 mer Anti-sense Strand	GUGAUUUUCCAUAUAACUUUCGUU CUG	1451
MTARC1-967	27 mer Anti-sense Strand	GGUGAUUUUCCAUAUAACUUUCGU UCU	1452
MTARC1-969	27 mer Anti-sense Strand	GUGGUUAUUUUCCAUAUAACUUUC GUU	1453
MTARC1-970	27 mer Anti-sense Strand	AGUGGUGAUUUUCCAUAUAACUUU CGU	1454
MTARC1-971	27 mer Anti-sense Strand	GAGUGUUGAUUUUCCAUAUAACUU UCG	1455
MTARC1-1107	27 mer Anti-sense Strand	UGUUGUCAUUUUUGAGAACAUUUU UAA	1456
MTARC1-1113	27 mer Anti-sense Strand	UUCAAUUGUUGUCAUUUUUGAGAA CAU	1457
MTARC1-1118	27 mer Anti-sense Strand	CAUGCUCUACAGUGUUGUCAUUUUU GAG	1458
MTARC1-1123	27 mer Anti-sense Strand	AACACUAUGCUUCAAGUGUUGUCA UUU	1459
MTARC1-1126	27 mer Anti-sense Strand	UGAAAUACCAUGCUUCAAGUGUUG UCA	1460
MTARC1-1127	27 mer Anti-sense Strand	CUGAAUCACCAUGCUUCAAGUGUU GUC	1461
MTARC1-1128	27 mer Anti-sense Strand	UCUGAUACACCAUGCUUCAAGUGU UGU	1462
MTARC1-1129	27 mer Anti-sense Strand	UUCUGUAACACCAUGCUUCAAGUG UUG	1463
MTARC1-1130	27 mer Anti-sense Strand	GUUCUUAACACCAUGCUUCAAGU GUU	1464

MTARC1-1132	27 mer Anti-sense Strand	CAGUUUUGAAACACCAUGCUUCAA GUG	1465
MTARC1-1133	27 mer Anti-sense Strand	UCAGUUCUGAAACACCAUGCUUCA AGU	1466
MTARC1-1134	27 mer Anti-sense Strand	CUCAGUUCUGAAACACCAUGCUUC AAG	1467
MTARC1-1135	27 mer Anti-sense Strand	UCUCAUUUCUGAAACACCAUGCUU CAA	1468
MTARC1-1139	27 mer Anti-sense Strand	GAGGUUUCAGUUCUGAAACACCAU GCU	1469
MTARC1-1144	27 mer Anti-sense Strand	AUGUAUAGGUCUCAGUUCUGAAAC ACC	1470
MTARC1-1165	27 mer Anti-sense Strand	AAAAUUACAAAUUUAAAGAAAAUG UAG	1471
MTARC1-1167	27 mer Anti-sense Strand	UGAAAUUCACAAAUUUAAAGAAAA UGU	1472
MTARC1-1173	27 mer Anti-sense Strand	AAAAUUUGAAAAUCACAAAUUUAA AGA	1473
MTARC1-1177	27 mer Anti-sense Strand	ACGAAUAAUGUGAAAAUCACAAAU UUA	1474
MTARC1-1179	27 mer Anti-sense Strand	AGACGUAAAAUGUGAAAAUCACAA AUU	1475
MTARC1-1329	27 mer Anti-sense Strand	AGAACUAUCCAUAUUCAGUUAAA CGG	1476
MTARC1-1330	27 mer Anti-sense Strand	AAGAAUUAUCCAUAUUCAGUUAA ACG	1477
MTARC1-1332	27 mer Anti-sense Strand	GAAAGUACUAUCCAUAUUCAGUU AAA	1478
MTARC1-1333	27 mer Anti-sense Strand	AGAAAUAAACUAUCCAUAUUCAGU UAA	1479
MTARC1-1334	27 mer Anti-sense Strand	GAGAAUGAACUAUCCAUAUUCAG UUA	1480
MTARC1-1335	27 mer Anti-sense Strand	GGAGAUAGAACUAUCCAUAUUCAG GUU	1481
MTARC1-1620	27 mer Anti-sense Strand	CAGAUUUUAUGGAAAAUUAUUAUCU GCA	1482
MTARC1-1622	27 mer Anti-sense Strand	UCCAGUUCUAUGGAAAAUUAUUAU CUG	1483
MTARC1-1660	27 mer Anti-sense Strand	AGGAAUCCAUGCUGUCUGAGAA GCA	1484
MTARC1-1663	27 mer Anti-sense Strand	UUUAGUAAAUCCAUGCUGUCUGA GAA	1485
MTARC1-1664	27 mer Anti-sense Strand	CUUUAUGAAAUCCAUGCUGUCUG AGA	1486
MTARC1-1812	27 mer Anti-sense Strand	UCUGAUUACACUGAAUCACUUUUC UUC	1487
MTARC1-1816	27 mer Anti-sense Strand	UCUAUUUGAAAUCACUGAAUCACU UUU	1488
MTARC1-1868	27 mer Anti-sense Strand	UUUAAUCAACUGACAUUAGCUUUC CUU	1489
MTARC1-1869	27 mer Anti-sense Strand	UUUUUAACAACUGACAUUAGCUUU CCU	1490
MTARC1-1876	27 mer Anti-sense Strand	UAUUGUGUUUUAAACAACUGACAU AUG	1491

MTARC1-1877	27 mer Anti-sense Strand	AUAUUUGGUUUUAAACAACUGACA UAU	1492
MTARC1-1878	27 mer Anti-sense Strand	GAUAUUGGGUUUUAAACAACUGAC AUA	1493
MTARC1-1879	27 mer Anti-sense Strand	AGAUAUUGGGUUUUAAACAACUGA CAU	1494
MTARC1-1882	27 mer Anti-sense Strand	AAUAGUUAUUGGGUUUUAAACAAC UGA	1495
MTARC1-1883	27 mer Anti-sense Strand	AAAUAUAUAUUGGGUUUUAAACAA CUG	1496
MTARC1-1884	27 mer Anti-sense Strand	AAAAUUGAUUAUUGGGUUUUAAACA ACU	1497
MTARC1-1885	27 mer Anti-sense Strand	AAAAAUAGAUUAUUGGGUUUUAAAC AAC	1498
MTARC1-1886	27 mer Anti-sense Strand	AAAAAUUAGAUUAUUGGGUUUUAAA CAA	1499
MTARC1-1935	27 mer Anti-sense Strand	UGGCAUUAUUUUUUUAUACUUCAUC AGA	1500
MTARC1-1936	27 mer Anti-sense Strand	AUGGCUAUAAAAAAUAUACUUCAU CAG	1501
MTARC1-1937	27 mer Anti-sense Strand	AAUGGUAAUAAAAAAUAUACUUCA UCA	1502
MTARC1-1939	27 mer Anti-sense Strand	AAAAUUGCAAUAAAAAAUAUACUU CAU	1503
MTARC1-1941	27 mer Anti-sense Strand	ACAAAUUGGCAAUAAAAAAUAUAC UUC	1504
MTARC1-1953	27 mer Anti-sense Strand	UAUAAUCAAAAGGACAAAUGGCAA UAA	1505
MTARC1-1955	27 mer Anti-sense Strand	AAUAUAUCAAAAGGACAAAUGGC AAU	1506
MTARC1-1981	27 mer Anti-sense Strand	CAUUUUUCAAGUUUAGUCAACUUC CCA	1507
MTARC1-1983	27 mer Anti-sense Strand	AACAUUUUUUCAAGUUUAGUCAACU UCC	1508
MTARC1-1985	27 mer Anti-sense Strand	AAAACUUUUUUUCAAGUUUAGUCA CUU	1509
MTARC1-1986	27 mer Anti-sense Strand	AAAAAUUUUUUCAAGUUUAGUCA ACU	1510
MTARC1-1988	27 mer Anti-sense Strand	UUAAAUACAUUUUUCAAGUUUAGU CAA	1511
MTARC1-1989	27 mer Anti-sense Strand	UUUAAUAACAUUUUUCAAGUUUAG UCA	1512
MTARC1-1990	27 mer Anti-sense Strand	UUUUAUAAACAUUUUUCAAGUUUA GUC	1513
MTARC1-1995	27 mer Anti-sense Strand	CACAGUUUUAAAAACAUUUUUCA GUU	1514
MTARC1-1996	27 mer Anti-sense Strand	UCACAUUUUUAAAAACAUUUUUCA AGU	1515
MTARC1-1998	27 mer Anti-sense Strand	AUUCAUAGUUUUAAAAACAUUUUU CAA	1516
MTARC1-1999	27 mer Anti-sense Strand	UAUUCUCAGUUUUAAAAACAUUUU UCA	1517
MTARC1-2000	27 mer Anti-sense Strand	UUAUUUACAGUUUUAAAAACAUUU UUC	1518

MTARC1-2001	27 mer Anti-sense Strand	UUUAUUCACAGUUUUAAAAACA UUU	1519
MTARC1-2002	27 mer Anti-sense Strand	AUUUAUUCACAGUUUUAAAAACA UUU	1520
MTARC1-2005	27 mer Anti-sense Strand	UCCAUUUAUUCACAGUUUUAAAA CAU	1521
MTARC1-2006	27 mer Anti-sense Strand	UCCAUUUAUUCACAGUUUUAAAA ACA	1522
MTARC1-2010	27 mer Anti-sense Strand	UAGCUUCCAUUUAUUCACAGUUUU AAA	1523
MTARC1-2011	27 mer Anti-sense Strand	GUAGCUUCCAUUUAUUCACAGUUUU UAA	1524
MTARC1-2012	27 mer Anti-sense Strand	AGUAGUUCCAUUUAUUCACAGUUUU UUA	1525
MTARC1-2013	27 mer Anti-sense Strand	AAGUAUCUCCAUUUAUUCACAGUUUU UUU	1526
MTARC1-2015	27 mer Anti-sense Strand	CAAAGUAGCUUCCAUUUAUUCACA GUU	1527
MTARC1-2016	27 mer Anti-sense Strand	UCAAUUAGCUUCCAUUUAUUCACAGU AGU	1528
MTARC1-2017	27 mer Anti-sense Strand	GUCAAUGUAGCUUCCAUUUAUUCACAG CAG	1529
MTARC1-2018	27 mer Anti-sense Strand	AGUCAUAGUAGCUUCCAUUUAUUCACA ACA	1530
MTARC1-2019	27 mer Anti-sense Strand	UAGUCUAAGUAGCUUCCAUUUAUUCAC CAC	1531
MTARC1-2020	27 mer Anti-sense Strand	CUAGUUAAGUAGCUUCCAUUUAUUCAC UCA	1532
MTARC1-2022	27 mer Anti-sense Strand	AACUAUUCAAAGUAGCUUCCAUUUAUUC AUU	1533
MTARC1-2023	27 mer Anti-sense Strand	AAACUUGUCAAGUAGCUUCCAUUUAUUC UAU	1534
MTARC1-2025	27 mer Anti-sense Strand	UGAAAUUAGUCAAGUAGCUUCCAUUUAUUC UUU	1535
MTARC1-2027	27 mer Anti-sense Strand	UCUGAUACUAGUCAAGUAGCUUCCA CAU	1536
MARC1-0324	36 mer Sense Strand	CGGGACAGGUUUUGGCUUGAGCAG CCGAAAGGCUGC	1537
MARC1-0326	36 mer Sense Strand	GGACAGGUUUUGGCUUGAGCAG CCGAAAGGCUGC	1538
MARC1-0327	36 mer Sense Strand	GACAGGUUUUGGCUUGAGCAG CCGAAAGGCUGC	1539
MARC1-0330	36 mer Sense Strand	AGGUUUUGGCUUGAGCAAGCAG CCGAAAGGCUGC	1540
MARC1-0331	36 mer Sense Strand	GGUUUUUGGCUUGAGCAAGCAG CCGAAAGGCUGC	1541
MARC1-0735	36 mer Sense Strand	AGGCUAGAGAAGAAAGUUAAGCAG CCGAAAGGCUGC	1542
MARC1-0736	36 mer Sense Strand	GGCUAGAGAAGAAAGUUAAGCAG CCGAAAGGCUGC	1543
MARC1-0788	36 mer Sense Strand	AGGAUGCGAUGUCAAGCAG CCGAAAGGCUGC	1544
MARC1-0863	36 mer Sense Strand	UUGUCCAGAUGCAUUUAAGCAG CCGAAAGGCUGC	1545

MARC1-1179	36 mer Sense Strand	UUUGUGAUUUUCACAUUUUAGCAG CCGAAAGGCUGC	1546
MARC1-2012	36 mer Sense Strand	AAACUGUGAAUAAAUGGAAAGCAG CCGAAAGGCUGC	1547
MARC1-2013	36 mer Sense Strand	AACUGUGAAUAAAUGGAAGAGCAG CCGAAAGGCUGC	1548
MARC1-0661	36 mer Sense Strand	AGGACCAGAUUGCUUACUCAGCAG CCGAAAGGCUGC	1549
MARC1-1869	36 mer Sense Strand	GAAAGCAUAUGUCAGUUGUAGCAG CCGAAAGGCUGC	1550
MARC1-1876	36 mer Sense Strand	UAUGUCAGUUGUUUAAAACAGCAG CCGAAAGGCUGC	1551
MARC1-1886	36 mer Sense Strand	GUUUAAAACCCAAUAUCUAAGCAG CCGAAAGGCUGC	1552
MARC1-2016	36 mer Sense Strand	UGUGAAUAAAUGGAAGCUAAGCAG CCGAAAGGCUGC	1553
MARC1-0413	36 mer Sense Strand	CGAUGGUGACACCCUGACUAGCAG CCGAAAGGCUGC	1554
MARC1-0416	36 mer Sense Strand	UGGUGACACCCUGACUCUCAGCAG CCGAAAGGCUGC	1555
MARC1-0622	36 mer Sense Strand	CGAGACGUCCUCAUCAAUAGCAG CCGAAAGGCUGC	1556
MARC1-0638	36 mer Sense Strand	AAUAGCAGACUUGUCCGAAGCAG CCGAAAGGCUGC	1557
MARC1-0657	36 mer Sense Strand	CCCAAGGACCAGAUUGCUUAGCAG CCGAAAGGCUGC	1558
MARC1-0660	36 mer Sense Strand	AAGGACCAGAUUGCUUACUAGCAG CCGAAAGGCUGC	1559
MARC1-0965	36 mer Sense Strand	AGAACGAAAGUUAUAUGGAAGCAG CCGAAAGGCUGC	1560
MARC1-0966	36 mer Sense Strand	GAACGAAAGUUAUAUGGAAAGCAG CCGAAAGGCUGC	1561
MARC1-0967	36 mer Sense Strand	AACGAAAGUUAUAUGGAAAAGCAG CCGAAAGGCUGC	1562
MARC1-0969	36 mer Sense Strand	CGAAAGUUAUAUGGAAAAUAGCAG CCGAAAGGCUGC	1563
MARC1-1177	36 mer Sense Strand	AAUUUGUGAUUUUCACAUUAGCAG CCGAAAGGCUGC	1564
MARC1-1884	36 mer Sense Strand	UUGUUUAAAACCCAAUAUCAGCAG CCGAAAGGCUGC	1565
MARC1-1885	36 mer Sense Strand	UGUUUAAAACCCAAUAUCUAGCAG CCGAAAGGCUGC	1566
MARC1-1955	36 mer Sense Strand	UGCCAUUUUGUCCUUGAUAGCAG CCGAAAGGCUGC	1567
MARC1-1983	36 mer Sense Strand	AAGUUGACUAAACUUGAAAAGCAG CCGAAAGGCUGC	1568
MARC1-1986	36 mer Sense Strand	UUGACUAAACUUGAAAAAUAGCAG CCGAAAGGCUGC	1569
MARC1-2011	36 mer Sense Strand	AAAACUGUGAAUAAAUGGAAGCAG CCGAAAGGCUGC	1570
MARC1-1113	36 mer Sense Strand	CGAGCAAGCACUAUAUGGAAGCAG CCGAAAGGCUGC	1571
MARC1-1575	36 mer Sense Strand	AAGAAUGUCCAGAAUGUUAGCAG CCGAAAGGCUGC	1572

MARC1-0324	22 mer Anti-sense Strand	UCAAGCCAAAACCUGUCCCGGG	1573
MARC1-0326	22 mer Anti-sense Strand	UCACAAGCCAAAACCUGUCCGG	1574
MARC1-0327	22 mer Anti-sense Strand	UUCACAAGCCAAAACCUGUCGG	1575
MARC1-0330	22 mer Anti-sense Strand	UUGAUCACAAGCCAAAACCUGG	1576
MARC1-0331	22 mer Anti-sense Strand	UUUGAUCACAAGCCAAAACCUGG	1577
MARC1-0735	22 mer Anti-sense Strand	UUAACUUUCUUCUCUAGCCUGG	1578
MARC1-0736	22 mer Anti-sense Strand	UUUAACUUUCUUCUCUAGCCGG	1579
MARC1-0788	22 mer Anti-sense Strand	UUGCAUAGACAUCGCAUCCUGG	1580
MARC1-0863	22 mer Anti-sense Strand	UUA AAA AUGCAUCUGGAACAAGG	1581
MARC1-1179	22 mer Anti-sense Strand	UAAAAUGUGAAAAUCACAAAGG	1582
MARC1-2012	22 mer Anti-sense Strand	UUUCCAUUUAUUCACAGUUUGG	1583
MARC1-2013	22 mer Anti-sense Strand	UCUCCAUUUAUUCACAGUUUGG	1584
MARC1-0661	22 mer Anti-sense Strand	UGAGUAAGCAAUCUGGUCCUGG	1585
MARC1-1869	22 mer Anti-sense Strand	UACAACUGACAUAUGCUUUCGG	1586
MARC1-1876	22 mer Anti-sense Strand	UGUUUUAAACAACUGACAUAAGG	1587
MARC1-1886	22 mer Anti-sense Strand	UUAGAUUUUGGGUUUUAAACGG	1588
MARC1-2016	22 mer Anti-sense Strand	UUAGCUUCCAUUUAUUCACAGG	1589
MARC1-0413	22 mer Anti-sense Strand	UAGUCAGGGUGUCACCAUCGGG	1590
MARC1-0416	22 mer Anti-sense Strand	UGAGAGUCAGGGUGUCACCAGG	1591
MARC1-0622	22 mer Anti-sense Strand	UAUUUGAUGAGGACGUCUCGGG	1592
MARC1-0638	22 mer Anti-sense Strand	UUCGGAACAAGUCUGCUAUUGG	1593
MARC1-0657	22 mer Anti-sense Strand	UAAGCAAUCUGGUCCUUGGGGG	1594
MARC1-0660	22 mer Anti-sense Strand	UAGUAAGCAAUCUGGUCCUUGG	1595
MARC1-0965	22 mer Anti-sense Strand	UUCCAUAUAACUUUCGUUCUGG	1596
MARC1-0966	22 mer Anti-sense Strand	UUCCAUAUAACUUUCGUUCGG	1597
MARC1-0967	22 mer Anti-sense Strand	UUUCCAUAUAACUUUCGUUGG	1598
MARC1-0969	22 mer Anti-sense Strand	UAUUUCCAUAUAACUUUCGGG	1599
MARC1-1177	22 mer Anti-sense Strand	UAAUGUGAAAAUCACAAAUUGG	1600
MARC1-1884	22 mer Anti-sense Strand	UGAUUUUGGGUUUUAAACAAGG	1601
MARC1-1885	22 mer Anti-sense Strand	UAGAUUUUGGGUUUUAAACAGG	1602
MARC1-1955	22 mer Anti-sense Strand	UAUCAAGGACAAAUGGCAGG	1603
MARC1-1983	22 mer Anti-sense Strand	UUUUCAAGUUUAGUCAACUUGG	1604
MARC1-1986	22 mer Anti-sense Strand	UAUUUUUCAAGUUUAGUCAAGG	1605
MARC1-2011	22 mer Anti-sense Strand	UCCAUAUUUACAGUUUUGG	1606
MARC1-1113	22 mer Anti-sense Strand	UUCCAUAUAGUCUUGCUCGGG	1607
MARC1-1575	22 mer Anti-sense Strand	UACAUCUGGAACAUUCUUGG	1608
MARC1-0324	36 mer Sense Strand	[mCs][mG][mG][mG][mA][mC][mA][fG][fG][fU][fU][mU][mU][mG][mC][mU][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1609
MARC1-0326	36 mer Sense Strand	[mGs][mG][mA][mC][mA][mG][mG][fU][fU][fU][fU][mG][mG][mC][mU][mU][mG][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1610
MARC1-0327	36 mer Sense Strand	[mGs][mA][mC][mA][mG][mG][mU][fU][fU][fU][fG][mG][mC][mU][mU][mG][mU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-	1611

		GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
MARC1-0330	36 mer Sense Strand	[mAs][mG][mG][mU][mU][mU][mU][fG][fG][fC][fU][mU][mG][mU][mG][mA][mU][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1612
MARC1-0331	36 mer Sense Strand	[mGs][mG][mU][mU][mU][mU][mG][fG][fC][fU][fU][mG][mU][mG][mA][mU][mC][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1613
MARC1-0735	36 mer Sense Strand	[mAs][mG][mG][mC][mU][mA][mG][fA][fG][fA][fA][mG][mA][mA][mA][mG][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1614
MARC1-0736	36 mer Sense Strand	[mGs][mG][mC][mU][mA][mG][mA][fG][fA][fA][fG][mA][mA][mA][mG][mU][mU][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1615
MARC1-0788	36 mer Sense Strand	[mAs][mG][mG][mA][mU][mG][mC][fG][fA][fU][fG][mU][mC][mU][mA][mU][mG][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1616
MARC1-0863	36 mer Sense Strand	[mUs][mU][mG][mU][mU][mC][mC][fA][fG][fA][fU][mG][mC][mA][mU][mU][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1617
MARC1-1179	36 mer Sense Strand	[mUs][mU][mU][mG][mU][mG][mA][fU][fU][fU][fU][mC][mA][mC][mA][mU][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1618
MARC1-2012	36 mer Sense Strand	[mAs][mA][mA][mC][mU][mG][mU][fG][fA][fA][fU][mA][mA][mA][mU][mG][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1619
MARC1-2013	36 mer Sense Strand	[mAs][mA][mC][mU][mG][mU][mG][fA][fA][fU][fA][mA][mA][mU][mG][mG][mA][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1620

		GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
MARC1-0661	36 mer Sense Strand	[mAs][mG][mG][mA][mC][mC][mA][fG][fA][fU][fU][mG][mC][mU][mU][mA][mC][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1621
MARC1-1869	36 mer Sense Strand	[mGs][mA][mA][mA][mG][mC][mA][fU][fA][fU][fG][mU][mC][mA][mG][mU][mU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1622
MARC1-1876	36 mer Sense Strand	[mUs][mA][mU][mG][mU][mC][mA][fG][fU][fU][fG][mU][mU][mU][mA][mA][mA][mA][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1623
MARC1-1886	36 mer Sense Strand	[mGs][mU][mU][mU][mA][mA][mA][fA][fC][fC][fC][mA][mA][mU][mA][mU][mC][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1624
MARC1-2016	36 mer Sense Strand	[mUs][mG][mU][mG][mA][mA][mU][fA][fA][fA][fU][mG][mG][mA][mA][mG][mC][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1625
MARC1-0413	36 mer Sense Strand	[mCs][mG][mA][mU][mG][mG][mU][fG][fA][fC][fA][mC][mC][mC][mU][mG][mA][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1626
MARC1-0416	36 mer Sense Strand	[mUs][mG][mG][mU][mG][mA][mC][fA][fC][fC][fC][mU][mG][mA][mC][mU][mC][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1627
MARC1-0622	36 mer Sense Strand	[mCs][mG][mA][mG][mA][mC][mG][fU][fC][fC][fU][mC][mA][mU][mC][mA][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1628
MARC1-0638	36 mer Sense Strand	[mAs][mA][mU][mA][mG][mC][mA][fG][fA][fC][fU][mU][mG][mU][mU][mC][mC][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1629

		GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
MARC1-0657	36 mer Sense Strand	[mCs][mC][mC][mA][mA][mG][mG][fA][fC][fC][fA][mG][mA][mU][mU][mG][mC][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1630
MARC1-0660	36 mer Sense Strand	[mAs][mA][mG][mG][mA][mC][mC][fA][fG][fA][fU][mU][mG][mC][mU][mU][mA][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1631
MARC1-0965	36 mer Sense Strand	[mAs][mG][mA][mA][mC][mG][mA][fA][fA][fG][fU][mU][mA][mU][mA][mU][mG][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1632
MARC1-0966	36 mer Sense Strand	[mGs][mA][mA][mC][mG][mA][mA][fA][fG][fU][fU][mA][mU][mA][mU][mG][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1633
MARC1-0967	36 mer Sense Strand	[mAs][mA][mC][mG][mA][mA][mA][fG][fU][fU][fA][mU][mA][mU][mG][mG][mA][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1634
MARC1-0969	36 mer Sense Strand	[mCs][mG][mA][mA][mA][mG][mU][fU][fA][fU][fA][mU][mG][mG][mA][mA][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1635
MARC1-1177	36 mer Sense Strand	[mAs][mA][mU][mU][mU][mG][mU][fG][fA][fU][fU][mU][mU][mC][mA][mC][mA][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1636
MARC1-1884	36 mer Sense Strand	[mUs][mU][mG][mU][mU][mU][mA][fA][fA][fA][fC][mC][mC][mA][mA][mU][mA][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1637
MARC1-1885	36 mer Sense Strand	[mUs][mG][mU][mU][mU][mA][mA][fA][fA][fC][fC][mC][mA][mA][mU][mA][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1638

		GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
MARC1-1955	36 mer Sense Strand	[mUs][mG][mC][mC][mA][mU][mU][fU][fU][fG][fU][mC][mC][mU][mU][mU][mG][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1639
MARC1-1983	36 mer Sense Strand	[mAs][mA][mG][mU][mU][mG][mA][fC][fU][fA][fA][mA][mC][mU][mU][mG][mA][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1640
MARC1-1986	36 mer Sense Strand	[mUs][mU][mG][mA][mC][mU][mA][fA][fA][fC][fU][mU][mG][mA][mA][mA][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1641
MARC1-2011	36 mer Sense Strand	[mAs][mA][mA][mA][mC][mU][mG][fU][fG][fA][fA][mU][mA][mA][mU][mG][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1642
MARC1-1113	36 mer Sense Strand	[mCs][mG][mA][mG][mC][mA][mA][fG][fC][fA][fC][mU][mA][mU][mA][mU][mG][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1643
MARC1-1575	36 mer Sense Strand	[mAs][mA][mG][mA][mA][mU][mG][fU][fU][fC][fC][mA][mG][mA][mA][mU][mG][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1644
MARC1-0324	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fCs][fAs][fA][fG][mC][fC][mA][mA][fA][mA][mC][mC][fU][mG][mU][mC][mC][mC][mGs][mGs][mG]	1645
MARC1-0326	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fCs][fAs][fC][fA][mA][fG][mC][mC][fA][mA][mA][mA][fC][mC][mU][mG][mU][mC][mCs][mGs][mG]	1646
MARC1-0327	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fCs][fA][fC][mA][fA][mG][mC][fC][mA][mA][mA][fA][mC][mC][mU][mG][mU][mCs][mGs][mG]	1647
MARC1-0330	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fGs][fA][fU][mC][fA][mC][mA][fA][mG][mC][mC][fA][mA][mA][mA][mC][mC][mUs][mGs][mG]	1648

MARC1-0331	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fUs][fG][fA][mU][fC][mA][mC][fA][mA][mG][mC][fC][mA][mA][mA][mA][mC][mCs][mGs][mG]	1649
MARC1-0735	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fAs][fA][fC][mU][fU][mU][mC][fU][mU][mC][mU][fC][mU][mA][mG][mC][mC][mUs][mGs][mG]	1650
MARC1-0736	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fUs][fA][fA][mC][fU][mU][mU][fC][mU][mU][mC][fU][mC][mU][mA][mG][mC][mCs][mGs][mG]	1651
MARC1-0788	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fGs][fC][fA][mU][fA][mG][mA][fC][mA][mU][mC][fG][mC][mA][mU][mC][mC][mUs][mGs][mG]	1652
MARC1-0863	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fAs][fA][fA][mA][fU][mG][mC][fA][mU][mC][mU][fG][mG][mA][mA][mC][mA][mAs][mGs][mG]	1653
MARC1-1179	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fAs][fA][fA][mU][fG][mU][mG][fA][mA][mA][mA][fU][mC][mA][mC][mA][mA][mAs][mGs][mG]	1654
MARC1-2012	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fUs][fC][fC][mA][fU][mU][mU][fA][mU][mU][mC][fA][mC][mA][mG][mU][mU][mUs][mGs][mG]	1655
MARC1-2013	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fCs][fUs][fU][fC][mC][fA][mU][mU][fU][mA][mU][mU][fC][mA][mC][mA][mG][mU][mUs][mGs][mG]	1656
MARC1-0661	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fGs][fAs][fG][fU][mA][fA][mG][mC][fA][mA][mU][mC][fU][mG][mG][mU][mC][mC][mUs][mGs][mG]	1657
MARC1-1869	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fCs][fA][fA][mC][fU][mG][mA][fC][mA][mU][mA][fU][mG][mC][mU][mU][mU][mCs][mGs][mG]	1658
MARC1-1876	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fGs][fUs][fU][fU][mU][fA][mA][mA][fC][mA][mA][mC][fU][mG][mA][mC][mA][mU][mAs][mGs][mG]	1659
MARC1-1886	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fAs][fG][fA][mU][fA][mU][mU][fG][mG][mG][mU][fU][mU][mU][mA][mA][mA][mCs][mGs][mG]	1660
MARC1-2016	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fAs][fG][fC][mU][fU][mC][mC][fA][mU][mU][mU][fA][mU][mU][mC][mA][mC][mAs][mGs][mG]	1661
MARC1-0413	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fGs][fU][fC][mA][fG][mG][m	1662

		G][fU][mG][mU][mC][fA][mC][mC][mA][mU][mC][mGs][mGs][mG]	
MARC1-0416	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fGs][fAs][fG][fA][mG][fU][mC][mA][fG][mG][mG][mU][fG][mU][mC][mA][mC][mC][mAs][mGs][mG]	1663
MARC1-0622	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fUs][fU][fU][mG][fA][mU][mG][fA][mG][mG][mA][fC][mG][mU][mC][mU][mC][mGs][mGs][mG]	1664
MARC1-0638	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fCs][fG][fG][mA][fA][mC][mA][fA][mG][mU][mC][fU][mG][mC][mU][mA][mU][mUs][mGs][mG]	1665
MARC1-0657	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fAs][fG][fC][mA][fA][mU][mC][fU][mG][mG][mU][fC][mC][mU][mU][mG][mG][mGs][mGs][mG]	1666
MARC1-0660	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fGs][fU][fA][mA][fG][mC][mA][fA][mU][mC][mU][fG][mG][mU][mC][mC][mU][mUs][mGs][mG]	1667
MARC1-0965	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fCs][fC][fA][mU][fA][mU][mA][fA][mC][mU][mU][fU][mC][mG][mU][mU][mC][mUs][mGs][mG]	1668
MARC1-0966	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fUs][fC][fC][mA][fU][mA][mU][fA][mA][mC][mU][fU][mU][mC][mG][mU][mU][mCs][mGs][mG]	1669
MARC1-0967	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fUs][fU][fC][mC][fA][mU][mA][fU][mA][mA][mC][fU][mU][mU][mC][mG][mU][mUs][mGs][mG]	1670
MARC1-0969	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fUs][fU][fU][mU][fC][mC][mA][fU][mA][mU][mA][fA][mC][mU][mU][mU][mC][mGs][mGs][mG]	1671
MARC1-1177	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fAs][fU][fG][mU][fG][mA][mA][fA][mA][mU][mC][fA][mC][mA][mA][mA][mU][mUs][mGs][mG]	1672
MARC1-1884	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fGs][fAs][fU][fA][mU][fU][mG][mG][fG][mU][mU][mU][fU][mA][mA][mA][mC][mA][mAs][mGs][mG]	1673
MARC1-1885	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fGs][fA][fU][mA][fU][mU][mG][fG][mG][mU][mU][fU][mU][mA][mA][mA][mC][mAs][mGs][mG]	1674
MARC1-1955	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fUs][fC][fA][mA][fA][mG][mG][fA][mA][mA][fA][mA][mU][mG][mG][mC][mAs][mGs][mG]	1675

MARC1-1983	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fUs][fU][fC][mA][fA][mG][mU][fU][mU][mA][mG][fU][mC][mA][mA][mC][mU][mUs][mGs][mG]	1676
MARC1-1986	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fUs][fU][fU][mU][fU][mC][mA][fA][mG][mU][mU][fU][mA][mG][mU][mC][mA][mAs][mGs][mG]	1677
MARC1-2011	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fCs][fC][fA][mU][fU][mU][mA][fU][mU][mC][mA][fC][mA][mG][mU][mU][mU][mUs][mGs][mG]	1678
MARC1-1113	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fUs][fC][fC][fA][mU][fA][mU][mA][fG][mU][mG][mC][fU][mU][mG][mC][mU][mC][mGs][mGs][mG]	1679
MARC1-1575	22 mer Anti-sense Strand	[MePhosphonate-4O-mUs][fAs][fA][fC][fA][mU][fU][mC][mU][fG][mG][mA][mA][fC][mA][mU][mU][mC][mU][mUs][mGs][mG]	1680
Stem Loop		GCAGCCGAAAGGCUGC	1681
MARC1 cDNA plasmid		GACGGATCGGGAGATCTCCCGATCC CCTATGGTTCGACTCTCAGTACAATC TGCTCTGATGCCGCATAGTTAAGCC AGTATCTGCTCCCTGCTTGTGTGTTG GAGGTCTGCTGAGTAGTGC GCGAGCA AAATTTAAGCTACAACAAGGCAAGG CTTGACCGACAATTGCATGAAGAAT CTGCTTAGGGTTAGGCGTTTTGCGCT GCTTCGCGATGTACGGGCCAGATAT ACGCGTTGACATTGATTATTGACTA GTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATG GAGTTCCGCGTTACATAACTTACGG TAAATGGCCCCGCCTGGCTGACCGCC CAACGACCCCCGCCCATTGACGTCA ATAATGACGTATGTTCCCATAGTAA CGCCAATAGGGACTTTCCATTGACG TCAATGGGTGGAGTATTTACGGTAA ACTGCCCCACTTGGCAGTACATCAAG TGTATCATATGCCAAGTACGCCCCC TATTGACGTCAATGACGGTAAATGG CCCGCCTGGCATTATGCCCAGTACA TGACCTTATGGGACTTTCCTACTTGG CAGTACATCTACGTATTAGTCATCG CTATTACCATGGTGATGCGGTTTTG GCAGTACATCAATGGGCGTGGATAG CGGTTTGACTCACGGGGATTTCCTAA GTCTCCACCCCATGACGTCAATGG GAGTTTGTTTTGGCACCAAAATCAA CGGGACTTTCCAAAATGTCGTAACA ACTCCGCCCCATTGACGCAAAATGGG CGGTAGGCGTGTACGGTGGGAGGTC TATATAAGCAGAGCTCTCTGGCTAA	1682

		CTAGAGAACCCACTGCTTACTGGCT TATCGAAATTAATACGACTCACTAT AGGGAGACCCAAGCTGGCTAGCGTT TAAACTTAAGCTTACAGCGCCCTGC AGCGCAGGCGACGGAAGGTTGCAG AGGCAGTGGGGCGCCGACCAAGTG GAAGCTGAGCCACCACCTCCCACTC CCCGCGCCGCCCCCAGAAGGACGC ACTGCTCTGATTGGCCCGGAAGGGT TCAGGAGCTGCCCAGCCTTTGGGCT CGGGGCCAAAGGCCGCACCTTCCCC CAGCGGCCCCGGGCGACCAGCGCGC TCCGGCCTTGCCGCGCCACCTCGC GGAGAAGCCAGCCATGGGCGCCGC CGGCTCCTCCGCGCTGGCGCGCTTT GTCCTCCTCGCGCAATCCCGGCCCG GGTGGCTCGGGGTTGCCGCGCTGGG CCTGACCGCGGTGGCGCTGGGGGCT GTCGCCTGGCGCCGCGCATGGCCCA CGCGGCGCCGGCGGCTGCTGCAGCA GGTGGGCACAGTGGCGCAGCTCTGG ATCTACCCTGTGAAATCCTGCAAGG GGGTGCCGGTGAGCGAGGCGGAGT GCACGGCCATGGGGCTGCGCAGCGG CAACCTGCGGGACAGGTTTTGGCTT GTGATCAACCAGGAGGGAAACATG GTTACTGCTCGCCAGGAACCTCGCC TGGTCCTGATTTCCCTGACCTGCGAT GGTGACACCCTGACTCTCAGTGCAG CCTACACAAAGGACCTACTACTGCC TATCAAAACGCCCACCACAAATGCA GTGCACAAGTGCAGAGTGCACGGCC TGGAGATAGAGGGCAGGGACTGTG GCGAGGCCACCGCCCAGTGGATAAC CAGCTTCCTGAAGTCACAGCCCTAC CGCCTGGTGCACTTCGAGCCTCACA TGCGACCGAGACGTCCTCATCAAAT AGCAGACTTGTTCCGACCCAAGGAC CAGATTGCTTACTCAGACACCAGCC CATTCTTGATCCTTTCTGAGGCGTCG CTGGCGGATCTCAACTCCAGGCTAG AGAAGAAAGTTAAAGCAACCAACTT CAGGCCCAATATTGTAATTTAGGA TGCGATGTCTATGCAGAGGTAACAC TATGCCCCCTTTGGATCTTTCCTTGGA TTTGACTTCTTTTTTAAGGATTCTTG GGATGAGCTTCTTATTGGTGACGTG GAACTGAAAAGGGTGATGGCTTGTT CCAGATGCATTTTAACCACAGTGGA CCCAGACACCGGTGTCATGAGCAGG AAGGAACCGCTGGAAACACTGAAG AGTTATCGCCAGTGTGACCCTTCAG AACGAAAGTTATATGGAAAATCACC ACTCTTTGGGCAGTATTTTGTGCTGG AAAACCCAGGGACCATCAAAGTGG	
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		GAGACCCTGTGTACCTGCTGGGCCA GTAATGGGAACCGTATGTCCTGGAA TATTAGATGCCTTTTAAAAATGTTCT CAAAAATGACAACACTTGAAGCATG GTGTTTCAGAACTGAGACCTCTACA TTTTCTTTAAATTTGTGATTTTCACA TTTTTCGTCTTTTGGACTTCTGGTGT CTCAATGCTTCAATGTCCCAGTGCA AAAAGTAAAGAAATATAGTCTCAAT AACTTAGTAGGACTTCAGTAAGTCA CTTAAATGACAAGACAGGATTCTGA AAACTCCCCGTTTAACTGATTATGG AATAGTTCTTTCTCCTGCTTCTCCGT TTATCTACCAAGAGCGCAGACTTGC ATCCTGTCACTACCACTCGTTAGAG AAAGAGAAGAAGAGAAAGAGGAAG AGTGGGTGGGCTGGAAGAATATCCT AGAATGTGTTATTGCCCTGTTTCATG AGGTACGCAATGAAAATTAAATTGC ACCCCAAATATGGCTGGAATGCCAC TTCCCTTTTCTTCTCAAGCCCCGGGC TAGCTTTTGAAATGGCATAAAGACT GAGGTGACCTTCAGGAAGCACTGCA GATATTAATTTTCCATAGATCTGGAT CTGGCCCTGCTGCTTCTCAGACAGC ATTGGATTTCTTAAAGGTGCTCAGG AGGATGGTTGTGTAGTCATGGAGGA CCCCTGGATCCTTGCCATTCCCCTCA GCTAATGACGGAGTGCTCCTTCTCC AGTTCCGGGTGAAAAAGTTCTGAAT TCTGTGGAGGAGAAGAAAAGTGATT CAGTGATTTTCAGATAGACTACTGAA AACCTTTAAAGGGGGAAAAGGAAA GCATATGTCAGTTGTTTAAACCCA ATATCTATTTTTTAACTGATTGTATA ACTCTAAGATCTGATGAAGTATATT TTTTATTGCCATTTTGTCTTTGATT ATATTGGGAAGTTGACTAACTTGA AAAATGTTTTTAAACTGTGAATAA ATGGAAGCTACTTTGACTAGTTTCA GAGCGGCCGCTCGAGTCTAGAGGGC CCGTTTAAACCCGCTGATCAGCCTC GACTGTGCCTTCTAGTTGCCAGCCA TCTGTTGTTTGCCCCCTCCCCGTGCC TTCCTTGACCCTGGAAGGTGCCACT CCCCTGTCTTTTCTAATAAAATG AGGAAATTGCATCGCATTGTCTGAG TAGGTGTCATTCTATTCTGGGGGGT GGGGTGGGGCAGGACAGCAAGGGG GAGGATTGGGAAGACAATAGCAGG CATGCTGGGGATGCGGTGGGCTCTA TGGCTTCTGAGGCGGAAAGAACCAG CTGGGGCTCTAGGGGGTATCCCCAC GCGCCCTGTAGCGGCGCATTAAAGCG CGGCGGGTGTGGTGGTTACGCGCAG	
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		CGTGACCGCTACACTTGCCAGCGCC CTAGCGCCCGCTCCTTTTCGCTTTCTT CCCTTCCTTTCTCGCCACGTTTCGCCG GCTTTCCCCGTCAAGCTCTAAATCG GGGGCTCCCTTTAGGGTTCCGATTT AGTGCTTTACGGCACCTCGACCCCA AAAAACTTGATTAGGGTGATGGTTC ACGTAGTGGGCCATCGCCCTGATAG ACGGTTTTTCGCCCTTTGACGTTGGA GTCCACGTTCTTTAATAGTGGACTCT TGTTCCAAACTGGAACAACACTCAA CCCTATCTCGGTCTATTCTTTTGATT TATAAGGGATTTTGGGGATTTCCGC CTATTGGTTAAAAAATGAGCTGATT TAACAAAAATTTAACGCGAATTAAT TCTGTGGAATGTGTGTCAGTTAGGG TGTGGAAAGTCCCCAGGCTCCCCAG GCAGGCAGAAGTATGCAAAGCATG CATCTCAATTAGTCAGCAACCAGGT GTGGAAAGTCCCCAGGCTCCCCAGC AGGCAGAAGTATGCAAAGCATGCAT CTCAATTAGTCAGCAACCATAGTCC CGCCCCTAACTCCGCCCATCCCGCC CCTAACTCCGCCCAGTTCCGCCATT CTCCGCCCCATGGCTGACTAATTTTT TTATTTATGCAGAGGCCGAGGCCG CCTCTGCCTCTGAGCTATTCCAGAA GTAGTGAGGAGGCTTTTTTGGAGGC CTAGGCTTTTGCAAAAAGCTCCCGG GAGCTTGTATATCCATTTTCGGATCT GATCAAGAGACAGGATGAGGATCG TTTCGCATGATTGAACAAGATGGAT TGCACGCAGGTTCTCCGGCCGCTTG GGTGGAGAGGCTATTCCGGCTATGAC TGGGCACAACAGACAATCGGCTGCT CTGATGCCGCCGTGTTCCGGCTGTC AGCGCAGGGGCGCCCGGTTCTTTTT GTCAAGACCGACCTGTCCGGTGCCC TGAATGAACTGCAGGACGAGGCAG CGCGGCTATCGTGGCTGGCCACGAC GGGCGTTCTTGCGCAGCTGTGCTC GACGTTGTCACTGAAGCGGGAAGGG ACTGGCTGCTATTGGGCGAAGTGCC GGGGCAGGATCTCCTGTCATCTCAC CTTGCTCCTGCCGAGAAAGTATCCA TCATGGCTGATGCAATGCGGCGGCT GCATACGCTTGATCCGGCTACCTGC CCATTTCGACCACCAAGCGAAACATC GCATCGAGCGAGCACGTACTCGGAT GGAAGCCGGTCTTGTCGATCAGGAT GATCTGGACGAAGAGCATCAGGGG CTCGCGCCAGCCGAACTGTTCCGCA GGCTCAAGGCGCGCATGCCCGACGG CGAGGATCTCGTTCGTGACCCATGGC GATGCCTGCTTGCCGAATATCATGG	
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		TGGAAAATGGCCGCTTTTCTGGATT CATCGACTGTGGCCGGCTGGGTGTG GCGGACCGCTATCAGGACATAGCGT TGGCTACCCGTGATATTGCTGAAGA GCTTGGCGGCGAATGGGCTGACCGC TTCCTCGTGCTTTACGGTATCGCCGC TCCCGATTTCGACGCGCATCGCCTTCT ATCGCCTTCTTGACGAGTTCTTCTGA GCGGGACTCTGGGGTTTCGAAATGAC CGACCAAGCGACGCCCAACCTGCCA TCACGAGATTTTCGATTCCACCGCCG CCTTCTATGAAAGGTTGGGCTTCGG AATCGTTTTCCGGGACGCCGGCTGG ATGATCCTCCAGCGCGGGGATCTCA TGCTGGAGTTCTTCGCCCACCCCAA CTTGTTTATTGCAGCTTATAATGGTT ACAAATAAAGCAATAGCATCACAA ATTCACAAATAAAGCATTTTTTCA CTGCATTCTAGTTGTGGTTTGTCCAA ACTCATCAATGTATCTTATCATGTCT GTATACCGTCGACCTCTAGCTAGAG CTTGGCGTAATCATGGTCATAGCTG TTTCCTGTGTGAAATTGTTATCCGCT CACAATTCCACACAACATACGAGCC GGAAGCATAAAGTGTAAGCCTGG GGTGCCTAATGAGTGAGCTAACTCA CATTAAATTGCGTTGCGCTCACTGCCC GCTTTCAGTCGGGAAACCTGTGCT GCCAGCTGCATTAATGAATCGGCCA ACGCGCGGGGAGAGGCGGTTTTCGT ATTGGGCGCTCTTCCGCTTCCTCGCT CACTGACTCGCTGCGCTCGGTCGTT CGGCTGCGGCGAGCGGTATCAGCTC ACTCAAAGGCGGTAATACGGTTATC CACAGAATCAGGGGATAACGCAGG AAAGAACATGTGAGCAAAAGGCCA GCAAAAGGCCAGGAACCGTAAAAA GGCCGCGTTGCTGGCGTTTTTCCATA GGCTCCGCCCCCTGACGAGCATCA CAAAAATCGACGCTCAAGTCAGAGG TGGCGAAACCCGACAGGACTATAAA GATACCAGGCGTTTCCCCCTGGAAG CTCCCTCGTGCGCTCTCCTGTTCCGA CCCTGCCGCTTACCGGATACCTGTC CGCCTTTCTCCCTTCGGGAAGCGTG GCGCTTTCTCAATGCTCACGCTGTA GGTATCTCAGTTCGGTGTAGGTCGT TCGCTCCAAGCTGGGCTGTGTGCAC GAACCCCCGTTTCAGCCCGACCGCT GCGCCTTATCCGGTAACTATCGTCTT GAGTCCAACCCGGTAAGACACGACT TATCGCCACTGGCAGCAGCCACTGG TAACAGGATTAGCAGAGCGAGGTAT GTAGGCGGTGCTACAGAGTTCCTGA AGTGGTGGCCTAACTACGGCTACAC	
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		TAGAAGGACAGTATTTGGTATCTGC GCTCTGCTGAAGCCAGTTACCTTCG GAAAAAGAGTTGGTAGCTCTTGATC CGGCAAACAAACCACCGCTGGTAGC GGTGGTTTTTTTGTGTTGCAAGCAGCA GATTACGCGCAGAAAAAAGGATCT CAAGAAGATCCTTTGATCTTTTCTAC GGGGTCTGACGCTCAGTGAACGAA AACTCACGTTAAGGGATTTTGGTCA TGAGATTATCAAAAAGGATCTTCAC CTAGATCCTTTTAAATTAATAATGA AGTTTTAAATCAATCTAAAGTATAT ATGAGTAAACTTGGTCTGACAGTTA CCAATGCTTAATCAGTGAGGCACCT ATCTCAGCGATCTGTCTATTTTCGTC ATCCATAGTTGCCTGACTCCCCGTC GTGTAGATAACTACGATACGGGAGG GCTTACCATCTGGCCCCAGTGCTGC AATGATACCGCGAGACCCACGCTCA CCGGCTCCAGATTTATCAGCAATAA ACCAGCCAGCCGGAAGGGCCGAGC GCAGAAAGTGGTCCTGCAACTTTATC CGCCTCCATCCAGTCTATTAATTGTT GCCGGGAAGCTAGAGTAAGTAGTTC GCCAGTTAATAGTTTGCACAACGTT GTTGCCATTGCTACAGGCATCGTGG TGTCACGCTCGTCGTTTGGTATGGCT TCATTACAGCTCCGGTTCCCAACGAT CAAGGCGAGTTACATGATCCCCCAT GTTGTGCAAAAAAGCGGTTAGCTCC TTCGGTCCTCCGATCGTTGTCAGAA GTAAGTTGGCCGCAGTGTTATCACT CATGGTTATGGCAGCACTGCATAAT TCTCTTACTGTCATGCCATCCGTAAG ATGCTTTTCTGTGACTGGTGAGTACT CAACCAAGTCATTCTGAGAATAGTG TATGCGGCGACCGAGTTGCTCTTGC CCGGCGTCAATACGGGATAATACCG CGCCACATAGCAGAACTTTAAAAGT GCTCATCATTGGAAAACGTTCTTCG GGGCGAAAACCTCTCAAGGATCTTAC CGCTGTTGAGATCCAGTTTCGATGTA ACCCACTCGTGCACCCAACTGATCT TCAGCATCTTTTACTTTCACCAGCGT TTCTGGGTGAGCAAAAACAGGAAG GCAAAATGCCGCAAAAAGGGAAT AAGGGCGACACGGAATGTTGAAT ACTCATACTCTTCCTTTTCAATATT ATTGAAGCATTATCAGGGTTATTG TTCATGAGCGGATACATATTTGAA TGTATTTAGAAAAATAAACAAATAG GGGTTCCGCGCACATTTCCCGAAA AGTGCCACCTGACGTC	
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MARC1 cDNA (XM_011509900 .3)		ACAGCGCCCTGCAGCGCAGGCGACG GAAGGTTGCAGAGGCAGTGGGGCG CCGACCAAGTGGAAGCTGAGCCACC ACCTCCCCTCCCCGCGCCGCCCCC CAGAAGGACGCACTGCTCTGATTGG CCCGGAAGGGTTCAGGAGCTGCCCA GCCTTTGGGCTCGGGGCCAAAGGCC GCACCTTCCCCCAGCGGCCCGGGC GACCAGCGCGCTCCGGCCTTGCCGC CGCCACCTCGCGGAGAAGCCAGCCA TGGGCGCCCGCGGCTCCTCCGCGCT GGCGCGCTTTGTCCTCCTCGCGCAA TCCCGGCCCGGGTGGCTCGGGGTTG CCGCGCTGGGCCTGACCGCGGTGGC GCTGGGGGCTGTGCTGCTGGCGCCGC GCATGGCCACGCGGCGCCGGCGGC TGCTGCAGCAGGTGGGCACAGTGGC GCAGCTCTGGATCTACCCTGTGAAA TCCTGCAAGGGGGTGCCGGTGAGCG AGGCGGAGTGACGGCCATGGGGCT GCGCAGCGGCAACCTGCGGGACAG GTTTTGGCTTGTGATCAACCAGGAG GGAAACATGGTTACTGCTCGCCAGG AACCTCGCCTGGTCCTGATTTCCCTG ACCTGCGATGGTGACACCCTGACTC TCAGTGCAGCCTACACAAAGGACCT ACTACTGCCTATCAAAACGCCCACC ACAAATGCAGTGCACAAGTGCAGA GTGCACGGCCTGGAGATAGAGGGC AGGGACTGTGGCGAGGCCACCGCCC AGTGGATAACCAGCTTCCTGAAGTC ACAGCCCTACCGCCTGGTGCACTTC GAGCCTCACATGCGACCGAGACGTC CTCATCAAATAGCAGACTTGTTCGG ACCCAAGGACCAGATTGCTTACTCA GACACCAGCCCATTCTTGATCCTTTC TGAGGCGTCGCTGGCGGATCTCAAC TCCAGGCTAGAGAAGAAAGTTAAA GCAACCAACTTCAGGCCCAATATTG TAATTTACAGGATGCGATGTCTATGC AGAGGTAACACTATGCCCCTTTGG TCTTTCCTTGGATTTGACTTCTTTTT AAGGATTCTTGGGATGAGCTTCTTA TTGGTGACGTGGAAGTGAAGGGT GATGGCTTGTTCAGATGCATTTTA ACCACAGTGGACCCAGACACCGGTG TCATGAGCAGGAAGGAACCGCTGG AAACACTGAAGAGTTATCGCCAGTG TGACCCTTCAGAACGAAAGTTATAT GGAAAATCACCCTCTTTGGGCAGT ATTTTGTGCTGGAAAACCCAGGGAC CATCAAAGTGGGAGACCCTGTGTAC CTGCTGGGCCAGTAATGGGAACCGT ATGTCCTGGAATATTAGATGCCTTTT AAAAATGTTCTCAAAAATGACAACA	1683
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		CTTGAAGCATGGTGTTCAGAACTG AGACCTCTACATTTTCTTTAAATTTG TGATTTTCACATTTTTCGTCTTTTGG ACTTCTGGTGTCTCAATGCTTCAATG TCCCAGTGCAAAAAGTAAAGAAATA TAGTCTCAATAACTTAGTAGGACTT CAGTAAGTCACTTAAATGACAAGAC AGGATTCTGAAAACCTCCCGTTTAA CTGATTATGGAATAGTTCTTTCTCCT GCTTCTCCGTTTATCTACCAAGAGC GCAGACTTGCATCCTGTCACCTACCA CTCGTTAGAGAAAGAGAAGAAGAG AAAGAGGAAGAGTGGGTGGGCTGG AAGAATATCCTAGAATGTGTTATTG CCCCTGTTTCATGAGGTACGCAATGA AAATTAAATTGCACCCCAAATATGG CTGGAATGCCACTTCCCTTTTCTTCT CAAGCCCCGGGCTAGCTTTTGAAAT GGCATAAAGACTGAGGTGACCTTCA GGAAGCACTGCAGATATTAATTTTC CATAGATCTGGATCTGGCCCTGCTG CTTCTCAGACAGCATTGGATTTCTTA AAGGTGCTCAGGAGGATGGTTGTGT AGTCATGGAGGACCCCTGGATCCTT GCCATTCCCCTCAGCTAATGACGGA GTGCTCCTTCTCCAGTTCGGGGTGA AAAAGTTCTGAATTCTGTGGAGGAG AAGAAAAGTGATTTCAGTGATTTTCAG ATAGACTACTGAAAACCTTTAAAGG GGGAAAAGGAAAGCATATGTCAGTT GTTTAAAACCCAATATCTATTTTTTA ACTGATTGTATAACTCTAAGATCTG ATGAAGTATATTTTTTATTGCCATTT TGTCCTTTGATTATATGGGAAGTTG ACTAACTTGAAAAATGTTTTTAAA ACTGTGAATAAATGGAAGCTACTTT GACTAGTTTCAGA	
3' Assay Forward Primer		GCTTCTCAGACAGCATTGGA	1684
3' Assay Reverse Primer		GAAGGAGCACTCCGTCATTAG	1685
5' Assay Forward Primer		AGTCCCTGCCCTCTATCTC	1686
5' Assay reverse Primer		CTACACAAAGGACCTACTACTGC	1687
HPRT Forward Primer		GACTTTGCTTTCCTTGGTCAG	1688
HPRT Reverse Primer		GGCTTATATCCAACACTTCGTGGG	1689
NHP MARC1 Forward Primer		GACCGAGACATCCTCACCAAA	1690
NHP MARC1 Reverse Primer		CCCAAGAATCCTCTGCATAGAC	1691

MARC1 Human cDNA (NM_022746.4)		CTTGCCGCCGCCACCTCGCGGAGAA GCCAGCCATGGGCGCCGCCGGCTCC TCCGCGCTGGCGCGCTTTGTCTCCT CGCGCAATCCCGGCCCGGGTGGCTC GGGGTTGCCGCGCTGGGCCTGACCG CGGTGGCGCTGGGG GCTGTGCGCTGGCGCCGCGCATGGC CCACGCGGCGCCGGCGGCTGCTGCA GCAGGTGGGCACAGTGGCGCAGCTC TGGATCTACCTGTGAAATCCTGCA AGGGGGTGCCGGTGAGCGAGGCGG AGTGACCGCCATGGG GCTGCGCAGCGGCAACCTGCGGGAC AGGTTTTGGCTTGTGATCAACCAGG AGGGAAACATGGTTACTGCTCGCCA GGAACCTCGCCTGGTCCTGATTTC CTGACCTGCGATGGTGACACCCTGA CTCTCAGTGCAGCCT ACACAAAGGACCTACTACTGCCTAT CAAAACGCCCACCACAAATGCAGTG CACAAGTGCAGAGTGCACGGCCTGG AGATAGAGGGCAGGGACTGTGGCG AGGCCACCGCCCAGTGGATAACCAG CTTCCTGAAGTCACAG CCCTACCGCCTGGTGCCTTCGAGC CTCACATGCGACCGAGACGTCCTCA TCAAATAGCAGACTTGTTCCGACCC AAGGACCAGATTGCTTACTCAGACA CCAGCCCATTCTTGATCCTTTCTGAG GCGTCGCTGGCGGA TCTCAACTCCAGGCTAGAGAAGAAA GTAAAGCAACCACTTCAGGCCCA ATATTGTAATTCAGGATGCGATGT CTATGCAGAGGATTCTTGGGATGAG CTTCTTATTGGTGACGTGGAACCTGA AAAGGGTGATGGCTT GTTCCAGATGCATTTTAACCACAGT GGACCCAGACACCGGTGTCATGAGC AGGAAGGAACCGCTGGAAACACTG AAGAGTTATCGCCAGTGTGACCCTT CAGAACGAAAGTTATATGGAAAATC ACCACTCTTTGGGCAG TATTTTGTGCTGGAAAACCCAGGGA CCATCAAAGTGGGAGACCCTGTGTA CCTGCTGGGCCAGTAATGGGAACCG TATGTCCTGGAATATTAGATGCCTTT	1692
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		TAAAAATGTTCTCAAAAATGACAAC ACTTGAAGCATGGT GTTTCAGAACTGAGACCTCTACATT TTCTTTAAATTTGTGATTTTCACATT TTTCGTCTTTTGGACTTCTGGTGTCT CAATGCTTCAATGTCCCAGTGCAAA AAGTAAAGAAATATAGTCTCAATAA CTTAGTAGGACTT CAGTAAGTCACTTAAATGACAAGAC AGGATTCTGAAAACCCCCGTTTAA CTGATTATGGAATAGTTCTTTCTCCT GCTTCTCCGTTTATCTACCAAGAGC GCAGACTTGCATCCTGTCACTACCA CTCGTTAGAGAAAG AGAAGAAGAGAAAAGAGGAAGAGTG GGTGGGCTGGAAGAATATCCTAGAA TGTGTTATTGCCCCGTTCATGAGGT ACGCAATGAAAATTAAATTGCACCC CAAATATGGCTGGAATGCCACTTCC CTTTCTTCTCAAGC CCCGGGCTAGCTTTTGAAATGGCAT AAAGACTGAGGTGACCTTCAGGAAG CACTGCAGATATTAATTTTCCATAG ATCTGGATCTGGCCCTGCTGCTTCTC AGACAGCATTGGATTTCTAAAGGT GCTCAGGAGGATGG TTGTGTAGTCATGGAGGACCCCTGG ATCCTTGCCATTCCCCTCAGCTAATG ACGGAGTGCTCCTTCTCCAGTTCCG GGTGAAAAAGTTCTGAATTCTGTGG AGGAGAAGAAAAGTGATTCAGTGA TTTCAGATAGACTAC TGAAAACCTTTAAAGGGGAAAAG GAAAGCATATGTCAGTTGTTTAAAA CCCAATATCTATTTTTTAACTGATTG TATAACTCTAAGATCTGATGAAGTA TATTTTTTATTGCCATTTTGTCCTTTG ATTATATTGGGAA GTTGACTAACTTGAAAAATGTTTT TAAAACGTGAATAAATGGAAGCTA CTTTGACTAGTTTCAGATCTTACTAA CTTCTTGGCACAAGTTAGACTGTG AAAGCTGACTGAGGCTGGGCACAG GGGCTCATGCCTGTA ATTCCAGCACTTTGGGAGGCCAAGG TGGGAGAATGGCTTGAGCCCAGGAG	
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		TTTGAGACCAGCCCAGAAAATATAA TGGGATCCTGTCGCTACAAAATGTT TTTAAAATGCACTCGGTGTGGTGGT GTGTGCCTGCAGTCC TGGCTATGGCTACTCGGGAGGATGA GGTAGAAGGATTGGTTGAGCCCAGG AGCGGGAGATTGAGGCTGCAGTGA GTTATGATTGCACCACTACACTCCA GCCTGAGTGATAGAGTGAGACCCTA TCTCTAAAAAAGAAAC AGGAAAAAAAAAGAAAGCTGACTG AGGTGAATGGGCAAAGCCAGTAATT CTGACACCTGACCACAGCTGGGTCT TCTGCATAATGGACCTCCTCACCCA CAGCCTCCCAGGCAAGCACCCATGT TTGAAGGACTATCAAG TCAACATGCTTTTTACCAAAGCTG CACATTTTTCACTTTGATTTTATAAA AGAGGTCAGTAATCGCTGAAATCTA GCTGAGCCCTGAAGTAAAGTTCTGA GCAAAGAGGTGCATGTGCTTGTTTT ATGGTTGGTGAATT ATTACAGTTTGTTTTCTGCATGCTTG GCATGAGGTGAATAATTACATCAAT TTTCCAGAGAACCTGGGCCATCACC TTCCCAACAAGTCCAGTTGATGTT GAACTACAGATAGATTGAGACAA AGCGAAGTGTTTCAGC AAGTAGCATTACTAATGGGACCGGG GGACCCGTGGGAGAGTGAGTGTACA CAGGATTTAGGAAACCATGTGAATA TGGGCTCTCTGGGAATAGCCAATAG GTAGGGAGCAATCAGAAACCCAAG GTTTGGTGGCTCTTCC TAGGTATTTATAATTAGTGGCAAGT GAAAGCCTTAGTCCTGAATTTCTAA CCACTTGTAAGAACTAACAGCCACT TCTCTGTGCCCCGTCCGGGCAGTAA CCATCATTCTCCATGGACAGGCTCT CGGGGTAGCTAGCTC TGCAGGGCAGCACCCACGTGGAAG GGAGCACCCAGAAACCCTCCTCACT GGGCAGACCTGTCCTTCTGTGCCTC ACAGTGTGAGGAAGATTCTGTTTG AAGAGAGAAGTTCCAGTGACCTCTA GAATCTCAGAGTAGTT	
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		GCCAAGCTTTCTGTCAGTGAGATTT AAAGGCCATTTACTTGTGTTTATTTT ATATTTAATGAGTTGGTTAATGCCA GAGACAAAGCTGATATCCCATTTAT TTTGGATACTGAGCATTGACACT ATTCCACTTGAAAT ATAGAATCAGGAATGTAGGCCATCC CAGACTTTCAGATCTTACAACAGCA AATGACAGATGTTTGAGATCAGGCC AAAATATCCACCCTCGGTGGGCATC TCCTCTGTGTGGCAACTTATGCTGCA GCCACAGTGGGGAG TCACAAACTCAGAGCTGGAGGTCTT GAAAAGGACAATGTGGGCCAGGCT CCGGAGGGGCTGCCTAAAGGCTTGC TTTTGTGACTCTCCTGCAGAAAATGT TAGAACTTCCAACCGAAAGACGAG GGCAGCAACTTATAC ACACGAAGGCAGAAAGAAATTGGG GAAGGGGAGGCTGTTGGAATTCAGG CCGTTGTCCTATAGGGAGAAATACT CCTCCTCTCCTTCTCCCTTTACTGAT AACGGGGCATGGTGAGGAGATGAG CTTGTGAGGGTCTGCC AGTTTGGTAAAGAGTGCATGGGGAGG TTGGGTAAATTAGACTAGCCAAATG GGACTTCGGGAAACCATTTATGAGG CTGTCACCAACAGTGATGGCAGGCT GAAATTCCAGGCAAGTGCTCCCAGC ATTCCAAGAGTGTAT CAAATTAAAGCAACCCATGATGGTG GAGAACAGATACATTAAAGTTCCTT GAAAATGACAGAGTGGCTCTCAGAC CAGACCTTGATTGTGGGTATAATCG GAGTGTTGCTACCACACCCTAACAC TGCATTTCCCGTGT TTATTGGTCCATGGAATTCTGAAAG TTTGCCTTTCGGGATGCTTCTAAAAA CAATTCCATGGACCAGTAAGTTTGG AAAGTCCTGCGTGCCTCACTTCTCTT CAAAGGCAAAAGGCTCTGGAGAGG CCTTCATGAAGACA TCTGTGTTTAATGCTGCCCTTCCCAA AGGTCTGTTTTTGA CTGTCTTTTGAG AAATGATCCTCTGATCTCTAGGCAG AATGCCAGTGAGCCAAGGAATCCCA	
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		GTTAGCAGGAGGGGTGCACTCATGG GAAGACTGAAGAA GTAAAAAGTTCCCGCCAAGTGAAGG AGACCTATCTTGGGACACTTCCCCTT GTCCTCTCCCTTGCCCCCTTGCTGG AGTAAAAGGATGGAAGTGGGACTTG ATAGGTTAAAGGAGGTGTGGAGAA GTGTCTTAGACCAG CTCTCCTGTTGTGGGCCTTAGGGAG AAGCACTCTCTTCTTCGGGATCATT TTCCAAACATGCATTTTGGATGGA TAGGGTGGATCAGGGTGAGGGAAG GGAAACCAAACCTCTCTAACCTTG CCCTTACAGCAATAC CTGTGATGTAAGTTACAAAACCACC TGTGATGAAAGTGCTCCAGGATGCT TCATGCACCAGGGAGGGGTGCCCTG TTTCTCTTCTGCTAGCTTCTCCTTCT TTTTTTTTTCTTCTTTTTTTTGAGA CAGTGTCTCAC TCTGTTGCCAGGCTGGAGTGCAGTG GTGAGATCTCAGCTCACTGCAGCCT CTGCCTCCAGGTTCAAGCAATTCTT CTGCCTCAGCCTCCCGAGTAGCTGG TGTGTCTGGAGTTGGTTCCTTCTGGT GGGTTCTTGGTCT CGCTGACTTCAAGAATGAAGCCACA GACCTTCGCAGTGAGTGTTACAGCT CTTAAAGGTGGCACGGACCCAAAGT GAGCAGTAGCAAGATTTATTGTGGA GAGCGAAAGAACAAAGCTTCGGAA GGGGACCCAAATGGGC TGCTGCTGCTGGCTGGGGTGGCCAC CTTTTATTCCTTATTTGTCCCTGCC CATGTCCTGCTGATTGCTCCATTTTA CAGAGTGCTGATTGGTCCATTTTAC AGAGTGCTGATTGGTGCATTTACAA TCCTTTAGCTAGA CACAGAGTGCCGATTGGTGAGTTTT TACAGTGCTGATTGGTGCATTTACA ATCCTTTAGCTAGACACAGAACACT GACTGGTGCATTTATAATCCTCTAG CTAGAAAGAAAAGTTCTCCAAGTCC CCACTAGACCCAGGA AGTCCAGCTGGCTTACCTCTCACT GGGACTACAGGTGCACACCACCACA	
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		CCCAGCTAATTTTTGTATTTTAGTA GAGACGGGGTTTCACCATGTTGTTTC AGGATGGTCTCGAACTCTTGATCTC GTGATCTGCCCCGCC TCGGCCTCCCAAAGTGCTGGGATTA CAGTTGTGAGCCACCACGCCCCGGCC CTAGCTTTTCCTTTCTGTTGCAAGTC CTCTCAACTAGTGTTGCCTTCCACCC TACAAAGCAGAATTACCTCAGAAGT CCTATGGCCCTGA CTCTATCTATGTCTGCACAAAGCAC TACTGTGCTTTGCTGTCTGCAAGAA CAGAGATTGTTTGCTTCAACCACTTT CTCTGAATGGATGAATGAGTTATGA TGATATCTAAAGTTACCCAATTTCA AGCAAGAGGAAGAA TCTGGCTCGGTACCACAGATGTTCTT GGAATTGGGATAGTAAAAAAGTCCC TGAGGCATCCCTTGGTCTGCTCTGA CCACACTCTCTTCACAGGAAGAGGC TTGGGCCACAGCTCTGACTATAACT CTGCTCTTCCTCCA AACACAGCTGAGGAATTGGGTGGTG GGGCACCTGCTCCCATGCTCTGTGG CCTGGCTCAGAGAGAAGAGTTGCCT TAATTACATTATTATTCTTCCTGGAC AGGCTGTAGGTTGTGTAAAGTAACA AAAAGGACTGAGAA GTGACTTCCCATTTCAGCCTCTTCCAA GGCCATTTTTGATAGGCAGGTCAAA TTCCTCACATTTGGTTATTTGTTGG CCAGTCTAGTGCATTACCCCTTGCTG GTCCTCAGTCATGCTCCTTTACCTTT ACAGAGCATCCTAGACTGCTCTTCC TCTTACCTTCCTTGTGAAACCCACAA CCCCTAGTCCCTCCCCTTCCCTGGCA TTTGTATGCCCTCTACCAATCCCTG ACCTGGTATTGGTCAGTCTCCAATC CTGGTGGATCCCTGTGGGAACCTAAG TTAAGTCTAACTTTTGTCTCCCTCTT TAGAATTTACTGGGAGTACTGTAAA TAAACTATTGTTGTTATAATTATTTT TGATTAACATTTTACACCTAACAA AGTCTCAGAGAGATTGAATTTACTG GGTTGAAGGGAGGAGCACCTTCCAC ATGACCTGCCCAGCAATTAAAGCCG	
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		CTTGTTAGTCCGAGGCCAGGACGG CCGAGG ACAGCTGGAGAGCTCTTCGTTGCAG GCAGCTCTGGTTAACATCAACCGGG AAAGCTCTTTGTAAACACATGAATA ATTGATCGTCCAGCGCTCACATAGC TACCGCGGATCTGAGCCCGTATGAC TCATTTGCGAGCCAT TCCTGTCGTCTGGATGCCATAACATT GGAGGAATGATGATCGTTTCTTGGA GGTTCTTCTGTGGCCAGAGTTGCCA AGACCAAGGCTGTAATGGTTTGTTA TGATGACCTTTGTTATTCCATTAGGC TCAATTGCTTTAA AAAATGATGTGTGCATACTTTAGGA ACGTTTTTACCCTTTATGTTGACCTG ACATCATAGTTTATATTATAAAATG TATTAATGACAGAAGAGTGTTTTCA TGTCCTCAAGGACAAATTTTAAACAAC CATAATCTGCCCTC AGTCATCATAAATATAAATGTATTG GTCAAACAGATCTCGTTAATGTGGC CAAGATAAATGCAAGTCTATATTTT AAGGCAGTCGAAGTCCTAGAGAATA TATCTGGAGCTTTTGTGGGGCTAAG AGATCTTGTATATAT GCTATCAAAAGGCTGAGAAAATTAA CATGTTCCCCCTCTGATTTTGCATT GGACAGATATAAATGTCTTGGGGAT GTCAAGTAAGATTGTTACATAGTT TCTGGACACCATTAATGCCTGATGG GGTGAATCTTAGTT CTTAAAGCTATATTCTGCTCATTATG CTCACAGGGCTTTTGAAAAGAGAAC AAAATAAAGATTTCAAGTCTTAGCA A	
MARCl Macaca fascicularis cDNA (XM_005540898 .2)		AAAAAAAAAGTGGTAAGTGAGCTG TAGCCCTGGGTAAATTCTGGAAGTG ATGAAATGGAAGAATCAGAACTTTA AAGTCAACCATTAAAATAGGGGAGC CATTTTTTCCTCTTAAATTTTCAAAG AGGAATTCAGGAGGG AGATAAACAGAAACACATATTTGGT GCCCCGGAGCTGCCTTTCCGAGGAG GATCAAGTGGTACGTCCTGCGGAGC TGTGTCCTTTACAGACAGGGTGTGA	1693

		CCTGGGGTTGGAAGAGAAGAGAAG AGAGCAGAAAAGCAGG ACAGATAAGTGTTTCAGGCCAGTAAA GACAGAGCCTCCCTGAGCACGGAAC TGCTCTGCAGTGAGTTGCCATCTGG AGGAGAGGGTTGTTCTTTTCTCTTGG CGAACTCCCGCTTCTCTCTTCCAAGG CACCTTGCCCTG CATGGACAATTCTGGCTGAGTCTTG AAATGTACACTCCTGGCTCAGGGGA CCATGGCTGAGCTGCGGATGACACA GGCTCTCGACCAAACCTTCAGTCTCC TCTGAGCCCTTTTCTTCGTGAGGCCT TGACCTTGCCACCC TACTCCCTGCAGAGCCCAGTTTAGC AAGAATCCTGCTTAGTCAGTTTCCA GAGTATTCTCCCATCCTTGATATCTG ATCATCCTTGATATCTGCTCAGATTC CTCATCTGTCACCCTCAGTGTGTAA GTCCTTGCCCTAGT TCAGTAGAATCCTGTAAAGTGGGTT TATCAAGAATCCTCTACACTTGATG TCTCCTCTTAGAGATTTTTCATTAC TGACCCCCAGGAACTTTGCTCTTTG GCTATAAACCCCCAGCAGTCTTCGC TGTAATACAGAGCT GAGCCTAATCTCTTTCCCCTATTGTG ATGCCCCGTGTACAATAGCCGTGAA TAGTCTTCCTTACCTTTTAAATAAGC GTTTGAGTAATTTTTCCTTTGATAG CTTGGTACATCAAACAGGAGCCTGA CTCCTAAACCAT GCTGTTCTGGGTGTGCTGATATTGTTG ACTGGAATATAACCTGATTTGGAAG TGACAAGTGACTGAGGTGAGTGCCT GCAGGACCAGGTGACATTCCTCCC GCCAGAAGCAGCCTGGGGACCTTGT GCAGTGCTGAACTT CTGAGCCAAGGCCTTGCCAATGCAG CTGCAGCTGAGGCTCCCCGCCGGA GCGTAGAAGGCGCTCTCAGACGCCC ATTGCCGCTCCGAACTGCCGCTGGG AGAACTCTGGCCTTGTCTCGCTGGC GCAGAGGGCCTGGTA GCATCCTCCTCCACCAGACCCCCAC TCTTGGAACCTCCCTAAACCCTGG	
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		GCAGCCTGCGGGGACGGCGGCCGC AGCAGAGAGCTGGACACTGCGCAG GCCAGGCAGGGCCAACCCGCTCTCT ACTATTCCTGGGAGAAG CTGCTGCCCCGCTGTCTGATTTTAAAT TTCAAATCACGCTTTGTCCTGCAA ATGTTGTCTATTGTTTATTTAGGTC AAATAACCCCATAAATACGTAAGTA AATAAACTGGTCACTTGCAGAGATC GTGGGGGAGGGCACGGCGCCCTGA GCTGCAGGCGACGGAAGGTTGCAG AAGCCATGGGGCGCAGACCAAGTG GAAGCTGAGCCGCCACCTCCCACTC CCCGCGCCGCCCCCAAAAGGACGC ACTGCTCTGATTGGCCCGGAAGGGT TTGGGAACTGCCCACCCTTTGGGCT CAGGGCCAAAGGCCGCACCTTCCCC CAGCTGCCCCGGGGCTACCAGCGCGC TGCGGCCTTGCCGCCGGCACCTCGC GGAGAAGCCAGCCATGGGCGCCGC CGGTTCTCCGCGCTGGCCGGC TTTGTCTCCTCGCTCAGCCCCGGCC CGGGTGGCTCGGGGTCGCCGTGCTG GGACTGACCGCGGTGGCGCTGGGGG CTGTCGCCTGGCGCCGCGCATGGCC CACGCAGCGCCGGCGGCTGCTGCAG CAGGTGGGCACAGT GGCGCAGCTCTGGATCTACCCTGTG AAATCCTGCAAGGGGGTGCCAGTGA GCGAGGCCGAGTGCAGTGCATGGG GCTGCGCAGCGGCAACCTGCGGGAC AGGTTTTGGCTTGTGATCAACCAGG AGGGAAACATGGTTA CCGCTCGCCAGGAACCTCGCCTGGT CCTGATTTCCCTGACCTGTGATGGTG ACACCCTGACTCTCAGTGCAGCCTA CACAAAGGATCTACTACTGCCCATC AAAACGCCCACCACAAATGCAGTGC GCAAGTGCAGAGTC CATGGCCTGGAGATTGAGGGCAGAG ACTGTGGTGAGGCCGCCGCCAGTG GATAACCAGCTTCCTGAAGTCACAG TCCTACCGCCTGGTGCACCTTCGAGC CTCACATGCGACCGAGACATCCTCA CCAAATAGCAGACTT GTTCCGACCCAAGGACCAGATTGCT TACTCAGACACCAGCCCATTTCATGA	
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		TCCTTTCTGAGGCGTCGCTAGCGGA TCTCAACTCCAGGCTAGAGAAGAAA GTTAAAGCAACCAACTTCAGGCCCA ATATTGTAATTTTCAG GATGCGATGTCTATGCAGAGGTAAC GCTATGCCCCTTTGCATCTTTCCTTG GATTTGACTTCTTTTTTAAGGATTCT TGGGACGAGCTTCTTATTGGTGACG TGGAAGTGAAGGTTGATGGCTTG TTCCAGATGCATT TTAACCACAGTGGACCCAGACACCG GCGTCATGAGCAGGAAGGAGCCGCT GGAAACACTGAAGAGTTATCGCCAG TGTGACCCTTCAGAACGAAAGTTAT ATGGAAAATCACCCTCTTTGGGCA GTATTTTGTGCTGGA AAACCCAGGGACCATCAAAGTGGG AGACCCTGTGTACCTGCTGGGCCAG TAATGGGAACTGTATGTCCTGGAAT ATTAGATGCCTTTAAAAAATGTTCT CAAAAATGACAACACTTGAAGCATG GTGTTTCAGAACTGAG ACCTCAACATTTTCTTTAAATTTGTG ATTTTCACATTTTCTCTTTTGGAC TTCTCGTGTCTCAATGCTTCAATGTC CCAGTGCACAAAGCAAAGAAATAT AGTCTTGATAACTTAGTAGGCTTTC AGTAAGACACTTAAGTGACAAGACA GGATTCTGAAAACCTCCCTGTTAAC TGATTATGGAATAGTTCTTCTCCTG CTTTGCCATTTATCTACCAAGAGTGC AGACTTCCATCCTGTCACTACCACTC ATGAGGGAAAGAGAAGAAGAGAAA GAGGAAGAGTGGGTAGGCCAGAAG AATGTCCTAGAATGTGTTATTACCC CTGTGCATGAGGTATGCAATGAAAA TTAAATAGCTCCCCAAATATGGCTG GAATGTCACTTGCCTTTTCTTCTGAA GCCCCGGGCTAGCTTTTGAAATGGC ATGAAGACTGAGGTGACCTTCAGGA AGCACTTCAGATATTAATTTTCCATA GATCTGGATCTGGCCCCGCTGCTTCT CAGACAGCATTGGATTTCTTAAAGG TGCTCAGGAGGGTGGTTGTGTAGTC ACGGAGGACCCCTGGATCCTTGCCA TTCCCCTCAGCTAATGACTGAGTGC TCCTTCTCCAGTTCTGGGTGAAAA	
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		AGTTCTGAAGTCTGTGGAGGAGAAG AAAAGTGATTCAGTGATTTCAAATG GATACTGAAAACCTTTAAAGGGGGA AAAGGAAAGCGTATGTCAGTTGTTT AAAACCCAATATCTACTTTTTTAACT GATTGCATAACTCTAAGATCTGATG AAGTATATTTTTTATTGCCATTTTGT CCTTTGATTGTATTGGGAAGTTGACT AAACTTGAAAAATGTTTTTAAACT GTGAATAAATGGAAGCTACTTTGAC TAGTT	
Probe		CAGGAGGATG GTTGT	1694
Probe		CCACCACAAA TGCA	1695
Probe		GTCGCAAGCT TGCTGGT	1696

LIST OF EMBODIMENTS

1. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.
2. The RNAi oligonucleotide of embodiment 1, wherein the sense strand is 15 to 50 nucleotides in length.
3. The RNAi oligonucleotide of embodiments 1 or 2, wherein the sense strand is 18 to 36 nucleotides in length.
4. The RNAi oligonucleotide of any one of embodiments 1 to 3, wherein the antisense strand is 15 to 30 nucleotides in length.
5. The RNAi oligonucleotide of any one of embodiments 1 to 4, wherein the antisense strand is 22 nucleotides in length and wherein antisense strand and the sense strand form a duplex region of at least 19 nucleotides in length, optionally at least 20 nucleotides in length.
6. The RNAi oligonucleotide of any one of embodiments 1 to 5, wherein the region of complementarity is at least 19 contiguous nucleotides in length, optionally at least 20 nucleotides in length.
7. The RNAi oligonucleotide of any one of embodiments 1 to 6, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length.
8. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ

ID NOs: 1-384, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

9. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

10. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is 19 contiguous nucleotides in length, differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

11. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is 19 contiguous nucleotides in length, differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

12. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is 19 contiguous nucleotides in length, differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

13. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is 19 contiguous nucleotides in length, differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

14. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is 19 contiguous nucleotides in length, differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

15. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region of at least 19 nucleotides in length, optionally 20 nucleotides in length, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is 19 contiguous nucleotides in length, differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

16. A double stranded RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising:

(i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARCI*

mRNA target sequence, wherein the region of complementarity is selected from SEQ ID NOs: 385-768, and

(ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

17. The RNAi oligonucleotide of embodiment 16, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3-5 nucleotides in length.

18. The RNAi oligonucleotide of any one of embodiments 7 and 13-17, wherein L is a triloop or a tetraloop.

19. The RNAi oligonucleotide of embodiment 18, wherein L is a tetraloop.

20. The RNAi oligonucleotide of embodiment 19, wherein the tetraloop comprises the sequence 5'-GAAA-3'.

21. The RNAi oligonucleotide of any one of embodiments 18-20, wherein the S1 and S2 are 1-10 nucleotides in length and have the same length.

22. The RNAi oligonucleotide of embodiment 21, wherein S1 and S2 are 1 nucleotide, 2 nucleotides, 3 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, or 10 nucleotides in length.

23. The RNAi oligonucleotide of embodiment 22, wherein S1 and S2 are 6 nucleotides in length.

24. The RNAi oligonucleotide of any one of embodiments 18 to 23, wherein the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 1681).

25. The RNAi oligonucleotide of any one of embodiments 1-24, comprising a nicked tetraloop structure.

26. The RNAi oligonucleotide of any one of embodiments 1-24, comprising a nick between the 3' terminus of the sense strand and the 5' terminus of the antisense strand.
27. The RNAi oligonucleotide of any one of embodiments 1-26, wherein the antisense and sense strands are not covalently linked.
28. The RNAi oligonucleotide of any one of embodiments 1 to 15 and 17-27, wherein the antisense strand comprises an overhang sequence of one or more nucleotides in length at the 3' terminus.
29. The RNAi oligonucleotide of any one of embodiments 16-28, wherein the overhang comprises purine nucleotides.
30. The RNAi oligonucleotide of embodiment 29, wherein the 3'-overhang sequence is 2 nucleotides in length.
31. The RNAi oligonucleotide of embodiment 30, wherein the 3'-overhang is selected from AA, GG, AG, and GA.
32. The RNAi oligonucleotide of embodiment 31, wherein the overhang is GG or AA.
33. The RNAi oligonucleotide of embodiment 31, wherein the overhang is GG.
34. The RNAi oligonucleotide of any one of the preceding embodiments, wherein the oligonucleotide comprises at least one modified nucleotide.
35. The RNAi oligonucleotide of embodiment 34, wherein the modified nucleotide comprises a 2'-modification.
36. The RNAi oligonucleotide of embodiment 35, wherein the 2'-modification is a modification selected from 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro- β -D-arabinonucleic acid.

37. The RNAi oligonucleotide of any one of embodiments 34 to 36, wherein all nucleotides comprising the oligonucleotide are modified, optionally wherein the modification is a 2'-modification selected from 2'-fluoro and 2'-O-methyl.
38. The RNAi oligonucleotide of any one of embodiments 34-37, wherein about 10-15%, 10%, 11%, 12%, 13%, 14%, or 15% of the nucleotides of the sense strand comprise a 2'-fluoro modification.
39. The RNAi oligonucleotide of any one of embodiments 34-38, wherein about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, or 35% of the nucleotides of the antisense strand comprise a 2'-fluoro modification.
40. The RNAi oligonucleotide of any one of embodiments 34-39, wherein about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, or 35% of the nucleotides of the oligonucleotide comprise a 2'-fluoro modification
41. The RNAi oligonucleotide of any one of embodiments 34-40, wherein the sense strand comprises 36 nucleotides with positions 1-36 from 5' to 3', wherein positions 8-11 comprise a 2'-fluoro modification.
42. The RNAi oligonucleotide of any one of embodiments 34-41, wherein the antisense strand comprises 22 nucleotides with positions 1-22 from 5' to 3', and wherein positions 2, 3, 4, 5, 7, 10, and 14 comprise a 2'-fluoro modification.
43. The RNAi oligonucleotide of any one of embodiments 34-42, wherein the remaining nucleotides comprise a 2'-O-methyl modification.
44. The RNAi oligonucleotide of any one of the preceding embodiments, wherein the oligonucleotide comprises at least one modified internucleotide linkage.
45. The RNAi oligonucleotide of embodiment 44, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

46. The RNAi oligonucleotide of embodiment 45, wherein the antisense strand comprises a phosphorothioate linkage (i) between positions 1 and 2, and between positions 2 and 3; or (ii) between positions 1 and 2, between positions 2 and 3, and between positions 3 and 4, wherein positions are numbered 1-4 from 5' to 3'.
47. The RNAi oligonucleotide of embodiment 45 or 64, wherein the antisense strand is 22 nucleotides in length, and wherein the antisense strand comprises a phosphorothioate linkage between positions 20 and 21 and between positions 21 and 22, wherein positions are numbered 1-22 from 5' to 3'.
48. The RNAi oligonucleotide of any one of embodiments 1-47, wherein the antisense strand comprises a phosphorylated nucleotide at the 5' terminus, wherein the phosphorylated nucleotide is selected from uridine and adenosine.
49. The RNAi oligonucleotide of embodiment 48, wherein the phosphorylated nucleotide is uridine.
50. The RNAi oligonucleotide of any one of the preceding embodiments, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog.
51. The RNAi oligonucleotide of embodiment 50, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate, or malonylphosphonate, optionally wherein the phosphate analog is a 4'-phosphate analog comprising 5'-methoxyphosphonate-4'-oxy.
52. The RNAi oligonucleotide of any one of the preceding embodiments, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands.
53. The RNAi oligonucleotide of embodiment 42, wherein each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid.
54. The RNAi oligonucleotide of any one of embodiments 17-53, wherein the stem loop comprises one or more targeting ligands conjugated to one or more nucleotides of the stem loop.

55. The RNAi oligonucleotide of embodiment 54, wherein the one or more targeting ligands is conjugated to one or more nucleotides of the loop.
56. The RNAi oligonucleotide of embodiment 55, wherein the loop comprises 4 nucleotides numbered 1-4 from 5' to 3', wherein nucleotides at positions 2, 3, and 4 each comprise one or more targeting ligands, wherein the targeting ligands are the same or different.
57. The RNAi oligonucleotide of any one of embodiments 52-56, wherein each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety.
58. The RNAi oligonucleotide of embodiment 57, wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety.
59. The RNAi oligonucleotide of any one of embodiments 17 to 58, wherein up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.
60. The RNAi oligonucleotide of any one of embodiments 1-59, wherein the region of complementarity is fully complementary to the *MARCI* mRNA target sequence at nucleotide positions 2-8 of the antisense strand, wherein nucleotide positions are numbered 5' to 3'.
61. The RNAi oligonucleotide of any one of embodiments 1-59, wherein the region of complementarity is fully complementary to the *MARCI* mRNA target sequence at nucleotide positions 2-11 of the antisense strand, wherein nucleotide positions are numbered 5' to 3'.
62. The RNAi oligonucleotide of any one of embodiments 1 to 61, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 1537-1570.
63. The RNAi oligonucleotide of any one of embodiments 1 to 62, wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 1573-1606.
64. The RNAi oligonucleotide of any one of embodiments 1 to 63, wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively.

65. The RNAi oligonucleotide of any one of embodiments 1 to 64, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1543, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1579.
66. The RNAi oligonucleotide of any one of embodiments 1 to 64, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1560, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1596.
67. The RNAi oligonucleotide of any one of embodiments 1 to 64, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1568, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1604.
68. The RNAi oligonucleotide of any one of embodiments 1 to 64, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1553, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1589.
69. The RNAi oligonucleotide of any one of embodiments 1-61, wherein the antisense strand is 22 nucleotides in length.
70. The RNAi oligonucleotide of embodiment 69, wherein the antisense strand comprises a nucleotide sequence selected from SEQ ID NOs: 1579, 1596, 1604, and 1589.
71. The RNAi oligonucleotide of any one of embodiments 1-61 and 69-70, wherein the sense strand comprises a nucleotide sequence selected from SEQ ID NOs: 234, 298, 356, and 376.
72. The RNAi oligonucleotide of any one of embodiments 1-61 and 69-71, wherein the sense strand is 36 nucleotides in length.
73. The RNAi oligonucleotide of embodiment 72, wherein the sense strand comprises a nucleotide sequence selected from SEQ ID NOs: 1543, 1560, 1568, and 1553.

74. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

75. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

76. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

77. An RNAi oligonucleotide for reducing *MARCI* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and the antisense strand are modified, wherein the antisense strand and the sense strand comprise one or more 2'-fluoro and 2'-O-methyl modified nucleotides and at least one phosphorothioate linkage, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and

wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

78. The RNAi oligonucleotide of any one of embodiments 1-77, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 1609-1642.

79. The RNAi oligonucleotide of any one of embodiments 1-78, wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 1645-1678.

80. The RNAi oligonucleotide of any one of embodiments 1-79, wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1609 and 1645, respectively;
- (b) SEQ ID NOs: 1610 and 1646, respectively;
- (c) SEQ ID NOs: 1611 and 1647, respectively;
- (d) SEQ ID NOs: 1612 and 1648, respectively;
- (e) SEQ ID NOs: 1613 and 1649, respectively;
- (f) SEQ ID NOs: 1614 and 1650, respectively;
- (g) SEQ ID NOs: 1615 and 1651, respectively;
- (h) SEQ ID NOs: 1616 and 1652, respectively;
- (i) SEQ ID NOs: 1617 and 1653, respectively;
- (j) SEQ ID NOs: 1618 and 1654, respectively;
- (k) SEQ ID NOs: 1619 and 1655, respectively;
- (l) SEQ ID NOs: 1620 and 1656, respectively;
- (m) SEQ ID NOs: 1621 and 1657, respectively;
- (n) SEQ ID NOs: 1622 and 1658, respectively;
- (o) SEQ ID NOs: 1623 and 1659, respectively;
- (p) SEQ ID NOs: 1624 and 1660, respectively;
- (q) SEQ ID NOs: 1625 and 1661, respectively;
- (r) SEQ ID NOs: 1626 and 1662, respectively;
- (s) SEQ ID NOs: 1627 and 1663, respectively;
- (t) SEQ ID NOs: 1628 and 1664, respectively;
- (u) SEQ ID NOs: 1628 and 1665, respectively;
- (v) SEQ ID NOs: 1630 and 1666, respectively;
- (w) SEQ ID NOs: 1631 and 1667, respectively;

- (x) SEQ ID NOs: 1632 and 1668, respectively;
- (y) SEQ ID NOs: 1633 and 1669, respectively;
- (z) SEQ ID NOs: 1634 and 1670, respectively;
- (aa) SEQ ID NOs: 1635 and 1671, respectively;
- (bb) SEQ ID NOs: 1636 and 1672, respectively;
- (cc) SEQ ID NOs: 1637 and 1673, respectively;
- (dd) SEQ ID NOs: 1638 and 1674, respectively;
- (ee) SEQ ID NOs: 1639 and 1675, respectively;
- (ff) SEQ ID NOs: 1640 and 1676, respectively;
- (gg) SEQ ID NOs: 1641 and 1677, respectively; and,
- (hh) SEQ ID NOs: 1642 and 1678, respectively.

81. The RNAi oligonucleotide of any one of embodiments 1-80, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1615 and 1651, respectively.

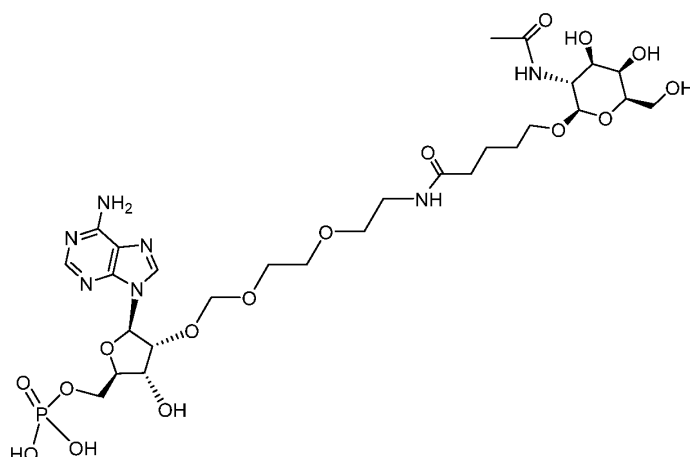
82. The RNAi oligonucleotide of any one of embodiments 1-80, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1632 and 1668, respectively.

83. The RNAi oligonucleotide of any one of embodiments 1-80, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1640 and 1676, respectively.

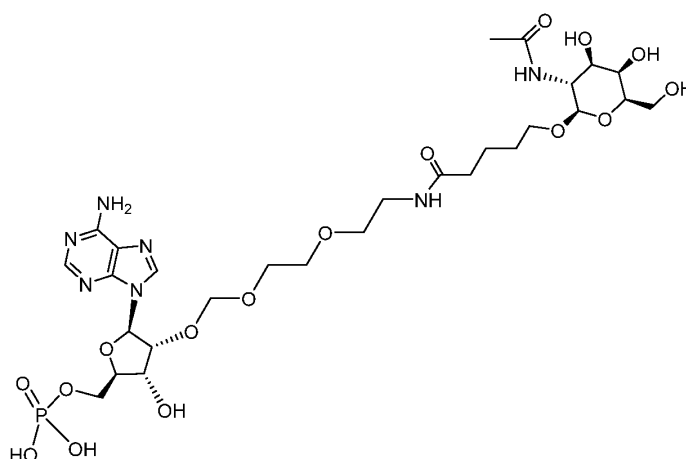
84. The RNAi oligonucleotide of any one of embodiments 1-80, wherein the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1625 and 1661, respectively.

85. An RNAi oligonucleotide for inhibiting expression of MARC1, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a MARC1 RNA transcript, wherein the sense strand comprises the sequence and all of the modifications of 5'-mGs-mG-mC-mU-mA-mG-mA-fG-fA-fA-fG-mA-mA-mA-mG-mU-mU-mA-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1615), and

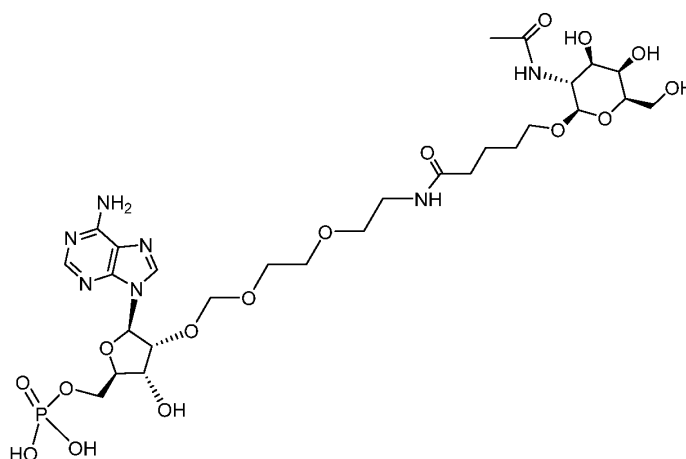
wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fUs-fA-fA-mC-fU-mU-mU-fC-mU-mU-mC-fU-mC-mU-mA-mG-mC-mCs-mGs-mG-3' (SEQ ID NO: 1651), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



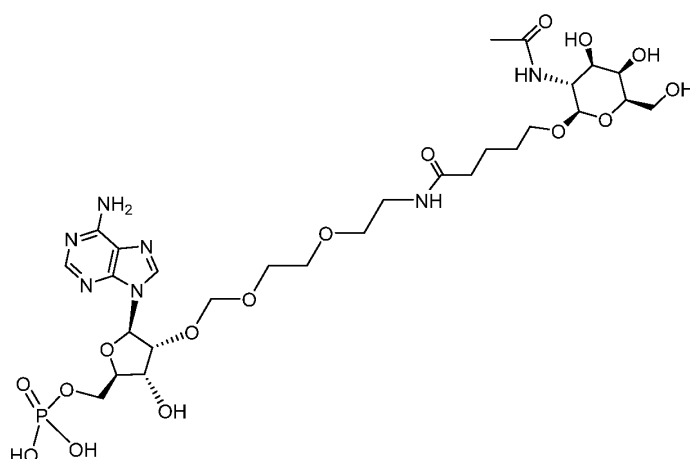
86. An RNAi oligonucleotide for inhibiting expression of MARC1, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a MARC1 RNA transcript, wherein the sense strand comprises the sequence and all of the modifications of 5'-mAs-mG-mA-mA-mC-mG-mA-fA-fA-fG-fU-mU-mA-mU-mA-mU-mG-mG-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1632), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fCs-fC-fA-mU-fA-mU-mA-fA-mC-mU-mU-fU-mC-mG-mU-mU-mC-mUs-mGs-mG-3' (SEQ ID NO: 1668), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



87. An RNAi oligonucleotide for inhibiting expression of MARC1, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a MARC1 RNA transcript, wherein the sense strand comprises the sequence and all of the modifications of 5'-mAs-mA-mG-mU-mU-mG-mA-fC-fU-fA-fA-mA-mC-mU-mU-mG-mA-mA-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1640), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fUs-fU-fC-mA-fA-mG-mU-fU-mU-mA-mG-fU-mC-mA-mA-mC-mU-mUs-mGs-mG-3' (SEQ ID NO: 1676), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



88. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of MARC1, wherein said dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity to a MARC1 RNA transcript, wherein the sense strand comprises the sequence and all of the modifications of 5'-mUs-mG-mU-mG-mA-mA-mU-fA-fA-fA-fU-mG-mG-mA-mA-mG-mC-mU-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1625), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fAs-fG-fC-mU-fU-mC-mC-fA-mU-mU-mU-fA-mU-mU-mC-mA-mC-mAs-mGs-mG-3' (SEQ ID NO: 1661), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



89. The RNAi oligonucleotide of any one of embodiments 1-88, wherein the oligonucleotide is a Dicer substrate.

90. The RNAi oligonucleotide of any one of embodiments 1-88, wherein the oligonucleotide is a Dicer substrate that, upon endogenous Dicer processing, yields double-stranded nucleic acids of 19-23 nucleotides in length capable of reducing *MARCI* expression in a mammalian cell.

91. A method for treating a subject having a disease, disorder or condition associated with *MARCI* expression, the method comprising administering to the subject a therapeutically effective amount of the RNAi oligonucleotide of any one of the preceding embodiments, or pharmaceutical composition thereof, thereby treating the subject.
92. A pharmaceutical composition comprising the RNAi oligonucleotide of any one of embodiments 1 to 90, and a pharmaceutically acceptable carrier, delivery agent or excipient.
93. A method of delivering an oligonucleotide to a subject, the method comprising administering pharmaceutical composition of embodiment 92 to the subject.
94. A method for reducing *MARCI* expression in a cell, a population of cells or a subject, the method comprising the step of:
- i. contacting the cell or the population of cells with the RNAi oligonucleotide of any one of embodiments 1 to 90, or the pharmaceutical composition of embodiment 92; or
 - ii. administering to the subject the RNAi oligonucleotide of any one of embodiments 1 to 90, or the pharmaceutical composition of embodiment 92.
95. The method of embodiment 94, wherein reducing *MARCI* expression comprises reducing an amount or level of *MARCI* mRNA, an amount or level of MARC1 protein, or both.
96. The method of embodiment 94 or 95, wherein the subject has a disease, disorder or condition associated with *MARCI* expression, for example *MARCI* expression in the liver.
97. The method of embodiment 96, wherein the subject has a disease, disorder or condition associated with *MARCI* expression in the liver.
98. The method of embodiment 97, wherein the subject has a disease, disorder or condition associated with *MARCI* expression in hepatocytes.
99. The method of embodiment 91 or 96 to 98, wherein the disease, disorder or condition associated with *MARCI* expression is non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and alcoholic steatohepatitis (ASH).

100. The method of any one of embodiments 91 and 94 to 99, wherein the RNAi oligonucleotide, or pharmaceutical composition, is administered in combination with a second composition or therapeutic agent.

101. A method for treating a subject having a disease, disorder or condition associated with *MARCI* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *MARCI* mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the *MARCI* mRNA target sequence.

102. A method for treating a subject having a disease, disorder or condition associated with *MARCI* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand selected from a row set forth in **Table 4 or Table 6**, or pharmaceutical composition thereof, thereby treating the subject.

103. A method for treating a subject having a disease, disorder or condition associated with *MARCI* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;

- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;
- (u) SEQ ID NOs: 1557 and 1593, respectively;
- (v) SEQ ID NOs: 1558 and 1594, respectively;
- (w) SEQ ID NOs: 1559 and 1595, respectively;
- (x) SEQ ID NOs: 1560 and 1596, respectively;
- (y) SEQ ID NOs: 1561 and 1597, respectively;
- (z) SEQ ID NOs: 1562 and 1598, respectively;
- (aa) SEQ ID NOs: 1563 and 1599, respectively;
- (bb) SEQ ID NOs: 1564 and 1600, respectively;
- (cc) SEQ ID NOs: 1565 and 1601, respectively;
- (dd) SEQ ID NOs: 1566 and 1602, respectively;
- (ee) SEQ ID NOs: 1567 and 1603, respectively;
- (ff) SEQ ID NOs: 1568 and 1604, respectively;
- (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
- (hh) SEQ ID NOs: 1570 and 1606, respectively.

104. The method of embodiment 103, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1543, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1579.

105. The method of embodiment 103, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1560, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1596.

106. The method of embodiment 103, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1568, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1604.

107. The method of embodiment 103, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1553, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1589.

108. A method for treating a subject having a disease, disorder or condition associated with *MARCI* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1609 and 1645, respectively;
- (b) SEQ ID NOs: 1610 and 1646, respectively;
- (c) SEQ ID NOs: 1611 and 1647, respectively;
- (d) SEQ ID NOs: 1612 and 1648, respectively;
- (e) SEQ ID NOs: 1613 and 1649, respectively;
- (f) SEQ ID NOs: 1614 and 1650, respectively;
- (g) SEQ ID NOs: 1615 and 1651, respectively;
- (h) SEQ ID NOs: 1616 and 1652, respectively;
- (i) SEQ ID NOs: 1617 and 1653, respectively;
- (j) SEQ ID NOs: 1618 and 1654, respectively;
- (k) SEQ ID NOs: 1619 and 1655, respectively;
- (l) SEQ ID NOs: 1620 and 1656, respectively;
- (m) SEQ ID NOs: 1621 and 1657, respectively;
- (n) SEQ ID NOs: 1622 and 1658, respectively;
- (o) SEQ ID NOs: 1623 and 1659, respectively;
- (p) SEQ ID NOs: 1624 and 1660, respectively;
- (q) SEQ ID NOs: 1625 and 1661, respectively;
- (r) SEQ ID NOs: 1626 and 1662, respectively;
- (s) SEQ ID NOs: 1627 and 1663, respectively;
- (t) SEQ ID NOs: 1628 and 1664, respectively;
- (u) SEQ ID NOs: 1628 and 1665, respectively;

- (v) SEQ ID NOs: 1630 and 1666, respectively;
- (w) SEQ ID NOs: 1631 and 1667, respectively;
- (x) SEQ ID NOs: 1632 and 1668, respectively;
- (y) SEQ ID NOs: 1633 and 1669, respectively;
- (z) SEQ ID NOs: 1634 and 1670, respectively;
- (aa) SEQ ID NOs: 1635 and 1671, respectively;
- (bb) SEQ ID NOs: 1636 and 1672, respectively;
- (cc) SEQ ID NOs: 1637 and 1673, respectively;
- (dd) SEQ ID NOs: 1638 and 1674, respectively;
- (ee) SEQ ID NOs: 1639 and 1675, respectively;
- (ff) SEQ ID NOs: 1640 and 1676, respectively;
- (gg) SEQ ID NOs: 1641 and 1677, respectively; and,
- (hh) SEQ ID NOs: 1642 and 1678, respectively.

109. The method of embodiment 108, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1615, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1651.

110. The method of embodiment 108, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1632, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1668.

111. The method of embodiment 108, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1640, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1676.

112. The method of embodiment 108, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1625, wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1661.

113. The method of any one of embodiments 101 to 112, wherein the disease, disorder or condition associated with *MARCI* expression is non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), or alcoholic steatohepatitis (ASH).

114. Use of the RNAi oligonucleotide of any one of embodiments 1 to 90, or the pharmaceutical composition of embodiment 92, in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with *MARCI* expression, optionally for the treatment of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), or alcoholic steatohepatitis (ASH).

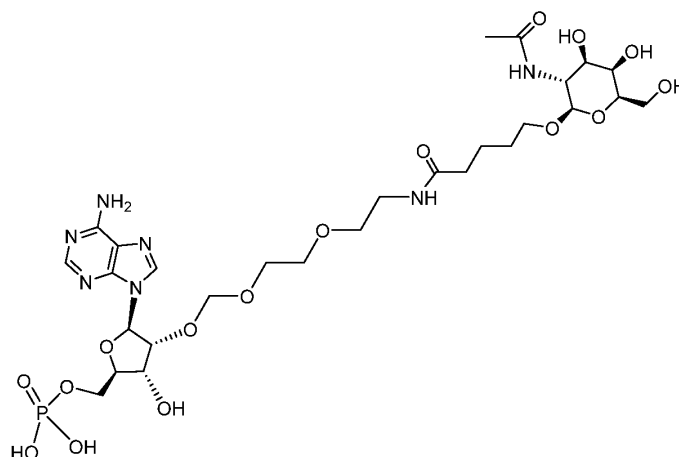
115. The RNAi oligonucleotide of any one of embodiments 1 to 90, or the pharmaceutical composition of embodiment 92, for use, or adaptable for use, in the treatment of a disease, disorder or condition associated with *MARCI* expression, optionally for the treatment of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), or alcoholic steatohepatitis (ASH).

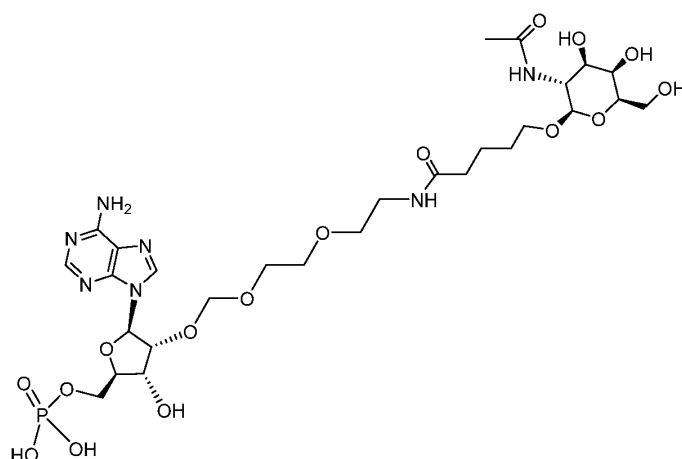
116. The RNAi oligonucleotide of any one of embodiments 1 to 90, or the pharmaceutical composition of embodiment 92, for use, or adaptable for use, in the treatment of a disease, disorder or condition associated with *MARCI* expression in the liver, for the treatment of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), or alcoholic steatohepatitis (ASH).

117. A kit comprising the RNAi oligonucleotide of any one of embodiments 1 to 90, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with *MARCI* expression.

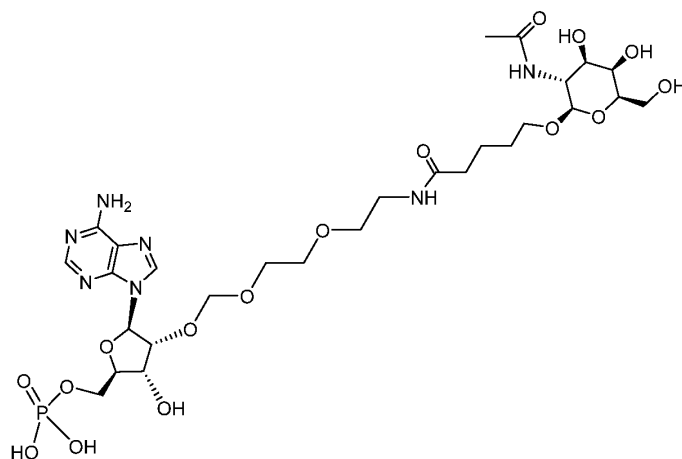
118. The use of embodiment 114, the RNAi oligonucleotide or pharmaceutical composition for use, or adaptable for use, of embodiment 115, or the kit of embodiment 116, wherein the disease, disorder or condition associated with *MARCI* expression is non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), or alcoholic steatohepatitis (ASH).

1. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of MARC1, wherein said dsRNAi comprises a sense strand and an antisense strand, wherein the sense strand comprises the sequence and all of the modifications of 5'-mGs-mG-mC-mU-mA-mG-mA-fG-fA-fA-fG-mA-mA-mA-mG-mU-mU-mA-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1615), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fUs-fA-fA-mC-fU-mU-mU-fC-mU-mU-mC-fU-mC-mU-mA-mG-mC-mCs-mGs-mG-3' (SEQ ID NO: 1651), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



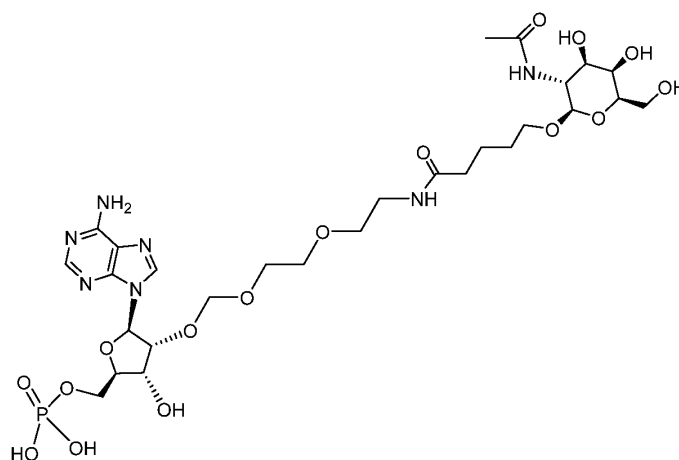


3. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of MARC1, wherein said dsRNAi comprises a sense strand and an antisense strand, wherein the sense strand comprises the sequence and all of the modifications of 5'-mAs-mA-mG-mU-mU-mG-mA-fC-fU-fA-fA-mA-mC-mU-mU-mG-mA-mA-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1640), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fUs-fU-fC-mA-fA-mG-mU-fU-mU-mA-mG-fU-mC-mA-mA-mC-mU-mUs-mGs-mG-3' (SEQ ID NO: 1676), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



4. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of MARC1, wherein said dsRNAi comprises a sense strand and an antisense strand, wherein the

sense strand comprises the sequence and all of the modifications of 5'-mUs-mG-mU-mG-mA-mA-mU-fA-fA-fA-fU-mG-mG-mA-mA-mG-mC-mU-mA-mA-mG-mC-mA-mG-mC-mC-mG-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC-3' (SEQ ID NO: 1625), and wherein the antisense strand comprises the sequence and all of the modifications of 5'-MePhosphonate-4O-mUs-fUs-fAs-fG-fC-mU-fU-mC-mC-fA-mU-mU-mU-fA-mU-mU-mC-mA-mC-mAs-mGs-mG-3' (SEQ ID NO: 1661), wherein mC, mA, mG, and mU = 2'-OMe ribonucleosides; fA, fC, fG, and fU = 2'F ribonucleosides; s = phosphorothioate, and wherein ademA-GalNAc =



5. An RNAi oligonucleotide for reducing MARC1 expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a MARC1 mRNA target sequence of any one of SEQ ID NOs: 1-384, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the MARC1 mRNA target sequence.

6. The RNAi oligonucleotide of claim 5, comprising:

(i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *MARC1* mRNA target sequence, wherein the region of complementarity is selected from SEQ ID NOs: 385-768, and

(ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate

strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

7. The RNAi oligonucleotide of any one of claims 5, wherein:

- (i) the sense strand is 15 to 50 or 18 to 36 nucleotides in length, optionally 36 nucleotides in length; optionally
- (ii) the antisense strand is 15 to 30 nucleotides in length, optionally 22 nucleotides in length; and optionally
- (iii) the duplex region is at least 19 nucleotides or at least 20 nucleotides in length.

8. The RNAi oligonucleotide of any one of claims 5 to 7, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein

(i) S1 is complementary to S2, optionally wherein S1 and S2 are each 1-10 nucleotides in length and have the same length, optionally wherein S1 and S2 are each 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, further optionally wherein S1 and S2 are 6 nucleotides in length; and

(ii) L forms a loop between S1 and S2 of 3-5 nucleotides in length, optionally wherein L is a triloop or a tetraloop, optionally wherein the tetraloop comprises the sequence 5'-GAAA-3', optionally wherein the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 1681).

9. The RNAi oligonucleotide of any one of claims 5 to 8, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands, optionally wherein:

(a) each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide or lipid;

(b) the stem loop comprises one or more targeting ligands conjugated to one or more nucleotides of the stem loop;

(c) the one or more targeting ligands is conjugated to one or more nucleotides of the loop, optionally wherein the loop comprises 4 nucleotides numbered 1-4 from 5' to 3', wherein nucleotides at positions 2, 3, and 4 each comprise one or more targeting ligands, wherein the targeting ligands are the same or different;

(d) the targeting ligand is a hepatocyte targeting ligand and each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety, optionally wherein the GalNAc moiety

is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety; and/or

(e) the targeting ligand is a hepatocyte targeting ligand and up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

10. The RNAi oligonucleotide of any one of claims 5 to 9, wherein:

(i) the oligonucleotide comprises at least one modified nucleotide, optionally wherein the modified nucleotide comprises a 2'-modification, optionally wherein:

(a) the 2'-modification is a modification selected from 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid, optionally wherein the modification is selected from 2'-fluoro and 2'-O-methyl, optionally wherein all nucleotides of the oligonucleotide are modified, wherein the modification is 2'-fluoro and 2'-O-methyl;

(b) about 10-15%, 10%, 11%, 12%, 13%, 14%, or 15% of the nucleotides of the sense strand comprise a 2'-fluoro modification;

(c) about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, or 35% of the nucleotides of the antisense strand comprise a 2'-fluoro modification;

(d) about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, or 35% of the nucleotides of the oligonucleotide comprise a 2'-fluoro modification;

(e) the sense strand comprises 36 nucleotides with positions 1-36 from 5' to 3', wherein positions 8-11 comprise a 2'-fluoro modification;

(f) the antisense strand comprises 22 nucleotides with positions 1-22 from 5' to 3', and wherein positions 2, 3, 4, 5, 7, 10, and 14 comprise a 2'-fluoro modification; and/or

(g) the remaining nucleotides comprise a 2'-O-methyl modification, and/or

(ii) the oligonucleotide comprises at least one modified internucleotide linkage, optionally wherein the at least one modified internucleotide linkage is a phosphorothioate linkage, optionally wherein:

(a) the antisense strand comprises a phosphorothioate linkage (i) between positions 1 and 2, and between positions 2 and 3; or (ii) between positions 1 and 2, between positions 2 and 3, and between positions 3 and 4, wherein positions are numbered 1-4 from 5' to 3'; and/or

(b) the antisense strand is 22 nucleotides in length, and wherein the antisense strand comprises a phosphorothioate linkage between positions 20 and 21 and between positions 21 and 22, wherein positions are numbered 1-22 from 5' to 3', and/or

(iii) the antisense strand comprises a phosphorylated nucleotide at the 5' terminus, wherein the phosphorylated nucleotide is selected from uridine and adenosine, optionally wherein the phosphorylated nucleotide is uridine, and/or

(iv) the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, optionally wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate, optionally wherein the phosphate analog is a 4'-phosphate analog comprising 5'-methoxyphosphonate-4'-oxy, and/or

(v) the antisense strand comprises an overhang sequence of one or more nucleotides in length at the 3' terminus, optionally wherein the overhang comprises purine nucleotides, optionally wherein the overhang sequence is 2 nucleotides in length, optionally wherein the overhang is selected from AA, GG, AG, and GA, optionally wherein the overhang is GG.

11. The RNAi oligonucleotide of any one of claims 5 to 10, wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1537 and 1573, respectively;
- (b) SEQ ID NOs: 1538 and 1574, respectively;
- (c) SEQ ID NOs: 1539 and 1575, respectively;
- (d) SEQ ID NOs: 1540 and 1576, respectively;
- (e) SEQ ID NOs: 1541 and 1577, respectively;
- (f) SEQ ID NOs: 1542 and 1578, respectively;
- (g) SEQ ID NOs: 1543 and 1579, respectively;
- (h) SEQ ID NOs: 1544 and 1580, respectively;
- (i) SEQ ID NOs: 1545 and 1581, respectively;
- (j) SEQ ID NOs: 1546 and 1582, respectively;
- (k) SEQ ID NOs: 1547 and 1583, respectively;
- (l) SEQ ID NOs: 1548 and 1584, respectively;
- (m) SEQ ID NOs: 1549 and 1585, respectively;
- (n) SEQ ID NOs: 1550 and 1586, respectively;
- (o) SEQ ID NOs: 1551 and 1587, respectively;
- (p) SEQ ID NOs: 1552 and 1588, respectively;
- (q) SEQ ID NOs: 1553 and 1589, respectively;
- (r) SEQ ID NOs: 1554 and 1590, respectively;
- (s) SEQ ID NOs: 1555 and 1591, respectively;
- (t) SEQ ID NOs: 1556 and 1592, respectively;

- (u) SEQ ID NOs: 1557 and 1593, respectively;
 - (v) SEQ ID NOs: 1558 and 1594, respectively;
 - (w) SEQ ID NOs: 1559 and 1595, respectively;
 - (x) SEQ ID NOs: 1560 and 1596, respectively;
 - (y) SEQ ID NOs: 1561 and 1597, respectively;
 - (z) SEQ ID NOs: 1562 and 1598, respectively;
 - (aa) SEQ ID NOs: 1563 and 1599, respectively;
 - (bb) SEQ ID NOs: 1564 and 1600, respectively;
 - (cc) SEQ ID NOs: 1565 and 1601, respectively;
 - (dd) SEQ ID NOs: 1566 and 1602, respectively;
 - (ee) SEQ ID NOs: 1567 and 1603, respectively;
 - (ff) SEQ ID NOs: 1568 and 1604, respectively;
 - (gg) SEQ ID NOs: 1569 and 1605, respectively; and,
 - (hh) SEQ ID NOs: 1570 and 1606, respectively; or,
- wherein the sense and antisense strands comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1609 and 1645, respectively;
- (b) SEQ ID NOs: 1610 and 1646, respectively;
- (c) SEQ ID NOs: 1611 and 1647, respectively;
- (d) SEQ ID NOs: 1612 and 1648, respectively;
- (e) SEQ ID NOs: 1613 and 1649, respectively;
- (f) SEQ ID NOs: 1614 and 1650, respectively;
- (g) SEQ ID NOs: 1615 and 1651, respectively;
- (h) SEQ ID NOs: 1616 and 1652, respectively;
- (i) SEQ ID NOs: 1617 and 1653, respectively;
- (j) SEQ ID NOs: 1618 and 1654, respectively;
- (k) SEQ ID NOs: 1619 and 1655, respectively;
- (l) SEQ ID NOs: 1620 and 1656, respectively;
- (m) SEQ ID NOs: 1621 and 1657, respectively;
- (n) SEQ ID NOs: 1622 and 1658, respectively;
- (o) SEQ ID NOs: 1623 and 1659, respectively;
- (p) SEQ ID NOs: 1624 and 1660, respectively;
- (q) SEQ ID NOs: 1625 and 1661, respectively;
- (r) SEQ ID NOs: 1626 and 1662, respectively;

- (s) SEQ ID NOs: 1627 and 1663, respectively;
- (t) SEQ ID NOs: 1628 and 1664, respectively;
- (u) SEQ ID NOs: 1628 and 1665, respectively;
- (v) SEQ ID NOs: 1630 and 1666, respectively;
- (w) SEQ ID NOs: 1631 and 1667, respectively;
- (x) SEQ ID NOs: 1632 and 1668, respectively;
- (y) SEQ ID NOs: 1633 and 1669, respectively;
- (z) SEQ ID NOs: 1634 and 1670, respectively;
- (aa) SEQ ID NOs: 1635 and 1671, respectively;
- (bb) SEQ ID NOs: 1636 and 1672, respectively;
- (cc) SEQ ID NOs: 1637 and 1673, respectively;
- (dd) SEQ ID NOs: 1638 and 1674, respectively;
- (ee) SEQ ID NOs: 1639 and 1675, respectively;
- (ff) SEQ ID NOs: 1640 and 1676, respectively;
- (gg) SEQ ID NOs: 1641 and 1677, respectively; and,
- (hh) SEQ ID NOs: 1642 and 1678, respectively.

12. A double stranded RNAi oligonucleotide (dsRNAi) for inhibiting expression of MARC1, wherein said dsRNAi comprises a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, and wherein

- (i) the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1615 and 1651, respectively;
- (ii) the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1632 and 1668, respectively;
- (iii) the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1640 and 1676, respectively; or
- (iv) the sense and antisense strands comprise the nucleotide sequences set forth in SEQ ID NOs: 1625 and 1661, respectively.

13. A pharmaceutical composition comprising the RNAi oligonucleotide of any one of claims 1-12, and a pharmaceutically acceptable carrier, delivery agent or excipient.

14. Use of the RNAi oligonucleotide of any one of claims 1 to 12, or the pharmaceutical composition of claim 13, as a medicament for the treatment of a disease, disorder or

condition associated with MARC1 expression, optionally for the treatment of a disease or condition associated with MARC1 expression in hepatocytes.

15. Use of the RNAi oligonucleotide of claim 14, as a medicament for the treatment of a disease selected from the group consisting of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and alcoholic steatohepatitis (ASH).