

SARM1 RNA INTERFERENCE AGENTS**SEQUENCE LISTING**

[0001] The present application is being filed along with a Sequence Listing in ST.26 XML format. The Sequence Listing is provided as a file titled “30243” created 13-Jan-2023 and is 361 kilobytes in size. The Sequence Listing information in the ST.26 XML format is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Axon degeneration is a pathological feature of many neurological diseases including peripheral neuropathies, traumatic brain injury, and neurodegenerative diseases (Gerdtts et al., *Science*, 2015, 348:453-457). Damaged or unhealthy axons are eliminated by an intrinsic self-destruction program known as Wallerian degeneration, which is an active process of retrograde degeneration of the distal end of an axon while keeping the proximal axon segment and cell body intact (Gerdtts, J., et al., *Neuron*, 2016, 89, 449-460; Whitmore, A. et al., *Cell Death Differ.*, 2003, 10, 260-261).

[0003] SARM1 (sterile alpha and TIR motif containing 1) is a NAD⁺ hydrolase that plays an important role in axon degeneration. It has been reported that knocking-down or eliminating the expression of SARM1 leads to long-lasting protection of sensory neurons against injury-induced axonal degeneration (Gerdtts et al., *J Neurosci*, 2013, 33, 13569-13580). WO2021/108602 describes SARM1 antisense oligonucleotides.

[0004] RNA interference (RNAi) is a highly conserved regulatory mechanism in which RNA molecules are involved in sequence-specific suppression of gene expression by double-stranded RNA molecules (dsRNA) (Fire et al., *Nature* 391:806-811, 1998).

[0005] There remains a need for therapeutic agents that can inhibit or adjust the expression of SARM1 for treating SARM1-mediated neurological diseases e.g., by utilizing RNAi.

SUMMARY OF INVENTION

[0006] Provided herein are SARM1 RNAi agents and compositions comprising a SARM1 RNAi agent. Also provided herein are methods of using the SARM1 RNAi agents or compositions

comprising a SARM1 RNAi agent for reducing SARM1 expression, reducing axon degeneration, and/or treating SARM1-mediated neurological diseases in a subject.

[0007] In one aspect, provided herein are SARM1 RNAi agents having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 1, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 2;
- (b) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 4;
- (c) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 6;
- (d) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 8;
- (e) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 10; and
- (f) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 12,

wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[0008] In some embodiments, the sense strand and the antisense strand of the SARM1 RNAi agent described herein comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 1, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 2;
 - (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 4;
 - (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 6;
 - (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 8;
 - (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 10; and
 - (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 12,
- wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[0009] In some embodiments, the sense strand and the antisense strand of the SARM1 RNAi agent described herein have a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 1, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 2;
- (b) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 3, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 4;
- (c) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 5, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 6;
- (d) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 8;

(e) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 10; and

(f) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 12.

[00010] The SARM1 RNAi agents described herein may include modifications. The modifications can be made to one or more nucleotides of the sense strand and/or antisense strand or to the internucleotide linkages. In some embodiments, one or more nucleotides of the sense strand are modified nucleotides. In some embodiments, each nucleotide of the sense strand is a modified nucleotide. In some embodiments, one or more nucleotides of the antisense strand are modified nucleotides. In some embodiments, each nucleotide of the antisense strand is a modified nucleotide. In some embodiments, the modified nucleotide is a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, or 2'-O-alkyl modified nucleotide, e.g., 2'-O-C12-16 alkyl modified nucleotide. In some embodiments, the sense strand has four 2'-fluoro modified nucleotides at positions 7, 9, 10, and 11 from the 5' end of the sense strand. In some embodiments, nucleotides at positions other than positions 7, 9, 10, and 11 of the sense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has four 2'-fluoro modified nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand. In some embodiments, nucleotides at positions other than positions 2, 6, 14 and 16 of the antisense strand are 2'-O-methyl modified nucleotides. In some embodiments, the sense strand has three 2'-fluoro modified nucleotides at positions 9, 10, and 11 from the 5' end of the sense strand. In some embodiments, the nucleotides at positions other than positions 9, 10, and 11 of the sense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has five 2'-fluoro modified nucleotides at positions 2, 5, 7, 14, and 16 from the 5' end of the antisense strand. In some embodiments, the nucleotides at positions other than positions 2, 5, 7, 14, and 16 of the antisense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has five 2'-fluoro modified nucleotides at positions 2, 5, 8, 14, and 16 from the 5' end of the antisense strand. In some embodiments, the nucleotides at positions other than positions 2, 5, 8, 14, and 16 of the antisense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has five 2'-fluoro modified nucleotides at positions 2, 3,

7, 14, and 16 from the 5' end of the antisense strand. In some embodiments, the nucleotides at positions other than positions 2, 3, 7, 14, and 16 of the antisense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has two 2'-fluoro modified nucleotides at positions 2 and 14 from the 5' end of the antisense strand. In some embodiments, the nucleotides at positions other than positions 2 and 14 of the antisense strand are 2'-O-methyl modified nucleotides.

[00011] In some embodiments, the first nucleotide from the 5' end of the antisense strand is a modified nucleotide that has a phosphate analog, e.g., a 5'-vinylphosphonate. In some embodiments, the first nucleotide from the 5' end of the antisense strand has a 5' phosphate. In some embodiments, the sense strand comprises an abasic moiety or inverted abasic moiety.

[00012] In some embodiments, the sense strand and the antisense strand have one or more modified internucleotide linkages, e.g., phosphorothioate linkage. In some embodiments, the sense strand has four or five phosphorothioate linkages. In some embodiments, the antisense strand has four or five phosphorothioate linkages. In some embodiments, the sense strand has four phosphorothioate linkages and the antisense strand has four phosphorothioate linkages.

[00013] In some embodiments, provided herein are SARM1 RNAi agents having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 14;
- (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16;
- (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 18;
- (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 20;
- (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 22;
- (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 24;

- (g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 27;
- (h) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 29;
- (i) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 30;
- (j) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 31;
- (k) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 32;
- (l) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 33;
- (m) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 35;
- (n) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 36;
- (o) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 37;
- (p) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 38;
- (q) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 39;
- (r) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 41;
- (s) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 42;
- (t) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 43;
- (u) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 44;
- (v) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and

the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 45;

(w) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and

the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 46; and

(x) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 47.

[00014] In some embodiments, provided herein are SARM1 RNAi agents having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, wherein the sense strand and the antisense strand have a pair of nucleic acid sequences selected from the group consisting of:

(a) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 14;

(b) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 16;

(c) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 18;

(d) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 20;

(e) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 22;

(f) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 24;

(g) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 27;

(h) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid

sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 29;

(i) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 30;

(j) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 31;

(k) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 32;

(l) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 33;

(m) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 35;

(n) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 36;

(o) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 37;

(p) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 38;

(q) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 39;

(r) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid

sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 41;

(s) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 42;

(t) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 43;

(u) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 44;

(v) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 45;

(w) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 46; and

(x) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 47.

[00015] In some embodiments, the sense strand of the SARM1 RNAi agent has a delivery moiety. In some embodiments, the sense strand of the SARM1 RNAi agent has a delivery moiety conjugated to the 3' end of the sense strand. In some embodiments, the sense strand of the SARM1 RNAi agent has a delivery moiety conjugated to the 5' end of the sense strand. In some embodiments, the sense strand of the SARM1 RNAi agent has delivery moieties conjugated to both the 5' end and the 3' end of the sense strand. In some embodiments, the sense strand of the SARM1 RNAi agent has a delivery moiety conjugated to a nucleotide of the sense strand. In some embodiments, the delivery moiety is a-tocopherol, palmitic acid, or another moiety in Table 4. In some embodiments, the delivery moiety is conjugated to the 5' or 3' end of the sense strand via a linker, e.g., a linker of Table 5. In some embodiments, the SARM1 RNAi agent is not a lipid conjugate. In some embodiments, the SARM1 RNAi agent has no delivery moiety.

[00016] In a further aspect, provided herein are SARM1 RNAi agents of Formula (I): R-L-D, wherein R is a double stranded RNA (dsRNA) having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex; wherein D is a delivery means (e.g., delivery moiety) for delivering the dsRNA into a cell; and wherein L is a linking means (e.g., linker) for linking the dsRNA to the delivery means, or optionally absent, wherein the sense strand and the antisense strand comprises a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 1, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 2;
 - (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 4;
 - (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 6;
 - (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 8;
 - (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 10; and
 - (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 12,
- wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00017] In some embodiments, provided herein are SARM1 RNAi agents of Formula (I): R-L-D, wherein R is a dsRNA having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex; wherein D is a delivery means (e.g., a delivery moiety) for delivering the dsRNA into a cell; and wherein L is a linking means (e.g., a linker) for linking the dsRNA to the delivery means, or optionally absent, wherein the sense strand and the antisense strand have a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 1, and the antisense strand has (e.g., consist of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 2;
 - (b) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 3, and the antisense strand has (e.g., consist of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 4;
 - (c) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 5, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 6;
 - (d) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 8;
 - (e) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 10; and
 - (f) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 12,
- wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00018] In some embodiments, provided herein are SARM1 RNAi agents of Formula (I): R-L-D, wherein R is a dsRNA having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex; wherein D is a delivery means (e.g., delivery moiety) for delivering the dsRNA into a cell; and wherein L is a linking means (e.g., linker) for linking the dsRNA to the delivery means, or optionally absent, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 14;

- (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16;
- (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 18;
- (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 20;
- (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 22;
- (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 24;
- (g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 27;
- (h) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 29;
- (i) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 30;
- (j) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 31;
- (k) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 32;
- (l) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 33;
- (m) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 35;
- (n) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 36;
- (o) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 37;
- (p) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 38;
- (q) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and

the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 39;

(r) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 41;

(s) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 42;

(t) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 43;

(u) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 44;

(v) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 45;

(w) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 46; and

(x) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 47.

[00019] In some embodiments, provided herein are SARM1 RNAi agents of Formula (I): R-L-D, wherein R is a dsRNA having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex; wherein D is a delivery means (e.g., delivery moiety) for delivering the dsRNA into a cell; and wherein L is a linking means (e.g., linker) for linking the dsRNA to the delivery means, or optionally absent, wherein the sense strand and the antisense strand have a pair of nucleic acid sequences selected from the group consisting of:

(a) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 14;

(b) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 16;

(c) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 18;

(d) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid

sequence of SEQ ID NO: 19, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 20;

(e) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 22; and

(f) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 24;

(e) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 27;

(f) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 29;

(g) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 30;

(h) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 31;

(i) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 32;

(j) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 33;

(k) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 35;

(l) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid

sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 36;

(m) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 37;

(n) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 38;

(o) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 39;

(p) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 41;

(q) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 42;

(r) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 43;

(s) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 44;

(t) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 45;

(u) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 46; and

(v) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid

sequence of SEQ ID NO: 23, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 47.

[00020] In another aspect, provided herein are pharmaceutical compositions comprising a SARM1 RNAi agent described herein and a pharmaceutically acceptable carrier. Also provided herein are pharmaceutical compositions comprising a means for reducing SARM1 expression in a cell and a pharmaceutically acceptable carrier.

[00021] In another aspect, provided herein are methods of reducing SARM1 expression in a patient in need thereof, and such method comprises administering to the patient an effective amount of a SARM1 RNAi agent or a pharmaceutical composition described herein.

[00022] In another aspect, provided herein are methods of reducing axon degeneration in a patient in need thereof, and such method comprises administering to the patient an effective amount of a SARM1 RNAi agent or a pharmaceutical composition described herein.

[00023] In another aspect, provided herein are methods of treating a SARM1-mediated neurological disease in a patient in need thereof, and such method comprises administering to the patient an effective amount of the SARM1 RNAi agent or a pharmaceutical composition described herein.

[00024] Also provided herein are methods of reducing SARM1 expression in a cell (e.g., a neuron), and such methods can include introducing a SARM1 RNAi agent described herein into the cell; and incubating the cell for a time sufficient for degradation of SARM1 mRNA, thereby reducing SARM1 expression in the cell.

[00025] In another aspect, provided herein are SARM1 RNAi agents or pharmaceutical compositions comprising a SARM1 RNAi agent for use in reducing SARM1 expression. In another aspect, provided herein are SARM1 RNAi agents or pharmaceutical compositions comprising a SARM1 RNAi agent for use in reducing axon degeneration. Also provided herein are SARM1 RNAi agents or the pharmaceutical composition comprising a SARM1 RNAi agent for use in a therapy. Also provided are SARM1 RNAi agents or pharmaceutical compositions comprising a SARM1 RNAi agent for use in the treatment of a SARM1-mediated neurological disease. Also provided herein are uses of SARM1 RNAi agents in the manufacture of a medicament for reducing axon degeneration. Also provided herein are uses of SARM1 RNAi agents in the manufacture of a medicament for the treatment of a SARM1-mediated neurological disease.

DETAILED DESCRIPTION

[00026] Provided herein are SARM1 RNAi agents and compositions comprising a SARM1 RNAi agent. Also provided herein are methods of using the SARM1 RNAi agents or compositions comprising a SARM1 RNAi agent for reducing SARM1 expression, reducing axon degeneration and/or treating SARM1-mediated neurological disease in a subject.

[00027] In some embodiments, provided herein are SARM1 RNAi agents having a sense strand and an antisense strand, and the sense strand and the antisense strand form a duplex. The antisense strand is complementary to a region of SARM1 mRNA. In a further embodiment, the sense strand and the antisense strand are each 15-30 nucleotides in length, e.g., 20-25 nucleotides in length. In some embodiments, provided herein are SARM1 RNAi agents having a sense strand of 21 nucleotides and an antisense strand of 23 nucleotides. In some embodiments, the sense strand and antisense strand of the SARM1 RNAi agent may have overhangs at either the 5' end or the 3' end (i.e., 5' overhang or 3' overhang). For example, the sense strand and the antisense strand may have 5' or 3' overhangs of 1 to 5 nucleotides or 1 to 3 nucleotides. In some embodiments, the antisense strand comprises a 3' overhang of two nucleotides. In some embodiments, the sense strand and antisense strand sequences of the SARM1 RNAi agents are provided in Table 1.

[00028] Provided herein are SARM1 RNAi agents having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 1, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 2;
- (b) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 4;
- (c) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 6;

- (d) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 8;
 - (e) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 10; and
 - (f) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 12,
- wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00029] Provided herein are SARM1 RNAi agents having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 1, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 2;
- (b) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 4;
- (c) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 6;
- (d) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 8;
- (e) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 10; and

(f) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 12, wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00030] In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 1, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 2, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 4, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 6, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 7, and the antisense

strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 8, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 10, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 12, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

Table 1. Unmodified Nucleic Acid Sequences of SARM1 RNAi Agents

SARM1 RNAi Agent No.	Sense Strand (5' to 3')	SEQ ID NO	Antisense Strand (5' to 3')	SEQ ID NO	Start position of antisense strand target region of human SARM1 transcript NM_015077.4*
1	GUUGCUCGACUCUAA CCGCUA	1	UAGCGGUUAGAGUCGAGC AACGG	2	1333
2	UUCGCCAACUAUUCU ACGUGA	3	UCACGUAGAAUAGUUGGC GAAGG	4	1763
3	ACCUUCGCCAACUAU UCUACA	5	UGUAGAAUAGUUGGCGA AGGUCU	6	1760
4	CGCCAACUAUUCUAC GUGCGA	7	UCGCACGUAGAAUAGUUG GCGAA	8	1765
5	CCGCAAGAGGUUCUU UAGGGA	9	UCCCUAAAGAACCUCUUG CGGGU	10	1723
6	AAACGCCUGGUUCC UACUCA	11	UGAGUAGGAAACCAGGCG UUUCA	12	1460

*Nucleotides 2-23 of the antisense strand are complementary to human SARM1 mRNA.

[00031] In some embodiments, the sense strand and the antisense strand of the SARM1 RNAi agent described herein comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 1, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 2;
- (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 4;
- (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 6;
- (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 8;

- (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 10; and
- (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 12, wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00032] In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 1, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 2, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 4, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 6, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 8, wherein one or more nucleotides of the sense strand and the

antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 10, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 12, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00033] In some embodiments, the sense strand and the antisense strand of the SARM1 RNAi agent described herein have a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 1, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 2;
- (b) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 3, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 4;
- (c) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 5, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 6;
- (d) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 8;

(e) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 10; and

(f) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 12,

wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00034] In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 1, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 2, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 3, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 4, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 5, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 6, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand has a second

nucleic acid sequence of SEQ ID NO: 8, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 10, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 12, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00035] The SARM1 RNAi agents described herein may include modifications. The modifications can be made to one or more nucleotides of the sense strand and/or antisense strand or to the internucleotide linkages, which are the bonds between two nucleotides in the sense or antisense strand. For example, some 2'-modifications of ribose or deoxyribose can increase RNA or DNA stability and half-life. Such 2'-modifications can be 2'-fluoro, 2'-O-methyl (i.e., 2'-methoxy), 2'-O-alkyl, or 2'-O-methoxyethyl (2'-O-MOE).

[00036] In some embodiments, one or more nucleotides of the sense strand and/or the antisense strand are independently modified nucleotides, which means the sense strand and the antisense strand can have different modified nucleotides. In some embodiments, one or more nucleotides of the sense strand are modified nucleotides. In some embodiments, each nucleotide of the sense strand is a modified nucleotide. In some embodiments, one or more nucleotides of the antisense strand are modified nucleotides. In some embodiments, each nucleotide of the antisense strand is a modified nucleotide. In some embodiments, the modified nucleotide is a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, or 2'-O-alkyl modified nucleotide, e.g., 2'-O-C₁₂₋₁₆ alkyl modified nucleotide. In some embodiments, each nucleotide of the sense

strand and the antisense strand is independently a modified nucleotide, e.g., a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, or 2'-O-alkyl modified nucleotide, e.g., 2'-O-C₁₂₋₁₆ alkyl modified nucleotide.

[00037] In some embodiments, the sense strand has four 2'-fluoro modified nucleotides, e.g., at positions 7, 9, 10, and 11 from the 5' end of the sense strand. In some embodiments, nucleotides at positions other than positions 7, 9, 10, and 11 of the sense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has four 2'-fluoro modified nucleotides, e.g., at positions 2, 6, 14, and 16 from the 5' end of the antisense strand. In some embodiments, nucleotides at positions other than positions 2, 6, 14 and 16 of the antisense strand are 2'-O-methyl modified nucleotides. In some embodiments, the sense strand has three 2'-fluoro modified nucleotides at positions 9, 10, and 11 from the 5' end of the sense strand. In some embodiments, the nucleotides at positions other than positions 9, 10, and 11 of the sense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has five 2'-fluoro modified nucleotides at positions 2, 5, 7, 14, and 16 from the 5' end of the antisense strand. In some embodiments, the nucleotides at positions other than positions 2, 5, 7, 14, and 16 of the antisense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has five 2'-fluoro modified nucleotides at positions 2, 5, 8, 14, and 16 from the 5' end of the antisense strand. In some embodiments, the nucleotides at positions other than positions 2, 5, 8, 14, and 16 of the antisense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has five 2'-fluoro modified nucleotides at positions 2, 3, 7, 14, and 16 from the 5' end of the antisense strand. In some embodiments, the nucleotides at positions other than positions 2, 3, 7, 14, and 16 of the antisense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has two 2'-fluoro modified nucleotides at positions 2 and 14 from the 5' end of the antisense strand. In some embodiments, the nucleotides at positions other than positions 2 and 14 of the antisense strand are 2'-O-methyl modified nucleotides.

[00038] In some embodiments, the modified nucleotide is a 2'-O-alkyl modified nucleotide, e.g., 2'-O-C₁₂₋₁₆ alkyl modified nucleotide, which can serve as a delivery moiety. In some embodiments, the 2'-O-alkyl modified nucleotide is a 2'-O-hexadecyl uridine, 2'-O-hexadecyl cytidine, 2'-O-hexadecyl guanine, or 2'-O-hexadecyl adenosine. In some

embodiments, 2'-O-hexadecyl uridine, 2'-O-hexadecyl cytidine, 2'-O-hexadecyl guanine, or 2'-O-hexadecyl adenosine is a modified nucleotide in the sense strand.

[00039] In some embodiments, the first nucleotide from the 5' end of the antisense strand is a modified nucleotide that has a phosphate analog, e.g., 5'-vinylphosphonate (5'-VP). In some embodiments, the first nucleotide from the 5' end of the antisense strand has a 5' phosphate.

[00040] In some embodiments, the sense strand comprises an abasic moiety or inverted abasic moiety, e.g., a moiety shown in Table 3.

[00041] In some embodiments, the sense strand and the antisense strand have one or more modified internucleotide linkages. In some embodiments, the modified internucleotide linkage is phosphorothioate linkage. In some embodiments, the sense strand has four or five phosphorothioate linkages. In some embodiments, the antisense strand has four or five phosphorothioate linkages. In some embodiments, the sense strand and the antisense strand each has four or five phosphorothioate linkages. In some embodiments, the sense strand has four phosphorothioate linkages and the antisense strand has four phosphorothioate linkages.

[00042] In a further aspect, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 14;
- (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16;
- (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 18;
- (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 20;
- (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 22;
- (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 24;
- (g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and

the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 27;

(h) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 29;

(i) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 30;

(j) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 31;

(k) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 32;

(l) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 33;

(m) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 35;

(n) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 36;

(o) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 37;

(p) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 38;

(q) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 39;

(r) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 41;

(s) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 42;

(t) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 43;

(u) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 44;

(v) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 45;

- (w) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 46; and
- (x) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 47.

[00043] In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 14. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 18. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 20. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 22. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 24. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 27. In some embodiments, provided herein are SARM1 RNAi

agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 29. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 30. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 31. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 32. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 33. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 35. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 36. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 37. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense

strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 38. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 39. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 41. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 42. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 43. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 44. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 45. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 46. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of

SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 47.

[00044] In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, wherein the sense strand and the antisense strand have a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 14;
- (b) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 16;
- (c) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 18;
- (d) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 20;
- (e) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 22;
- (f) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 24;
- (g) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 27;
- (h) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 29;
- (i) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid

sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 30;

(j) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 31;

(k) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid

(l) sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 32;

(m) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 33;

(n) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 35;

(o) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 36;

(p) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 37;

(q) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 38;

(r) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 39;

(s) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 41;

(t) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid

sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 42;

(u) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 43;

(v) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 44;

(v) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 45;

(w) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 46; and

(x) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 47.

[00045] In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 14. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 18. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand has a second

nucleic acid sequence of SEQ ID NO: 20. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 22. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 24. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 27. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 29. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 30. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 31. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 32. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 33. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence

of SEQ ID NO: 34, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 35. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 36. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 37. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 38. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 39. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 41. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 42. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 43. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 44. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein

the sense strand has a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 45. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 46. In some embodiments, provided herein are SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 47.

Table 2: SARM1 RNAi Agents with Modifications

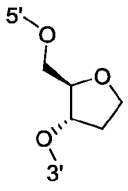
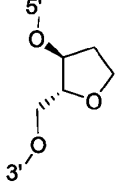
SARM1 RNAi Agent No.	Strand	Sequence from 5' to 3' end	SEQ ID NO
13	S	mG*mU*mUmGmCmUfCmGfAfCfUmCmUmAmAmCmCmGmC*mU*mA	13
	AS	VPmU*fA*mGmCmGfGmUmUmAmGmAmGmUfCmGfAmGmCmAmAmC*mG*mG	14
14	S	mU*mU*mCmGmCmCfAmAfCfUfAmUmUmCmUmAmCmGmU*mG*mA	15
	AS	VPmU*fC*mAmCmGfUmAmGmAmAmUmAmGfUmUfGmGmCmGmAmA*mG*mG	16
15	S	mA*mC*mCmUmUmCfGmCfCfAfAmCmUmAmUmUmCmUmA*mC*mA	17
	AS	VPmU*fG*mUmAmGfAmAmUmAmGmUmUmGfGmCfGmAmAmGmGmU*mC*mU	18
16	S	mC*mG*mCmCmAmAfCmUfAfUfUmCmUmAmCmGmUmGmC*mG*mA	19
	AS	VPmU*fC*mGmCmAfCmGmUmAmGmAmAmUfAmGfUmUmGmGmCmG*mA*mA	20
17	S	mC*mC*mGmCmAmAfGmAfGfGfUmUmCmUmUmUmAmGmG*mG*mA	21
	AS	VPmU*fC*mCmCmUfAmAmAmGmAmAmCmCfUmCfUmUmGmCmGmG*mG*mU	22
18	S	mA*mA*mAmCmGmCfCmUfGfGfUmUmUmCmCmUmAmCmU*mC*mA	23
	AS	VPmU*fG*mAmGmUfAmGmGmAmAmAmCmCfAmGfGmCmGmUmUmU*mC*mA	24
19	S	mU*mU*mCmGmCmCmAmAfCfUfAmUmUmCmUmAmCmGmU*mG*mA	28

	AS	mU*fC*mAmCfGmUfAmGmAmAmUmAmGfUmUfGmGmCmGmAmA*mG*mG	29
20	S	mU*mU*mCmGmCmCmAmAfCfUfAmUmUmCmUmAmCmGmU*mG*mA	28
	AS	mU*fC*fAmCmGmUfAmGmAmAmUmAmGfUmUfGmGmCmGmAmA*mG*mG	30
21	S	mU*mU*mCmGmCmCmAmAfCfUfAmUmUmCmUmAmCmGmU*mG*mA	28
	AS	mU*fC*mAmCfGmUmAfGmAmAmUmAmGfUmUfGmGmCmGmAmA*mG*mG	31
22	S	mU*mU*mCmGmCmCmAmAfCfUfAmUmUmCmUmAmCmGmU*mG*mA	28
	AS	mU*fC*mAmCmGmUmAmGmAmAmUmAmGfUmUmGmGmCmGmAmA*mG*mG	32
23	S	mG*mU*mUmGmCmUmCmGfAfCfUmCmUmAmAmCmCmGmC*mU*mA	34
	AS	mU*fA*mGmCfGmGfUmUmAmGmAmGmUfCmGfAmGmCmAmAmC*mG*mG	35
24	S	mG*mU*mUmGmCmUmCmGfAfCfUmCmUmAmAmCmCmGmC*mU*mA	34
	AS	mU*fA*fGmCmGmGfUmUmAmGmAmGmUfCmGfAmGmCmAmAmC*mG*mG	36
25	S	mG*mU*mUmGmCmUmCmGfAfCfUmCmUmAmAmCmCmGmC*mU*mA	34
	AS	mU*fA*mGmCfGmGmUfUmAmGmAmGmUfCmGfAmGmCmAmAmC*mG*mG	37
26	S	mG*mU*mUmGmCmUmCmGfAfCfUmCmUmAmAmCmCmGmC*mU*mA	34
	AS	mU*fA*mGmCmGmGmUmUmAmGmAmGmUfCmGmAmGmCmAmAmC*mG*mG	38
27	S	mC*mC*mGmCmAmAmGmAfGfGfUmUmCmUmUmUmAmGmG*mG*mA	40
	AS	mU*fC*mCmCfUmAfAmAmGmAmAmCmCfUmCfUmUmGmCmGmG*mG*mU	41
28	S	mC*mC*mGmCmAmAmGmAfGfGfUmUmCmUmUmUmAmGmG*mG*mA	40
	AS	mU*fC*fCmCmUmAfAmAmGmAmAmCmCfUmCfUmUmGmCmGmG*mG*mU	42
29	S	mC*mC*mGmCmAmAmGmAfGfGfUmUmCmUmUmUmAmGmG*mG*mA	40
	AS	mU*fC*mCmCfUmAmAfAmGmAmAmCmCfUmCfUmUmGmCmGmG*mG*mU	43
30	S	mC*mC*mGmCmAmAmGmAfGfGfUmUmCmUmUmUmAmGmG*mG*mA	40
	AS	mU*fC*mCmCmUmAmAmAmGmAmAmCmCfUmCmUmUmGmCmGmG*mG*mU	44

7	S	mG*mU*mUmGmCmUfCmGfAfCfUmCmUmAmAmCmCmGmC*mU*mA	13
	AS	mU*fA*mGmCmGfGmUmUmAmGmAmGmUfCmGfAmGmCmAmAmC*mG*mG	33
8	S	mU*mU*mCmGmCmCfAmAfCfUfAmUmUmCmUmAmCmGmU*mG*mA	15
	AS	mU*fC*mAmCmGfUmAmGmAmAmUmAmGfUmUfGmGmCmGmAmA*mG*mG	27
9	S	mA*mC*mCmUmUmCfGmCfCfAfAmCmUmAmUmUmCmUmA*mC*mA	17
	AS	mU*fG*mUmAmGfAmAmUmAmGmUmUmGfGmCfGmAmAmGmGmU*mC*mU	45
10	S	mC*mG*mCmCmAmAfCmUfAfUfUmCmUmAmCmGmUmGmC*mG*mA	19
	AS	mU*fC*mGmCmAfCmGmUmAmGmAmAmUfAmGfUmUmGmGmCmG*mA*mA	46
11	S	mC*mC*mGmCmAmAfGmAfGfGfUmUmCmUmUmUmAmGmG*mG*mA	21
	AS	mU*fC*mCmCmUfAmAmAmGmAmAmCmCfUmCfUmUmGmCmGmG*mG*mU	39
12	S	mA*mA*mAmCmGmCfCmUfGfGfUmUmUmCmCmUmAmCmU*mC*mA	23
	AS	mU*fG*mAmGmUfAmGmGmAmAmAmCmCfAmGfGmCmGmUmUmU*mC*mA	47

Abbreviations – “m” indicates 2’-OMe; “f” indicates 2’-fluoro; “*” indicates phosphorothioate linkage; “VP” indicates 5’-vinylphosphonate; “S” means the sense strand; “AS” means the antisense strand; unless otherwise noted, the 5’ position of the AS can include 5’-phosphate or 5’-vinylphosphonate.

Table 3. Abasic or inverted abasic (iAb) moieties

	Structure
1 (abasic)	
2 (iAb)	

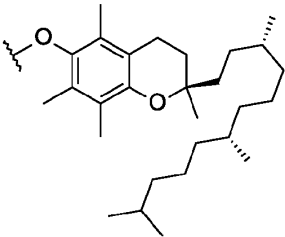
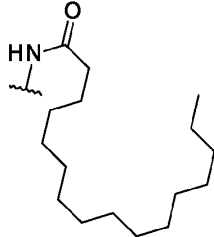
“5’” and “3’” indicate the 5’ to 3’ direction of the sequences.

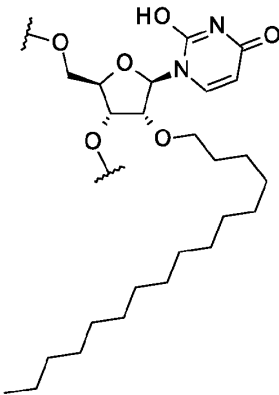
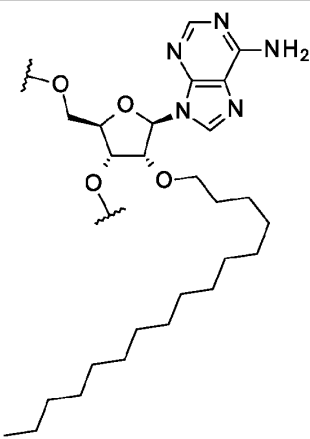
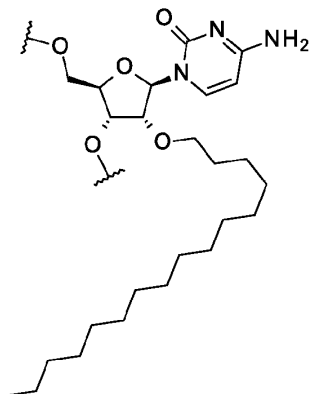
[00046] In some embodiments, the sense strand of the SARM1 RNAi agent has a delivery moiety. In some embodiments, the sense strand of the SARM1 RNAi agent has a delivery moiety conjugated to the 3’ end of the sense strand. In some embodiments, the sense strand of the SARM1 RNAi agent has a delivery moiety conjugated to the 5’ end of the sense strand. In some embodiments, the sense strand of the SARM1 RNAi agent has delivery moieties conjugated to both the 5’ end and the 3’ end of the sense strand. In some embodiments, the sense strand of the SARM1 RNAi agent has a delivery moiety conjugated to a nucleotide of the sense strand. The delivery moiety can facilitate the entry of RNAi agent into the cells. In some embodiments, the delivery moiety is α -tocopherol, palmitic acid, or another moiety in Table 4. In some embodiments, the delivery moiety is a known delivery moiety for delivering RNAi agent into a cell. Placement of a delivery moiety on the RNAi agent needs to overcome potential inefficient loading of AGO2 (Argonaute-2), or other hindrance of the RNA-induced silencing complex (RISC) complex activity. In some embodiments, the SARM1 RNAi agent is not a lipid conjugate. In some embodiments, the SARM1 RNAi agent has no delivery moiety.

[00047] In some embodiments, the delivery moiety is conjugated to the 5’ or 3’ end of the sense strand via a linker. In some embodiments, the linker is selected from Linker 1, Linker 2, Linker 3, or Linker 4 of Table 5. Other suitable linkers are known in the art. Exemplary linker - delivery moiety pairs are shown in Table 6. In some embodiments, the SARM1 RNAi agent has a linker - delivery moiety pair of Table 6.

[00048] In some embodiments, the delivery moiety is conjugated to a nucleotide of the sense strand. In that case, the delivery moiety is a modified nucleotide (e.g., a 2'-O-C₁₂₋₁₆ alkyl modified nucleotide) located in the sense strand. In some embodiments, the modified nucleotide is 2'-O-hexadecyl uridine, 2'-O-hexadecyl cytidine, 2'-O-hexadecyl guanine, or 2'-O-hexadecyl adenosine (Table 4).

Table 4. Delivery Moieties

Delivery Moiety	Structure
1	α-Tocopherol
	
2	Palmitic Acid
	
3	Uhd (2'-O-hexadecyl uridine)

	 <p>The structure shows a uracil base (a pyrimidine ring with carbonyl groups at positions 2 and 4, and a hydroxyl group at position 6) attached to a ribose sugar at the N1 position. The ribose sugar has a phosphate group at the 5' position and a long alkyl chain (hexadecyl) at the 2' position. The alkyl chain is represented by a zigzag line.</p>
4	Ahd (2'-O-hexadecyl adenosine)  <p>The structure shows an adenine base (a purine ring with an amino group at position 6) attached to a ribose sugar at the N9 position. The ribose sugar has a phosphate group at the 5' position and a long alkyl chain (hexadecyl) at the 2' position. The alkyl chain is represented by a zigzag line.</p>
5	Chd (2'-O-hexadecyl cytidine)  <p>The structure shows a cytosine base (a pyrimidine ring with a carbonyl group at position 2 and an amino group at position 4) attached to a ribose sugar at the N1 position. The ribose sugar has a phosphate group at the 5' position and a long alkyl chain (hexadecyl) at the 2' position. The alkyl chain is represented by a zigzag line.</p>

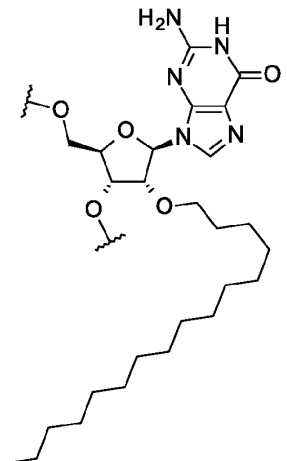
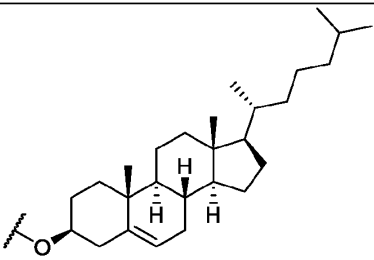
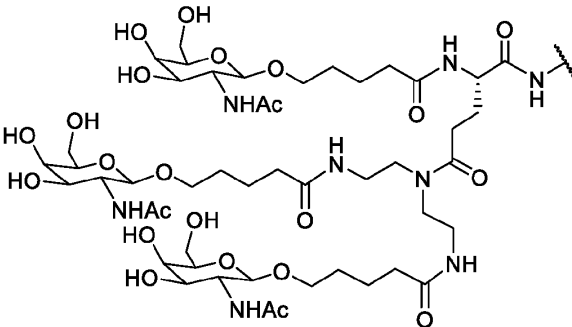
6	Ghd (2'-O-hexadecyl guanine) 
7	Cholesterol 
8	GalNAc 

Table 5. Linkers

Linker	Structure
1	<p>Teg (tetraethylene glycol) linker</p>
2	<p>Piperidinol-PEG linker</p>
3	<p>Teg (tetraethylene glycol) linker PS</p>
4	<p>Piperidinol-PEG linker PS</p>

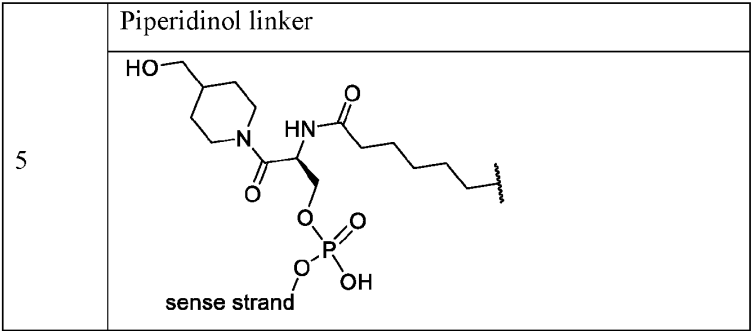
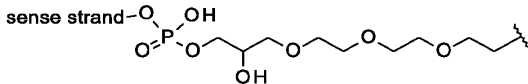
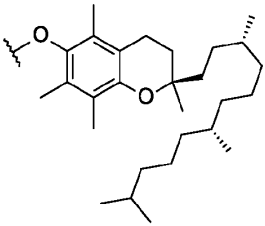
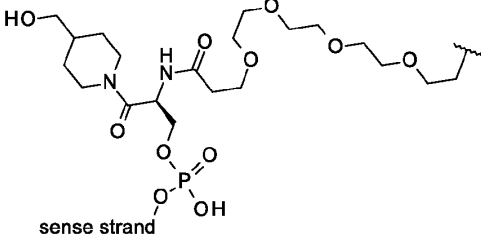
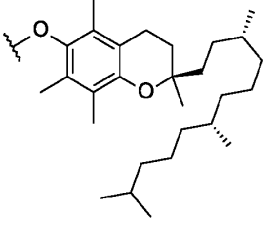
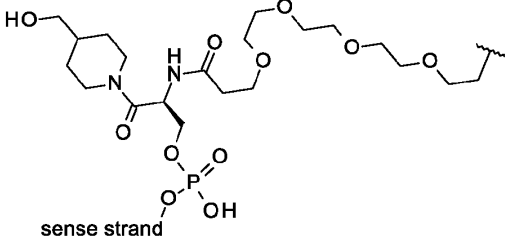
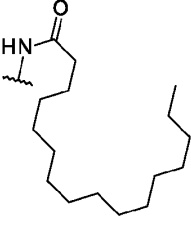
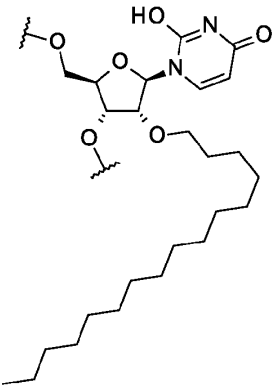
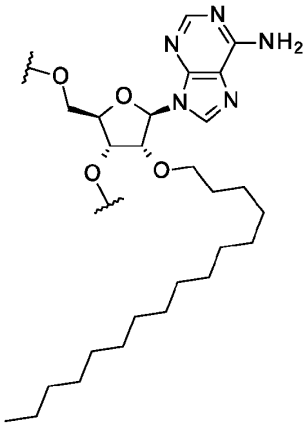
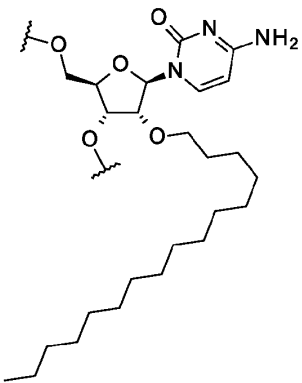
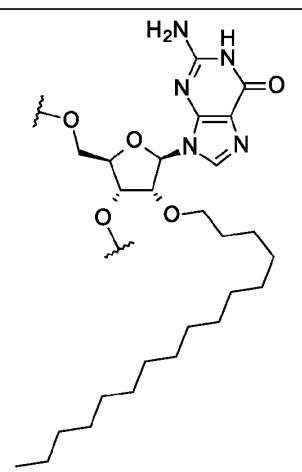
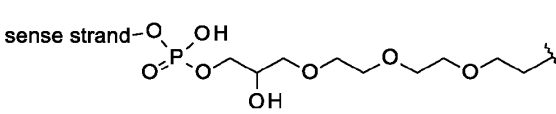
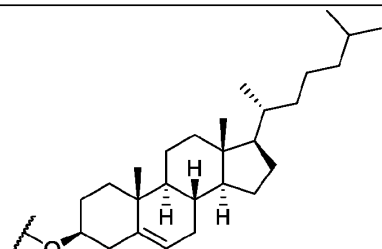


Table 6. Linker Delivery Moiety Pairs (LDP)

LDP	Linker	Delivery Moiety
1	Teg (tetraethylene glycol) linker	α -Tocopherol
		
2	Piperidinol-PEG linker	α -Tocopherol
		
3	Piperidinol-PEG linker	Palmitic Acid
		

4	None	Uhd
		 <p>The chemical structure shows a nucleotide derivative. It features a ribose sugar ring with a uracil base attached at the C5 position. The uracil base has a carbonyl group at C2 and a hydroxyl group at C4. The ribose sugar is linked to a long alkyl chain (octyl group) via an ether linkage at the C3' position. The C1' position of the ribose is also linked to a polymer chain, indicated by wavy lines.</p>
5	None	Ahd
		 <p>The chemical structure shows a nucleotide derivative. It features a ribose sugar ring with an adenine base attached at the C9 position. The adenine base has an amino group at C6. The ribose sugar is linked to a long alkyl chain (octyl group) via an ether linkage at the C3' position. The C1' position of the ribose is also linked to a polymer chain, indicated by wavy lines.</p>

6	None	Chd
		
7	None	Ghd
		
8	Teg (tetraethylene glycol) linker	Cholesterol
		

	Piperidinol linker	GalNAc
9		

[00049] In a further aspect, provided herein are SARM1 RNAi agents of Formula (I): R-L-D, wherein R is a double stranded RNA (dsRNA) having a sense stand and an antisense strand, wherein the sense strand and the antisense strand form a duplex; wherein D is a delivery means (e.g., a delivery moiety) for delivering the dsRNA into a cell; and wherein L is a linking means (e.g., a linker) for linking the dsRNA to the delivery means, or optionally absent, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 1, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 2;
 - (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 4;
 - (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 6;
 - (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 8;
 - (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 10; and
 - (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 12,
- wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00050] In some embodiments, provided herein are SARM1 RNAi agents of Formula (I): R-L-D, wherein R is a double stranded RNA (dsRNA) having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex; wherein D is a delivery means (e.g., a delivery moiety) for delivering the dsRNA into a cell; and wherein L is a linking means (e.g., a linker) for linking the dsRNA to the delivery means, or optionally absent, wherein the sense strand and the antisense strand have a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 1, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 2;
- (b) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 3, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 4;
- (c) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 5, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 6;
- (d) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 8;
- (e) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 10; and
- (f) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 12,

wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00051] In some embodiments, provided herein are SARM1 RNAi agents of Formula (I): R-L-D, wherein R is a double stranded RNA (dsRNA) having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex; wherein D is a delivery

means (e.g., a delivery moiety) for delivering the dsRNA into a cell; and wherein L is a linking means (e.g., a linker) for linking the dsRNA to the delivery means, or optionally absent, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 14;
- (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16;
- (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 18;
- (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 20;
- (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 22;
- (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 24;
- (g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 27;
- (h) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 29;
- (i) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 30;
- (j) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 31;
- (k) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 32;
- (l) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 33;
- (m) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 35;
- (n) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and

the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 36;

(o) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 37;

(p) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 38;

(q) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 39;

(r) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 41;

(s) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 42;

(t) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 43;

(u) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 44;

(v) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 45;

(w) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 46; and

(x) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 47.

[00052] In some embodiments, provided herein are SARM1 RNAi agents of Formula (I): R-L-D, wherein R is a double stranded RNA (dsRNA) having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex; wherein D is a delivery means (e.g., a delivery moiety) for delivering the dsRNA into a cell; and wherein L is a linking means (e.g., a linker) for linking the dsRNA to the delivery means, or optionally absent, wherein the sense strand and the antisense strand have a pair of nucleic acid sequences selected from the group consisting of:

(a) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 14;

- (b) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 16;
- (c) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 18;
- (d) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 20;
- (e) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 22;
- (f) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 24;
- (g) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 27;
- (h) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 29;
- (i) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 30;
- (j) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 31;
- (k) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 32;
- (l) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid

sequence of SEQ ID NO: 13, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 33;

(m) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 35;

(n) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 36;

(o) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 37;

(p) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 38;

(q) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 39;

(r) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 41;

(s) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 42;

(t) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 43;

(u) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 44;

(v) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid

sequence of SEQ ID NO: 17, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 45;

(w) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 46; and

(x) the sense strand has (e.g., consists of, or consists essentially of) a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand has (e.g., consists of, or consists essentially of) a second nucleic acid sequence of SEQ ID NO: 47.

[00053] In some embodiments, the delivery means is conjugated to the 3' end of the sense strand. In some embodiments, the delivery means is conjugated to the 5' end of the sense strand. In some embodiments, the delivery means is conjugated to a nucleotide of the sense strand. In some embodiments, the delivery means is palmitic acid, α -tocopherol, or another moiety in Table 4. In some embodiments, the linking means is selected from the group consisting of Linker 1, Linker 2, Linker 3, and Linker 4 of Table 5.

[00054] The sense strand and antisense strand of SARM1 RNAi agent can be synthesized using any nucleic acid polymerization methods known in the art, for example, solid-phase synthesis by employing phosphoramidite chemistry methodology (e.g., Current Protocols in Nucleic Acid Chemistry, Beaucage, S.L. et al. (Eds.), John Wiley & Sons, Inc., New York, NY, USA), H-phosphonate, phosphotriester chemistry, or enzymatic synthesis. Automated commercial synthesizers can be used, for example, MerMade™ 12 from LGC Biosearch Technologies, or other synthesizers from BioAutomation or Applied Biosystems. Phosphorothioate linkages can be introduced using a sulfurizing reagent such as phenylacetyl disulfide or DDTT (((dimethylaminomethylidene) amino)-3H-1,2,4-dithiazoline-3-thione). It is well known to use similar techniques and commercially available modified amidites and controlled-pore glass (CPG) products to synthesize modified oligonucleotides or conjugated oligonucleotides.

[00055] Purification methods can be used to exclude the unwanted impurities from the final oligonucleotide product. Commonly used purification techniques for single stranded oligonucleotides include reverse-phase ion pair high performance liquid chromatography (RP-IP-HPLC), capillary gel electrophoresis (CGE), anion exchange HPLC (AX-HPLC), and size exclusion chromatography (SEC). After purification, oligonucleotides can be analyzed by mass

spectrometry and quantified by spectrophotometry at a wavelength of 260 nm. The sense strand and antisense strand can then be annealed to form a duplex.

[00056] In another aspect, provided herein are pharmaceutical compositions comprising a SARM1 RNAi agent described herein and a pharmaceutically acceptable carrier. Also provided herein are pharmaceutical compositions comprising a means for reducing SARM1 expression in a cell and a pharmaceutically acceptable carrier. Such pharmaceutical compositions can also comprise one or more pharmaceutically acceptable excipient, diluent, or carrier. Pharmaceutical compositions can be prepared by methods well known in the art (e.g., Remington: The Science and Practice of Pharmacy, 23rd edition (2020), A. Loyd et al., Academic Press).

[00057] In a further aspect, provided herein are methods of reducing SARM1 expression in a cell (e.g., a neuron), such methods can include introducing a SARM1 RNAi agent described herein into the cell; and incubating the cell for a time sufficient for degradation of SARM1 mRNA, thereby reducing SARM1 expression in the cell. The SARM1 RNAi agent can be introduced into the cell (e.g., a neuron) using a method known in the art, e.g., transfection, electroporation, microinjection, or uptake by the cell via natural transport mechanisms.

[00058] In another aspect, provided herein are methods of reducing SARM1 expression in a patient in need thereof, and such method comprises administering to the patient an effective amount of a SARM1 RNAi agent or a pharmaceutical composition described herein.

[00059] In another aspect, provided herein are methods of reducing axon degeneration in a patient in need thereof, and such method comprises administering to the patient an effective amount of a SARM1 RNAi agent or a pharmaceutical composition described herein.

[00060] In another aspect, provided herein are methods of treating a SARM1-mediated neurological disease in a patient in need thereof, and such method comprises administering to the patient an effective amount of the SARM1 RNAi agent or a pharmaceutical composition described herein. Exemplary SARM1-mediated neurological disease includes, but are not limited to, amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), Alzheimer's disease, Parkinson's disease, multiple sclerosis (MS), Huntington's disease (HD), senile dementia, Pick's disease, Gaucher's disease, Hurler syndrome, progressive multifocal leukoencephalopathy, Alexander's disease, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelinolysis, osmotic hyponatremia, Tay-Sachs disease, motor neuron disease, ataxia, spinal muscular atrophy (SMA), Niemann-Pick disease, acute

hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, cerebral ischemia, multiple system atrophy, Pelizaeus Merzbacher disease, periventricular leukomalacia, a hereditary ataxia, noise-induced hearing loss, congenital hearing loss, age-related hearing loss, Creutzfeldt-Jakob disease, transmissible spongiform encephalopathy, Lewy Body Dementia, frontotemporal dementia, tauopathy, synucleinopathy, amyloidosis, diabetic neuropathy, globoid cell leukodystrophy (Krabbe's disease), Bassen-Komzweig syndrome, transverse myelitis, motor neuron disease, spinocerebellar ataxia, pre-eclampsia, hereditary spastic paraplegias, spastic paraparesis, familial spastic paraplegia, French settlement disease, Strumpell-Lorrain disease, non-alcoholic steatohepatitis (NASH), adrenomyeloneuropathy, progressive supra nuclear palsy (PSP), Friedrich's ataxia, spinal cord injury, acute optic neuropathy (AON), a genetic or idiopathic retinal condition, Leber congenital amaurosis (LCA), Leber hereditary optic neuropathy (LHON), primary open-angle glaucoma (POAG), acute angle-closure glaucoma (AACG), autosomal dominant optic atrophy, retinal ganglion degeneration, retinitis pigmentosa, an outer retinal neuropathy, optic nerve neuritis, optic nerve degeneration associated with multiple sclerosis, Kjer's optic neuropathy, ischemic optic neuropathy, chemotherapy-induced peripheral neuropathy, neuromyelitis optica, Charcot Marie Tooth disease, deficiency in vitamin B12, deficiency in folic acid (vitamin B9), isolated vitamin E deficiency syndrome, non-arteritic anterior ischemic optic neuropathy, exposure to ethambutol, exposure to cyanide, traumatic brain injury (TBI), spinal cord injury, traumatic axonal injury or chronic traumatic encephalopathy (CTE). In some embodiments, the SARM1-mediated neurological disease is amyotrophic lateral sclerosis, multiple sclerosis, chemotherapy-induced peripheral neuropathy (CIPN), diabetic peripheral neuropathy (DPN), tauopathy, or Charcot Marie Tooth disease. In some embodiments, the SARM1-mediated neurological disease is amyotrophic lateral sclerosis.

[00061] The SARM1 RNAi agent can be administered to the patient intrathecally, intracerebroventricularly, or via intracisternal magna injection. In some embodiments, the SARM1 RNAi agent is administered to the patient intrathecally, e.g., via a catheter or direct injection into the intrathecal space.

[00062] RNAi dosage regimens may be adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time, or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation.

[00063] Dosage values may vary with the type and severity of the condition to be alleviated. It is further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

[00064] In another aspect, provided herein are SARM1 RNAi agents or pharmaceutical compositions comprising a SARM1 RNAi agent for use in reducing SARM1 expression. Also provided herein are SARM1 RNAi agents or pharmaceutical compositions comprising a SARM1 RNAi agent for use in reducing axon degeneration. Also provided herein are SARM1 RNAi agents or the pharmaceutical composition comprising a SARM1 RNAi agent for use in a therapy. Also provided herein are SARM1 RNAi agents or pharmaceutical compositions comprising a SARM1 RNAi agent for use in the treatment of a SARM1-mediated neurological disease. Also provided herein are uses of SARM1 RNAi agents in the manufacture of a medicament for reducing axon degeneration. Also provided herein are uses of SARM1 RNAi agents in the manufacture of a medicament for the treatment of a SARM1-mediated neurological disease.

[00065] As used herein, the terms “a,” “an,” “the,” and similar terms used in the context of the present disclosure (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

[00066] As used herein, the term “alkyl” means saturated linear or branched-chain monovalent hydrocarbon radical, containing the indicated number of carbon atoms. For example, “C₁-C₂₀ alkyl” means a radical having 1-20 carbon atoms in a linear or branched arrangement.

[00067] As used herein, “antisense strand” means a single-stranded oligonucleotide that is complementary to a region of a target sequence. Likewise, and as used herein, “sense strand” means a single-stranded oligonucleotide that is complementary to a region of an antisense strand.

[00068] As used herein, “complementary” means a structural relationship between two nucleotides (*e.g.*, on two opposing nucleic acids or on opposing regions of a single nucleic acid strand, *e.g.*, a hairpin) 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. Complementary nucleotides can base pair in the Watson-Crick manner or in any other manner that allows for the formation of stable duplexes. Likewise, two nucleic acids may

have regions of multiple nucleotides that are complementary with each other to form regions of complementarity, as described herein.

[00069] As used herein, a “delivery moiety” refers to a moiety that facilitates the entry of an oligonucleotide or RNAi agent into a cell. The delivery moiety can be lipid, cholesterol, vitamin E, carbohydrate, amino sugar, polypeptide, or combination thereof.

[00070] As used herein, “duplex,” in reference to nucleic acids or oligonucleotides, means a structure formed through complementary base pairing of two antiparallel sequences of nucleotides (i.e., in opposite directions), whether formed by two covalently separate nucleic acid strands or by a single, folded strand (*e.g.*, via a hairpin).

[00071] An “effective amount” refers to an amount necessary (for periods of time and for the means of administration) to achieve the desired therapeutic result. An effective amount of a RNAi agent may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the RNAi agent to elicit a desired response in the individual. An effective amount is also one in which any toxic or detrimental effects of the RNAi agent are outweighed by the therapeutically beneficial effects.

[00072] The term “knockdown” or “expression knockdown” refers to reduced mRNA or protein expression of a gene after treatment of a reagent, *e.g.*, a RNAi agent.

[00073] As used herein, “modified internucleotide linkage” means an internucleotide linkage having one or more chemical modifications when compared with a reference internucleotide linkage having a phosphodiester bond. A modified internucleotide linkage can be a non-naturally occurring linkage. In some embodiments, the modified internucleotide linkage is phosphorothioate linkage.

[00074] 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. A modified nucleotide can have, for example, one or more chemical modification in its sugar, nucleobase, and/or phosphate group. Additionally, or alternatively, a modified nucleotide can have one or more chemical moieties conjugated to a corresponding reference nucleotide. In some embodiments, the modified nucleotide is a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, or 2'-O-alkyl modified nucleotide. In

some embodiments, the modified nucleotide has a phosphate analog, e.g., 5'-vinylphosphonate. In some embodiments, the modified nucleotide has an abasic moiety or inverted abasic moiety, e.g., a moiety shown in Table 3.

[00075] As used herein, the term “SARM1-mediated neurological disease” refers to a neurological disease, disorder, or injury mediated by SARM1 and/or by axonal degeneration.

[00076] As used herein, “nucleotide” means an organic compound having a nucleoside (a nucleobase, e.g., adenine, cytosine, guanine, thymine, or uracil, and a pentose sugar, e.g., ribose or 2'-deoxyribose) linked to a phosphate group. A “nucleotide” can serve as a monomeric unit of nucleic acid polymers such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

[00077] As used herein, “oligonucleotide” means a polymer of linked nucleotides, each of which can be modified or unmodified. An oligonucleotide is typically less than about 100 nucleotides in length.

[00078] As used herein, “overhang” means the unpaired nucleotide or nucleotides that protrude from the duplex structure of a double stranded oligonucleotide. An overhang may include one or more unpaired nucleotides extending from a duplex region at the 5' terminus or 3' terminus of a double stranded oligonucleotide. The overhang can be a 3' or 5' overhang on the antisense strand or sense strand of a double stranded oligonucleotide.

[00079] The term “patient”, as used herein, refers to a human patient.

[00080] As used herein, “phosphate analog” means a chemical moiety that mimics the electrostatic and/or steric properties of a phosphate group. 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. A 5' phosphate analog can include a phosphatase-resistant linkage. Examples of phosphate analogs include 5' methylene phosphonate (5'-MP) and 5'-(E)-vinylphosphonate (5'-VP). In some embodiments, the phosphate analog is 5'-VP.

[00081] The term “% sequence identity” or “percentage sequence identity” with respect to a reference nucleic acid sequence is defined as the percentage of nucleotides, nucleosides, or nucleobases in a candidate sequence that are identical with the nucleotides, nucleosides, or nucleobases in the reference nucleic acid sequence, after optimally aligning the sequences and introducing gaps or overhangs, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in

various ways that are within the skill in the art, for instance, using publicly available computer software programs, for example, those described in Current Protocols in Molecular Biology (Ausubel *et al.*, eds., 1987, Supp. 30, section 7.7.18, Table 7.7.1), and including BLAST, BLAST-2, ALIGN, Megalign (DNASTAR), Clustal W2.0 or Clustal X2.0 software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. Percentage of “sequence identity” can be determined by comparing two optimally aligned sequences over a comparison window, where the fragment of the nucleic acid sequence in the comparison window may comprise additions or deletions (e.g., gaps or overhangs) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage can be calculated by determining the number of positions at which the identical nucleotide, nucleoside, or nucleobase occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison, and multiplying the result by 100 to yield the percentage of sequence identity. The output is the percent identity of the subject sequence with respect to the query sequence.

[00082] As used herein, “RNAi,” “RNAi agent,” “iRNA,” “iRNA agent,” and “RNA interference agent” means an agent that mediates sequence-specific degradation of a target mRNA by RNA interference, e.g., via RNA-induced silencing complex (RISC) pathway. In some embodiments, the RNAi agent has a sense strand and an antisense strand, and the sense strand and the antisense strand form a duplex (e.g., a double stranded RNA). In some embodiments, the sense strand has a delivery moiety conjugated to the 5’ or 3’ end of the sense strand or a nucleotide of the sense strand.

[00083] As used herein, “strand” refers to a single, contiguous sequence of nucleotides linked together through internucleotide linkages (e.g., phosphodiester linkages or phosphorothioate linkages). A strand can have two free ends (e.g., a 5’ end and a 3’ end).

[00084] As used herein, “SARM1” (sterile alpha and TIR motif containing 1, also known as SARM; HsTIR; SAMD2; hSARM1; MyD88-5) refers to a human SARM1 mRNA transcript or a human SARM1 protein. The nucleotide sequence of human SARM1 mRNA can be found at NM_015077.4:

1 ATCTCCAGC TCAGCCGAGC CCGTGCCAG GCCACGCTTT GTTCCAGCCG CCGCCTCCTC

61 TACCCTACGG CGTCCGGAGC CATCCCTCGC CTGCTCGCTC TCTCCTTTCG CCCACTCCCT
121 GCATCTGGGC CTGCATCACC TTTGCCAACC GCTCCCCCGA TCCTGCCGAC ACTCCTCCCC
181 CAAACTTCTG ACCGGCACCC TTGCCTGGTA CCCTTCTCTC CATTCCTCCC CCTCCATCTT
241 CTTTCCCCGA CCCCTCTCGG GTCCCTCTTT TCCCAAAACC CGGTCTCTC CGCGTGGCCC
301 CGCTCCAGG CCGGGGATGT CCCCCGCGC CCGCGCCCA TGGTCTGAC GCTGCTTCTC
361 TCCGCTACA AGCTGTGTG CTTCTTCGCC ATGTCGGGCC CACGGCCGGG CGCCGAGCGG
421 CTGGCGGTGC CTGGGCCAGA TGGGGGCGGT GGCACGGGCC CATGGTGGGC TGCGGTGGC
481 CGCGGGCCCC GCGAAGTGC GCCGGGGGCA GGCACCGAGG TGCAGGACGC CCTGGAGCGC
541 GCGCTGCCGG AGCTGCAGCA GGCCTTGTCC GCGCTGAAGC AGGCGGGCGG CGCGCGGGCC
601 GTGGGCGCGG GCCTGGCCGA GGTCTTCAA CTGGTGGAGG AGGCCTGGCT GCTGCCGGCC
661 GTGGGCCGCG AGGTAGCCCA GGTCTGTGC GACGCCATCC GCCTCGATGG CGGCCTCGAC
721 CTGTGTTGC GGCTGTGCA GGCGCCGAG TTGGAGACGC GTGTGCAGGC CGCGCGCCTG
781 CTGGAGCAGA TCCTGGTGGC TGAGAACCGA GACCGCTGG CGCGCATTGG GCTGGGCGTG
841 ATCTGAACC TGGCGAAGGA ACGCGAACC GTAGAGCTGG CGCGGAGCGT GGCAGGCATC
901 TTGGAGCACA TGTTCAAGCA TTCGAGGAG ACATGCCAGA GGCTGGTGGC GGCCGGCGGC
961 CTGGACGCGG TGCTGTATTG GTGCCGCCG ACGGACCCG CGCTGCTGCG CCACTGCGCG
1021 CTGGCGCTGG GCAACTGCGC GCTGCACGGG GGCCAGGCGG TGCAGCGACG CATGGTAGAG
1081 AAGCGCGCAG CCGAGTGGCT CTTCCCGCTC GCCTTCTCCA AGGAGGACGA GCTGCTTCGG
1141 CTGCACGCCT GCCTCGCAGT AGCGGTGTTG GCGACTAACA AGGAGGTGGA GCGCGAGGTG
1201 GAGCGCTCGG GCACGCTGGC GCTCGTGGAG CCGCTTGTGG CCTCGCTGGA CCCTGGCCGC
1261 TTCGCCCGCT GTCTGGTGGA CGCCAGCGAC ACAAGCCAGG GCCGCGGGCC CGACGACCTG
1321 CAGCGCCTCG TGCCGTGCT CGACTCTAAC CGCTTGAGG CGCAGTGCAT CGGGGCTTTC
1381 TACCTCTGCG CCGAGGCTGC CATCAAGAGC CTGCAAGGCA AGACCAAGGT GTTCAGCGAC
1441 ATCGGCGCCA TCCAGAGCCT GAAACGCCTG GTTTCCTACT CTACCAATGG CACTAAGTCG
1501 GCGCTGGCCA AGCGCGCGCT GCGCCTGCTG GCGAGGAGG TGCCACGGCC CATCCTGCCC
1561 TCCGTGCCCA GCTGGAAGGA GGCCGAGGTT CAGACGTGGC TGCAGCAGAT CGGTTTCTCC
1621 AAGTACTGCG AGAGCTTCCG GGAGCAGCAG GTGGATGGCG ACCTGCTTCT GCGGCTCAGC
1681 GAGGAGGAAC TCCAGACCGA CCTGGGCATG AAATCGGGCA TCACCCGCAA GAGGTTCTTT
1741 AGGGAGCTCA CGGAGCTCAA GACCTTCGCC AACTATTCTA CGTGCGACCG CAGCAACCTG
1801 GCGGACTGGC TGGGCAGCCT GGACCCGCGC TTCCGCCAGT ACACCTACGG CCTGGTCAGC
1861 TGCGGCCTGG ACCGCTCCCT GCTGCACCGC GTGTCTGAGC AGCAGCTGCT GGAAGACTGC
1921 GGCATCCACC TGGGCGTGCA CCGCGCCCGC ATCCTCACGG CGGCCAGAGA AATGCTACAC
1981 TCCCCGCTGC CCTGTACTGG TGGCAAACCC AGTGGGACA CTCCAGATGT CTTTCATCAGC
2041 TACCGCCGGA ACTCAGGTTC CCAGCTGGCC AGTCTCCTGA AGGTGCACCT GCAGCTGCAT
2101 GGCTTCAGTG TCTTCATTGA TGTGGAGAAG CTGGAAGCAG GCAAGTTCGA GGACAACTC
2161 ATCCAGAGTG TCATGGGTGC CCGCAACTTT GTGTGGTG C TATCACCTGG AGCACTGGAC
2221 AAGTGCATGC AAGACCATGA CTGCAAGGAT TGGGTGCATA AGGAGATTGT GACTGCTTTA
2281 AGTGCGGCA AGAACATTGT GCCCATCATT GATGGCTTCG AGTGGCCTGA GCGCCAGGTC

2341 CTGCCTGAGG ACATGCAGGC TGTGCTTACT TTCAACGGTA TCAAGTGGTC CCACGAATAC
2401 CAGGAGGCCA CCATTGAGAA GATCATCCGC TTCCTGCAGG GCCGCTCCTC CCGGGACTCA
2461 TCTGCAGGCT CTGACACCAG TTTGGAGGGT GCTGCACCCA TGGGTCCAAC CTAACCAGTC
2521 CCCAGTTCCC CAGCCCTGCT GTGACTTCCA TTTCCATCGT CCTTTCTGAA GGAACAGCTC
2581 CTGAAACCAG TCTCCCTGGG CTGAGACAAC CTGGGCTCTT CTTAGGAAAT GGCTCTCCCT
2641 CCCCTGTCC CCCACCCTCA TGGCCACCT CCAACCCACT TTCCTCAGTA TCTGGAGAGG
2701 GAAGGGAAGT CAGGCTTGGG CACGGGAGGT TAGAACTCCC CCAGGCCCTG CCATTGGGTT
2761 GTCTGTCTCC GTCATGGGGA GGTCCCTGC TCAGTTCTGG AGACACTGGA GTTGGGGTGG
2821 GGGTGGTTCT GCATTCCCTT CTCCTGCTGA TAGCAGTCAG CTTGAGGAGG ATGACGGAAG
2881 GCAGCCTCAG ACAGGAATTA AGGCAATGCC CAGGCGGGCC TGGGCACTGT ATTCTGAGCA
2941 AGGGCCTGGG CCCAGGAGCC AGCCAGGGAT GAGTGCCATC ATGGCTCTCC ACTCAGACTG
3001 TGCTTGCCCTGCTGCACTTAC AACTTCCTGC CGCTCTGTGG CCTTGCCCTG TAATCACTCA
3061 GTGCCCTTAG CTAGCCTGAC TAAGTCCCAG ATCCCCTACA GCTTCCTTCG GTGTGGTATC
3121 TTTTGCCACA TCCAGGGCGA GGGTTGAGGC AAACCAGCCC TCCCTCTGAC TTCCTTGTC
3181 CTGCAGCCAG CTTTGCTGCA CTGCTGGTG CACAGGAGCC TCCTGTTTGG GCCTGGGTCT
3241 GGGCATGGGG AGGCCGTGCC TCAAAGCCCA CCCTACCCCA TGCCTTGGTG TGTGCTCA
3301 GGCTCCTTCC TGGTCTGGCC CAGCTGGCTT CCCCAGCCCC TCAGCCATCC AGGGCTACCC
3361 ACTGCTTACT CAGGGACCAG GCAGCCCCCA TGGCAGTAAA AGCAGCCTAG ACAGAACCTG
3421 CAGCTCTGTG GAAAGAGGCA AAGTCCTGAA AAGGCAAAGG GTTGTCACCT AGGGCAGCTT
3481 CTCCAACTTT AACATGCATC CAAGTCACCT GGAATGTTG TTAAAATCAG GAGATCTGGG
3541 GTGGGGCCTA GGA CTGCA TTTCTTACAG ATTCCCAGGT GAGCTGATGC TGGTGGTTAA
3601 GGGTAGCAAA TCTCTAAAGC ACGAAGCCCT CACAAATCTT TGCCATTTC CAAACTCC
3661 GCTCCATGGT CTCCAGTCAT CAGAGCAACT CTACCTGGTA TTATCATCCC CATTTTACAG
3721 ATAATGACAC TGAGGCTCAG AAAGGTTGAG GATAAGCCCA CTTTCCTGTC ATTAGTGGCA
3781 GCCCCAGATC CAGACCTAGG CCTCCTGGCA CCCAGTCCAC TGGCAGTGGA ATTGCTTTCC
3841 TGAGAATCAT TCTGAGGCTG GGCTATTGCT TCTCCCTTGC TTCAAAGAAT CTAGCAGCGG
3901 GGGATAGGAT TTTGCAACAA AAAGCTGACC CAGAGGCCAT ACAGAGCAGG AATATCCCAT
3961 TGCCCCCTCC TCCACTGGGT TCAGAGGGTA AGAAAGCACC CTCCAATAAA CCCAGGCTCC
4021 AGGCCGTGGG GGCTGCTGAA GGCTCTTTCC CCGCAAGGGC CAGGTGTTGA CACCTTAAAG
4081 CTGGCTGCGC CCCCAGCCCC ACTCTTGGCT GTGCTGGCCA GGTGACTCCT AGTTCTTGGC
4141 CACATCATCA GAAAGTCAAA GTCTCACTC CAGGTTTGGG GTCCTTCCT TCCACTCCCC
4201 TCCCTGCCAG AGTCTGTCTT GGCCAGTGCC AGCCTCGATG CTTTGGTTTT GACCCACCT
4261 GATCCTCCTT TCCTCATGCA GCACAAGTGC TCACCGGGGC CAGAGCCAGG GCATGGATAT
4321 GACAAGCAGG GCAGCCTGGA CACTGCCCTC ACAGGACAGC GCCAATAACA ATACAGTGTC
4381 TGAGTATCTC CAGGGGATGA TTTCTGGCTC TTTGTCTCCA ATCAGTCCCA CTCCCTCTG
4441 AGGTCCCCAA GGGCAGTATT CAGAGAGGTT TCCTGCGTTT TATTTCTATT TGGTATACCC
4501 TCCACTGTTG TCCACTGCCC TGTGTGGCCT TCTGGTTGAC CTCTGCCCGA TCTTCTGTCT
4561 CTCTGAGGGA ATCAGAGTCC AGCATCCAGC CCCAGCTGGA ACAGCTGAAG TCACAAGCCT

4621 CCTCTAAGCC AAGGCCAGTG TGTTCAGAGG TGACTGCCAC CCATACTAGG ACAAACACAG
4681 CTCAGATCAC CAGGTCAAGC ACCTAGGCCT GGCTTCTCCT GAGACAGAGG ACTCAGAAGT
4741 GGCTTTTCCT CCAAAGCCTG CTCAGACACA GGTCTGTAGG GCCAGGGTGT TCTGCTTGGC
4801 TGGGCTGCAG CTGCTACCCC TCGGTTGGGG CTGAGTCAGC CAGATCCTCC CCCTACTTCT
4861 CCCAAGGGC CAAGAACTGC TCAGGGACAT TAAAGGTCAA AAGTCCAGCC ACACCTCATTC
4921 ATCCTTTTCC CAGGCCCATG AAGAGAGGCA TCTCATTGTA GAATGTATGA GGAAGTGGGA
4981 AGTATCTCAG AGAATCAGCT AAGTTTCCTA ACTTGTCCTT CCAAATGTGA TCACCACGAT
5041 TCAACAATTT GGGGCATTGC TGATCTAGCC GTTCCTAGTG GGGCTTGCTC AAGGTTGCAC
5101 AGCGAGTCAG TAGAAGCCCT GGCTGGCCCC ACTTGGTACC AATCCACCAG GCAGCTCAGG
5161 GCTCCTGCCC AGCCCAGCAG CTCTGTGTGT CTAACGTATG GCAGGCAGAC TGGGAGCAGG
5221 AAAACAGAGG GCCCCAAAGC CCAAGGCACC AGAAGGTTTG TTTCAGTTTG CTGAAGCTGA
5281 TTTGTAATGA TTGGCACTCT TCAGCCAGGG GAGTGGGTAG GCCATAGCCA AGGATCGATT
5341 CCCCAACCAC AGCAAAGGCA ACACTCTTCC TCCAGAGATC ACCAAGCCCC TCTTACCTCC
5401 CTCCTCTCCT CCCAAGGCTG GCACTAACCA GGTACCACAT TCATTGTATA GGAATGGCTG
5461 ATGACTGCTA CACGTGTTGG GAACCTGGTT GGGGCTGTGC AGTTTGGGCT GGAAGGAGAG
5521 ATGCCAGCCC TCGTGCTGCC TCTGGTCCCT GAAGTGTAC CTCTCTCAGG ACCTCTCTCT
5581 TGGCTGTGG GGTATAAGT GATGGATAGC AGAAAGGGAG AACTGACTCC TGTCCCAAAT
5641 AGCTCCTCTG CCACCTGTCC TGCAGTGGGC CTGTGTGGGT TATGATTCTA GATCCTAGAC
5701 AGAGGCTGGG TCAGCTGTGG ATGGGGTGGT GCCTTGGTCT CTCTTGACTA CCTCGTCCAA
5761 AGAGAGCACT GCCCTTAGAC AAGAGTTGCT TGTCTGCTG TGGGCTGGGC TTCCAGCTGC
5821 AGACCTCCAG TTGCTTGGTG TTCACCTTGC TCCTCTTGCC CTCTGTCTTC TGGTCCAGGC
5881 AGATCAGGGG CTCTGGGGAA ACTGCTGGAA CTCGAGGTGA GGATCAGCCT TTTCCAGCAT
5941 CCTGTGAGAG ACCAGAGAGA GAGTTTGGAT TTCATGTGGG GAACCTCAA GGCCTGTCTG
6001 GAGAAGTGAC ACAGGATTTA CTGGGGTGGG CTGGTCCAGG TAGCTCTCCT GAACCTCCTC
6061 CTTCCCCAAG CTGAGAAGCT GAGAGCTGGA GGACAATATC CAGGGACATG GCTCTGAAAA
6121 ATAACCTTTT TTTTTTTAAG AGACAGGGTC TTGCTCTGTT GTCCAGGCTG GAGGGCAGTG
6181 ACATAATCAT AGCTCACTGT ACCCTTGAAC TCCTGGGCTC AAGTGATCCT CCTGCCTCAG
6241 CCTCCTTAGT AGCTGGGACT ACCAGTGCAT ACCACCATGC CTGGGTGATT TTTTAAATTT
6301 TTTATACAGA CAAGGTCTTG CTATGTTGCC CAGGCTGATC TTGAATTCCT GGGCTCAAGT
6361 GGTCTCTCTG CCTCAGCCTC CCACAGGATC GGGATTACAG GCAAGAGCCT CCACGCCCCG
6421 CCATGAAATA TAATTCTTAA TATCATACAG GAAAAAGTCA GCGGGTCAAG CTAGCCTGTG
6481 GCCCAGCCAC AACTAGCTGA CAAAGCTTCC TGGCCTTCCC TTTAACACAG TTCTGCTGCC
6541 ATAGTTCCAT CTATAAAATG GGAATGGAGG GAAATAGGGG AACTGGGAGA GAGAACACAG
6601 CCTTGCCAAG CAGCAATGTT AGCCTGATCC TTCCTCCACC TAGCTCGCCA TCTCGCCCTT
6661 GGGAAATGGC TCCTGGAGGA TTAGGCAGCC ATCTGCAAGG AGAGGGGCAA CCTGGGACAA
6721 GACACCCAGA GGGTAAGGAT TCCAGGAATG AAGCTGCCAT TTCTGGTTGG GAGGAGAAGA
6781 GGAAACTTTT AAGAGAAAGG GCTCCATTAT GAGCATGGGT TCAGGGCCCT GCATTACCCA
6841 ATCAGAACAG CCGGATGAG CAGGAGGCCA GCTCCCAGGA GGAAGGGGAA CCCCTTCATA

6901 AAGTTCAGAG TGGCTGGGTA GAGTGAGTTG AAGATGCCGG AGGCCGTCAG CATGGCCAGG
6961 CTATTCACAC AGGCCACAGC AGAAAAGAGA GCACCTGTGA AGAAATAAAT ACCATACTCT
7021 GGAGTCCGAA AGGGCCATAT TCCAACCTCTG GCACCACCAC CTCACAGCTG TGTGACCGGG
7081 AGTAGTCACT TAACCTATGT CTCCCCTTCC TCACCAGTAA ATCCTGCTAC ATCATGTACT
7141 GTGACAAGGA TTCAGTAAGG TCATATGTGG ACAGTAGCTG GCACAGAGGG GCTACTAAAC
7201 AAATGGCTGC TATTAAATCC ACATTAAAAG TACATGTGAT CTGACAGAAC CCAGCACATA
7261 AAAGAAAAAA AAAGTACATG TGATATTGTC TGATGAAAGC TTGATGGAAA TGGCTTTTTT
7321 CTGGTTTATC CTCTTTGGAA TCATCTCCTG TTTGGGATTA ACTGCTGGTC TGATCAGTTC
7381 CAATATTCAT AGCGGTGTCA CCACTGAATA GCTTCTTATC CTTTGGGTTC CTGTTCTCTC
7441 TTCTGCTAAA TAAGGATAAT ACCTATTTCC TAGATTGTGA GCAACATTAA GTTCACATGG
7501 AAATCACCCA TCACTGGGCC TGGTCCCCTG GAAGTAGCTA GTTAGTAAGG GCTGTTCTTT
7561 TCTCTGTTT CTCTTGACAT CTCTGGGCAC AGAGAAAGTG CTGGGAAAAA AAGTTTAGGT
7621 GAATGAATGA AGACACATGG ATTCTGGGGA CACCAGAACC CACAGTGGGC TCTGTATGGC
7681 ACCAGAGTCT CTGTCAATCAT CAGATCCTCA TTCCAGGACA GATGGAAAAA GATGAATGTT
7741 TCCAGACTGG GGCATAAAGA CCCAGAGGCT GGAGAAGCTG TTCTTTATAG ATATACCAGG
7801 AGAACCCACA GTTTACAAAA TGTGCAACAA CCCAACAGAA GTTGAGATTA AATTCTGTCA
7861 CATCTAGAGG GGTCTGTGAT GTCATCAAAA GCAAACCACC CACATCACAG ATGAAGAAAC
7921 AGGCCTGTGG CAGGGCTCGG ACTAAAACCC AGATCCTGAG ACCAGCTGCT TTAAACACA
7981 GACGTAGGTT TGCATCCTAG CTCCACCATT TACTGAGTAA CCTTGGGTGA GCCAATGTAA
8041 CCCCTGGGT CTCTGTTTCT TTATCTGTCA ACTGTGAAA ATGAAACCCA TGTCACAAGG
8101 TTGTTCACTT CTGGGCTTGT ACACGCTGAC CCCAGAGAAA CAGGGAACCT TGGCATCACC
8161 ACACCCATCT TACAGACGGA AAAGCTGAGG TCTGCAGAGA GTAAATCCTC TGCTCTGGTT
8221 ATCTAGAAAG AACATAATTG TGCTCTGCTG ACTGCAAATC CCAACTCTGC GGTTTGAAAA
8281 TCCAAGGTGG CATGATCCTC TGCCATTGT GGGCAATTTC ACAGAAATGT GTTTGTTTTG
8341 GCCACTTACT TCTCCAGGGT GAGAGGGGGG AAGGCAAGCT GTTCCCCAG CCATGGCTGC
8401 CCATCAGCCC GTTTCGGGCA GCACTGGACA TGAGGAACCA GACACAGGTG GGTTCTGACA
8461 CTCACCTGCT TCTGTCTCTC TCACCAGCTT GGAGAGTTTA GCCCGGATGA CAGGTGTGAT
8521 GACTAATGAC AGGAAAAGCA ACCCATATCC TGTGGAGAAA CAAACACTCA TCAGGAAAAT
8581 GGGGCTGGGG AGAGGGGCGT CCAAGGGAAA GGCAGCAGAG CTCCTATCCA TACCCACGT
8641 GGGGCTTAGG TTAGACCCAG GAAGAACTTC CTTGATGGTG AGGGTGGGAA GACAGTAGTC
8701 AAGGAGGAAT GGAGACTGCC CTTGTCTGGG CTTGGCCACC TGCTAGCTCT CATGAATGAA
8761 TGCTAATTCC CATTGATTGC TTTCTTGTCT GAACCTCTTG TGGTCACAGC AGGCATCACC
8821 CACCCACTTG GCACTTAGTA GGGATATGGC AGGGCACAGA AAACAAGCAT GGGCTTTGGA
8881 GTCAGCCCTG AGTTCAAAAC CTGATGCCAT TACATATTAT CTGTGTGGCC TGGGGTACTT
8941 ACCCTCTCTG ATCCTGACTC CCTGTATGAG GAAGATAATA AGGCCTTCAT CACAGGATGG
9001 TTCTGAGGCA TAGGAGGCTG AATAATGGTG CCCAATGGCA TCAGATTCAT AGCCCTGGAA
9061 CCTGTAAATA CTACCTTATT TGGAAAATGA GTCTATGCAG GTGTGCAGTT AAGCCTCCTG
9121 AGAGAGCAGA GTTATCCTGG ATTAGGTTGG GCCCTAAATG CCGTCACACA TATCTTTATA

9181 AGAGGAAAGC AGACGGAGAT TTGGCACCGA CAGAATTGAG AAGGCACAAA GAGGAGGAGA
9241 GTCAATGTGA GCACAGAGGC AGAGACTGGT GATGGCCGCC CCAAGCCAAG GAATGCCAGC
9301 AGCCCCAGAA GCTGGAAGAA ATGAGAAACA CGTTCTCTCC TGGAGGCTTG CAAGGGAGCA
9361 CTGCCTGCTG ACTGCTTCCA TTCAGCCCGG TGGTACTGAC TTTGGACTTC TGGCCTCCAG
9421 AACTGTGAGA GAATATGTTT CTGTTGTGTT AAGCCCCCAA GTTTGTGGTA TGTCATTACA
9481 GCAATCTCAG GGAACCAATA CATGAGGTAA AAAGGTAACA TCTATGAAGA GCATGGCATA
9541 GGGACACAGC AAATGGGAGT TCCTTTTCCC TTTGCATTCA GTTACTTACA GGCTTCCTGT
9601 TTTCTTCATA ACCATTCTC TCCCTGTGCG ACTGCTGACT CCTCAGCAAA ACTGCAAAC
9661 CCTACAGGAC AGTGGATCCT CCAAAGAAGG TATACGATGA GGCATCCAGG GACCCTAGCA
9721 GTGTCAGGCC CCTCAAATCC CACTCTGTTG AGACCTCCCC CCGACCCAGA GCAATGACAG
9781 CATCTTTATC ATCTCTGCAT CCCCAGGGC CATCAGCAGG AGGGAAAGGT TCCCTTCTGC
9841 TTAATTGTCA GACAAGCAGT TGAGTTAAGA AATCTGTGAT TATTGTATTG TTGACTATAC
9901 ACAGCACATT TTAGGGCTCT ATCAAATAA ATCTGTCCCT TTAATAAAG TTAATAAAG
9961 CCGGGCACGG TGGCTCATGC CTGTAATCCC AACACTTTGG GAGGCTGAGG CAGGCGGATC
10021 CTGAGCTCA GGAGTTAGAG ACCTGGACTG GGCAAAATGG TGAGGACCCC ATCTCTATAA
10081 AAAATACAAA AATTAGCAAG GTGTGGTAAT GTGCACCAGT GGTCCCAGCT ACTAGAGAGG
10141 CCAAGGTGGG AGGATCATCT GGGCCCGGGG GATGAGGCTG CAGTGAGCCA TGATCGTGCC
10201 ACTGCACTCT AGCCTGGGTA ACAAAGCGAG ACCCTGTCTC TAAATACATC AATCAAATAA
10261 AAATTTTAAA AAGTTAA

(SEQ ID NO: 25).

The corresponding amino acid sequence of human SARM1 protein can be found at

NP_055892.2:

1 MVLTLILLSAY KLCRFFAMSG PRPGAERLAV PGPDGGGGTG PWWAAGGRGP REVSPGAGTE
61 VQDALERALP ELQQALSALK QAGGARAVGA GLAEVFQLVE EAWLLPAVGR EVAQGLCDAI
121 RLDGGDLDDL RLLQAPELET RVQAARLLEQ ILVAENRDRV ARIGLGVLN LAKEREPELV
181 ARSVAGILEH MFKHSEETCQ RLVAAGGLDA VLYWCRRTDP ALLRHCALAL GNCALHGGQA
241 VQRRMVEKRA AEWLFPLAFS KEDELLRLHA CLAVAVLATN KEVEREVERS GTLALVEPLV
301 ASLDPGRFAR CLVDASDTSQ GRGPDDLQRL VPLLDNRLE AQCIGAFYLC AEAAIKSLQG
361 KTKVFSDIGA IQSLKRLVSY STNGTKSALA KRALRLLGEE VPRPILPSVP SWKEAEVQTW
421 LQQIGFSKYC ESFREQQVDG DLLLRLTEEE LQTDLMKSG ITRKRFFREL TELKTFANYS
481 TCDRSNLADW LGSLDPRFRQ YTYGLVSCGL DRSLLRHVSE QQLLEDCGIH LGVHRARILT
541 AAREMLHSPL PCTGGKPSGD TPDVFISYRR NSGSQLASLL KVHLQLHGFS VFIDVEKLEA
601 GKFEKLIQS VMGARNFVLV LSPGALDKCM QDHDCKDWVH KEIVTALSCG KNIVPIIDGF
661 EWPEPQVLPE DMQAVLTFNG IKWSHEYQEA TIEKIIRFLQ GRSSRDSSAG SDTSLEGAAP
721 MGPT

(SEQ ID NO: 26).

[00085] As used herein, “subject” means a mammal, including cat, dog, mouse, rat, chimpanzee, ape, monkey, and human. Preferably the subject is a human.

[00086] As used herein, “treatment” or “treating” refers to all processes wherein there may be a slowing, controlling, delaying, or stopping of the progression of the disorders or disease disclosed herein, or ameliorating disorder or disease symptoms, but does not necessarily indicate a total elimination of all disorder or disease symptoms. Treatment includes administration of a protein or nucleic acid or vector or composition for treatment of a disease or condition in a patient, particularly in a human.

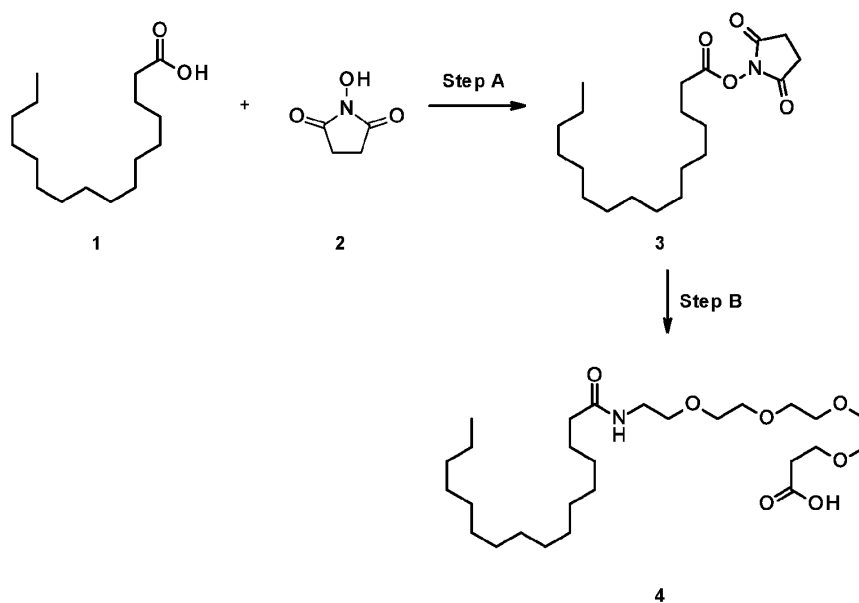
EXAMPLES

Example 1. Synthesis of Linker - Delivery Moiety Pairs

[00087] Certain abbreviations are defined as follows: “ACN” refers to acetonitrile; “AEX” refers to anion exchange; “C/D” refers to cleavage and deprotection; “CPG” refers to controlled pore glass; “DCM” refers to dichloromethane; “DEA” refers to diethylamine; “DIEA” refers to N,N-diisopropylethylamine; “DMAP” refers to 4-dimethylaminopyridine; “DMF” refers to dimethylformamide; “DMSO” refers to dimethyl sulfoxide; “DMTCl” refers to 4,4’-dimethoxytrityl chloride; “ES/MS” refers to electrospray mass spectrometry; “EtOAc” refers to ethyl acetate; “EtOH” refers to ethanol and ethyl alcohol; “HBTU” refers to 3-[bis(dimethylamino)methyl]-1,2,3,4-tetrahydro-1H-benzotriazin-4-yl hexafluorophosphate; “HOBt” refers to 1-hydroxybenzotriazole; “IP-RP” refers to ion-pair reverse phase; “LCAA CPG” refers to long chain alkylamine controlled pore glass; “LC/MS” refers to liquid chromatography-mass spectrometry; “MeOH” refers to methanol and methyl alcohol; “MPA” refers to mobile phase A; “MPB” refers to mobile phase B; “MWCO” refers to molecular weight cut-off; “NMR” refers to nuclear magnetic resonance; “PBS” phosphate-buffered saline; “PEG” refers to polyethylene glycol; “PVDF” refers to polyvinylidene fluoride; “RP” refers to reverse phase; “RPM” refers to revolutions per minute; “siRNA” refers to small interfering ribonucleic acid; “TEA” refers to triethylamine; “THF” refers to tetrahydrofuran; “TLC” refers to thin line chromatography; “TMP” refers to 2,2,6,6-tetramethylpiperidine; “UPLC” refers to ultra-performance liquid chromatography; and “UV” refers to ultraviolet.

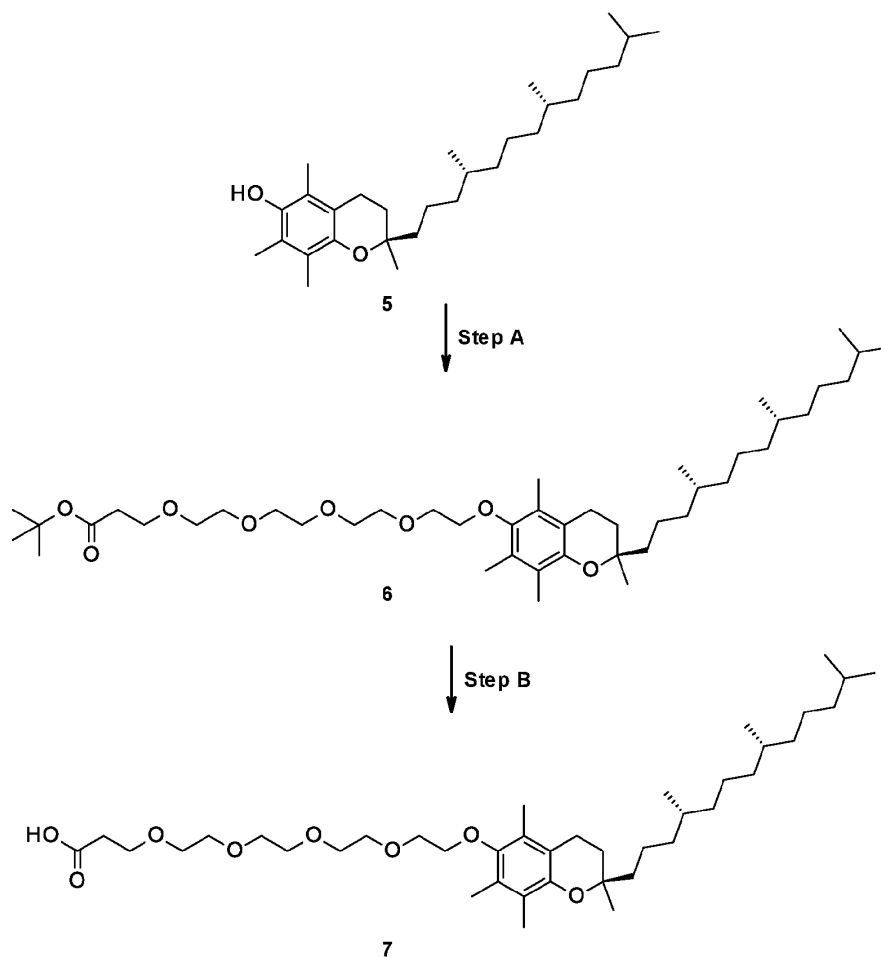
Scheme 1

67



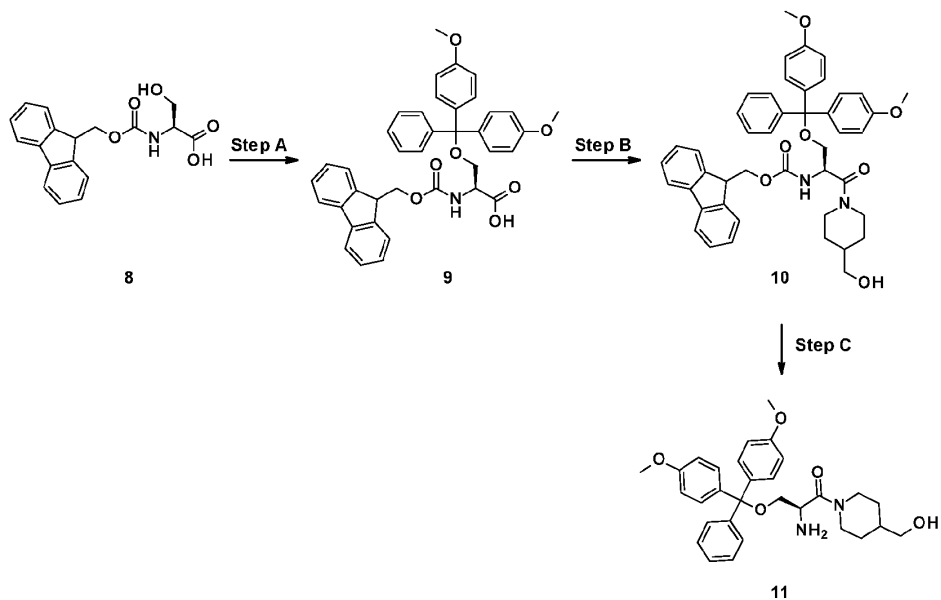
[00088] Scheme 1, step A depicts the coupling of compounds (1) and (2) using an appropriate base such as DMAP in a suitable solvent such as DCM to give compound (3). Step B shows the coupling of compound (3) with 1-amino-3,6,9,12-tetraoxapentadecan-15-oic acid in the presence of a base such as potassium carbonate and in a solvent system such as water and THF to give compound (4).

68

Scheme 2

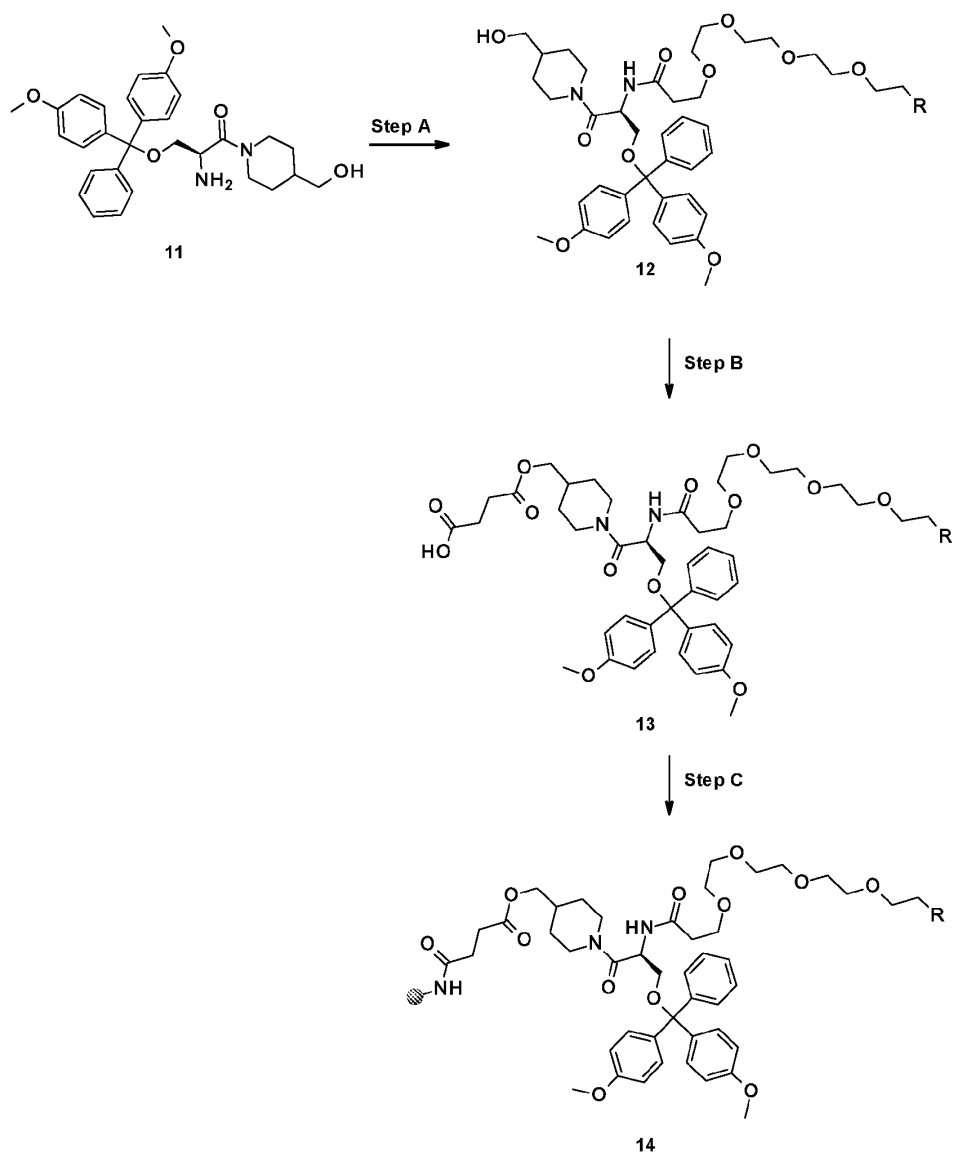
[00089] Scheme 2, step A depicts a Mitsunobu reaction between compound (5) and *tert*-butyl 1-hydroxy-3,6,9,12-tetraoxapentadecan-15-oate using triphenyl phosphine and diisopropyl azodicarboxylate in a solvent such as THF to give compound (6). Step B shows the acidic deprotection of compound (6) using an acid such as HCl in a solvent such as 1,4-dioxane to give compound (7).

Scheme 3



[00091] Scheme 3, step A depicts the protection of compound (8) using DMTCI with a suitable base such as DIEA in a solvent such as DCM to give compound (9). Step B shows an amide coupling between compound (9) and piperidin-4-yl methanol using HBTU and HOBt with TMP in a solvent such as DCM to give compound (10). The deprotection of compound (10) with 20% piperidine in DMF to give compound (11) is shown in step C.

Scheme 4

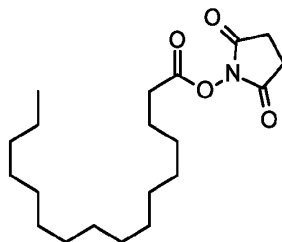


[00093] Scheme 4, step A depicts an amide coupling between compound (11) and either compound (4) or compound (7) using standard coupling reagents such as HBTU and HOBt with a base such as DIEA in a solvent such as DMF to give compound (12). One skilled in the art will recognize the variety of conditions which could be used to perform this amide coupling. Step B shows the coupling of compound (12) to succinic anhydride using a base such as TEA

with catalytic DMAP in a solvent such as DCM to give compound (13). Step C shows the amide coupling of compound (13) to amino LCAA CPG using HBTU with a base such as DIEA in a solvent such as ACN followed by a multistep work up to give compound (14).

Preparation 1

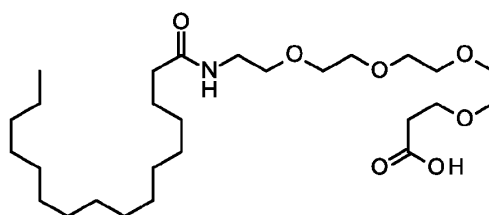
2,5-Dioxopyrrolidin-1-yl palmitate



[00094] Added palmitic acid (2.00 g, 7.80 mmol) to a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.79 g, 9.36 mmol) and DMAP (0.19 g, 1.56 mmol) in DCM (31 mL). Stirred the mixture at ambient temperature for 5 minutes then added N-hydroxysuccinimide (0.99 g, 8.58 mmol) and stirred at ambient temperature for 18 hours. Concentrated *in vacuo* and purified the resulting crude material via silica gel flash chromatography eluting with a gradient of 0-80% EtOAc in hexanes to give the title compound as a white solid (2.65 g, 96%). ¹H NMR (DMSO-*d*₆) δ 2.81 (s, 4H), 2.66 (t, 2H), 1.62 (m, 2H), 1.25 (br s, 24H), 0.87 (t, 3H).

Preparation 2

3-[2-[2-[2-[2-(Hexadecanoylamino)ethoxy]ethoxy]ethoxy]ethoxy]propanoic acid

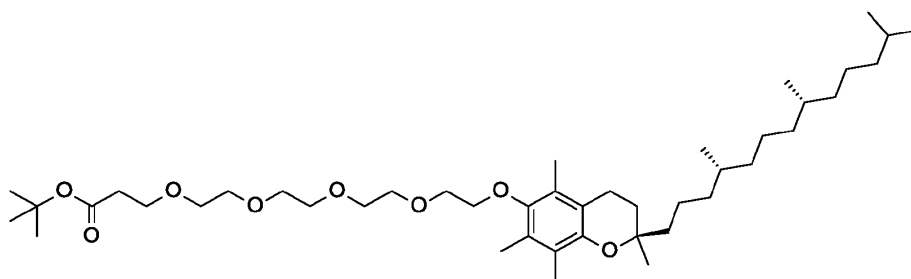


[00095] Added 1-amino-3,6,9,12-tetraoxapentadecan-15-oic acid (0.14 g, 0.53 mmol) to a solution of potassium carbonate (0.14 g, 1.00 mmol) in THF (1 mL) and water (2 mL). Added 2,5-dioxopyrrolidin-1-yl palmitate (0.18 g, 0.51 mmol) and stirred the reaction at ambient temperature for 18 hours. Quenched the reaction with water (30 mL) and adjusted the pH to ~3

with 1N aqueous HCl. A precipitate formed and was collected by vacuum filtration to give the title compound as a white solid (0.19 g, 74%). ES/MS m/z 504 (M+H).

Preparation 3

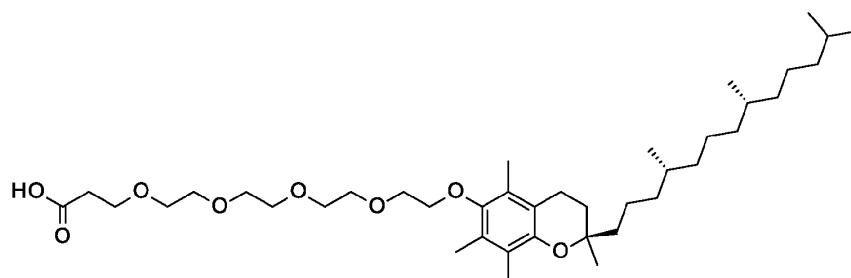
tert-Butyl 3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propanoate



[00096] Combined (2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-ol (3.00 g, 6.90 mmol), *tert*-butyl 1-hydroxy-3,6,9,12-tetraoxapentadecan-15-oate (2.50 g, 7.60 mmol), and triphenylphosphine (2.00 g, 7.60 mmol) in THF (28.0 mL) and added diisopropyl azodicarboxylate (1.50 mL, 7.60 mmol) dropwise over 5 minutes. Heated the mixture at 60 °C for 16 hours. Cooled the mixture to ambient temperature, added silica gel, and concentrated *in vacuo* to give an off-white solid. Purified the mixture via silica gel flash chromatography, eluting with 0- 40% EtOAc/hexanes, to give the title compound as an oil (3.33 g, 66%). ¹H NMR (CDCl₃): 3.84 (s, 4H), 3.77-3.71 (m, 13H), 2.59 (t, J= 6.8 Hz, 2H), 2.52 (t, J= 6.6 Hz, 2H), 2.20-2.20 (m, 3H), 2.15-2.12 (m, 3H), 2.10 (s, 3H), 1.87-1.73 (m, 2H), 1.58-1.51 (m, 4H), 1.47 (s, 9H), 1.35-1.27 (m, 21H), 0.90-0.86 (m, 12H).

Preparation 4

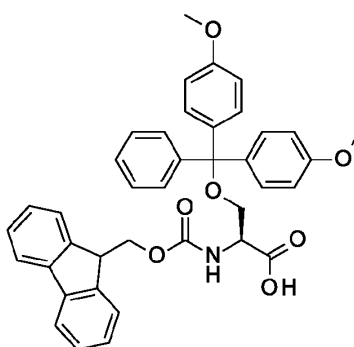
3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propanoic acid



[00097] Dissolved *tert*-butyl 3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propanoate (3.33 g, 4.53 mmol) in 4M HCl in dioxane (22.6 mL, 90.6 mmol) and stirred for 16 hours at ambient temperature. Removed the solvent under reduced pressure to give the title compound as an off-white solid (3.08 g, 100%). ES/MS m/z 678.0 (M-H).

Preparation 5

(2S)-3-[Bis(4-methoxyphenyl)-phenyl-methoxy]-2-(9H-fluoren-9-ylmethoxycarbonylamino) propanoic acid

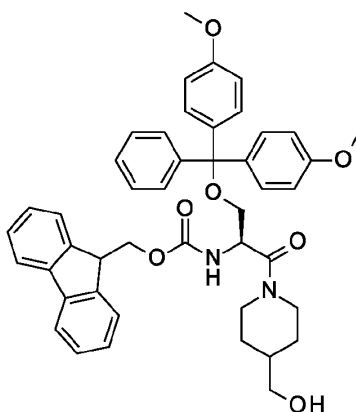


[00098] Added DIEA (64 mL, 0.366 mol) to a stirring solution of (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-hydroxy-propanoic acid (40 g, 0.122 mol) in dry DCM (400 mL) at 0 °C under an inert atmosphere. To this mixture, slowly added a solution of DMTCI (49.6 g, 0.146 mol) in DCM (200 mL). Allowed to warm to ambient temperature and stirred for 16 hours. After this time, diluted the reaction mixture with water and extracted with DCM. Dried organics over anhydrous sodium sulphate, filtered, and concentrated *in vacuo*. Washed the crude

residue with 10% EtOAc/ hexane and dried under vacuum to give the crude title compound as a pale brown solid (62 g, crude). TLC: 5% MeOH/ CH₂Cl₂ (*R_f*: 0.5) UV, 254 nm.

Preparation 6

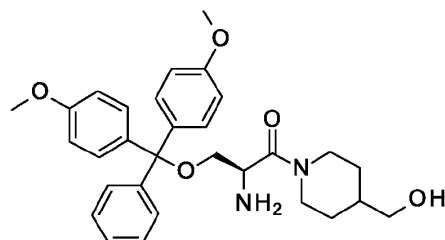
9H-Fluoren-9-ylmethyl N-[(1S)-1-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-2-[4 - (hydroxymethyl)-1-piperidyl]-2-oxo-ethyl]carbamate



[00099] Slowly added HBTU (78.3 g, 0.206 mol), HOBt (27.9 g, 0.206 mol), and piperidin-4-yl methanol (15.4 g, 0.134 mol) followed by TMP (15 mL, 0.113 mol) to a stirring solution of (2S)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-(9H-fluoren-9-ylmethoxycarbonylamino) propanoic acid (62 g, 0.103 mol) in DCM (750 mL) at 0 °C under inert atmosphere. Allowed the resulting reaction mixture to reach ambient temperature and stirred for 4 hours. After this time, diluted the mixture with water and extracted with DCM. Dried the organics over anhydrous sodium sulphate, filtered, and concentrated *in vacuo*. Purified the resulting residue via silica gel flash chromatography eluting with 20-40% EtOAc/hexane and 1% MeOH/DCM to give the title compound (40 g, 52% over two steps). ¹H NMR (DMSO-d₆) δ 7.88 (br d, *J* = 7.5 Hz, 2H), 7.79 - 7.59 (m, 3H), 7.45 - 7.12 (m, 13H), 6.92 - 6.76 (m, 4H), 4.79 - 4.44 (m, 2H), 4.32 (br d, *J* = 11.4 Hz, 2H), 4.20 (br s, 2H), 3.71 (s, 6H), 3.21 (br s, 4H), 2.99 - 2.79 (m, 1H), 2.69 (br s, 2H), 1.81 - 1.43 (m, 3H), 1.08 - 0.73 (m, 2H).

Preparation 7

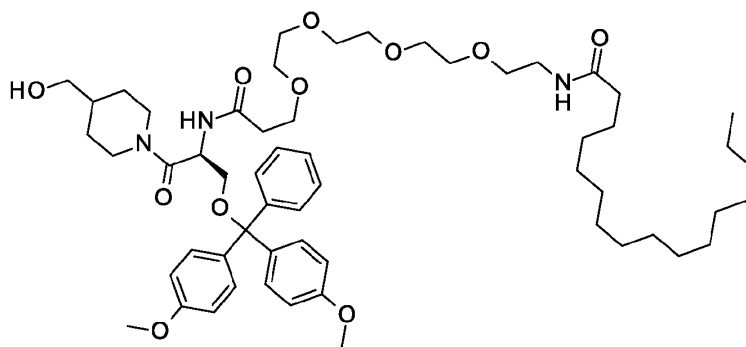
(2S)-2-Amino-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-1-[4-(hydroxymethyl)-1-piperidyl]propan-1-one



[000101] Slowly added a solution of 20% piperidine in DMF (400 mL) to 9H-fluoren-9-ylmethyl N-[(1S)-1-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-2-[4-(hydroxymethyl)-1-piperidyl]-2-oxo-ethyl]carbamate (40 g, 0.055 mol) at 0 °C under inert atmosphere. Allowed the mixture to warm to ambient temperature and stirred for 1 hour. After this time, diluted the mixture with water and extracted with EtOAc. Dried organics over anhydrous sodium sulphate, filtered, and concentrated *in vacuo*. Purified the resulting residue via silica gel flash chromatography eluting with 1-8% MeOH/DCM to give the title compound as an off-white solid (13 g, 47%). ES/MS m/z 1009.5 (2M+H).

Preparation 8

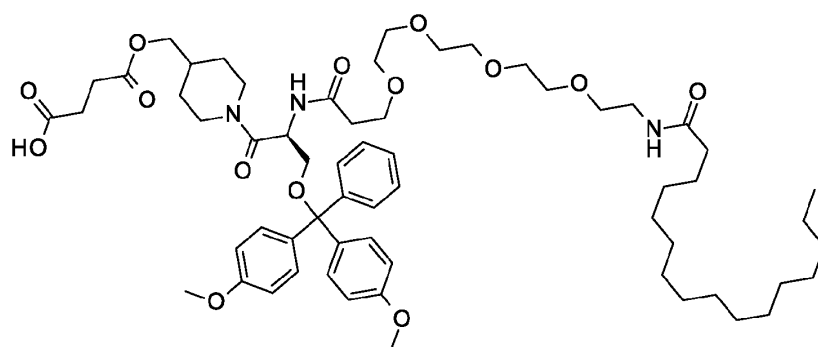
N-[2-[2-[2-[2-[3-[[[(1S)-1-[[Bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-2-[4-(hydroxymethyl)-1-piperidyl]-2-oxo-ethyl]amino]-3-oxo-propoxy]ethoxy]ethoxy]ethyl]hexadecanamide



[000103] Combined 3-[2-[2-[2-[2-(hexadecanoylamino)ethoxy]ethoxy]ethoxy]ethoxy]propanoic acid (496 mg, 0.984 mmol), HOBt (146 mg, 1.08 mmol), HBTU (410 mg, 1.08 mmol), and DIEA (1.03 mL, 5.90 mmol) in DMF (9.84 mL) and stirred at ambient temperature for 10 minutes. Added (2S)-2-amino-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-1-[4-(hydroxymethyl)-1-piperidyl]propan-1-one (546 mg, 1.08 mmol) to the mixture and stirred at ambient temperature for 16 hours. Partitioned the mixture between EtOAc and saturated aqueous sodium chloride solution. Separated the layers and washed the organics with saturated aqueous sodium chloride solution. Dried the organics over sodium sulfate, filtered, and concentrated *in vacuo*. Purified the resulting residue by silica gel flash chromatography eluting with 0-10% MeOH/DCM to give the title compound as an oil (327 mg, 34%). ¹H NMR (DMSO-*d*₆) 8.21 (d, *J* = 8.5 Hz, 1H), 7.80 (t, *J* = 5.6 Hz, 1H), 7.37-7.28 (m, 4H), 7.23-7.20 (m, 5H), 6.88 (d, *J* = 8.3 Hz, 4H), 5.06-5.02 (m, 1H), 4.51-4.49 (m, 1H), 4.45-4.40 (m, 1H), 3.97-3.93 (m, 1H), 3.74 (s, 5H), 3.63-3.56 (m, 2H), 3.49-3.48 (m, 4H), 3.47-3.45 (m, 7H), 3.40-3.35 (m, 2H), 3.30 (s, 1H), 3.23-3.13 (m, 7H), 2.41-2.33 (m, 2H), 2.04 (t, *J* = 7.4 Hz, 2H), 1.74-1.69 (m, 3H), 1.51-1.44 (m, 2H), 1.26-1.24 (m, 24H), 1.00-0.97 (m, 1H), 0.88-0.82 (m, 5H).

Preparation 9

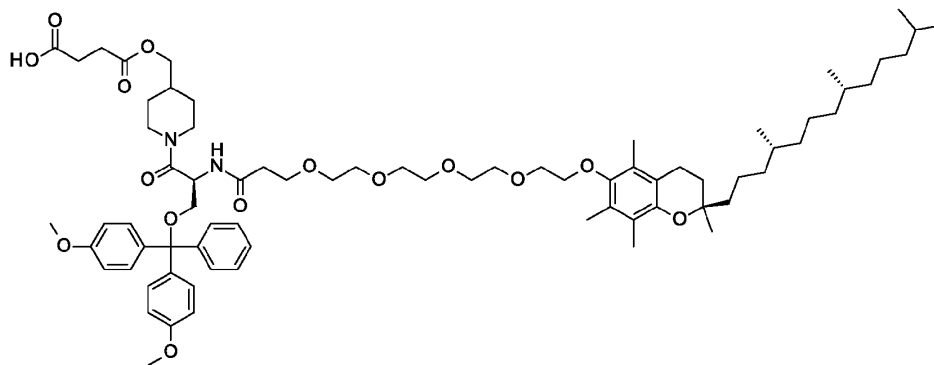
4-[[1-[(2S)-3-[Bis(4-methoxyphenyl)-phenyl-methoxy]-2-[3-[2-[2-[2-[2-(hexadecanoylamino)ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]propanoyl]-4-piperidyl]methoxy]-4-oxo-butanoic acid



[000104] Combined N-[2-[2-[2-[2-[3-[[1S)-1-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-2-[4-(hydroxymethyl)-1-piperidyl]-2-oxo-ethyl]amino]-3-oxo-propoxy]ethoxy]ethoxy]ethoxy]ethyl]hexadecanamide (320 mg, 0.323 mmol), DMAP (120 mg, 0.969 mmol), TEA (225 μ L, 1.62 mmol), and succinic anhydride (64.7 mg, 0.646 mmol) in DCM (6.46 mL) and stirred the mixture for 16 hours at ambient temperature. Purified the mixture directly via silica gel flash chromatography, eluting with 0% to 40% MeOH/DCM, to give the title compound as a colorless oil (279 mg, 79%). ^1H NMR (DMSO- d_6) 12.65-12.64 (m, 1H), 8.24-8.19 (m, 1H), 7.80 (t, J = 5.6 Hz, 1H), 7.37-7.28 (m, 4H), 7.24-7.20 (m, 5H), 6.88 (d, J = 8.6 Hz, 4H), 5.05-5.01 (m, 1H), 4.44-4.40 (m, 1H), 3.97-3.95 (m, 3H), 3.74 (s, 6H), 3.61-3.56 (m, 2H), 3.49-3.45 (m, 11H), 3.38 (t, J = 5.9 Hz, 3H), 3.22-3.14 (m, 6H), 2.48-2.31 (m, 7H), 2.04 (t, J = 7.4 Hz, 2H), 1.90-1.87 (m, 5H), 1.24 (s, 23H), 0.98-0.96 (m, 1H), 0.87-0.82 (m, 4H).

Preparation 10

4-[[1-[(2S)-3-[Bis(4-methoxyphenyl)-phenyl-methoxy]-2-[3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]propanoyl]-4-piperidyl]methoxy]-4-oxo-butanoic acid

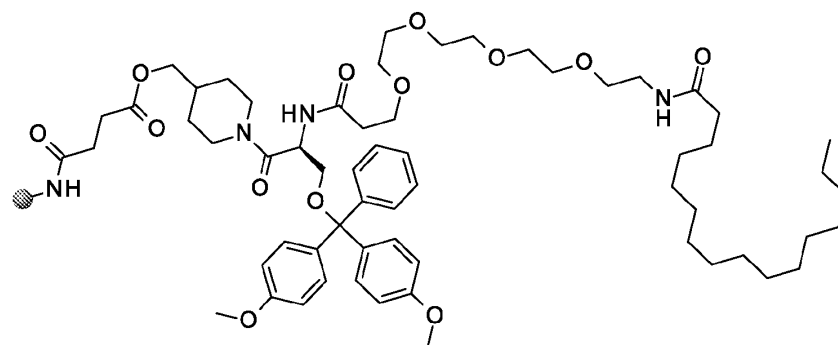


[000105] Combined 3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propanoic acid (1.20 g, 1.80 mmol), HOBt (260 mg, 1.90 mmol), HBTU (740 mg, 1.90 mmol), and DIEA (1.80 mL, 11.0 mmol) in DMF (18.0 mL) and stirred at ambient temperature for 10 minutes. Added (2S)-2-amino-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-1-[4-(hydroxymethyl)-1-piperidyl]propan-1-

one (980 mg, 1.90 mmol) to the mixture and stirred at ambient temperature for 16 hours. Partitioned the mixture between EtOAc and saturated aqueous sodium chloride solution. Separated the layers and washed the organics with saturated aqueous sodium chloride solution. Dried the organic layer over sodium sulfate, filtered, and concentrated *in vacuo*. Purified the resulting residue by silica gel flash chromatography, eluting with 0-10% MeOH/DCM, to give N-[(1S)-1-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-2-[4-(hydroxymethyl)-1-piperidyl]-2-oxo-ethyl]-3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propenamide as a yellow oil. [000106] Combined N-[(1S)-1-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-2-[4-(hydroxymethyl)-1-piperidyl]-2-oxo-ethyl]-3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propenamide (1.45 g, 1.24 mmol), DMAP (456 mg, 3.73 mmol), TEA (867 μ L, 6.22 mmol), and succinic anhydride (249 mg, 2.49 mmol) in DCM (24.9 mL) and stirred for 16 hours at ambient temperature. Concentrated *in vacuo* and purified the resulting residue via silica gel flash chromatography, eluting with 0-40% MeOH/DCM, to give the title compound as an oil (1.36 g, 60%). ES/MS m/z 1264.4 (M-H).

Preparation 11

[[4-[[1-[(2S)-3-[Bis(4-methoxyphenyl)-phenyl-methoxy]-2-[3-[2-[2-[2-[2-(hexadecanoylamino)ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]propanoyl]-4-piperidyl]methoxy]-4-oxo-butanoyl]amino] on CPG

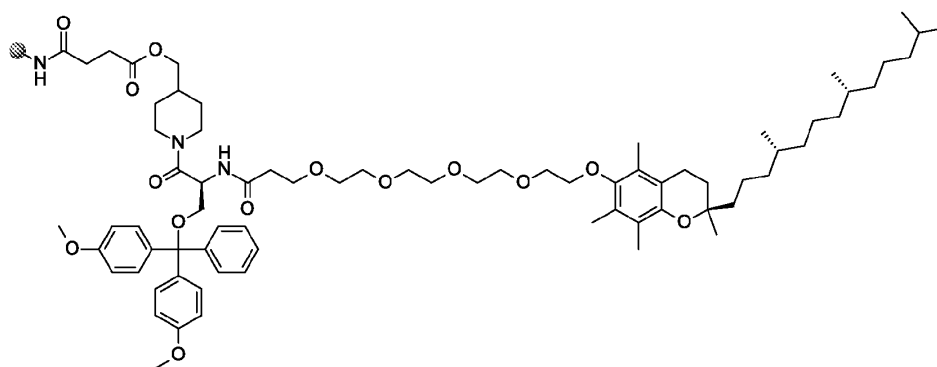


[000107] Dissolved 4-[[1-[(2S)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-[3-[2-[2-[2-[2-(hexadecanoylamino)ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]propanoyl]-4-

piperidyl]methoxy]-4-oxo-butanoic acid (270 mg, 0.248 mmol) in ACN (12.5 mL) and transferred the solution to a fritted glass dropping funnel. Added DIEA (150 μ L, 0.860 mmol) and HBTU (190 mg, 0.500 mmol) to the solution and shook the mixture at ambient temperature for 10 minutes. Added native amino LCAA CPG 500Å (1.92 g, 129 μ mol/g,) to the solution and shook the mixture at 500 RPM for 16 hours at ambient temperature. Drained the CPG and dried under nitrogen for 5 minutes. Washed the CPG with DCM (50 mL), 10% MeOH/DCM (50 mL), and then diethyl ether (50 mL). Dried the CPG for 30 minutes under nitrogen and then resuspended in pyridine (15 mL). Added acetic anhydride (3.30 mL, 35.0 mmol) and TEA (0.50 mL) and shook the mixture at 500 RPM for 2 hours at ambient temperature. Drained the CPG and dried for 5 minutes under nitrogen. Washed the CPG with DCM (50 mL), 10% MeOH/DCM (50 mL), and then diethyl ether (50 mL). Dried the CPG for 45 minutes under nitrogen and determined the ligand loading at 505 nm to give the title compound (1.92 g, 75.5 μ mol/g).

Preparation 12

[[4-[[1-[(2S)-3-[Bis(4-methoxyphenyl)-phenyl-methoxy]-2-[3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]propanoyl]-4-piperidyl]methoxy]-4-oxo-butanoyl]amino] on CPG

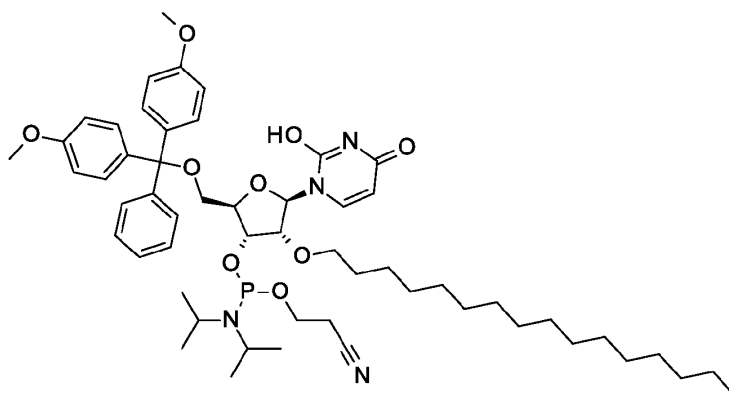


[000108] Prepared the title compound from 4-[[1-[(2S)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-[3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]propanoyl]-4-

piperidyl]methoxy]-4-oxo-butanoic acid in a manner essentially analogous to Preparation 11. Determined the ligand loading at 505 nm to give the title compound (4.01 g, 66.9 $\mu\text{mol/g}$).

Preparation 13

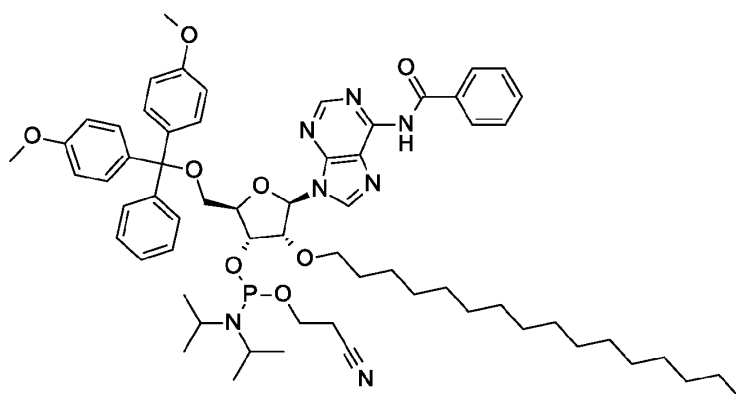
3-[[[(2R,3R,4R,5R)-2-[[Bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hexadecoxy-5-(2-hydroxy-4-oxo-pyrimidin-1-yl)THF-3-yl]oxy-(diisopropylamino)phosphanyl]oxypropanenitrile



[000109] Prepared the title compound according to the protocols described in WO2019217459. ^1H NMR (CD_3CN): 7.86-7.73 (m, 1H), 7.51-7.43 (m, 2H), 7.40-7.23 (m, 7H), 6.95-6.87 (m, 4H), 5.90-5.84 (m, 1H), 5.29-5.21 (m, 1H), 4.54-4.40 (m, 1H), 4.21-4.13 (m, 1H), 4.10-3.56 (m, 13H), 3.50-3.34 (m, 2H), 2.75-2.62 (m, 1H), 2.55 (t, $J=6.0$ Hz, 1H), 1.66-1.51 (m, 2H), 1.40-1.14 (m, 35H), 1.08 (d, $J=6.8$ Hz, 3H), 0.91 (t, $J=6.8$ Hz, 3H). ^{31}P NMR (CD_3CN): 149.6, 149.2.

Preparation 14

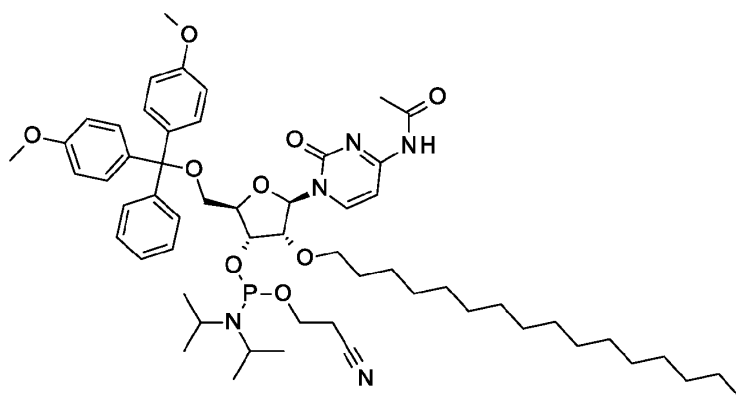
N-[9-[(2R,3R,4R,5R)-5-[[Bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-[2-cyanoethoxy-(diisopropylamino)phosphanyl]oxy-3-hexadecoxy-tetrahydrofuran-2-yl]purin-6-yl]benzamide



[000110] Prepared the title compound according to the protocols described in WO2019217459. $^1\text{H-NMR}$ (CD_3CN) δ 9.37 (s, 1H), 8.57 (d, $J = 9.4$ Hz, 1H), 8.27 (d, $J = 10.3$ Hz, 1H), 7.99 (d, $J = 7.6$ Hz, 2H), 7.61 (d, $J = 7.4$ Hz, 1H), 7.52 (t, $J = 7.6$ Hz, 2H), 7.42 (t, $J = 7.3$ Hz, 2H), 7.34 - 7.16 (m, 7H), 6.85 - 6.77 (m, 4H), 6.11 (dd, $J = 5.0, 2.5$ Hz, 1H), 4.80 (m, 1H), 4.69 (m, 1H), 4.32 (m, 1H), 3.97 - 3.78 (m, 1H), 3.74 (d, $J = 3.1$ Hz, 7H), 3.64 (m, 4H), 3.56 - 3.40 (m, 2H), 3.33 (m, 1H), 2.73 - 2.59 (m, 1H), 2.50 (t, $J = 6.0$ Hz, 1H), 1.52 - 1.45 (m, 2H), 1.33 - 1.12 (m, 37H), 1.09 (d, $J = 6.8$ Hz, 3H), 0.87 (t, $J = 6.8$ Hz, 3H). ^{31}P NMR (CD_3CN) δ 151.19, 150.78.

Preparation 15

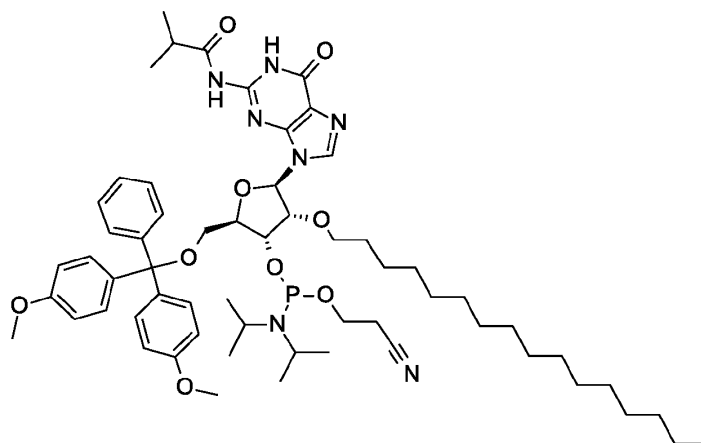
N-[1-[(2R,3R,4R,5R)-5-[[Bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-[2-cyanoethoxy-(diisopropylamino)phosphanyloxy]-3-hexadecoxy-tetrahydrofuran-2-yl]-2-oxo-pyrimidin-4-yl]acetamide



[000111] Prepared the title compound according to the protocols described in WO2019217459. ¹H-NMR (CD₃CN) 9.15 (s, 1H), 8.46 (dd, J = 7.5 Hz, 1H), 7.95 (d, J = 7.6 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.57 - 7.41 (m, 5H), 7.41 - 7.31 (m, 6H), 7.28 (m, 1H), 7.04 (d, J = 15.8 Hz, 1H), 6.90 (t, J = 7.9 Hz, 4H), 5.90 (d, J = 7.8 Hz, 1H), 4.51 (m, 1H), 4.20 (dd, J = 10.6, 8.1 Hz, 1H), 4.04 (dd, J = 31.3, 4.6 Hz, 1H), 3.91 - 3.81 (m, 2H), 3.79 (d, J = 3.1 Hz, 6H), 3.74 (m, 2H), 3.69 - 3.41 (m, 6H), 2.67 - 2.59 (m, 1H), 2.54 - 2.48 (m, 1H), 1.58 (m, 2H), 1.36 (m, 2H), 1.25 (d, J = 4.7 Hz, 26H), 1.21 - 1.09 (m, 10H), 1.04 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H). ³¹P NMR (CD₃CN) δ 151.10, 150.19.

Preparation 16

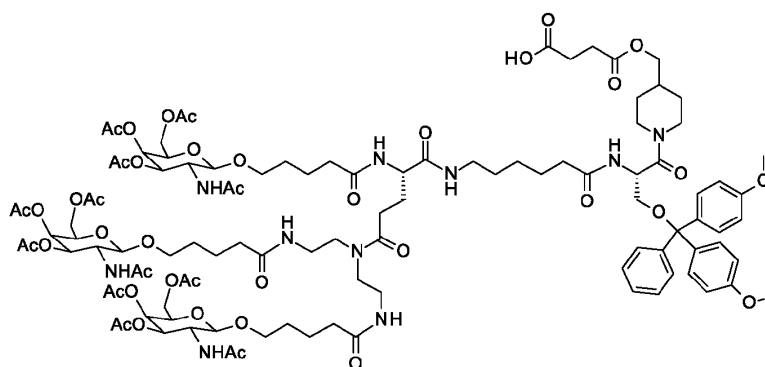
N-[9-[(2R,3R,4R,5R)-5-[[Bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-[2-cyanoethoxy-(diisopropylamino)phosphanyl]oxy-3-hexadecoxy-tetrahydrofuran-2-yl]-6-oxo-1H-purin-2-yl]-2-methyl-propanamide



[000112] Prepared the title compound according to the protocols described in WO2019217459. ¹H-NMR (CDCl₃) δ 12.01-11.96 (m, 1H), 7.82-7.78 (m, 1H), 7.59-7.53 (m, 1H), 7.47-7.42 (m, 1H), 7.41-7.37 (m, 2H), 7.34-7.29 (m, 2H), 7.27-7.22 (m, 3H), 6.85-6.80 (m, 4H), 5.99-5.82 (m, 1H), 4.40-4.36 (m, 1H), 4.17-4.11 (m, 1H), 3.80-3.77 (m, 6H), 3.76-3.68 (m, 6H), 3.22-3.17 (m, 1H), 2.84-2.79 (m, 1H), 1.60-1.54 (m, 4H), 1.35-1.30 (m, 6H), 1.27 (s, 19H), 1.24-1.15 (m, 13H), 1.06-1.03 (m, 5H), 0.93-0.88 (m, 6H), 0.74-0.70 (m, 1H). ³¹P NMR (CDCl₃) δ 150.20, 149.92.

Preparation 17

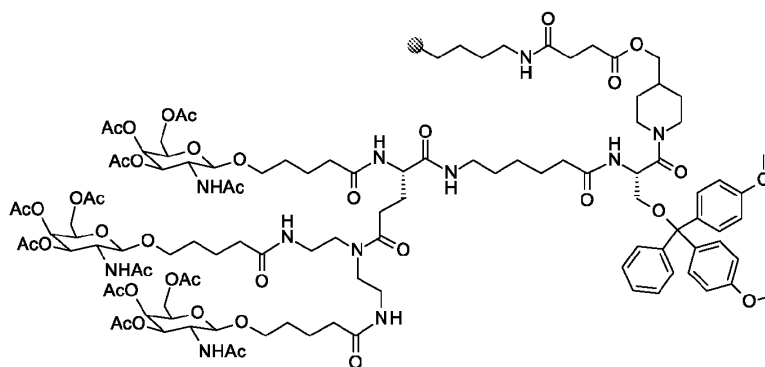
4-[[1-[(2S)-2-[6-[[[(2S)-2-[5-[3-Acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydropyran-2-yl]oxypentanoylamino]-5-[bis[2-[5-[3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydropyran-2-yl]oxypentanoylamino]ethyl]amino]-5-oxo-pentanoyl]amino]hexanoylamino]-3-[bis(4-methoxyphenyl)-phenyl-methoxy]propanoyl]-4-piperidyl]methoxy]-4-oxo-butanoic acid



[000113] Prepared the title compound according to the protocols described in WO2022271806. ES/MS m/z 1109.60 (M-2H)/2.

Preparation 18

Resin loading



[000114] Prepared the title compound from 4-[[1-[(2S)-2-[6-[[[(2S)-2-[5-[3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydropyran-2-yl]oxypentanoylamino]-5-[bis[2-[5-[3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydropyran-2-yl]oxypentanoylamino]ethyl]amino]-5-oxo-pentanoyl]amino]hexanoylamino]-3-[bis(4-

methoxyphenyl)-phenyl-methoxy]propanoyl]-4-piperidyl]methoxy]-4-oxo-butanoic acid according to the protocols described in WO2022271806. The resin loading was calculated to be 34.7 $\mu\text{mol/g}$.

Example 2. Synthesis of SARMI RNAi Agents and Conjugated RNAi Agents

[000115] Single strands (sense and antisense) of the RNA duplexes were synthesized on solid support via a MerMade™ 12 (LGC Biosearch Technologies). The sequences of the sense and antisense strands were shown in Table 2. The oligonucleotides were synthesized via phosphoramidite chemistry at either 5, 10, 25 or 50 μmol scales.

[000116] For the sense strands, the types of solid supports were universal CPG: (3'-Piperidinol-PEG- Palmitate) and (3'-Piperidinol-PEG-Tocopherol) were synthesized in house (see Example 1) while the Universal UnyLinker (Chemgenes, Catalog No. AT273-27), 3'-Teg-Tocopherol (LGC Biosearch Technologies, Catalog No. BG7-1190), and 3'-Cholesterol-TEG CPG (Glen Research, Catalog No. 20-2975) were purchased commercially. For all the antisense strands, commercially available standard support mA was utilized. Standard reagents were used in the oligo synthesis (Table 7), where 0.1M xanthane hydride in pyridine was used as the sulfurization reagent and 20% DEA in ACN was used as an auxiliary wash post synthesis. All monomers (Table 8) were made at 0.1M in ACN and contained a molecular sieves trap bag.

[000117] The oligonucleotides were cleaved and deprotected (C/D) at 45 °C for 20 hours. The sense strands were C/D from the CPG using ammonia hydroxide (28-30%, cold), whereas 3% DEA in ammonia hydroxide (28-30%, cold) was used for the antisense strands. C/D was determined complete by IP-RP LCMS when the resulting mass data confirmed the identity of sequence. Dependent on scale, the CPG was filtered via 0.45 μm PVDF syringeless filter, 0.22 μm PVDF Steriflip® vacuum filtration or 0.22 μm PVDF Stericup® Quick release. The CPG was back washed/rinsed with either 30% ACN/RNase free water or 30% EtOH/RNase free water then filtered through the same filtering device and combined with the first filtrate. This was repeated twice. The material was then divided evenly into 50 mL falcon tubes to remove organics via Genevac™. After concentration, the crude oligonucleotides were diluted back to synthesized scale with RNase free water and filtered either by 0.45 μm PVDF syringeless filter, 0.22 μm PVDF Steriflip® vacuum filtration or 0.22 μm PVDF Stericup® Quick release.

[000118] The crude oligonucleotides were purified via AKTA™ Pure purification system using either anion-exchange (AEX) or reverse phase (RP) a source 15Q-RP column. For AEX, an ES Industry Source™ 15Q column maintaining column temperature at 65 °C with MPA: 20mM NaH₂PO₄, 15% ACN, pH 7.4 and MPB: 20 mM NaH₂PO₄, 1M NaBr, 15% ACN, pH 7.4. For RP, a Source™ 15Q-RP column with MPA: 50mM NaOAc with 10% ACN and MPB: 50mM NaOAc with 80% ACN. In all cases, fractions which contained a mass purity greater than 85% without impurities >5% were combined.

[000119] The purified oligonucleotides were desalted using 15 mL 3K MWCO centrifugal spin tubes at 3500xg for ~30 min. The oligonucleotides were rinsed with RNase free water until the eluent conductivity reached < 100 usem/cm. After desalting was complete, 2-3 mL of RNase free water was added then aspirated 10x, the retainment was transferred to a 50 mL falcon tube, this was repeated until complete transfer of oligo by measuring concentration of compound on filter via nanodrop. The final oligonucleotide was then nano filtered 2x via 15 mL 100K MWCO centrifugal spin tubes at 3500xg for 2 min. The final desalted oligonucleotides were analyzed for concentration (nano drop at A260), characterized by IP-RP LCMS for mass purity and UPLC for UV-purity.

[000120] For the preparation of duplexes, equimolar amounts of sense and antisense strand were combined and heated at 65 °C for 10 minutes then slowly cooled to ambient temperature over 40 minutes. Integrity of the duplex was confirmed by UPLC analysis and characterized by LCMS using IP-RP. All duplexes were nano filtered then endotoxin levels measured via Charles River Endosafe® Cartridge Device to give the final compounds of conjugated RNAi (Table 9). For in vivo analysis, the appropriate amount of duplex was lyophilized then reconstituted in 1X PBS for rodent studies and a CSF for non-human primate studies.

Table 7 - Oligonucleotide Synthesis Reagents

Reagents
Activator Solution (0.5M ETT in ACN)
Cap A (Acetic Anhydride, Pyridine in THF, 1:1:8)
Cap B (1-Methylimidazole in THF, 16:84)

Oxidation Solution (0.02M Iodine in THF/Pyridine/Water, 70:20:10)
Deblock Solution, 3% TCA in DCM (w/v)
Acetonitrile (Anhydrosolv, Water max. 10 ppm)
Xanthane Hydride (0.1 M in Pyridine)
Diethylamine (20 % in Acetonitrile)

Table 8 - Phosphoramidites

Phosphoramidite	Abbreviation	Supplier	Catalog #	CAS
DMT-2'-F-A(Bz)-CE Phosphoramidite	fA	Hongene	PD1-001	136834-22-5
DMT-2'-F-C(Ac)-CE Phosphoramidite	fC	Hongene	PD3-001	159414-99-0
DMT-2'-F-G(iBu)-CE Phosphoramidite	fG	Hongene	PD2-002	144089-97-4
DMT-2'-F-U-CE Phosphoramidite	fU	Hongene	PD5-001	146954-75-8
DMT-2'-O-Me-A(Bz)-CE Phosphoramidite	mA	Hongene	PR1-001	110782-31-5
DMT-2'-O-Me-C(Ac)-CE Phosphoramidite	mC	Hongene	PR3-001	199593-09-4
DMT-2'-O-Me-G(iBu)-CE Phosphoramidite	mG	Hongene	PR2-002	150780-67-9
DMT-2'-O-Me-U-CE Phosphoramidite	mU	Hongene	PR5-001	110764-79-9
5'bis(POM) vinyl phosphate-2'-Ome-U3'CE phosphoramidite	POM-VPmU	Hongene	PR5-032	BVPMUP23B2A1
Reverse Abasic phosphoramidite	iAb	Chemgenes	ANP-1422	401813-16-9

Abasic phosphoroamidite	Ab	Chemgenes	ANP-7058	129821-76-7
Uhd	Uhd	Lilly		
Chd	Chd	Lilly		
Ahd	Ahd	Lilly		
Ghd	Ghd	Lilly		

Table 9 – Conjugated SARM1 RNAi Agents

Conjugated RNAi Agent No.	RNAi Agent No.	Strand	LDP	MW Cal. (g/mol)	MW Obs. (g/mol)
1	13	S: SEQ ID NO: 13	1*	7618.5	7619.1
		AS: SEQ ID NO: 14		7880.2	7881.3
2	14	S: SEQ ID NO: 15	1	7603.5	7604.7
		AS: SEQ ID NO: 16		7865.2	7866.2
3	15	S: SEQ ID NO: 17	1	7546.5	7547.4
		AS: SEQ ID NO: 18		7843.2	7844.4
4	16	S: SEQ ID NO: 19	1	7641.6	7642.7
		AS: SEQ ID NO: 20		7825.2	7827.1
5	17	S: SEQ ID NO: 21	1	7761.6	7762.3
		AS: SEQ ID NO: 22		7698.1	7699.4
6	18	S: SEQ ID NO: 23	1	7602.5	7603.2

		AS: SEQ ID NO: 24		7825.2	7826.5
7	7	S: SEQ ID NO: 13	8*	7675.6	7675.8
		AS: SEQ ID NO: 33		7884.2	7884.8
8	8	S: SEQ ID NO: 15	8	7660.5	7660.9
		AS: SEQ ID NO: 27		7869.2	7869.5
9	9	S: SEQ ID NO: 17	8	7603.5	7604.0
		AS: SEQ ID NO: 45		7847.1	7847.3
10	10	S: SEQ ID NO: 19	8	7698.6	7698.7
		AS: SEQ ID NO: 46		7829.2	7829.2
11	11	S: SEQ ID NO: 21	8	7818.7	7818.5
		AS: SEQ ID NO: 39		7702.1	7702.3
12	12	S: SEQ ID NO: 23	8	7659.6	7660.0
		AS: SEQ ID NO: 47		7829.2	7829.7
13	8	S: SEQ ID NO: 15	9*	8406.2	8407.6
		AS: SEQ ID NO: 27		7869.2	7870.5
14	19	S: SEQ ID NO: 28	9	8418.2	8418.6

		AS: SEQ ID NO: 29		7857.2	7857.2
15	20	S: SEQ ID NO: 28	9	8418.2	8418.7
		AS: SEQ ID NO: 30		7857.2	7857.3
16	21	S: SEQ ID NO: 28	9	8418.2	8418.7
		AS: SEQ ID NO: 31		7857.2	7857.2
17	22	S: SEQ ID NO: 28	9	8418.2	8418.6
		AS: SEQ ID NO: 32		7893.3	7893.4
18	7	S: SEQ ID NO: 13	9	8421.2	8421.9
		AS: SEQ ID NO: 33		7884.2	7885.7
19	23	S: SEQ ID NO: 34	9	8433.2	8433.7
		AS: SEQ ID NO: 35		7872.2	7872.5
20	24	S: SEQ ID NO: 34	9	8433.2	8433.5
		AS: SEQ ID NO: 36		7872.2	7872.6
21	25	S: SEQ ID NO: 34	9	8433.2	8433.5
		AS: SEQ ID NO: 37		7872.2	7872.5
22	26	S: SEQ ID NO: 34	9	8433.2	8433.5
		AS: SEQ ID NO: 38		7908.3	7908.6
23	11	S: SEQ ID NO: 21	9	8564.3	8564.3

		AS: SEQ ID NO: 39		7702.1	7702.3
24	27	S: SEQ ID NO: 40	9	8576.3	8576.9
		AS: SEQ ID NO: 41		7690.0	7690.3
25	28	S: SEQ ID NO: 40	9	8576.3	8576.8
		AS: SEQ ID NO: 42		7690.0	7690.4
26	29	S: SEQ ID NO: 40	9	8576.3	8576.8
		AS: SEQ ID NO: 43		7690.0	7690.3
27	30	S: SEQ ID NO: 40	9	8576.3	8577.1
		AS: SEQ ID NO: 44		7726.1	7726.3

“S” means the sense strand; “AS” means the antisense strand. * LDP 1, 8, 9 is linked to the 3' end of the sense strand. AS SEQ ID NOs: 14, 16, 18, 20, 22, and 24 include a 5'-vinylphosphonate; and all the other AS in this table include a 5'-phosphate.

Example 3. Characterization of SARM1 RNAi Agents

[000121] Selected SARM1 RNAi agents were tested *in vitro* for SARM1 inhibition in cultured cells, including SH-SY5Y cells and/or human induced pluripotent stem cells (hiPSC).

Materials and Methods

[000122] **SH-SY5Y Cell Culture and RNAi Treatment and Analysis:** SH-SY5Y cells (ATCC CRL-2266) were derived from the SK-N-SH neuroblastoma cell line (Ross, R. A., et al., 1983. J Natl Cancer Inst 71, 741-747). The base medium was composed of a 1:1 mixture of ATCC-formulated Eagle's Minimum Essential Medium, (Cat No. 30-2003), and F12 Medium. The complete growth medium was supplemented with 10% fetal bovine serum, 1X amino acids, 1X sodium bicarbonate, and 1X penicillin-streptomycin (Gibco) and cells incubated at 37 °C in a humidified atmosphere of 5% CO₂. On Day One, SH-SY5Y cells were plated in 96 well fibronectin coated tissue culture plates and allowed to attach overnight. On Day Two, complete

media was removed and replaced with RNAi agent in serum free media. Cells were incubated with RNAi agent for 72 hours before analysis of gene expression. Analysis of changes in gene expression in RNAi treated SH-SY5Y cells was measured using Cells-to-CT Kits following the manufacturer's protocol (ThermoFisher A35377). Predesigned gene expression assays (supplied as 20X mixtures) were selected from Applied Bio-systems (Foster City, CA, USA). The efficiencies of these assays (ThermoFisher Hs00240906_m1 SARM1 and ThermoFisher Hs99999905_m1 GAPDH) were characterized with a dilution series of cDNA. RT-QPCR was performed in MicroAmp Optical 384-well reaction plates using QuantStudio 7 Flex system. The delta-delta CT method of normalizing to the housekeeping gene GAPDH was used to determine relative amounts of gene expression. GraphPad Prism v9.0 was used to determine IC50 with a four parameter logistic fit.

[000123] **Human Induced Pluripotent Stem Cell-derived Neuron (hiPSC Neuron)**
Culture and RNAi Treatment and Analysis: Doxycycline-inducible Neurogenin2 (NGN2) human induced Pluripotent Stem Cells (hiPSC) were developed by Bioneer for Eli Lilly. The hiPSC were doxycycline-induced for three days (DIV3) to initiate neuronal differentiation and plated on 96-well PDL and laminin coated plates at 30k/well and grown in Neuronal Differentiation Media (NDM) consisting of DMEM/F12 (Life Technologies 11330-057), Neurobasal media (Gibco 15240062), antibiotics, supplements, growth factors and doxycycline in an incubator (37°C/ 5%CO2). Cells were half-fed every seven days, and on DIV21, RNAi agent was serially diluted in NDM, and cells were treated with RNAi by aspirating 75 µL and adding 75 µL of 2x RNAi concentration for a final of 1x RNAi according to dilutions. Cells were half-fed every seven days after treatment by removing half of media and adding back fresh NDM. Cell lysates were harvested at DIV35 (14 days after RNAi treatment) or DIV42 (21 days after RNAi treatment) and RT-qPCR was performed using TaqMan Fast Advanced Cells-to-CT Kit (ThermoFisher, A35377) and to determine mRNA knock down using SARM1 probe as the gene of interest (ThermoFisher, Hs00240907_m1) and ACTb probe as the housekeeping gene (ThermoFisher, Hs99999903_m1).

Results

[000124] Table 10 summarizes the percentage knockdown of SARM1 mRNA and IC₅₀ of the SARM RNAi agents in human SH-SY5Y cells. The tested SARM1 RNAi agents achieved robust SARM1 mRNA knockdown in human SH-SY5Y cells.

Table 10. *In vitro* activities of selected SARM1 RNAi agents

SARM1 RNAi Agent	SH-SY5Y, 3d IC₅₀ (nM)	SH-SY5Y, 3d % KD (knockdown) of SARM1 at 1 μM	hiPSC Neurons, 21d IC₅₀ (nM)	hiPSC Neurons, 21d % KD (knockdown) of SARM1 at 1 μM
Conjugated RNAi Agent NO. 1	99.41	71.91	NA	NA
Conjugated RNAi Agent NO. 2	28.27	80.41	NA	NA
Conjugated RNAi Agent NO. 3	23.7	77.28	NA	NA
Conjugated RNAi Agent NO. 4	61.95	75.45	NA	NA
Conjugated RNAi Agent NO. 5	53.11	75.68	NA	NA
Conjugated RNAi Agent NO. 6	113.9	83.94	NA	NA
Conjugated RNAi Agent NO. 7	6.30	82.25	13.05	70.37
Conjugated RNAi Agent NO. 8	4.16	77.08	7.11	68.11
Conjugated RNAi Agent NO. 9	4.63	84.37	14.31	68.05
Conjugated RNAi Agent NO. 10	6.84	87.74	9.54	84

Conjugated RNAi Agent NO. 11	5.16	83.84	8.86	67.96
Conjugated RNAi Agent NO. 12	12.23	84.51	26.29	68.15

“NA” means not available.

Example 4. Knockdown of SARM1 mRNA in the Cynomolgus Monkey following a single intrathecal administration of selected RNAi Agent

[000125] The efficacy of selected SARM1 RNAi agents were tested in cynomolgus monkey (*Macaca fascicularis*). To assess the efficacy of the RNAi agent in knocking down SARM1; five groups of four cynomolgus monkeys per group were ported with indwelling catheters at L4/L5 with the catheter tip placed at T12/L1. The monkeys were infused with either aCSF (cerebrospinal fluid) or 20 mg of the Conjugated RNAi Agent No. 1-4 (8mg/ml in aCSF) over 15 minutes and were perfused 28 days later. Tissues collected at necropsy included spinal cord (lumbar, cervical, thoracic) and brain (motor cortex, medulla, pons, and midbrain). qPCR was performed to determine mRNA knockdown in multiple spinal cord and brain regions.

[000126] Table 11 summarizes the percentage knockdown of SARM1 mRNA in cynomolgus monkey. As shown in Table 11, robust SARM1 mRNA knockdown was observed in all the tested regions 28 days after a single intrathecal administration of the RNAi agent.

Table 11. The Percentage Knockdown (KD) of SARM1 mRNA in Cynomolgus Monkey following a single intrathecal administration of selected RNAi Agent.

Conjugated RNAi Agent No.	% KD Lumbar Spinal Cord	% KD Cervical Spinal Cord	% KD Thoracic Spinal Cord	% KD Motor Cortex	%KD Medulla	% KD Pons	% KD Midbrain
1	76.93	57.80	71.20	72.46	68.31	31.13	32.07
2	79.38	69.82	76.63	78.31	78.28	60.38	46.89
3	78.83	68.22	73.99	74.06	67.33	56.47	42.90
4	59.99	38.46	49.01	62.27	68.22	27.73	22.92

Example 5. Knockdown of human SARM1 mRNA in the liver of AAV mouse model

[000127] All animals were individually housed in a temperature-controlled facility with 12h/12h light/dark cycle. Animal protocols in this study were approved by the Eli Lilly and Co., Animal Use and Care Committee (Protocol No. 20-025). A liver centric model over-expressing human SARM1 was generated using ~8-week-old C57BL/6 male mice through a single dose administration of 10^{11} genome copies (GC) of AAV8-TBG vector harboring *Homo sapiens* SARM1 in PBS by intravenous injection. At 14 days post-AAV administration, a selected RNAi agent or control agent (PBS) were subcutaneously injected at 3 mg/kg (n=6 per group). Mice were sacrificed and livers assessed for human SARM1 mRNA levels at 14 days post-subcutaneous injection of RNAi agent or control. Knockdown levels of in vivo human SARM1 mRNA were determined by comparison to control group.

[000128] Table 12 summarizes the percentage knockdown of human SARM1 mRNA in the liver of AAV mouse model.

Table 12. The Percentage Knockdown (KD) of human SARM1 mRNA in the liver of AAV mouse model.

Agent	% KD of human SARM1 in the liver of AAV mouse model	Standard Error
Control	0	0.1
Conjugated RNAi Agent No. 13	47.9	3.9
Conjugated RNAi Agent No. 14	60.3	3.9
Conjugated RNAi Agent No. 15	59.1	3.2
Conjugated RNAi Agent No. 16	64.5	5.8
Conjugated RNAi Agent No. 17	36.2	15.3
Conjugated RNAi Agent No. 18	9.4	15.3

Conjugated RNAi Agent No. 19	29.6	5.9
Conjugated RNAi Agent No. 20	47.5	5.7
Conjugated RNAi Agent No. 21	47.4	1.8
Conjugated RNAi Agent No. 22	40.7	5.5
Conjugated RNAi Agent No. 23	24.9	4.5
Conjugated RNAi Agent No. 24	57.9	3.4
Conjugated RNAi Agent No. 25	58.6	2.9
Conjugated RNAi Agent No. 26	55.6	3.4
Conjugated RNAi Agent No. 27	32.9	2.8

SEQUENCE LISTING

SEQ ID NO	Sequence
1	GUUGCUCGACUCUAACCGCUA
2	UAGCGGUUAGAGUCGAGCAACGG
3	UUCGCCAACUAUUCUACGUGA
4	UCACGUAGAAUAGUUGGCGAAGG
5	ACCUUCGCCAACUAUUCUACA
6	UGUAGAAUAGUUGGCGAAGGUCU
7	CGCCAACUAUUCUACGUGCGA
8	UCGCACGUAGAAUAGUUGGCGAA
9	CCGCAAGAGGUUCUUUAGGGA
10	UCCCUAAAGAACCUCUUGCGGGU
11	AAACGCCUGGUUCCUACUCA
12	UGAGUAGGAAACCAGGCGUUUCA
13	mG*mU*mUmGmCmUfCmGfAfCfUmCmUmAmAmCmCmGmC*mU*mA
14	VPmU*fA*mGmCmGfGmUmUmAmGmAmGmUfCmGfAmGmCmAmAmC*mG*mG
15	mU*mU*mCmGmCmCfAmAfCfUfAmUmUmCmUmAmCmGmU*mG*mA
16	VPmU*fC*mAmCmGfUmAmGmAmAmUmAmGfUmUfGmGmCmGmAmA*mG*mG
17	mA*mC*mCmUmUmCfGmCfCfAfAmCmUmAmUmUmCmUmA*mC*mA
18	VPmU*fG*mUmAmGfAmAmUmAmGmUmUmGfGmCfGmAmAmGmGmU*mC*mU
19	mC*mG*mCmCmAmAfCmUfAfUfUmCmUmAmCmGmUmGmC*mG*mA
20	VPmU*fC*mGmCmAfCmGmUmAmGmAmAmUfAmGfUmUmGmGmCmG*mA*mA
21	mC*mC*mGmCmAmAfGmAfGfGfUmUmCmUmUmUmAmGmG*mG*mA
22	VPmU*fC*mCmCmUfAmAmAmGmAmAmCmCfUmCfUmUmGmCmGmG*mG*mU
23	mA*mA*mAmCmGmCfCmUfGfGfUmUmUmCmCmUmAmCmU*mC*mA
24	VPmU*fG*mAmGmUfAmGmGmAmAmAmCmCfAmGfGmCmGmUmUmU*mC*mA
25	1 ATCTCCAGC TCAGCCGAGC CCGTGCCAG GCCACGCTTT GTTCCAGCCG CCGCTCCTC 61 TACCCTACGG CGTCCGGAGC CATCCCTCGC CTGCTCGCTC TCTCCTTTTCG CCCACTCCCT 121 GCATCTGGGC CTGCATCACC TTGCCAACC GCTCCCCGA TCCTGCCGAC ACTCCTCCCC 181 CAAACTTCTG ACCGGCACCC TTGCTGGTA CCCTTCTCTC CATTCCTCCC CCTCCATCTT 241 CTTTCCCCGA CCCCTCTCGG GTCCCTCTTT TCCAAAACC CGGGTCTCTC CGCGTGCCCC 301 CGCTCCAGG CCGGGGATGT CCCCCGCGC CCCGCGCCA TGGTCTGAC GCTGCTTCTC 361 TCCGCCTACA AGCTGTGTCG CTTCTTCGCC ATGTGCGGCC CACGGCCGGG CGCCGAGCGG 421 CTGGCGGTGC CTGGGCCAGA TGGGGCGGT GGCACGGGCC CATGGTGGGC TGCGGGTGGC 481 CGCGGGCCCC GCGAAGTGTG GCCGGGGCA GGCACGAGG TGCAGGACGC CCTGGAGCGC 541 GCGTGCCGG AGCTGCAGCA GGCCTTGTC GCGTGAAGC AGCGGGCGG CGCGGGGCC

601	GTGGGCGCCG GCCTGGCCGA GGTCTTCAA CTGGTGGAGG AGGCCTGGCT GCTGCCGGCC
661	GTGGGCGCG AGGTAGCCCA GGGTCTGTGC GACGCCATCC GCCTCGATGG CGGCCTCGAC
721	CTGCTGTGC GGCTGCTGCA GGCGCCGAG TTGGAGACGC GTGTGCAGGC CGCGCGCCTG
781	CTGGAGCAGA TCCTGGTGGC TGAGAACCGA GACCGCGTGG CGCGCATTTG GCTGGGCGTG
841	ATCCTGAACC TGGCGAAGGA ACGCGAACCC GTAGAGCTGG CGCGGAGCGT GGCAGGCATC
901	TTGGAGCACA TGTTCAGCA TTCGAGGAG ACATGCCAGA GGCTGGTGGC GGCCGGCGGC
961	CTGGACGCGG TGCTGTATTG GTGCCGCCG ACGGACCCCG CGCTGCTGCG CCACTGCGCG
1021	CTGGCGCTGG GCAACTGCGC GTGCACGGG GGCCAGGCGG TGCAGCGACG CATGGTAGAG
1081	AAGCGCGCAG CCGAGTGGCT CTTCCCGCTC GCCTTCTCCA AGGAGGACGA GCTGCTTCGG
1141	CTGCACGCCT GCCTCGCAGT AGCGGTGTTG GCGACTAACA AGGAGGTGGA GCGCGAGGTG
1201	GAGCGCTCGG GCACGCTGGC GCTCGTGGAG CCGCTTGTGG CCTCGCTGGA CCCTGGCCGC
1261	TTGCCCCGCT GTCTGGTGGG CGCCAGCGAC ACAAGCCAGG GCCGCGGGCC CGACGACCTG
1321	CAGCGCCTCG TGCCGTGTCT CGACTCTAAC CGTTGGAGG CGCAGTGCAT CGGGGCTTTC
1381	TACCTCTGCG CCGAGGTGC CATCAAGAGC CTGCAAGGCA AGACCAAGGT GTTCAGCGAC
1441	ATCGGCGCCA TCCAGAGCCT GAAACGCCTG GTTTCCTACT CTACCAATGG CACTAAGTCG
1501	GCGCTGGCCA AGCGCGCCT GCGCTGCTG GCGCAGGAGG TGCCACGGCC CATCTTGCCC
1561	TCCGTGCCCA GCTGGAAGGA GGCCGAGGTT CAGACGTGGC TGCAGCAGAT CGGTTTCTCC
1621	AAGTACTGCG AGAGCTTCCG GGAGCAGCAG GTGGATGGCG ACCTGCTTCT GCGGCTCAGC
1681	GAGGAGGAAC TCCAGACCGA CCTGGGCATG AAATCGGGCA TCACCCGCAA GAGGTTCTTT
1741	AGGGAGCTCA CGGAGCTCAA GACCTTCGCC AACTATTCTA CGTGCACCG CAGCAACCTG
1801	GCGGACTGGC TGGGCAGCCT GGACCCGCGC TTCCGCCAGT ACACCTACGG CCTGGTCAGC
1861	TGCGGCTGG ACCGCTCCCT GCTGCACCG GTGTCTGAGC AGCAGCTGCT GGAAGACTGC
1921	GGCATCCACC TGGGCGTGCA CCGCGCCCGC ATCTCACGG CGGCCAGAGA AATGCTACAC
1981	TCCCCGCTGC CTGTACTGG TGGCAAACCC AGTGGGGACA CTCCAGATGT CTTTCATCAGC
2041	TACCGCCGGA ACTCAGGTTT CCAGCTGGCC AGTCTCCTGA AGGTGCACCT GCAGCTGCAT
2101	GGCTTCAGTG TCTTCATTGA TGTGGAGAAG CTGGAAGCAG GCAAGTTCGA GGACAACTC
2161	ATCCAGAGTG TCATGGGTGC CCGCAACTTT GTGTTGGTGC TATCACCTGG AGCACTGGAC
2221	AAGTGCATGC AAGACCATGA CTGCAAGGAT TGGGTGCATA AGGAGATTGT GATGCTTTA
2281	AGTGCGGCA AGAACATTG GCCCATCATT GATGGCTTCG AGTGGCTGA GCCCGACTC
2341	CTGCCCTGAGG ACATGCAGGC TGTGCTTACT TTCAACGCTA TCAAGTGGTC CCACGAATAC
2401	CAGGAGGCCA CCATTGAGAA GATCATCCGC TTCTGCAGG GCCGCTCCTC CCGGGACTCA
2461	TCTGCAGGCT CTGACACCAG TTTGAGGGT GCTGCACCCA TGGGTCCAAC CTAACCACTC
2521	CCCACTTCCC CAGCCCTGCT GTGACTTCCA TTTCCATCGT CCTTCTGAA GGAACAGCTC
2581	CTGAAACCAG TCTCCCTGGG CTGAGACAAC CTGGGCTCTT CTTAGGAAAT GGCTCTCCCT
2641	CCCCCTGTCC CCCACCTCA TGGCCCACT CCAACCACT TTCCTCAGTA TCTGGAGAGG
2701	GAAGGGAAGT CAGGCTTGGG CACGGGAGGT TAGAACTCCC CCAGGCCCTG CCATTGGGTT
2761	GTCTGTCTCC GTCATGGGGA GGGTCCCTGC TCAGTTCTGG AGACACTGGA GTTGGGTTGG
2821	GGGTGGTTCT GCATTCCCTT CTCCTGCTGA TAGCAGTCAG CTTGAGGAGG ATGACGGAAG
2881	GCAGCTCAG ACAGGAATTA AGGCAATGCC CAGGCGGGCC TGGGCACTGT ATTCTGAGCA
2941	AGGGCTGGG CCCAGGAGCC AGCCAGGGAT GAGTGCCATC ATGGCTCTCC ACTCAGACTG
3001	TGCCTGGCCC CTGCACTTAC AACTTCCTGC CGCTCTGTGG CCTTGCCCTG TAATCACTCA
3061	GTGCCCTTAG CTAGCCTGAC TAAGTCCCAG ATCCCCTACA GCTTCCTTCG GTGTGGTATC
3121	TTTTGCCACA TCCAGGGCGA GGGTTGAGGC AAACCAGCCC TCCCTCTGAC TTCCTTGTC
3181	CTGCAGCCAG CTTTGTGCA CTTGCTGGT CACAGGAGCC TCCTGTTTGG GCCTGGGTCT
3241	GGGCATGGGG AGGCCGTGCC TCAAAGCCCA CCCTACCCCA TGCCTTGGTG CTGTGCCTCA
3301	GGCTCCTTCC TGGTCTGGCC CAGCTGGCTT CCCCAGCCCC TCAGCCATCC AGGGCTACCC

3361	ACTGCTTACT CAGGGACCAG GCAGCCCCA TGGCAGTAAA AGCAGCCTAG ACAGAACCTG
3421	CAGCTCTGTG GAAAGAGGCA AAGTCCTGAA AAGGCAAAGG GTTGTCACCT AGGGCAGCTT
3481	CTCCAACTTT AACATGCATC CAAGTCACCT GGGAATGTTG TTAATCAG GAGATCTGGG
3541	GTGGGGCCTA GGAAGCTGCA TTCTTACAG ATTCCAGGT GAGCTGATGC TGGTGGTTAA
3601	GGGTAGCAAA TCTCTAAAGC ACGAAGCCCT CACAAATCTT TGCCATTTC CAAACACTCC
3661	GCTCCATGGT CTCCAGTCAT CAGAGCAACT CTACCTGGTA TTATCATCCC CATTTTACAG
3721	ATAATGACAC TGAGGCTCAG AAAGGTTGAG GATAAGCCCA CTTTCTGTC ATTAGTGGCA
3781	GCCCCAGATC CAGACCTAGG CTTCTGGCA CCCAGTCCAC TGGCAGTGA ATTGCTTTCC
3841	TGAGAATCAT TCTGAGGCTG GGCTATTGCT TCTCCCTGTC TTCAAAGAAT CTAGCAGCGG
3901	GGGATAGGAT TTGCAACAA AAAGCTGACC CAGAGGCCAT ACAGAGCAGG AATATCCCAT
3961	TGCCCCCTCC TCCACTGGGT TCAGAGGGTA AGAAAGCACC CTCCAATAAA CCCAGGCTCC
4021	AGGCCGTGGG GGCTGCTGAA GGCTCTTTCC CCGCAAGGGC CAGGTGTTGA CACCTTAAAG
4081	CTGGCTGCGC CCCCAGCCCC ACTCTGGCT GTGCTGGCCA GGTGACTCCT AGTTCTTGGC
4141	CACATCATCA GAAAGTCAAA GGTCTACTC CAGGTTTGGG GCTCCTTCTC TCCACTCCCC
4201	TCCCTGCCAG AGTCTGTCTT GGCCAGTGCC AGCCTCGATG CTTTGGTTT GACCCCACT
4261	GATCTCTCTT TCCTCATGCA GCACAAGTGC TCACCGGGGC CAGAGCCAGG GCATGGATAT
4321	GACAAGCAGG GCAGCCTGGA CACTGCCCTC ACAGGACAGC GCCAATAACA ATACAGTGTC
4381	TGAGTATCTC CAGGGGATGA TTCTGGCTC TTGTCTCCA ATCAGTCCCA CTCCCTCCTG
4441	AGGTCCCAA GGGCAGTATT CAGAGAGGTT TCCTGCGTTT TATTTCTATT TGGTATACCC
4501	TCCACTGTTG TCCACTGCCC TGTGTGGCCT TCTGGTTGAC CTCGCCCCGA TCTTCTGTCT
4561	CTCTGAGGGA ATCAGAGTCC AGCATCCAGC CCCAGCTGGA ACAGCTGAAG TCACAAGCCT
4621	CCTCTAAGCC AAGGCCAGTG GTTCAGAGG TGAAGTCCAC CCATACTAGG ACAAACACAG
4681	CTCAGATCAC CAGGTCAAGC ACCTAGGCCT GGCTTCTCTC GAGACAGAGG ACTCAGAAGT
4741	GGCCTTTCTC CCAAAGCCTG CTCAGACACA GGTCTGTAGG GCCAGGGTGT TCTGCTTGGC
4801	TGGGCTGCAG CTGCTACCCC TCGGTTGGGG CTGAGTCAGC CAGATCCTCC CCCTACTTCT
4861	CCCCAAGGGC CAAGAAGTGC TCAGGGACAT TAAAGGTCAA AAGTCCAGCC ACCTCATTC
4921	ATCCTTTCCC CAGGCCCATG AAGAGAGGCA TCTATTGTA GAATGTATGA GGAAGTGGGA
4981	AGTATCTCAG AGAATCAGCT AAGTTTCCTA ACTGTCCAT CCAATGTGA TCACCACGAT
5041	TCAACAATTT GGGGCAATGC TGATCTAGCC GTTCTAGTG GGGCTTGCTC AAGCTTGAC
5101	AGCAGTCAAG TAGAAGCCCT GGCTGGCCCC ACTTGGTACC AATCCACCAG CAGCTCAGG
5161	GCTCCTGCCC AGCCCAGCAG CTTCTGTGT CTAACGTATG GCAGGCAGAC TGGGAGCAGG
5221	AAAACAGAGG GCCCAAAGC CCAAGGCACC AGAAGGTTG TTTCAGTTG CTGAAGCTGA
5281	TTTGTAAATGA TTGGCACTCT TCAGCCAGGG GAGTGGGTAG GCCATAGCCA AGGATCGATT
5341	CCCCAACAC AGCAAAGGCA ACCTCTTCC TCCAGAGATC ACCAAGCCCC TCTTACCTCC
5401	CTCCCTCCTT CCAAAGGCTG GCACTAACCA GGTACCACAT TCATTGTAA GGAATGGCTG
5461	ATGACTGCTA CACGTGTTGG GAACCTGGTT GGGGCTGTGC AGTTTGGGCT GGAAGGAGAG
5521	ATGCCAGCCC TCGTGTGCC TCTGTCCCT GAAGTGTAC CTCTCTCAGG ACCTCTCCTC
5581	TGGCCTGTGG GGTATAAGT GATGGATAGC AGAAAGGGAG AACTGACTCC TGTCCTAAAT
5641	AGTCTCTCTG CCACCTGTCC TGCAGTGGGC CTGTGTGGGT TATGATTCTA GATCCTAGAC
5701	AGAGGCTGGG TCAGCTGTGG ATGGGGTGGT GCCTTGGTCT CTCTTGACTA CCTCGTCCAA
5761	AGAGAGCACT GCCCTTAGAC AAGAGTTGCT TGTCTGTCTG TGGGCTGGGC TTCCAGCTGC
5821	AGACCTCCAG TTGCTTGGTG TTCACCTTGC TCCTCTTGCC CTCTGTCTTC TGGTCCAGGC
5881	AGATCAGGGG CTCTGGGGAA ACTGCTGGAA CTCGAGGTGA GGATCAGCCT TTTCCAGCAT
5941	CCTGTGAGAG ACCAGAGAGA GAGTTTGGAT TTCATGTGGG GAACCTCAA GGCCTGTCTG
6001	GAGAAAGTAC ACAGGATTTA CTGGGGTGGG CTGGTCCAGG TAGCTCTCCT GAACCTCCTC
6061	CTTCCCCAAG CTGAGAAGCT GAGAGCTGGA GGACAATATC CAGGGACATG GCTCTGAAAA

6121	ATAACTTTTT TTTTTTAAG AGACAGGGTC TTGCTCTGTT GTCCAGGCTG GAGGGCAGTG
6181	ACATAATCAT AGCTCACTGT ACCCTTGAAC TCCTGGGCTC AAGTGATCCT CCTGCCTCAG
6241	CCTCCTTAGT AGCTGGGACT ACCAGTGCAT ACCACCATGC CTGGGTGATT TTTTAAATTT
6301	TTTATACAGA CAAGGTCTTG CTATGTTGCC CAGGCTGATC TTGAATTCCC GGGCTCAAGT
6361	GGTCCTCCTG CCTCAGCCTC CCACAGGATC GGGATTACAG GCAAGAGCCT CCACGCCCGG
6421	CCATGAAATA TAATTCTTAA TATCATAACAG GAAAAAGTCA GCGGGTCAAG CTAGCCTGTG
6481	GCCCAGCCAC AACTAGCTGA CAAAGCTTCC TGGCCTTCCC TTAAACACAG TTCTGTGTC
6541	ATAGTTCCAT CTATAAAATG GGAATGGAGG GAAATAGGGG AACTGGGAGA GAGAACACAG
6601	CCTTGCCAAG CAGCAATGTT AGCCTGATCC TTCCTCCACC TAGCTCGCCA TCTCGCCCTT
6661	GGAAAAATGGC TCCTGGAGGA TTAGGCAGCC ATCTGCAAGG AGAGGGGGCAA CCTGGGACAA
6721	GACACCCAGA GGGTAAGGAT TCCAGGAATG AAGCTGCCAT TTCTGGTTGG GAGGAGAAGA
6781	GGAAACTTTT AAGAGAAAGG GCTCCATTAT GAGCATGGGT TCAGGGCCCT GCATTACCCA
6841	ATCAGAACAG CCGGGATGAG CAGGAGGCCA GCTCCAGGA GGAAGGGGAA CCCCTTCATA
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7021	GGAGTCCGAA AGGGCCATAT TCCAACCTCT GCACCACCAC CTCACAGCTG TGTGACCGG
7081	AGTAGTCACT TAACCTATGT CTCCCCTTCC TCACCAGTAA ATCCTGCTAC ATCATGTACT
7141	GTGACAAGGA TTCAGTAAGG TCATATGTGG ACAGTAGCTG GCACAGAGGG GCTACTAAAC
7201	AAATGGCTGC TATTAATCC ACATTAAGG TACATGTGAT CTGACAGAAC CCAGCACATA
7261	AAAGAAAAAA AAAGTACATG TGATATTGTC TGATGAAAGC TTGATGAAAA TGGCTTTTTT
7321	CTGGTTTATC CTCITTGGAA TCAICTCCTG TTIGGGATTA ACIGCTGGTC TGATCAGTTC
7381	CAATATTCAT AGCGGTGTCA CCACTGAATA GCTTCTTATC CTTTGGGTTC CTGTTCTCTC
7441	TTCTGCTAAA TAAGGATAAT ACCTATTCC TAGATTGTGA GCAACATTAA GTTCACATGG
7501	AAATCACCCA TCACTGGGCC TGGTCCCCTG GAAGTAGCTA GTTAGTAAGG GCTGTTCTTT
7561	TCTCTGTTT CTCTTGACAT CTCTGGGCAC AGAGAAAGTG CTGGGAAAAA AAGTTTAGGT
7621	GAATGAATGA AGACACATGG ATTCTGGGGA CACCAGAACC CACAGTGGGC TCTGTATGGC
7681	ACCAGAGTCT CTGTCAATCAT CAGATCCTCA TTCCAGGACA GATGGAAAAA GATGAATGTT
7741	TCCAGACTGG GGCATAAAGA CCCAGAGGCT GGAGAAAGCTG TTCTTTATAG ATATAACAGG
7801	AGAACCCACA GTTTACAAAA TGTGCAACAA CCAACAGAA GTTGAGATTA AATTCTGTCA
7861	CATCTAGAGG GGTCTGTGAT GTCATCAAAA GCAAACCACC CACATCACAG ATGAAGAAAC
7921	AGGCCTGTGG CAGGGCTCGG ACTAAAACCC AGATCCTGAG ACCAGCTGCT TTAAACACA
7981	GACGTAGGTT TGCATCCTAG CTCCACCATT TACTGAGTAA CCTTGGGTGA GCCAATGTAA
8041	CCCCCTGGGT CTCTGTTTCT TTATCTGTCA ACTGTGGAAA ATGAAACCCA TGTACAAGG
8101	TTGTTCACTT CTGGGCTTGT ACACGCTGAC CCCAGAGAAA CAGGGAACCT TGGCATCACC
8161	ACACCCATCT TACAGACGGA AAAGCTGAGG TCTGCAGAGA GTAAATCCTC TGCTCTGGTT
8221	ATCTAGAAAAG AACATAATTG TGCTCTGCTG ACTGCAAATC CCAACTCTGC GGTTTGAAAA
8281	TCCAAGGTGG CATGATCCTC TGCCCATGTT GGGCAATTC ACAGAAATGT GTTGTGTTTG
8341	GCCACTTACT TCTCCAGGTG GAGAGGGGGG AAGGCAAGCT GTTCCCCCAG CCATGGCTGC
8401	CCATCAGCCC GTTTCGGGCA GCACTGGACA TGAGGAACCA GACACAGGTG GGTCTGTACA
8461	CTCACCTGCT TCTGTCTCTC TCACCAGCTT GGAGAGTTTA GCCCGGATGA CAGGTGTGAT
8521	GACTAATGAC AGGAAAAGCA ACCCATATCC TGTGGAGAAA CAAACACTCA TCAGGAAAAAT
8581	GGGGCTGGGG AGAGGGGCGT CCAAGGGAAA GGCAGCAGAG CTCCTATCCA TACCCACGT
8641	GGGGCTTAGG TTAGACCCAG GAAGAACTTC CTTGATGGTG AGGGTGGGAA GACAGTAGTC
8701	AAGGAGGAAT GGAGACTGCC CTTGTCTGGG CTTGGCCACC TGCTAGCTCT CATGAATGAA
8761	TGCTAATTC CATTGATTGC TTTCTGTCT GAACCTCTTG TGGTCACAGC AGGCATCACC
8821	CACCCACTTG GCACTTAGTA GGGATATGGC AGGGCACAGA AAACAAGCAT GGGCTTTGGA

	<p>8881 GTCAGCCCTG AGTTCAAAC CTGATGCCAT TACATATTAT CTGTGTGGCC TGGGGTACTT 8941 ACCCTCTCTG ATCCTGACTC CCTGTATGAG GAAGATAATA AGGCCTTCAT CACAGGATGG 9001 TTCTGAGGCA TAGGAGGCTG AATAATGGTG CCCAATGGCA TCAGATTTCAT AGCCCTGGAA 9061 CCTGTAAATA CTACCTTATT TGGAAAATGA GTCTATGCAG GTGTGCAGTT AAGCCTCCTG 9121 AGAGAGCAGA GTTATCCTGG ATTAGGTTGG GCCCTAAATG CCGTCACACA TATCTTTATA 9181 AGAGGAAAGC AGACGGAGAT TTGGCACCGA CAGAATTGAG AAGGCACAAA GAGGAGGAGA 9241 GTCAATGTGA GCACAGAGGC AGAGACTGGT GATGGCCGCC CCAAGCCAAG GAATGCCAGC 9301 AGCCCCAGAA GCTGGAAGAA ATGAGAAACA CGTTCTCTCC TGGAGGCTTG CAAGGGAGCA 9361 CTGCCTGCTG ACTGCTTCCA TTCAGCCCGG TGGTACTGAC TTTGGACTTC TGGCCTCCAG 9421 AACTGTGAGA GAATATGTTT CTGTTGTGTT AAGCCCCCAA GTTGTGGTA TGTCAATACA 9481 GCAATCTCAG GGAACCAATA CATGAGGTAA AAAGGTAAACA TCTATGAAGA GCATGGCATA 9541 GGGACACAGC AAATGGGAGT TCCTTTTCCC TTTGCATTCA GTTACTTACA GGCTTCTGT 9601 TTTCTTCATA ACCATTTCTC TCCCTGTGCG ACTGCTGACT CCTCAGCAAA ACTGCAAACT 9661 CCTACAGGAC AGTGGATCCT CCAAAGAAAG TATACGATGA GGCATCCAGG GACCCTAGCA 9721 GTGTCAGGCC CCTCAAATCC CACTCTGTTG AGACCTCCCC CCGACCCAGA GCAATGACAG 9781 CATCTTTATC ATCTCTGCAT CCCCAGGGC CATCAGCAGG AGGGAAAGGT TCCCTTCTGC 9841 TTAATTGTCA GACAAGCAGT TGAGTTAAGA AATCTGTGAT TATTGTATTG TTGACTATAC 9901 ACAGCACATT TTAGGGCTCT ATCAAAATAA ATCTGTCCCT TAAAAAAG TTAATAAAG 9961 CCGGGCACGG TGGCTCATGC CTGTAATCCC AACACTTTGG GAGGCTGAGG CAGGCGGATC 10021 CTTGAGCTCA GGAGTTAGAG ACCTGGACTG GGCAAAATGG TGAGGACCCC ATCTCTATAA 10081 AAAATACAAA AATTAGCAAG GTGTGGTAAT GTGCACCAGT GGTCCAGCT ACTAGAGAGG 10141 CCAAGGTGGG AGGATCATCT GGGCCCGGGG GATGAGGCTG CAGTGAGCCA TGATCGTGCC 10201 ACTGCACTCT AGCCTGGGTA ACAAAGCGAG ACCCTGTCTC TAAATACATC AATCAAATAA 10261 AAATTTTAAA AAGTTAA</p>
26	<p>1 MVLTLLSAY KLCRFFAMSG PRPGAERLAV PGPDGGGGTG PWWAAGGRGP REVSPGAGTE 61 VQDALERALP ELQQALSALK QAGGARAVGA GLAEVFQVE EAWLLPAVGR EVAQGLCDAI 121 RLDGGLDLLL RLLQAPELET RVQAARLLEQ ILVAENRDRV ARIGLGVLN LAKEREPELV 181 ARSVAGILEH MFKHSEETCQ RLVAAGGLDA VLYWCRRTDP ALLRHICALAL GNCALHGGQA 241 VQRRMVEKRA AEWLFLAFLS KEDELLRLHA CLAVAVLATN KEVEREVERS GTLALVEPLV 301 ASLDPGRFAR CLVDASDTSQ GRGPDDLQRL VPLDSNRLE AQCIGAFYLC AEAIAKSLQG 361 KTKVFSDIGA IQSLKRLVSY STNGTKSALA KRALRLLGEE VPRPILPSVP SWKEAEVQTW 421 LQQIGFSKYC ESFREQQVDG DLLLRLTEEE LQTDLGKMSG ITRKRFFREL TELKTFANY 481 TCDRSLNADW LGSLDPRFRQ YTYGLVSCGL DRSLLRHVSE QQLLEDGCIH LGVHRARILT 541 REMLHSPPL PCTGKGKPSGD TPDVFISYRR NSGSQLASLL KVHLQLHGFS VFIDVEKLEA 601 FEDKLIQS VMGARNFVLV LSPGALDKCM QDHDCKDWVH KEIVTALSCG KNIVPIIDGF 661 PEPQVLPE DMQAVLTFNG IKWSHEYQEA TIEKIIRFLQ GRSSRDSSAG SDTSLEGAAP 721 MGPT</p>
27	mU*fC*mAmCmGfUmAmGmAmAmUmAmGfUmUfGmGmCmGmA*mG*mG
28	mU*mU*mCmGmCmCmAmAfCfUfAmUmUmCmUmAmCmGmU*mG*mA
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30	mU*fC*fAmCmGmUfAmGmAmAmUmAmGfUmUfGmGmCmGmA*mG*mG
31	mU*fC*mAmCfGmUmAfGmAmAmUmAmGfUmUfGmGmCmGmA*mG*mG
32	mU*fC*mAmCmGmUmAmGmAmAmUmAmGfUmUmGmGmCmGmA*mG*mG
33	mU*fA*mGmCmGfGmUmUmAmGmAmGmUfCmGfAmGmCmAmAmC*mG*mG

34	mG*mU*mUmGmCmUmCmGfAfCfUmCmUmAmAmCmCmGmC*mU*mA
35	mU*fA*mGmCfGmGfUmUmAmGmAmGmUfCmGfAmGmCmAmAmC*mG*mG
36	mU*fA*fGmCmGmGfUmUmAmGmAmGmUfCmGfAmGmCmAmAmC*mG*mG
37	mU*fA*mGmCfGmGmUfUmAmGmAmGmUfCmGfAmGmCmAmAmC*mG*mG
38	mU*fA*mGmCmGmGmUmUmAmGmAmGmUfCmGmAmGmCmAmAmC*mG*mG
39	mU*fC*mCmCmUfAmAmAmGmAmAmCmCfUmCfUmUmGmCmGmG*mG*mU
40	mC*mC*mGmCmAmAmGmAfGfGfUmUmCmUmUmUmAmGmG*mG*mA
41	mU*fC*mCmCfUmAfAmAmGmAmAmCmCfUmCfUmUmGmCmGmG*mG*mU
42	mU*fC*fCmCmUmAfAmAmGmAmAmCmCfUmCfUmUmGmCmGmG*mG*mU
43	mU*fC*mCmCfUmAmAfAmGmAmAmCmCfUmCfUmUmGmCmGmG*mG*mU
44	mU*fC*mCmCmUmAmAmAmGmAmAmCmCfUmCmUmUmGmCmGmG*mG*mU
45	mU*fG*mUmAmGfAmAmUmAmGmUmUmGfGmCfGmAmAmGmGmU*mC*mU
46	mU*fC*mGmCmAfCmGmUmAmGmAmAmUfAmGfUmUmGmGmCmG*mA*mA
47	mU*fG*mAmGmUfAmGmGmAmAmAmCmCfAmGfGmCmGmUmUmU*mC*mA

CLAIMS

1. A SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex,
wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:
 - (a) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 1, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 2;
 - (b) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 4;
 - (c) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 6;
 - (d) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 8;
 - (e) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 10; and
 - (f) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 12,wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and
wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

2. The SARM1 RNAi agent of claim 1, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:
 - (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 1, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 2;
 - (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 4;
 - (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 6;
 - (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 8;
 - (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 10; and
 - (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 12.

3. The SARM1 RNAi agent of claim 1 or 2, wherein the sense strand and the antisense strand have a pair of nucleic acid sequences selected from the group consisting of:
 - (a) the sense strand has a first nucleic acid sequence of SEQ ID NO: 1, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 2;
 - (b) the sense strand has a first nucleic acid sequence of SEQ ID NO: 3, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 4;
 - (c) the sense strand has a first nucleic acid sequence of SEQ ID NO: 5, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 6;
 - (d) the sense strand has a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 8;
 - (e) the sense strand has a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 10; and
 - (f) the sense strand has a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 12.

4. The SARM1 RNAi agent of any one of claims 1-3, wherein one or more nucleotides of the sense strand are modified nucleotides.
5. The SARM1 RNAi agent of any one of claims 1-4, wherein each nucleotide of the sense strand is a modified nucleotide.
6. The SARM1 RNAi agent of any one of claims 1-5, wherein one or more nucleotides of the antisense strand are modified nucleotides.
7. The SARM1 RNAi agent of any one of claims 1-6, wherein each nucleotide of the antisense strand is a modified nucleotide.
8. The SARM1 RNAi agent of any one of claims 1-7, wherein the modified nucleotide is a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide or 2'-O-alkyl modified nucleotide.
9. The SARM1 RNAi agent of any one of claims 1-8, wherein the sense strand has four 2'-fluoro modified nucleotides at positions 7, 9, 10, and 11 from the 5' end of the sense strand.
10. The SARM1 RNAi agent of claim 9, wherein nucleotides at positions other than positions 7, 9, 10, and 11 of the sense strand are 2'-O-methyl modified nucleotides.
11. The SARM1 RNAi agent of any one of claims 8-10, wherein the antisense strand has four 2'-fluoro modified nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand.
12. The SARM1 RNAi agent of claim 11, wherein nucleotides at positions other than positions 2, 6, 14 and 16 of the antisense strand are 2'-O-methyl modified nucleotides.
13. The SARM1 RNAi agent of any one of claims 1-8, wherein the sense strand has three 2'-fluoro modified nucleotides at positions 9, 10, and 11 from the 5' end of the sense strand.

14. The SARM1 RNAi agent of claim 13, wherein nucleotides at positions other than positions 9, 10, and 11 of the sense strand are 2'-O-methyl modified nucleotides.
15. The SARM1 RNAi agent of any one of claims 1-10, 13, 14, wherein the antisense strand has five 2'-fluoro modified nucleotides at positions 2, 5, 7, 14, and 16 from the 5' end of the antisense strand.
16. The SARM1 RNAi agent of claim 15, wherein nucleotides at positions other than positions 2, 5, 7, 14, and 16 of the antisense strand are 2'-O-methyl modified nucleotides.
17. The SARM1 RNAi agent of any one of claims 1-10, 13, 14, wherein the antisense strand has five 2'-fluoro modified nucleotides at positions 2, 5, 8, 14, and 16 from the 5' end of the antisense strand.
18. The SARM1 RNAi agent of claim 17, wherein nucleotides at positions other than positions 2, 5, 8, 14, and 16 of the antisense strand are 2'-O-methyl modified nucleotides.
19. The SARM1 RNAi agent of any one of claims 1-10, 13, 14, wherein the antisense strand has five 2'-fluoro modified nucleotides at positions 2, 3, 7, 14, and 16 from the 5' end of the antisense strand.
20. The SARM1 RNAi agent of claim 19, wherein nucleotides at positions other than positions 2, 3, 7, 14, and 16 of the antisense strand are 2'-O-methyl modified nucleotides.
21. The SARM1 RNAi agent of any one of claims 1-10, 13, 14, wherein the antisense strand has two 2'-fluoro modified nucleotides at positions 2 and 14 from the 5' end of the antisense strand.
22. The SARM1 RNAi agent of claim 21, wherein nucleotides at positions other than positions 2 and 14 of the antisense strand are 2'-O-methyl modified nucleotides.
23. The SARM1 RNAi agent of any one of claims 1-22, wherein the sense strand and the antisense strand have one or more modified internucleotide linkages.

24. The SARM1 RNAi agent of claim 23, wherein the modified internucleotide linkage is phosphorothioate linkage.
25. The SARM1 RNAi agent of claim 24, wherein the sense strand has four or five phosphorothioate linkages.
26. The SARM1 RNAi agent of claim 24 or 25, wherein the antisense strand has four or five phosphorothioate linkages.
27. The SARM1 RNAi agent of any one of claims 1-26, wherein the first nucleotide from the 5' end of the antisense strand is a modified nucleotide that has a phosphate analog.
28. The SARM1 RNAi agent of claim 27, wherein the phosphate analog is 5'-vinylphosphonate.
29. The SARM1 RNAi agent of any one of claims 1-28, wherein the sense strand comprises an abasic moiety or inverted abasic moiety.
30. A SARM1 RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:
- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 14;
 - (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16;
 - (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 18;
 - (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 20;
 - (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 22;

- (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 24;
- (g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 27;
- (h) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 29;
- (i) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 30;
- (j) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 31;
- (k) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 32;
- (l) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 33;
- (m) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 35;
- (n) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 36;
- (o) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 37;
- (p) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 38;
- (q) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 39;
- (r) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 41;
- (s) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 42;
- (t) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 43;

- (u) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 44;
- (v) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 45;
- (w) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 46; and
- (x) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 47.

31. The SARM1 RNAi agent of claim 30, wherein the sense strand and the antisense strand have a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand has a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 14;
- (b) the sense strand has a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16;
- (c) the sense strand has a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 18;
- (d) the sense strand has a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 20;
- (e) the sense strand has a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 22;
- (f) the sense strand has a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 24;
- (g) the sense strand has a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 27;
- (h) the sense strand has a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 29;
- (i) the sense strand has a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 30;
- (j) the sense strand has a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 31;

- (k) the sense strand has a first nucleic acid sequence of SEQ ID NO: 28, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 32;
- (l) the sense strand has a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 33;
- (m) the sense strand has a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 35;
- (n) the sense strand has a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 36;
- (o) the sense strand has a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 37;
- (p) the sense strand has a first nucleic acid sequence of SEQ ID NO: 34, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 38;
- (q) the sense strand has a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 39;
- (r) the sense strand has a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 41;
- (s) the sense strand has a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 42;
- (t) the sense strand has a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 43;
- (u) the sense strand has a first nucleic acid sequence of SEQ ID NO: 40, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 44;
- (v) the sense strand has a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 45;
- (w) the sense strand has a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 46; and
- (x) the sense strand has a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 47.

32. The SARM1 RNAi agent of any one of claims 1-31, wherein the sense strand has a delivery moiety conjugated to the 3' end of the sense strand.

33. The SARM1 RNAi agent of any one of claims 1-32, wherein the sense strand has a delivery moiety conjugated to the 5' end of the sense strand.
34. The SARM1 RNAi agent of any one of claims 1-31, wherein the sense strand has a delivery moiety conjugated to a nucleotide of the sense strand.
35. The SARM1 RNAi agent of claim 32 or 33, wherein the delivery moiety is conjugated to the 5' or 3' end of the sense strand via a linker.
36. A pharmaceutical composition comprising the SARM1 RNAi agent of any one of claims 1-35 and a pharmaceutically acceptable carrier.
37. A pharmaceutical composition comprising a means for reducing SARM1 expression in a cell and a pharmaceutically acceptable carrier.
38. A method of reducing SARM1 expression in a patient in need thereof, the method comprising administering to the patient an effective amount of the SARM1 RNAi agent of any one of claims 1-35, or the pharmaceutical composition of claim 36 or 37.
39. A method of reducing axon degeneration in a patient in need thereof, the method comprising administering to the patient an effective amount of the SARM1 RNAi agent of any one of claims 1-35, or the pharmaceutical composition of claim 36 or 37.
40. A method of treating a SARM1-mediated neurological disease in a patient in need thereof, the method comprising administering to the patient an effective amount of the SARM1 RNAi agent of any one of claims 1-35, or the pharmaceutical composition of claim 36 or 37.
41. The method of claim 40, wherein the SARM1-mediated neurological disease is selected from amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), Alzheimer's disease,

Parkinson's disease, multiple sclerosis (MS), Huntington's disease (HD), senile dementia, Pick's disease, Gaucher's disease, Hurler syndrome, progressive multifocal leukoencephalopathy, Alexander's disease, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelinolysis, osmotic hyponatremia, Tay-Sachs disease, motor neuron disease, ataxia, spinal muscular atrophy (SMA), Niemann-Pick disease, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, cerebral ischemia, multiple system atrophy, Pelizaeus Merzbacher disease, periventricular leukomalacia, a hereditary ataxia, noise-induced hearing loss, congenital hearing loss, age-related hearing loss, Creutzfeldt-Jakob disease, transmissible spongiform encephalopathy, Lewy Body Dementia, frontotemporal dementia, tauopathy, synucleinopathy, amyloidosis, diabetic neuropathy, globoid cell leukodystrophy (Krabbe's disease), Bassen-Komzweig syndrome, transverse myelitis, motor neuron disease, spinocerebellar ataxia, pre-eclampsia, hereditary spastic paraplegias, spastic paraparesis, familial spastic paraplegia, French settlement disease, Strumpell-Lorrain disease, non-alcoholic steatohepatitis (NASH), adrenomyeloneuropathy, progressive supra nuclear palsy (PSP), Friedrich's ataxia, spinal cord injury, acute optic neuropathy (AON), a genetic or idiopathic retinal condition, Leber congenital amaurosis (LCA), Leber hereditary optic neuropathy (LHON), primary open-angle glaucoma (POAG), acute angle-closure glaucoma (AACG), autosomal dominant optic atrophy, retinal ganglion degeneration, retinitis pigmentosa, an outer retinal neuropathy, optic nerve neuritis, optic nerve degeneration associated with multiple sclerosis, Kjer's optic neuropathy, ischemic optic neuropathy, chemotherapy-induced peripheral neuropathy, neuromyelitis optica, Charcot Marie Tooth disease, deficiency in vitamin B12, deficiency in folic acid (vitamin B9), isolated vitamin E deficiency syndrome, non-arteritic anterior ischemic optic neuropathy, exposure to ethambutol, exposure to cyanide, traumatic brain injury (TBI), spinal cord injury, traumatic axonal injury or chronic traumatic encephalopathy (CTE).

42. The method of claim 40 or 41, wherein the SARM1-mediated neurological disease is amyotrophic lateral sclerosis, multiple sclerosis, chemotherapy-induced peripheral

neuropathy (CIPN), diabetic peripheral neuropathy (DPN), tauopathy, or Charcot Marie Tooth disease.

43. The method of any one of claims 40-42, wherein the SARM1-mediated neurological disease is amyotrophic lateral sclerosis.
44. The method of any one of claims 40-43, wherein the SARM1 RNAi agent is administered to the patient intrathecally, intracerebroventricularly, or via intracisternal magnainjection.
45. A method of reducing SARM1 expression in a cell, the method comprising:
 - (a) introducing the SARM1 RNAi agent of any one of claims 1-35 into the cell; and
 - (b) incubating the cell for a time sufficient for degradation of SARM1 mRNA, thereby reducing SARM1 expression in the cell.
46. The SARM1 RNAi agent of any one of claims 1-35, or the pharmaceutical composition of claim 36, for use in a therapy.
47. The SARM1 RNAi agent of any one of claims 1-35, or the pharmaceutical composition of claim 36, for use in reducing SARM1 expression.
48. The SARM1 RNAi agent of any one of claims 1-35, or the pharmaceutical composition of claim 36, for use in reducing axon degeneration.
49. The SARM1 RNAi agent of any one of claims 1-35, or the pharmaceutical composition of claim 36, for use in the treatment of a SARM1-mediated neurological disease.
50. The SARM1 RNAi agent or the pharmaceutical composition for use of claim 49, wherein the SARM1-mediated neurological disease is selected from amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), Alzheimer's disease, Parkinson's disease, multiple sclerosis (MS), Huntington's disease (HD), senile dementia, Pick's disease, Gaucher's disease, Hurler syndrome, progressive multifocal leukoencephalopathy, Alexander's

disease, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelinolysis, osmotic hyponatremia, Tay-Sachs disease, motor neuron disease, ataxia, spinal muscular atrophy (SMA), Niemann-Pick disease, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, cerebral ischemia, multiple system atrophy, Pelizaeus Merzbacher disease, periventricular leukomalacia, a hereditary ataxia, noise-induced hearing loss, congenital hearing loss, age-related hearing loss, Creutzfeldt-Jakob disease, transmissible spongiform encephalopathy, Lewy Body Dementia, frontotemporal dementia, tauopathy, synucleinopathy, amyloidosis, diabetic neuropathy, globoid cell leukodystrophy (Krabbe's disease), Bassen-Komzweig syndrome, transverse myelitis, motor neuron disease, spinocerebellar ataxia, pre-eclampsia, hereditary spastic paraplegias, spastic paraparesis, familial spastic paraplegia, French settlement disease, Strumpell-Lorrain disease, non-alcoholic steatohepatitis (NASH), adrenomyeloneuropathy, progressive supra nuclear palsy (PSP), Friedrich's ataxia, spinal cord injury, acute optic neuropathy (AON), a genetic or idiopathic retinal condition, Leber congenital amaurosis (LCA), Leber hereditary optic neuropathy (LHON), primary open-angle glaucoma (POAG), acute angle-closure glaucoma (AACG), autosomal dominant optic atrophy, retinal ganglion degeneration, retinitis pigmentosa, an outer retinal neuropathy, optic nerve neuritis, optic nerve degeneration associated with multiple sclerosis, Kjer's optic neuropathy, ischemic optic neuropathy, chemotherapy-induced peripheral neuropathy, neuromyelitis optica, Charcot Marie Tooth disease, deficiency in vitamin B12, deficiency in folic acid (vitamin B9), isolated vitamin E deficiency syndrome, non-arteritic anterior ischemic optic neuropathy, exposure to ethambutol, exposure to cyanide, traumatic brain injury (TBI), spinal cord injury, traumatic axonal injury or chronic traumatic encephalopathy (CTE).

51. The SARM1 RNAi agent or the pharmaceutical composition for use of claim 49 or 50, wherein the SARM1-mediated neurological disease is amyotrophic lateral sclerosis, multiple sclerosis, chemotherapy-induced peripheral neuropathy (CIPN), diabetic peripheral neuropathy (DPN), tauopathy, or Charcot Marie Tooth disease.

52. The SARM1 RNAi agent or the pharmaceutical composition for use of any one of claims 49-51, wherein the SARM1-mediated neurological disease is amyotrophic lateral sclerosis.
53. Use of the SARM1 RNAi agent of any one of claims 1-35, in the manufacture of a medicament for reducing axon degeneration.
54. Use of the SARM1 RNAi agent of any one of claims 1-35, in the manufacture of a medicament for the treatment of a SARM1-mediated neurological disease.
55. The use of claim 54, wherein the SARM1-mediated neurological disease is selected from amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), Alzheimer's disease, Parkinson's disease, multiple sclerosis (MS), Huntington's disease (HD), senile dementia, Pick's disease, Gaucher's disease, Hurler syndrome, progressive multifocal leukoencephalopathy, Alexander's disease, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelinolysis, osmotic hyponatremia, Tay-Sachs disease, motor neuron disease, ataxia, spinal muscular atrophy (SMA), Niemann-Pick disease, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, cerebral ischemia, multiple system atrophy, Pelizaeus Merzbacher disease, periventricular leukomalacia, a hereditary ataxia, noise-induced hearing loss, congenital hearing loss, age-related hearing loss, Creutzfeldt-Jakob disease, transmissible spongiform encephalopathy, Lewy Body Dementia, frontotemporal dementia, tauopathy, synucleinopathy, amyloidosis, diabetic neuropathy, globoid cell leukodystrophy (Krabbe's disease), Bassen-Komzweig syndrome, transverse myelitis, motor neuron disease, spinocerebellar ataxia, pre-eclampsia, hereditary spastic paraplegias, spastic paraparesis, familial spastic paraplegia, French settlement disease, Strumpell-Lorrain disease, non-alcoholic steatohepatitis (NASH), adrenomyeloneuropathy, progressive supra nuclear palsy (PSP), Friedrich's ataxia, spinal cord injury, acute optic neuropathy (AON), a genetic or idiopathic retinal condition, Leber congenital amaurosis (LCA), Leber hereditary optic neuropathy (LHON), primary open-angle glaucoma (POAG), acute angle-closure glaucoma (AACG), autosomal dominant optic atrophy, retinal

ganglion degeneration, retinitis pigmentosa, an outer retinal neuropathy, optic nerve neuritis, optic nerve degeneration associated with multiple sclerosis, Kjer's optic neuropathy, ischemic optic neuropathy, chemotherapy-induced peripheral neuropathy, neuromyelitis optica, Charcot Marie Tooth disease, deficiency in vitamin B12, deficiency in folic acid (vitamin B9), isolated vitamin E deficiency syndrome, non-arteritic anterior ischemic optic neuropathy, exposure to ethambutol, exposure to cyanide, traumatic brain injury (TBI), spinal cord injury, traumatic axonal injury or chronic traumatic encephalopathy (CTE).

56. The use of claim 54 or 55, wherein the SARM1-mediated neurological disease is amyotrophic lateral sclerosis, multiple sclerosis, chemotherapy-induced peripheral neuropathy (CIPN), diabetic peripheral neuropathy (DPN), tauopathy, or Charcot Marie Tooth disease.
57. The use of any one of claims 54-56, wherein the SARM1-mediated neurological disease is amyotrophic lateral sclerosis.