

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 (Gerdts 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 (Gerdts, 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 (Gerdts 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

[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 examples, 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 examples, the sense strand and the antisense strand of the SARMI 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 examples, one or more nucleotides of the sense strand are modified nucleotides. In some examples, each nucleotide of the sense strand is a modified nucleotide. In some examples, one or more nucleotides of the antisense strand are modified nucleotides. In some examples, each nucleotide of the antisense strand is a modified nucleotide. In some examples, 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 examples, 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 examples, nucleotides at positions other than positions 7, 9, 10, and 11 of the sense strand are 2'-O-methyl modified nucleotides. In some examples, 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 examples, nucleotides at positions other than positions 2, 6, 14 and 16 of the antisense strand are 2'-O-methyl modified nucleotides. In some examples, 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 examples, the nucleotides at positions other than positions 9, 10, and 11 of the sense strand are 2'-O-methyl modified nucleotides. In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the antisense strand has two 2'-fluoro modified nucleotides at positions 2 and 14 from the 5' end of the antisense strand. In some examples, the nucleotides at positions other than positions 2 and 14 of the antisense strand are 2'-O-methyl modified nucleotides.

[00011] In some examples, 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 examples, the first nucleotide from the 5' end of the antisense strand has a 5' phosphate. In some examples, the sense strand comprises an abasic moiety or inverted abasic moiety.

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

[00013] In another 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 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;

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 examples, 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: 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 examples, the sense strand of the SARM1 RNAi agent has a delivery moiety. In some examples, the sense strand of the SARM1 RNAi agent has a delivery moiety conjugated to the 3' end of the sense strand. In some examples, the sense strand of the SARM1 RNAi agent has a delivery moiety conjugated to the 5' end of the sense strand. In some examples, 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 examples, the sense strand of the SARM1 RNAi agent has a delivery moiety conjugated to a nucleotide of the sense strand. In some examples, the delivery moiety is a-tocopherol, palmitic acid, or another moiety in Table 4. In some examples, 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 examples, the SARM1 RNAi agent is not a lipid conjugate. In some examples, the SARM1 RNAi agent has no delivery moiety.

[00016] In some examples, 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 examples, 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 examples, provided herein are SARM1 RNAi agents of Formula (I): R-L-D, wherein R is a 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., 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;

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 examples, provided herein are SARMI 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: 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. In another aspect, provided herein are pharmaceutical compositions comprising a means for reducing SARM1 expression in a cell and a pharmaceutically acceptable carrier.

[00021] In some examples, 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 some examples, 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 some examples, 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. In another aspect, provided herein are in vitro methods of reducing SARM1 expression in a cell, the method comprising: (a) introducing the SARM1 RNAi agent as described herein into the cell; and (b) incubating the cell for a time sufficient for degradation of SARM1 mRNA, thereby reducing SARM1 expression in the cell.

[00025] In some examples, provided herein are SARM1 RNAi agents or pharmaceutical compositions comprising a SARM1 RNAi agent for use in reducing SARM1 expression. In some examples, 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.

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

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. An in vitro 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.
39. The SARM1 RNAi agent of any one of claims 1-35, or the pharmaceutical composition of claim 36, for use in a therapy.
40. The SARM1 RNAi agent of any one of claims 1-35, or the pharmaceutical composition of claim 36, for use in reducing SARM1 expression.
41. The SARM1 RNAi agent of any one of claims 1-35, or the pharmaceutical composition of claim 36, for use in reducing axon degeneration.

42. 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.
43. The SARM1 RNAi agent or the pharmaceutical composition for use of claim 42, 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).

44. The SARM1 RNAi agent or the pharmaceutical composition for use of claim 42 or 43, 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.
45. The SARM1 RNAi agent or the pharmaceutical composition for use of any one of claims 42-44, wherein the SARM1-mediated neurological disease is amyotrophic lateral sclerosis.
46. Use of the SARM1 RNAi agent of any one of claims 1-35, in the manufacture of a medicament for reducing axon degeneration.
47. 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.
48. The use of claim 47, 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).

49. The use of claim 47 or 48, 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.
50. The use of any one of claims 47-49, wherein the SARM1-mediated neurological disease is amyotrophic lateral sclerosis.