

disease. Accordingly, there remains a need for therapeutic agents that can inhibit or adjust the expression of the MAPT gene for treating tauopathies, e.g., by utilizing RNAi.

SUMMARY

In a first aspect of the present disclosure, there is provided a MAPT 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:15, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 16;
- (b) 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;
- (c) 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;
- (d) 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;
- (e) 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;
- (f) 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;

- (g) 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;
- (h) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:13, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 14;
- (i) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:17, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 18;
- (j) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:19, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 20;
- (k) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:21, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 22;
- (l) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:23, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 24;
- (m)the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 55, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 16;
- (n) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 56, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 16;
- (o) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 57, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 58;

- (p) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 59, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 58;
- (q) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 60, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 61;
- (r) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 62, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 61;
- (s) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 117, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 118; and
- (t) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 119, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 16,

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.

In another aspect of the present disclosure, there is provided a MAPT 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: 63, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 40;
- (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 25, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 26;

- (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 27, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 28;
- (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 29, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 30;
- (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 31, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 32;
- (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 33, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 34;
- (g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 35, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 36;
- (h) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 37, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 38;
- (i) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 39, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 40;
- (j) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 41, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 42;
- (k) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 43, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 44;
- (l) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 45, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 46; and
- (m) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 47, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 48;
- (n) the sense strand comprises a first nucleic acid sequence selected from any one of SEQ ID NOs: 64, 66-69, 71, 75-86, 93-100, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 65;
- (o) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 64, and the antisense strand comprises a second nucleic acid sequence selected from any one of SEQ ID NOs: 70, 72-74;

- (p) the sense strand comprises a first nucleic acid sequence selected from SEQ ID NO: 87 or 89, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 88;
- (q) the sense strand comprises a first nucleic acid sequence selected from SEQ ID NO: 90 or 92, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 91;
- (r) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 101, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 102;
- (s) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 103, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 104;
- (t) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 105, and the antisense strand comprises a second nucleic acid sequence selected from any one of SEQ ID NOs: 65, 106-108;
- (u) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 109, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 65;
- (v) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 110, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 40;
- (w) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 111, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 112;
- (x) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 113, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 114; and
- (y) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 115, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 116.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the MAPT RNAi agent as disclosed herein and a pharmaceutically acceptable carrier.

In a further aspect of the present disclosure, there is provided an *ex-vivo* method of reducing MAPT expression in a cell, the method comprising:

introducing the MAPT RNAi agent as disclosed herein into the cell; and

incubating the cell for a time sufficient for degradation of MAPT mRNA, thereby reducing MAPT expression in the cell.

In another aspect of the present disclosure, there is provided a use of the MAPT RNAi agent as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for reducing MAPT expression.

In yet another aspect of the present disclosure, there is provided the MAPT RNAi agent as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in therapy.

In a further aspect of the present disclosure, there is provided a use of the MAPT RNAi agent as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a tauopathy.

Provided herein are MAPT RNAi agents and compositions comprising a MAPT RNAi agent. Also provided herein are methods of using the MAPT RNAi agents or compositions comprising a MAPT RNAi agent for reducing MAPT expression and/or treating tauopathy in a subject.

In one example, provided herein are MAPT 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;
- (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;

- (q) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 60, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 61;
- (r) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 62, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 61;
- (s) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 117, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 118; and
- (t) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 119, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 16,

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.

In some examples, the sense strand and the antisense strand of the MAPT 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;
- (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;

In some examples, the sense strand and the antisense strand of the MAPT RNAi agent described herein 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;
- (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;
- (g) 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;
- (h) 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;
- (i) 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;
- (j) 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;
- (k) 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;
- (l) 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;
- (m) the sense strand has a first nucleic acid sequence of SEQ ID NO: 55, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16;
- (n) the sense strand has a first nucleic acid sequence of SEQ ID NO: 56, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16;

- (o) the sense strand has a first nucleic acid sequence of SEQ ID NO: 57, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 58;
- (p) the sense strand has a first nucleic acid sequence of SEQ ID NO: 59, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 58;
- (q) the sense strand has a first nucleic acid sequence of SEQ ID NO: 60, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 61;
- (r) the sense strand has a first nucleic acid sequence of SEQ ID NO: 62, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 61;
- (s) the sense strand has a first nucleic acid sequence of SEQ ID NO: 117, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 118; and
- (t) the sense strand has a first nucleic acid sequence of SEQ ID NO: 119, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16.

The MAPT 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., e.g., 2'-O-C16 alkyl modified nucleotide. In some examples, the sense strand has four 2'-fluoro modified nucleotides at positions 7, 9, 10, 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 or 2'-O-C16 alkyl modified nucleotides. In some examples, the antisense strand has four 2'-fluoro modified nucleotides at positions 2, 6, 14, 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 or 2'-O-C16 alkyl modified nucleotides. In some examples, the sense strand has three 2'-fluoro modified nucleotides, e.g., at positions 9, 10, 11 from the 5' end of the sense strand. In some examples, the other nucleotides of the sense strand are 2'-O-methyl modified nucleotides. In some examples, the antisense strand has five 2'-fluoro modified nucleotides, e.g., at positions

2, 5, 7, 14, 16 from the 5' end of the antisense strand. In some examples, the antisense strand has five 2'-fluoro modified nucleotides, e.g., at positions 2, 5, 8, 14, 16 from the 5' end of the antisense strand. In some examples, the antisense strand has five 2'-fluoro modified nucleotides, e.g., at positions 2, 3, 7, 14, 16 from the 5' end of the antisense strand. In some examples, the other nucleotides of the antisense strand are 2'-O-methyl modified nucleotides. In some examples, the sense strand comprises an abasic moiety or inverted abasic moiety.

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 sense strand comprises an abasic moiety or inverted abasic moiety. 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.

In some examples, provided herein are MAPT 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: 25, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 26;
- (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 27, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 28;
- (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 29, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 30;
- (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 31, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 32;
- (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 33, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 34;
- (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 35, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 36;

- (t) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 105, and the antisense strand comprises a second nucleic acid sequence selected from any one of SEQ ID NOs: 65, 106-108;
- (u) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 109, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 65;
- (v) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 110, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 40;
- (w) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 111, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 112;
- (x) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 113, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 114; and
- (y) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 115, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 116.

In some examples, provided herein are MAPT 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 a first nucleic acid sequence of SEQ ID NO: 25, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 26;
- (b) the sense strand has a first nucleic acid sequence of SEQ ID NO: 27, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 28;
- (c) the sense strand has a first nucleic acid sequence of SEQ ID NO: 29, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 30;
- (d) the sense strand has a first nucleic acid sequence of SEQ ID NO: 31, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 32;
- (e) the sense strand has a first nucleic acid sequence of SEQ ID NO: 33, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 34;
- (f) the sense strand has a first nucleic acid sequence of SEQ ID NO: 35, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 36;

- (u) the sense strand has a first nucleic acid sequence of SEQ ID NO: 109, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 65;
- (v) the sense strand has a first nucleic acid sequence of SEQ ID NO: 110, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 40;
- (w) the sense strand has a first nucleic acid sequence of SEQ ID NO: 111, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 112;
- (x) the sense strand has a first nucleic acid sequence of SEQ ID NO: 113, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 114; and
- (y) the sense strand has a first nucleic acid sequence of SEQ ID NO: 115, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 116.

In some examples, the sense strand of the MAPT RNAi agent has a delivery moiety. In some examples, the sense strand of the MAPT RNAi agent has a delivery moiety conjugated to the 5' or 3' end of the sense strand. In some examples, the sense strand of the MAPT RNAi agent has a delivery moiety conjugated to a nucleotide of the sense strand. In some examples, the delivery moiety is α -tocopherol or palmitic acid. 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 a further example, provided herein are MAPT 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 for delivering the dsRNA into a cell; and wherein L is a linking means 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;

- (s) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 117, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 118; and
- (t) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 119, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16,

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.

In some examples, provided herein are MAPT 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 for delivering the dsRNA into a cell; and wherein L is a linking means 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 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;
- (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;
- (g) 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;
- (h) 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;

- (i) 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;
- (j) 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;
- (k) 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;
- (l) 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;
- (m) the sense strand has a first nucleic acid sequence of SEQ ID NO: 55, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16;
- (n) the sense strand has a first nucleic acid sequence of SEQ ID NO: 56, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16;
- (o) the sense strand has a first nucleic acid sequence of SEQ ID NO: 57, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 58;
- (p) the sense strand has a first nucleic acid sequence of SEQ ID NO: 59, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 58;
- (q) the sense strand has a first nucleic acid sequence of SEQ ID NO: 60, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 61;
- (r) the sense strand has a first nucleic acid sequence of SEQ ID NO: 62, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 61;
- (s) the sense strand has a first nucleic acid sequence of SEQ ID NO: 117, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 118; and
- (t) the sense strand has a first nucleic acid sequence of SEQ ID NO: 119, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16,

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.

In some examples, provided herein are MAPT 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 for delivering the dsRNA into a cell; and wherein L is a linking means for linking the dsRNA to the delivery means, or

- (o) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 110, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 40;
- (p) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 111, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 112;
- (q) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 113, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 114; and
- (r) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 115, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 116.

In some examples, provided herein are MAPT 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 for delivering the dsRNA into a cell; and wherein L is a linking means 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 a first nucleic acid sequence of SEQ ID NO: 25, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 26;
- (b) the sense strand has a first nucleic acid sequence of SEQ ID NO: 27, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 28;
- (c) the sense strand has a first nucleic acid sequence of SEQ ID NO: 29, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 30;
- (d) the sense strand has a first nucleic acid sequence of SEQ ID NO: 31, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 32;
- (e) the sense strand has a first nucleic acid sequence of SEQ ID NO: 33, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 34;
- (f) the sense strand has a first nucleic acid sequence of SEQ ID NO: 35, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 36;
- (g) the sense strand has a first nucleic acid sequence of SEQ ID NO: 37, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 38;
- (h) the sense strand has a first nucleic acid sequence of SEQ ID NO: 39, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 40;

- (i) the sense strand has a first nucleic acid sequence of SEQ ID NO: 41, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 42;
- (j) the sense strand has a first nucleic acid sequence of SEQ ID NO: 43, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 44;
- (k) the sense strand has a first nucleic acid sequence of SEQ ID NO: 45, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 46;
- (l) the sense strand has a first nucleic acid sequence of SEQ ID NO: 47, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 48;
- (m) the sense strand has a first nucleic acid sequence of SEQ ID NO: 105, and the antisense strand has a second nucleic acid sequence selected from SEQ ID NO: 65, 106-108;
- (n) the sense strand has a first nucleic acid sequence of SEQ ID NO: 109, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 65;
- (o) the sense strand has a first nucleic acid sequence of SEQ ID NO: 110, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 40;
- (p) the sense strand has a first nucleic acid sequence of SEQ ID NO: 111, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 112;
- (q) the sense strand has a first nucleic acid sequence of SEQ ID NO: 113, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 114; and
- (r) the sense strand has a first nucleic acid sequence of SEQ ID NO: 115, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 116.

In another example, provided herein are pharmaceutical compositions comprising a MAPT RNAi agent described herein and a pharmaceutically acceptable carrier. Also provided herein are pharmaceutical compositions comprising a means for reducing MAPT expression in a cell and a pharmaceutically acceptable carrier.

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

In another example, provided herein are methods of treating a tauopathy in a patient in need thereof, and such method comprises administering to the patient an effective amount of the MAPT RNAi agent or a pharmaceutical composition described herein.

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

In another example, provided herein are MAPT RNAi agents or pharmaceutical compositions comprising a MAPT RNAi agent for use in reducing MAPT expression. Also provided herein are MAPT RNAi agents or the pharmaceutical composition comprising a MAPT RNAi agent for use in a therapy. Also provided herein are MAPT RNAi agents or pharmaceutical compositions comprising a MAPT RNAi agent for use in the treatment of a tauopathy. Also provided herein are uses of MAPT RNAi agents in the manufacture of a medicament for the treatment of a tauopathy.

DETAILED DESCRIPTION

Provided herein are MAPT RNAi agents and compositions comprising a MAPT RNAi agent. Also provided herein are methods of using the MAPT RNAi agents or compositions comprising a MAPT RNAi agent for reducing MAPT expression and/or treating tauopathy in a subject.

In some embodiments, provided herein are MAPT 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 MAPT 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 MAPT 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 MAPT 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

Conjugated RNAi Agent NO. 7	431.3	65.4	68.0	34.4
Conjugated RNAi Agent NO. 8	286.2	72.9	65.9	46.1
Conjugated RNAi Agent NO. 9	124.9	86	64.9	44.9
Conjugated RNAi Agent NO. 10	516.1	70.7	52.1	22.4
Conjugated RNAi Agent NO. 11	424.3	60.1	41.4	29.1
Conjugated RNAi Agent No. 12	309.3	73.4	54.7	22.5

*NE means no observed effect.

Additional RNAi agents with different modification patterns were also tested. Table 10B shows the *in vitro* and *in vivo* activities of additional MAPT RNAi agents with different modification patterns.

Table 10B. *In vitro* and *in vivo* activities of additional MAPT RNAi agents with different modification patterns

MAPT RNAi Agent No. or Conjugate No.	SHSY5Y, 3d IC50 (nM)	SHSY5Y, 3d % KD (knockdown) of MAPT at 1 μ M	MCN, 7d IC50 (nM)	MCN, 7d % KD (knockdown) of MAPT at 1uM	Mouse ICV, 14d % KD Brain stem	Mouse ICV, 14d % KD Frontal Cortex
31	ND*	ND	7.24	85.6	67	58
32	ND	ND	5.648	86.8	66	57
33	ND	ND	12.38	83.2	48	45
34	ND	ND	28.32	79.3	48	52
35	ND	ND	64.94	73	56	56
36	ND	ND	16.01	83	71	70
37	ND	ND	9.5	86.5	68	68
38	ND	ND	9.01	87.8	72	46

CLAIMS

1. A MAPT 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:15, and the antisense strand comprises a second nucleic acid
sequence having at least 95% sequence identity to SEQ ID NO: 16;
 - (b) 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;
 - (c) 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;
 - (d) 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;
 - (e) 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;
 - (f) 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;
 - (g) 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;
 - (h) the sense strand comprises a first nucleic acid sequence having at least 95% sequence
identity to SEQ ID NO:13, and the antisense strand comprises a second nucleic acid
sequence having at least 95% sequence identity to SEQ ID NO: 14;

- (i) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:17, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 18;
- (j) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:19, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 20;
- (k) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:21, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 22;
- (l) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:23, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 24;
- (m) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 55, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 16;
- (n) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 56, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 16;
- (o) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 57, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 58;
- (p) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 59, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 58;
- (q) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 60, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 61;
- (r) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 62, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 61;

- (s) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 117, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 118; and
- (t) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 119, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 16,

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 MAPT 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:15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16;
 - (b) 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;
 - (c) 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;
 - (d) 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;
 - (e) 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;
 - (f) 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;
 - (g) 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;
 - (h) 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;
 - (i) 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;

- (j) 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;
 - (k) 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;
 - (l) 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;
 - (m) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 55, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16;
 - (n) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 56, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16;
 - (o) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 57, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 58;
 - (p) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 59, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 58;
 - (q) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 60, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 61;
 - (r) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 62, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 61;
 - (s) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 117, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 118; and
 - (t) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 119, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16.
3. The MAPT 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:15, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16;
 - (b) 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;
 - (c) 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;

- (d) 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;
- (e) 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;
- (f) 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;
- (g) 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;
- (h) 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;
- (i) 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;
- (j) 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;
- (k) 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;
- (l) 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;
- (m) the sense strand has a first nucleic acid sequence of SEQ ID NO: 55, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16;
- (n) the sense strand has a first nucleic acid sequence of SEQ ID NO: 56, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16;
- (o) the sense strand has a first nucleic acid sequence of SEQ ID NO: 57, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 58;
- (p) the sense strand has a first nucleic acid sequence of SEQ ID NO: 59, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 58;
- (q) the sense strand has a first nucleic acid sequence of SEQ ID NO: 60, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 61;
- (r) the sense strand has a first nucleic acid sequence of SEQ ID NO: 62, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 61;

- (s) the sense strand has a first nucleic acid sequence of SEQ ID NO: 117, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 118; and
 - (t) the sense strand has a first nucleic acid sequence of SEQ ID NO: 119, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16.
4. The MAPT RNAi agent of any one of claims 1-3, wherein one or more nucleotides of the sense strand are modified nucleotides.
 5. The MAPT RNAi agent of any one of claims 1-4, wherein each nucleotide of the sense strand is a modified nucleotide.
 6. The MAPT RNAi agent of any one of claims 1-5, wherein one or more nucleotides of the antisense strand are modified nucleotides.
 7. The MAPT RNAi agent of any one of claims 1-6, wherein each nucleotide of the antisense strand is a modified nucleotide.
 8. The MAPT 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-C16 alkyl modified nucleotide.
 9. The MAPT RNAi agent of any one of claims 1-8, wherein the sense strand has four 2'-fluoro modified nucleotides at positions 7, 9, 10, 11 from the 5' end of the sense strand.
 10. The MAPT 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 or 2'-O-C16 alkyl modified nucleotides.
 11. The MAPT RNAi agent of any one of claims 8-10, wherein the antisense strand has four 2'-fluoro modified nucleotides at positions 2, 6, 14, 16 from the 5' end of the antisense strand.

12. The MAPT 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 or 2'-O-C16 alkyl modified nucleotides.
13. The MAPT 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 MAPT 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 or 2'-O-C16 alkyl modified nucleotides.
15. The MAPT RNAi agent of any one of claims 1-8, 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 MAPT 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 or 2'-O-C16 alkyl modified nucleotides.
17. The MAPT RNAi agent of any one of claims 1-8, 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 MAPT 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 or 2'-O-C16 alkyl modified nucleotides.
19. The MAPT RNAi agent of any one of claims 1-18, wherein the sense strand and the antisense strand have one or more modified internucleotide linkages.
20. The MAPT RNAi agent of claim 19, wherein the modified internucleotide linkage is phosphorothioate linkage.

21. The MAPT RNAi agent of claim 20, wherein the sense strand has four or five phosphorothioate linkages.
22. The MAPT RNAi agent of claim 20 or 21, wherein the antisense strand has four or five phosphorothioate linkages.
23. The MAPT RNAi agent of any one of claims 1-22, wherein the first nucleotide from the 5' end of the antisense strand is a modified nucleotide that has a phosphate analog.
24. The MAPT RNAi agent of claim 23, wherein the phosphate analog is 5'-vinylphosphonate.
25. The MAPT RNAi agent of any one of claims 1-24, wherein the sense strand comprises an abasic moiety or inverted abasic moiety.
26. A MAPT 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: 63, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 40;
 - (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 25, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 26;
 - (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 27, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 28;
 - (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 29, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 30;
 - (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 31, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 32;
 - (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 33, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 34;
 - (g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 35, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 36;

- (h) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 37, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 38;
- (i) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 39, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 40;
- (j) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 41, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 42;
- (k) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 43, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 44;
- (l) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 45, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 46; and
- (m) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 47, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 48;
- (n) the sense strand comprises a first nucleic acid sequence selected from any one of SEQ ID NOs: 64, 66-69, 71, 75-86, 93-100, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 65;
- (o) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 64, and the antisense strand comprises a second nucleic acid sequence selected from any one of SEQ ID NOs: 70, 72-74;
- (p) the sense strand comprises a first nucleic acid sequence selected from SEQ ID NO: 87 or 89, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 88;
- (q) the sense strand comprises a first nucleic acid sequence selected from SEQ ID NO: 90 or 92, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 91;
- (r) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 101, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 102;
- (s) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 103, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 104;
- (t) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 105, and the antisense strand comprises a second nucleic acid sequence selected from any one of SEQ ID NOs: 65, 106-108;

- (u) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 109, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 65;
- (v) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 110, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 40;
- (w) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 111, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 112;
- (x) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 113, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 114; and
- (y) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 115, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 116.

27. The MAPT RNAi agent of claim 26, 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: 63, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 40;
- (b) the sense strand has a first nucleic acid sequence of SEQ ID NO: 25, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 26;
- (c) the sense strand has a first nucleic acid sequence of SEQ ID NO: 27, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 28;
- (d) the sense strand has a first nucleic acid sequence of SEQ ID NO: 29, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 30;
- (e) the sense strand has a first nucleic acid sequence of SEQ ID NO: 31, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 32;
- (f) the sense strand has a first nucleic acid sequence of SEQ ID NO: 33, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 34;
- (g) the sense strand has a first nucleic acid sequence of SEQ ID NO: 35, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 36;
- (h) the sense strand has a first nucleic acid sequence of SEQ ID NO: 37, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 38;
- (i) the sense strand has a first nucleic acid sequence of SEQ ID NO: 39, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 40;

- (j) the sense strand has a first nucleic acid sequence of SEQ ID NO: 41, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 42;
- (k) the sense strand has a first nucleic acid sequence of SEQ ID NO: 43, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 44;
- (l) the sense strand has a first nucleic acid sequence of SEQ ID NO: 45, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 46;
- (m) the sense strand has a first nucleic acid sequence of SEQ ID NO: 47, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 48;
- (n) the sense strand has a first nucleic acid sequence selected from any one of SEQ ID NOs: 64, 66-69, 71, 75-86, 93-100, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 65;
- (o) the sense strand has a first nucleic acid sequence of SEQ ID NO: 64, and the antisense strand has a second nucleic acid sequence selected from any one of SEQ ID NOs: 70, 72-74;
- (p) the sense strand has a first nucleic acid sequence selected from SEQ ID NO: 87 or 89, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 88;
- (q) the sense strand has a first nucleic acid sequence selected from SEQ ID NO: 90 or 92, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 91;
- (r) the sense strand has a first nucleic acid sequence of SEQ ID NO: 101, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 102;
- (s) the sense strand has a first nucleic acid sequence of SEQ ID NO: 103, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 104;
- (t) the sense strand has a first nucleic acid sequence of SEQ ID NO: 105, and the antisense strand has a second nucleic acid sequence selected from any one of SEQ ID NOs: 65, 106-108;
- (u) the sense strand has a first nucleic acid sequence of SEQ ID NO: 109, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 65;
- (v) the sense strand has a first nucleic acid sequence of SEQ ID NO: 110, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 40;
- (w) the sense strand has a first nucleic acid sequence of SEQ ID NO: 111, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 112;

- (x) the sense strand has a first nucleic acid sequence of SEQ ID NO: 113, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 114; and
- (y) the sense strand has a first nucleic acid sequence of SEQ ID NO: 115, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 116.

- 28. The MAPT RNAi agent of any one of claims 1-27, wherein the sense strand has a delivery moiety conjugated to the 5' or 3' end of the sense strand.
- 29. The MAPT RNAi agent of any one of claims 1-28, wherein the sense strand has a delivery moiety conjugated to a nucleotide of the sense strand.
- 30. The MAPT RNAi agent of claim 28, wherein the delivery moiety is conjugated to the 3' end of the sense strand, optionally via a linker.
- 31. A pharmaceutical composition comprising the MAPT RNAi agent of any one of claims 1-30 and a pharmaceutically acceptable carrier.
- 32. An *ex-vivo* method of reducing MAPT expression in a cell, the method comprising:
 - introducing the MAPT RNAi agent of any one of claims 1-30 into the cell; and
 - incubating the cell for a time sufficient for degradation of MAPT mRNA, thereby reducing MAPT expression in the cell.
- 33. Use of the MAPT RNAi agent of any one of claims 1-30, or the pharmaceutical composition of claim 31, in the manufacture of a medicament for reducing MAPT expression.
- 34. The MAPT RNAi agent of any one of claims 1-30, or the pharmaceutical composition of claim 31, for use in therapy.
- 35. Use of the MAPT RNAi agent of any one of claims 1-30, or the pharmaceutical composition of claim 31, in the manufacture of a medicament for the treatment of a tauopathy.

36. The use of claim 35, wherein the tauopathy is selected from Alzheimer's disease (AD), frontotemporal dementia (FTD), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), Parkinson's disease, Pick's disease (PiD), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), multiple system tauopathy with presenile dementia (MSTD), neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, progressive supranuclear palsy (PSP), amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS-PDC), argyrophilic grain dementia (AGD), British type amyloid angiopathy, cerebral amyloid angiopathy, chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, epilepsy, Gerstmann-Straussler-Scheinker disease, Hallervorden-Spatz disease, Huntington's disease, inclusion body myositis, lead encephalopathy, Lytico-Bodig disease, meningioangiomas, multiple system atrophy, myotonic dystrophy, Niemann-Pick disease type C (NP-C), non-Guamanian motor neuron disease with neurofibrillary tangles, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, tangle only dementia, tangle-predominant dementia, ganglioglioma, gangliocytoma, subacute sclerosing pan encephalitis, tuberous sclerosis, lipofuscinosis, primary age-related tauopathy (PART), or globular glial tauopathies (GGT).

37. The use of claim 35, wherein the tauopathy is Alzheimer's disease (AD), frontotemporal dementia (FTD), or progressive supranuclear palsy (PSP).