

MAPT RNA INTERFERENCE AGENTS

SEQUENCE LISTING

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 “30170” created 2-Nov-2022 and is 835 kilobytes in size. The Sequence Listing information in the ST.26 XML format is incorporated herein by reference in its entirety.

BACKGROUND

Microtubule associated protein Tau is encoded by the MAPT gene located on chromosome 17. Tau protein interacts with tubulin to stabilize the microtubules and promote tubulin assembly into microtubules. MAPT transcripts are differentially expressed throughout the body, predominantly in the central and peripheral nervous system.

The MAPT gene consists of 16 exons. Alternative mRNA splicing gives rise to multiple MAPT isoforms. At least six Tau isoforms exist in human brain, ranging from 352 to 441 amino acids long. Alternative splicing of exons 2 and/or 3 leads to inclusion of zero, one, or two copies of the N-terminal acidic domain, which are referred to as 0N, 1N, or 2N Tau, respectively. The Tau isoforms that include exon 10, which encodes an additional microtubule-binding domain, are referred to as “4R Tau”, as it has four microtubule-binding domains. The Tau isoforms without exon 10 are referred to as “3R Tau”, as it has three microtubule-binding domains.

Mutations in MAPT and hyperphosphorylation of Tau protein can cause aggregation and deposition of Tau in pathogenic neurofibrillary tangles, causing progressive neurodegenerative disorders such as Alzheimer’s disease, frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), and other tauopathies.

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).

There are currently no FDA-approved disease-modifying therapeutic agents specifically for reducing MAPT and treating tauopathies. Aducanumab, which targets amyloid beta protein (A β), is the only disease-modifying medication currently approved to treat Alzheimer’s

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 OF INVENTION

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 aspect, 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;

- (g) 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;
- (h) 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;
- (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; and
- (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 some embodiments, 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;

- (g) 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;
- (h) 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;
- (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.

In some embodiments, 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 embodiments, one or more nucleotides of the sense strand are modified nucleotides. In some embodiments, each nucleotide of the sense strand is a modified nucleotide. In some embodiments, one or more nucleotides of the antisense strand are modified nucleotides. In some embodiments, each nucleotide of the antisense strand is a modified nucleotide. In some embodiments, the modified nucleotide is a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, or 2'-O-alkyl modified nucleotide, e.g., e.g., 2'-O-C16 alkyl modified nucleotide. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the other nucleotides of the sense strand are 2'-O-methyl modified nucleotides. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the other nucleotides of the antisense strand are 2'-O-methyl modified nucleotides. In some embodiments, the sense strand comprises an abasic moiety or inverted abasic moiety.

In some embodiments, the first nucleotide from the 5' end of the antisense strand is a modified nucleotide that has a phosphate analog, e.g., a 5'-vinylphosphonate. In some embodiments, the sense strand comprises an abasic moiety or inverted abasic moiety. In some embodiments, the sense strand and the antisense strand have one or more modified internucleotide linkages, e.g., phosphorothioate linkage. In some embodiments, the sense strand has four or five phosphorothioate linkages. In some embodiments, the antisense strand has four or five phosphorothioate linkages. In some embodiments, the sense strand has four phosphorothioate linkages and the antisense strand has four phosphorothioate linkages.

In some embodiments, 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;

- (g) 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;
- (h) 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;
- (i) 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;
- (j) 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;
- (k) 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;
- (l) 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;
- (m) 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;
- (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 some embodiments, 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;

- (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: 63, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 40;
- (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.

In some embodiments, the sense strand of the MAPT RNAi agent has a delivery moiety. In some embodiments, 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 embodiments, the sense strand of the MAPT RNAi agent has a delivery moiety conjugated to a nucleotide of the sense strand. In some embodiments, the delivery moiety is α -tocopherol or palmitic acid. In some embodiments, the delivery moiety is conjugated to the 5' or 3' end of the sense strand via a linker, e.g., a linker of Table 5.

In a further aspect, 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;

- (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;
- (g) 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;
- (h) 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;
- (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,

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 embodiments, 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 embodiments, 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 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;
- (g) 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;
- (h) 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;
- (i) 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;
- (j) 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;
- (k) 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;
- (l) 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;
- (m) 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 SEQ ID NO: 65, 106-108;
- (n) 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;

- (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 embodiments, 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 aspect, 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 aspect, 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 aspect, 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 aspect, 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 complimentary 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

embodiments, the sense strand and antisense strand sequences of the MAPT RNAi agents are provided in Table 1.

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 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 1, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 2;
- (b) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 4;
- (c) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 6;
- (d) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence having at least

- 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 8;
- (e) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 10;
- (f) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 12;
- (g) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 14;
- (h) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 16;

- (i) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO:17, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 18;
- (j) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO:19, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 20;
- (k) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO:21, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 22; and
- (l) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO:23, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 24;
- (m) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO:

- 55, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 16;
- (n) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 56, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 16;
- (o) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 57, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 58;
- (p) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 59, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 58;
- (q) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 60, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%,

- about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 61;
- (r) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 62, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 61;
- (s) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 117, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 118;
- (t) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 119, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID

NO: 1, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 2, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 3, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 4, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 5, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 6, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 8, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more

internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 10, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 12, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 14, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about

95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 16, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 18, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 20, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 22, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 24, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 55, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 16, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 56, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 16, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and

wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 57, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 58, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 59, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 58, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 60, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 61, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 62, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence

identity to SEQ ID NO: 61, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 117, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 118, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 119, and the antisense strand comprises a second nucleic acid sequence having at least 95% (e.g., about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 16, wherein 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.

Table 1. Nucleic Acid Sequences of MAPT RNAi Agents

MAPT RNAi Agent No.	Sense Strand (5' to 3')	SEQ ID NO	Start position of sense strand target region of human MAPT transcript NM_0011 23067.4	Antisense Strand (5' to 3')	SEQ ID NO	Start position of antisense strand target region of human MAPT transcript NM_0011 23067.4
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1	ACAAGCUGACCUUCCG CGAGA	1	1184	UCUCGCGGAAGGUCAGCU UGUGG	2	1182
2	AGAUUGAAACCCACAA GCUGA	3	1172	UCAGCUUGUGGGUUUCAA UCUUU	4	1170
3	AAUAAAAAGAUUGAA ACCCAA	5	1165	UUGGGUUUCAAUCUUUU UAUUUC	6	1163
4	GGAAAUAAAAAGAUU GAAACA	7	1162	UGUUUCAAUCUUUUUAU UCCUC	8	1160
5	GGCGGAGGAAAUAAAA AGAU	9	1156	UAUCUUUUUAUUUCCUCC GCCAG	10	1154
6	GAAGUAAAAUCUGAGA AGCUA	11	1075	UAGCUUCUCAGAUUUUAC UCCA	12	1073
7	GGAAGUAAAAUCUGAG AAGCA	13	1074	UGCUUCUCAGAUUUUACU UCCAC	14	1072
8	GUGGAAGUAAAAUCUG AGAAA	15	1072	UUUCUCAGAUUUUACUUC CACCU	16	1070
9	CCAGGUGGAAGUAAAA UCUGA	17	1068	UCAGAUUUUACUCCACC UGGCC	18	1066
10	CAAGUCCAAGAUCGGC UCCAA	19	831	UUGGAGCCGAUCUUGGAC UUGAC	20	829
11	UCUGGUGAACCUCCAA AAUCA	21	616	UGAUUUUGGAGGUUCACC AGAGC	22	614
12	CAGGUGGAAGUAAAAU CUGAA	23	1069	UUCAGAUUUUACUCCAC CUGGC	24	1067
25	GUGGAAGUA(n)AAUCU GAGAAA, wherein (n) indicates an abasic moiety.	55	1072	UUUCUCAGAUUUUACUUC CACCU	16	1070
26	GUGGAAGU(n)AAAUCU GAGAAA, wherein (n) indicates an abasic moiety.	56	1072	UUUCUCAGAUUUUACUUC CACCU	16	1070
27	CCAAGUGUGGCUCAUU AGGCA	57	1022	UGCCUAAUGAGCCACACU UGGAG	58	1020
28	CCAAGUGU(n)GCUCAU UAGGCA, wherein (n) indicates an abasic moiety.	59	1022	UGCCUAAUGAGCCACACU UGGAG	58	1020
29	UGCAAAUA(n)UCUACA AACCAA, wherein (n) indicates an abasic moiety.	60	980	UUGGUUUUGUAGACUAUU UGCACC	61	978*
30	UGCAAAUAGUCUACAA ACCAA	62	980	UUGGUUUUGUAGACUAUU UGCACC	61	978*
77	GUGGAAGUAAAAUCUG AGAAATT	117	1072	UUUCUCAGAUUUUACUUC CACTT	118	1070**
78	GUGGAAGUAAAAUCUG AGAAG	119	1072	UUUCUCAGAUUUUACUUC CACCU	16	1070

* The last nucleotide does not match the transcript.
 ** The last two nucleotides do not match the transcript.

In some embodiments, 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;
- (g) 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;
- (h) 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;
- (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,

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

strand comprises a second nucleic acid sequence of SEQ ID NO: 6, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 8, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 10, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 12, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 14, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the

antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 18, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 20, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 22, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 24, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 55, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 56, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 57, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 58, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 59, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 58, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 57, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 58, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 60, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 61, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 62, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 61, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 117, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 118, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 119, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 16, wherein 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 embodiments, 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,

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

strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 7, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 8, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 9, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 10, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 11, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 12, wherein one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 13, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 14, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 15, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 17, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 18, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 19, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 20, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 21, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 22, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 23, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 24, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 55, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 56, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 57, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 58, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 59, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 58, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 60, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 61, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 62, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 61, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 117, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 118, wherein 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 embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 119, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 16, wherein 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 embodiments, the MAPT RNAi agent described herein can comprise a sense strand that comprises a sequence that has 1, 2, or 3 differences from SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 55, 56, 57, 59, 60, 62, 117, 119. In some embodiments, the MAPT RNAi agent described herein can comprise an antisense strand that comprises a sequence that has 1, 2, or 3 differences from SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 58, 61, 118.

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, which are the bonds between two nucleotides in the sense or antisense strand. For example, some 2'-modifications of ribose or deoxyribose can increase RNA or DNA stability and half-life. Such 2'-modifications can be 2'-fluoro, 2'-O-methyl (i.e., 2'-methoxy), 2'-O-alkyl, e.g., 2'-O-C16 alkyl modified nucleotide, or 2'-O-methoxyethyl (2'-O-MOE).

In some embodiments, one or more nucleotides of the sense strand and/or the antisense strand are independently modified nucleotides, which means the sense strand and the antisense strand can have different modified nucleotides. In some embodiments, one or more nucleotides of the sense strand are modified nucleotides. In some embodiments, each nucleotide of the sense

strand is a modified nucleotide. In some embodiments, one or more nucleotides of the antisense strand are modified nucleotides. In some embodiments, each nucleotide of the antisense strand is a modified nucleotide. In some embodiments, the modified nucleotide is a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, or 2'-O-alkyl modified nucleotide, e.g., 2'-O-C16 alkyl modified nucleotide. In some embodiments, each nucleotide of the sense strand and the antisense strand is independently a modified nucleotide, e.g., a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, or 2'-O-alkyl modified nucleotide, e.g., 2'-O-C16 alkyl modified nucleotide.

In some embodiments, the sense strand has four 2'-fluoro modified nucleotides, e.g., at positions 7, 9, 10, 11 from the 5' end of the sense strand. In some embodiments, nucleotides at positions other than positions 7, 9, 10, and 11 of the sense strand are 2'-O-methyl modified nucleotides or 2'-O-C16 alkyl modified nucleotides. In some embodiments, the antisense strand has four 2'-fluoro modified nucleotides, e.g., at positions 2, 6, 14, 16 from the 5' end of the antisense strand. In some embodiments, nucleotides at positions other than positions 2, 6, 14 and 16 of the antisense strand are 2'-O-methyl modified nucleotides or 2'-O-C16 alkyl modified nucleotides.

In some embodiments, 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 embodiments, the other nucleotides of the sense strand are 2'-O-methyl modified nucleotides. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the other nucleotides of the antisense strand are 2'-O-methyl modified nucleotides. In some embodiments, the sense strand comprises an abasic moiety or inverted abasic moiety.

In some embodiments, the modified nucleotide is a 2'-O-alkyl modified nucleotide, e.g., 2'-O-C16 alkyl modified nucleotide, which can serve as a delivery moiety. In some embodiments, the 2'-O-alkyl modified nucleotide is a 2'-O-hexadecyl uridine, 2'-O-hexadecyl cytidine, 2'-O-hexadecyl guanine, or 2'-O-hexadecyl adenosine. In some embodiments, 2'-O-

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

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

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

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

In a further aspect, provided herein are 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 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 25, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 26;
- (b) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 27, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%,

- about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 28;
- (c) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 29, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 30;
- (d) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 31, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 32;
- (e) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 33, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 34;
- (f) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 35, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 36;

- (g) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 37, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 38;
- (h) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 39, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 40;
- (i) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 41, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 42;
- (j) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 43, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 44;
- (k) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO:

- 45, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 46;
- (l) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 47, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 48;
- (m) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 63, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 40;
- (n) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to any one of SEQ ID NOs: 64, 66-69, 71, 75-86, 93-100, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 65;
- (o) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 64, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%,

- about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to any one of SEQ ID NOs: 70, 72-74;
- (p) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 87 or 89, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 88;
- (q) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 90 or 92, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 91;
- (r) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 101, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 102;
- (s) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 103, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 104;

- (t) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 105, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to any one of SEQ ID NOs: 65, 106-108;
- (u) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 109, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 65;
- (v) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 110, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 40;
- (w) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 111, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 112;
- (x) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO:

113, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 114; and

- (y) the sense strand comprises a first nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 115, and the antisense strand comprises a second nucleic acid sequence having at least 90% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%) sequence identity to SEQ ID NO: 116.

In some embodiments, provided herein are 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: 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;
- (g) 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;

- (h) 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;
- (i) 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;
- (j) 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;
- (k) 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;
- (l) 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;
- (m) 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;
- (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 some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 25, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 26. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 27, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 28. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 29, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 30. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 31, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 32. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 33, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 34. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first

nucleic acid sequence of SEQ ID NO: 35, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 36. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 37, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 38. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 39, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 40. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 41, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 42. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 43, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 44. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 45, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 46. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 47, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 48.

In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 63, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 40. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence 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. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 64, and the antisense strand comprises a second nucleic acid sequence selected from any one of SEQ ID NOs: 70, 72-74. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence selected from SEQ ID NO: 87 or 89, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 88. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence selected from SEQ ID NO: 90 or 92, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 91. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 101, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 102. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 103, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 104.

In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 105, and the antisense strand comprises a second nucleic acid sequence selected from any one of SEQ ID NOs: 65, 106-108. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 109, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 65. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a

first nucleic acid sequence of SEQ ID NO: 110, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 40. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 111, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 112. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 113, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 114. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 115, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 116.

In some embodiments, the MAPT RNAi agent described herein can comprise a sense strand that comprises a sequence that has 1, 2, or 3 differences from SEQ ID NO: 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 63, 64, 66-69, 71, 75-87, 89, 90, 92-101, 103, 105, 109-111, 113, 115. In some embodiments, the MAPT RNAi agent described herein can comprise an antisense strand that comprises a sequence that has 1, 2, or 3 differences from SEQ ID NO: 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 65, 70, 72-74, 88, 91, 102, 104, 106-108, 112, 114, 116.

In some embodiments, provided herein are 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 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: 63, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 40;
- (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.

In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 25, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 26. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 27, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 28. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 29, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 30. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 31, and the antisense strand has a second nucleic acid sequence of SEQ ID NO:

32. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 33, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 34. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 35, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 36. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 37, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 38. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 39, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 40. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 41, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 42. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 43, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 44. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 45, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 46. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 47, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 48.

In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein

the sense strand has a first nucleic acid sequence of SEQ ID NO: 63, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 40. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence 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. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 64, and the antisense strand has a second nucleic acid sequence selected from any one of SEQ ID NOs: 70, 72-74. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence selected from SEQ ID NO: 87 or 89, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 88. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence selected from SEQ ID NO: 90 or 92, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 91. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 101, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 102. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 103, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 104.

In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 105, and the antisense strand has a second nucleic acid sequence selected from any one of SEQ ID NOs: 65, 106-108. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense

strand has a first nucleic acid sequence of SEQ ID NO: 109, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 65. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 110, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 40. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 111, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 112. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 113, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 114. In some embodiments, provided herein are MAPT RNAi agent having a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the sense strand has a first nucleic acid sequence of SEQ ID NO: 115, and the antisense strand has a second nucleic acid sequence of SEQ ID NO: 116.

Table 2: MAPT RNAi Agents with Modifications

MAPT RNAi Agent No.	Strand	Sequence from 5' to 3' end	SEQ ID NO
13	S	mA*mC*mAmAmGmCfUmGfAfCfCmUmUmCmCmGmCmGmA*mG*mA	25
	AS	VPmU*fC*mUmCmGfCmGmGmAmAmGmGmUfCmAfGmCmUmUmGmU*mG*mG	26
14	S	mA*mG*mAmUmUmGfAmAfAfCfCmCmAmCmAmAmGmCmU*mG*mA	27
	AS	VPmU*fC*mAmGmCfUmUmGmUmGmGmGmUfUmUfCmAmAmUmCmU*mU*mU	28
15	S	mA*mA*mUmAmAmAfAmAfGfAfUmUmGmAmAmAmCmCmC*mA*mA	29
	AS	VPmU*fU*mGmGmGfUmUmUmCmAmAmUmCfUmUfUmUmUmAmUmU*mU*mC	30

16	S	mG*mG*mAmAmAmUfAmAfAfAmGmAmUmUmGmAmAmA*mC*mA	31
	AS	VPmU*fG*mUmUmUfCmAmAmUmCmUmUmUfUmUfAmUmUmUmCmC*mU*mC	32
17	S	mG*mG*mCmGmGmAfGmGfAfAmUmAmAmAmAmGmA*mU*mA	33
	AS	VPmU*fA*mUmCmUfUmUmUmAmUmUmUfCmCfUmCmCmGmCmC*mA*mG	34
18	S	mG*mA*mAmGmUmAfAmAfAfUfCmUmGmAmGmAmAmGmC*mU*mA	35
	AS	VPmU*fA*mGmCmUfUmCmUmCmAmGmAmUfUmUfUmAmCmUmUmC*mC*mA	36
19	S	mG*mG*mAmAmGmUfAmAfAfAfUmCmUmGmAmGmAmAmG*mC*mA	37
	AS	VPmU*fG*mCmUmUfCmUmCmAmGmAmUmUfUmUfAmCmUmUmCmC*mA*mC	38
20	S	mG*mU*mGmGmAmAfGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA	39
	AS	VPmU*fU*mUmCmUfCmAmGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU	40
21	S	mC*mC*mAmGmGmUfGmGfAfAfGmUmAmAmAmAmUmCmU*mG*mA	41
	AS	VPmU*fC*mAmGmAfUmUmUmAmCmUmUfCmCfAmCmCmUmGmG*mC*mC	42
22	S	mC*mA*mAmGmUmCfCmAfAfGfAmUmCmGmGmCmUmCmC*mA*mA	43
	AS	VPmU*fU*mGmGmAfGmCmCmGmAmUmCmUfUmGfGmAmCmUmUmG*mA*mC	44
23	S	mU*mC*mUmGmGmUfGmAfAfCfCmUmCmCmAmAmAmAmU*mC*mA	45
	AS	VPmU*fG*mAmUmUfUmUmGmGmAmGmGmUfUmCfAmCmCmAmGmA*mG*mC	46
24	S	mC*mA*mGmGmUmGfGmAfAfGfUmAmAmAmAmUmCmUmG*mA*mA	47
	AS	VPmU*fU*mCmAmGfAmUmUmUmAmCmUfUmCfCmAmCmCmUmG*mG*mC	48
31	S	mG*mU*mGmGmAmAfGmUfAfAfAmA(Uhd)mCmUmGmAmGmA*mA*mA	63
	AS	VPmU*fU*mUmCmUfCmAmGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU	40
32	S	mG*mU*mGmGmAmAmGmUfAfAfAmA(Uhd)mCmUmGmAmGmA*mA*mA	64
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU	65
33	S	mG*mU*mGmGmAmAmGmUfAfAfA(Ahd)mUmCmUmGmAmGmA*mA*mA	66

	AS	VPmU*fU*mUmCfUmCmAfGmAmmUmUmUfAmCfUmUmCmCmAmmC*mU	65
34	S	mG*mU*mGmGmAmmGmUfA(n)fAmA(Uhd)mCmUmGmAmmGmA*mA*mA	67
	AS	VPmU*fU*mUmCfUmCmAfGmAmmUmUmUfAmCfUmUmCmCmAmmC*mU	65
35	S	mG*mU*mGmGmAmmGmUfA(n)fAmA(Uhd)mCmUmGmAmmGmA*mA*mA	68
	AS	VPmU*fU*mUmCfUmCmAfGmAmmUmUmUfAmCfUmUmCmCmAmmC*mU	65
36	S	mG*mU*mGmGmAmmGmU(n)fAfAmA(Uhd)mCmUmGmAmmGmA*mA*mA	69
	AS	VPmU*fU*mUmCfUmCmAfGmAmmUmUmUfAmCfUmUmCmCmAmmC*mU	65
37	S	mG*mU*mGmGmAmmGmUfAfAfAmA(Uhd)mCmUmGmAmmGmA*mA*mA	64
	AS	VPmU*fU*mUmCmUfCmAmmGmAmmUmUmUfAmCfUmUfCmCfAmC*mC*mU	70
38	S	mG*mU*mGmGmAmmGmUfAfAfAmA(Uhd)mCfUmGmAmmGmA*mA*mA	71
	AS	VPmU*fU*mUmCfUmCmAfGmAmmUmUmUfAmCfUmUmCmCmAmmC*mU	65
39	S	mG*mU*mGmGmAmmGmUfAfAfAmA(Uhd)mCmUmGmAmmGmA*mA*mA	64
	AS	VPmU*fU*mUmCfUmCfAmGmAmmUmUmUfAmCfUmUmCmCmAmmC*mU	72
40	S	mG*mU*mGmGmAmmGmUfAfAfAmA(Uhd)mCmUmGmAmmGmA*mA*mA	64
	AS	VPmU*fU*fUmCmUmCfAmGmAmmUmUmUfAmCfUmUmCmCmAmmC*mU	73
41	S	mG*mU*mGmGmAmmGmUfAfAfAmA(Uhd)mCmUmGmAmmGmA*mA*mA	64
	AS	VPmU*fU*mUmCfUmCmAmmGmAmmUmUmUfAmCmUmUmCmCmAmmC*mU	74
42	S	mG*mU*mGmGmAmmGmUfAfAfA(Uhd)fUmCfUmGmAmmGmA*mA*mA	75
	AS	VPmU*fU*mUmCfUmCmAfGmAmmUmUmUfAmCfUmUmCmCmAmmC*mU	65
43	S	(Ghd)*mU*mGmGmAmmGmUfAfAfAmAmUmCmUmGmAmmGmA*mA*mA	76
	AS	VPmU*fU*mUmCfUmCmAfGmAmmUmUmUfAmCfUmUmCmCmAmmC*mU	65
44	S	mG*(Uhd)*mGmGmAmmGmUfAfAfAmAmUmCmUmGmAmmGmA*mA*mA	77
	AS	VPmU*fU*mUmCfUmCmAfGmAmmUmUmUfAmCfUmUmCmCmAmmC*mU	65

45	S	mG*mU*(Ghd)mGmAmAmGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA	78
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
46	S	mG*mU*mGmGmA(Ahd)mGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA	79
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
47	S	mG*mU*mGmGmA(Ahd)fAfAfAmAmUmCmUmGmAmGmA*mA*mA	80
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
48	S	mG*mU*mGmGmA(Ahd)fAfAmAmUmCmUmGmAmGmA*mA*mA	81
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
49	S	mG*mU*mGmGmA(Ahd)fAmAmUmCmUmGmAmGmA*mA*mA	82
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
50	S	mG*mU*mGmGmA(Ahd)fAfAfAmAmUmC(Uhd)mGmAmGmA*mA*mA	83
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
51	S	mG*mU*mGmGmA(Ahd)fAfAfAmAmUmCmUmGmAmG(Ahd)*mA*mA	84
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
52	S	mG*mU*mGmGmA(Ahd)fAfAfAmAmUmCmUmGmAmGmA*(Ahd)*mA	85
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
53	S	mG*mU*mGmGmA(Ahd)fAfAfAmAmUmCmUmGmAmGmA*mA*(Ahd)	86
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
54	S	mC*mC*mAmAmGmUmGmUfGfGfCmU(Chd)mAmUmUmAmGmG*mC*mA	87
	AS	VPmU*fG*mCmCfUmAmAfUmGmAmGmCmCfAmCfAmCmUmUmGmG*mA*mG	88
55	S	mC*mC*mAmAmGmUmGmU(n)fGfCmU(Chd)mAmUmUmAmGmG*mC*mA	89
	AS	VPmU*fG*mCmCfUmAmAfUmGmAmGmCmCfAmCfAmCmUmUmGmG*mA*mG	88
56	S	mU*mG*mCmA(Ahd)mCmA(Ahd)mCmA(Ahd)mCmA(Ahd)mCmA(Ahd)	90

	AS	VPmU*fU*mGmGfUmUmUfGmUmAmGmAmCfUmAfUmUmUmGmCmA*mC*mC	91
57	S	mU*mG*mCmAmAmAmUmAfGfUfCmU(Ahd)mCmAmAmAmCmC*mA*mA	92
	AS	VPmU*fU*mGmGfUmUmUfGmUmAmGmAmCfUmAfUmUmUmGmCmA*mC*mC	91
58	S	mG*mU*mG(Ghd)mAmAmGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA	93
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
59	S	mG*mU*mGmG(Ahd)mAmGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA	94
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
60	S	mG*mU*mGmGmA(Ahd)mUfAfAfAmAmUmCmUmGmAmGmA*mA*mA	95
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
61	S	mG*mU*mGmGmA(Ahd)mAmUmCmUmGmAmGmA*mA*mA	96
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
62	S	mG*mU*mGmGmA(Ahd)mUmGmAmGmA*mA*mA	97
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
63	S	mG*mU*mGmGmA(Ahd)mAmGmA*mA*mA	98
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
64	S	mG*mU*mGmGmA(Ahd)mGmA*mA*mA	99
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
65	S	mG*mU*mGmGmA(Ahd)mA*mA*mA	100
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mU	65
66	S	mC*mC*mAmGmGmUmGmGfAfAfGmU(Ahd)mAmAmAmUmCmU*mG*mA	101
	AS	VPmU*fC*mAmGfAmUmUfUmUmAmCmUmUfCmCfAmCmCmUmGmG*mC*mC	102
67	S	mG*mG*mAmAmGmUmAmAfAfAfUmC(Uhd)mGmAmGmAmAmG*mC*mA	103
	AS	VPmU*fG*mCmUfUmCmUfCmAfGmAmUmUfUmUfAmCmUmUmCmC*mA*mC	104

68	S	mG*mU*mGmGmAmAfGmUfAfAfAmAmUmCmUmGmAmGmAmA*mA*	105
	AS	VPmU*fU*mUmCmUmCmAmGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU	106
69	S	mG*mU*mGmGmAmAfGmUfAfAfAmAmUmCmUmGmAmGmAmA*mA*	105
	AS	VPmU*fU*mUfCmUfCfAmGfAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU	107
70	S	mG*mU*mGmGmAmAfGmUfAfAfAmAmUmCmUmGmAmGmAmA*mA*	105
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU	65
71	S	mG*mU*mGmGmAmAfGmUfAfAfAmAmUmCmUmGmAmGmAmA*mA*	105
	AS	VPmU*fU*mUmCfUfCfAfGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU	108
72	S	mG*mU*mGmGmAmAfGmUfA(n)fAmAmUmCmUmGmAmGmAmA*mA*	109
	AS	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU	65
73	S	mG*mU*mGmGmAmAfGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mG	110
	AS	VPmU*fU*mUmCmUfCmAmGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU	40
74	S	mA*mA*fGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA	111
	AS	VPmU*fU*mUmCmUfCmAmGmAmUmUmUmUfAmCfUmU*mC*mC*mA*mC*mC*mU	112
75	S	mG*mU*mGmGmAmAfGmUfAfAfAmAmUmCmUmGmAmGmAmAmAdTdT*	113
	AS	VPmU*fU*mUmCmUfCmAmGmAmUmUmUmUfAmCfUmUmCmC*mA*mCdTdT	114
76	S	mG*mU*mGmGmAmAmGmUfAfAfAmAmUmCmUmGmAmGmAmA*mA*	115
	AS	VPmU*fU*mUmCmUfCmAmGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mC*mU	116

Abbreviations – “m” indicates 2'-OMe; “f” indicated 2'-fluoro; “*” indicates phosphorothioate linkage; “VP” indicates 5'-vinylphosphonate; “Uhd” indicates 2'-O-hexadecyl uridine; “Chd” indicates 2'-O-hexadecyl cytidine; “Ahd” indicates 2'-O-hexadecyl adenosine; “iAb” indicates inverted abasic moiety; “n” indicates abasic moiety; “S” means the sense strand; “AS” means the antisense strand.

Table 3. Abasic or inverted abasic (iAb) moieties

	Structure
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1 (abasic)	
2 (iAb)	

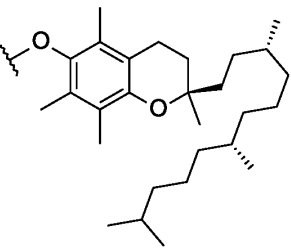
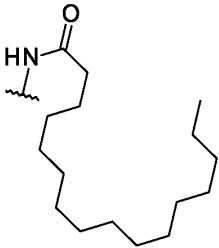
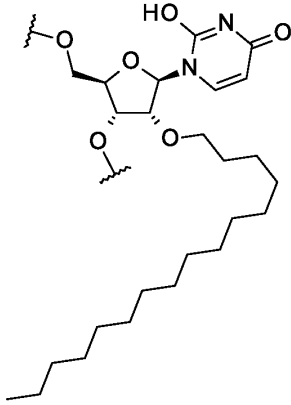
“5” and “3” indicate the 5' to 3' direction of the sequences.

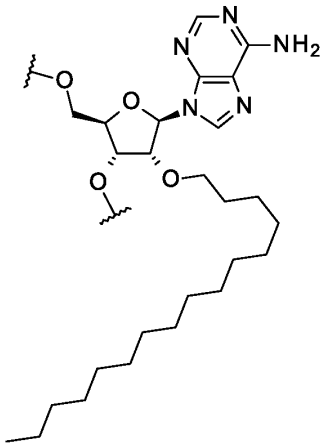
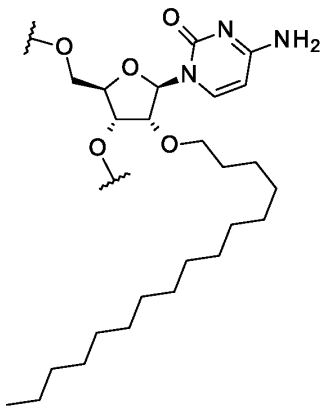
In some embodiments, the sense strand of the MAPT RNAi agent has a delivery moiety. In some embodiments, the sense strand of the MAPT RNAi agent has a delivery moiety conjugated to the 5' or 3' end of the sense strand. In some embodiments, the sense strand of the MAPT RNAi agent has a delivery moiety conjugated to a nucleotide of the sense strand. The delivery moiety can facilitate the entry of RNAi agent into the cells. In some embodiments, the delivery moiety is α -tocopherol or palmitic acid (see Table 4). In some embodiments, the delivery moiety is a known delivery moiety for delivering RNAi agent into a cell, e.g., a delivery moiety described in Hu et al., *Signal Transduction and Targeted Therapy* (2020) 5:101. Placement of a delivery moiety on the RNAi agent needs to overcome potential inefficient loading of AGO2 (Argonaute-2), or other hindrance of the RNA-induced silencing complex (RISC) complex activity.

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

In some embodiments, the delivery moiety is conjugated to a nucleotide of the sense strand. In that case, the delivery moiety is a modified nucleotide located in the sense strand. In some embodiments, the modified nucleotide is 2'-O-hexadecyl uridine, 2'-O-hexadecyl cytidine, 2'-O-hexadecyl guanine, or 2'-O-hexadecyl adenosine (Table 4).

Table 4. Delivery Moieties

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

	
	Chd (2'-O-hexadecyl cytidine)
5	
6	Ghd (2'-O-hexadecyl guanine)

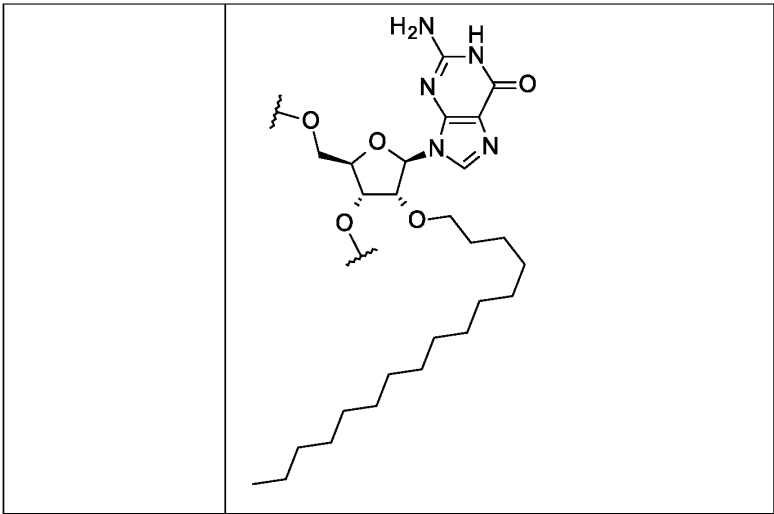


Table 5. Linkers

Linker	Structure
1	Teg (tetraethylene glycol) linker
	sense strand- The structure shows a sense strand with a phosphate group (O⁻-P(=O)(OH)-O-) attached to a tetraethylene glycol linker (O-CH₂-CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-). The linker is terminated with a wavy line.
2	Piperidinol-PEG linker
	The structure shows a piperidinol-PEG linker attached to a sense strand. The piperidine ring is connected to a hydroxyl group (HO-) and a carbonyl group (C=O). The carbonyl group is connected to a piperidine ring, which is further connected to a PEG linker (O-CH₂-CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-). The linker is terminated with a wavy line. The sense strand is attached to the piperidine ring via a phosphate group (O⁻-P(=O)(OH)-O-).
3	Teg (tetraethylene glycol) linker PS
	sense strand- The structure shows a sense strand with a phosphorothioate group (O⁻-P(=S)(OH)-O-) attached to a tetraethylene glycol linker (O-CH₂-CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-). The linker is terminated with a wavy line.
	Piperidinol-PEG linker PS

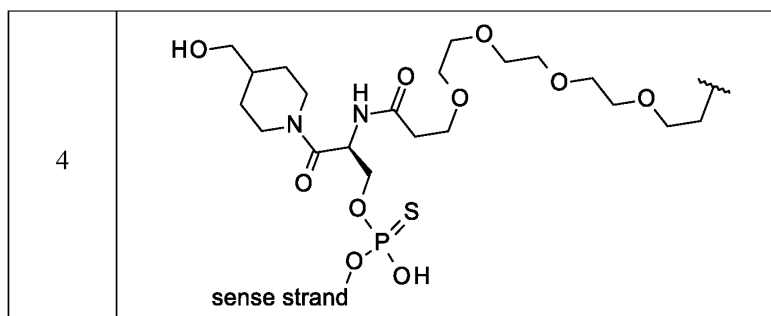
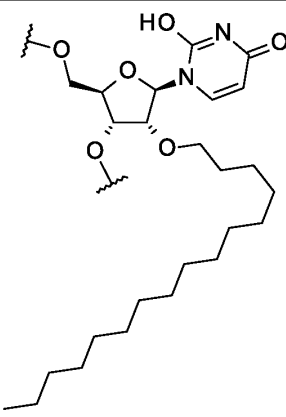
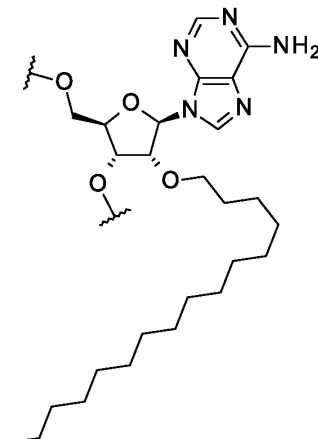
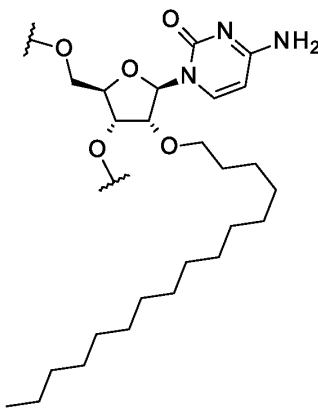
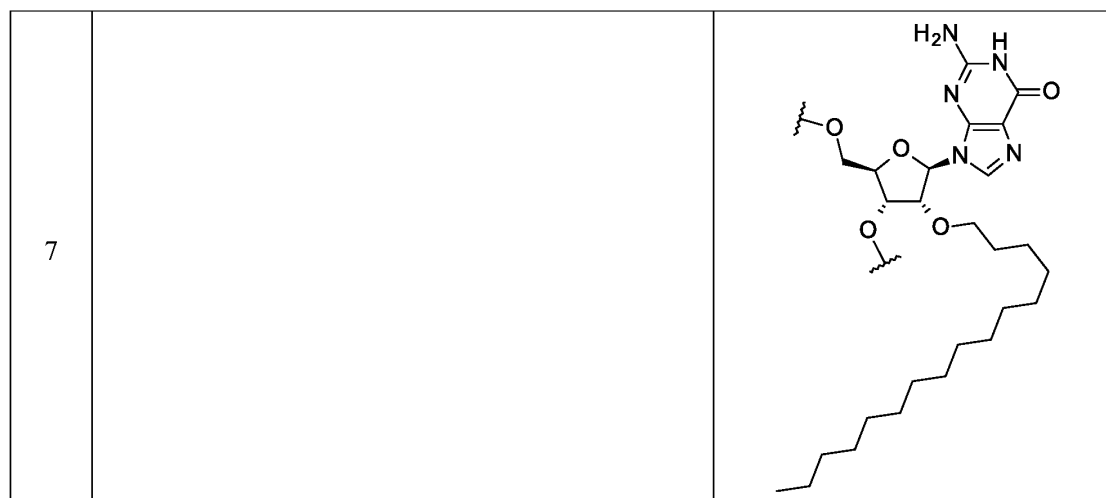


Table 6. Linker Delivery Moiety Pairs (LDP)

LDP	Linker	Delivery Moiety
1	Teg (tetraethylene glycol) linker	α -Tocopherol
	sense strand	
2	Piperidinol-PEG linker	α -Tocopherol
	sense strand	
3	Piperidinol-PEG linker	Palmitic Acid
	sense strand	
	None	Uhd

4		
5	None	Ahd 
6	None	Chd 
	None	Ghd



In a further aspect, 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 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;

- (g) 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;
- (h) 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;
- (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;
- (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 embodiments, 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 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 embodiments, 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 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;
- (g) 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;
- (h) 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;
- (i) 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;
- (j) 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;
- (k) 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;
- (l) 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;
- (m) 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 SEQ ID NO: 65, 106-108;
- (n) 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;
- (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 embodiments, 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 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 some embodiments, the delivery means is conjugated to the sense strand. In some embodiments, the delivery means is conjugated to the 5' or 3' end of the sense strand. In some embodiments, the delivery means is conjugated to a nucleotide of the sense strand. In some embodiments, the delivery means is palmitic acid or α -tocopherol. In some embodiments, the linking means is selected from the group consisting of Linker 1, Linker 2, Linker 3, and Linker 4 of Table 5.

The sense strand and antisense strand of MAPT RNAi agent can be synthesized using any nucleic acid polymerization methods known in the art, for example, solid-phase synthesis by employing phosphoramidite chemistry methodology (e.g., Current Protocols in Nucleic Acid Chemistry, Beaucage, S.L. et al. (Eds.), John Wiley & Sons, Inc., New York, NY, USA), H-phosphonate, phosphotriester chemistry, or enzymatic synthesis. Automated commercial synthesizers can be used, for example, MerMade™ 12 from LGC Biosearch Technologies, or other synthesizers from BioAutomation or Applied Biosystems. Phosphorothioate linkages can

be introduced using a sulfurizing reagent such as phenylacetyl disulfide or DDTT (((dimethylaminomethylidene) amino)-3H-1,2,4-dithiazaoline-3-thione). It is well known to use similar techniques and commercially available modified amidites and controlled-pore glass (CPG) products to synthesize modified oligonucleotides or conjugated oligonucleotides.

Purification methods can be used to exclude the unwanted impurities from the final oligonucleotide product. Commonly used purification techniques for single stranded oligonucleotides include reverse-phase ion pair high performance liquid chromatography (RP-IP-HPLC), capillary gel electrophoresis (CGE), anion exchange HPLC (AX-HPLC), and size exclusion chromatography (SEC). After purification, oligonucleotides can be analyzed by mass spectrometry and quantified by spectrophotometry at a wavelength of 260 nm. The sense strand and antisense strand can then be annealed to form a duplex.

In another aspect, 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. Such pharmaceutical compositions can also comprise one or more pharmaceutically acceptable excipient, diluent, or carrier. Pharmaceutical compositions can be prepared by methods well known in the art (e.g., Remington: The Science and Practice of Pharmacy, 23rd edition (2020), A. Loyd et al., Academic Press).

In a further aspect, provided herein are methods of reducing MAPT expression in a cell (e.g., a neuron), 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. The MAPT RNAi agent can be introduced into the cell (e.g., a neuron) using a method known in the art, e.g., transfection, electroporation, microinjection, or uptake by the cell via natural transport mechanisms.

In another aspect, 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. Aggregation of MAPT can be caused by overexpression of the MAPT protein or a mutation that affects the structure of the protein, resulting in an increased tendency of the MAPT protein to self-associate. Therefore, reducing MAPT expression level can be beneficial to the patient with tauopathy.

In another aspect, 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. Exemplary tauopathy includes, but are not limited to, 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 (Parkinson-dementia complex of Guam), 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 sclerosingpan encephalitis, tuberous sclerosis, lipofuscinosis, primary age-related tauopathy (PART), globular glial tauopathies (GGT). In some embodiments, the tauopathy is Alzheimer's disease (AD), frontotemporal dementia (FTD), or progressive supranuclear palsy (PSP).

The MAPT RNAi agent can be administered to the patient intrathecally, intracerebroventricularly, or via intracisternal magna injection. In some embodiments, the MAPT RNAi agent is administered to the patient intrathecally via a catheter.

RNAi dosage regimens may be adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus may be administered, several divided doses

may be administered over time, or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation.

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

In another aspect, 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.

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

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

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

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

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

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

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

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

The term “have”, “having” or “has”, when referring to a sequence, means consists of or consists essentially of.

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

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

As used herein, “modified nucleotide” refers to a nucleotide having one or more chemical modifications when compared with a corresponding reference nucleotide selected from: adenine

ribonucleotide, guanine ribonucleotide, cytosine ribonucleotide, uracil ribonucleotide, adenine deoxyribonucleotide, guanine deoxyribonucleotide, cytosine deoxyribonucleotide, and thymidine deoxyribonucleotide. A modified nucleotide can have, for example, one or more chemical modification in its sugar, nucleobase, and/or phosphate group. Additionally, or alternatively, a modified nucleotide can have one or more chemical moieties conjugated to a corresponding reference nucleotide. In some embodiments, the modified nucleotide is a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, or 2'-O-alkyl modified nucleotide, e.g., 2'-O-C16 alkyl modified nucleotide. In some embodiments, the modified nucleotide has a phosphate analog, e.g., 5'-vinylphosphonate. In some embodiments, the modified nucleotide is an abasic moiety or inverted abasic moiety, e.g., a moiety shown in Table 3.

As used herein, the term “tauopathy” refers to a disease associated with abnormal tau protein expression, secretion, phosphorylation, cleavage, and/or aggregation.

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

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

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

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

As used herein, “phosphate analog” means a chemical moiety that mimics the electrostatic and/or steric properties of a phosphate group. In some embodiments, a phosphate analog is positioned at the 5' terminal nucleotide of an oligonucleotide in place of a 5'-phosphate, which is often susceptible to enzymatic removal. A 5' phosphate analog can include a

phosphatase-resistant linkage. Examples of phosphate analogs include 5' methylene phosphonate (5'-MP) and 5'-(E)-vinylphosphonate (5'-VP). In some embodiments, the phosphate analog is 5'-VP.

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

As used herein, “RNAi,” “RNAi agent,” “iRNA,” “iRNA agent,” and “RNA interference agent” means an agent that mediates sequence-specific degradation of a target mRNA by RNA interference, e.g., via RNA-induced silencing complex (RISC) pathway. In some embodiments, the RNAi agent has a sense strand and an antisense strand, and the sense strand and the antisense strand form a duplex. In some embodiments, the sense strand has a delivery moiety, e.g., a

delivery moiety conjugated to the 5' or 3' end of the sense strand or a nucleotide of the sense strand.

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

As used herein, “MAPT” refers to a human MAPT mRNA transcript, encoding a microtubule associated protein Tau. The nucleotide sequences of human MAPT transcript variants and amino acid sequences of human Tau protein isoforms can be found at:

- i. MAPT transcript variant 1 → Tau protein isoform 1: NM_016835.5 (nucleotide sequence) → NP_058519.3 (amino acid sequence);
- ii. MAPT transcript variant 2 → Tau protein isoform 2: NM_005910.6 (nucleotide sequence) → NP_005901.2 (amino acid sequence);
- iii. MAPT transcript variant 3 → Tau protein isoform 3: NM_016834.5 (nucleotide sequence) → NP_058518.1 (amino acid sequence);
- iv. MAPT transcript variant 4 → Tau protein isoform 4: NM_016841.5 (nucleotide sequence) → NP_058525.1 (amino acid sequence);
- v. MAPT transcript variant 5 → Tau protein isoform 5: NM_001123067.4 (nucleotide sequence) → NP_001116539.1 (amino acid sequence);
- vi. MAPT transcript variant 6 → Tau protein isoform 6: NM_001123066.4 (nucleotide sequence) → NP_001116538.2 (amino acid sequence);
- vii. MAPT transcript variant 7 → Tau protein isoform 7: NM_001203251.2 (nucleotide sequence) → NP_001190180.1 (amino acid sequence);
- viii. MAPT transcript variant 8 → Tau protein isoform 8: NM_001203252.2 (nucleotide sequence) → NP_001190181.1 (amino acid sequence);
- ix. MAPT transcript variant 9 → Tau protein isoform 9: NM_001377265.1 (nucleotide sequence) → NP_001364194.1 (amino acid sequence);
- x. MAPT transcript variant 10 → Tau protein isoform 10: NM_001377266.1 (nucleotide sequence) → NP_001364195.1 (amino acid sequence);
- xi. MAPT transcript variant 11 → Tau protein isoform 11: NM_001377267.1 (nucleotide sequence) → NP_001364196.1 (amino acid sequence);

- xii. MAPT transcript variant 12 → Tau protein isoform 4: NM_001377268.1 (nucleotide sequence) → NP_001364197.1 (amino acid sequence).

The nucleotide sequence of the human MAPT transcript variant 6 (encoding 2N4R Tau) can be found at NM_001123066.4:

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1  GCAGTCACCG  CCACCCACCA  GCTCCGGCAC  CAACAGCAGC  GCCGCTGCCA  CCGCCCACCT
61  TCTGCCGCCG  CCACCACAGC  CACCTTCTCC  TCCTCCGCTG  TCCTCTCCCG  TCCTCGCCTC
121  TGTGCGACTAT  CAGGTGAACT  TTGAACCAGG  ATGGCTGAGC  CCCGCCAGGA  GTTCGAAGTG
181  ATGGAAGATC  ACGCTGGGAC  GTACGGGTTG  GGGGACAGGA  AAGATCAGGG  GGGCTACACC
241  ATGCACCAAG  ACCAAGAGGG  TGACACGGAC  GCTGGCCTGA  AAGAATCTCC  CCTGCAGACC
301  CCCACTGAGG  ACGGATCTGA  GGAACCGGGC  TCTGAAACCT  CTGATGCTAA  GAGCACTCCA
361  ACAGCGGAAG  ATGTGACAGC  ACCCTTAGTG  GATGAGGGAG  CTCCCGGCAA  GCAGGCTGCC
421  GCGCAGCCCC  ACACGGAGAT  CCCAGAAGGA  ACCACAGCTG  AAGAAGCAGG  CATTTGAGAC
481  ACCCCCAGCC  TGGAAAGACG  AGCTGCTGGT  CACGTGACCC  AAGAGCCTGA  AAGTGGTAAG
541  GTGGTCCAGG  AAGGCTTCTT  CCGAGAGCCA  GGCCCCCAG  GTCTGAGCCA  CCAGCTCATG
601  TCCGGCATGC  CTGGGGCTCC  CCTCTGCTT  GAGGGCCCCA  GAGAGGCCAC  ACGCCAACCT
661  TCGGGGACAG  GACCTGAGGA  CACAGAGGGC  GGCCGCCACG  CCCCTGAGCT  GCTCAAGCAC
721  CAGCTTCTAG  GAGACCTGCA  CCAGGAGGGG  CCGCCGCTGA  AGGGGGCAGG  GGGCAAAGAG
781  AGGCCGGGGA  GCAAGGAGGA  GGTGGATGAA  GACCGCGACG  TCGATGAGTC  CTCCCCCAA
841  GACTCCCTC  CCTCCAAGGC  CTCCCAGCC  CAAGATGGGC  GGCCTCCCA  GACAGCCGCC
901  AGAGAAGCCA  CCAGCATCCC  AGGCTTCCCA  GCGGAGGGTG  CCATCCCCCT  CCCTGTGGAT
961  TTCCTCTCCA  AAGTTTCCAC  AGAGATCCCA  GCCTCAGAGC  CCGACGGGCC  CAGTGTAGGG
1021  CGGGCCAAAG  GGCAGGATGC  CCCCCTGGAG  TTCACGTTTC  ACGTGGAAT  CACACCCAAC
1081  GTGCAGAAGG  AGCAGGCGCA  CTCGGAGGAG  CATTTGGGAA  GGGCTGCATT  TCCAGGGGCC
1141  CCTGGAGAGG  GGCCAGAGGC  CCGGGGCCCC  TCTTTGGGAG  AGGACACAAA  AGAGGCTGAC
1201  CTTCCAGAGC  CCTCTGAAAA  GCAGCCTGCT  GCTGCTCCGC  GGGGGAAGCC  CGTCAGCCGG
1261  GTCCCTCAAC  TCAAAGCTCG  CATGGTCAGT  AAAAGCAAAG  ACGGACTTGG  AAGCGATGAC
1321  AAAAAAGCCA  AGACATCCAC  ACGTTCCTCT  GCTAAAACCT  TGAAAAATAG  GCCTTGCCCTT
1381  AGCCCCAAAC  ACCCACTCC  TGGTAGCTCA  GACCCTCTGA  TCCAACCTC  CAGCCCTGCT
1441  GTGTGCCCAG  AGCCACCTTC  CTCTCCTAAA  TACGTCTCTT  CTGTCACTTC  CCGAACTGGC
1501  AGTTCTGGAG  CAAAGGAGAT  GAAACTCAAG  GGGGCTGATG  GTAAAACGAA  GATCGCCACA
1561  CCGCGGGGAG  CAGCCCTCC  AGGCCAGAAG  GGCCAGGCCA  ACGCCACCAG  GATTCCAGCA
1621  AAAACCCCGC  CCGCTCCAAA  GACACCACCC  AGCTCTGCGA  CTAAGCAAGT  CCAGAGAAGA
1681  CCACCCCTG  CAGGGCCAG  ATCTGAGAGA  GGTGAACCTC  CAAAATCAGG  GGATCGCAGC
1741  GGCTACAGCA  GCCCCGGCTC  CCCAGGCACT  CCGGCGAGCC  GCTCCCGCAC  CCGTCCCTT
1801  CCAACCCAC  CCACCCGGA  GCCAAGAAG  GTGGCAGTGG  TCCGTACTCC  ACCCAAGTCG
1861  CCGTCTTCCG  CCAAGAGCCG  CCTGCAGACA  GCCCCCGTGC  CCATGCCAGA  CCTGAAGAAT
1921  GTCAAGTCCA  AGATCGGCTC  CACTGAGAAC  CTGAAGCACC  AGCCGGGAGG  CGGGAAGGTG
1981  CAGATAATTA  ATAAGAAGCT  GGATCTTAGC  AACGTCCAGT  CCAAGTGTGG  CTCAAAGGAT
2041  AATATCAAAC  ACGTCCCGGG  AGGCGGCAGT  GTGCAAATAG  TCTACAAACC  AGTTGACCTG
2101  AGCAAGGTGA  CCTCCAAGTG  TGGCTCATT  GGCAACATCC  ATCATAAACC  AGGAGGTGGC
2161  CAGGTGGAAG  TAAAATCTGA  GAAGCTTGAC  TTCAAGGACA  GAGTCCAGTC  GAAGATTGGG
2221  TCCCTGGACA  ATATACCCA  CGTCCCTGGC  GGAGGAAATA  AAAAGATTGA  AACCACAAG
2281  CTGACCTTCC  GCGAGAACGC  CAAAGCCAAG  ACAGACCACG  GGGCGGAGAT  CGTGTACAAG
2341  TCGCCAGTGG  TGTCTGGGGA  CACGTCTCCA  CGGCATCTCA  GCAATGTCTC  CTCCACCGGC
2401  AGCATCGACA  TGGTAGACTC  GCCCAGCTC  GCCACGCTAG  CTGACGAGGT  GTCTGCCTCC
2461  CTGGCCAAGC  AGGGTTTGTG  ATCAGGCCCC  TGGGGCGGTC  AATAATTGTG  GAGAGGAGAG
2521  AATGAGAGAG  TGTGAAAAA  AAAAGAATAA  TGACCCGGCC  CCCGCCCTCT  GCCCCAGCT
2581  GCTCCTCGCA  GTTCGGTTAA  TTGGTTAATC  ACTTAACCTG  CTTTTGTGAC  TCGGCTTTGG
2641  CTCGGGACTT  CAAAATCAGT  GATGGGAGTA  AGAGCAAATT  TCATCTTTCC  AAATTGATGG
2701  GTGGGCTAGT  AATAAAATAT  TTAATAAAAA  ACATTCAAAA  ACATGGCCAC  ATCCAACATT
2761  TCCTCAGGCA  ATTCTTTTGG  ATTCTTTTTC  CTTCCCCCTC  CATGTAGAAG  AGGGAGAAGG
2821  AGAGGCTCTG  AAAGCTGCTT  CTGGGGGATT  TCAAGGGACT  GGGGGTGCCA  ACCACCTCTG

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2881 GCCCTGTTGT GGGGGTGTCA CAGAGGCAGT GGCAGCAACA AAGGATTTGA AACTTGGTGT
 2941 GTTCGTGGAG CCACAGGCAG ACGATGTCAA CCTTGTGTGA GTGTGACGGG GGTGAGGGTG
 3001 GGGCGGGGAGG CCACGGGGGA GGCCGAGGCA GGGGCTGGGC AGAGGGGAGA GGAAGCACAA
 3061 GAAGTGGGAG TGGGAGAGGA AGCCACGTGC TGGAGAGTAG ACATCCCCCT CCTTGCCGCT
 3121 GGGAGAGCCA AGGCCTATGC CACCTGCAGC GTCTGAGCGG CCGCCTGTCC TTGGTGGCCG
 3181 GGGGTGGGGG CCTGCTGTGG GTCACTGTGC CACCCTCTGC AGGGCAGCCT GTGGGAGAAG
 3241 GGACAGCGGG TAAAAAGAGA AGGCAAGCTG GCAGGAGGGT GGCACCTCGT GGATGACCTC
 3301 CTTAGAAAAG ACTGACCTTG ATGTCTTGAG AGCGCTGGCC TCTTCCTCCC TCCCTGCAGG
 3361 GTAGGGGGCC TGAGTTGAGG GGCTTCCCTC TGCTCCACAG AAACCCGTGT TTATTGAGTT
 3421 CTGAAGGTTG GAACTGCTGC CATGATTTTG GCCACTTTGC AGACCTGGGA CTTTAGGGCT
 3481 AACCAGTTCT CTTTGTAAAG ACTTGTGCCT CTTGGGAGAC GTCCACCCGT TCCCAAGCCT
 3541 GGGCCACTGG CATCTCTGGA GTGTGTGGGG GTCTGGGAGG CAGGTCCCGA GCCCCCTGTC
 3601 CTTCCACAGG CCACTGCAGT CACCCCGTCT GCGCCGCTGT GCTGTTGTCT GCCGTGAGAG
 3661 CCAATCACT GCCTATACCC CTCATCACAC GTCACAATGT CCCGAATTCC CAGCCTCACC
 3721 ACCCCTTCTC AGTAATGACC CTGGTTGGTT GCAGGAGGTA CCTACTCCAT ACTGAGGGTG
 3781 AAATTAAAGG AAGGCAAAGT CCAGGCACAA GAGTGGGACC CCAGCCTCTC ACTCTCAGTT
 3841 CCACTCATCC AACTGGGACC CTCACCACGA ATCTCATGAT CTGATTCCGT TCCCTGTCTC
 3901 CTCCTCCCGT CACAGATGTG AGCCAGGGCA CTGCTCAGCT GTGACCCTAG GTGTTTCTGC
 3961 CTTGTTGACA TGGAGAGAGC CCTTCCCCCT GAGAAGGCCT GGCCCCTTCC TGTGCTGAGC
 4021 CCACAGCAGC AGGCTGGGTG TCTTGGTTGT CAGTGGTGGC ACCAGGATGG AAGGGCAAGG
 4081 ACCCAGGGC AGGCCACAG TCCCGCTGTC CCCCCTTGC ACCCTAGCTT GTAGCTGCCA
 4141 ACCTCCAGA CAGCCAGCC CGTGTCTCAG CTCCACATGC ATAGTATCAG CCCCACAC
 4201 CCGACAAAGG GGAACACACC CCCTTGGAAA TGGTTCTTTT CCCCAGTCC CAGCTGGAAG
 4261 CCATGCTGTC TGTCTGCTG GAGCAGCTGA ACATATACAT AGATGTTGCC CTGCCCTCCC
 4321 CATCTGACC CTGTTGAGTT GTAGTTGGAT TTGTCTGTTT ATGCTTGAT TCACCAGAGT
 4381 GACTATGATA GTGAAAAGAA AAAAAAAAAA AAAAAAGGAC GCATGTATCT TGAAATGCTT
 4441 GTAAAGAGGT TTCTAACCCA CCCTCACGAG GTGTCTCTCA CCCCACACT GGGACTCGTG
 4501 TGGCCTGTGT GGTGCCACCC TGCTGGGGCC TCCCAAGTTT TGAAAGGCTT TCCTCAGCAC
 4561 CTGGGACCCA ACAGAGACCA GCTTCTAGCA GCTAAGGAGG CCGTTCAGCT GTGACGAAGG
 4621 CCTGAAGCAC AGGATTAGGA CTGAAGCGAT GATGTCCCCT TCCCTACTTC CCCTGGGGC
 4681 TCCCTGTGTC AGGGCACAGA CTAGGTCTTG TGGCTGGTCT GGCTTGCCGC GCGAGGATGG
 4741 TTCTCTCTGG TCATAGCCCC AAGTCTCATG GCAGTCCCAA AGGAGGCTTA CAACTCCTGC
 4801 ATCACAAGAA AAAGGAAGCC ACTGCCAGCT GGGGGGATCT GCAGCTCCCA GAAGCTCCGT
 4861 GAGCCTCAGC CACCCTCAG ACTGGGTTCC TCTCCAAGCT CGCCCTTGG AGGGGACGCG
 4921 CAGCCTCCCA CCAAGGGCCC TGCAGACCACA GCAGGGATTG GGATGAATTG CCTGTCTTGG
 4981 ATCTGCTCTA GAGGCCCAAG CTGCCTGCCT GAGGAAGGAT GACTTGACAA GTCAGGAGAC
 5041 ACTGTTCCCA AAGCCTTGAC CAGAGCACCT CAGCCCGCTG ACCTTGACAA AACTCCATCT
 5101 GCTGCCATGA GAAAAGGGAA GCCGCCTTTG CAAAACATTG CTGCCTAAAG AACTCAGCA
 5161 GCCTCAGGCC CAATTCTGCC ACTTCTGGTT TGGGTACAGT TAAAGGCAAC CCTGAGGGAC
 5221 TTGGCAGTAG AAATCCAGGG CCTCCCCTGG GGCTGGCAGC TTCGTGTGCA GCTAGAGCTT
 5281 TACCTGAAAG GAAGTCTCTG GGCCAGAAC TCTCCACCAA GAGCCTCCCT GCCGTTCTCT
 5341 GAGTCCAGC AATTCTCCTA AGTTGAAGGG ATCTGAGAAG GAGAAGGAAA TGTGGGGTAG
 5401 ATTTGGTGGT GGTTAGAGAT ATGCCCCCTT CATTACTGCC AACAGTTTCG GCTGCATTTC
 5461 TTCACGCACC TCGGTTCCCTC TTCTGAAGT TCTTGTGCCC TGCTCTTCCAG CACCATGGGC
 5521 CTTCTTATAC GGAAGGCTCT GGGATCTCCC CCTTGTGGGG CAGGCTCTTG GGGCCAGCCT
 5581 AAGATCATGG TTTAGGGTGA TCAGTGCTGG CAGATAAATT GAAAAGGCAC GCTGGCTTGT
 5641 GATCTTAAAT GAGGACAATC CCCCCAGGGC TGGGCACTCC TCCCCCTCCC TCACTTCTCC
 5701 CACCTGCAGA GCCAGTGTCC TTGGGTGGGC TAGATAGGAT ATACTGTATG CCGGCTCCTT
 5761 CAAGCTGCTG ACTCACTTTA TCAATAGTTC CATTTAAATT GACTTCAGTG GTGAGACTGT
 5821 ATCCTGTTTG CTATTGCTTG TTGTGCTATG GGGGGAGGGG GGAGGAATGT GTAAGATAGT
 5881 TAACATGGGC AAAGGGAGAT CTTGGGGTGC AGCACTTAAA CTGCCCTGTA ACCCTTTTCA
 5941 TGATTTCAAC CACATTTGCT AGAGGGAGGG AGCAGCCACG GAGTTAGAGG CCCTTGGGGT
 6001 TTCTCTTTTC CACTGACAGG CTTTCCCAGG CAGCTGGCTA GTTCATTCCC TCCCCAGCCA
 6061 GGTGCAGGCG TAGGAATATG GACATCTGGT TGCTTTGGCC TGCTGCCCTC TTTCAGGGGT
 6121 CCTAAGCCCA CAATCATGCC TCCTAAGAC CTTGGCATCC TTCCCTCTAA GCCGTGGCA
 6181 CCTCTGTGCC ACCTCTCACA CTGGCTCCAG ACACACAGCC TGTGCTTTTG GAGCTGAGAT
 6241 CACTCGCTTC ACCCTCCTCA TCTTTGTTCT CCAAGTAAAG CCACGAGGTC GGGGCGAGGG

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6301 CAGAGGTGAT CACCTGCGTG TCCCATCTAC AGACCTGCAG CTTCATAAAA CTTCTGATTT
6361 CTCTTCAGCT TTGAAAAGGG TTACCCTGGG CACTGGCCTA GAGCCTCACC TCCTAATAGA
6421 CTTAGCCCCA TGAGTTTGCC ATGTTGAGCA GGACTATTTC TGGCACTTGC AAGTCCCATG
6481 ATTTCTTCGG TAATTCTGAG GGTGGGGGGA GGGACATGAA ATCATCTTAG CTTAGCTTTC
6541 TGTCTGTGAA TGTCTATATA GTGTATTGTG TGTTTTAACA AATGATTTAC ACTGACTGTT
6601 GCTGTAAAAG TGAATTTGGA AATAAAGTTA TTA CTCTGAT TAAA

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(SEQ ID NO: 49).

The corresponding amino acid sequence of human Tau protein isoform 6 can be found at NP_001116538.2:

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1 MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61 SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEAEAGIGD TPSLEDEAAG
121 HVTQEPESGK VVQEGFLREP GPPGLSHQLM SGMPGAPLLP EGPREATRQP SGTGPEDTEG
181 GRHAPELLKH QLLGDLHQEG PPLKGAGGKE RFGSKKEEVDE DRDVDESSPQ DSPPSKASPA
241 QDGRPPQTAA REATSIPGFP AEGAIPLPVD FLSKVSTEIP ASEPDGSPVG RAKGQDAPLE
301 FTFHVEITPN VQKEQAHSEE HLGRAAFPGA PGEGPEARGP SLGEDTKEAD LPEPSEKQPA
361 AAPRGKPVSR VPQLKARMVS KSKDGTGSDD KKA KTSTRSS AKTLKNRPCL SPKHPTFGSS
421 DPLIQPSSPA VCPEPPSSPK YVSSVTSRTG SSGAKEMKLLK GADGKTKIAT PRGAAPFGQK
481 GQANATRIPA KTPPA PKTTP SSATKQVQRR PPPAGPRSER GEPPKSGDRS GYSSPGSPGT
541 PGSRSRTPSL PTPPTREPKK VAVVRTPKS PSSAKSRLQT APVPMPLDN VKSKIGSTEN
601 LKHQPGGGKV QIINKKLDLS NVQSKCGSKD NIKHVPGGGS VQIVYKPDV SKVTSKCGSL
661 GNIHHKPGGG QVEVKSEKLD FKDRVQSKIG SLDNITHVPG GGNKKIETHK LTFRENAKAK
721 TDHGA EIVYK SPVVS GDTSP RHLSNVSSTG SIDMVDSPQL ATLADEV SAS LAKQGL

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(SEQ ID NO: 50).

The nucleotide sequence of a human MAPT transcript variant 5 (encoding 1N4R Tau) can be found at NM_001123067.4:

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1 GCAGTCACCG CCACCCACCA GCTCCGGCAC CAACAGCAGC GCCGCTGCCA CCGCCCACCT
61 TCTGCCGCGG CCACACACAG CACCTTCTCC TCCTCCGCTG TCCTCTCCCG TCCTCGCCTC
121 TGTGCGACTAT CAGGTGAACT TTGAACCAGG ATGGCTGAGC CCCGCCAGGA GTTCGAAGTG
181 ATGGAAGATC ACGCTGGGAC GTACGGGTTG GGGGACAGGA AAGATCAGGG GGGCTACACC
241 ATGCACCAAG ACCAAGAGGG TGACACGGAC GCTGGCCTGA AAGAATCTCC CCTGCAGACC
301 CCCACTGAGG ACGGATCTGA GGAACCGGGC TCTGAAACCT CTGATGCTAA GAGCACTCCA
361 ACAGCGGAAG CTGAAGAAGC AGGCATTGGA GACACCCCA GCCTGGAAGA CGAAGCTGCT
421 GGTCACGTGA CCCAAGCTCG CATGGTCAGT AAAAGCAAAG ACGGGACTGG AAGCGATGAC
481 AAAAAAGCCA AGGGGGCTGA TGGTAAAACG AAGATCGCCA CACCGCGGGG AGCAGCCCCT
541 CCAGGCCAGA AGGGCCAGGC CAACGCCACC AGGATTCCAG CAAAAACCCC GCGCGTCCA
601 AAGACACCAC CCAGCTCTGG TGAACCTCCA AAATCAGGGG ATCGCAGCGG CTACAGCAGC
661 CCCGGCTCCC CAGGCACTCC CGGCAGCCGC TCCCGCACCC CGTCCCTTCC AACCCACCC
721 ACCCGGGAGC CCAAGAAGGT GGCAGTGGTC CGTACTCCAC CCAAGTCGCC GTCTTCGCC
781 AAGAGCCGCC TGCAGACAGC CCCCGTGCCC ATGCCAGACC TGAAGAATGT CAAGTCCAAG
841 ATCGGCTCCA CTGAGAACCT GAAGCACCAG CCGGGAGGCG GGAAGGTGCA GATAATTAAT
901 AAGAAGCTGG ATCTTAGCAA CGTCCAGTCC AAGTGTGGCT CAAAGGATAA TATCAAACAC
961 GTCCCGGGAG GCGGCAGTGT GCAAATAGTC TACAAACCAG TTGACCTGAG CAAGGTGACC
1021 TCCAAGTGTG GCTCATTAGG CAACATCCAT CATAAACCCAG GAGGTGGCCA GGTGGAAGTA
1081 AAATCTGAGA AGCTTGACTT CAAGGACAGA GTCCAGTCGA AGATTGGGTC CCTGGACAAT
1141 ATCACCCACG TCCCTGGCGG AGGAAATAAA AAGATTGAAA CCCACAAGCT GACCTTCCGC
1201 GAGAACGCCA AAGCCAAGAC AGACCACGGG GCGGAGATCG TGTACAAGTC GCCAGTGGTG
1261 TCTGGGGACA CGTCTCCACG GCATCTCAGC AATGTCTCCT CCACCGGCAG CATCGACATG
1321 GTAGACTCGC CCCAGCTCGC CACGCTAGCT GACGAGGTGT CTGCCTCCCT GGCCAGCAG
1381 GGTGTGTGAT CAGGCCCTG GGGCGGTCAA TAATTGTGGA GAGGAGAGAA TGAGAGAGTG

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1441 TGGAAAAAAA AAGAATAATG ACCCGGCCCC CGCCCTCTGC CCCCAGCTGC TCCTCGCAGT
 1501 TCGGTTAATT GGTTAATCAC TTAACCTGCT TTTGTCACTC GGCTTTGGCT CGGGACTTCA
 1561 AAATCAGTGA TGGGAGTAAG AGCAAATTTT ATCTTTCCAA ATTGATGGGT GGGCTAGTAA
 1621 TAAAATATTT AAAAAAAAC ATTCAAAAAC ATGGCCACAT CCAACATTTC CTCAGGCAAT
 1681 TCCTTTTGAT TCTTTTCT TCCCCCTCCA TGTAAGAAGAG GGAGAAGGAG AGGCTCTGAA
 1741 AGCTGCTTCT GGGGGATTTC AAGGGACTGG GGGTGCCAAC CACCTCTGGC CCTGTTGTGG
 1801 GGGTGTCA CA GAGGCAGTGG CAGCAACAAA GGATTTGAAA CTTGGTGTGT TCGTGGAGCC
 1861 ACAGGCAGAC GATGTCAACC TTGTGTGAGT GTGACGGGGG TTGGGGTGGG GCGGGAGGCC
 1921 ACGGGGGAGG CCGAGGCAGG GGCTGGGCAG AGGGGAGAGG AAGCACAAGA AGTGGGAGTG
 1981 GGAGAGGAAG CCACGTGCTG GAGAGTAGAC ATCCCCCTCC TTGCCGCTGG GAGAGCCAAG
 2041 GCCTATGCCA CCTGCAGCGT CTGAGCGGCC GCCTGTCCTT GGTGGCCGGG GGTGGGGGCC
 2101 TGCTGTGGGT CAGTGTGCCA CCCTCTGCAG GGCAGCCTGT GGGAGAAGGG ACAGCGGGTA
 2161 AAAAGAGAAG GCAAGCTGGC AGGAGGGTGG CACTTCGTGG ATGACCTCCT TAGAAAAGAC
 2221 TGACCTTGAT GTCTTGAGAG CGCTGGCCTC TTCCTCCCTC CCTGCAGGGT AGGGGGCCTG
 2281 AGTTGAGGGG CTTCCCTCTG CTCACAGAA ACCCTGTTTT ATTGAGTTCT GAAGGTTGGA
 2341 ACTGCTGCCA TGATTTTGGC CACTTTGCAG ACCTGGGACT TTAGGGCTAA CCAGTTCTCT
 2401 TTGTAAGGAC TTGTGCCTCT TGGGAGACGT CCACCCGTTT CCAAGCCTGG GCCACTGGCA
 2461 TCTCTGGAGT GTGTGGGGGT CTGGGAGGCA GGTCCCGAGC CCCCTGTCCT TCCCACGGCC
 2521 ACTGCAGTCA CCCCCTCTGC GCCGCTGTGC TGTGTCTGCG CGTGAGAGCC CAATCACTGC
 2581 CTATACCCCT CATCACACGT CACAATGTCC CGAATTCCCA GCCTCACCAC CCCTTCTCAG
 2641 TAATGACCCCT GGTGGTTTGC AGGAGGTACC TACTCCATAC TGAGGGTGAA ATTAAGGGAA
 2701 GGCAAAGTCC AGGCACAAGA GTGGGACCCC AGCCTCTCAC TCTCAGTTCC ACTCATCCAA
 2761 CTGGGACCCCT CACCACGAAT CTCATGATCT GATTGCGTTC CCTGTCTCCT CCTCCCGTCA
 2821 CAGATGTGAG CCAGGGCACT GCTCAGCTGT GACCCTAGGT GTTTCTGCCT TGTGTGACATG
 2881 GAGAGAGCCC TTTCCCTGA GAAGGCCTGG CCCCTTCCTG TGCTGAGCCC ACAGCAGCAG
 2941 GCTGGGTGTC TTGGTTGTCA GTGGTGGCAC CAGGATGGAA GGGCAAGGCA CCCAGGGCAG
 3001 GCCCACAGTC CCGCTGTCCC CCACTTGAC CCTAGCTTGT AGCTGCCAAC CTCCAGACA
 3061 GCGCAGCCCG CTGCTCAGCT CCACATGCAT AGTATCAGCC CTCCACACCC GACAAAGGGG
 3121 AACACACCCC CTTGGAAATG GTTCTTTTCC CCCAGTCCCA GCTGGAAGCC ATGCTGTCTG
 3181 TTCTGTGGA GCAGCTGAAC ATATACATAG ATGTTGCCCT GCCCTCCCA TCTGCACCCT
 3241 GTTGAGTTGT AGTTGGATTT GTCTGTTTAT GCTTGATTC ACCAGAGTGA CTATGATAGT
 3301 GAAAAGAAAA AAAAAAAAAA AAAAGGACGC ATGTATCTTG AAATGCTTGT AAAGAGGTTT
 3361 CTAACCCACC CTCACGAGGT GTCTCTCACC CCCACACTGG GACTCGTGTG GCCTGTGTGG
 3421 TGCCACCCCG CTGGGGCCTC CCAAGTTTTG AAAGGCTTTC CTCAGCACCT GGGACCCAAC
 3481 AGAGACCAGC TTCTAGCAGC TAAGGAGGCC GTTCAGCTGT GACGAAGGCC TGAAGCACAG
 3541 GATTAGGACT GAAGCGATGA TGTCCCTTC CTTACTTCCC CTTGGGGCTC CCTGTGTCTG
 3601 GGCACAGACT AGGTCTGTGT GCTGGTCTGG CTTGCGGCGC GAGGATGGTT CTCTCTGGTC
 3661 ATAGCCCGAA GTCTCATGGC AGTCCCAAAG GAGGCTTACA ACTCCTGCAT CACAAGAAAA
 3721 AGGAAGCCAC TGCCAGCTGG GGGGATCTGC AGCTCCCAGA AGCTCCGTGA GCCTCAGCCA
 3781 CCCCTCAGAC TGGGTTCCTC TCCAAGCTCG CCCTCTGGAG GGGCAGCGCA GCCTCCCAAC
 3841 AAGGGCCCTG CGACCACAGC AGGGATTGGG ATGAATTGCC TGTCTGGAT CTGCTCTAGA
 3901 GGCCCAAGCT GCCTGCCTGA GGAAGGATGA CTTGACAAGT CAGGAGACAC TGTTCCTAAA
 3961 GCCTTGACCA GAGCACCTCA GCCCCTGAC CTTGCACAAA CTCCATCTGC TGCCATGAGA
 4021 AAAGGGAAGC CGCCTTTGCA AAACATTGCT GCCTAAAGAA ACTCAGCAGC CTCAGGCCCA
 4081 ATTCTGCCAC TTCTGGTTTG GGTACAGTTA AAGGCAACCC TGAGGGACTT GGCAGTAGAA
 4141 ATCCAGGGCC TCCCCTGGGG CTGGCAGCTT CGTGTGCAGC TAGAGCTTAA CCTGAAAGGA
 4201 AGTCTCTGGG CCCAGAACTC TCCACCAAGA GCCTCCCTGC CGTTCTGCTGA GTCCACAGCA
 4261 TTCTCCTAAG TTGAAGGGAT CTGAGAAGGA GAAGGAAATG TGGGGTAGAT TTGGTGGTGG
 4321 TTAGAGATAT GCCCCCTCA TTAAGTCCAA CAGTTTCGGC TGCATTTCTT CACGCACCTC
 4381 GGTTCCTCTT CCTGAAGTTC TTGTGCCCTG CTCTTCAGCA CCATGGGCCT TCTTATACGG
 4441 AAGGCTCTGG GATCTCCCC TTGTGGGGCA GGCTCTTGGG GCCAGCCTAA GATCATGGTT
 4501 TAGGGTGATC AGTGCTGGCA GATAAATTGA AAAGGCACGC TGGCTTGTGA TCTTAAATGA
 4561 GGACAATCCC CCCAGGGCTG GGCACCTCTC CCCTCCCTC ACTTCTCCCA CCTGCAGAGC
 4621 CAGTGTCTTT GGGTGGGCTA GATAGGATAT ACTGTATGCC GGCTCCTTCA AGCTGCTGAC
 4681 TCACTTTATC AATAGTTCCA TTAAATTTGA CTTCAAGTGT GAGACTGTAT CCTGTTTGCT
 4741 ATTGCTTGTG GTGCTATGGG GGGAGGGGGG AGGAATGTGT AAGATAGTTA ACATGGGCAA
 4801 AGGGAGATCT TGGGTGTCAG CACTTAAACT GCCTCGTAAC CCTTTTCATG ATTTCAACCA

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4861 CATTGCTAG AGGGAGGGAG CAGCCACGGA GTTAGAGGCC CTTGGGGTTT CTCTTTTCCA
4921 CTGACAGGCT TTCCAGGCA GCTGGCTAGT TCATTCCCTC CCCAGCCAGG TGCAGGCGTA
4981 GGAATATGGA CATCTGGTTG CTTTGGCCTG CTGCCCTCTT TCAGGGGTCC TAAGCCCACA
5041 ATCATGCCTC CCTAAGACCT TGGCATCCTT CCCTCTAAGC CGTTGGCACC TCTGTGCCAC
5101 CTCTCACACT GGCTCCAGAC ACACAGCCTG TGCTTTTGGA GCTGAGATCA CTCGCTTCAC
5161 CCTCCTCATC TTTGTTCTCC AAGTAAAGCC ACGAGGTCGG GCGAGGGCA GAGGTGATCA
5221 CCTGCGTGTC CCATCTACAG ACCTGCAGCT TCATAAACT TCTGATTTCT CTTAGCTTTT
5281 GAAAAGGGTT ACCCTGGGCA CTGGCCTAGA GCCTCACCTC CTAATAGACT TAGCCCATG
5341 AGTTTGCCAT GTTGAGCAGG ACTATTTCTG GCACTTGCAA GTCCCATGAT TTCTTCGGTA
5401 ATTCTGAGGG TGGGGGAGG GACATGAAAT CATCTTAGCT TAGCTTTCTG TCTGTGAATG
5461 TCTATATAGT GTATGTGTG TTTTAACAAA TGATTTACAC TGACTGTTGC TGTAAGGTG
5521 AATTTGAAA TAAAGTTATT ACTCTGATTA AA

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(SEQ ID NO: 51).

The corresponding amino acid sequence of human Tau protein isoform 5 can be found at NP_001116539.1:

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1 MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61 SETSDAKSTP TAEAEAGIG DTPSLEDEAA GHVTQARMVS KSKDGTGSDD KKAKGADGKT
121 KIATPRGAAP PGQKQANAT RIPAKTTPAP KTPSSGEP KSGDRSGYSS PGSPGTPGSR
181 SRTPSLPTFP TREPKKVAVV RTPPKSPSSA KSRLQTAPVP MPDLKNVSK IGSTENLKHQ
241 PGGGKVQIIN KKLDLSNVQS KCGSKDNIKH VPGGGSVQIV YKPVDSLKV SKCGSLGNIH
301 HKPGGGQVEV KSEKLDKDR VQSKIGSLDN ITHVPGGGNK KIETHKLTFR ENAKAKTDHG
361 AEIVYKSPVV SGDTSPRHLS NVSSTGSIDM VDSPQLATLA DEVSASLAKQ GL

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(SEQ ID NO: 52).

The nucleotide sequence of the human MAPT transcript variant 4 (encoding 0N3R Tau) can be found at NM_016841.5:

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1 GCAGTCACCG CCACCCACCA GCTCCGGCAC CAACAGCAGC GCCGCTGCCA CCGCCACCT
61 TCTGCCGCCG CCACACAGC CACCTTCTCC TCCTCCGCTG TCCTCTCCCG TCCTCGCCTC
121 TGTCGACTAT CAGGTGAAC TGAACCAGG ATGGCTGAGC CCCGCCAGGA GTTCGAAGTG
181 ATGGAAGATC ACGCTGGGAC GTACGGGTTG GGGGACAGGA AAGATCAGGG GGGCTACACC
241 ATGCACCAAG ACCAAGAGGG TGACACGGAC GCTGGCCTGA AAGCTGAAGA AGCAGGCATT
301 GGAGACACCC CCAGCCTGGA AGACGAAGCT GCTGGTCACG TGACCCAAGC TCGCATGGTC
361 AGTAAAAGCA AAGACGGGAC TGGGAAGCGAT GACAAAAAAG CCAAGGGGGC TGATGGTAAA
421 ACGAAGATCG CCACACCGCG GGGAGCAGCC CCTCCAGGCC AGAAGGGCCA GGCCAACGCC
481 ACCAGGATTC CAGCAAAAAC CCCGCCGCT CCAAAGACAC CACCCAGCTC TGGTGAACCT
541 CCAAAATCAG GGGATCGCAG CGGCTACAGC AGCCCCGGCT CCCAGGCAC TCCCGGCAGC
601 CGCTCCCGCA CCCCCTCCCT TCCAACCCCA CCCACCCGGG AGCCCAAGAA GGTGGCAGTG
661 GTCCGTACTC CACCAAGTC GCCGTCTTCC GCCAAGAGCC GCCTGCAGAC AGCCCCGTG
721 CCCATGCCAG ACCTGAAGAA TGTCAAGTCC AAGATCGGCT CCACTGAGAA CCTGAAGCAC
781 CAGCCGGGAG GCGGGAAGGT GCAAAATAGT TACAAACCAG TTGACCTGAG CAAGGTGACC
841 TCCAAGTGTG GCTCATTAG CAACATCCAT CATAAACCAG GAGGTGGCCA GGTGGAAGTA
901 AAATCTGAGA AGCTTGACTT CAAGGACAGA GTCCAGTCGA AGATTGGGTC CCTGGACAAT
961 ATCACCCACG TCCCTGGCGG AGGAAATAAA AAGATTGAAA CCCACAAGCT GACCTTCCGC
1021 GAGAACGCCA AAGCCAAGAC AGACCACGGG GCGGAGATCG TGTACAAGTC GCCAGTGGTG
1081 TCTGGGGACA CGTCTCCACG GCATCTCAGC AATGTCTCCT CCACCGGCAG CATCGCATG
1141 GTAGACTCGC CCCAGCTCGC CACGCTAGCT GACGAGGTGT CTGCCTCCCT GGCCAAGCAG
1201 GGTTTGTGAT CAGGCCCTG GGGCGGTCAA TAATTGTGGA GAGGAGAGAA TGAGAGAGTG
1261 TGGAATAAATA AAGAATAATG ACCCGGCCCC CGCCCTCTGC CCCAGCTGC TCCTCGCAGT
1321 TCGGTTAATT GGTTAATCAC TTAACCTGCT TTTGTCACTC GGCTTTGGCT CGGGACTTCA
1381 AAATCAGTGA TGGGAGTAAG AGCAAATTTT ATCTTTCCAA ATTGATGGGT GGGCTAGTAA
1441 TAAAATATTT AAAAAAATC ATTCAAAAAC ATGGCCACAT CCAACATTTC CTCAGGCAAT
1501 TCCTTTTGAT TCTTTTCTT TCCCCCTCCA TGTAGAAGAG GGAGAAGGAG AGGCTCTGAA

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1561 AGCTGCTTCT GGGGGATTTC AAGGGACTGG GGGTGCCAAC CACCTCTGGC CCTGTTGTGG
 1621 GGGTGTGACA GAGGCAGTGG CAGCAACAAA GGATTTGAAA CTTGGTGTGT TCGTGGAGCC
 1681 ACAGGCAGAC GATGTCAACC TTGTGTGAGT GTGACGGGGG TTGGGGTGGG GCGGGAGGCC
 1741 ACGGGGGAGG CCGAGGCAGG GGCTGGGCAG AGGGGAGAGG AAGCACAAGA AGTGGGAGTG
 1801 GGAGAGGAAG CCACGTGCTG GAGAGTAGAC ATCCCCCTCC TTGCCGTGGG GAGAGCCAAG
 1861 GCCTATGCCA CCTGCAGCGT CTGAGCGGCC GCCTGTCCTT GGTGGCCGGG GGTGGGGGCC
 1921 TGCTGTGGGT CAGTGTGCCA CCCTCTGCAG GGCAGCCTGT GGGAGAAGGG ACAGCGGGTA
 1981 AAAAGAGAAG GCAAGCTGGC AGGAGGGTGG CACTTCGTGG ATGACCTCCT TAGAAAAGAC
 2041 TGACCTTGAT GTCTTGAGAG CGCTGGCCTC TTCCTCCCTC CCTGCAGGGT AGGGGGCCTG
 2101 AGTTGAGGGG CTTCCTCTG CTCCACAGAA ACCCTGTTTT ATTGAGTTCT GAAGGTTGGA
 2161 ACTGCTGCCA TGATTTTGGC CACTTTGCAG ACCCTGGGACT TTAGGGCTAA CCAGTTCTCT
 2221 TTGTAAGGAC TTGTGCCTCT TGGGAGACGT CCACCCGTTT CCAAGCCTGG GCCACTGGCA
 2281 TCTCTGGAGT GTGTGGGGGT CTGGGAGGCA GGTCCCGAGC CCCCTGTCCT TCCCACGGCC
 2341 ACTGCAGTCA CCCCCTCTGC GCCGCTGTGC TGTGTCTGCG CGTGAGAGCC CAATCACTGC
 2401 CTATACCCCT CATCACACGT CACAATGTCC CGAATTCCCA GCCTCACCAC CCCTTCTCAG
 2461 TAATGACCCT GGTGTTGTTG AGGAGGTACC TACTCCATAC TGAGGGTGAA ATTAAGGGAA
 2521 GGCACCAAGT AGGCACAAGA GTGGGACCCC AGCCTCTCAC TCTCAGTTCC ACTCATCCAA
 2581 CTGGGACCCT CACCACGAAT CTCATGATCT GATTGCGTTC CCTGTCTCCT CCTCCCGTCA
 2641 CAGATGTGAG CCAGGGCACT GCTCAGCTGT GACCCTAGGT GTTTCTGCCT TGTGTACATG
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 2761 GCTGGGTGTC TTGGTTGTCA GTGGTGGCAC CAGGATGGAA GGGCAAGGCA CCCAGGGCAG
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 2881 GCCCAGCCCG CTGCTCAGCT CCACATGCAT AGTATCAGCC CTCCACACCC GACAAAGGGG
 2941 AACACACCCC CTTGGAAATG GTTCTTTTCC CCCAGTCCCA GCTGGAAGCC ATGCTGTCTG
 3001 TTCTGCTGGA GCAGCTGAAC ATATACATAG ATGTTGCCCT GCCCTCCCA TCTGCACCCT
 3061 GTTGAGTTGT AGTTGGATTT GTCTGTTTAT GCTTGGATTC ACCAGAGTGA CTATGATAGT
 3121 GAAAAGAAAA AAAAAAAAAA AAAAGGACGC ATGTATCTTG AAATGCTTGT AAAGAGGTTT
 3181 CTAACCCACC CTCACGAGGT GTCTCTCACC CCCACACTGG GACTCGTGTG CCCTGTGTGG
 3241 TGCCACCCTG CTGGGGCCTC CCAAGTTTTG AAAGGCTTTC CTCAGCACCT GGGACCCAAC
 3301 AGAGACCAGC TTCTAGCAGC TAAGGAGGCC GTTCAGCTGT GACGAAGGCC TGAAGCACAG
 3361 GATTAGGACT GAAGCGATGA TGTCCCCTTC CCTACTTCCC CTTGGGGCTC CCTGTGTCAG
 3421 GGCACAGACT AGGTCTTGTG GCTGGTCTGG CTTGCGGCGC GAGGATGGTT CTCTCTGGTC
 3481 ATAGCCCGAA GTCTCATGGC AGTCCCAAAG GAGGCTTACA ACTCCTGCAT CACAAGAAAA
 3541 AGGAAGCCAC TGCCAGCTGG GGGGATCTGC AGCTCCAGA AGCTCCGTGA GCCTCAGCCA
 3601 CCCCTCAGAC TGGGTTCCCTC TCCAAGCTCG CCCTCTGGAG GGGCAGCGCA GCCTCCACCC
 3661 AAGGGCCCTG CGACCACAGC AGGGATTGGG ATGAATTGCC TGTCTTGGAT CTGCTCTAGA
 3721 GGCCCAAGCT GCCTGCCTGA GGAAGGATGA CTTGACAAGT CAGGAGACAC TGTTCCTAAA
 3781 GCCTTGACCA GAGCACCTCA GCCCGCTGAC CTTGCACAAA CTCCATCTGC TGCCATGAGA
 3841 AAAGGGAAGC CGCCTTTGCA AAACATTGCT GCCTAAAGAA ACTCAGCAGC CTCAGGCCCA
 3901 ATTCTGCCAC TTCTGGTTTG GGTACAGTTA AAGGCAACCC TGAGGGACTT GGCAGTAGAA
 3961 ATCCAGGGCC TCCCCTGGGG CTGGCAGCTT CGTGTGCAGC TAGAGCTTTA CCTGAAAGGA
 4021 AGTCTCTGGG CCCAGAACTC TCCACCAAGA GCCTCCCTGC CGTTCGCTGA GTCCCAGCAA
 4081 TTCTCCTAAG TTGAAGGGAT CTGAGAAGGA GAAGGAAATG TGGGGTAGAT TTGGTGGTGG
 4141 TTAGAGATAT GCCCCCTCA TTAAGTCCAA CAGTTTCGGC TGCATTTCTT CACGCACCTC
 4201 GGTTCCTCTT CCTGAAGTTC TTGTGCCCTG CTCTTCAGCA CCATGGGCCT TCTTATACGG
 4261 AAGGCTCTGG GATCTCCCCC TTGTGGGGCA GGCTCTTGGG GCCAGCCTAA GATCATGGTT
 4321 TAGGGTGATC AGTGTCTGGCA GATAAATTGA AAAGGCACGC TGGCTTGTGA TCTTAAATGA
 4381 GGACAATCCC CCCAGGGCTG GGCACCTCCTC CCCTCCCCTC ACTTCTCCCA CCTGCAGAGC
 4441 CAGTGTCTCT GGGTGGGCTA GATAGGATAT ACTGTATGCC GGCTCCTTCA AGCTGCTGAC
 4501 TCACTTTATC AATAGTTCCA TTTAAATTGA CTTCAAGTGT GAGACTGTAT CCTGTTTGCT
 4561 ATTGCTTGTT GTGCTATGGG GGGAGGGGGG AGGAATGTGT AAGATAGTTA ACATGGGCAA
 4621 AGGGAGATCT TGGGTGTCAG CACTTAAACT GCCTCGTAAC CCTTTTCATG ATTTCAACCA
 4681 CATTTGCTAG AGGGAGGGAG CAGCCACGGA GTTAGAGGCC CTTGGGGTTT CTCTTTTCCA
 4741 CTGACAGGCT TTCCAGGCA GCTGGCTAGT TCATTCCCTC CCCAGCCAGG TGCAGGCGTA
 4801 GGAATATGGA CATCTGGTTG CTTTGGCCTG CTGCCCTCTT TCAGGGGTCC TAAGCCACCA
 4861 ATCATGCCTC CCTAAGACCT TGGCATCCTT CCCTCTAAGC CGTTGGCACC TCTGTGCCAC
 4921 CTCTCACACT GGCTCCAGAC ACACAGCCTG TGCTTTTGGA GCTGAGATCA CTCGCTTCAC

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4981 CCTCCTCATC TTTGTTCTCC AAGTAAAGCC ACGAGGTCGG GCGAGGGCA GAGGTGATCA
5041 CCTGCGTGTC CCATCTACAG ACCTGCAGCT TCATAAACT TCTGATTTCT CTTTCAGCTTT
5101 GAAAAGGGTT ACCCTGGGCA CTGGCCTAGA GCCTCACCTC CTAATAGACT TAGCCCCATG
5161 AGTTTGCCAT GTTGAGCAGG ACTATTTCTG GCACTTGCAA GTCCCATGAT TTCTTCGGTA
5221 ATTCTGAGGG TGGGGGGAGG GACATGAAAT CATCTTAGCT TAGCTTTCTG TCTGTGAATG
5281 TCTATATAGT GTATTGTGTG TTTTAACAAA TGATTTACAC TGACTGTTGC TGTAAGTATG
5341 AATTTGGAAA TAAAGTTATT ACTCTGATTA AA

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(SEQ ID NO: 53).

The corresponding amino acid sequence of human Tau protein isoform 4 can be found at NP_058525.1:

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1 MAEPRQEFV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKAEEAGI GDTPSLEDEA
61 AGHVTQARMV SKSKDGTGSD DKKAKGADGK TKIATPRGAA PPGQKGQANA TRIPAKTPPA
121 PKTPPSSGEP PKSGDRSGYS SPGSPGTPGS RSRTPSLPTP PTREP KKVAV VRTPPKSPSS
181 AKSRLQTAPV PMPDLKNVKS KIGSTENLKH QPGGGKVQIV YKPVDLSKVT SKCGSLGNIH
241 HKPGGGQVEV KSEKLDFKDR VQSKIGSLDN ITHVPGGGNK KIETHKLTFR ENAKAKTDHG
301 AEIVYKSPVV SGDTSPRHLS NVSSTGSIDM VDSPQLATLA DEVSASLAKQ GL

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(SEQ ID NO: 54).

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

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

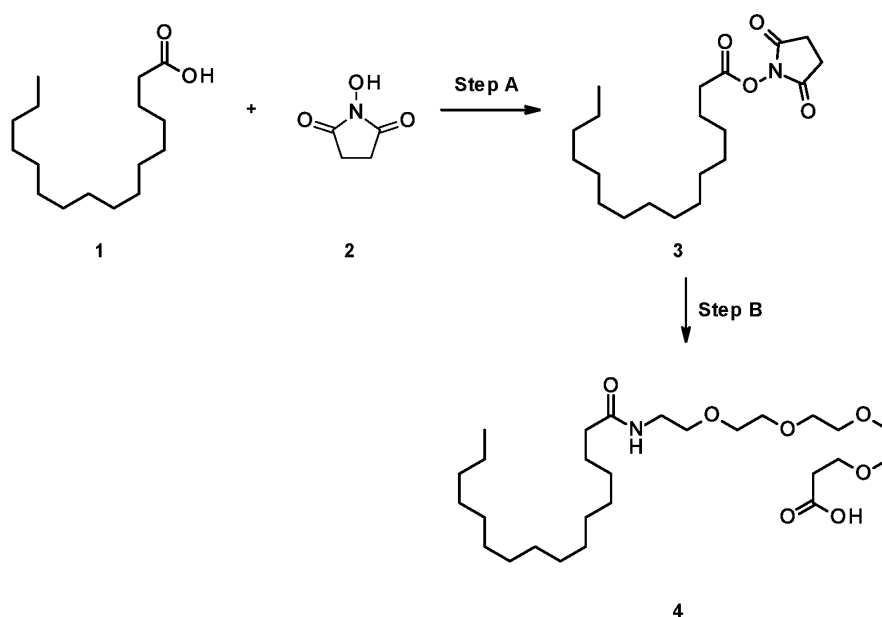
EXAMPLES

Example 1. Synthesis of Linker - Delivery Moiety Pairs

Certain abbreviations are defined as follows: “ACN” refers to acetonitrile; “AEX” refers to anion exchange; “C/D” refers to cleavage and deprotection; “CPG” refers to controlled pore glass; “DCM” refers to dichloromethane; “DEA” refers to diethylamine; “DIEA” refers to N,N-diisopropylethylamine; “DMAP” refers to 4-dimethylaminopyridine; “DMF” refers to dimethylformamide; “DMSO” refers to dimethyl sulfoxide; “DMTCl” refers to 4,4’-dimethoxytrityl chloride; “ES/MS” refers to electrospray mass spectrometry; “EtOAc” refers to ethyl acetate; “EtOH” refers to ethanol and ethyl alcohol; “HBTU” refers to 3-[bis(dimethylamino)methyl]-3H-benzotriazol-1-yl hexafluorophosphate; “HOBt” refers

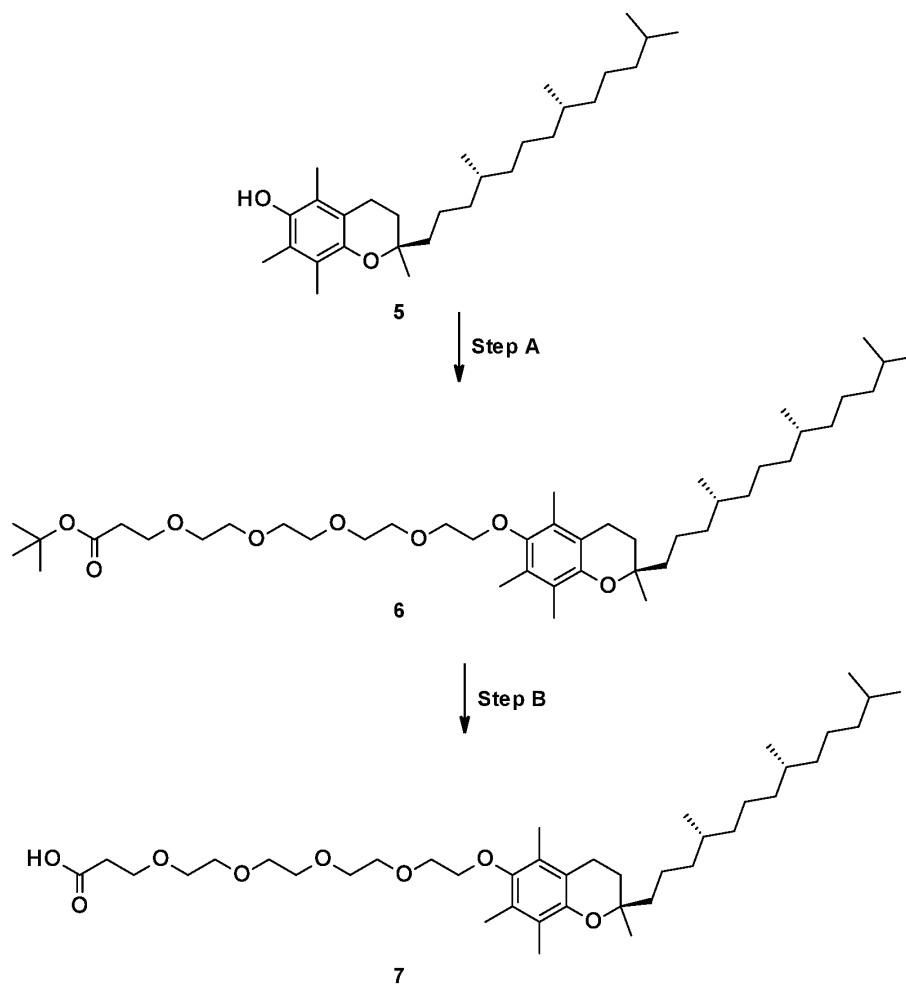
to 1-hydroxybenzotriazole; “IP-RP” refers to ion-pair reverse phase; “LCAA CPG” refers to long chain alkylamine controlled pore glass; “LC/MS” refers to liquid chromatography-mass spectrometry; “MeOH” refers to methanol and methyl alcohol; “MPA” refers to mobile phase A; “MPB” refers to mobile phase B; “MWCO” refers to molecular weight cut-off; “NMR” refers to nuclear magnetic resonance; “PBS” phosphate-buffered saline; “PEG” refers to polyethylene glycol; “PVDF” refers to polyvinylidene fluoride; “RP” refers to reverse phase; “RPM” refers to revolutions per minute; “siRNA” refers to small interfering ribonucleic acid; “TEA” refers to triethylamine; “THF” refers to tetrahydrofuran; “TLC” refers to thin line chromatography; “TMP” refers to 2,2,6,6-tetramethylpiperidine; “UPLC” refers to ultra-performance liquid chromatography; and “UV” refers to ultraviolet.

Scheme 1



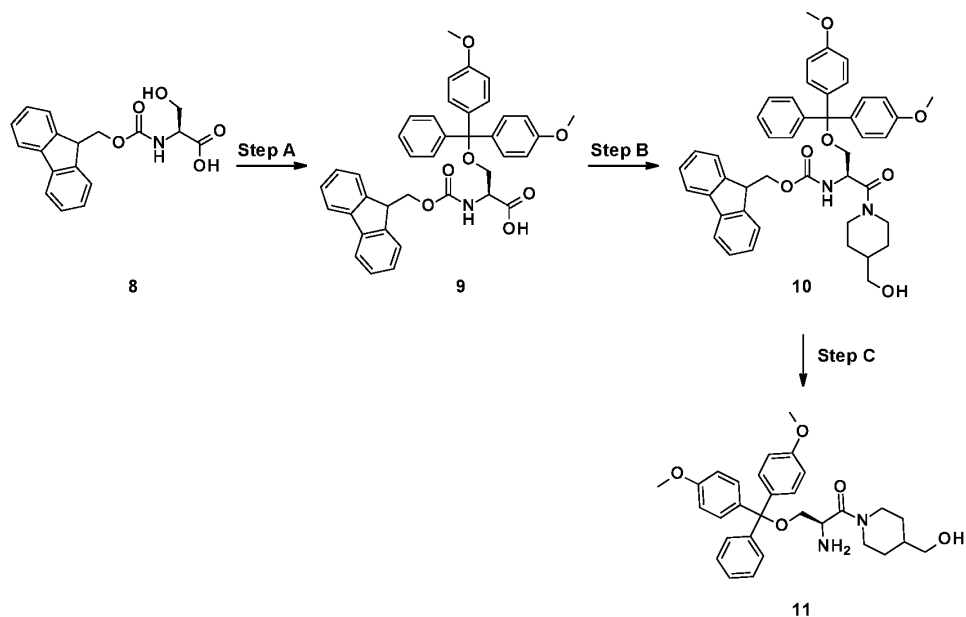
Scheme 1, step A depicts the coupling of compounds (1) and (2) using an appropriate base such as DMAP in a suitable solvent such as DCM to give compound (3). Step B shows the coupling of compound (3) with 1-amino-3,6,9,12-tetraoxapentadecan-15-oic acid in the presence of a base such as potassium carbonate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

Scheme 2



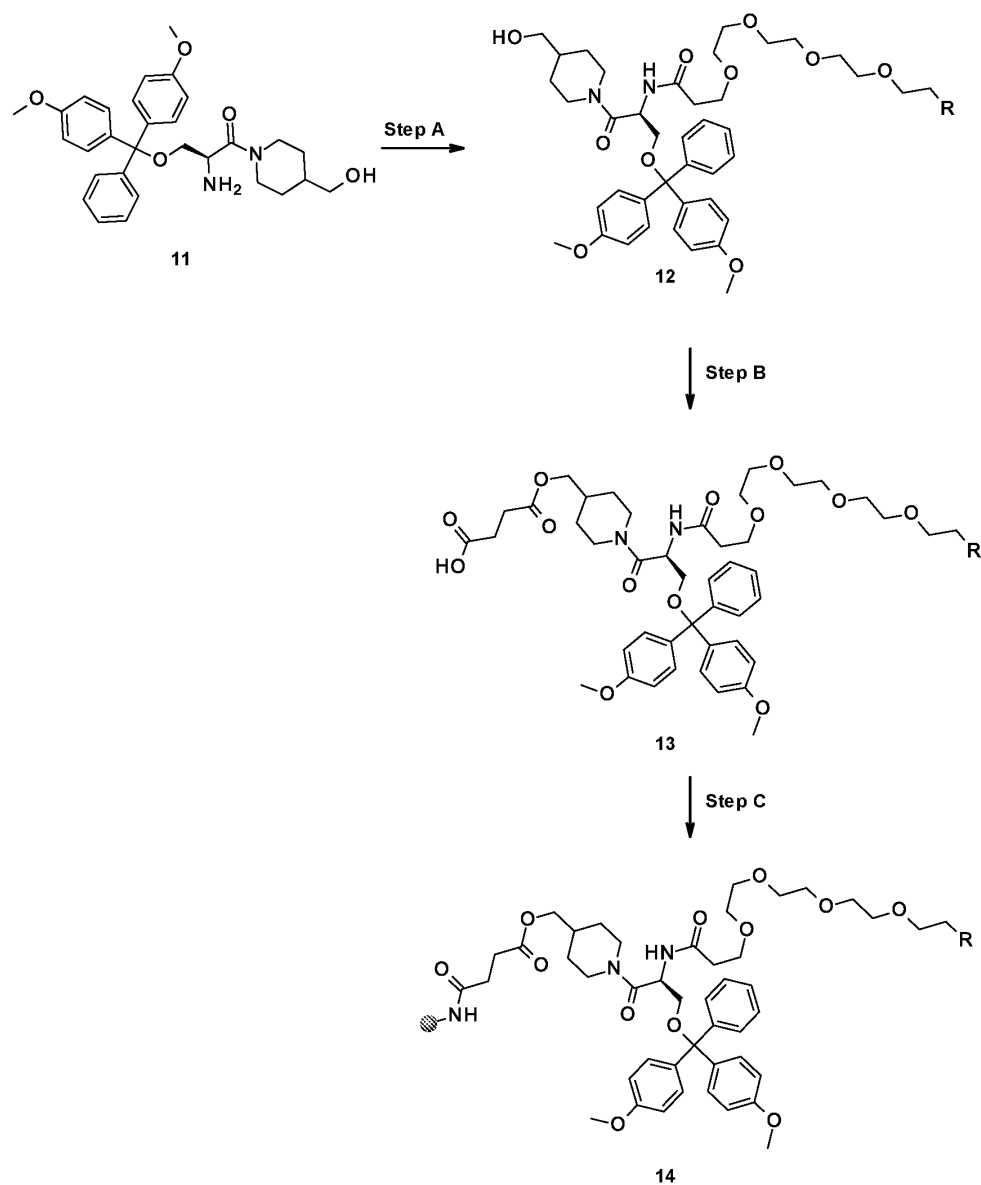
Scheme 2, step A depicts a Mitsunobu reaction between compound (5) and *tert*-butyl 1-hydroxy-3,6,9,12-tetraoxapentadecan-15-oate using triphenyl phosphene and diisopropyl azodicarboxylate in a solvent such as THF to give compound (6). Step B shows the acidic deprotection of compound (6) using an acid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

Scheme 3



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

Scheme 4

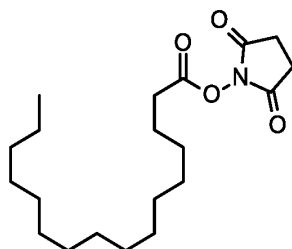


Scheme 4, step A depicts an amide coupling between compound (11) and either compound (4) or compound (7) using standard coupling reagents such as HBTU and HOBt with a base such as DIEA in a solvent such as DMF to give compound (12). One skilled in the art will recognize the variety of conditions which could be used to perform this amide coupling. Step B shows the coupling of compound (12) to succinic anhydride using a base such as TEA with catalytic DMAP in a solvent such as DCM to give compound (13). Step C shows the amide

coupling of compound (13) to amino LCAA CPG using HBTU with a base such as DIEA in a solvent such as ACN followed by a multistep work up to give compound (14).

Preparation 1

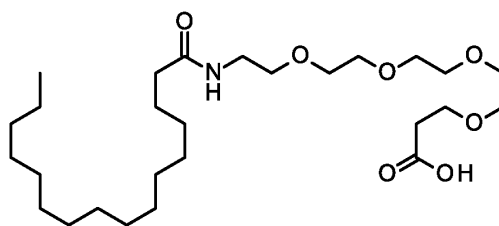
2,5-Dioxopyrrolidin-1-yl palmitate



Added palmitic acid (2.00 g, 7.80 mmol) to a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.79 g, 9.36 mmol) and DMAP (0.19 g, 1.56 mmol) in DCM (31 mL). Stirred the mixture at ambient temperature for 5 minutes then added N-hydroxysuccinimide (0.99 g, 8.58 mmol) and stirred at ambient temperature for 18 hours. Concentrated *in vacuo* and purified the resulting crude material via silica gel flash chromatography eluting with a gradient of 0-80% EtOAc in hexanes to give the title compound as a white solid (2.65 g, 96%). ^1H NMR (DMSO- d_6) δ 2.81 (s, 4H), 2.66 (t, 2H), 1.62 (m, 2H), 1.25 (br s, 24H), 0.87 (t, 3H).

Preparation 2

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

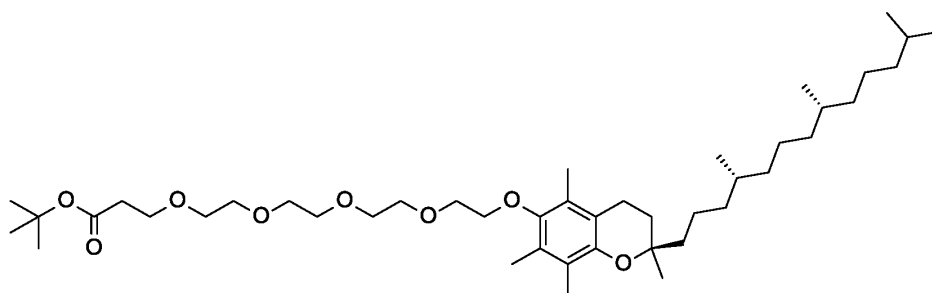


Added 1-amino-3,6,9,12-tetraoxapentadecan-15-oic acid (0.14 g, 0.53 mmol) to a solution of potassium carbonate (0.14 g, 1.00 mmol) in THF (1 mL) and water (2 mL). Added 2,5-dioxopyrrolidin-1-yl palmitate (0.18 g, 0.51 mmol) and stirred the reaction at ambient temperature for 18 hours. Quenched the reaction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

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

Preparation 3

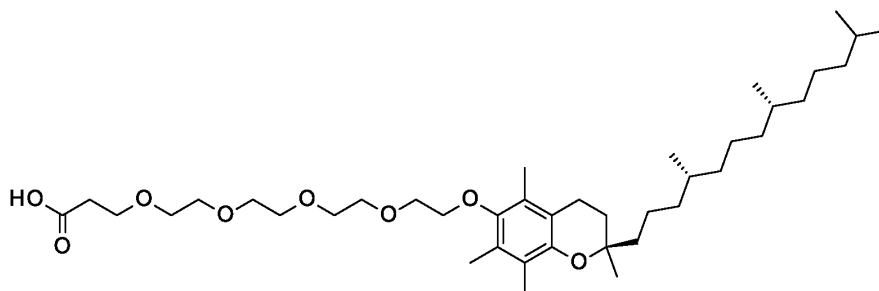
tert-Butyl 3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propanoate



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

Preparation 4

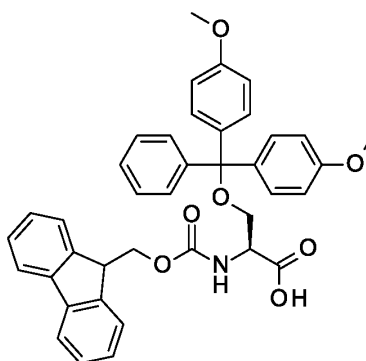
3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propanoic acid



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

Preparation 5

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

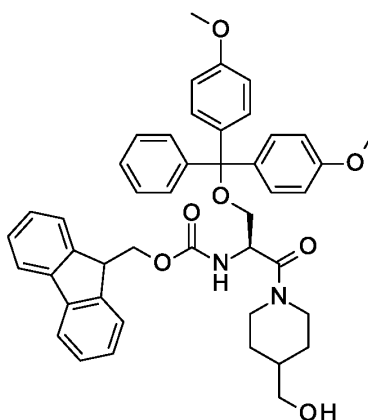


Added DIEA (64 mL, 0.366 mol) to a stirring solution of (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-hydroxy-propanoic acid (40 g, 0.122 mol) in dry DCM (400 mL) at 0 °C under an inert atmosphere. To this mixture, slowly added a solution of DMTCI (49.6 g, 0.146 mol) in DCM (200 mL). Allowed to warm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

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

Preparation 6

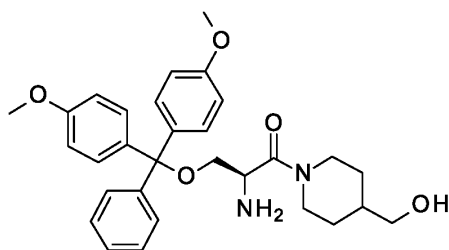
9H-Fluoren-9-ylmethyl N-[(1S)-1-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-2-[4-(hydroxymethyl)-1-piperidyl]-2-oxo-ethyl]carbamate



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

Preparation 7

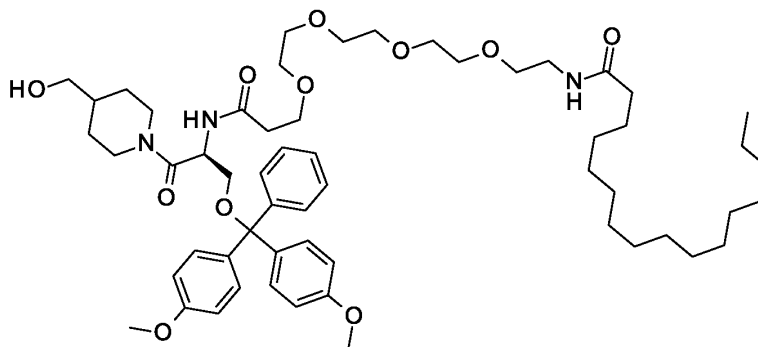
(2S)-2-Amino-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-1-[4-(hydroxymethyl)-1-piperidyl]propan-1-one



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

Preparation 8

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

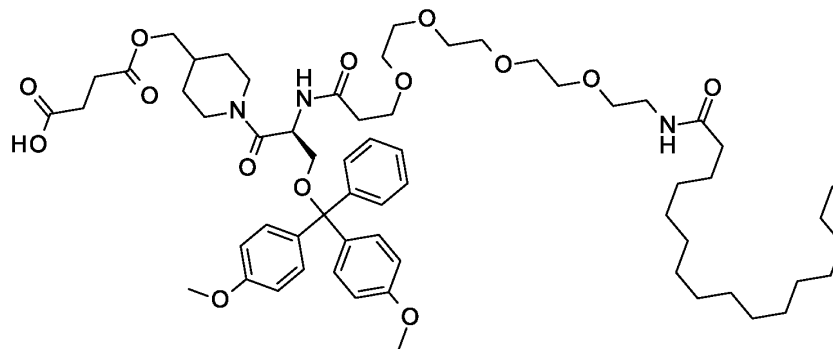


Combined 3-[2-[2-[2-[2-(hexadecanoylamino)ethoxy]ethoxy]ethoxy]propanoic acid (496 mg, 0.984 mmol), HOBt (146 mg, 1.08 mmol), HBTU (410 mg, 1.08 mmol), and DIEA (1.03 mL, 5.90 mmol) in DMF (9.84 mL) and stirred at ambient temperature for 10 minutes. Added (2S)-2-amino-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-1-[4-

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

Preparation 9

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

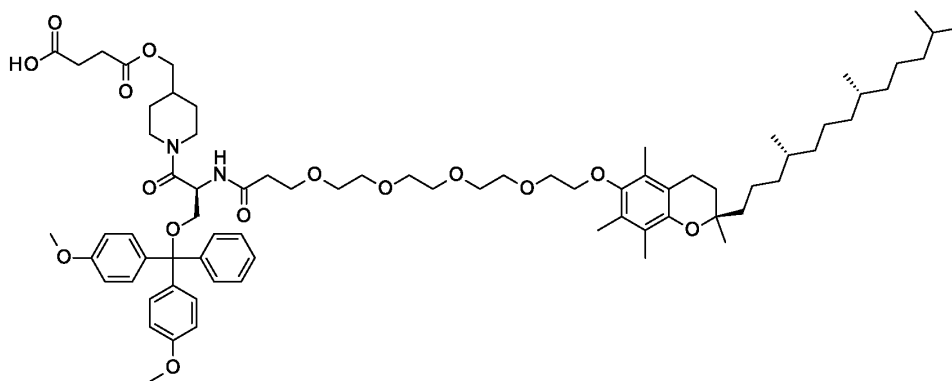


Combined N-[2-[2-[2-[2-[3-[[1*S*]-1-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-2-[4-(hydroxymethyl)-1-piperidyl]-2-oxo-ethyl]amino]-3-oxo-propoxy]ethoxy]ethoxy]ethoxy]ethyl]hexadecanamide (320 mg, 0.323 mmol), DMAP (120 mg, 0.969 mmol), TEA (225 μ L, 1.62 mmol), and succinic anhydride (64.7 mg, 0.646 mmol) in DCM (6.46 mL) and stirred the mixture for 16 hours at ambient temperature. Purified the mixture directly via silica gel flash chromatography, eluting with 0% to 40% MeOH/DCM, to

give the title compound as a colorless oil (279 mg, 79%). ^1H NMR (DMSO-d_6) 12.65-12.64 (m, 1H), 8.24-8.19 (m, 1H), 7.80 (t, $J = 5.6$ Hz, 1H), 7.37-7.28 (m, 4H), 7.24-7.20 (m, 5H), 6.88 (d, $J = 8.6$ Hz, 4H), 5.05-5.01 (m, 1H), 4.44-4.40 (m, 1H), 3.97-3.95 (m, 3H), 3.74 (s, 6H), 3.61-3.56 (m, 2H), 3.49-3.45 (m, 11H), 3.38 (t, $J = 5.9$ Hz, 3H), 3.22-3.14 (m, 6H), 2.48-2.31 (m, 7H), 2.04 (t, $J = 7.4$ Hz, 2H), 1.90-1.87 (m, 5H), 1.24 (s, 23H), 0.98-0.96 (m, 1H), 0.87-0.82 (m, 4H).

Preparation 10

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



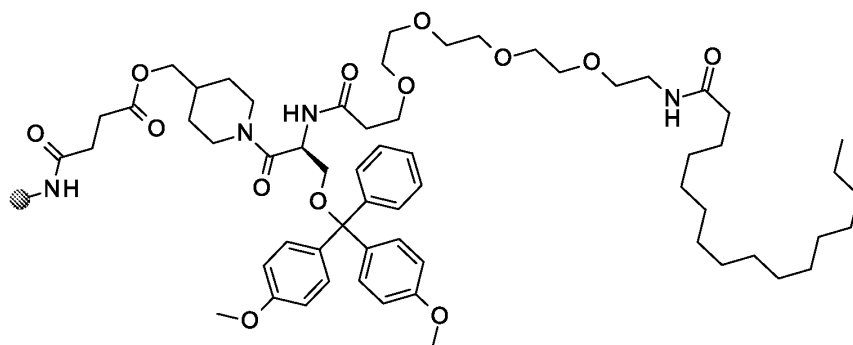
Combined 3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propanoic acid (1.20 g, 1.80 mmol), HOBt (260 mg, 1.90 mmol), HBTU (740 mg, 1.90 mmol), and DIEA (1.80 mL, 11.0 mmol) in DMF (18.0 mL) and stirred at ambient temperature for 10 minutes. Added (2S)-2-amino-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-1-[4-(hydroxymethyl)-1-piperidyl]propan-1-one (980 mg, 1.90 mmol) to the mixture and stirred at ambient temperature for 16 hours. Partitioned the mixture between EtOAc and saturated aqueous sodium chloride solution. Separated the layers and washed the organics with saturated aqueous sodium chloride solution. Dried the organic layer over sodium sulfate, filtered, and concentrated *in vacuo*. Purified the resulting residue by silica gel flash chromatography, eluting with 0-10% MeOH/DCM, to give N-[(1S)-1-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-2-[4-(hydroxymethyl)-1-piperidyl]-

2-oxo-ethyl]-3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propenamide as a yellow oil.

Combined N-[(1S)-1-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-2-[4-(hydroxymethyl)-1-piperidyl]-2-oxo-ethyl]-3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propenamide (1.45 g, 1.24 mmol), DMAP (456 mg, 3.73 mmol), TEA (867 μ L, 6.22 mmol), and succinic anhydride (249 mg, 2.49 mmol) in DCM (24.9 mL) and stirred for 16 hours at ambient temperature. Concentrated *in vacuo* and purified the resulting residue via silica gel flash chromatography, eluting with 0-40% MeOH/DCM, to give the title compound as an oil (1.36 g, 60%). ES/MS m/z 1264.4 (M-H).

Preparation 11

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

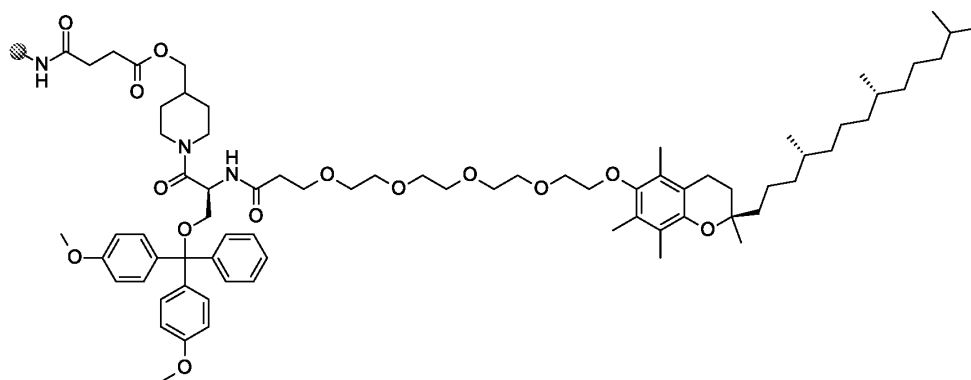


Dissolved 4-[[1-[(2S)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-[3-[2-[2-[2-[2-(hexadecanoylamino)ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]propanoyl]-4-piperidyl]methoxy]-4-oxo-butanoyl]amino] acid (270 mg, 0.248 mmol) in ACN (12.5 mL) and transferred the solution to a fritted glass dropping funnel. Added DIEA (150 μ L, 0.860 mmol) and HBTU (190 mg, 0.500 mmol) to the solution and shook the mixture at ambient temperature for 10 minutes. Added native amino LCAA CPG 500Å (1.92 g, 129 μ mol/g) to the solution and shook the mixture at 500 RPM for 16 hours at ambient temperature. Drained the CPG and dried under nitrogen for 5 minutes. Washed the CPG with DCM (50 mL), 10% MeOH/DCM (50 mL),

and then diethyl ether (50 mL). Dried the CPG for 30 minutes under nitrogen and then resuspended in pyridine (15 mL). Added acetic anhydride (3.30 mL, 35.0 mmol) and TEA (0.50 mL) and shook the mixture at 500 RPM for 2 hours at ambient temperature. Drained the CPG and dried for 5 minutes under nitrogen. Washed the CPG with DCM (50 mL), 10% MeOH/DCM (50 mL), and then diethyl ether (50 mL). Dried the CPG for 45 minutes under nitrogen and determined the ligand loading at 505 nm to give the title compound (1.92 g, 75.5 $\mu\text{mol/g}$).

Preparation 12

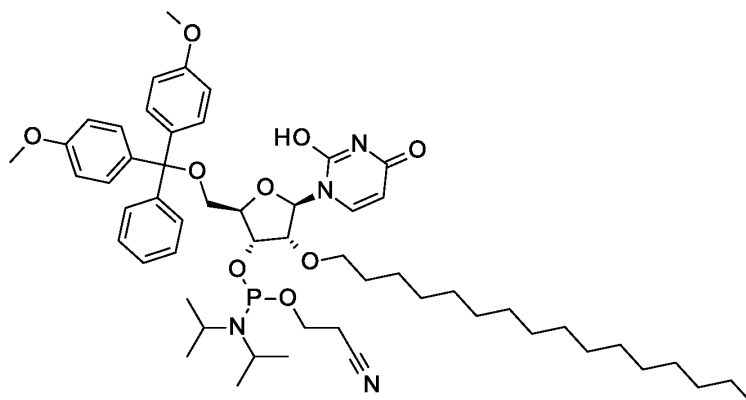
[[4-[[1-[(2S)-3-[Bis(4-methoxyphenyl)-phenyl-methoxy]-2-[3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]propanoyl]-4-piperidyl]methoxy]-4-oxo-butanoyl]amino] on CPG



Prepared the title compound from 4-[[1-[(2S)-3-[bis(4-methoxyphenyl)-phenyl-methoxy]-2-[3-[2-[2-[2-[2-[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]chroman-6-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]propanoyl]-4-piperidyl]methoxy]-4-oxo-butanoyl]amino] acid in a manner essentially analogous to Preparation 11. Determined the ligand loading at 505 nm to give the title compound (4.01 g, 66.9 $\mu\text{mol/g}$).

Preparation 13

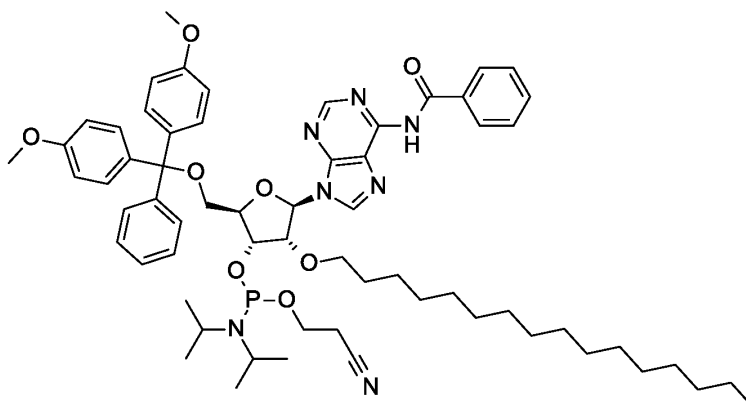
3-[[[(2R,3R,4R,5R)-2-[[Bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-hexadecoxy-5-(2-hydroxy-4-oxo-pyrimidin-1-yl)THF-3-yl]oxy-(diisopropylamino)phosphanyl]oxypropanenitrile



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

Preparation 14

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

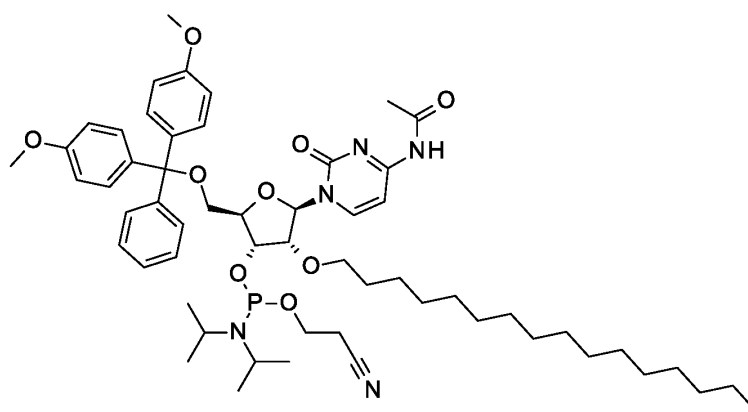


Prepared the title compound according to the protocols described in WO2019217459. ^1H -NMR (CD_3CN) δ 9.37 (s, 1H), 8.57 (d, $J = 9.4$ Hz, 1H), 8.27 (d, $J = 10.3$ Hz, 1H), 7.99 (d, $J = 7.6$ Hz, 2H), 7.61 (d, $J = 7.4$ Hz, 1H), 7.52 (t, $J = 7.6$ Hz, 2H), 7.42 (t, $J = 7.3$ Hz, 2H), 7.34 - 7.16 (m, 7H), 6.85 - 6.77 (m, 4H), 6.11 (dd, $J = 5.0, 2.5$ Hz, 1H), 4.80 (m, 1H), 4.69 (m, 1H),

4.32 (m, 1H), 3.97 - 3.78 (m, 1H), 3.74 (d, J = 3.1 Hz, 7H), 3.64 (m, 4H), 3.56 - 3.40 (m, 2H), 3.33 (m, 1H), 2.73 - 2.59 (m, 1H), 2.50 (t, J = 6.0 Hz, 1H), 1.52 - 1.45 (m, 2H), 1.33 - 1.12 (m, 37H), 1.09 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H). ^{31}P NMR (CD_3CN) δ 151.19, 150.78.

Preparation 15

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

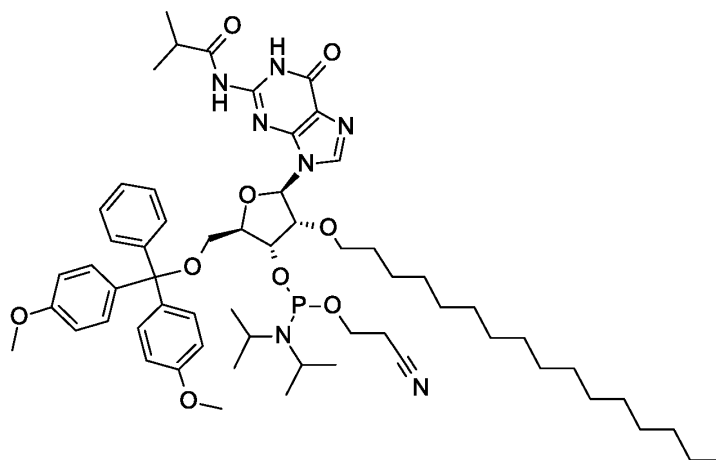


Prepared the title compound according to the protocols described in WO2019217459.

^1H -NMR (CD_3CN) 9.15 (s, 1H), 8.46 (dd, J = 7.5 Hz, 1H), 7.95 (d, J = 7.6 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.57 - 7.41 (m, 5H), 7.41 - 7.31 (m, 6H), 7.28 (m, 1H), 7.04 (d, J = 15.8 Hz, 1H), 6.90 (t, J = 7.9 Hz, 4H), 5.90 (d, J = 7.8 Hz, 1H), 4.51 (m, 1H), 4.20 (dd, J = 10.6, 8.1 Hz, 1H), 4.04 (dd, J = 31.3, 4.6 Hz, 1H), 3.91 - 3.81 (m, 2H), 3.79 (d, J = 3.1 Hz, 6H), 3.74 (m, 2H), 3.69 - 3.41 (m, 6H), 2.67 - 2.59 (m, 1H), 2.54 - 2.48 (m, 1H), 1.58 (m, 2H), 1.36 (m, 2H), 1.25 (d, J = 4.7 Hz, 26H), 1.21 - 1.09 (m, 10H), 1.04 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H). ^{31}P NMR (CD_3CN) δ 151.10, 150.19.

Preparation 16

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



Prepared the title compound according to the protocols described in WO2019217459.

$^1\text{H-NMR}$ (CDCl_3) δ 12.01-11.96 (m, 1H), 7.82-7.78 (m, 1H), 7.59-7.53 (m, 1H), 7.47-7.42 (m, 1H), 7.41-7.37 (m, 2H), 7.34-7.29 (m, 2H), 7.27-7.22 (m, 3H), 6.85-6.80 (m, 4H), 5.99-5.82 (m, 1H), 4.40-4.36 (m, 1H), 4.17-4.11 (m, 1H), 3.80-3.77 (m, 6H), 3.76-3.68 (m, 6H), 3.22-3.17 (m, 1H), 2.84-2.79 (m, 1H), 1.60-1.54 (m, 4H), 1.35-1.30 (m, 6H), 1.27 (s, 19H), 1.24-1.15 (m, 13H), 1.06-1.03 (m, 5H), 0.93-0.88 (m, 6H), 0.74-0.70 (m, 1H). ^{31}P NMR (CDCl_3) δ 150.20, 149.92.

Example 2. Synthesis of MAPT RNAi Agents

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

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

synthesis. All monomers (Table 8) were made at 0.1M in ACN and contained a molecular sieves trap bag.

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

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

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

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

Table 7 - Oligonucleotide Synthesis Reagents

Reagents
Activator Solution (0.5M ETT in ACN)
Cap A (Acetic Anhydride, Pyridine in THF, 1:1:8)
Cap B (1-Methylimidazole in THF, 16:84)
Oxidation Solution (0.02M Iodine in THF/Pyridine/Water, 70:20:10)
Deblock Solution, 3% TCA in DCM (w/v)
Acetonitrile (Anhydrosolv, Water max. 10 ppm)
Xanthane Hydride (0.1 M in Pyridine)
Diethylamine (20 % in Acetonitrile)

Table 8 - Phosphoramidites

Phosphoramidite	Abbreviation	Supplier	Catalog #	CAS
DMT-2'-F-A(Bz)-CE Phosphoamidite	fA	Hongene	PD1-001	136834-22-5

DMT-2'-F-C(Ac)-CE Phosphoamidite	fC	Hongene	PD3-001	159414-99-0
DMT-2'-F-G(iBu)-CE Phosphoamidite	fG	Hongene	PD2-002	144089-97-4
DMT-2'-F-U-CE Phosphoamidite	fU	Hongene	PD5-001	146954-75-8
DMT-2'-O-Me-A(Bz)- CE Phosphoamidite	mA	Hongene	PR1-001	110782-31-5
DMT-2'-O-Me-C(Ac)- CE Phosphoamidite	mC	Hongene	PR3-001	199593-09-4
DMT-2'-O-Me-G(iBu)- CE Phosphoamidite	mG	Hongene	PR2-002	150780-67-9
DMT-2'-O-Me-U-CE Phosphoamidite	mU	Hongene	PR5-001	110764-79-9
5'bis(POM) vinyl phosphate-2'-Ome- U3'CE phosphoroamidite	POM-VPmU	Hongene	PR5-032	BVPMUP23B2A1
Reverse Abasic phosphoroamidite	iAb	Chemgenes	ANP-1422	401813-16-9
Uhd	Uhd	Lilly		
Chd	Chd	Lilly		
Ahd	Ahd	Lilly		
Ghd	Ghd	Lilly		

Table 9 – Conjugated MAPT RNAi Agents

Conjugated MAPT RNAi Agent No.	RNAi Agent No.	Strand	LDP	MW Cal. (g/mol)	MW Obs. (g/mol)
1	13	S: SEQ ID NO: 25	1	7703.75	7704.3
		AS: SEQ ID NO: 26		7810.25	7810.7
2	14	S: SEQ ID NO: 27	1	7735.81	7736.4
		AS: SEQ ID NO: 28		7655.08	7656.1
3	15	S: SEQ ID NO: 29	1	7751.87	7752.7
		AS: SEQ ID NO: 30		7577.99	7579.0
4	16	S: SEQ ID NO: 31	1	7831.93	7832.4
		AS: SEQ ID NO: 32		7497.93	7498.5
5	17	S: SEQ ID NO: 33	1	7902.97	7903.1
		AS: SEQ ID NO: 34		7534.99	7535.3
6	18	S: SEQ ID NO: 35	1	7800.86	7801.2
		AS: SEQ ID NO: 36		7582.06	7582.6
7	19	S: SEQ ID NO: 37	1	7839.9	7840.1
		AS: SEQ ID NO: 38		7558.03	7558.5
8	20	S: SEQ ID NO: 39	1	7840.89	7841.5
		AS: SEQ ID NO: 40		7518.99	7520.0
9	21	S: SEQ ID NO: 41	1	7792.83	7793.2
		AS: SEQ ID NO: 42		7596.08	7596.9
10	22	S: SEQ ID NO: 43	1	7687.75	7688.7
		AS: SEQ ID NO: 44		7755.21	7756.2
11	23	S: SEQ ID NO: 45	1	7649.7	7650.3
		AS: SEQ ID NO: 46		7779.24	7779.3
12	24	S: SEQ ID NO: 47	1	7816.86	7817.6
		AS: SEQ ID NO: 48		7597.07	7597.7

/	31	S: SEQ ID NO: 63	4	7352.24	7352.5
		AS: SEQ ID NO: 40		7518.87	7519.1
/	32	S: SEQ ID NO: 64	4	7364.27	7364.7
		AS: SEQ ID NO: 65		7506.84	7507.4
/	33	S: SEQ ID NO: 66	5	7364.27	7364.0
		AS: SEQ ID NO: 65		7506.84	7507.4
/	34	S: SEQ ID NO: 67	4	7213.17	7213.7
		AS: SEQ ID NO: 65		7506.84	7507.4
/	35	S: SEQ ID NO: 68	4	7199.15	7199.6
		AS: SEQ ID NO: 65		7506.84	7507.4
/	36	S: SEQ ID NO: 69	4	7213.17	7213.5
		AS: SEQ ID NO: 65		7506.84	7507.4
/	37	S: SEQ ID NO: 64	4	7364.27	7364.8
		AS: SEQ ID NO: 70		7482.76	7482.9
/	38	S: SEQ ID NO: 71	4	7352.24	7352.7
		AS: SEQ ID NO: 65		7506.84	7507.5
/	39	S: SEQ ID NO: 64	4	7364.27	7364.8
		AS: SEQ ID NO: 72		7506.84	7507.5
/	40	S: SEQ ID NO: 64	4	7364.27	7365.0
		AS: SEQ ID NO: 73		7506.84	7507.4
/	41	S: SEQ ID NO: 64	4	7364.27	7364.9
		AS: SEQ ID NO: 74		7530.91	7531.6
/	42	S: SEQ ID NO: 75	4	7340.20	7340.7
		AS: SEQ ID NO: 65		7506.84	7507.5
/	43	S: SEQ ID NO: 76	7	7364.27	7365.4
		AS: SEQ ID NO: 65		7506.84	7508.0
/	44	S: SEQ ID NO: 77	4	7364.27	7365.5
		AS: SEQ ID NO: 65		7506.84	7507.9
/	45	S: SEQ ID NO: 78	7	7364.27	7365.5

		AS: SEQ ID NO: 65		7506.84	7508.1
/	46	S: SEQ ID NO: 79	5	7364.27	7365.5
		AS: SEQ ID NO: 65		7506.84	7508.1
/	47	S: SEQ ID NO: 80	4	7364.27	7365.6
		AS: SEQ ID NO: 65		7506.84	7508.0
/	48	S: SEQ ID NO: 81	5	7376.31	7377.7
		AS: SEQ ID NO: 65		7506.84	7508.1
/	49	S: SEQ ID NO: 82	5	7376.31	7377.7
		AS: SEQ ID NO: 65		7506.84	7508.2
/	50	S: SEQ ID NO: 83	4	7364.27	7365.5
		AS: SEQ ID NO: 65		7506.84	7508.2
/	51	S: SEQ ID NO: 84	5	7364.27	7365.9
		AS: SEQ ID NO: 65		7506.84	7508.2
/	52	S: SEQ ID NO: 85	5	7364.27	7365.7
		AS: SEQ ID NO: 65		7506.84	7508.0
/	53	S: SEQ ID NO: 86	5	7364.27	7365.6
		AS: SEQ ID NO: 65		7506.84	7508.0
/	54	S: SEQ ID NO: 87	6	7245.13	7245.7
		AS: SEQ ID NO: 88		7749.10	7749.5
/	55	S: SEQ ID NO: 89	6	7078.03	7079.3
		AS: SEQ ID NO: 88		7749.10	7750.7
/	56	S: SEQ ID NO: 90	5	7037.08	7038.6
		AS: SEQ ID NO: 91		7665.95	7667.5
/	57	S: SEQ ID NO: 92	5	7204.18	7204.2
		AS: SEQ ID NO: 91		7665.95	7665.9
/	58	S: SEQ ID NO: 93	7	7364.27	7365.5
		AS: SEQ ID NO: 65		7506.84	7508.1
/	59	S: SEQ ID NO: 94	5	7364.27	7365.4
		AS: SEQ ID NO: 65		7506.84	7508.1

/	60	S: SEQ ID NO: 95	7	7364.27	7365.5
		AS: SEQ ID NO: 65		7506.84	7508.1
/	61	S: SEQ ID NO: 96	5	7376.31	7377.6
		AS: SEQ ID NO: 65		7506.84	7508.1
/	62	S: SEQ ID NO: 97	6	7364.27	7365.4
		AS: SEQ ID NO: 65		7506.84	7508.1
/	63	S: SEQ ID NO: 98	7	7364.27	7365.4
		AS: SEQ ID NO: 65		7506.84	7508.1
/	64	S: SEQ ID NO: 99	5	7364.27	7365.5
		AS: SEQ ID NO: 65		7506.84	7508.1
/	65	S: SEQ ID NO: 100	7	7364.27	7365.4
		AS: SEQ ID NO: 65		7506.84	7508.1
/	66	S: SEQ ID NO: 101	5	7316.22	7315.2
		AS: SEQ ID NO: 102		7583.93	7582.9
/	67	S: SEQ ID NO: 103	4	7363.29	7362.5
		AS: SEQ ID NO: 104		7545.87	7544.8
13	68	S: SEQ ID NO: 105	1	7840.74	7841.4
		AS: SEQ ID NO: 106		7530.90	7532.0
14	69	S: SEQ ID NO: 105	1	7840.74	7841.5
		AS: SEQ ID NO: 107		7482.76	7483.6
15	70	S: SEQ ID NO: 105	1	7840.74	7841.4
		AS: SEQ ID NO: 65		7506.83	7507.5
16	71	S: SEQ ID NO: 105	1	7840.74	7841.4
		AS: SEQ ID NO: 108		7482.76	7483.6
17	72	S: SEQ ID NO: 109	1	7689.64	7690.6
		AS: SEQ ID NO: 65		7506.83	7507.6
18	73	S: SEQ ID NO: 110	1	7856.74	7857.3
		AS: SEQ ID NO: 40		7518.87	7520.0
19	74	S: SEQ ID NO: 111	1	6442.86	6443.5

		AS: SEQ ID NO: 112		7583.13	7584.1
20	75	S: SEQ ID NO: 113	1	8433.06	8434.3
		AS: SEQ ID NO: 114		7487.86	7488.9
21	76	S: SEQ ID NO: 115	1	7852.78	7854.4
		AS: SEQ ID NO: 116		7534.93	7535.9

“S” means the sense strand; “AS” means the antisense strand. * LDP 1 is linked to the 3’ of the sense strand. ** LDPs 4-7 are Uhd, Ahd, Chd, Ghd respectively linked to a nucleotide in the sense strand.

Example 3. Characterization of MAPT RNAi Agents

Selected MAPT RNAi agents were tested *in vitro* for MAPT inhibition in cultured cells, including SH-SY5Y cells, mouse cortical neurons (MCN) and/or human induced pluripotent stem cells (hiPSC). A subset of the selected MAPT RNAi agents were tested *in vivo* in transgenic human Tau mouse.

Materials and Methods

SH-SY5Y Cell Culture and RNAi Treatment and Analysis: SH-SY5Y cells (ATCC CRL-2266) were derived from the SK-N-SH neuroblastoma cell line (Ross, R. A., et al., 1983. J Natl Cancer Inst 71, 741-747). The base medium was composed of a 1:1 mixture of ATCC-formulated Eagle's Minimum Essential Medium, (Cat No. 30-2003), and F12 Medium. The complete growth medium was supplemented with 10% fetal bovine serum, 1X amino acids, 1X sodium bicarbonate, and 1X penicillin-streptomycin (Gibco) and cells incubated at 37 °C in a humidified atmosphere of 5% CO₂. On Day One, SH-SY5Y cells were plated in 96 well fibronectin coated tissue culture plates and allowed to attach overnight. On Day Two, complete media was removed and replaced with RNAi agent in serum free media. Cells were incubated with RNAi agent for 72 hours before analysis of gene expression. Analysis of changes in gene expression in RNAi treated SH-SY5Y cells was measured using Cells-to-C_T Kits following the manufacturer's protocol (ThermoFisher A35377). Predesigned gene expression assays (supplied as 20X mixtures) were selected from Applied Bio-systems (Foster City, CA, USA). The efficiencies of these assays (ThermoFisher Hs00902194_m1 MAPT and ThermoFisher Hs99999905_m1 GAPDH) were characterized with a dilution series of cDNA. RT-QPCR was

performed in MicroAmp Optical 384-well reaction plates using QuantStudio 7 Flex system. The delta-delta CT method of normalizing to the housekeeping gene GAPDH was used to determine relative amounts of gene expression. GraphPad Prism v9.0 was used to determine IC50 with a four parameter logistic fit.

Mouse Primary Cortical Neuron (MCN) Culture and RNAi Treatment and

Analysis: Mouse primary cortical neurons were isolated from hTau C57BL6 transgenic mouse embryos expressing human tau transgene at E18. Cells were plated in poly-D-lysine coated 96-well plates at a density of 40k cells/well and cultured in NbActiv1 (BrainBits, LLC) containing 1% Antibiotic/Antimycotic (Corning) for 7 days at 37 °C in a tissue culture incubator in a humidified chamber with 5% CO₂. On Day 7, half of the medium was removed from each well and 2x concentration of RNAi in culture media with 2% FBS was added for treatment as CRC and incubated with cells for additional 7, 14 or 21 days. Half media change was done every 7 days with fresh culture media. At the end of RNAi treatment, RT-qPCR was performed to quantify MAPT mRNA levels using TaqMan Fast Advanced Cell-to-CT kit. Specifically, cells were lysed, cDNA was generated on Mastercycler X50a (Eppendorf), and qPCR was carried out on QuantStudio 7 Flex Real-Time PCR System (Applied Biosystems). Human MAPT (ThermoFisher, Hs00902194_m1) gene expression levels were normalized by β -actin (ThermoFisher, Mm02619580_g1) using respective probes.

Human Induced Pluripotent Stem Cell-derived Neuron (hiPSC Neuron) Culture

and RNAi Treatment and Analysis: Doxycycline-inducible Neurogenin2 (NGN2) human induced Pluripotent Stem Cells (hiPSC) were developed by Bioneer for Eli Lilly. The hiPSC were doxycycline-induced for three days (DIV3) to initiate neuronal differentiation and plated on 96-well PDL and laminin coated plates at 30k/well and grown in Neuronal Differentiation Media (NDM) consisting of DMEM/F12 (Life Technologies 11330-057), Neurobasal media (Gibco 15240062), antibiotics, supplements, growth factors and doxycycline in an incubator (37°C/ 5%CO₂). Cells were half-fed every seven days, and on DIV21, RNAi agent was serially diluted in NDM, and cells were treated with RNAi by aspirating 75 μ L and adding 75 μ L of 2x RNAi concentration for a final of 1x RNAi according to dilutions. Cells were half-fed every seven days after treatment by removing half of media and adding back fresh NDM. Cell lysates were harvested at DIV35 (14 days later) or DIV42 (21 days later) and RT-qPCR was performed using

TaqMan Fast Advanced Cells-to-CT Kit (ThermoFisher, A35377) and to determine mRNA knock down using MAPT probe as the gene of interest (ThermoFisher, Hs00902194_m1) and ACTb probe as the housekeeping gene (ThermoFisher, Hs99999903_m1).

***In vivo* Characterization of Selected RNAi Agents in Transgenic Mice**

The efficacy of selected RNAi agents was also studied in hTau transgenic mice expressing human MAPT RNA and lacking murine MAPT RNA (Andorfer et al., J Neurochem 2003, 86, 582–590). Six mice received intracerebroventricular (ICV) injection of 100 µg of the RNAi agent or PBS (phosphate buffered saline) and were sacrificed on Day 14 after the injection. MAPT mRNA expression in the brain was measured and analyzed by quantitative PCR (qPCR).

Results

Table 10A summarizes the *in vitro* and *in vivo* activities of selected MAPT RNAi agents. As shown in Table 10A, the tested RNAi agents knock down MAPT expression *in vitro* and *in vivo*.

Table 10A. *In vitro* and *in vivo* activities of selected MAPT RNAi agents

MAPT RNAi Agent	SHSY5Y, 3d IC50 (nM)	SHSY5Y, 3d % KD (knockdown) of MAPT at 1 µM	Mouse ICV, 14d % KD Brain stem	Mouse ICV, 14d % KD Frontal Cortex
Conjugated RNAi Agent NO. 1	204.2	77.3	37.8	32.6
Conjugated RNAi Agent NO. 2	231.7	74.8	36.3	36.0
Conjugated RNAi Agent NO. 3	210.1	84.1	48.0	36.0
Conjugated RNAi Agent NO. 4	11051	69.6	54.4	33.7
Conjugated RNAi Agent NO. 5	60503	59.4	53.7	NE*
Conjugated RNAi Agent NO. 6	275.6	66.7	47.9	26.6

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 μM	MCN, 7d IC50 (nM)	MCN, 7d % KD (knockdown) of SNCA 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

39	ND	ND	8.58	88.5	78	61
40	ND	ND	7.3	88.3	79	59
41	ND	ND	57.6	84.3	61	38
42	ND	ND	16.16	86.1	69	45
43	ND	ND	71.82	89.4	ND	ND
44	ND	ND	64.11	87.3	ND	ND
45	ND	ND	89.05	85.5	ND	ND
46	ND	ND	25.06	87.2	ND	ND
47	ND	ND	68.9	86.3	ND	ND
48	ND	ND	45.8	59.9	ND	ND
49	ND	ND	333.7	84	ND	ND
50	ND	ND	15.02	81.6	ND	ND
51	ND	ND	72.72	81.4	ND	ND
52	ND	ND	99.63	86.2	ND	ND
53	ND	ND	157.9	88.1	ND	ND
54	ND	ND	2.01	88.3	81	54
55	ND	ND	10.33	82.5	ND	ND
56	ND	ND	25.05	77.8	ND	ND
57	ND	ND	1.12	87.2	ND	ND
58	ND	ND	22.8	87.2	ND	ND
59	ND	ND	18.1	88.4	ND	ND
60	ND	ND	20.6	89.7	ND	ND

61	ND	ND	99.1	66.8	ND	ND
62	ND	ND	23.2	89.0	ND	ND
63	ND	ND	36.7	89.3	ND	ND
64	ND	ND	39.5	90.6	ND	ND
65	ND	ND	76.0	89.1	ND	ND
66	ND	ND	22.3	87.9	ND	ND
67	ND	ND	39.2	84.5	ND	ND
Conjugated RNAi Agent No. 13	384.56	71.02	ND	ND	68	42
Conjugated RNAi Agent No. 14	320.53	79.53	ND	ND	67	41
Conjugated RNAi Agent No. 15	630.91	64.37	ND	ND	68	48
Conjugated RNAi Agent No. 16	232.42	77.03	ND	ND	71	41
Conjugated RNAi Agent No. 17	>1000	24.79	ND	ND	68	51
Conjugated RNAi Agent No. 18	>1000	54.08	ND	ND	ND	ND
Conjugated RNAi Agent No. 19	625.79	60.91	ND	ND	ND	ND
Conjugated RNAi Agent No. 20	406.76	66.69	ND	ND	ND	ND

Conjugated RNAi Agent No. 21	683.09	58.54	ND	ND	ND	ND
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*ND means not determined.

Example 4. Knockdown of MAPT mRNA in Cynomolgus monkey following a single administration of MAPT siRNA by intrathecal injection

In vivo testing of MAPT RNAi agent No. 31 (sense strand of SEQ ID NO: 63 and antisense strand of SEQ ID NO: 40) in Cynomolgus monkey (*Macaca fascicularis*) was conducted to assess the efficacy of MAPT siRNA. In order to elucidate the efficacy of the siRNA in silencing the target gene; n=4/group cynomolgus monkeys were ported with indwelling catheters intrathecally in the lumbar region. The monkeys were infused with either aCSF or MAPT RNAi agent No. 31 (2.4 mg/ml in aCSF) over 15 minutes and were perfused 78 days later. Tissues collected at necropsy included spinal cord (lumbar) and brain (prefrontal cortex, motor cortex, parietal cortex, hippocampus and thalamus). qPCR and ELISA was performed to determine MAPT mRNA and protein knockdown respectively in the CNS regions. Tables 11 and 12 below show MAPT mRNA and protein knockdown observed in all the regions, 78 days after a single administration of the siRNA.

Table 11. Mean MAPT mRNA knockdown following a single intrathecal administration of MAPT RNAi agent No. 31.

Route of administration	Dose [mg]	Lumbar Spinal Cord	Prefrontal Cortex	Motor Cortex	Parietal Cortex	Hippocampus	Thalamus
Intrathecal-Catheter	6	80%	73%	62%	72%	61%	34%

Table 12. Mean MAPT protein knockdown following a single intrathecal administration of MAPT RNAi agent No. 31.

Route of administration	Dose [mg]	Lumbar Spinal Cord	Prefrontal Cortex	Motor Cortex	Parietal Cortex	Hippocampus	Thalamus
Intrathecal-Catheter	6	75%	70%	72%	77%	63%	67%

SEQUENCE LISTING

SEQ ID NO	Sequence
1	ACAAGCUGACCUCCGCGAGA
2	UCUCGCGGAAGGUCAGCUUGUGG
3	AGAUUGAAACCCACAAGCUGA
4	UCAGCUUGUGGGUUUCAAUUUU
5	AAUAAAAAGAUUGAAACCCAA
6	UUGGGUUUCAUUCUUUUUAUUUC
7	GGAAAUAAAAAGAUUGAAACA
8	UGUUUCAAUUCUUUUUAUUUCCUC
9	GGCGGAGGAAAUAAAAAGAUUA
10	UAUCUUUUUAUUUCCUCCGCCAG
11	GAAGUAAAAUCUGAGAAGCUA
12	UAGCUUCUCAGAUUUUACUUCCA
13	GGAAGUAAAAUCUGAGAAGCA
14	UGCUCUCAGAUUUUACUUCCAC
15	GUGGAAGUAAAAUCUGAGAAA
16	UUUCUCAGAUUUUACUUCCACCU
17	CCAGGUGGAAGUAAAAUCUGA
18	UCAGAUUUUACUUCCACCUGGCC
19	CAAGUCCAAGAUCGGCUCCAA
20	UUGGAGCCGAUCUUGGACUUGAC
21	UCUGGUGAACCUCCAAAAUCA
22	UGAUUUUGGAGGUUACCAGAGC
23	CAGGUGGAAGUAAAAUCUGAA
24	UUCAGAUUUUACUUCCACCUGGC
25	mA*mC*mAmAmGmCfUmGfAfCfCmUmUmCmCmGmCmGmA*mG*mA
26	VPmU*fC*mUmCmGfCmGmGmAmAmGmGmUfCmAfGmCmUmUmGmU*mG*mG
27	mA*mG*mAmUmUmGfAmAfAfCfCmCmAmCmAmAmGmCmU*mG*mA
28	VPmU*fC*mAmGmCfUmUmGmUmGmGmGmUfUmUfCmAmAmUmCmU*mU*mU
29	mA*mA*mUmAmAmAfAmAfGfAfUmUmGmAmAmAmCmC*mA*mA
30	VPmU*fU*mGmGmGfUmUmUmCmAmAmUmCfUmUfUmUmAmUmU*mU*mC
31	mG*mG*mAmAmAmUfAmAfAfAfAmGmAmUmUmGmAmAmA*mC*mA
32	VPmU*fG*mUmUmUfCmAmAmUmCmUmUmUfUmUfAmUmUmUmCmC*mU*mC
33	mG*mG*mCmGmGmAfGmGfAfAfAmUmAmAmAmAmAmGmA*mU*mA

34	VPmU*fA*mUmCmUfUmUmUmUmAmUmUmUfCmCfUmCmCmGmCmC*mA*mG
35	mG*mA*mAmGmUmAfAmAfAfUfCmUmGmAmGmAmAmGmC*mU*mA
36	VPmU*fA*mGmCmUfUmCmUmCmAmGmAmUfUmUfUmAmCmUmUmC*mC*mA
37	mG*mG*mAmAmGmUfAmAfAfAfUmCmUmGmAmGmAmAmG*mC*mA
38	VPmU*fG*mCmUmUfCmUmCmAmGmAmUmUfUmUfAmCmUmUmCmC*mA*mC
39	mG*mU*mGmGmAmAfGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA
40	VPmU*fU*mUmCmUfCmAmGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU
41	mC*mC*mAmGmGmUfGmGfAfAfGmUmAmAmAmAmUmCmU*mG*mA
42	VPmU*fC*mAmGmAfUmUmUmUmAmCmUmUfCmCfAmCmCmUmGmG*mC*mC
43	mC*mA*mAmGmUmCfCmAfAfGfAmUmCmGmGmCmUmCmC*mA*mA
44	VPmU*fU*mGmGmAfGmCmCmGmAmUmCmUfUmGfGmAmCmUmUmG*mA*mC
45	mU*mC*mUmGmGmUfGmAfAfCfCmUmCmCmAmAmAmAmU*mC*mA
46	VPmU*fG*mAmUmUfUmUmGmGmAmGmGmUfUmCfAmCmCmAmGmA*mG*mC
47	mC*mA*mGmGmUmGfGmAfAfGfUmAmAmAmAmUmCmUmG*mA*mA
48	VPmU*fU*mCmAmGfAmUmUmUmUmAmCmUfUmCfCmAmCmCmUmG*mG*mC
49	GCAGTCACCG CCACCCACCA GTCCTGGCAC CAACAGCAGC GCCGCTGCCA CCGCCACCTT TCTGCCGCGG CCACCACAGC CACCTTCTCC TCCTCCGCTG TCCTCTCCCG TCCTCGCCTC TGTCGACTAT CAGGTGAAGT TTGAACCAGG ATGGCTGAGC CCCGCCAGGA GTTCGAAGTG ATGGAAGATC ACGCTGGGAC GTACGGGTG GGGGACAGGA AAGATCAGGG GGGCTACACC ATGCACCAAG ACCAAGAGGG TGACACGGAC GCTGGCCTGA AAGAATCTCC CCTGCAGACC CCCACTGAGG ACGGATCTGA GGAACCGGGC TCTGAAACCT CTGATGCTAA GAGCACTCCA ACAGCGGAAG ATGTGACAGC ACCCTTAGTG GATGAGGGAG CTCCCGGCAA GCAGGCTGCC GCGCAGCCCC ACACGGAGAT CCCAGAAGGA ACCACAGCTG AAGAAGCAGG CATTGGAGAC ACCCCCAGCC TGGAAGACGA AGCTGCTGGT CACGTGACCC AAGAGCCTGA AAGTGGTAAG GTGGTCCAGG AAGGCTTCCT CCGAGAGCCA GGCCCCCAG GTCTGAGCCA CCAGCTCATG TCCGGCATGC CTGGGGCTCC CCTCCTGCCT GAGGGCCCCA GAGAGGCCAC ACGCCAACCT TCGGGGACAG GACCTGAGGA CACAGAGGGC GGCCGCCACG CCCCTGAGCT GCTCAAGCAC CAGCTTCTAG GAGACCTGCA CCAGGAGGGG CCGCCGCTGA AGGGGGCAGG GGGCAAGAG AGGCCGGGGA GCAAGGAGGA GGTGGATGAA GACCGCGACG TCGATGAGTC CTCCCCCAA GACTCCCCCT CCTCCAAGGC CTCCCCAGCC CAAGATGGGC GGCCTCCCCA GACAGCCGCC AGAGAAGCCA CCAGCATCCC AGGCTTCCA GCGGAGGGTG CCATCCCCCT CCCTGTGGAT TTCCTCTCCA AAGTTTCCAC AGAGATCCA GCCTCAGAGC CCGACGGGCC CAGTGTAGGG CGGGCCAAAG GGCAGGATGC CCCCCTGGAG TTCACGTTTC ACGTGGAAT CACACCCAAC GTGCAGAAGG AGCAGGCGCA CTCGGAGGAG CATTTGGGAA GGGCTGCATT TCCAGGGGCC CCTGGAGAGG GGCCAGAGGC CCGGGGCCCC TCTTTGGGAG AGGACACAAA AGAGGCTGAC CTTCCAGAGC CCTCTGAAAA GCAGCCTGCT GCTGCTCCGC GGGGGAAGCC CGTCAGCCGG GTCCCTCAAC TCAAAGCTCG CATGGTCAGT AAAAGCAAAG ACGGGACTGG AAGCGATGAC AAAAAAGCCA AGACATCCAC ACGTTCCTCT GTAAAAACCT TGAAAAATAG GCCTTGCCTT AGCCCCAAAC ACCCACTTCC TGGTAGCTCA GACCCTCTGA TCCAACCTC CAGCCCTGCT GTGTGCCCCAG AGCCACCTTC CTCTCCTAAA TACGTCTCTT CTGTCACTC CGAACTGGC AGTTCTGGAG CAAAGGAGAT GAAACTCAAG GGGGCTGATG GTAAAACGAA GATCGCCACA CCGCGGGGAG CAGCCCCCTC AGGCCAGAAG GGCCAGGCCA ACGCCACCAG GATTCCAGCA AAAACCCCGC CCGCTCCAAA GACACCACCC AGCTCTGCGA CTAAGCAAGT CCAGAGAAGA CCACCCCTG CAGGGCCAG ATCTGAGAGA GGTGAACCTC CAAAATCAGG GGATCGCAGC GGCTACAGCA GCCCCGGCTC CCCAGGCACT CCCGGCAGCC GCTCCCGCAC CCCGTCCCTT CCAACCCAC CCACCCGGGA GCCCAAGAAG GTGGCAGTGG TCCGTACTCC CCCCAGTCG CCGTCTTCCG CCAAGAGCCG CCTGCAGACA GCCCCGTGC CCATGCCAGA CCTGAAGAAT GTCAAGTCCA AGATCGGCTC CACTGAGAAC CTGAAGCACC AGCCGGGAGG CGGGAAGGTG

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	GCTGTAAAAG	TGAATTTGGA	AATAAAGTTA	TTACTCTGAT	TAAA	
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	PGSRSRTPSL	PTPPTREPCK	VAVVRTPPKS	PSSAKSRLQT	APVPMPLDKN	VKSKIGSTEN
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AACACACCCC	CTTGGAATATG	GTTCTTTTCC	CCCAGTCCCA	GCTGGAAGCC	ATGCTGTCTG
TTCTGCTGGA	GCAGCTGAAC	ATATACATAG	ATGTTGCCCT	GCCCTCCCCA	GCCCTACCCCT
GTTGAGTTGT	AGTTGGATTT	GTCTGTTTAT	GCTTGGATTTC	ACCAGAGTGA	CTATGATAGT
GAAAAGAAAA	AAAAAAAAAA	AAAAGGACGC	ATGTATCTTG	AAATGCTTGT	AAAGAGGTTT
CTAACCCACC	CTCACGAGGT	GTCTCTCACC	CCCACACTGG	GACTCGTGTG	GCCTGTGTGG
TGCCACCCCTG	CTGGGGCCTC	CCAAGTTTTC	AAAGGCTTTC	CTCAGCACCT	GGGACCCAAC
AGAGACCAGC	TTCTAGCAGC	TAAGGAGGCC	GTTTCTGCTG	GACGAAGGCC	TGAAGCACAG
GATTAGGACT	GAAGCGATGA	TGTCCCTTTC	CCTACTTCCC	CTTGGGGCTC	CCTGTGTCTG
GGCACAGACT	AGGTCTTGTG	GCTGGTCTGG	CTTGCGGCGC	GAGGATGGTT	CTCTCTGGTC
ATAGCCCGAA	GTCTCATGGC	AGTCCCAAAG	GAGGCTTACA	ACTCCTGCAT	CACAAGAAAA
AGGAAGCCAC	TGCCAGCTGG	GGGGATCTGC	AGCTCCAGAA	AGCTCCGTGA	GCCTCAGCCA
CCCCTCAGAC	TGGGTTCCTC	TCCAAGCTCG	CCCTCTGGAG	GGGCAGCGCA	GCCTCCCACC
AAGGGCCCTG	CGACCACAGC	AGGGATTGGG	ATGAATTGCC	TGTCCTGGAT	CTGCTCTAGA
GGCCCAAGCT	GCCTGCCTGA	GGAAGGATGA	CTTGACAAGT	CAGGAGACAC	TGTTCCCAAA
GCCTTGACCA	GAGCACCTCA	GCCCCGTGAC	CTTGACAAAA	CTCCATCTGC	TGCCATGAGA
AAAGGGAAGC	CGCCTTTGCA	AAACATTGCT	GCCTAAAGAA	ACTCAGCAGC	CTCAGGCCCA
ATTCTGCCAC	TTCTGGTTTG	GGTACAGTTA	AAGGCAACCC	TGAGGGACTT	GGCAGTAGAA
ATCCAGGGCC	TCCCCTGGGG	CTGGCAGCTT	CGTGTGCAGC	TAGAGCTTTA	CCTGAAAGGA
AGTCTCTGGG	CCCAGAACTC	TCCACCAAGA	GCCTCCCTGC	CGTTCGCTGA	GTCCCAGCAA
TTCTCCTAAG	TTGAAGGGAT	CTGAGAAGGA	GAAGGAAATG	TGGGGTAGAT	TTGGTGGTGG
TTAGAGATAT	GCCCCCTCA	TTACTGCCAA	CAGTTTCGGC	TGCATTTCTT	CACGCACCTC
GGTTCTCTCT	CCTGAAGTTC	TTGTGCCCTG	CTCTTCAGCA	CCATGGGCCT	TCTTATACGG
AAGGCTCTGG	GATCTCCCCC	TTGTGGGGCA	GGCTCTTGGG	GCCAGCCTAA	GATCATGGTT
TAGGGTGATC	AGTGCTGGCA	GATAAATTGA	AAAGGCACGC	TGGCTTGTGA	TCTTAAATGA
GGACAATCCC	CCCAGGGCTG	GGCACTCCTC	CCCTCCCCTC	ACTTCTCCCA	CCTGCAGAGC

	CAGTGTCTT	GGGTGGGCTA	GATAGGATAT	ACTGTATGCC	GGCTCCTTCA	AGCTGCTGAC
	TCACCTTTATC	AATAGTTCCA	TTTAAATTGA	CTTCAGTGGT	GAGACTGTAT	CCTGTTTGTCT
	ATTGCTTGTT	GTGCTATGGG	GGGAGGGGGG	AGGAATGTGT	AAGATAGTTA	ACATGGGCAA
	AGGGAGATCT	TGGGGTGCAG	CACCTAAACT	GCCTCGTAAC	CCTTTTCATG	ATTTCAACCA
	CATTTGCTAG	AGGGAGGGAG	CAGCCACGGA	GTTAGAGGCC	CTTGGGGTTT	CTCTTTTCCA
	CTGACAGGCT	TTCCCAGGCA	GCTGGCTAGT	TCATTCCCTC	CCCAGCCAGG	TGCAGGCGTA
	GGAATATGGA	CATCTGGTTG	CTTTGGCCTG	CTGCCCTCTT	TCAGGGGTCC	TAAGCCCACA
	ATCATGCCTC	CCTAAGACCT	TGGCATCCTT	CCCTCTAAGC	CGTTGGCACC	TCTGTGCCAC
	CTCTCACACT	GGCTCCAGAC	ACACAGCCTG	TGCTTTTGGA	GCTGAGATCA	CTCGCTTCAC
	CCTCCTCATC	TTTGTTCCTC	AAGTAAAGCC	ACGAGGTCCG	GGCGAGGGCA	GAGGTGATCA
	CCTGCGTGTG	CCATCTACAG	ACCTGCAGCT	TCATAAAACT	TCTGATTTCT	CTTCAGCTTT
	GAAAAGGGTT	ACCCTGGGCA	CTGGCCTAGA	GCCTCACCTC	CTAATAGACT	TAGCCCCATG
	AGTTTGCCAT	GTTGAGCAGG	ACTATTCTG	GCACTTGCAA	GTCCCATGAT	TTCTTCGGTA
	ATTCTGAGGG	TGGGGGGAGG	GACATGAAAT	CATCTTAGCT	TAGCTTTCTG	TCTGTGAATG
	TCTATATAGT	GTATTGTGTG	TTTTAACAAA	TGATTTACAC	TGACTGTTGC	TGTAAGAGTG
	AATTTGGAAA	TAAAGTTATT	ACTCTGATTA	AA		
52	MAEPRQEFEV	MEDHAGTYGL	GDRKDQGGYT	MHQDQEGDTD	AGLKESPLQT	PTEDGSEEPG
	SETSDAKSTP	TAEAEAGIG	DTPSLEDEAA	GHVTQARMVS	KSKDGTGSDD	KKAKGADGKT
	KIATPRGAAP	PGQKGQANAT	RIPAKTTPAP	KTPPSSGEPP	KSGDRSGYSS	PGSPGTPGSR
	SRTPSLPTPP	TREPKKVAVV	RTPPKSPSSA	KSRLQTAPVP	MPDLKNVSKS	IGSTENLKHQ
	PGGGKVQIIN	KKLDLSNVQS	KCGSKDNIKH	VPGGGSVQIV	YKPVDLKSVT	SKCGSLGNIH
	HKPGGGQVEV	KSEKLDKFKDR	VQSKI GSLDN	ITHVPGGGNK	KIETHKLTFR	ENAKAKTDHG
	AEIVYKSPVV	SGDTSPRHLS	NVSSTGSIDM	VDSPQLATLA	DEVSASLAKQ	GL
53	GCAGTCACCG	CCACCCACCA	GCTCCGGCAC	CAACAGCAGC	GCCGCTGCCA	CCGCCCACCT
	TCTGCCGCCG	CCACCACAGC	CACCTTCTCC	TCCTCCGCTG	TCCTCTCCCG	TCCTCGCCTC
	TGTCGACTAT	CAGGTGAACT	TTGAACCAGG	ATGGCTGAGC	CCCGCCAGGA	GTTTCAAGTG
	ATGGAAGATC	ACGCTGGGAC	GTACGGGTG	GGGGACAGGA	AAGATCAGGG	GGGCTACACC
	ATGCACCAAG	ACCAAGAGGG	TGACACGGAC	GCTGGCCTGA	AAGCTGAAGA	AGCAGGCATT
	GGAGACACCC	CCAGCCTGGA	AGACGAAGCT	GCTGGTCACG	TGACCCAAGC	TCGCATGGTC
	AGTAAAAGCA	AAGACGGGAC	TGGAAGCGAT	GACAAAAAAG	CCAAGGGGGC	TGATGGTAAA
	ACGAAGATCG	CCACACCGCG	GGGAGCAGCC	CCTCCAGGCC	AGAAGGGCCA	GGCCAACGCC
	ACCAAGGATC	CAGCAAAAAC	CCCGCCCGCT	CCAAAGACAC	CACCCAGCTC	TGGTGAACCT
	CCAAAATCAG	GGGATCGCAG	CGGCTACAGC	AGCCCCGGCT	CCCCAGGCAC	TCCCGGCAGC
	CGCTCCCGCA	CCCCGTCCCT	TCCAACCCCA	CCCAACCGGG	AGCCCAAGAA	GGTGGCAGTG
	GTCCGTACTC	CACCCAAGTC	GCCGTCTTCC	GCCAAGAGCC	GCCTGCAGAC	AGCCCCCGTG
	CCCATGCCAG	ACCTGAAGAA	TGTCAAGTCC	AAGATCGGCT	CCACTGAGAA	CCTGAAGCAC
	CAGCCGGGAG	GCGGGAAGGT	GCAAATAGTC	TACAAACCAG	TTGACCTGAG	CAAGGTGACC
	TCCAAGTGTG	GCTCATTAGG	CAACATCCAT	CATAAACAG	GAGGTGGCCA	GGTGGAAGTA
	AAATCTGAGA	AGCTTGACTT	CAAGGACAGA	GTCCAGTCGA	AGATTGGGTC	CCTGGACAAT
	ATCACCCACG	TCCCTGGCGG	AGGAAATAAA	AAGATTGAAA	CCCACAAGCT	GACCTTCCGC
	GAGAACGCCA	AAGCCAAGAC	AGACCACGGG	GCGGAGATCG	TGTACAAGTC	GCCAGTGGTG
	TCTGGGGACA	CGTCTCCACG	GCATCTCAGC	AATGTCTCCT	CCACCGGCAG	CATCGACATG
	GTAGACTCGC	CCCAGCTCGC	CACGCTAGCT	GACGAGGTGT	CTGCCTCCCT	GGCCAAGCAG
	GGTTTGTGAT	CAGGCCCTG	GGGCGGTCAA	TAATTGTGGA	GAGGAGAGAA	TGAGAGAGTG
	TGGAAAAAAA	AAGAATAATG	ACCCGGCCCC	CGCCCTCTGC	CCCCAGCTGC	TCCTCGCAGT
	TCGGTTAATT	GGTTAATCAC	TTAACCTGCT	TTTGTCACTC	GGCTTTGGCT	CGGGACTTCA
	AAATCAGTGA	TGGGAGTAAG	AGCAAATTTT	ATCTTTCCAA	ATTGATGGGT	GGGCTAGTAA
	TAAAATATTT	AAAAAAAAC	ATTCAAAAAC	ATGGCCACAT	CCAACATTTT	CTCAGGCAAT
	TCCTTTTGAT	TCTTTTTTCT	TCCCCCTCCA	TGTAGAAGAG	GGAGAAGGAG	AGGCTCTGAA
	AGCTGCTTCT	GGGGGATTTC	AAGGGACTGG	GGGTGCCAAC	CACCTCTGGC	CCTGTTGTGG
	GGGTGTCACA	GAGGCAGTGG	CAGCAACAAA	GGATTTGAAA	CTTGGTGTGT	TCGTGGAGCC
	ACAGGCAGAC	GATGTCAACC	TTGTGTGAGT	GTGACGGGGG	TTGGGGTGGG	GCGGGAGGCC
	ACGGGGGAGG	CCGAGGCAGG	GGCTGGGCAG	AGGGGAGAGG	AAGCACAAAG	AGTGGGAGTG
	GGAGAGGAAG	CCACGTGCTG	GAGAGTAGAC	ATCCCCCTCC	TTGCCGCTGG	GAGAGCCAAG
	GCCTATGCCA	CCTGCAGCGT	CTGAGCGGCC	GCCTGTCTTT	GGTGGCCGGG	GGTGGGGGCC

TGCTGTGGGT	CAGTGTGCCA	CCCTCTGCAG	GGCAGCCTGT	GGGAGAAGGG	ACAGCGGGTA
AAAAGAGAAG	GCAAGCTGGC	AGGAGGGTGG	CACTTCGTGG	ATGACCTCCT	TAGAAAAGAC
TGACCTTGAT	GTCTTGAGAG	CGCTGGCCTC	TTCTCCCTC	CCTGCAGGGT	AGGGGGCCTG
AGTTGAGGGG	CTTCCCCTCTG	CTCCACAGAA	ACCCTGTTTT	ATTGAGTTCT	GAAGGTTGGA
ACTGCTGCCA	TGATTTTGGC	CACTTTGCAG	ACCTGGGACT	TTAGGGCTAA	CCAGTTCTCT
TTGTAAGGAC	TTGTGCCTCT	TGGGAGACGT	CCACCCGTTT	CCAAGCCTGG	GCCACTGGCA
TCTCTGGAGT	GTGTGGGGGT	CTGGGAGGCA	GGTCCCAGC	CCCCTGTCCT	TCCCACGGCC
ACTGCAGTCA	CCCCGTCTGC	GCCGCTGTGC	TGTTGTCTGC	CGTGAGAGCC	CAATCACTGC
CTATACCCCT	CATCACACGT	CACAATGTCC	CGAATTCCCA	GCCTCACCAC	CCCTTCTCAG
TAATGACCCT	GGTTGGTTGC	AGGAGGTACC	TACTCCATAC	TGAGGGTGAA	ATTAAGGGAA
GGCAAAGTCC	AGGCACAAGA	GTGGGACCCC	AGCCTCTCAC	TCTCAGTTCC	ACTCATCCAA
CTGGGACCCT	CACCACGAAT	CTCATGATCT	GATTTCGGTTC	CCTGTCTCCT	CCTCCCCTCA
CAGATGTGAG	CCAGGGCACT	GCTCAGCTGT	GACCCTAGGT	GTTTCTGCCT	TGTTGACATG
GAGAGAGCCC	TTTCCCCTGA	GAAGGCCTGG	CCCCTTCCTG	TGCTGAGCCC	ACAGCAGCAG
GCTGGGTGTC	TTGGTTGTCA	GTGGTGGCAC	CAGGATGGAA	GGGCAAGGCA	CCCAGGGCAG
GGCCACAGTC	CCGCTGTCCC	CCACTTGCAC	CCTAGCTTGT	AGCTGCCAAC	CTCCCAGACA
GCCCAGCCCC	CTGCTCAGCT	CCACATGCAT	AGTATCAGCC	CTCCACACCC	GACAAAGGGG
AACACACCCC	CTTGGAATG	GTTCTTTTCC	CCCAGTCCCA	GCTGGAAGCC	ATGCTGTCTG
TTCTGCTGGA	GCAGCTGAAC	ATATACATAG	ATGTTGCCCT	GCCCTCCCCA	TCTGCACCCT
GTTGAGTTGT	AGTTGGATTT	GTCTGTTTAT	GCTTGGATTG	ACCAGAGTGA	CTATGATAGT
GAAAAGAAAA	AAAAAAAAAA	AAAAGGACGC	ATGTATCTTG	AAATGCTTGT	AAAGAGGTTT
CTAACCCACC	CTCACGAGGT	GTCTCTCACC	CCCACACTGG	GACTCGTGTG	GCCTGTGTGG
TGCCACCCTG	CTGGGGCCTC	CCAAGTTTTG	AAAGGCCTTC	CTCAGCACCT	GGGACCCAAC
AGAGACCAGC	TTCTAGCAGC	TAAGGAGGCC	GTTTCAGCTGT	GACGAAGGCC	TGAAGCACAG
GATTAGGACT	GAAGCGATGA	TGTCCCCTTC	CCTACTTCCC	CTTGGGGCTC	CCTGTGTGAG
GGCACAGACT	AGGTCTTGTG	GCTGGTCTGG	CTTGCGGCGC	GAGGATGGTT	CTCTCTGTCT
ATAGCCCCGAA	GTCTCATGGC	AGTCCCAAAG	GAGGCTTACA	ACTCTGCAT	CACAAGAAAA
AGGAAGCCAC	TGCCAGCTGG	GGGGATCTGC	AGCTCCCAGA	AGCTCCGTGA	GACTCAGCCA
CCCCTCAGAC	TGGGTTCCCTC	TCCAAGCTCG	CCCTCTGGAG	GGGCAGCGCA	GCCTCCCACC
AAGGGCCCTG	CGACCACAGC	AGGGATTGGG	ATGAATTGCC	TGTCCTGGAT	CTGCTCTAGA
GGCCCCAAGCT	GCCTGCCTGA	GGAAGGATGA	CTTGACAAGT	CAGGAGACAC	TGTTCCCAAA
GCCTTGACCA	GAGCACCTCA	GCCCCGTGAC	CTTGACACAA	CTCCATCTGC	TGCCATGAGA
AAAGGGGAAGC	CGCCTTTGCA	AAACATTGCT	GCCTAAAGAA	ACTCAGCAGC	CTCAGGCCCC
ATTCTGCCAC	TTCTGGTTTG	GGTACAGTTA	AAGGCAACCC	TGAGGGACTT	GGCAGTAGAA
ATCCAGGGCC	TCCCCTGGGG	CTGGCAGCTT	CGTGTGCAGC	TAGAGCTTTA	CCTGAAAGGA
AGTCTCTGGG	CCCAGAACTC	TCCACCAAGA	GCCTCCCTGC	CGTTCGCTGA	GTCCCAGCAA
TTCTCCTAAG	TTGAAGGGAT	CTGAGAAGGA	GAAGGAAATG	TGGGGTAGAT	TTGGTGGTGG
TTAGAGATAT	GCCCCCTCA	TTACTGCCAA	CAGTTTCGGC	TGCATTTCTT	CACGCACCTC
GGTTCCTCTT	CCTGAAGTTC	TTGTGCCCTG	CTCTTCAGCA	CCATGGGCCT	TCTTATACGG
AAGGCTCTGG	GATCTCCCCC	TTGTGGGGCA	GGCTCTTGGG	GCCAGCCTAA	GATCATGGTT
TAGGGTGATC	AGTGCTGGCA	GATAAATTGA	AAAGGCACGC	TGGCTTGTGA	TCTTAAATGA
GGACAATCCC	CCCAGGGCTG	GGCACTCCTC	CCCTCCCCTC	ACTTCTCCCA	CCTGCAGAGC
CAGTGTCCCT	GGGTGGGCTA	GATAGGATAT	ACTGTATGCC	GGCTCCTTCA	AGCTGCTGAC
TCACCTTTATC	AATAGTTCCA	TTTAAATTGA	CTTCAGTGGT	GAGACTGTAT	CCTGTTTGCT
ATTGCTTGTT	GTGCTATGGG	GGGAGGGGGG	AGGAATGTGT	AAGATAGTTA	ACATGGGCAG
AGGGAGATCT	TGGGGTGCA	CACCTAAACT	GCCTCGTAAC	CCTTTTCATG	ATTTCAACCA
CATTTGCTAG	AGGGAGGGAG	CAGCCACGGA	GTTAGAGGCC	CTTGGGGTTT	CTCTTTTCCA
CTGACAGGCT	TTCCCAGGCA	GCTGGCTAGT	TCATTCCCTC	CCCAGCCAGG	TGCAGGCGTA
GGAATATGGA	CATCTGGTTG	CTTTGGCCTG	CTGCCCTCTT	TCAGGGGTCC	TAAGCCCACA
ATCATGCCTC	CCTAAGACCT	TGGCATCCTT	CCCTCTAAGC	CGTTGGCACC	TCTGTGCCAC
CTCTCACACT	GGCTCCAGAC	ACACAGCCTG	TGCTTTTGGA	GCTGAGATCA	CTCGCTTCAC
CCTCCTCATC	TTTGTTCTCC	AAGTAAAGCC	ACGAGGTCGG	GGCGAGGGCA	GAGGTGATCA
CCTGCGTGTC	CCATCTACAG	ACCTGCAGCT	TCATAAAACT	TCTGATTTCT	CTTCAGCTTT
GAAAAGGGTT	ACCCTGGGCA	CTGGCCTAGA	GCCTCACCTC	CTAATAGACT	TAGCCCCATG
AGTTTGCCAT	GTTGAGCAGG	ACTATTTCTG	GCACTTGCAA	GTCCCATGAT	TTCTTCGGTA
ATTCTGAGGG	TGGGGGGAGG	GACATGAAAT	CATCTTAGCT	TAGCTTTCTG	TCTGTGAATG
TCTATATAGT	GTATTGTGTG	TTTTAACAAA	TGATTTACAC	TGACTGTTGC	TGTAAAAGTG

	AATTTGGAAA TAAAGTTATT ACTCTGATTA AA
54	MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKAE EAGI GDTPSLEDEA AGHVTQARMV SKSKDGTGSD DKKAKGADGK TKIATPRGAA PPGQKGQANA TRIPAKTPPA PKTPSSGEP PKSGDRSGYS SPGSPGTPGS RSRTPSLPTP PTREPKKVAV VRTPPKSPSS AKSRLQTAPV PMPDLKNVKS KIGSTENLKH QPGGGKVQIV YKPVDL SKVT SKCGSLGNIH HKPGGGQVEV KSEKLD FKDR VQSKIGSLDN ITHVPGGGNK KIETHKLTFR ENAKAKTDHG AEIVYKSPVV SGDTSPRHLS NVSSTGSIDM VDSPQLATLA DEVSASLAKQ GL
55	GUGGAAGUA(n)AAUCUGAGAAA, wherein (n) indicates an abasic moiety.
56	GUGGAAGU(n)AAAUCUGAGAAA, wherein (n) indicates an abasic moiety.
57	CCAAGUGUGGCUCAUUAGGCA
58	UGCCUAAUGAGCCACACUUGGAG
59	CCAAGUGU(n)GCUCAUUAGGCA, wherein (n) indicates an abasic moiety.
60	UGCAAAUA(n)UCUACAAACCAA, wherein (n) indicates an abasic moiety.
61	UUGGUUUUGUAGACUAAUUGCACC
62	UGCAAAUAGUCUACAAACCAA
63	mG*mU*mGmGmAmAfGmUfAfAfAmA(Uhd)mCmUmGmAmGmA*mA*mA
64	mG*mU*mGmGmAmAmGmUfAfAfAmA(Uhd)mCmUmGmAmGmA*mA*mA
65	VPmU*fU*mUmCfUmCmAfGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU
66	mG*mU*mGmGmAmAmGmUfAfAfA(Ahd)mUmCmUmGmAmGmA*mA*mA
67	mG*mU*mGmGmAmAmGmUfA(n)fAmA(Uhd)mCmUmGmAmGmA*mA*mA
68	mG*mU*mGmGmAmAmGmUfA(n)fAmA(Uhd)mCmUmGmAmGmA*mA*mA
69	mG*mU*mGmGmAmAmGmU(n)fAfAmA(Uhd)mCmUmGmAmGmA*mA*mA
70	VPmU*fU*mUmCmUfCmAmGmAfUmUmUmUfAmCfUmUfCmCfAmC*mC*mU
71	mG*mU*mGmGmAmAmGmUfAfAfAmA(Uhd)mCfUmGmAmGmA*mA*mA
72	VPmU*fU*mUmCfUmCfAmGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU
73	VPmU*fU*fUmCmUmCfAmGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU
74	VPmU*fU*mUmCfUmCmAmGmAmUmUmUmUfAmCmUmUmCmCmAmC*mC*mU
75	mG*mU*mGmGmAmAmGmUfAfAfA(Uhd)fUmCfUmGmAmGmA*mA*mA
76	(Ghd)*mU*mGmGmAmAmGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA
77	mG*(Uhd)*mGmGmAmAmGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA
78	mG*mU*(Ghd)mGmAmAmGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA
79	mG*mU*mGmGmA(Ahd)mGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA
80	mG*mU*mGmGmAmAmG(Uhd)fAfAfAmAmUmCmUmGmAmGmA*mA*mA
81	mG*mU*mGmGmAmAmGmU(Ahd)fAfAmAmUmCmUmGmAmGmA*mA*mA
82	mG*mU*mGmGmAmAmGmUfA(Ahd)fAfAmAmUmCmUmGmAmGmA*mA*mA
83	mG*mU*mGmGmAmAmGmUfAfAfAmAmUmC(Uhd)mGmAmGmA*mA*mA
84	mG*mU*mGmGmAmAmGmUfAfAfAmAmUmCmUmGmAmG(Ahd)*mA*mA

85	mG*mU*mGmGmAmAmGmUfAfAfAmAmUmCmUmGmAmGmA*(Ahd)*mA
86	mG*mU*mGmGmAmAmGmUfAfAfAmAmUmCmUmGmAmGmA*mA*(Ahd)
87	mC*mC*mAmAmGmUmGmUfGfGfCmU(Chd)mAmUmUmAmGmG*mC*mA
88	VPmU*fG*mCmCfUmAmAfUmGmAmGmCmCfAmCfAmCmUmUmGmG*mA*mG
89	mC*mC*mAmAmGmUmGmU(n)fGfCmU(Chd)mAmUmUmAmGmG*mC*mA
90	mU*mG*mCmAmAmAmUmA(n)fUfCmU(Ahd)mCmAmAmAmCmC*mA*mA
91	VPmU*fU*mGmGfUmUmUfGmUmAmGmAmCfUmAfUmUmUmGmCmA*mC*mC
92	mU*mG*mCmAmAmAmUmAfGfUfCmU(Ahd)mCmAmAmAmCmC*mA*mA
93	mG*mU*mG(Ghd)mAmAmGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA
94	mG*mU*mGmG(Ahd)mAmGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA
95	mG*mU*mGmGmAmA(Ghd)mUfAfAfAmAmUmCmUmGmAmGmA*mA*mA
96	mG*mU*mGmGmAmAmGmUfAfA(Ahd)mAmUmCmUmGmAmGmA*mA*mA
97	mG*mU*mGmGmAmAmGmUfAfAfAmAmU(Chd)mUmGmAmGmA*mA*mA
98	mG*mU*mGmGmAmAmGmUfAfAfAmAmUmCmU(Ghd)mAmGmA*mA*mA
99	mG*mU*mGmGmAmAmGmUfAfAfAmAmUmCmUmG(Ahd)mGmA*mA*mA
100	mG*mU*mGmGmAmAmGmUfAfAfAmAmUmCmUmGmA(Ghd)mA*mA*mA
101	mC*mC*mAmGmGmUmGmGfAfAfGmU(Ahd)mAmAmAmUmCmU*mG*mA
102	VPmU*fC*mAmGfAmUmUfUmUmAmCmUmUfCmCfAmCmCmUmGmG*mC*mC
103	mG*mG*mAmAmGmUmAmAfAfAfUmC(Uhd)mGmAmGmAmAmG*mC*mA
104	VPmU*fG*mCmUfUmCmUfCmAmGmAmUmUfUmUfAmCmUmUmCmC*mA*mC
105	mG*mU*mGmGmAmAfGmUfAfAfAmAmUmCmUmGmAmGmA*mA*
106	VPmU*fU*mUmCmUmCmAmGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU
107	VPmU*fU*mUfCmUfCfAmGfAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU
108	VPmU*fU*mUmCfUfCfAfGmAmUmUmUmUfAmCfUmUmCmCmAmC*mC*mU
109	mG*mU*mGmGmAmAfGmUfA(n)fAmAmUmCmUmGmAmGmA*mA*
110	mG*mU*mGmGmAmAfGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mG
111	mA*mA*fGmUfAfAfAmAmUmCmUmGmAmGmA*mA*mA
112	VPmU*fU*mUmCmUfCmAmGmAmUmUmUmUfAmCfUmU*mC*mC*mA*mC*mC*mU
113	mG*mU*mGmGmAmAfGmUfAfAfAmAmUmCmUmGmAmGmAAdTdT*
114	VPmU*fU*mUmCmUfCmAmGmAmUmUmUmUfAmCfUmUmCmC*mA*mCdTdT
115	mG*mU*mGmGmAmAmGmUfAfAfAmAmUmCmUmGmAmGmA*mA*
116	VPmU*fU*mUmCmUfCmAmGmAmUmUmUmUfAmCfUmUmCmCmA*mC*mC*mU
117	GUGGAAGUAAAAUCUGAGAAATT
118	UUUCUCAGAUUUUACUCCACTT
119	GUGGAAGUAAAAUCUGAGAAG

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. A method of reducing MAPT expression in a patient in need thereof, the method comprising administering to the patient an effective amount of the MAPT RNAi agent of any one of claims 1-30, or the pharmaceutical composition of claim 31.
33. A method of treating a tauopathy in a patient in need thereof, the method comprising administering to the patient an effective amount of the MAPT RNAi agent of any one of claims 1-30, or the pharmaceutical composition of claim 31.
34. The method of claim 33, 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 sclerosingpan encephalitis, tuberous sclerosis, lipofuscinosis, primary age-related tauopathy (PART), or globular glial tauopathies (GGT).

35. The method of claim 33 or 34, wherein the tauopathy is Alzheimer's disease (AD), frontotemporal dementia (FTD), or progressive supranuclear palsy (PSP).
36. The method of any one of claims 33-35, wherein the MAPT RNAi agent is administered to the patient intrathecally, intracerebroventricularly, or via intracisternal magna injection.
37. A 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.
38. The MAPT RNAi agent of any one of claims 1-30, or the pharmaceutical composition of claim 31, for use in a therapy.
39. The MAPT RNAi agent of any one of claims 1-30, or the pharmaceutical composition of claim 31, for use in reducing MAPT expression.

40. The MAPT RNAi agent of any one of claims 1-30, or the pharmaceutical composition of claim 31, for use in the treatment of a tauopathy.
41. The MAPT RNAi agent or the pharmaceutical composition for use of claim 40, 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).
42. The MAPT RNAi agent or the pharmaceutical composition for use of claim 40 or 41, wherein the tauopathy is Alzheimer's disease (AD), frontotemporal dementia (FTD), or progressive supranuclear palsy (PSP).

43. Use of the MAPT RNAi agent of any one of claims 1-30, in the manufacture of a medicament for the treatment of a tauopathy.
44. The use of claim 43, 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 sclerosingpan encephalitis, tuberous sclerosis, lipofuscinosis, primary age-related tauopathy (PART), or globular glial tauopathies (GGT).
45. The use of claim 43 or 44, wherein the tauopathy is Alzheimer's disease (AD), frontotemporal dementia (FTD), or progressive supranuclear palsy (PSP).