siRNA COMPOSITIONS AND METHODS TARGETING MICROTUBULE ASSOCIATED PROTEIN TAU NUCLEIC ACIDS

1. SEQUENCE LISTING

[0001] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on September 27, 2023, is named "51436-041WO2_Sequence_Listing_9_27_23" and is 843,776 bytes in size.

2. BACKGROUND

[0002] Expression of the microtubule associated protein tau (MAPT) gene produces the protein tau. Mutations in the MAPT gene have been linked to a number of disorders referred to as tauopathies. For example, mutations in the MAPT gene have been linked to Alzheimer's disease. Additional tauopathies include frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration. Currently, there are limited treatment options available for neurodegenerative tauopathies. Accordingly, there remains a need for therapeutics that can selectively diminish MAPT activity in a manner that provides effective treatment for tauopathies.

3. SUMMARY

[0003] The instant application is directed to single- or double-stranded interfering RNA molecules (e.g., siRNA) that target a MAPT gene. The interfering RNA molecules may contain specific patterns of nucleoside modifications and internucleoside linkage modifications. The disclosure also features pharmaceutical compositions including the same. The siRNA molecules may be branched siRNA molecules, such as di-branched, tri-branched, or tetra-branched siRNA molecules. The disclosed siRNA molecules may further feature a 5' phosphorus stabilizing moiety and/or a hydrophobic moiety. Additionally, the disclosure provides methods for delivering the siRNA molecule of the disclosure to the central nervous system of a subject, such as a subject identified as having a tauopathy. In certain embodiments, an interfering RNA molecule of the present disclosure is a di-branched siRNA molecule. In certain embodiments, the di-branched siRNA molecules of the present disclosure comprise:

a) a sense strand comprising the sequence (mG)#(mA)#(mA)(fU)(mG)(fA)(mG)(fA)(mG)(fA)(mG)(mU)(mG)(fU)#(mG)#(mA)-DIO (SEQ ID NO: 847) and an antisense

strand comprising the sequence
V(mU)#(fC)#(mA)(fC)(fA)(fC)(mU)(fC)(mU)(fC)(mU)(fC)(mA)(fU)(mU)
(fC)#(mU)#(mC)#(mU)#(mC)#(mC) (SEQ ID NO: 832);

b) a sense strand comprising the sequence (mU)#(mC)#(mU)(fG)(mU)(fC)(mG)(fA)
(mC)(fU)(mA)(mU)(mC)(fA)#(mG)#(mA)-DIO (SEQ ID NO: 848) and an antisense
strand comprising the sequence
V(mU)#(fC)#(mU)(fG)(fA)(fU)(mA)(fG)(mU)(fC)(mG)(fA)(mC)(fA)(mG)
(fA)#(mG)#(mG)#(mC)#(mG)#(mA) (SEQ ID NO: 833);

c) a sense strand comprising the sequence
(mA)#(mG)#(mA)(fG)(mG)(fA)(mG)(fA)(mG)
(fA)(mA)(mU)(mG)(fA)#(mG)#(mA)-DIO (SEQ ID NO: 849) and an antisense
strand comprising the sequence
V(mU)#(fC)#(mU)(fC)(fA)(fU)(mU)(fC)(mU)(fC)(mU)(fC)(mC)
(fU)(mC)(fU)#(mC)#(mC)#(mA)#(mC)#(mA) (SEQ ID NO: 834);

d) a sense strand comprising the sequence (mU)#(mC)#(mA)(fC)(mG)(fC)(mU)(fG)
(mG)(fG)(mA)(mC)(mG)(fU)#(mA)#(mA)-DIO (SEQ ID NO: 850) and an antisense
strand comprising the sequence
V(mU)#(fU)#(mA)(fC)(fG)(fU)(mC)(fC)(mC)(fA)(mG)(fC)(mG)(fU)
(mG)(fA)#(mU)#(mC)#(mU)#(mU)#(mC) (SEQ ID NO: 835);

e) a sense strand comprising the sequence (mG)#(mA)#(mA)(fG)(mU)(fA)(mA)(fA)
(mA)(fU)(mC)(mU)(mG)(fA)#(mG)#(mA)-DIO (SEQ ID NO: 851) and an antisense
strand comprising the sequence
V(mU)#(fC)#(mU)(fC)(fA)(fG)(mA)(fU)(mU)(fU)(mU)(fA)
(mC)(fU)(mU)(fC)#(mC)#(mA)#(mC)#(mC)#(mU) (SEQ ID NO: 836);

f) a sense strand comprising the sequence
(mU)#(mC)#(mA)(fA)(mA)(fA)(mU)(fC)(mA)
(fG)(mU)(mG)(mA)(fU)#(mG)#(mA)-DIO (SEQ ID NO: 852) and an antisense
strand comprising the sequence
V(mU)#(fC)#(mA)(fU)(fC)(fA)(mC)(fU)(mG)(fA)(mU)(fU)(mU)(fU)
(mG)(fA)#(mA)#(mG)#(mU)#(mC)#(mC) (SEQ ID NO: 837);

g) a sense strand comprising the sequence
(mC)#(mC)#(mA)(fG)(mG)(fU)(mG)(fG)(mA)
(fA)(mG)(mU)(mA)(fA)#(mA)#(mA)-DIO (SEQ ID NO: 853) and an antisense
strand comprising the sequence

V(mU)#(fU)#(mU)(fU)(fA)(fC)(mU)(fU)(mC)(fC)(mA)(fC)(mC)(fU)
(mG)(fG)#(mC)#(mC)#(mA)#(mC)#(mC) (SEQ ID NO: 838);

h) a sense strand comprising the sequence (mA)#(mU)#(mG)(fA)(mG)(fA)(mG)(fA)
(mG)(fU)(mG)(mU)(mG)(fG)#(mA)#(mA)-DIO (SEQ ID NO: 854) and an antisense
strand comprising the sequence
V(mU)#(fU)#(mC)(fC)(fA)(fC)(mA)(fC)(mU)(fC)(mU)(fC)(mU)(fC)
(mA)(fU)#(mU)#(mC)#(mU)#(mC)#(mU) (SEQ ID NO: 839);

i) a sense strand comprising the sequence (mA)#(mG)#(mG)(fA)(mG)(fA)(mG)(fA)
(mA)(fU)(mG)(mA)(mG)(fA)#(mG)#(mA)-DIO (SEQ ID NO: 855) and an antisense
strand comprising the sequence
V(mU)#(fC)#(mU)(fC)(fU)(fC)(mA)(fU)(mU)(fC)(mU)(fC)(mU)(fC)
(mC)(fU)#(mC)#(mU)#(mC)#(mC)#(mA) (SEQ ID NO: 840);

j) a sense strand comprising the sequence (mU)#(mC)#(mU)(fU)(mU)(fC)(mC)(fA)
(mA)(fA)(mU)(mU)(mG)(fA)#(mU)#(mA)-DIO (SEQ ID NO: 856) and an antisense
strand comprising the sequence
V(mU)#(fA)#(mU)(fC)(fA)(fA)(mU)(fU)(mU)(fG)(mG)(fA)(mA)(fA)(mG)
(fA)#(mU)#(mG)#(mA)#(mA)#(mA) (SEQ ID NO: 841);

k) a sense strand comprising the sequence
(mG)#(mG)#(mU)(fG)(mG)(fA)(mA)(fG)(mU)
(fA)(mA)(mA)(mA)(fU)#(mC)#(mA)-DIO (SEQ ID NO: 857) and an antisense
strand comprising the sequence
V(mU)#(fG)#(mA)(fU)(fU)(fU)(mU)(fA)(mC)(fU)(mU)(fC)(mC)
(fA)(mC)(fC)#(mU)#(mG)#(mG)#(mC)#(mC) (SEQ ID NO: 842);

l) a sense strand comprising the sequence (mA)#(mG)#(mA)(fA)(mU)(fG)(mA)(fG)
(mA)(fG)(mA)(mG)(mU)(fG)#(mU)#(mA)-DIO (SEQ ID NO: 858) and an antisense
strand comprising the sequence
V(mU)#(fA)#(mC)(fA)(fC)(fU)(mC)(fU)(mC)(fU)(mC)(fA)(mU)(fU)(mC)(fU)#(mC
)# (mU)#(mC)#(mC)#(mU) (SEQ ID NO: 843);

m) a sense strand comprising the sequence (mU)#(mG)#(mA)(fG)(mA)(fG)(mA)(fG)
(mU)(fG)(mU)(mG)(mG)(fA)#(mA)#(mA)-DIO (SEQ ID NO: 859) and an antisense
strand comprising the sequence
V(mU)#(fU)#(mU)(fC)(fC)(fA)(mC)(fA)(mC)(fU)(mC)(fU)(mC)(fU)
(mC)(fA)#(mU)#(mU)#(mC)#(mU)#(mC) (SEQ ID NO: 844);

n) a sense strand comprising the sequence (mA)#(mC)#(mU)(fU)(mC)(fA)(mA)(fA)(mA)(fU)(mC)(mA)(mG)(fU)#(mG)#(mA)-DIO (SEQ ID NO: 860) and an antisense strand comprising the sequence VP(mU)#(fC)#(mA)(fC)(fU)(fG)(mA)(fU)(mU)(fU)(mU)(fG)(mA)(fA)(mG)(fU)#(mC)#(mC)#(mC)#(mG)#(mA) (SEQ ID NO: 845); or

o) a sense strand comprising the sequence (mG)#(mC)#(mA)(fA)(mA)(fU)(mU)(fU)(mC)(fA)(mU)(mC)(mU)(fU)#(mU)#(mA)-DIO (SEQ ID NO: 861) and an antisense strand comprising the sequence VP(mU)#(fA)#(mA)(fA)(fG)(fA)(mU)(fG)(mA)(fA)(mA)(fU)(mU)(fU)(mG)(fC)#(mU)#(mC)#(mU)#(mU)#(mA) (SEQ ID NO: 846),

wherein m represents a 2'-O-Me ribonucleoside, f represents a 2'-F ribonucleoside, # represents a phosphorothioate internucleoside linkage, -DIO represents a divalent oligonucleotide (DIO) linker; and V represents a vinyl phosphonate.

[0004] In another aspect, the disclosure features a small interfering RNA (siRNA) molecule comprising an antisense strand and sense strand having complementarity to the antisense strand. The antisense strand may be, e.g., from 10 to 30 nucleotides in length and may have complementarity sufficient to hybridize to a region within a microtubule-associated protein tau (*MAPT*) mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0005] In some embodiments, the antisense strand has at least 70% complementarity to a region of 21 contiguous nucleobases within the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816. In some embodiments, the antisense strand has at least 75% complementarity to a region of 21 contiguous nucleobases within the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816. In some embodiments, the antisense strand has at least 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementarity to the region within the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID Nos: 409-816.

[0006] In some embodiments, the antisense strand comprises at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0007] In some embodiments, the antisense strand comprises from 10 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0008] In some embodiments, the antisense strand comprises from 12 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0009] In some embodiments, the antisense strand comprises from 15 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0010] In some embodiments, the antisense strand comprises from 18 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0011] In some embodiments, the antisense strand comprises from 21 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0012] In some embodiments, the antisense strand comprises from 24 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0013] In some embodiments, the antisense strand comprises 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0014] In some embodiments, the antisense strand comprises 9 or fewer nucleotide mismatches relative to a region of 21 contiguous nucleobases of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816. In some embodiments, the antisense strand comprises 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or only 1 mismatch relative to the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0015] In some embodiments, the region of the *MAPT* mRNA transcript has the nucleic acid sequence of any one of SEQ ID NOs: 817-831.

[0016] In some embodiments, the region of the *MAPT* mRNA transcript has the nucleic acid sequence of any one of SEQ ID NOs: 817-821, 823-825, and 827-830.

[0017] In some embodiments, the antisense strand has a nucleic acid sequence that is at least 85% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-408.

[0018] In some embodiments, the antisense strand has a nucleic acid sequence that is at least 90% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-408.

[0019] In some embodiments, the antisense strand has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of SEQ ID NOs: 1-408. In some embodiments, the antisense strand has a nucleic acid sequence that is at least 96%, 97%, 98%, or 99% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-408.

[0020] In some embodiments, the antisense strand has the nucleic acid sequence of any one of SEQ ID NOs: 1-408.

[0021] In some embodiments, the nucleic acid sequence is any one of SEQ ID NOs: 834-846.

[0022] In some embodiments, the nucleic acid sequence is any one of SEQ ID NOs: 834-836, 838-840, and 842-845.

[0023] In some embodiments, the sense strand has a nucleic acid sequence that is at least 85% identical to the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0024] In some embodiments, the sense strand has a nucleic acid sequence that is at least 90% identical to the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0025] In some embodiments, the sense strand has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of SEQ ID NOs: 409-816. In some embodiments, the sense strand has a nucleic acid sequence that is at least 96%, 97%, 98%, or 99% identical to the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0026] In some embodiments, the sense strand has the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0027] In some embodiments, the nucleic acid sequence is any one of SEQ ID NOs: 817-831.

[0028] In some embodiments, the nucleic acid sequence is any one of SEQ ID NOs: 817-821, 823-825, and 827-830.

[0029] In some embodiments, the antisense strand comprises a structure represented by Formula I, wherein Formula I is, in the 5'-to-3' direction:

$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C'\text{-}P^1)_k\text{-}C'$

Formula I;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;

each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;

B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$;

each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;

each D is a 2'-F ribonucleoside;

each P^1 is a phosphorothioate internucleoside linkage;

each P^2 is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7; and

k is an integer from 1 to 7.

[0030] In some embodiments, the antisense strand comprises a structure represented by Formula A1, wherein Formula A1 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0031] In some embodiments, the antisense strand comprises a structure represented by Formula II, wherein Formula II is, in the 5'-to-3' direction:

$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C\text{-}P^1)_k\text{-}C'$

Formula II;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;

each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;

B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$;

each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;

each D is a 2'-F ribonucleoside;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7; and
k is an integer from 1 to 7.

[0032] In some embodiments, the antisense strand comprises a structure represented by Formula A2, wherein Formula A2 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-A-S-A

Formula A2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0033] In some embodiments, the sense strand comprises a structure represented by Formula III, wherein Formula III is, in the 5'-to-3' direction:

$$E\text{-}(A')_m\text{-}F$$

Formula III;

wherein E is represented by the formula $(C\text{-}P^1)_2$;
F is represented by the formula $(C\text{-}P^2)_3\text{-}D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $(C\text{-}P^2)_3\text{-}D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $(C\text{-}P^2)_3\text{-}D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $(C\text{-}P^2)_3\text{-}D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$;
A', C, D, P^1, and P^2 are as defined in Formula II; and
m is an integer from 1 to 7.

[0034] In some embodiments, the sense strand comprises a structure represented by Formula S1, wherein Formula S1 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-A

Formula S1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0035] In some embodiments, the sense strand comprises a structure represented by Formula S2, wherein Formula S2 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-A

Formula S2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0036] In some embodiments, the sense strand comprises a structure represented by Formula S3, wherein Formula S3 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-B

Formula S3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0037] In some embodiments, the sense strand comprises a structure represented by Formula S4, wherein Formula S4 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-B

Formula S4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0038] In some embodiments, the antisense strand comprises a structure represented by Formula IV, wherein Formula IV is, in the 5'-to-3' direction:

$A\text{-}(A')_j\text{-}C\text{-}P^2\text{-}B\text{-}(C\text{-}P^1)_k\text{-}C'$

Formula IV;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;

each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;

B is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D\text{-}P^1$;

each C is a 2'-O-Me ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;

each D is a 2'-F ribonucleoside;

each P^1 is a phosphorothioate internucleoside linkage;

each P^2 is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7; and

k is an integer from 1 to 7.

[0039] In some embodiments, the antisense strand comprises a structure represented by Formula A3, wherein Formula A3 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B-S-A-S-A-S-A

Formula A3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0040] In some embodiments, the sense strand comprises a structure represented by Formula V, wherein Formula V is, in the 5'-to-3' direction:

$$E\text{-}(A')_m\text{-}C\text{-}P^2\text{-}F$$

Formula V;

wherein E is represented by the formula $(C\text{-}P^1)_2$;
F is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$;
A', C, D, P^1 and P^2 are as defined in Formula IV; and
m is an integer from 1 to 7.

[0041] In some embodiments, the sense strand comprises a structure represented by Formula S5, wherein Formula S5 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A

Formula S5;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0042] In some embodiments, the sense strand comprises a structure represented by Formula S6, wherein Formula S6 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A

Formula S6;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0043] In some embodiments, the sense strand comprises a structure represented by Formula S7, wherein Formula S7 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B

Formula S7;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0044] In some embodiments, the sense strand comprises a structure represented by Formula S8, wherein Formula S8 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B

Formula S8;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0045] In some embodiments, the antisense strand comprises a structure represented by Formula VI, wherein Formula VI is, in the 5'-to-3' direction:

$$A\text{-}B_j\text{-}E\text{-}B_k\text{-}E\text{-}F\text{-}G_l\text{-}D\text{-}P^1\text{-}C'$$

Formula VI;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;

each B is represented by the formula $C\text{-}P^2$;

each C is a 2'-O-Me ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;

each D is a 2'-F ribonucleoside;

each E is represented by the formula $D\text{-}P^2\text{-}C\text{-}P^2$;

F is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1$;

each G is represented by the formula $C\text{-}P^1$;

each P^1 is a phosphorothioate internucleoside linkage;

each P^2 is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7;

k is an integer from 1 to 7; and

l is an integer from 1 to 7.

[0046] In some embodiments, the antisense strand comprises a structure represented by Formula A4, wherein Formula A4 is, in the 5'-to-3' direction:

A-S-B-S-A-O-A-O-A-O-B-O-A-O-A-O-A-O-A-O-A-O-A-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0047] In some embodiments, the sense strand comprises a structure represented by Formula VII, wherein Formula VII is, in the 5'-to-3' direction:

$$H\text{-}B_m\text{-}I_n\text{-}A'\text{-}B_o\text{-}H\text{-}C$$

Formula VII;

wherein A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;

each H is represented by the formula $(C\text{-}P^1)_2$;

each I is represented by the formula $(D\text{-}P^2)$;

B, C, D, P^1 and P^2 are as defined in Formula VI;

m is an integer from 1 to 7;

n is an integer from 1 to 7; and

o is an integer from 1 to 7.

[0048] In some embodiments, the sense strand comprises a structure represented by Formula S9, wherein Formula S9 is, in the 5'-to-3' direction:

A-S-A-S-A-O-A-O-A-O-B-O-B-O-B-O-A-O-B-O-A-O-A-O-A-O-A-S-A-S-A

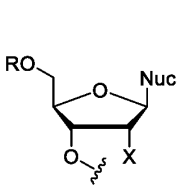
Formula S9;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

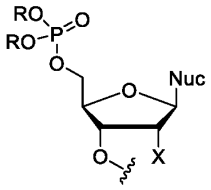
[0049] In some embodiments, the antisense strand further comprises a 5' phosphorus stabilizing moiety at the 5' end of the antisense strand.

[0050] In some embodiments, the sense strand further comprises a 5' phosphorus stabilizing moiety at the 5' end of the sense strand.

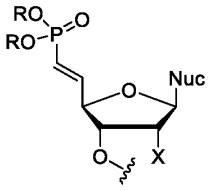
[0051] In some embodiments, each 5' phosphorus stabilizing moiety is, independently, represented by any one of Formulas IX-XVI:



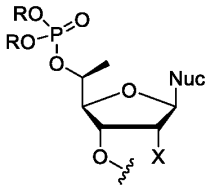
Formula IX



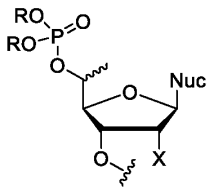
Formula X



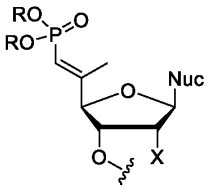
Formula XI



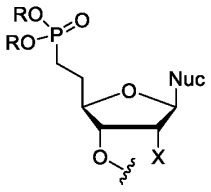
Formula XII



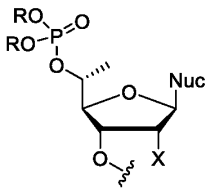
Formula XIII



Formula XIV



Formula XV



Formula XVI

wherein Nuc represents a nucleobase selected from the group consisting of adenine, uracil, guanine, thymine, and cytosine, and R represents an optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, phenyl, benzyl, hydroxy, or hydrogen.

[0052] In some embodiments, the nucleobase is an adenine, uracil, guanine, thymine, or cytosine.

[0053] In some embodiments, the 5' phosphorus stabilizing moiety is (E)-vinylphosphonate represented by Formula XI.

[0054] In some embodiments, the siRNA molecule further comprises a hydrophobic moiety at the 5' or the 3' end of the siRNA molecule.

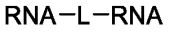
[0055] In some embodiments, the hydrophobic moiety is selected from a group consisting of cholesterol, vitamin D, or tocopherol.

[0056] In some embodiments, the length of the sense strand is between 12 and 30 nucleotides.

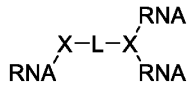
[0057] In some embodiments, the siRNA molecule is a branched siRNA molecule.

[0058] In some embodiments, the branched siRNA molecule is di-branched, tri-branched, or tetra-branched.

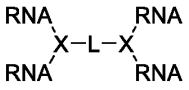
[0059] In some embodiments, the siRNA molecule is a di-branched siRNA molecule. In some embodiments, the di-branched siRNA molecule is represented by any one of Formulas XVII-XIX:



Formula XVII;



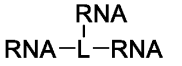
Formula XVIII;



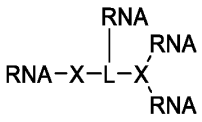
Formula XIX;

wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

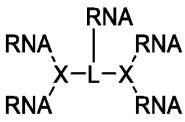
[0060] In some embodiments, the siRNA molecule is a tri-branched siRNA molecule, optionally wherein the tri-branched siRNA molecule is represented by any one of Formulas XX-XXIII:



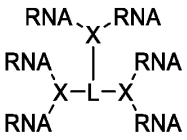
Formula XX;



Formula XXI;



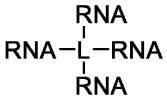
Formula XXII;

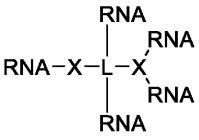


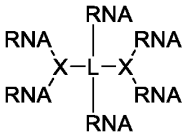
Formula XXIII;

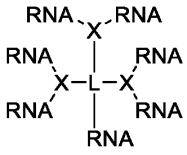
wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

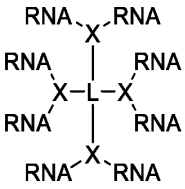
[0061] In some embodiments, the siRNA molecule is a tetra-branched siRNA molecule, optionally wherein the tetra-branched siRNA molecule is represented by any one of Formulas XXIV-XXVIII:











Formula XXIV; Formula XXV; Formula XXVI; Formula XXVII; Formula XXVIII;

wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

[0062] In some embodiments, the linker is selected from a group consisting of one or more contiguous subunits of an ethylene glycol, alkyl, carbohydrate, block copolymer, peptide, RNA, and DNA.

[0063] In some embodiments, the one or more contiguous subunits is 2 to 20 contiguous subunits.

[0064] In another aspect, the disclosure features a pharmaceutical composition comprising the siRNA molecule of any of the foregoing aspects or embodiments of the disclosure, in combination with a pharmaceutically acceptable excipient, carrier, or diluent.

[0065] In another aspect, the disclosure features a method of delivering an siRNA molecule to a subject diagnosed as having a tauopathy, the method comprising administering to the subject a therapeutically effective amount of the siRNA molecule of any of the foregoing aspects or embodiments of the disclosure, optionally in combination with a pharmaceutically acceptable excipient, carrier, or diluent.

[0066] In another aspect, the disclosure features a method of treating a tauopathy in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the siRNA molecule of any of the foregoing aspects or embodiments of the disclosure, optionally in combination with a pharmaceutically acceptable excipient, carrier, or diluent.

[0067] In some embodiments, the tauopathy is Alzheimer's disease. In some embodiments, the tauopathy is frontotemporal dementia. In some embodiments, the tauopathy is progressive supranuclear palsy. In some embodiments, the tauopathy is corticobasal degeneration.

[0068] In another aspect, the disclosure features a method of reducing *MAPT* expression in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the siRNA molecule of any of the foregoing aspects or embodiments of the disclosure, optionally in combination with a pharmaceutically acceptable excipient, carrier, or diluent.

[0069] In some embodiments, the siRNA molecule or the pharmaceutical composition is administered to the subject by way of intracerebroventricular, intrastriatal, intraparenchymal, or intrathecal injection. In some embodiments, the siRNA molecule or the pharmaceutical composition is administered to the subject by way of intravenous, intramuscular, or subcutaneous injection.

[0070] In some embodiments, the subject is a human.

[0071] In a further aspect, the disclosure features a kit comprising (a) the siRNA molecule of any of the foregoing aspects or embodiments of the disclosure, optionally in combination with

a pharmaceutically acceptable excipient, carrier, or diluent, and (b) a package insert. In some embodiments, the package insert instructs a user of the kit to perform the method of any of the above aspects or embodiments of the disclosure.

4. BRIEF DESCRIPTION OF THE FIGURES

[0072] FIG. 1A is a graph showing reduction in MAPT mRNA in hMAPT mice in frontal cortex (fCTx), striatum (Cpu), thalamus (Thal), temporal cortex (tCTx), and hippocampus (Hp) at 1, 2, 3, or 4 months after administration of a di-siRNA molecule of the disclosure.

[0073] FIG. 1B is a graph showing reduction in MAPT mRNA in hMAPT mice in Midbrain (Mb), Pons, medulla (Med), and cerebellum (Cb) at 1, 2, 3, or 4 months after administration of a di-siRNA molecule of the disclosure.

[0074] FIG. 1C is a graph showing reduction in MAPT mRNA in hMAPT mice in cervical spinal cord (SC-C), thoracic spinal cord (SC-T), and lumbar spinal cord (SC-L) at 1, 2, 3, or 4 months after administration of a di-siRNA molecule of the disclosure.

[0075] FIG. 2A is a graph showing reduction in MAPT protein in hMAPT mice in fCTx, tCTx, Cpu, Hp, Thal, Cb, and Mb at 1, 2, 3, or 4 months after administration of a di-siRNA molecule of the disclosure.

[0076] FIG. 2B is a graph showing reduction in MAPT protein in hMAPT mice in Med, Pons, SC-C, SC-T, and SC-L at 1, 2, 3, or 4 months after administration of a di-siRNA molecule of the disclosure.

5. DETAILED DESCRIPTION

[0077] The instant application is directed to single- or double-stranded interfering RNA molecules (e.g., siRNA) that target a MAPT gene. The interfering RNA molecules may contain specific patterns of nucleoside modifications and internucleoside linkage modifications, as pharmaceutical compositions including the same. The siRNA molecules may be branched siRNA molecules, such as di-branched, tri-branched, or tetra-branched siRNA molecules. The disclosed siRNA molecules may further feature a 5' phosphorus stabilizing moiety and/or a hydrophobic moiety. Additionally, the disclosure provides methods for delivering the siRNA molecule of the disclosure to the central nervous system of a subject, such as a subject identified as having a tauopathy

5.1. Definitions

[0078] Unless otherwise defined herein, scientific, and technical terms used herein have the meanings that are commonly understood by those of ordinary skill in the art. In the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The use of "or" means "and/or" unless stated otherwise. The use of the term "including," as well as other forms, such as "includes" and "included," is not limiting.

[0079] As used herein, the term "nucleic acids" refers to RNA or DNA molecules consisting of a chain of ribonucleotides or deoxyribonucleotides, respectively. As used herein, the term "therapeutic nucleic acid" refers to a nucleic acid molecule (e.g., ribonucleic acid) that has partial or complete complementarity to, and interacts with, a disease-associated target mRNA and mediates silencing of expression of the mRNA.

[0080] As used herein, the term "carrier nucleic acid" refers to a nucleic acid molecule (e.g., ribonucleic acid) that has sequence complementarity with, and hybridizes with, a therapeutic nucleic acid. As used herein, the term "3' end" refers to the end of the nucleic acid that contains an unmodified hydroxyl group at the 3' carbon of the ribose ring.

[0081] As used herein, the term "nucleoside" refers to a molecule made up of a heterocyclic base and its sugar.

[0082] As used herein, the term "nucleotide" refers to a nucleoside having a phosphate group on its 3' or 5' sugar hydroxyl group.

[0083] As used herein, the term "siRNA" refers to small interfering RNA duplexes that induce the RNA interference (RNAi) pathway. siRNA molecules can vary in length (generally, between 18 and 30 base pairs) and contain varying degrees of complementarity to their target mRNA. The term "siRNA" includes duplexes of two separate strands, as well as single strands that optionally form hairpin structures including a duplex region.

[0084] As used herein, the term "antisense strand" refers to the strand of the siRNA duplex that contains some degree of complementarity to the target gene.

[0085] As used herein, the term "sense strand" refers to the strand of the siRNA duplex that contains complementarity to the antisense strand.

[0086] As used herein, the terms "chemically modified nucleotide" refers to a non-standard nucleotide, including non-naturally occurring ribonucleotides or deoxyribonucleotides. Exemplary chemically modified nucleotides are modified at any position so as to alter certain

chemical properties of the nucleotide yet retain the ability of the chemically modified nucleotide to perform its intended function.

[0087] As used herein, the term "metabolically stabilized" refers to RNA molecules that contain ribonucleotides that have been chemically modified from 2'-hydroxyl groups to 2'-O-methyl groups , 2' fluoro groups, or other modifications known in the art to stabilized RNA to enzymatic and/or non-enzymatic degradation.

[0088] As used herein, the term "phosphorothioate" refers to a phosphate group of a nucleotide that is modified by substituting one or more of the oxygens of the phosphate group with sulfur.

[0089] As used herein, the term "ethylene glycol chain" refers to a carbon chain with the formula $((CH_2OH)_2)$.

[0090] As used herein, "alkyl" refers to a saturated hydrocarbon group. Alkyl groups may be acyclic or cyclic and contain only C and H when unsubstituted. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, "butyl" is meant to include n-butyl, sec-butyl, and iso-butyl. Examples of alkyl include ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. In some embodiments, alkyl may be substituted. Suitable substituents that may be introduced into an alkyl group include, for example, hydroxy, alkoxy, amino, alkylamino, and halo, among others.

[0091] As used herein, "alkenyl" refers to an acyclic or cyclic unsaturated hydrocarbon group having at least one site of olefinic unsaturation (i.e., having at least one moiety of the formula C=C). Alkenyl groups contain only C and H when unsubstituted. When an alkenyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, "butenyl" is meant to include n-butenyl, sec-butenyl, and iso-butenyl. Examples of alkenyl include $–CH=CH_2$, $–CH_2-CH=CH_2$, and $–CH_2-CH=CH-CH=CH_2$. In some embodiments, alkenyl may be substituted. Suitable substituents that may be introduced into an alkenyl group include, for example, hydroxy, alkoxy, amino, alkylamino, and halo, among others.

[0092] As used herein, "alkynyl" refers to an acyclic or cyclic unsaturated hydrocarbon group having at least one site of acetylenic unsaturation (i.e., having at least one moiety of the formula C≡C). Alkynyl groups contain only C and H when unsubstituted. When an alkynyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, "pentynyl" is meant to include n-pentynyl, sec-pentynyl, iso-pentynyl, and tert-pentynyl. Examples of alkynyl

include –C≡CH and –C≡C-CH_3. In some embodiments, alkynyl may be substituted. Suitable substituents that may be introduced into an alkynyl group include, for example, hydroxy, alkoxy, amino, alkylamino, and halo, among others.

[0093] As used herein the term "phenyl" denotes a monocyclic arene in which one hydrogen atom from a carbon atom of the ring has been removed. A phenyl group can be unsubstituted or substituted with one or more suitable substituents, wherein the substituent replaces an H of the phenyl group.

[0094] As used herein, the term “benzyl” refers to monovalent radical obtained when a hydrogen atom attached to the methyl group of toluene is removed. A benzyl generally has the formula of phenyl-CH_2-.

[0095] A benzyl group can be unsubstituted or substituted with one or more suitable substituents. For example, the substituent may replace an H of the phenyl component and/or an H of the methylene (-CH_2-) component.

[0096] As used herein, the term "amide" refers to an alkyl, alkenyl, alkynyl, or aromatic group that is attached to an amino-carbonyl functional group.

[0097] As used herein, the term "internucleoside" and "internucleotide" refer to the bonds between nucleosides and nucleotides, respectively.

[0098] As used herein, the term "triazol" refers to heterocyclic compounds with the formula ($C_2H_3N_3$), having a five-membered ring of two carbons and three nitrogens, the positions of which can change resulting in multiple isomers.

[0099] As used herein, the term "terminal group" refers to the group at which a carbon chain or nucleic acid ends.

[0100] As used herein, the term "lipophilic amino acid" refers to an amino acid including a hydrophobic moiety (e.g., an alkyl chain or an aromatic ring).

[0101] As used herein, the term "target of delivery" refers to the organ or part of the body that is desired to deliver the branched oligonucleotide compositions to.

[0102] As used herein, the term “branched siRNA” refers to a compound containing two or more double-stranded siRNA molecules covalently bound to one another. Branched siRNA molecules may be “di-branched,” also referred to herein as “di-siRNA,” wherein the siRNA molecule includes 2 siRNA molecules covalently bound to one another, e.g., by way of a linker. Branched siRNA molecules may be “tri-branched,” also referred to herein as “tri-siRNA,” wherein the siRNA molecule includes 3 siRNA molecules covalently bound to one another, e.g., by way of a linker. Branched siRNA molecules may be “tetra-branched,” also referred to

herein as “tetra-siRNA,” wherein the siRNA molecule includes 4 siRNA molecules covalently bound to one another, e.g., by way of a linker.

[0103] As used herein, the term “branch point moiety” refers to a chemical moiety of a branched siRNA structure of the disclosure that may be covalently linked to a 5’ end or a 3’ end of an antisense strand or a sense strand of an siRNA molecule and which may support the attachment of additional single- or double-stranded siRNA molecules. Non-limiting examples of branch point moieties suitable for use in conjunction with the disclosed methods and compositions include, e.g., phosphoroamidite, tosylated solketal, 1,3-diaminopropanol, pentaerythritol, and any one of the branch point moieties described in US 10,478,503.

[0104] As used herein, the term “5′ phosphorus stabilizing moiety” refers to a terminal phosphate group that includes phosphates as well as modified phosphates (e.g., phosphorothioates, phosphodiesters, phosphonates). The phosphate moiety can be located at either terminus, e.g., at the 5′-terminal nucleoside. In one aspect, the terminal phosphate is unmodified having the formula –O–P(=O)(OH)OH. In another aspect, the terminal phosphate is modified such that one or more of the O and OH groups are replaced with H, O, S, N(R’), or alkyl where R’ is H, an amino protecting group, or unsubstituted or substituted alkyl. In some embodiments, the 5′ and or 3′ terminal group can include from 1 to 3 phosphate moieties that are each, independently, unmodified (di- or tri-phosphates) or modified.

[0105] As used herein, the term “between X and Y” is inclusive of the values of X and Y. For example, “between X and Y” refers to the range of values between the value of X and the value of Y, as well as the value of X and the value of Y.

[0106] As used herein, an "amino acid" refers to a molecule containing amine and carboxyl functional groups and a side chain specific to the amino acid.

[0107] In some embodiments the amino acid is chosen from the group of proteinogenic amino acids. In some embodiments, the amino acid is an L-amino acid or a D-amino acid. In some embodiments, the amino acid is a synthetic amino acid (e.g., a beta-amino acid).

[0108] It is understood that certain internucleoside linkages provided herein, including, e.g., phosphodiester and phosphorothioate, include a formal charge of -1 at physiological pH, and that said formal charge will be balanced by a cationic moiety, e.g., an alkali metal such as sodium or potassium, an alkali earth metal such as calcium or magnesium, or an ammonium or guanidinium ion.

[0109] The phosphate group of the nucleotide may also be modified, e.g., by substituting one or more of the oxygens of the phosphate group with sulfur (e.g., phosphorothioates), or by making other substitutions which allow the nucleotide to perform its intended function such as

described in, for example, Eckstein, *Antisense Nucleic Acid Drug Dev.* 10:117-21, 2000; Rusckowski et al., *Antisense Nucleic Acid Drug Dev.* 10:333-45, 2000; Stein, *Antisense Nucleic Acid Drug Dev.* 11:317-25, 2001; Vorobjev et al., *Antisense Nucleic Acid Drug Dev.* 11:77-85, 2001; and US 5,684,143. Certain of the above-referenced modifications (e.g., phosphate group modifications) can decrease the rate of hydrolysis of, for example, polynucleotides including said modifications *in vivo* or *in vitro*.

[0110] As used herein, the term "complementary" refers to two nucleotides that form canonical Watson-Crick base pairs. For the avoidance of doubt, Watson-Crick base pairs in the context of the present disclosure include adenine-thymine, adenine-uracil, and cytosine-guanine base pairs. A proper Watson-Crick base pair is referred to in this context as a "match," while each unpaired nucleotide, and each incorrectly paired nucleotide, is referred to as a "mismatch." Alignment for purposes of determining percent nucleic acid sequence complementarity can be achieved in various ways that are within the capabilities of one of skill in the art, for example, using publicly available computer software such as BLAST, BLAST-2, or Megalign software.

[0111] "Percent (%) sequence complementarity" with respect to a reference polynucleotide sequence is defined as the percentage of nucleic acids in a candidate sequence that are complementary to the nucleic acids in the reference polynucleotide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence complementarity. A given nucleotide is considered to be "complementary" to a reference nucleotide as described herein if the two nucleotides form canonical Watson-Crick base pairs. For the avoidance of doubt, Watson-Crick base pairs in the context of the present disclosure include adenine-thymine, adenine-uracil, and cytosine-guanine base pairs. A proper Watson-Crick base pair is referred to in this context as a "match," while each unpaired nucleotide, and each incorrectly paired nucleotide, is referred to as a "mismatch." Alignment for purposes of determining percent nucleic acid sequence complementarity can be achieved in various ways that are within the capabilities of one of skill in the art, for example, using publicly available computer software such as BLAST, BLAST-2, or Megalign software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal complementarity over the full length of the sequences being compared. As an illustration, the percent sequence complementarity of a given nucleic acid sequence, A, to a given nucleic acid sequence, B, (which can alternatively be phrased as a given nucleic acid sequence, A that has a certain percent complementarity to a given nucleic acid sequence, B) is calculated as follows:

100 multiplied by (the fraction X/Y)

where X is the number of complementary base pairs in an alignment (e.g., as executed by computer software, such as BLAST) in that program's alignment of A and B, and where Y is the total number of nucleic acids in B. It will be appreciated that where the length of nucleic acid sequence A is not equal to the length of nucleic acid sequence B, the percent sequence complementarity of A to B will not equal the percent sequence complementarity of B to A. As used herein, a query nucleic acid sequence is considered to be "completely complementary" to a reference nucleic acid sequence if the query nucleic acid sequence has 100% sequence complementarity to the reference nucleic acid sequence.

[0112] The term "gene silencing" refers to the suppression of gene expression, e.g., transgene, heterologous gene and/or endogenous gene expression, which may be mediated through processes that affect transcription and/or through processes that affect post-transcriptional mechanisms. In some embodiments, gene silencing occurs when an RNAi molecule initiates the inhibition or degradation of the mRNA transcribed from a gene of interest in a sequence-specific manner via RNA interference, thereby preventing translation of the gene's product.

[0113] The phrase "overactive disease driver gene," as used herein, refers to a gene having increased activity and/or expression that contributes to or causes a disease state in a subject (e.g., a human). The disease state may be caused or exacerbated by the overactive disease driver gene directly or by way of an intermediate gene(s).

[0114] The term "negative regulator," as used herein, refers to a gene that negatively regulates (e.g., reduces or inhibits) the expression and/or activity of another gene or set of genes.

[0115] The term "positive regulator," as used herein, refers to a gene that positively regulates (e.g., increases or saturates) the expression and/or activity of another gene or set of genes.

[0116] The term "phosphate moiety" as used herein, refers to a terminal phosphate group that includes phosphates as well as modified phosphates. The phosphate moiety can be located at either terminus, e.g., at the 5′-terminal nucleoside. In one aspect, the terminal phosphate is unmodified having the formula —O—P(═O)(OH)OH. In another aspect, the terminal phosphate is modified such that one or more of the O and OH groups are replaced with H, O, S, N(R') or alkyl where R' is H, an amino protecting group or unsubstituted or substituted alkyl. In some embodiments, the 5′ and or 3′ terminal group can include from 1 to 3 phosphate moieties that are each, independently, unmodified (di or tri-phosphates) or modified.

[0117] In the context of the instant disclosure, the term "oligonucleotide" refers to an oligomer or polymer of ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) or other nucleic acids.

This term includes oligonucleotides composed of naturally-occurring nucleobases, sugars and covalent internucleoside (backbone) linkages as well as oligonucleotides having non-naturally-occurring (e.g., modified) portions that function similarly. Such chemically modified oligonucleotides can exhibit desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases.

[0118] The term "treatment" refers to clinical intervention designed to alter the natural course of the patient or cell being treated during the course of clinical pathology. Desirable effects of treatment include decreasing the rate of disease progression, ameliorating or palliating the disease state, and remission or improved prognosis. For example, a patient is successfully "treated" if one or more symptoms associated with a synucleinopathy described herein are mitigated or eliminated, including, but are not limited to, decreasing symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, and/or prolonging survival of patients.

[0119] The term "delaying progression" of a disease refers to deferring, hindering, slowing, retarding, stabilizing, and/or postponing development of a cancer described herein. This delay can be of varying lengths of time, depending on the history of the synucleinopathy and/or patient being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the patient does not develop a synucleinopathy or relapse.

5.2. Anti-MAPT siRNAs

[0120] The instant application is directed to single- or double-stranded interfering RNA molecules (e.g., siRNA) targeting an MAPT gene. For example, but not by way of limitation, siRNA molecules targeting an MAPT gene can be designed to target an MAPT mRNA sequence.

[0121] In certain embodiments, the MAPT gene targeted by an siRNA of the instant disclosure expresses a mRNA comprising the sequence of NM_001123066.3 (Homo sapiens microtubule associated protein tau (MAPT), transcript variant 6, mRNA):
GGACGGCCGAGCGGCAGGGCGCTCGCGCGCGCCCACTAGTGGCCGGAGGAGAA
GGCTCCCGCGGAGGCCGCGCTGCCCGCCCCCTCCCCTGGGGAGGCTCGCGTTCCC
GCTGCTCGCGCCTGCGCCGCCCGCCGGCCTCAGGAACGCGCCCTCTTCGCCGGCG
CGCGCCCTCGCAGTCACCGCCACCCACCAGCTCCGGCACCAACAGCAGCGCCGC

TGCCACCGCCCACCTTCTGCCGCCGCCACCACAGCCACCTTCTCCTCCTCCGCTGT
CCTCTCCCGTCCTCGCCTCTGTCGACTATCAGGTGAACTTTGAACCAGGATGGCT
GAGCCCCGCCAGGAGTTCGAAGTGATGGAAGATCACGCTGGGACGTACGGGTTG
GGGGACAGGAAAGATCAGGGGGGCTACACCATGCACCAAGACCAAGAGGGTGA
CACGGACGCTGGCCTGAAAGAATCTCCCCTGCAGACCCCCACTGAGGACGGATC
TGAGGAACCGGGCTCTGAAACCTCTGATGCTAAGAGCACTCCAACAGCGGAAGA
TGTGACAGCACCCTTAGTGGATGAGGGAGCTCCCGGCAAGCAGGCTGCCGCGCA
GCCCCACACGGAGATCCCAGAAGGAACCACAGCTGAAGAAGCAGGCATTGGAG
ACACCCCCAGCCTGGAAGACGAAGCTGCTGGTCACGTGACCCAAGAGCCTGAAA
GTGGTAAGGTGGTCCAGGAAGGCTTCCTCCGAGAGCCAGGCCCCCCAGGTCTGA
GCCACCAGCTCATGTCCGGCATGCCTGGGGCTCCCCTCCTGCCTGAGGGCCCCAG
AGAGGCCACACGCCAACCTTCGGGGACAGGACCTGAGGACACAGAGGGCGGCC
GCCACGCCCCTGAGCTGCTCAAGCACCAGCTTCTAGGAGACCTGCACCAGGAGG
GGCCGCCGCTGAAGGGGGCAGGGGGCAAAGAGAGGCCGGGGAGCAAGGAGGA
GGTGGATGAAGACCGCGACGTCGATGAGTCCTCCCCCCAAGACTCCCCTCCCTCC
AAGGCCTCCCCAGCCCAAGATGGGCGGCCTCCCCAGACAGCCGCCAGAGAAGCC
ACCAGCATCCCAGGCTTCCCAGCGGAGGGTGCCATCCCCCTCCCTGTGGATTTCC
TCTCCAAAGTTTCCACAGAGATCCCAGCCTCAGAGCCCGACGGGCCCAGTGTAG
GGCGGGCCAAAGGGCAGGATGCCCCCCTGGAGTTCACGTTTCACGTGGAAATCA
CACCCAACGTGCAGAAGGAGCAGGCGCACTCGGAGGAGCATTTGGGAAGGGCT
GCATTTCCAGGGGCCCCTGGAGAGGGGCCAGAGGCCCGGGGCCCCTCTTTGGGA
GAGGACACAAAAGAGGCTGACCTTCCAGAGCCCTCTGAAAAGCAGCCTGCTGCT
GCTCCGCGGGGGAAGCCCGTCAGCCGGGTCCCTCAACTCAAAGCTCGCATGGTC
AGTAAAAGCAAAGACGGGACTGGAAGCGATGACAAAAAAGCCAAGACATCCAC
ACGTTCCTCTGCTAAAACCTTGAAAAATAGGCCTTGCCTTAGCCCCAAACACCCC
ACTCCTGGTAGCTCAGACCCTCTGATCCAACCCTCCAGCCCTGCTGTGTGCCCAG
AGCCACCTTCCTCTCCTAAATACGTCTCTTCTGTCACTTCCCGAACTGGCAGTTCT
GGAGCAAAGGAGATGAAACTCAAGGGGGCTGATGGTAAAACGAAGATCGCCAC
ACCGCGGGGAGCAGCCCCTCCAGGCCAGAAGGGCCAGGCCAACGCCACCAGGA
TTCCAGCAAAAACCCCGCCCGCTCCAAAGACACCACCCAGCTCTGCGACTAAGC
AAGTCCAGAGAAGACCACCCCCTGCAGGGCCCAGATCTGAGAGAGGTGAACCTC
CAAAATCAGGGGATCGCAGCGGCTACAGCAGCCCCGGCTCCCCAGGCACTCCCG
GCAGCCGCTCCCGCACCCCGTCCCTTCCAACCCCACCCACCCGGGAGCCCAAGA
AGGTGGCAGTGGTCCGTACTCCACCCAAGTCGCCGTCTTCCGCCAAGAGCCGCCT

GCAGACAGCCCCCGTGCCCATGCCAGACCTGAAGAATGTCAAGTCCAAGATCGG
CTCCACTGAGAACCTGAAGCACCAGCCGGGAGGCGGGAAGGTGCAGATAATTAA
TAAGAAGCTGGATCTTAGCAACGTCCAGTCCAAGTGTGGCTCAAAGGATAATAT
CAAACACGTCCCGGGAGGCGGCAGTGTGCAAATAGTCTACAAACCAGTTGACCT
GAGCAAGGTGACCTCCAAGTGTGGCTCATTAGGCAACATCCATCATAAACCAGG
AGGTGGCCAGGTGGAAGTAAAATCTGAGAAGCTTGACTTCAAGGACAGAGTCCA
GTCGAAGATTGGGTCCCTGGACAATATCACCCACGTCCCTGGCGGAGGAAATAA
AAAGATTGAAACCCACAAGCTGACCTTCCGCGAGAACGCCAAAGCCAAGACAGA
CCACGGGGCGGAGATCGTGTACAAGTCGCCAGTGGTGTCTGGGGACACGTCTCC
ACGGCATCTCAGCAATGTCTCCTCCACCGGCAGCATCGACATGGTAGACTCGCCC
CAGCTCGCCACGCTAGCTGACGAGGTGTCTGCCTCCCTGGCCAAGCAGGGTTTGT
GATCAGGCCCCTGGGGCGGTCAATAATTGTGGAGAGGAGAGAATGAGAGAGTGT
GGAAAAAAAAAGAATAATGACCCGGCCCCCGCCCTCTGCCCCCAGCTGCTCCTC
GCAGTTCGGTTAATTGGTTAATCACTTAACCTGCTTTTGTCACTCGGCTTTGGCTC
GGGACTTCAAAATCAGTGATGGGAGTAAGAGCAAATTTCATCTTTCCAAATTGAT
GGGTGGGCTAGTAATAAAATATTTAAAAAAAAACATTCAAAAACATGGCCACAT
CCAACATTTCCTCAGGCAATTCCTTTTGATTCTTTTTTCTTCCCCCTCCATGTAGA
AGAGGGAGAAGGAGAGGCTCTGAAAGCTGCTTCTGGGGGATTTCAAGGGACTGG
GGGTGCCAACCACCTCTGGCCCTGTTGTGGGGGTGTCACAGAGGCAGTGGCAGC
AACAAAGGATTTGAAACTTGGTGTGTTCGTGGAGCCACAGGCAGACGATGTCAA
CCTTGTGTGAGTGTGACGGGGGTTGGGGTGGGGCGGGAGGCCACGGGGGAGGCC
GAGGCAGGGGCTGGGCAGAGGGGAGAGGAAGCACAAGAAGTGGGAGTGGGAG
AGGAAGCCACGTGCTGGAGAGTAGACATCCCCCTCCTTGCCGCTGGGAGAGCCA
AGGCCTATGCCACCTGCAGCGTCTGAGCGGCCGCCTGTCCTTGGTGGCCGGGGGT
GGGGGCCTGCTGTGGGTCAGTGTGCCACCCTCTGCAGGGCAGCCTGTGGGAGAA
GGGACAGCGGGTAAAAAGAGAAGGCAAGCTGGCAGGAGGGTGGCACTTCGTGG
ATGACCTCCTTAGAAAAGACTGACCTTGATGTCTTGAGAGCGCTGGCCTCTTCCT
CCCTCCCTGCAGGGTAGGGGGCCTGAGTTGAGGGGCTTCCCTCTGCTCCACAGAA
ACCCTGTTTTATTGAGTTCTGAAGGTTGGAACTGCTGCCATGATTTTGGCCACTTT
GCAGACCTGGGACTTTAGGGCTAACCAGTTCTCTTTGTAAGGACTTGTGCCTCTT
GGGAGACGTCCACCCGTTTCCAAGCCTGGGCCACTGGCATCTCTGGAGTGTGTGG
GGGTCTGGGAGGCAGGTCCCGAGCCCCCTGTCCTTCCCACGGCCACTGCAGTCAC
CCCGTCTGCGCCGCTGTGCTGTTGTCTGCCGTGAGAGCCCAATCACTGCCTATAC
CCCTCATCACACGTCACAATGTCCCGAATTCCCAGCCTCACCACCCCTTCTCAGT

AATGACCCTGGTTGGTTGCAGGAGGTACCTACTCCATACTGAGGGTGAAATTAA
GGGAAGGCAAAGTCCAGGCACAAGAGTGGGACCCCAGCCTCTCACTCTCAGTTC
CACTCATCCAACTGGGACCCTCACCACGAATCTCATGATCTGATTCGGTTCCCTG
TCTCCTCCTCCCGTCACAGATGTGAGCCAGGGCACTGCTCAGCTGTGACCCTAGG
TGTTTCTGCCTTGTTGACATGGAGAGAGCCCTTTCCCCTGAGAAGGCCTGGCCCC
TTCCTGTGCTGAGCCCACAGCAGCAGGCTGGGTGTCTTGGTTGTCAGTGGTGGCA
CCAGGATGGAAGGGCAAGGCACCCAGGGCAGGCCCACAGTCCCGCTGTCCCCCA
CTTGCACCCTAGCTTGTAGCTGCCAACCTCCCAGACAGCCCAGCCCGCTGCTCAG
CTCCACATGCATAGTATCAGCCCTCCACACCCGACAAAGGGGAACACACCCCCTT
GGAAATGGTTCTTTTCCCCCAGTCCCAGCTGGAAGCCATGCTGTCTGTTCTGCTG
GAGCAGCTGAACATATACATAGATGTTGCCCTGCCCTCCCCATCTGCACCCTGTT
GAGTTGTAGTTGGATTTGTCTGTTTATGCTTGGATTCACCAGAGTGACTATGATA
GTGAAAAGAAAAAAAAAAAAAAAAAAAGGACGCATGTATCTTGAAATGCTTGTA
AAGAGGTTTCTAACCCACCCTCACGAGGTGTCTCTCACCCCCACACTGGGACTCG
TGTGGCCTGTGTGGTGCCACCCTGCTGGGGCCTCCCAAGTTTTGAAAGGCTTTCC
TCAGCACCTGGGACCCAACAGAGACCAGCTTCTAGCAGCTAAGGAGGCCGTTCA
GCTGTGACGAAGGCCTGAAGCACAGGATTAGGACTGAAGCGATGATGTCCCCTT
CCCTACTTCCCCTTGGGGCTCCCTGTGTCAGGGCACAGACTAGGTCTTGTGGCTG
GTCTGGCTTGCGGCGCGAGGATGGTTCTCTCTGGTCATAGCCCGAAGTCTCATGG
CAGTCCCAAAGGAGGCTTACAACTCCTGCATCACAAGAAAAAGGAAGCCACTGC
CAGCTGGGGGGATCTGCAGCTCCCAGAAGCTCCGTGAGCCTCAGCCACCCCTCA
GACTGGGTTCCTCTCCAAGCTCGCCCTCTGGAGGGGCAGCGCAGCCTCCCACCAA
GGGCCCTGCGACCACAGCAGGGATTGGGATGAATTGCCTGTCCTGGATCTGCTCT
AGAGGCCCAAGCTGCCTGCCTGAGGAAGGATGACTTGACAAGTCAGGAGACACT
GTTCCCAAAGCCTTGACCAGAGCACCTCAGCCCGCTGACCTTGCACAAACTCCAT
CTGCTGCCATGAGAAAAGGGAAGCCGCCTTTGCAAAACATTGCTGCCTAAAGAA
ACTCAGCAGCCTCAGGCCCAATTCTGCCACTTCTGGTTTGGGTACAGTTAAAGGC
AACCCTGAGGGACTTGGCAGTAGAAATCCAGGGCCTCCCCTGGGGCTGGCAGCT
TCGTGTGCAGCTAGAGCTTTACCTGAAAGGAAGTCTCTGGGCCCAGAACTCTCCA
CCAAGAGCCTCCCTGCCGTTCGCTGAGTCCCAGCAATTCTCCTAAGTTGAAGGGA
TCTGAGAAGGAGAAGGAAATGTGGGGTAGATTTGGTGGTGGTTAGAGATATGCC
CCCCTCATTACTGCCAACAGTTTCGGCTGCATTTCTTCACGCACCTCGGTTCCTCT
TCCTGAAGTTCTTGTGCCCTGCTCTTCAGCACCATGGGCCTTCTTATACGGAAGG
CTCTGGGATCTCCCCCTTGTGGGGCAGGCTCTTGGGGCCAGCCTAAGATCATGGT

TTAGGGTGATCAGTGCTGGCAGATAAATTGAAAAGGCACGCTGGCTTGTGATCTT
AAATGAGGACAATCCCCCCAGGGCTGGGCACTCCTCCCCTCCCCTCACTTCTCCC
ACCTGCAGAGCCAGTGTCCTTGGGTGGGCTAGATAGGATATACTGTATGCCGGCT
CCTTCAAGCTGCTGACTCACTTTATCAATAGTTCCATTTAAATTGACTTCAGTGGT
GAGACTGTATCCTGTTTGCTATTGCTTGTTGTGCTATGGGGGGAGGGGGGAGGAA
TGTGTAAGATAGTTAACATGGGCAAAGGGAGATCTTGGGGTGCAGCACTTAAAC
TGCCTCGTAACCCTTTTCATGATTTCAACCACATTTGCTAGAGGGAGGGAGCAGC
CACGGAGTTAGAGGCCCTTGGGGTTTCTCTTTTCCACTGACAGGCTTTCCCAGGC
AGCTGGCTAGTTCATTCCCTCCCCAGCCAGGTGCAGGCGTAGGAATATGGACATC
TGGTTGCTTTGGCCTGCTGCCCTCTTTCAGGGGTCCTAAGCCCACAATCATGCCTC
CCTAAGACCTTGGCATCCTTCCCTCTAAGCCGTTGGCACCTCTGTGCCACCTCTCA
CACTGGCTCCAGACACACAGCCTGTGCTTTTGGAGCTGAGATCACTCGCTTCACC
CTCCTCATCTTTGTTCTCCAAGTAAAGCCACGAGGTCGGGGCGAGGGCAGAGGT
GATCACCTGCGTGTCCCATCTACAGACCTGCAGCTTCATAAAACTTCTGATTTCTC
TTCAGCTTTGAAAAGGGTTACCCTGGGCACTGGCCTAGAGCCTCACCTCCTAATA
GACTTAGCCCCATGAGTTTGCCATGTTGAGCAGGACTATTTCTGGCACTTGCAAG
TCCCATGATTTCTTCGGTAATTCTGAGGGTGGGGGGAGGGACATGAAATCATCTT
AGCTTAGCTTTCTGTCTGTGAATGTCTATATAGTGTATTGTGTGTTTTAACAAATG
ATTTACACTGACTGTTGCTGTAAAAGTGAATTTGGAAATAAAGTTATTACTCTGA
TTAAA (SEQ ID NO: 862).

[0122] In certain embodiments, the antisense strand comprises at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the MAPT RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816. In certain embodiments, the antisense strand comprises from 10 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the MAPT RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816. In certain embodiments, the antisense strand comprises from 12 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the MAPT RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816. In certain embodiments, the antisense strand comprises from 15 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal

length within the region of the MAPT RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816. In certain embodiments, the antisense strand comprises from 18 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the MAPT RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816. In certain embodiments, the antisense strand comprises from 21 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the MAPT RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816. In certain embodiments, the antisense strand comprises from 24 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the MAPT RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816. In certain embodiments, the antisense strand comprises 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the MAPT RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0123] In certain embodiments, the antisense strand comprises 9 or fewer nucleotide mismatches relative to a region of 21 contiguous nucleobases of the MAPT RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816. For example, but not by way of limitation, the antisense strand can comprise 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or only 1 mismatch relative to the region of the MAPT RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0124] In certain embodiments, the siRNA molecule of the present disclosure targets a region of an MAPT RNA transcript that has the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

[0125] In certain embodiments, the present disclosure is directed to an siRNA molecule comprising a sense strand comprising a modified sense strand of Table 1. In certain embodiments, the present disclosure is directed to an siRNA molecule comprising an antisense strand comprising a modified antisense strand of Table 1. In certain embodiments the sense strand is selected from SEQ ID Nos. 847-861 and the antisense strand is selected from SEQ ID Nos. 832-846 (where m = 2'Ome; f = 2'F; # = phosphorothioate; -DIO = DIO oligo linker; V = vinyl phosphonate. In certain embodiments the sense strand is SEQ ID NO. 847 and the antisense strand is SEQ ID NO 832. In certain embodiments the sense strand is SEQ ID NO. 848 and the antisense strand is SEQ ID NO. 833. In certain embodiments the sense strand is SEQ ID NO. 849 and the antisense strand is SEQ ID NO. 834. In certain embodiments the

sense strand is SEQ ID NO. 850 and the antisense strand is SEQ ID NO. 835. In certain embodiments the sense strand is SEQ ID NO. 851 and the antisense strand is SEQ ID NO. 836. In certain embodiments the sense strand is SEQ ID NO. 852 and the antisense strand is SEQ ID NO. 837. In certain embodiments the sense strand is SEQ ID NO. 853 and the antisense strand is SEQ ID NO. 838. In certain embodiments the sense strand is SEQ ID NO. 854 and the antisense strand is SEQ ID NO. 839. In certain embodiments the sense strand is SEQ ID NO. 855 and the antisense strand is SEQ ID NO. 840. In certain embodiments the sense strand is SEQ ID NO. 856 and the antisense strand is SEQ ID NO. 841. In certain embodiments the sense strand is SEQ ID NO. 857 and the antisense strand is SEQ ID NO. 842. In certain embodiments the sense strand is SEQ ID NO. 858 and the antisense strand is SEQ ID NO. 843. In certain embodiments the sense strand is SEQ ID NO. 859 and the antisense strand is SEQ ID NO. 844. In certain embodiments the sense strand is SEQ ID NO. 860 and the antisense strand is SEQ ID NO. 845. In certain embodiments the sense strand is SEQ ID NO. 861 and the antisense strand is SEQ ID NO. 846.

Table 1. Modified siRNA Sequences

Pos.	Target mRNA sequence	SEQ ID NO.	Modified antisense sequence	SEQ ID NO.	Modified sense sequence	SEQ ID NO.	*In vivo* duplex ID#	AX Duplex ID#
MAPT_2687	GGAGAGAATGAGAGAGTGTGG	817	5'-VP(mU)#(fC)#(mA)(fC)(fA)(fC)(mU)(fC)(mU)(fC)(mU)(fC)(mA)(fU)(mU)(fC)#(mU)#(mC)#(mU)#(mC)#(mC)	832	(mG)#(mA)#(mA)(fU)(mG)(fA)(mG)(fA)(mG)(fA)(mG)(mU)(mG)(fU)#(mG)#(mA)-DIO	847	AT4692-4693	AX001049
MAPT_286	TCGCCTCTGTCGACTATCAGG	818	5'-VP(mU)#(fC)#(mU)(fG)(fA)(fU)(mA)(fG)(mU)(fC)(mG)(fA)(mC)(fA)(mG)(fA)#(mG)#(mG)#(mC)#(mG)#(mA)	833	(mU)#(mC)#(mU)(fG)(mU)(fC)(mG)(fA)(mC)(fU)(mA)(mU)(mC)(fA)#(mG)#(mA)-DIO	848	AT4688-4689	AX001047
Pos.	**Target mRNA sequence**		**Modified antisense sequence**		**Modified sense sequence**		***In vivo* duplex ID#**	***In vivo* duplex ID#**
MAPT_2679	TGTGGAGAGGAGAGAATGAGA	819	5'-VP(mU)#(fC)#(mU)(fC)(fA)(fU)(mU)(fC)(mU)(fC)(mU)(fC)(mC)(fU)(mC)(fU)#(mC)#(mC)#(mA)#(mC)#(mA)	834	(mA)#(mG)#(mA)(fG)(mG)(fA)(mG)(fA)(mG)(fA)(mA)(mU)(mG)(fA)#(mG)#(mA)-DIO	849	AT4694-4695	AX001050
MAPT_356	GAAGATCACGCTGGGACGTAC	820	5'-VP(mU)#(fU)#(mA)(fC)(fG)(fU)(mC)(fC)(mC)(fA)(mG)(fC)(mG)(fU)(mG)(fA)#(mU)#(mC)#(mU)#(mU)#(mC)	835	(mU)#(mC)#(mA)(fC)(mG)(fC)(mU)(fG)(mG)(fG)(mA)(mC)(mG)(fU)#(mA)#(mA)-DIO	850	AT4690-4691	AX001048
MAPT_2334	AGGTGGAAGTAAAATCTGAGA	821	5'-VP(mU)#(fC)#(mU)(fC)(fA)(fG)(mA)(fU)(mU)(fU)(mU)(fA)(mC)(fU)(mU)(fC)#(mC)#(mA)#(mC)#(mC)#(mU)	836	(mG)#(mA)#(mA)(fG)(mU)(fA)(mA)(fA)(mA)(fU)(mC)(mU)(mG)(fA)#(mG)#(mA)-DIO	851	AT4684-4685	AX001045
MAPT_2817	GGACTTCAAAATCAGTGATGG	822	5'-VP(mU)#(fC)#(mA)(fU)(fC)(fA)(mC)(fU)(mG)(fA)(mU)(fU)(mU)(fU)(mG)(fA)#(mA)#(mG)#(mU)#(mC)#(mC)	837	(mU)#(mC)#(mA)(fA)(mA)(fA)(mU)(fC)(mA)(fG)(mU)(mG)(mA)(fU)#(mG)#(mA)-DIO	852	AT4686-4687	AX001046
MAPT_2327	GGTGGCCAGGTGGAAGTAAAA	823	5'-VP(mU)#(fU)#(mU)(fU)(fA)(fC)(mU)(fU)(mC)(fC)(mA)(fC)(mC)(fU)(mG)(fG)#(mC)#(mC)#(mA)#(mC)#(mC)	838	(mC)#(mC)#(mA)(fG)(mG)(fU)(mG)(fG)(mA)(fA)(mG)(mU)(mA)(fA)#(mA)#(mA)-DIO	853	AT4696-4697	AX001051

			5'-				
MAPT_2689	AGAGAATGAGAG AGTGTGGAA	824	VP(mU)#(fU)#(mC)(fC)(fA)(fC)(mA)(fC)(mU)(fC)(mU)(fC)(mU)(fC)(mA)(fU)#(mU)#(mC)#(mU)#(mC)#(mU)	839	(mA)#(mU)#(mG)(fA)(mG)(fA)(mG)(fG)#(mA)#(mA)-DIO	854	AT4700-4701	AX001053
MAPT_2681	TGGAGAGGAGAG AATGAGAGA	825	5'-VP(mU)#(fC)#(mU)(fC)(fU)(fC)(mA)(fU)(mU)(fC)(mU)(fC)(mU)(fC)(mC)(fU)#(mC)#(mU)#(mC)#(mC)#(mA)	840	(mA)#(mG)#(mG)(fA)(mG)(fA)(mG)(fA)(mA)(fU)(mG)(mA)(mG)(fA)#(mG)#(mA)-DIO	855	AT4698-4699	AX001052
MAPT_2851	TTTCATCTTTCCA AATTGATG	826	5'-VP(mU)#(fA)#(mU)(fC)(fA)(fA)(mU)(fU)(mU)(fG)(mG)(fA)(mA)(fA)(mG)(fA)#(mU)#(mG)#(mA)#(mA)#(mA)	841	(mU)#(mC)#(mU)(fU)(mU)(fC)(mC)(fA)(mA)(fA)(mU)(mU)(mG)(fA)#(mU)#(mA)-DIO	856	AT4702-4703	AX001054
MAPT_2330	GGCCAGGTGGAAG TAAAATCT	827	5'-VP(mU)#(fG)#(mA)(fU)(fU)(fU)(mU)(fA)(mC)(fU)(mU)(fC)(mC)(fA)(mC)(fC)#(mU)#(mG)#(mC)#(mC)	842	(mG)#(mG)#(mU)(fG)(mG)(fA)(mA)(mA)(fG)(mU)(fA)(mA)(mA)(fU)#(mC)#(mA)-DIO	857	AT4704-4705	AX001055
MAPT_2686	AGGAGAGAATGA GAGAGTGTG	828	5'-VP(mU)#(fA)#(mC)(fA)(fC)(fU)(mC)(fU)(mC)(fU)(mC)(fA)(mU)(fU)(mC)(fU)#(mC)#(mU)#(mC)#(mC)#(mU)	843	(mA)#(mG)#(mA)(fA)(mU)(fG)(mA)(fG)(mA)(fG)(mA)(mG)(fU)(fG)#(mU)#(mA)-DIO	858	AT4706-4707	AX001056
MAPT_2690	GAGAATGAGAGA GTGTGGAAA	829	5'-VP(mU)#(fU)#(mU)(fC)(fC)(fA)(mC)(fA)(mC)(fU)(mC)(fU)(mC)(fU)(mC)(fC)(fA)#(mU)#(mC)#(mU)#(mC)	844	(mU)#(mG)#(mA)(fG)(mA)(fG)(mA)(fG)(mA)(fG)(mU)(fG)(mU)(mG)(fA)#(mA)#(mA)-DIO	859	AT4708-4709	AX001057
MAPT_2814	TCGGGACTTCAAA ATCAGTGA	830	5'-VP(mU)#(fC)#(mA)(fC)(fU)(fG)(mA)(fU)(mU)(fU)(mU)(fG)(mA)(fA)(mG)(fU)#(mC)#(mC)#(mG)#(mA)	845	(mA)#(mC)#(mU)(fU)(mC)(fA)(mA)(fA)(mA)(fU)(mC)(mA)(mG)(fU)#(mG)#(mA)-DIO	860	AT4710-4711	AX001058
MAPT_2841	TAAGAGCAAATTT CATCTTTC	831	5'-VP(mU)#(fA)#(mA)(fA)(fG)(fG)(fA)(mU)(fG)(mA)(fA)(mA)(fU)(mU)(fU)(mG)(fC)#(mU)#(mC)#(mU)#(mC)#(mA)	846	(mG)#(mC)#(mA)(fA)(mA)(fA)(mA)(fU)(mU)(fU)(mC)(fA)(mU)(mC)(mU)(fU)#(mU)#(mA)-DIO	861	AT4712-4713	AX001059

Note: m = 2'Ome; f = 2'F; # = phosphorothioate; -DIO = DIO oligo linker; V = vinyl phosphonate.

5.3. siRNA Structure

[0126] The siRNA molecules of the disclosure may be in the form of a single-stranded (ss) or double-stranded (ds) oligonucleotide structure. In some embodiments, the siRNA molecules may be di-branched, tri-branched, or tetra-branched molecules. Furthermore, the siRNA molecules of the disclosure may contain one or more phosphodiester internucleoside linkages and/or an analog thereof, such as a phosphorothioate internucleoside linkage. The siRNA molecules of the disclosure may further contain chemically modified nucleosides having 2' sugar modifications.

[0127] The simplest siRNAs consist of a ribonucleic acid, including a ss- or ds- structure, formed by a first strand (i.e., antisense strand), and in the case of a ds-siRNA, a second strand (i.e., sense strand). The first strand includes a stretch of contiguous nucleotides that is at least partially complementary to a target nucleic acid. The second strand also includes a stretch of contiguous nucleotides where the second stretch is at least partially identical to a target nucleic acid. The first strand and said second strand may be hybridized to each other to form a double-stranded structure. The hybridization typically occurs by Watson Crick base pairing.

[0128] Depending on the sequence of the first and second strand, the hybridization or base pairing is not necessarily complete or perfect, which means that the first and second strand are not 100% base-paired due to mismatches. One or more mismatches may also be present within the duplex without necessarily impacting the siRNA RNAi activity.

[0129] The first strand contains a stretch of contiguous nucleotides which is essentially complementary to a target nucleic acid. Typically, the target nucleic acid sequence is, in accordance with the mode of action of interfering ribonucleic acids, a ss-RNA, e.g., an mRNA. Such hybridization occurs most likely through Watson Crick base pairing but is not necessarily limited thereto. The extent to which the first strand has a complementary stretch of contiguous nucleotides to a target nucleic acid sequence may be between 80% and 100%, e.g., 80%, 85%, 90%, 95%, or 100% complementary.

[0130] The siRNA molecules described herein may employ modifications to the nucleobase, phosphate backbone, ribose core, 5′- and 3′-ends, and branching, wherein multiple strands of siRNA may be covalently linked.

[0131] The siRNA molecules described herein may contain one or more phosphodiester internucleoside linkages and/or an analog thereof, such as a phosphorothioate internucleoside linkage, in which oxyanion moieties are electrostatically neutralized by ionic bonding to a

divalent metal cation, such as Ba^{2+}, Be^{2+}, Ca^{2+}, Cu^{2+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, or Zn^{2+}. In certain embodiments, the one or more divalent cations includes Ca^{2+} and Mg^{2+}, optionally wherein the ratio of Ca^{2+} to Mg^{2+} is from 1:100 to 100:1 (e.g., 1:75, 1:50, 1:25, 1:10, 1:5, 1:1, 5:1, 10:1, 25:1. 50:1, 75:1, or 100:1). In certain embodiments, the Ca^{2+} and Mg^{2+} are present in a 1:1 ratio. In certain embodiments, the one or more divalent cations displace water from a cationic binding site of the siRNA molecule. In certain embodiments, the degree of saturation of the cationic binding sites by the one or more divalent cations is from about 10% to about 100% (e.g., from about 20% to about 100%, from about 30% to about 100%, from about 40% to about 100%, from about 50% to about 100%, from about 60% to about 100%, from about 70% to about 100%, from about 80% to about 100%, or from about 90% to about 100%). In certain embodiments, the cationic binding site is located within an internucleoside linkage, such as a phosphodiester linkage and/or a phosphorothioate linkage. For example, the cationic binding site may be an oxyanion moiety within a phosphodiester linage or phosphorothioate linkage. In certain embodiments, the one or more divalent cations are characterized as having an ionic radius ranging from about 30 picometers to about 150 picometers (e.g., from about 30 picometers to about 140 picometers, from about 40 picometers to about 130 picometers, from about 50 picometers to about 120 picometers, from about 60 picometers to about 110 picometers, from about 60 picometers to about 100 picometers, or from about 60 picometers to about 90 picometers).

5.3.1. Lengths of siRNA Molecules

[0132] It is within the scope of the disclosure that any length, known and previously unknown in the art, may be employed for the current invention. As described herein, potential lengths for an antisense strand of the siRNA molecules of the present disclosure is between 10 and 30 nucleotides (e.g., 10 nucleotides, 11 nucleotides, 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, or 30 nucleotides), 15 and 25 nucleotides (e.g., 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, or 25 nucleotides), or 18 and 23 nucleotides (e.g., 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, or 23 nucleotides). In some embodiments, the antisense strand is 20 nucleotides. In some embodiments, the antisense strand is 21 nucleotides. In some

embodiments, the antisense strand is 22 nucleotides. In some embodiments, the antisense strand is 23 nucleotides. In some embodiments, the antisense strand is 24 nucleotides. In some embodiments, the antisense strand is 25 nucleotides. In some embodiments, the antisense strand is 26 nucleotides. In some embodiments, the antisense strand is 27 nucleotides. In some embodiments, the antisense strand is 28 nucleotides. In some embodiments, the antisense strand is 29 nucleotides. In some embodiments, the antisense strand is 30 nucleotides.

[0133] In some embodiments, the sense strand of the siRNA molecules of the present disclosure is between 12 and 30 nucleotides (e.g., 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, or 30 nucleotides), or 14 and 23 nucleotides (e.g., 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, or 23 nucleotides). In some embodiments, the sense strand is 15 nucleotides. In some embodiments, the sense strand is 16 nucleotides. In some embodiments, the sense strand is 17 nucleotides. In some embodiments, the sense strand is 18 nucleotides. In some embodiments, the sense strand is 19 nucleotides. In some embodiments, the sense strand is 20 nucleotides. In some embodiments, the sense strand is 21 nucleotides. In some embodiments, the sense strand is 22 nucleotides. In some embodiments, the sense strand is 23 nucleotides. In some embodiments, the sense strand is 24 nucleotides. In some embodiments, the sense strand is 25 nucleotides. In some embodiments, the sense strand is 26 nucleotides. In some embodiments, the sense strand is 27 nucleotides. In some embodiments, the sense strand is 28 nucleotides. In some embodiments, the sense strand is 29 nucleotides. In some embodiments, the sense strand is 30 nucleotides.

5.3.2. 2' Sugar Modifications

[0134] The present disclosure may include ss- and ds- siRNA molecule compositions including at least one (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or more) nucleosides having 2' sugar modifications. Possible 2′-modifications include all possible orientations of OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C1 to C10 alkyl or C2 to C10 alkenyl and alkynyl. In some embodiments, the modification includes a 2'-O-methyl (2'-O-Me) modification. Other potential sugar substituent groups include: C1 to C10 lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3,

OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. In some embodiments, the modification includes 2′-methoxyethoxy (2′-O-$CH_2CH_2OCH_3$, also known as 2′-O-(2-methoxyethyl) or 2′-MOE). In some embodiments, the modification includes 2′-dimethylaminooxyethoxy, i.e., a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2′-DMAOE, and 2′-dimethylaminoethoxyethoxy (also known in the art as 2′-O-dimethylamino-ethoxy-ethyl or 2′-DMAEOE), i.e., 2′-O-$CH_2OCH_2N(CH_3)_2$. Other potential sugar substituent groups include, e.g., aminopropoxy (-$OCH_2CH_2CH_2NH_2$), allyl (-CH_2-$CH=CH_2$), -O-allyl (-O-CH_2-$CH=CH_2$) and fluoro (F). 2′-sugar substituent groups may be in the arabino (up) position or ribo (down) position. In some embodiments, the 2′-arabino modification is 2′-F. Similar modifications may also be made at other positions on the siRNA molecule, particularly the 3′ position of the sugar on the 3′ terminal nucleoside or in 2′-5′ linked oligonucleotides and the 5′ position of 5′ terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar.

5.3.3. Nucleobase Modifications

[0135] The siRNA molecules of the disclosure may also include nucleosides or other surrogate or mimetic monomeric subunits that include a nucleobase (often referred to in the art simply as "base" or "heterocyclic base moiety"). The nucleobase is another moiety that has been extensively modified or substituted and such modified and or substituted nucleobases are amenable to the present disclosure. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases also referred herein as heterocyclic base moieties include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (-C=C-CH3) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and

7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in US 3,687,808, those disclosed in Kroschwitz, J.I., ed. *The Concise Encyclopedia of Polymer Science and Engineering,* New York, John Wiley & Sons, 1990, pp. 858-859; those disclosed by Englisch et al., *Angewandte Chemie,* International Edition 30:613, 1991; and those disclosed by Sanghvi, Y.S., Chapter 16, *Antisense Research and Applications,* CRC Press, Gait, M.J. ed., 1993, pp. 289-302. The siRNA molecules of the present disclosure may also include polycyclic heterocyclic compounds in place of one or more heterocyclic base moieties. A number of tricyclic heterocyclic compounds have been previously reported. These compounds are routinely used in antisense applications to increase the binding properties of the modified strand to a target strand.

[0136] Representative cytosine analogs that make three hydrogen bonds with a guanosine in a second strand include 1,3-diazaphenoxazine-2-one (Kurchavov *et al., Nucleosides and Nucleotides,* 16:1837-46, 1997), 1,3-diazaphenothiazine-2-one (Lin et al. *Am. Chem. Soc.,* 117:3873-4, 1995), and 6,7,8,9-tetrafluoro-l,3-diazaphenoxazine-2-one (Wang et al., *Tetrahedron Lett.,* 39:8385-8, 1998). Incorporated into oligonucleotides, these base modifications were shown to hybridize with complementary guanine and the latter was also shown to hybridize with adenine and to enhance helical thermal stability by extended stacking interactions (also see US 10/155,920 and US 10/013,295, both of which are herein incorporated by reference in their entirety). Further helix-stabilizing properties have been observed when a cytosine analog/substitute has an aminoethoxy moiety attached to the rigid 1,3-diazaphenoxazine-2-one scaffold (Lin et al., *Am. Chem. Soc.,* 120:8531-2, 1998).

5.3.4. Internucleoside Linkage Modifications

[0137] Another variable in the design of the present disclosure is the internucleoside linkage making up the phosphate backbone of the siRNA molecule. Although the natural RNA phosphate backbone may be employed here, derivatives thereof may be used which enhance desirable characteristics of the siRNA molecule. In certain embodiments, the siRNA molecule will be modified to exhibit reduced hydrolysis relative to the unmodified siRNA. One example of a modification that decreases the rate of hydrolysis is phosphorothioates. Any portion or the

whole of the backbone may contain phosphate substitutions (e.g., phosphorothioates). For instance, the internucleoside linkages may be between 0 and 100% phosphorothioate, e.g., between 0 and 100%, 10 and 100%, 20 and 100%, 30 and 100%, 40 and 100%, 50 and 100%, 60 and 100%, 70 and 100%, 80 and 100%, 90 and 100%, 0 and 90%, 0 and 80%, 0 and 70%, 0 and 60%, 0 and 50%, 0 and 40%, 0 and 30%, 0 and 20%, 0 and 10%, 10 and 90%, 20 and 80%, 30 and 70%, 40 and 60%, 10 and 40%, 20 and 50%, 30 and 60%, 40 and 70%, 50 and 80%, or 60 and 90% phosphorothioate linkages. Similarly, the internucleoside linkages may be between 0 and 100% phosphodiester linkages, e.g., between 0 and 100%, 10 and 100%, 20 and 100%, 30 and 100%, 40 and 100%, 50 and 100%, 60 and 100% 70 and 100%, 80 and 100%, 90 and 100%, 0 and 90%, 0 and 80%, 0 and 70%, 0 and 60%, 0 and 50%, 0 and 40%, 0 and 30%, 0 and 20%, 0 and 10%, 10 and 90%, 20 and 80%, 30 and 70%, 40 and 60%, 10 and 40%, 20 and 50%, 30 and 60%, 40 and 70%, 50 and 80%, or 60 and 90% phosphodiester linkages.

[0138] Specific examples of some potential siRNA molecules useful in this invention include oligonucleotides containing modified e.g., non-naturally occurring internucleoside linkages. As defined in this specification, oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom and internucleoside linkages that do not have a phosphorus atom. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. An exemplary phosphorus containing modified internucleoside linkage is the phosphorothioate internucleoside linkage. In some embodiments, the modified oligonucleotide backbones containing a phosphorus atom therein include, for example, phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates, 5'-alkylene phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkyl-phosphonates, thionoalkylphosphotriesters, selenophosphates, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. Exemplary U.S. patents describing the preparation of phosphorus-containing linkages include but are not limited to, U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,625,050;

6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6,239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and U.S. Pat. RE39464, the entire contents of each of which are hereby incorporated herein by reference.

[0139] In some embodiments, the modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; riboacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH_2 component parts. Non-limiting examples of U.S. patents that teach the preparation of non-phosphorus backbones include, but are not limited to, U.S. Pat. Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439, the entire contents of each of which are hereby incorporated herein by reference.

5.4. Patterns of Modifications of siRNA Molecules

[0140] The following section provides a set of exemplary scaffolds into which the siRNA molecules of the disclosure may be incorporated.

[0141] In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region represented by Formula I, wherein Formula I is, in the 5'-to-3' direction

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C'\text{-}P^1)_k\text{-}C'$$

Formula I;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$; each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$; B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$; each C is a 2'-O-methyl (2'-O-Me) ribonucleoside; each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-

F) ribonucleoside; each D is a 2'-F ribonucleoside; each P^1 is a phosphorothioate internucleoside linkage; each P^2 is a phosphodiester internucleoside linkage; j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, j is 4. In some embodiments, k is 4. In some embodiments, j is 4 and k is 4. The antisense is complementary (e.g., fully or partially complementary) to a target nucleic acid sequence.

[0142] In some embodiments, the antisense strand includes a structure represented by Formula A1, wherein Formula A1 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0143] In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region represented by Formula II, wherein Formula II is, in the 5'-to-3' direction:

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C\text{-}P^1)_k\text{-}C'$$

Formula II;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$; each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$; B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$; each C is a 2'-O-methyl (2'-O-Me) ribonucleoside; each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside; each D is a 2'-F ribonucleoside; each P^1 is a phosphorothioate internucleoside linkage; each P^2 is a phosphodiester internucleoside linkage; j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, j is 4. In some embodiments, k is 4. In some embodiments, j is 4 and k is 4. The antisense is complementary (e.g., fully or partially complementary) to a target nucleic acid sequence.

[0144] In some embodiments of the disclosure, the antisense strand includes a structure represented by Formula A2, wherein Formula A2 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-A-S-A

Formula A2;

[0145] wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0146] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula III, wherein Formula III is, in the 5'-to-3' direction:

$$E\text{-}(A')_m\text{-}F$$

Formula III;

wherein E is represented by the formula $(C\text{-}P^1)_2$; F is represented by the formula $(C\text{-}P^2)_3\text{-}D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $(C\text{-}P^2)_3\text{-}D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $(C\text{-}P^2)_3\text{-}D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $(C\text{-}P^2)_3\text{-}D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$; A', C, D, P^1, and P^2 are as defined in Formula I; and m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, m is 4. The sense strand is complementary (e.g., fully or partially complementary) to the antisense strand.

[0147] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S1, wherein Formula S1 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-A

Formula S1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0148] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S2, wherein Formula S2 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-A

Formula S2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0149] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S3, wherein Formula S3 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-B

Formula S3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0150] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S4, wherein Formula S4 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-B

Formula S4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0151] In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region represented by Formula IV, wherein Formula IV is, in the 5'-to-3' direction:

$$A\text{-}(A')_j\text{-}C\text{-}P^2\text{-}B\text{-}(C\text{-}P^1)_k\text{-}C'$$

Formula IV;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$; each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$; B is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D\text{-}P^1$; each C is a 2'-O-Me ribonucleoside; each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside; each D is a 2'-F ribonucleoside; each P^1 is a phosphorothioate internucleoside linkage; each P^2 is a phosphodiester internucleoside linkage; j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and k is an integer from 1 to7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, j is 6. In some

embodiments, k is 4. In some embodiments, j is 6 and k is 4. The antisense strand is complementary (e.g., fully or partially complementary) to a target nucleic acid.

[0152] In some embodiments of the disclosure, the antisense strand includes a structure represented by Formula A3, wherein Formula A3 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B-S-A-S-A-S-A

Formula A3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0153] In some embodiments of the disclosure, the siRNA of the disclosure may have a sense strand represented by Formula V, wherein Formula V is, in the 5'-to-3' direction:

$$E\text{-}(A')_m\text{-}C\text{-}P^2\text{-}F$$

Formula V;

[0154] wherein E is represented by the formula $(C\text{-}P^1)_2$; F is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$; A', C, D, P^1, and P^2 are as defined in Formula IV; and m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, m is 5. The sense strand is complementary (e.g., fully or partially complementary) to the antisense strand.

[0155] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S5, wherein Formula S5 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A

Formula S5;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0156] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S6, wherein Formula S6 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A

Formula S6;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0157] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S7, wherein Formula S7 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B

Formula S7;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0158] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S8, wherein Formula S8 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B

Formula S8;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0159] In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region represented by Formula VI, wherein Formula VI is, in the 5'-to-3' direction:

2- B_j-E-B_k-E-F-G_l-D-P^1-C'

Formula VI;

wherein A is represented by the formula C-P^1-D-P^1; each B is represented by the formula C-P^2; each C is a 2'-O-Me ribonucleoside; each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside; each D is a 2'-F ribonucleoside; each E is represented by the formula

D-P^2-C-P^2; F is represented by the formula D-P^1-C-P^1; each G is represented by the formula C-P^1; each P^1 is a phosphorothioate internucleoside linkage; each P^2 is a phosphodiester internucleoside linkage; j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and l is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, j is 3. In some embodiments, k is 6. In some embodiments, l is 2. In some embodiments, j is 3, k is 6, and l is 2. The antisense strand is complementary (e.g., fully or partially complementary) to a target nucleic acid.

[0160] In some embodiments of the disclosure, the antisense strand includes a structure represented by Formula A4, wherein Formula A4 is, in the 5'-to-3' direction:

A-S-B-S-A-O-A-O-A-O-B-O-A-O-A-O-A-O-A-O-A-O-A-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0161] In some embodiments of the disclosure, the siRNA may contain a sense strand including a region represented by Formula VII, wherein Formula VII is, in the 5'-to-3' direction:

$H\text{-}B_m\text{-}I_n\text{-}A'\text{-}B_o\text{-}H\text{-}C$

Formula VII;

wherein A' is represented by the formula C-P^2-D-P^2; each H is represented by the formula (C-P^1)$_2$; each I is represented by the formula (D-P^2); B, C, D, P^1, and P^2 are as defined in Formula VI; m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); n is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and o is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, m is 3. In some embodiments, n is 3. In some embodiments, o is 3. In some embodiments, m is 3, n is 3, and o is 3. The sense strand is complementary (e.g., fully or partially complementary) to the antisense strand.

[0162] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S9, wherein Formula S9 is, in the 5'-to-3' direction:

A-S-A-S-A-O-A-O-A-O-B-O-B-O-B-O-A-O-B-O-A-O-A-O-A-O-A-S-A-S-A

Formula S9;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0163] In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region that is represented by Formula VIII:

$$Z\text{-}((A\text{-}P\text{-})_n(B\text{-}P\text{-})_m)_q;$$

Formula VIII

wherein Z is a 5' phosphorus stabilizing moiety; each A is a 2'-O-methyl (2′-O-Me) ribonucleoside; each B is a 2′-fluoro-ribonucleoside; each P is, independently, an internucleoside linkage selected from a phosphodiester linkage and a phosphorothioate linkage; n is an integer from 1 to 5 (e.g., 1, 2, 3, 4, or 5); m is an integer from 1 to 5 (e.g., 1, 2, 3, 4, or 5); and q is an integer between 1 and 30 (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30).

5.5. Methods of siRNA Synthesis

[0164] The siRNA molecules of the disclosure can be synthesized by standard methods known in the art as further discussed below, e.g., by use of an automated DNA synthesizer, such as are commercially available from, for example, Biosearch, Applied Biosystems, Inc.

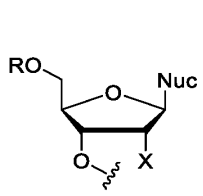
[0165] The siRNA agent can be prepared using solution-phase or solid-phase organic synthesis or both. Organic synthesis offers the advantage that the oligonucleotide including unnatural or modified nucleotides can be easily prepared. siRNA molecules of the disclosure can be prepared using solution-phase or solid-phase organic synthesis or both.

[0166] Further, it is contemplated that for any siRNA agent disclosed herein, further optimization could be achieved by systematically either adding or removing linked nucleosides to generate longer or shorter sequences. Further still, such optimized sequences can be adjusted by, e.g., the introduction of modified nucleosides, and/or modified internucleoside linkages as described herein or as known in the art, including alternative nucleosides, alternative sugar moieties, and/or alternative internucleoside linkages as known in the art and/or discussed herein

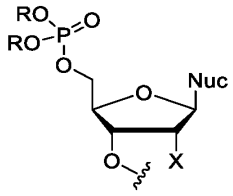
to further optimize the molecule (e.g., increasing serum stability or circulating half-life, increasing thermal stability, enhancing transmembrane delivery, and/or targeting to a particular location or cell type).

5.6. 5′ Phosphorus Stabilizing Moieties

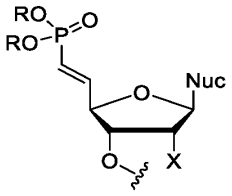
[0167] To further protect the siRNA molecules of this disclosure from degradation, a 5′-phosphorus stabilizing moiety may be employed. A 5′-phosphorus stabilizing moiety replaces the 5′-phosphate to prevent hydrolysis of the phosphate. Hydrolysis of the 5′-phosphate prevents binding to RISC, a necessary step in gene silencing. Any replacement for phosphate that does not impede binding to RISC is contemplated in this disclosure. In some embodiments, the replacement for the 5′-phosphate is also stable to *in vivo* hydrolysis. Each strand of a siRNA molecule may independently and optionally employ any suitable 5′-phosphorus stabilizing moiety.



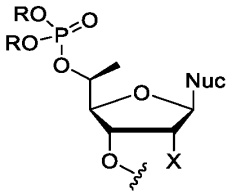
Formula IX



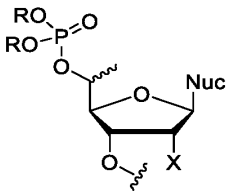
Formula X



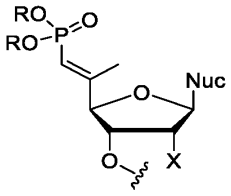
Formula XI



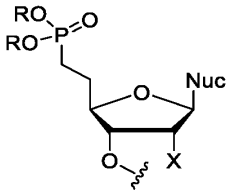
Formula XII



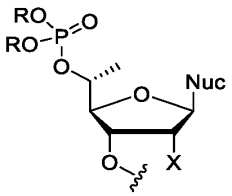
Formula XIII



Formula XIV



Formula XV



Formula XVI

[0168] Some exemplary endcaps are demonstrated in Formulas IX-XVI. Nuc in Formulas IX-XVI represents a nucleobase or nucleobase derivative or replacement as described herein. X in formula IX-XVI represents a 2'-modification as described herein. Some embodiments employ hydroxy as in Formula IX, phosphate as in Formula X, vinylphosphonates as in Formula XI and XIV, 5'-methyl-substitued phosphates as in Formula XII, XIII, and XVI, methylenephosphonates as in Formula XV, or vinyl 5′-vinylphsophonate as a 5′-phosphorus stabilizing moiety as demonstrated in Formula XI.

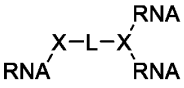
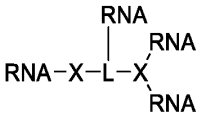
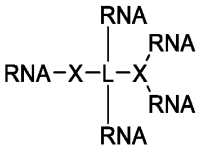
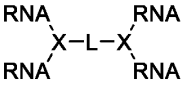
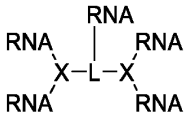
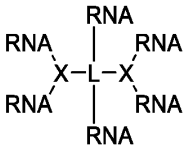
[0169] The present disclosure further provides siRNA molecules having one or more hydrophobic moieties attached thereto. The hydrophobic moiety may be covalently attached to the 5' end or the 3' end of the siRNA molecules of the disclosure. Non-limiting examples of hydrophobic moieties suitable for use with the siRNA molecules of the disclosure may include cholesterol, vitamin D, tocopherol, phosphatidylcholine (PC), docosahexaenoic acid, docosanoic acid, PC-docosanoic acid, eicosapentaenoic acid, lithocholic acid or any combination of the aforementioned hydrophobic moieties with PC.

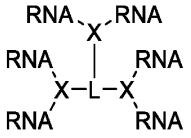
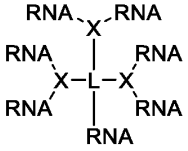
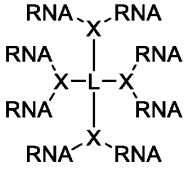
5.7. siRNA Branching

[0170] The siRNA molecules of the disclosure may be branched. For example, the siRNA molecules of the disclosure may have one of several branching patterns, as described herein.

[0171] According to the present disclosure, the siRNA molecules disclosed herein may be branched siRNA molecules. The siRNA molecule may not be branched, or may be di-branched, tri-branched, or tetra-branched, connected through a linker. Each main branch may be further branched to allow for 2, 3, 4, 5, 6, 7, or 8 separate RNA single- or double-strands. The branch points on the linker may stem from the same atom, or separate atoms along the linker. Some exemplary embodiments are listed in Table 2.

Table 2. Branched siRNA structures

Di-branched	Tri-branched	Tetra-branched
RNA−L−RNA **Formula XVII**	RNA RNA−L−RNA **Formula XX**	RNA RNA−L−RNA RNA **Formula XXIV**
 **Formula XVIII**	 **Formula XXI**	 **Formula XXV**
 **Formula XIX**	 **Formula XXII**	 **Formula XXVI**

	 Formula XXIII	 Formula XXVII
		 Formula XXVIII

[0172] In some embodiments, the siRNA molecule is a branched siRNA molecule. In some embodiments, the branched siRNA molecule is di-branched, tri-branched, or tetra-branched. In some embodiments, the di-branched siRNA molecule is represented by any one of Formulas XVII-XIX, wherein each RNA, independently, is an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety (e.g., phosphoroamidite, tosylated solketal, 1,3-diaminopropanol, pentaerythritol, or any one of the branch point moieties described in US 10,478,503).

[0173] In some embodiments, the tri-branched siRNA molecule represented by any one of Formulas XX-XXIII, wherein each RNA, independently, is an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

[0174] In some embodiments, the tetra-branched siRNA molecule represented by any one of Formulas XXIV-XXVIII, wherein each RNA, independently, is an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

[0175] Multiple strands of siRNA described herein may be covalently attached by way of a linker. The effect of this branching improves, *inter alia*, cell permeability allowing better access into cells (e.g., neurons or glial cells) in the CNS. Any linking moiety may be employed which is not incompatible with the siRNAs of the present invention. Linkers include ethylene glycol chains of 2 to 10 subunits (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 subunits), alkyl chains, carbohydrate chains, block copolymers, peptides, RNA, DNA, and others. In some embodiments, any carbon or oxygen atom of the linker is optionally replaced with a nitrogen atom, bears a hydroxyl substituent, or bears an oxo substituent. In some embodiments, the linker is a poly-ethylene glycol (PEG) linker. The PEG linkers suitable for use with the

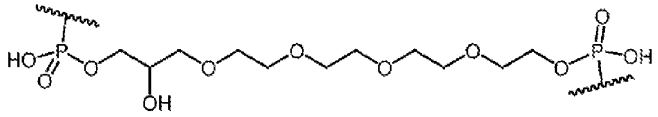
disclosed compositions and methods include linear or non-linear PEG linkers. Examples of non-linear PEG linkers include branched PEGs, linear forked PEGs, or branched forked PEGs.

[0176] PEG linkers of various weights may be used with the disclosed compositions and methods. For example, the PEG linker may have a weight that is between 5 and 500 Daltons. In some embodiments, a PEG linker having a weight that is between 500 and 1,000 Dalton may be used. In some embodiments, a PEG linker having a weight that is between 1,000 and 10,000 Dalton may be used. In some embodiments, a PEG linker having a weight that is between 200 and 20,000 Dalton may be used. In some embodiments, the linker is covalently attached to a sense strand of the siRNA. In some embodiments, the linker is covalently attached to an antisense strand of the siRNA. In some embodiments, the PEG linker is a triethylene glycol (TrEG) linker. In some embodiments, the PEG linker is a tetraethylene glycol (TEG) linker.

[0177] In some embodiments, the linker is an alkyl chain linker. In some embodiments, the linker is a peptide linker. In some embodiments, the linker is an RNA linker. In some embodiments, the linker is a DNA linker.

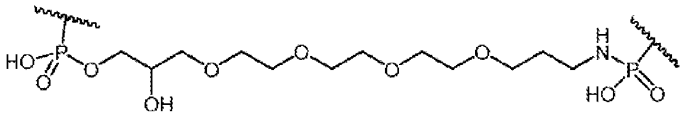
[0178] Linkers may covalently link 2, 3, 4, or 5 unique siRNA strands. The linker may covalently bind to any part of the siRNA oligomer. In some embodiments, the linker attaches to the 3′ end of nucleosides of each siRNA strand. In some embodiments, the linker attaches to the 5′ end of nucleosides of each siRNA strand. In some embodiments, the linker attaches to a nucleoside of an siRNA strand (e.g., sense or antisense strand) by way of a covalent bond-forming moiety. In some embodiments, the covalent-bond-forming moiety is selected from the group consisting of an alkyl, ester, amide, carbonate, carbamate, triazole, urea, formacetal, phosphonate, phosphate, and phosphate derivative (e.g., phosphorothioate, phosphoramidate, etc.). In certain embodiments the linker is a divalent oligonucleotide (DIO) linker

[0179] In some embodiments, the linker has a structure of Formula L1:



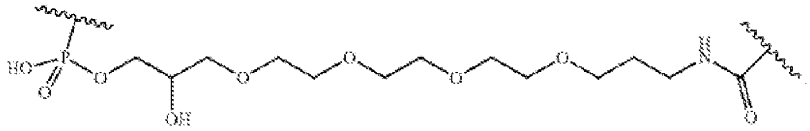
(Formula L1)

[0180] In some embodiments, the linker has a structure of Formula L2:



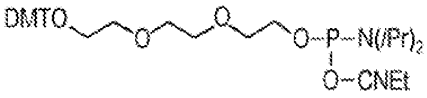
(**Formula L2**)

[0181] In some embodiments, the linker has a structure of Formula L3:



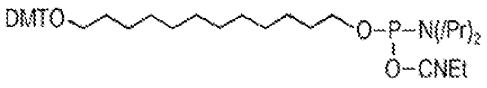
(**Formula L3**)

[0182] In some embodiments, the linker has a structure of Formula L4:



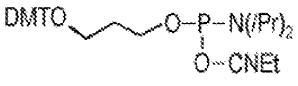
(**Formula L4**)

[0183] In some embodiments, the linker has a structure of Formula L5:



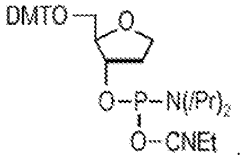
(**Formula L5**)

[0184] In some embodiments, the linker has a structure of Formula L6:



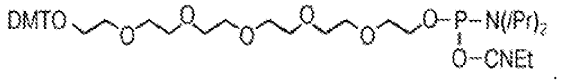
(**Formula L6**)

[0185] In some embodiments, the linker has a structure of Formula L7, as is shown below:



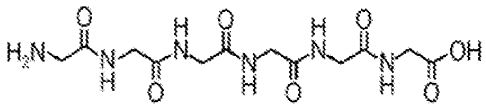
(**Formula L7**)

[0186] In some embodiments, the linker has a structure of Formula L8:



(Formula L8)

[0187] In some embodiments, the linker has a structure of Formula L9:



(Formula L9)

[0188] In some embodiments, the selection of a linker for use with one or more of the branched siRNA molecules disclosed herein may be based on the hydrophobicity of the linker, such that, e.g., desirable hydrophobicity is achieved for the one or more branched siRNA molecules of the disclosure. For example, a linker containing an alkyl chain may be used to increase the hydrophobicity of the branched siRNA molecule as compared to a branched siRNA molecule having a less hydrophobic linker or a hydrophilic linker.

[0189] The siRNA agents disclosed herein may be synthesized and/or modified by methods well established in the art, such as those described in Beaucage, S. L. et al. (edrs.), *Current Protocols in Nucleic Acid Chemistry*, John Wiley & Sons, Inc., New York, N.Y., 2000, which is hereby incorporated herein by reference.

5.8. Methods of Treatment

[0190] The *MAPT*-targeting siRNA molecules of the disclosure may be delivered to a subject, thereby treating a tauopathy. Exemplary tauopathies include Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration or any other medical risk(s) associated with the *MAPT* gene. Furthermore, the siRNA molecules of the disclosure may also be delivered to a subject having a variant of the *MAPT* gene for which siRNA-mediated gene silencing of the *MAPT* variant gene reduces the expression level of *MAPT* transcript, thereby treating a tauopathy, e.g., Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration or any other medical risk(s) associated with the *MAPT* gene

[0191] The disclosure provides methods of treating a subject by way of *MAPT* gene silencing with one or more of the siRNA molecules described herein. The gene silencing may be performed in a subject to silence wild type *MAPT* transcripts, mutant *MAPT* transcripts, splice isoforms of *MAPT* transcripts, and/or overexpressed *MAPT* transcripts thereof, relative to a

healthy subject. The method may include delivering to the CNS or affected tissues of the subject (e.g., a human) the siRNA molecules of the disclosure or a pharmaceutical composition containing the same by any appropriate route of administration (e.g., intracerebroventricular, intrathecal injection, intrastriatal injection, intra-cisterna magna injection by catheterization, intraparenchymal injection, intravenous injection, subcutaneous injection, or intramuscular injection). The active compound can be administered in any suitable dose. The actual dosage amount of a composition of the present disclosure administered to a patient can be determined by physical and physiological factors such as body weight, severity of condition, previous or concurrent therapeutic interventions, idiopathy of the patient and on the route of administration. Depending upon the dosage and the route of administration, the number of administrations of an exemplary dosage and/or an effective amount may vary according to the response of the subject. The practitioner responsible for administration will, in any event, determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject. Administration may occur any suitable number of times per day, and for as long as necessary. Subjects may be adult or pediatric humans, with or without comorbid diseases.

5.8.1. Selection of Subjects

[0192] Subjects that may be treated with the siRNA molecules disclosed herein are subjects in need of treatment of, for example, a tauopathy, Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration or any other medical risk(s) associated with the *MAPT* gene. Subjects that may be treated with the siRNA molecules disclosed herein may include, for example, humans, monkeys, rats, mice, pigs, and other mammals containing at least one orthologous copy of the *MAPT* gene. Subjects may be adult or pediatric humans, with or without comorbid diseases.

5.8.2. Pharmaceutical Compositions

[0193] The siRNA molecules in the present disclosure may be formulated into a pharmaceutical composition for administration to a subject in a biologically compatible form suitable for administration *in vivo*. Accordingly, the present disclosure provides a pharmaceutical composition containing a siRNA molecule of the disclosure in admixture with a suitable diluent, carrier, or excipient. The siRNA molecules may be administered, for example, directly into the CNS or affected tissues of the subject (e.g., by way of intracerebroventricular, intrastriatally, intrathecal injection, intra-cisterna magna injection by

catheterization, intraparenchymal injection, intravenous injection, subcutaneous injection, or intramuscular injection).

[0194] Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington, J.P. *The Science and Practice of Pharmacy*, Easton, PA. Mack Publishers, 2012, 22nd ed. and in The United States Pharmacopeial Convention, *The National Formulary*, United States Pharmacopeial, 2015, USP 38 NF 33).

[0195] Under ordinary conditions of storage and use, a pharmaceutical composition may contain a preservative, e.g., to prevent the growth of microorganisms. Pharmaceutical compositions may include sterile aqueous solutions, dispersions, or powders, e.g., for the extemporaneous preparation of sterile solutions or dispersions. In all cases the form may be sterilized using techniques known in the art and may be fluidized to the extent that may be easily administered to a subject in need of treatment.

[0196] A pharmaceutical composition may be administered to a subject, e.g., a human subject, alone or in combination with pharmaceutically acceptable carriers, as noted herein, the proportion of which may be determined by the solubility and/or chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice.

5.8.3. Dosing Regimens

[0197] A physician having ordinary skill in the art can readily determine an effective amount of the siRNA molecule for administration to a mammalian subject (e.g., a human) in need thereof. For example, a physician could start prescribing doses of one the siRNA molecules of the disclosure at levels lower than that required to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. Alternatively, a physician may begin a treatment regimen by administering one of the siRNA molecules of the disclosure at a high dose and subsequently administer progressively lower doses until reaching a minimal dosage at which a therapeutic effect is achieved (e.g., a reduction in expression of a target gene sequence). In general, a suitable daily dose of one of the siRNA molecules of the disclosure will be an amount of the siRNA molecule which is the lowest dose effective to produce a therapeutic effect. The ss- or ds-siRNA molecules of the disclosure may be administered by injection, e.g., intrathecally, intracerebroventricularly, by intra-cisterna magna injection by catheterization, intraparenchy-mally, intravenously, subcutaneously, or intramuscularly. A daily dose of a therapeutic composition of the siRNA molecules of the disclosure may be

administered as a single dose or as two, three, four, five, six or more doses administered separately at appropriate intervals throughout the day, week, month, or year, optionally, in unit dosage forms. While it is possible for the siRNA molecules of the disclosure to be administered alone, it may also be administered as a pharmaceutical formulation in combination with excipients, carriers, and optionally, additional therapeutic agents.

5.8.4. Routes of Administration

[0198] The method of the disclosure contemplates any route of administration tolerated by the therapeutic composition. Some embodiments of the method include injection intrathecally, intracerebroventricularly, intrastriatally, intraparenchymally, or by intra-cisterna magna injection by catheterization.

[0199] Intrathecal injection is the direct injection into the spinal column or subarachnoid space. By injecting directly into the CSF of the spinal column the siRNA molecules of the disclosure have direct access to cells (e.g., neurons and glial cells) in the spinal column and a route to access the cells in the brain by bypassing the blood brain barrier.

[0200] Intracerebroventricular (ICV) injection is a method to directly inject into the CSF of the cerebral ventricles. Similar to intrathecal injection, ICV is a method of injection which bypasses the blood brain barrier. Using ICV allows the advantage of access to the cells of the brain and spinal column without the danger of the therapeutic being degraded in the blood.

[0201] Intrastriatal injection is the direct injection into the striatum, or corpus striatum. The striatum is an area in the subcortical basal ganglia in the brain. Injecting into the striatum bypasses the blood brain barrier and the pharmacokinetic challenges of injection into the blood stream and allows for direct access to the cells of the brain.

[0202] Intraparenchymal administration is the direct injection into the parenchyma (e.g., the brain parenchyma). Injection into the brain parenchyma allows for injection directly into brain regions affected by a disease or disorder while bypassing the blood brain barrier.

[0203] Intra-cisterna magna injection by catheterization is the direct injection into the cisterna magna. The cisterna magna is the area of the brain located between the cerebellum and the dorsal surface of the medulla oblongata. Injecting into the cisterna magna results in more direct delivery to the cells of the cerebellum, brainstem, and spinal cord.

[0204] In some embodiments of the methods described herein, the therapeutic composition may be delivered to the subject by way of systemic administration, e.g., intravenously, intramuscularly, or subcutaneously.

[0205] Intravenous (IV) injection is a method to directly inject into the bloodstream of a subject. The IV administration may be in the form of a bolus dose or by way of continuous infusion, or any other method tolerated by the therapeutic composition.

[0206] Intramuscular (IM) injection is injection into a muscle of a subject, such as the deltoid muscle or gluteal muscle. IM may allow for rapid absorption of the therapeutic composition.

[0207] Subcutaneous injection is injection into subcutaneous tissue. Absorption of compositions delivered subcutaneously may be slower than IV or IM injection, which may be beneficial for compositions requiring continuous absorption.

6. ENUMERATED EMBODIMENTS OF THE DISCLOSURE

[0208] The compositions, methods, and kits described herein include the following non-limiting, exemplary, enumerated embodiments of the disclosure. In some embodiments, the disclosure provides:

Embodiment 1. A small interfering RNA (siRNA) molecule comprising an antisense strand and sense strand having complementarity to the antisense strand, wherein the antisense strand is from 10 to 30 nucleotides in length and has complementarity sufficient to hybridize to a region within a microtubule-associated protein tau (*MAPT*) mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 2. The siRNA molecule of embodiment 1, wherein the antisense strand has at least 70% complementarity to a region of 21 contiguous nucleobases within the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 3. The siRNA molecule of embodiment 2, wherein the antisense strand has at least 75% complementarity to a region of 21 contiguous nucleobases within the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816, optionally wherein the antisense strand has at least 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementarity to the region within the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID Nos: 409-816.

Embodiment 4. The siRNA molecule of any one of embodiments 1-3, wherein the antisense strand comprises at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or 30 contiguous nucleotides that

are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 5. The siRNA molecule of embodiment 4, wherein the antisense strand comprises from 10 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 6. The siRNA molecule of embodiment 5, wherein the antisense strand comprises from 12 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 7. The siRNA molecule of embodiment 6, wherein the antisense strand comprises from 15 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 8. The siRNA molecule of embodiment 7, wherein the antisense strand comprises from 18 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 9. The siRNA molecule of embodiment 8, wherein the antisense strand comprises from 21 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 10. The siRNA molecule of any one of embodiments 1-9, wherein the antisense strand comprises from 24 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 11. The siRNA molecule of embodiment 10, wherein the antisense strand comprises 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 12. The siRNA molecule of any one of embodiments 1-11, wherein the antisense strand comprises 9 or fewer nucleotide mismatches relative to a region of 21

contiguous nucleobases of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816, optionally wherein the antisense strand comprises 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or only 1 mismatch relative to the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 13. The siRNA molecule of any one of embodiments 1-12, wherein the region of the *MAPT* mRNA transcript has the nucleic acid sequence of any one of SEQ ID NOs: 817-831.

Embodiment 14. The siRNA molecule of embodiment 13, wherein the region of the *MAPT* mRNA transcript has the nucleic acid sequence of any one of SEQ ID NOs: 817-821, 823-825, and 827-830.

Embodiment 15. The siRNA molecule of any one of embodiments 1-14, wherein the antisense strand has a nucleic acid sequence that is at least 85% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-408.

Embodiment 16. The siRNA molecule of embodiment 15, wherein the antisense strand has a nucleic acid sequence that is at least 90% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-408.

Embodiment 17. The siRNA molecule of embodiment 16, wherein the antisense strand has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of SEQ ID NOs: 1-408, optionally wherein the antisense strand has a nucleic acid sequence that is at least 96%, 97%, 98%, or 99% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-408.

Embodiment 18. The siRNA molecule of embodiment 17, wherein the antisense strand has the nucleic acid sequence of any one of SEQ ID NOs: 1-408.

Embodiment 19. The siRNA molecule of any one of embodiments 15-18, wherein the nucleic acid sequence is any one of SEQ ID NOs: 834-846.

Embodiment 20. The siRNA molecule of embodiment 19, wherein the nucleic acid sequence is any one of SEQ ID NOs: 834-836, 838-840, and 842-845.

Embodiment 21. The siRNA molecule of any one of embodiments 1-20, wherein the sense strand has a nucleic acid sequence that is at least 85% identical to the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 22. The siRNA molecule of embodiment 21, wherein the sense strand has a nucleic acid sequence that is at least 90% identical to the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 23. The siRNA molecule of embodiment 22, wherein the sense strand has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of SEQ ID NOs: 409-816, optionally wherein the sense strand has a nucleic acid sequence that is at least 96%, 97%, 98%, or 99% identical to the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 24. The siRNA molecule of embodiment 23, wherein the sense strand has the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

Embodiment 25. The siRNA molecule of any one of embodiments 21-24, wherein the nucleic acid sequence is any one of SEQ ID NOs: 817-831.

Embodiment 26. The siRNA molecule of embodiment 25, wherein the nucleic acid sequence is any one of SEQ ID NOs: 817-821, 823-825, and 827-830.

Embodiment 27. The siRNA molecule of any one of embodiments 1-26, wherein the antisense strand comprises a structure represented by Formula I, wherein Formula I is, in the 5'-to-3' direction:

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C'\text{-}P^1)_k\text{-}C'$$

Formula I;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;

each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;

B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$;

each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;

each D is a 2'-F ribonucleoside;

each P^1 is a phosphorothioate internucleoside linkage;

each P^2 is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7; and

k is an integer from 1 to 7.

Embodiment 28. The siRNA molecule of embodiment 27, wherein the antisense strand comprises a structure represented by Formula A1, wherein Formula A1 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 29. The siRNA molecule of any one of embodiments 1-26, wherein the antisense strand comprises a structure represented by Formula II, wherein Formula II is, in the 5'-to-3' direction:

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C\text{-}P^1)_k\text{-}C'$$

Formula II;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$;
each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;
each D is a 2'-F ribonucleoside;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7; and
k is an integer from 1 to 7.

Embodiment 30. The siRNA molecule of embodiment 29, wherein the antisense strand comprises a structure represented by Formula A2, wherein Formula A2 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-A-S-A

Formula A2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 31. The siRNA molecule of any one of embodiments 1-30, wherein the sense strand comprises a structure represented by Formula III, wherein Formula III is, in the 5'-to-3' direction:

$$E\text{-}(A')_m\text{-}F$$

Formula III;

wherein E is represented by the formula $(C\text{-}P^1)_2$;

F is represented by the formula $(C\text{-}P^2)_3\text{-}D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $(C\text{-}P^2)_3\text{-}D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $(C\text{-}P^2)_3\text{-}D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $(C\text{-}P^2)_3\text{-}D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$;

A', C, D, P^1, and P^2 are as defined in Formula II; and

m is an integer from 1 to 7.

Embodiment 32. The siRNA molecule of embodiment 31, wherein the sense strand comprises a structure represented by Formula S1, wherein Formula S1 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-A

Formula S1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 33. The siRNA molecule of embodiment 31, wherein the sense strand comprises a structure represented by Formula S2, wherein Formula S2 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-A

Formula S2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 34. The siRNA molecule of embodiment 31, wherein the sense strand comprises a structure represented by Formula S3, wherein Formula S3 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-B

Formula S3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 35. The siRNA molecule of embodiment 31, wherein the sense strand comprises a structure represented by Formula S4, wherein Formula S4 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-B

Formula S4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 36. The siRNA molecule of any one of embodiments 1-26 and 31-35, wherein the antisense strand comprises a structure represented by Formula IV, wherein Formula IV is, in the 5'-to-3' direction:

$A\text{-}(A')_j\text{-}C\text{-}P^2\text{-}B\text{-}(C\text{-}P^1)_k\text{-}C'$

Formula IV;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;

each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;

B is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D\text{-}P^1$;

each C is a 2'-O-Me ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;
each D is a 2'-F ribonucleoside;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7; and
k is an integer from 1 to 7.

Embodiment 37. The siRNA molecule of embodiment 36, wherein the antisense strand comprises a structure represented by Formula A3, wherein Formula A3 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B-S-A-S-A-S-A

Formula A3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 38. The siRNA molecule of any one of embodiments 1-30, 36, and 37, wherein the sense strand comprises a structure represented by Formula V, wherein Formula V is, in the 5'-to-3' direction:

$$E\text{-}(A')_m\text{-}C\text{-}P^2\text{-}F$$

Formula V;

wherein E is represented by the formula $(C\text{-}P^1)_2$;
F is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$;
A', C, D, P^1 and P^2 are as defined in Formula IV; and
m is an integer from 1 to 7.

Embodiment 39. The siRNA molecule of embodiment 38, wherein the sense strand comprises a structure represented by Formula S5, wherein Formula S5 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A

Formula S5;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 40. The siRNA molecule of embodiment 38, wherein the sense strand comprises a structure represented by Formula S6, wherein Formula S6 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A

Formula S6;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 41. The siRNA molecule of embodiment 38, wherein the sense strand comprises a structure represented by Formula S7, wherein Formula S7 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B

Formula S7;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 42. The siRNA molecule of embodiment 38, wherein the sense strand comprises a structure represented by Formula S8, wherein Formula S8 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B

Formula S8;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 43. The siRNA molecule of any one of embodiments 1-26, 31-35 and 38-42, wherein the antisense strand comprises a structure represented by Formula VI, wherein Formula VI is, in the 5'-to-3' direction:

$$A\text{-}B_j\text{-}E\text{-}B_k\text{-}E\text{-}F\text{-}G_l\text{-}D\text{-}P^1\text{-}C'$$

Formula VI;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each B is represented by the formula $C\text{-}P^2$;
each C is a 2'-O-Me ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;
each D is a 2'-F ribonucleoside;
each E is represented by the formula $D\text{-}P^2\text{-}C\text{-}P^2$;
F is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1$;
each G is represented by the formula $C\text{-}P^1$;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7;
k is an integer from 1 to 7; and
l is an integer from 1 to 7.

Embodiment 44. The siRNA molecule of embodiment 43, wherein the antisense strand comprises a structure represented by Formula A4, wherein Formula A4 is, in the 5'-to-3' direction:

A-S-B-S-A-O-A-O-A-O-B-O-A-O-A-O-A-O-A-O-A-O-A-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 45. The siRNA molecule of any one of embodiments 1-30, 36, 37, 43, and 44, wherein the sense strand comprises a structure represented by Formula VII, wherein Formula VII is, in the 5'-to-3' direction:

$H\text{-}B_m\text{-}I_n\text{-}A'\text{-}B_o\text{-}H\text{-}C$

Formula VII;

wherein A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
each H is represented by the formula $(C\text{-}P^1)_2$;
each I is represented by the formula $(D\text{-}P^2)$;
B, C, D, P^1 and P^2 are as defined in Formula VI;
m is an integer from 1 to 7;
n is an integer from 1 to 7; and
o is an integer from 1 to 7.

Embodiment 46. The siRNA molecule of embodiment 45, wherein the sense strand comprises a structure represented by Formula S9, wherein Formula S9 is, in the 5'-to-3' direction:

A-S-A-S-A-O-A-O-A-O-B-O-B-O-B-O-A-O-B-O-A-O-A-O-A-O-A-S-A-S-A

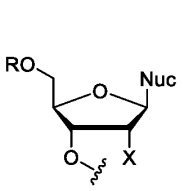
Formula S9;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

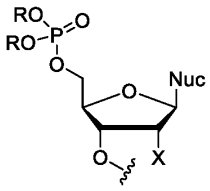
Embodiment 47. The siRNA molecule of any one of embodiments 1-46, wherein the antisense strand further comprises a 5' phosphorus stabilizing moiety at the 5' end of the antisense strand.

Embodiment 48. The siRNA molecule of any one of embodiments 1-47, wherein the sense strand further comprises a 5' phosphorus stabilizing moiety at the 5' end of the sense strand.

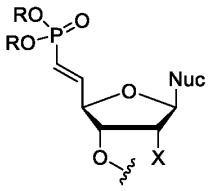
Embodiment 49. The siRNA molecule of embodiment 47 or 48, wherein each 5' phosphorus stabilizing moiety is, independently, represented by any one of Formulas IX-XVI:



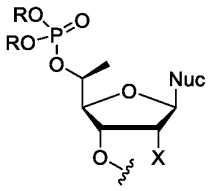
Formula IX



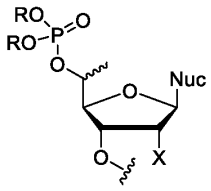
Formula X



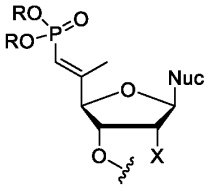
Formula XI



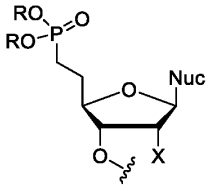
Formula XII



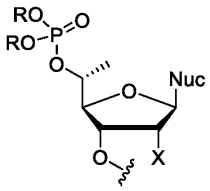
Formula XIII



Formula XIV



Formula XV



Formula XVI

wherein Nuc represents a nucleobase selected from the group consisting of adenine, uracil, guanine, thymine, and cytosine, and R represents an optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, phenyl, benzyl, hydroxy, or hydrogen.

Embodiment 50. The siRNA molecule of embodiment 49, wherein the nucleobase is an adenine, uracil, guanine, thymine, or cytosine.

Embodiment 51. The siRNA molecule of any one of embodiments 47-50, wherein the 5' phosphorus stabilizing moiety is (E)-vinylphosphonate represented by Formula XI.

Embodiment 52. The siRNA molecule of any one of embodiments 1-51, wherein the siRNA molecule further comprises a hydrophobic moiety at the 5' or the 3' end of the siRNA molecule.

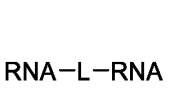
Embodiment 53. The siRNA molecule of embodiment 52, wherein the hydrophobic moiety is selected from a group consisting of cholesterol, vitamin D, or tocopherol.

Embodiment 54. The siRNA molecule of any one of embodiments 1-53, wherein the length of the sense strand is between 12 and 30 nucleotides.

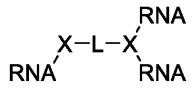
Embodiment 55. The siRNA molecule of any one of embodiments 1-54, wherein the siRNA molecule is a branched siRNA molecule.

Embodiment 56. The siRNA molecule of embodiment 55, wherein the branched siRNA molecule is di-branched, tri-branched, or tetra-branched.

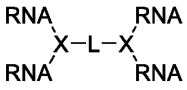
Embodiment 57. The siRNA molecule of embodiment 56, wherein the siRNA molecule is a di-branched siRNA molecule, optionally wherein the di-branched siRNA molecule is represented by any one of Formulas XVII-XIX:



Formula XVII;



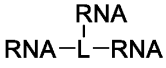
Formula XVIII;



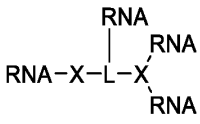
Formula XIX;

wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

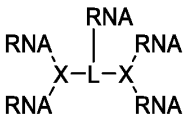
Embodiment 58. The siRNA molecule of embodiment 56, wherein the siRNA molecule is a tri-branched siRNA molecule, optionally wherein the tri-branched siRNA molecule is represented by any one of Formulas XX-XXIII:



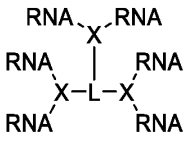
Formula XX;



Formula XXI;



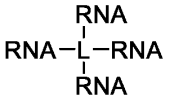
Formula XXII;

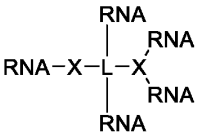


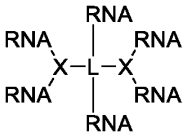
Formula XXIII;

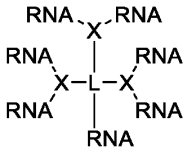
wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

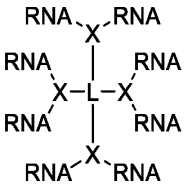
Embodiment 59. The siRNA molecule of embodiment 56, wherein the siRNA molecule is a tetra-branched siRNA molecule, optionally wherein the tetra-branched siRNA molecule is represented by any one of Formulas XXIV-XXVIII:











Formula XXIV; Formula XXV; Formula XXVI; Formula XXVII; Formula XXVIII;

wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

Embodiment 60. The siRNA molecule of any one of embodiments 57-59, wherein the linker is selected from a group consisting of one or more contiguous subunits of an ethylene glycol, alkyl, carbohydrate, block copolymer, peptide, RNA, and DNA.

Embodiment 61. The siRNA molecule of embodiment 60, wherein the one or more contiguous subunits is 2 to 20 contiguous subunits.

Embodiment 62. An siRNA molecule comprising:

a) a sense strand comprising the sequence (mG)#(mA)#(mA)(fU)(mG)(fA)(mG)(fA)(mG)(fA)(mG)(mU)(mG)(fU)#(mG)#(mA)-DIO (SEQ ID NO: 847) and an antisense strand comprising the sequence V(mU)#(fC)#(mA)(fC)(fA)(fC)(mU)(fC)(mU)(fC)(mU)(fC)(mA)(fU)(mU)(fC)#(mU)#(mC)#(mU)#(mC)#(mC) (SEQ ID NO: 832);

b) a sense strand comprising the sequence (mU)#(mC)#(mU)(fG)(mU)(fC)(mG)(fA)(mC)(fU)(mA)(mU)(mC)(fA)#(mG)#(mA)-DIO (SEQ ID NO: 848) and an antisense strand comprising the sequence V(mU)#(fC)#(mU)(fG)(fA)(fU)(mA)(fG)(mU)(fC)(mG)(fA)(mC)(fA)(mG)(fA)#(mG)#(mG)#(mC)#(mG)#(mA) (SEQ ID NO: 833);

c) a sense strand comprising the sequence (mA)#(mG)#(mA)(fG)(mG)(fA)(mG)(fA)(mG)(fA)(mA)(mU)(mG)(fA)#(mG)#(mA)-DIO (SEQ ID NO: 849) and an antisense strand comprising the sequence V(mU)#(fC)#(mU)(fC)(fA)(fU)(mU)(fC)(mU)(fC)(mU)(fC)(mC)(fU)(mC)(fU)#(mC)#(mC)#(mA)#(mC)#(mA) (SEQ ID NO: 834);

d) a sense strand comprising the sequence (mU)#(mC)#(mA)(fC)(mG)(fC)(mU)(fG)(mG)(fG)(mA)(mC)(mG)(fU)#(mA)#(mA)-DIO (SEQ ID NO: 850) and an antisense strand comprising the sequence V(mU)#(fU)#(mA)(fC)(fG)(fU)(mC)(fC)(mC)(fA)(mG)(fC)(mG)(fU)(mG)(fA)#(mU)#(mC)#(mU)#(mU)#(mC) (SEQ ID NO: 835);

e) a sense strand comprising the sequence (mG)#(mA)#(mA)(fG)(mU)(fA)(mA)(fA)(mA)(fU)(mC)(mU)(mG)(fA)#(mG)#(mA)-DIO (SEQ ID NO: 851) and an antisense strand comprising the sequence V(mU)#(fC)#(mU)(fC)(fA)(fG)(mA)(fU)(mU)(fU)(mU)(fA)(mC)(fU)(mU)(fC)#(mC)#(mA)#(mC)#(mC)#(mU) (SEQ ID NO: 836);

f) a sense strand comprising the sequence (mU)#(mC)#(mA)(fA)(mA)(fA)(mU)(fC)(mA)

(fG)(mU)(mG)(mA)(fU)#(mG)#(mA)-DIO (SEQ ID NO: 852) and an antisense strand comprising the sequence V(mU)#(fC)#(mA)(fU)(fC)(fA)(mC)(fU)(mG)(fA)(mU)(fU)(mU)(fU) (mG)(fA)#(mA)#(mG)#(mU)#(mC)#(mC) (SEQ ID NO: 837);

g) a sense strand comprising the sequence (mC)#(mC)#(mA)(fG)(mG)(fU)(mG)(fG)(mA) (fA)(mG)(mU)(mA)(fA)#(mA)#(mA)-DIO (SEQ ID NO: 853) and an antisense strand comprising the sequence V(mU)#(fU)#(mU)(fU)(fA)(fC)(mU)(fU)(mC)(fC)(mA)(fC)(mC)(fU) (mG)(fG)#(mC)#(mC)#(mA)#(mC)#(mC) (SEQ ID NO: 838);

h) a sense strand comprising the sequence (mA)#(mU)#(mG)(fA)(mG)(fA)(mG)(fA) (mG)(fU)(mG)(mU)(mG)(fG)#(mA)#(mA)-DIO (SEQ ID NO: 854) and an antisense strand comprising the sequence V(mU)#(fU)#(mC)(fC)(fA)(fC)(mA)(fC)(mU)(fC)(mU)(fC)(mU)(fC) (mA)(fU)#(mU)#(mC)#(mU)#(mC)#(mU) (SEQ ID NO: 839);

i) a sense strand comprising the sequence (mA)#(mG)#(mG)(fA)(mG)(fA)(mG)(fA) (mA)(fU)(mG)(mA)(mG)(fA)#(mG)#(mA)-DIO (SEQ ID NO: 855) and an antisense strand comprising the sequence V(mU)#(fC)#(mU)(fC)(fU)(fC)(mA)(fU)(mU)(fC)(mU)(fC)(mU)(fC) (mC)(fU)#(mC)#(mU)#(mC)#(mC)#(mA) (SEQ ID NO: 840);

j) a sense strand comprising the sequence (mU)#(mC)#(mU)(fU)(mU)(fC)(mC)(fA) (mA)(fA)(mU)(mU)(mG)(fA)#(mU)#(mA)-DIO (SEQ ID NO: 856) and an antisense strand comprising the sequence V(mU)#(fA)#(mU)(fC)(fA)(fA)(mU)(fU)(mU)(fG)(mG)(fA)(mA)(fA)(mG) (fA)#(mU)#(mG)#(mA)#(mA)#(mA) (SEQ ID NO: 841);

k) a sense strand comprising the sequence (mG)#(mG)#(mU)(fG)(mG)(fA)(mA)(fG)(mU) (fA)(mA)(mA)(mA)(fU)#(mC)#(mA)-DIO (SEQ ID NO: 857) and an antisense strand comprising the sequence V(mU)#(fG)#(mA)(fU)(fU)(fU)(mU)(fA)(mC)(fU)(mU)(fC)(mC) (fA)(mC)(fC)#(mU)#(mG)#(mG)#(mC)#(mC) (SEQ ID NO: 842);

l) a sense strand comprising the sequence (mA)#(mG)#(mA)(fA)(mU)(fG)(mA)(fG) (mA)(fG)(mA)(mG)(mU)(fG)#(mU)#(mA)-DIO (SEQ ID NO: 858) and an antisense strand comprising the sequence

V(mU)#(fA)#(mC)(fA)(fC)(fU)(mC)(fU)(mC)(fU)(mC)(fA)(mU)
(fU)(mC)(fU)#(mC)#(mU)#(mC)#(mC)#(mU) (SEQ ID NO: 843);

m) a sense strand comprising the sequence (mU)#(mG)#(mA)(fG)(mA)(fG)(mA)(fG)
(mU)(fG)(mU)(mG)(mG)(fA)#(mA)#(mA)-DIO (SEQ ID NO: 859) and an antisense strand comprising the sequence
V(mU)#(fU)#(mU)(fC)(fC)(fA)(mC)(fA)(mC)(fU)(mC)(fU)(mC)(fU)
(mC)(fA)#(mU)#(mU)#(mC)#(mU)#(mC) (SEQ ID NO: 844);

n) a sense strand comprising the sequence (mA)#(mC)#(mU)(fU)(mC)(fA)(mA)(fA)
(mA)(fU)(mC)(mA)(mG)(fU)#(mG)#(mA)-DIO (SEQ ID NO: 860) and an antisense strand comprising the sequence
VP(mU)#(fC)#(mA)(fC)(fU)(fG)(mA)(fU)(mU)(fU)(mU)(fG)(mA)(fA)
(mG)(fU)#(mC)#(mC)#(mC)#(mG)#(mA) (SEQ ID NO: 845); or

o) a sense strand comprising the sequence (mG)#(mC)#(mA)(fA)(mA)(fU)(mU)(fU
)(mC)(fA)(mU)(mC)(mU)(fU)#(mU)#(mA)-DIO (SEQ ID NO: 861) and an antisense strand comprising the sequence
VP(mU)#(fA)#(mA)(fA)(fG)(fA)(mU)(fG)(mA)(fA)(mA)(fU)(mU)
(fU)(mG)(fC)#(mU)#(mC)#(mU)#(mU)#(mA) (SEQ ID NO: 846),

wherein m represents a 2'-O-Me ribonucleoside, f represents a 2'-F ribonucleoside, # represents a phosphorothioate internucleoside linkage, -DIO represents a divalent oligonucleotide (DIO) linker; and V represents a vinyl phosphonate.

Embodiment 63. A pharmaceutical composition comprising the siRNA molecule of any one of embodiments 1-62 and a pharmaceutically acceptable excipient, carrier, or diluent.

Embodiment 64. A method of delivering an siRNA molecule to a subject diagnosed as having an , the method comprising administering a therapeutically effective amount of the siRNA molecule of any one of embodiments 1-62 or the pharmaceutical composition of embodiment 63 to the subject.

Embodiment 65. A method of treating a tauopathy in a subject in need thereof, the method comprising administering a therapeutically effective amount of the siRNA molecule of any one of embodiments 1-62 or the pharmaceutical composition of embodiment 63 to the subject.

Embodiment 66. The method of embodiment 65, wherein the tauopathy is Alzheimer's disease.

Embodiment 67. The method of embodiment 65, wherein the tauopathy is frontotemporal dementia.

Embodiment 68. The method of embodiment 65, wherein the tauopathy is progressive supranuclear palsy.

Embodiment 69. The method of embodiment 65, wherein the tauopathy is corticobasal degeneration.

Embodiment 70. A method of reducing *MAPT* expression in a subject in need thereof, the method comprising administering a therapeutically effective amount of the siRNA molecule of any one of embodiments 1-62 or the pharmaceutical composition of embodiment 63 to the subject.

Embodiment 71. The method of any one of embodiments 64-70, wherein the siRNA molecule or the pharmaceutical composition is administered to the subject by way of intracerebroventricular, intrastriatal, intraparenchymal, or intrathecal injection.

Embodiment 72. The method of any one of embodiments 64-71, wherein the siRNA molecule or the pharmaceutical composition is administered to the subject by way of intravenous, intramuscular, or subcutaneous injection.

Embodiment 73. The method of any one of embodiments 64-72, wherein the subject is a human.

Embodiment 74. A kit comprising the siRNA molecule of any one of embodiments 1-62, or the pharmaceutical composition of embodiment 63, and a package insert, wherein the package insert instructs a user of the kit to perform the method of any one of embodiments 64-73.

7. EXAMPLES

[0209] The following examples are put forth so as to provide those of ordinary skill in the art with a description of how the compositions and methods described herein may be used, made, and evaluated, and are intended to be purely exemplary of the disclosure and are not intended to limit the scope of what the inventors regard as their disclosure.

Example 1. *In Vitro* Screening

[0210] *In vitro* screening was performed using human SHSY-5Y cells in a 96-well format. In some embodiments, MeWo cells may be used. Briefly, cholesterol-conjugated, mono-siRNA was passively administered to cells in culture for 72 hours at 2 uM or 0.5 uM concentrations (single point format) or at serial 1:2.5 dilutions from 3 uM to 0.00196608 uM (IC50 format). Cells were lysed using the Cells-to-Ct kit (Thermo) and quantitative reverse transcriptase

polymerase change reaction (QRT-PCR) was performed to assess target (MAPT) gene expression relative to housekeeping (ATP5B) gene expression using TaqMan primer/probes and Fast Advanced master mix (Thermo). Data are presented as mean % MAPT target expression (N=2-3 biological replicates, 2 technical replicates each) relative to untreated control cells, where 100% represents no knockdown and 0% represents complete target knockdown. The results are reported in Table 2, below.

Table 2. In Vitro Screening

Name	Position in NM_001123066.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	*In vitro* duplex ID#	% UNT MAPT mRNA expression @ 2uM	ST DEV	% UNT MAPT mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
MAPT_2690	2690	UUUCCACACUCUCUCAUUCUC	1	UGAGAGAGUGUGGAAA	409	AT4336-4337	13.84	0.19	21.68	0.83	68.7
MAPT_2688	2688	UCCACACUCUCUCAUUCUCUC	2	AAUGAGAGAGUGUGGA	410	AT4332-4333	15.62	0.45	18.41	0.58	48.1
MAPT_2686	2686	UACACUCUCUCAUUCUCUCCU	3	AGAAUGAGAGAGUGUA	411	AT4330-4331	16.38	0.56	24.69	0.06	90.2
MAPT_2684	2684	UACUCUCUCAUUCUCUCCUCU	4	AGAGAAUGAGAGAGUA	412	AT4326-4327	17.03	0.73	17.88	0.43	92.4
MAPT_2679	2679	UCUCAUUCUCUCCUCUCACA	5	AGAGGAGAGAAUGAGA	413	AT2590-2591	17.51	0.97	30.50	29.61	38.1
MAPT_2665	2665	UUCCACAAUUAUUGACCGCCC	6	GUCAAUAAUUGUGGAA	414	AT4290-4291	18.99	0.16	21.87	0.57	
MAPT_2685	2685	UCACUCUCUCAUUCUCCUCC	7	GAGAAUGAGAGAGUGA	415	AT4328-4329	19.25	0.09	39.51	0.18	143
MAPT_2689	2689	UUCCACACUCUCUCAUUCUCU	8	AUGAGAGAGUGUGGAA	416	AT4334-4335	19.33	1.29	20.69	0.97	33
MAPT_2681	2681	UCUCUCAUUCUCUCCUCCCA	9	AGGAGAGAAUGAGAGA	417	AT4320-4321	19.54	2.34	21.30	0.26	44.3
MAPT_2666	2666	UCUCCACAAUUAUUGACCGCC	10	UCAAUAAUUGUGGAGA	418	AT4292-4293	19.55	2.11	25.98	2.56	

MAPT_2687	2687	UCACACUCUCUC AUUCUCUCC	11	GAAUGAGAG AGUGUGA	419	AT2592-2593	20.12	0.37	32.85	33.70	32.2
MAPT_2841	2841	UAAAGAUGAAA UUUGCUCUUA	12	GCAAAUUUC AUCUUUA	420	AT2614-2615	20.65	1.56	49.15	47.04	210
MAPT_2674	2674	UUCUCUCCUCUC CACAAUUAU	13	UGUGGAGAG GAGAGAA	421	AT4308-4309	20.86	0.73	19.23	1.05	
MAPT_2367	2367	UCUUCGACUGGA CUCUGUCCU	14	AGAGUCCAG UCGAAGA	422	AT4256-4257	21.15	0.23	24.89	2.04	330
MAPT_2836	2836	UUGAAAUUUGC UCUUACUCCC	15	UAAGAGCAA AUUUCAA	423	AT2612-2613	21.70	0.32	39.34	36.28	186
MAPT_2691	2691	UUUUCCACACUC UCUCAUUCU	16	GAGAGAGUG UGGAAAA	424	AT4338-4339	22.30	0.07	27.01	0.64	149
MAPT_2667	2667	UUCUCCACAAUU AUUGACCGC	17	CAAUAAUUG UGGAGAA	425	AT4294-4295	22.38	1.71	27.14	0.25	
MAPT_1473	1473	UGUCAUCGCUUC CAGUCCCGU	18	ACUGGAAGCG AUGACA	426	AT2520-2521	22.43	0.12	48.66	0.64	498
MAPT_2673	2673	UCUCUCCUCUCC ACAAUUAUU	19	UUGUGGAGA GGAGAGA	427	AT4306-4307	23.77	0.92	27.15	0.54	
MAPT_2680	2680	UUCUCAUUCUCU CCUCUCCAC	20	GAGGAGAGA AUGAGAA	428	AT4318-4319	24.46	0.17	25.38	1.37	104
MAPT_2776	2776	UAAGCAGGUUAA GUGAUUAAC	21	UCACUUAACC UGCUUA	429	AT4344-4345	26.18	1.56	36.42	3.83	195
MAPT_2671	2671	UCUCCUCUCCAC AAUUAUUGA	22	AAUUGUGGA GAGGAGA	430	AT4302-4303	26.65	1.93	37.36	0.84	
MAPT_2683	2683	UCUCUCUCAUUC UCUCCUCUC	23	GAGAGAAUG AGAGAGA	431	AT4324-4325	26.79	2.43	26.36	0.24	111

MAPT_2352	2352	UGUCCUUGAAGUCAAGCUUCU	24	CUUGACUUCAAGGACA	432	AT4254-4255	27.05	0.41	32.25	3.01	483	
MAPT_2835	2835	UGAAAUUUGCUCUUACUCCCA	25	GUAAGAGCAAAUUUCA	433	AT2610-2611	27.49	0.19	41.82	39.17	98.7	
MAPT_2334	2334	UCUCAGAUUUUACUUCCACCU	26	GAAGUAAAAUCUGAGA	434	AT4250-4251	27.70	2.36	33.60	0.88	326	
MAPT_307	307	UCCAUCCUGGUUCAAAGUUCA	27	UUUGAACCAGGAUGGA	435	AT4142-4143	28.68	1.93	35.60	2.89	370	
MAPT_356	356	UUACGUCCCAGCGUGAUCUUC	28	UCACGCUGGGACGUAA	436	AT4150-4151	28.82	5.36	32.10	2.50	268	
MAPT_1774	1774	UUUGCUGGAAUCCUGGUGGCG	29	CCAGGAUUCCAGCAAA	437	AT4170-4171	30.49	4.86	28.16	0.46	323	
MAPT_2668	2668	UCUCUCCACAAUUAUUGACCG	30	AAUAAUUGUGGAGAGA	438	AT4296-4297	30.85	5.77	41.92	0.78		
MAPT_2670	2670	UUCCUCUCCACAAUUAUUGAC	31	UAAUUGUGGAGAGGAA	439	AT4300-4301	30.89	2.01	34.30	1.07		
MAPT_2843	2843	UGGAAAGAUGAAAUUUGCUCU	32	AAAUUUCAUCUUUCCA	440	AT4382-4383	31.22	3.49	31.29	3.12	158	
MAPT_2676	2676	UAUUCUCUCCUCUCCACAAUU	33	UGGAGAGGAGAGAAUA	441	AT4312-4313	31.48	0.56	33.82	2.84	189	
MAPT_2669	2669	UCCUCUCCACAAUUAUUGACC	34	AUAAUUGUGGAGAGGA	442	AT4298-4299	31.52	0.74	42.44	0.32		
MAPT_2327	2327	UUUUACUUCCACCUGGCCACC	35	CCAGGUGGAAGUAAAA	443	AT4244-4245	32.20	3.01	36.84	3.18	246	
MAPT_303	303	UCCUGGUUCAAAGUUCACCUG	36	GAACUUUGAACCAGGA	444	AT4136-4137	32.39	3.12	39.46	1.35	292	

MAPT_286	286	UCUGAUAGUCGACAGAGGCGA	37	UCUGUCGACUAUCAGA	445	AT2512-2513	32.80	0.31	43.76	0.43	120
MAPT_2672	2672	UUCUCCUCUCCACAAUUAUUG	38	AUUGUGGAGAGGAGAA	446	AT4304-4305	32.86	0.21	33.24	0.47	
MAPT_2845	2845	UUUGGAAAGAUGAAAUUUGCU	39	AUUUCAUCUUUCCAAA	447	AT4386-4387	33.00	1.43	36.06	1.57	
MAPT_306	306	UCAUCCUGGUUCAAAGUUCAC	40	CUUUGAACCAGGAUGA	448	AT4140-4141	33.09	8.35	40.14	6.05	
MAPT_2340	2340	UAAGCUUCUCAGAUUUUACUU	41	AAAUCUGAGAAGCUUA	449	AT4252-4253	34.00	3.16	36.67	3.97	
MAPT_2248	2248	UCAACUGGUUUGUAGACUAUU	42	UCUACAAACCAGUUGA	450	AT4228-4229	34.12	1.45	38.49	0.43	
MAPT_288	288	UACCUGAUAGUCGACAGAGGC	43	UGUCGACUAUCAGGUA	451	AT4126-4127	34.24	0.84	46.04	1.34	
MAPT_2844	2844	UUGGAAAGAUGAAAUUUGCUC	44	AAUUUCAUCUUUCCAA	452	AT4384-4385	34.35	3.51	40.01	0.40	
MAPT_2682	2682	UUCUCUCAUUCUCUCCUCCC	45	GGAGAGAAUGAGAAGAA	453	AT4322-4323	34.62	5.87	35.74	0.14	
MAPT_302	302	UCUGGUUCAAAGUUCACCUGA	46	UGAACUUUGAACCAGA	454	AT4134-4135	34.90	1.99	48.29	0.58	
MAPT_2329	2329	UAUUUUACUUCCACCUGGCCA	47	AGGUGGAAGUAAAAUA	455	AT4246-4247	35.42	1.55	75.75	7.05	
MAPT_1469	1469	UUCGCUUCCAGUCCGUCUUU	48	CGGGACUGGAAGCGAA	456	AT4158-4159	35.86	4.27	35.31	2.82	
MAPT_2810	2810	UGAUUUUGAAGUCCCGAGCCA	49	CGGGACUUCAAAAUCA	457	AT2602-2603	36.06	0.76	82.47	80.01	684

MAPT_2295	2295	UAUGGAUGUUG CCUAAUGAGC	50	UUAGGCAAC AUCCAUA	458	AT4238-4239	36.58	4.33	40.46	1.52	
MAPT_2842	2842	UGAAAGAUGAA AUUUGCUCUU	51	CAAAUUUCA UCUUUCA	459	AT4380-4381	36.76	3.67	35.70	0.02	
MAPT_2566	2566	UCCAUGUCGAUG CUGCCGGUG	52	GCAGCAUCGA CAUGGA	460	AT4288-4289	37.10	0.46	45.99	0.95	1360
MAPT_290	290	UUCACCUGAUAG UCGACAGAG	53	UCGACUAUCA GGUGAA	461	AT4130-4131	37.16	0.41	54.14	9.76	
MAPT_4523	4523	UAUCCAAGCAUA AACAGACAA	54	UGUUUAUGC UUGGAUA	462	AT4430-4431	37.54	0.89	48.91	4.00	
MAPT_2868	2868	UUUAUUACUAG CCCACCCAUC	55	GUGGGCUAG UAAUAAA	463	AT2622-2623	37.88	0.07	67.07	64.79	
MAPT_6510	6510	UUCAGAAGUUU UAUGAAGCUG	56	UCAUAAAAC UUCUGAA	464	AT2884-2885	39.09	0.11	73.79	0.24	
MAPT_2082	2082	UGGACUUGACAU UCUUCAGGU	57	AAGAAUGUC AAGUCCA	465	AT4176-4177	39.13	6.29	42.10	0.04	
MAPT_2330	2330	UGAUUUUACUU CCACCUGGCC	58	GGUGGAAGU AAAAUCA	466	AT4248-4249	40.13	0.99	50.94	3.02	282
MAPT_2817	2817	UCAUCACUGAUU UUGAAGUCC	59	UCAAAAUCA GUGAUGA	467	AT4360-4361	40.16	1.22	45.24	4.97	353
MAPT_2390	2390	UGUGAUAUUGU CCAGGGACCC	60	CCUGGACAAU AUCACA	468	AT2576-2577	40.24	0.46	55.77	54.32	
MAPT_2433	2433	UCUUGUGGGUU UCAAUCUUUU	61	AUUGAAACCC ACAAGA	469	AT4274-4275	40.38	4.14	52.71	1.84	12800
MAPT_305	305	UAUCCUGGUUCA AAGUUCACC	62	ACUUUGAACC AGGAUA	470	AT2514-2515	40.87	1.39	63.27	0.13	

MAPT_2830	2830	UUUGCUCUUACUCCCAUCACU	63	UGGGAGUAAGAGCAAA	471	AT4366-4367	41.92	0.60	42.47	3.10	
MAPT_6748	6748	UUCAGUGUAAAUCAUUUGUUA	64	AAUGAUUUACACUGAA	472	AT2920-2921	42.40	1.57	54.89	0.69	
MAPT_2540	2540	UACAUUGCUGAGAUGCCGUGG	65	GCAUCUCAGCAAUGUA	473	AT4286-4287	42.57	3.34	46.74	2.65	
MAPT_2851	2851	UAUCAAUUUGGAAAGAUGAAA	66	UCUUUCCAAAUUGAUA	474	AT4388-4389	43.15	3.13	47.93	0.69	327
MAPT_2832	2832	UAUUUGCUCUUACUCCCAUCA	67	GGAGUAAGAGCAAAUA	475	AT4370-4371	43.72	1.71	42.40	2.25	
MAPT_2675	2675	UUUCUCUCCUCUCCACAAUUA	68	GUGGAGAGGAGAGAAA	476	AT4310-4311	44.10	1.59	40.21	1.26	
MAPT_6710	6710	UAUAGACAUUCACAGACAGAA	69	UCUGUGAAUGUCUAUA	477	AT2904-2905	44.23	4.47	58.37	2.86	
MAPT_2299	2299	UUAUGAUGGAUGUUGCCUAAU	70	GCAACAUCCAUCAUAA	478	AT4242-4243	44.28	2.24	49.51	2.46	
MAPT_2292	2292	UGAUGUUGCCUAAUGAGCCAC	71	UCAUUAGGCAACAUCA	479	AT4236-4237	44.71	2.38	47.52	0.45	
MAPT_2819	2819	UCCCAUCACUGAUUUUGAAGU	72	AAAAUCAGUGAUGGGA	480	AT4364-4365	44.94	2.60	47.61	1.57	474
MAPT_2677	2677	UCAUUCUCUCCUCUCCACAAU	73	GGAGAGGAGAGAAUGA	481	AT4314-4315	45.11	3.10	50.07	0.63	
MAPT_2837	2837	UAUGAAAUUUGCUCUUACUCC	74	AAGAGCAAAUUUCAUA	482	AT4374-4375	45.87	3.78	44.42	0.42	
MAPT_287	287	UCCUGAUAGUCGACAGAGGCG	75	CUGUCGACUAUCAGGA	483	AT4124-4125	45.97	1.35	69.01	6.25	

MAPT_2371	2371	UCAAUCUUCGACUGGACUCUG	76	UCCAGUCGAAGAUUGA	484	AT4258-4259	47.07	0.82	51.02	2.19	
MAPT_4511	4511	UACAGACAAAUCCAACUACAA	77	GUUGGAUUUGUCUGUA	485	AT4426-4427	47.26	3.30	60.45	1.77	82.7
MAPT_4515	4515	UAUAAACAGACAAAUCCAACU	78	GAUUUGUCUGUUUAUA	486	AT4428-4429	48.24	1.23	71.18	9.85	
MAPT_2815	2815	UUCACUGAUUUUGAAGUCCCG	79	CUUCAAAAUCAGUGAA	487	AT2606-2607	48.42	0.87	67.65	70.88	481
MAPT_2773	2773	UCAGGUUAAGUGAUUAACCAA	80	UAAUCACUUAACCUGA	488	AT2594-2595	48.70	0.04	60.73	62.65	
MAPT_2252	2252	UAGGUCAACUGGUUUGUAGAC	81	CAAACCAGUUGACCUA	489	AT4232-4233	49.61	2.28	48.91	2.63	
MAPT_2814	2814	UCACUGAUUUUGAAGUCCCGA	82	ACUUCAAAAUCAGUGA	490	AT4356-4357	49.65	2.78	61.32	6.79	385
MAPT_2678	2678	UUCAUUCUCUCCUCUCCACAA	83	GAGAGGAGAGAAUGAA	491	AT4316-4317	49.80	0.57	54.96	3.87	
MAPT_6708	6708	UAGACAUUCACAGACAGAAAG	84	UGUCUGUGAAUGUCUA	492	AT4466-4467	50.15	0.48	53.23	0.06	
MAPT_2816	2816	UAUCACUGAUUUUGAAGUCCC	85	UUCAAAAAUCAGUGAUA	493	AT4358-4359	50.18	0.31	58.99	3.21	
MAPT_6731	6731	UUUAAAACACACAAUACACUA	86	UAUUGUGUGUUUUAAA	494	AT2918-2919	50.24	0.35	66.25	0.56	
MAPT_6723	6723	UCACAAUACACUAUAUAGACA	87	AUAUAGUGUAUUGUGA	495	AT2916-2917	50.28	1.23	80.93	13.09	
MAPT_4509	4509	UAGACAAAUCCAACUACAACU	88	UAGUUGGAUUUUGUCUA	496	AT4424-4425	50.31	1.39	55.19	3.88	

MAPT_2812	2812	UCUGAUUUUGAAGUCCCGAGC	89	GGACUUCAAAAUCAGA	497	AT2604-2605	50.32	1.45	58.28	56.20	
MAPT_2871	2871	UAUUUUAUUACUAGCCCACCC	90	GGCUAGUAAUAAAAUA	498	AT4398-4399	50.93	1.61	48.58	1.08	
MAPT_5942	5942	UAACUAUUGAUAAAGUGAGUC	91	ACUUUAUCAAUAGUUA	499	AT2820-2821	51.34	1.34	53.60	5.05	
MAPT_4525	4525	UGAAUCCAAGCAUAAACAGAC	92	UUUAUGCUUGGAUUCA	500	AT4432-4433	51.43	1.73	59.94	1.42	
MAPT_2872	2872	UUAUUUUAUUACUAGCCCACC	93	GCUAGUAAUAAAAUAA	501	AT2626-2627	51.82	4.18	78.87	76.61	
MAPT_2834	2834	UAAAUUUGCUCUUACUCCCAU	94	AGUAAGAGCAAAUUUA	502	AT2608-2609	51.98	0.02	72.42	75.74	
MAPT_6757	6757	UCAGCAACAGUCAGUGUAAAU	95	CACUGACUGUUGCUGA	503	AT2922-2923	52.06	0.83	67.82	1.30	
MAPT_6749	6749	UGUCAGUGUAAAUCAUUUGUU	96	AUGAUUUACACUGACA	504	AT4476-4477	52.77	3.62	50.61	0.04	
MAPT_309	309	UAGCCAUCCUGGUUCAAAGUU	97	UGAACCAGGAUGGCUA	505	AT4146-4147	52.80	6.50	55.89	3.69	
MAPT_5940	5940	UCUAUUGAUAAAGUGAGUCAG	98	UCACUUUAUCAAUAGA	506	AT4454-4455	53.12	0.98	64.79	2.46	
MAPT_4544	4544	UCUAUCAUAGUCACUCUGGUG	99	GAGUGACUAUGAUAGA	507	AT4436-4437	53.48	0.57	63.45	2.62	
MAPT_285	285	UUGAUAGUCGACAGAGGCGAG	100	CUCUGUCGACUAUCAA	508	AT4122-4123	53.79	3.79	73.43	5.77	
MAPT_2813	2813	UACUGAUUUUGAAGUCCCGAG	101	GACUUCAAAAUCAGUA	509	AT4354-4355	54.43	1.33	68.26	2.60	

MAPT_6707	6707	UGACAUUCACAG ACAGAAAGC	102	CUGUCUGUG AAUGUCA	510	AT4464-4465	55.09	1.98	59.91	4.84	
MAPT_2414	2414	UUUAUUUCCUCC GCCAGGGAC	103	UGGCGGAGG AAAUAAA	511	AT2580-2581	55.10	0.79	87.84	88.16	
MAPT_5941	5941	UACUAUUGAUA AAGUGAGUCA	104	CACUUUAUC AAUAGUA	512	AT2818-2819	55.11	1.34	52.88	2.46	
MAPT_2839	2839	UAGAUGAAAUU UGCUCUUACU	105	GAGCAAAUU UCAUCUA	513	AT4378-4379	55.45	2.12	50.35	0.66	
MAPT_2777	2777	UAAAGCAGGUUA AGUGAUUAA	106	CACUUAACCU GCUUUA	514	AT4346-4347	55.50	2.01	66.69	5.98	
MAPT_6504	6504	UGUUUUAUGAA GCUGCAGGUC	107	GCAGCUUCAU AAAACA	515	AT2880-2881	56.21	2.45	65.80	2.24	
MAPT_2818	2818	UCCAUCACUGAU UUUGAAGUC	108	CAAAAUCAG UGAUGGA	516	AT4362-4363	56.29	0.54	58.19	3.82	
MAPT_5978	5978	UAGGAUACAGUC UCACCACUG	109	GUGAGACUG UAUCCUA	517	AT2832-2833	56.93	2.18	55.49	1.64	
MAPT_5943	5943	UGAACUAUUGA UAAAGUGAGU	110	CUUUAUCAA UAGUUCA	518	AT2822-2823	57.01	1.32	54.19	2.36	
MAPT_289	289	UCACCUGAUAGU CGACAGAGG	111	GUCGACUAUC AGGUGA	519	AT4128-4129	57.15	4.11	71.78	2.81	
MAPT_301	301	UUGGUUCAAAG UUCACCUGAU	112	GUGAACUUU GAACCAA	520	AT4132-4133	57.42	5.26	67.09	1.91	
MAPT_5938	5938	UAUUGAUAAAG UGAGUCAGCA	113	ACUCACUUU AUCAAUA	521	AT4450-4451	57.47	3.28	67.48	1.39	
MAPT_5944	5944	UGGAACUAUUG AUAAAGUGAG	114	UUUAUCAAU AGUUCCA	522	AT2824-2825	57.66	0.27	53.93	5.87	

MAPT_5645	5645	UGAACUUCAGGAAGAGGAACC	115	CUCUUCCUGAAGUUCA	523	AT2812-2813	57.94	3.43	57.21	0.95	
MAPT_2575	2575	UGCGAGUCUACCAUGUCGAUG	116	ACAUGGUAGACUCGCA	524	AT2588-2589	58.19	0.18	80.35	79.01	
MAPT_6524	6524	UAAGCUGAAGAGAAAUCAGAA	117	AUUUCUCUUCAGCUUA	525	AT2886-2887	58.38	3.07	63.91	2.23	
MAPT_6753	6753	UAACAGUCAGUGUAAAUCAUU	118	UUUACACUGACUGUUA	526	AT4484-4485	58.43	0.52	59.71	1.81	
MAPT_6750	6750	UAGUCAGUGUAAAUCAUUUGU	119	UGAUUUACACUGACUA	527	AT4478-4479	58.72	1.42	57.33	1.75	
MAPT_4548	4548	UUUCACUAUCAUAGUCACUCU	120	GACUAUGAUAGUGAAA	528	AT4438-4439	58.83	0.41	60.81	1.37	
MAPT_1475	1475	UUUGUCAUCGCUUCCAGUCCC	121	UGGAAGCGAUGACAAA	529	AT4168-4169	58.92	5.24	57.57	1.15	
MAPT_6754	6754	UCAACAGUCAGUGUAAAUCAU	122	UUACACUGACUGUUGA	530	AT4486-4487	58.95	0.57	64.19	4.53	
MAPT_2377	2377	UGGGACCCAAUCUUCGACUGG	123	CGAAGAUUGGGUCCCA	531	AT4260-4261	59.23	0.27	56.43	2.85	
MAPT_6699	6699	UCAGACAGAAAGCUAAGCUAA	124	UUAGCUUUCUGUCUGA	532	AT2898-2899	59.32	1.41	64.01	0.49	
MAPT_6732	6732	UGUUAAAACACACAAUACACU	125	AUUGUGUGUUUUAACA	533	AT4474-4475	59.42	4.99	58.68	3.72	
MAPT_6751	6751	UCAGUCAGUGUAAAUCAUUUG	126	GAUUUACACUGACUGA	534	AT4480-4481	59.68	3.74	67.50	2.81	
MAPT_6431	6431	UUUACUUGGAGAACAAAGAUG	127	UUGUUCUCCAAGUAAA	535	AT2872-2873	59.84	1.18	77.12	6.59	

MAPT_6759	6759	UUACAGCAACAG UCAGUGUAA	128	CUGACUGUU GCUGUAA	536	AT4492-4493	59.86	0.18	57.55	2.60	
MAPT_6511	6511	UAUCAGAAGUU UUAUGAAGCU	129	CAUAAAACU UCUGAUA	537	AT4462-4463	59.92	1.66	59.89	1.22	
MAPT_2264	2264	UGUCACCUUGCU CAGGUCAAC	130	CCUGAGCAAG GUGACA	538	AT4234-4235	59.93	0.38	58.22	4.23	
MAPT_4551	4551	UCUUUUCACUAU CAUAGUCAC	131	UAUGAUAGU GAAAAGA	539	AT4442-4443	59.97	2.91	65.07	6.93	
MAPT_6430	6430	UUACUUGGAGA ACAAAGAUGA	132	UUUGUUCUC CAAGUAA	540	AT2870-2871	60.17	1.92	76.72	5.84	
MAPT_5960	5960	UUGAAGUCAAU UUAAAUGGAA	133	UUUAAAUUG ACUUCAA	541	AT2826-2827	60.26	1.70	59.18	1.24	
MAPT_6752	6752	UACAGUCAGUGU AAAUCAUUU	134	AUUUACACU GACUGUA	542	AT4482-4483	60.34	0.22	70.43	4.58	
MAPT_350	350	UCCAGCGUGAUC UUCCAUCAC	135	GGAAGAUCAC GCUGGA	543	AT4148-4149	60.38	6.66	60.17	0.04	
MAPT_4549	4549	UUUUCACUAUCA UAGUCACUC	136	ACUAUGAUA GUGAAAA	544	AT4440-4441	60.49	0.12	62.19	2.92	
MAPT_6034	6034	UAACUAUCUUAC ACAUUCCUC	137	AUGUGUAAG AUAGUUA	545	AT2838-2839	60.70	0.79	63.18	1.93	
MAPT_6724	6724	UACACAAUACAC UAUAUAGAC	138	UAUAGUGUA UUGUGUA	546	AT4470-4471	61.07	2.55	71.79	4.45	
MAPT_6700	6700	UACAGACAGAAA GCUAAGCUA	139	UAGCUUUCU GUCUGUA	547	AT2900-2901	61.30	0.84	85.53	1.94	
MAPT_6709	6709	UUAGACAUUCAC AGACAGAAA	140	GUCUGUGAA UGUCUAA	548	AT2902-2903	61.70	1.83	68.36	1.16	

MAPT_2809	2809	UAUUUUGAAGU CCCGAGCCAA	141	UCGGGACUUC AAAAUA	549	AT2600-2601	62.07	1.08	76.41	76.41	
MAPT_6725	6725	UCACACAAUACA CUAUAUAGA	142	AUAGUGUAU UGUGUGA	550	AT4472-4473	62.17	0.51	75.16	7.37	
MAPT_6711	6711	UUAUAGACAUUC ACAGACAGA	143	CUGUGAAUG UCUAUAA	551	AT2906-2907	62.27	10.85	74.69	4.00	
MAPT_6758	6758	UACAGCAACAGU CAGUGUAAA	144	ACUGACUGU UGCUGUA	552	AT2924-2925	62.42	4.50	66.15	2.61	
MAPT_4613	4613	UUGGGUUAGAA ACCUCUUUAC	145	GAGGUUUCU AACCCAA	553	AT2746-2747	62.53	0.66	74.76	2.55	
MAPT_4291	4291	UGCAGCUACAAG CUAGGGUGC	146	CUAGCUUGU AGCUGCA	554	AT2696-2697	62.54	4.95	72.74	0.47	
MAPT_6756	6756	UAGCAACAGUCA GUGUAAAUC	147	ACACUGACUG UUGCUA	555	AT4490-4491	62.87	1.84	61.03	0.56	
MAPT_6770	6770	UAAAUUCACUU UUACAGCAAC	148	UGUAAAAGU GAAUUUA	556	AT2930-2931	62.95	8.63	69.75	6.03	
MAPT_2250	2250	UGUCAACUGGUU UGUAGACUA	149	UACAAACCAG UUGACA	557	AT4230-4231	63.26	2.76	65.65	0.93	
MAPT_6769	6769	UAAUUCACUUU UACAGCAACA	150	CUGUAAAAG UGAAUUA	558	AT2928-2929	63.33	3.74	68.75	0.82	
MAPT_2831	2831	UUUUGCUCUUAC UCCCAUCAC	151	GGGAGUAAG AGCAAAA	559	AT4368-4369	63.36	1.17	70.42	7.66	
MAPT_5990	5990	UGCAAUAGCAAA CAGGAUACA	152	CCUGUUUGC UAUUGCA	560	AT2836-2837	63.37	3.31	56.91	4.50	
MAPT_6760	6760	UUUACAGCAACA GUCAGUGUA	153	UGACUGUUG CUGUAAA	561	AT2926-2927	63.57	5.11	70.06	3.36	

MAPT_6761	6761	UUUUACAGCAACAGUCAGUGU	154	GACUGUUGCUGUAAAA	562	AT4494-4495	63.60	3.44	62.46	3.57	
MAPT_2867	2867	UUAUUACUAGCCCACCCAUCA	155	GGUGGGCUAGUAAUAA	563	AT4396-4397	63.73	4.45	66.77	6.36	
MAPT_2804	2804	UGAAGUCCCGAGCCAAAGCCG	156	UUGGCUCGGGACUUCA	564	AT2598-2599	63.82	1.15	95.98	91.64	
MAPT_4450	4450	UUAUAUGUUCAGCUGCUCCAG	157	GCAGCUGAACAUAUAA	565	AT2714-2715	64.32	1.48	80.87	6.18	
MAPT_3082	3082	UCAAAUCCUUUGUUGCUGCCA	158	GCAACAAAGGAUUUGA	566	AT2646-2647	64.41	2.32	83.45	78.07	
MAPT_1474	1474	UUGUCAUCGCUUCCAGUCCCG	159	CUGGAAGCGAUGACAA	567	AT4166-4167	64.58	1.45	54.98	1.83	
MAPT_6527	6527	UUCAAAGCUGAAGAGAAAUCA	160	UCUCUUCAGCUUUGAA	568	AT2890-2891	64.84	2.55	67.70	0.97	
MAPT_6508	6508	UAGAAGUUUUAUGAAGCUGCA	161	CUUCAUAAAACUUCUA	569	AT2882-2883	64.93	0.52	59.09	0.68	
MAPT_6526	6526	UCAAAGCUGAAGAGAAAUCAG	162	UUCUCUUCAGCUUUGA	570	AT2888-2889	65.19	2.47	64.29	0.29	
MAPT_2869	2869	UUUUAUUACUAGCCCACCCAU	163	UGGGCUAGUAAUAAAA	571	AT2624-2625	65.21	2.03	83.97	84.39	
MAPT_4961	4961	UCUUGUGAUGCAGGAGUUGUA	164	CUCCUGCAUCACAAGA	572	AT2756-2757	65.21	3.82	78.05	1.20	
MAPT_5450	5450	UAGACUUCCUUUCAGGUAAAG	165	CCUGAAAGGAAGUCUA	573	AT2794-2795	65.21	5.55	71.80	3.26	
MAPT_406	406	UGGUCUUGGUGCAUGGUGUAG	166	CCAUGCACCAAGACCA	574	AT4152-4153	65.33	0.74	64.78	1.86	

MAPT_4506	4506	UCAAAUCCAACUACAACUCAA	167	UUGUAGUUGGAUUUGA	575	AT2718-2719	65.44	0.59	75.54	2.61	
MAPT_4538	4538	UUAGUCACUCUGGUGAAUCCA	168	UCACCAGAGUGACUAA	576	AT2728-2729	65.74	3.36	94.94	1.98	
MAPT_5975	5975	UAUACAGUCUCACCACUGAAG	169	GUGGUGAGACUGUAUA	577	AT2828-2829	65.95	1.58	60.49	2.39	
MAPT_5939	5939	UUAUUGAUAAAGUGAGUCAGC	170	CUCACUUUAUCAAUAA	578	AT4452-4453	66.03	0.15	75.74	8.17	
MAPT_4530	4530	UCUGGUGAAUCCAAGCAUAAA	171	GCUUGGAUUCACCAGA	579	AT2724-2725	66.22	0.00	72.56	3.48	
MAPT_2240	2240	UUUGUAGACUAUUUGCACACU	172	GCAAAUAGUCUACAAA	580	AT4226-4227	66.47	2.43	69.33	0.20	
MAPT_5981	5981	UAACAGGAUACAGUCUCACCA	173	AGACUGUAUCCUGUUA	581	AT2834-2835	66.79	1.04	61.37	1.56	
MAPT_6755	6755	UGCAACAGUCAGUGUAAAUCA	174	UACACUGACUGUUGCA	582	AT4488-4489	66.88	1.11	67.48	4.43	
MAPT_4507	4507	UACAAAUCCAACUACAACUCA	175	UGUAGUUGGAUUUGUA	583	AT2720-2721	67.09	1.99	72.90	3.27	
MAPT_2778	2778	UAAAAGCAGGUUAAGUGAUUA	176	ACUUAACCUGCUUUUA	584	AT2596-2597	67.33	2.27	79.79	82.19	
MAPT_283	283	UAUAGUCGACAGAGGCGAGGA	177	GCCUCUGUCGACUAUA	585	AT4118-4119	68.12	0.59	88.15	4.29	
MAPT_4592	4592	UAGCAUUUCAAGAUACAUGCG	178	GUAUCUUGAAAUGCUA	586	AT2742-2743	68.16	3.45	74.73	2.27	
MAPT_4612	4612	UGGGUUAGAAACCUCUUUACA	179	AGAGGUUUCUAACCCA	587	AT2744-2745	68.22	0.54	74.13	1.38	

MAPT_4547	4547	UUCACUAUCAUA GUCACUCUG	180	UGACUAUGA UAGUGAA	588	AT2738-2739	68.82	0.04	76.72	2.54	
MAPT_6425	6425	UGGAGAACAAAG AUGAGGAGG	181	UCAUCUUUG UUCUCCA	589	AT2868-2869	68.83	6.56	68.45	2.35	
MAPT_4541	4541	UUCAUAGUCACU CUGGUGAAU	182	CCAGAGUGAC UAUGAA	590	AT2732-2733	69.35	2.51	80.08	14.24	
MAPT_2838	2838	UGAUGAAAUUU GCUCUUACUC	183	AGAGCAAAU UUCAUCA	591	AT4376-4377	69.46	1.16	61.19	4.90	
MAPT_3079	3079	UAUCCUUUGUU GCUGCCACUG	184	GCAGCAACAA AGGAUA	592	AT2644-2645	69.63	3.98	72.53	76.92	
MAPT_6722	6722	UACAAUACACUA UAUAGACAU	185	UAUAUAGUG UAUUGUA	593	AT4468-4469	69.66	1.47	77.76	4.91	
MAPT_284	284	UGAUAGUCGACA GAGGCGAGG	186	CCUCUGUCGA CUAUCA	594	AT4120-4121	69.89	0.78	86.24	5.21	
MAPT_6506	6506	UAAGUUUUAUG AAGCUGCAGG	187	AGCUUCAUA AAACUUA	595	AT4458-4459	69.89	0.13	80.87	1.26	
MAPT_4546	4546	UCACUAUCAUAG UCACUCUGG	188	GUGACUAUG AUAGUGA	596	AT2736-2737	69.94	4.25	79.39	0.74	
MAPT_4958	4958	UGUGAUGCAGGA GUUGUAAGC	189	CAACUCCUGC AUCACA	597	AT2752-2753	70.85	4.24	68.49	0.14	
MAPT_6528	6528	UUUCAAAGCUGA AGAGAAAUC	190	CUCUUCAGCU UUGAAA	598	AT2892-2893	71.84	1.16	72.93	2.71	
MAPT_4787	4787	UUCCUGUGCUUC AGGCCUUCG	191	GCCUGAAGCA CAGGAA	599	AT4446-4447	71.95	3.18	80.69	0.17	
MAPT_2772	2772	UAGGUUAAGUG AUUAACCAAU	192	UUAAUCACU UAACCUA	600	AT4342-4343	72.11	1.90	85.06	6.71	

MAPT_6640	6640	UAAGAAAUCAUG GGACUUGCA	193	GUCCCAUGAU UUCUUA	601	AT2896-2897	72.36	1.18	78.48	3.41	
MAPT_4962	4962	UUCUUGUGAUGC AGGAGUUGU	194	UCCUGCAUCA CAAGAA	602	AT2758-2759	72.48	1.09	78.48	0.11	
MAPT_5536	5536	UCUCCUUCUCAG AUCCCUUCA	195	GGAUCUGAG AAGGAGA	603	AT2804-2805	72.80	5.46	90.43	3.04	
MAPT_6100	6100	UGAAAUCAUGAA AAGGGUUAC	196	CCUUUUCAU GAUUUCA	604	AT2842-2843	72.84	4.09	86.26	0.12	
MAPT_2931	2931	UAAAGGAAUUGC CUGAGGAAA	197	UCAGGCAAU UCCUUUA	605	AT2638-2639	73.07	1.20	69.39	72.50	
MAPT_6712	6712	UAUAUAGACAU UCACAGACAG	198	UGUGAAUGU CUAUAUA	606	AT2908-2909	73.28	8.91	69.14	0.71	
MAPT_3578	3578	UUUCAGAACUCA AUAAAACAG	199	UUAUUGAGU UCUGAAA	607	AT2656-2657	73.65	0.13	85.77	3.31	
MAPT_4545	4545	UACUAUCAUAGU CACUCUGGU	200	AGUGACUAU GAUAGUA	608	AT2734-2735	73.85	2.85	78.88	0.23	
MAPT_5213	5213	UGUCAAGGCUUU GGGAACAGU	201	UCCCAAAGCC UUGACA	609	AT2772-2773	74.16	3.65	97.54	3.94	
MAPT_2935	2935	UAUCAAAAGGAA UUGCCUGAG	202	GCAAUUCCU UUUGAUA	610	AT2642-2643	74.21	3.03	75.33	74.98	
MAPT_2359	2359	UGGACUCUGUCC UUGAAGUCA	203	UCAAGGACAG AGUCCA	611	AT2572-2573	74.34	2.43	83.47	83.36	
MAPT_5667	5667	UGGUGCUGAAGA GCAGGGCAC	204	CUGCUCUUCA GCACCA	612	AT2814-2815	74.36	1.58	73.48	3.35	
MAPT_6319	6319	UAGGGAAGGAUG CCAAGGUCU	205	UUGGCAUCC UUCCCUA	613	AT2858-2859	74.56	6.07	84.03	2.52	

MAPT_4529	4529	UUGGUGAAUCCAAGCAUAAAC	206	UGCUUGGAUUCACCAA	614	AT2722-2723	74.64	0.01	86.72	1.59	
MAPT_5976	5976	UGAUACAGUCUCACCACUGAA	207	UGGUGAGACUGUAUCA	615	AT2830-2831	75.17	0.61	71.31	4.90	
MAPT_4552	4552	UUCUUUUCACUAUCAUAGUCA	208	AUGAUAGUGAAAAGAA	616	AT2740-2741	75.88	1.72	91.16	3.21	
MAPT_4539	4539	UAUAGUCACUCUGGUGAAUCC	209	CACCAGAGUGACUAUA	617	AT4434-4435	76.05	1.70	90.11	1.87	177
MAPT_2440	2440	UAGGUCAGCUUGUGGGUUUCA	210	CCCACAAGCUGACCUA	618	AT4278-4279	76.09	2.53	77.08	0.20	
MAPT_4786	4786	UCCUGUGCUUCAGGCCUUCGU	211	GGCCUGAAGCACAGGA	619	AT4444-4445	76.20	1.80	88.12	2.82	
MAPT_6509	6509	UCAGAAGUUUUAUGAAGCUGC	212	UUCAUAAAACUUCUGA	620	AT4460-4461	76.25	0.59	93.29	8.67	unstable
MAPT_3473	3473	UCAAGGUCAGUCUUUUCUAAG	213	AAAAGACUGACCUUGA	621	AT2648-2649	76.28	4.13	108.98	103.74	
MAPT_2386	2386	UUAUUGUCCAGGGACCCAAUC	214	GGUCCCUGGACAAUAA	622	AT4262-4263	76.31	0.97	72.99	5.13	
MAPT_5571	5571	UCUCUAACCACCACCAAAUCU	215	UGGUGGUGGUUAGAGA	623	AT2808-2809	76.75	3.39	68.56	1.49	
MAPT_5945	5945	UUGGAACUAUUGAUAAAGUGA	216	UUAUCAAUAGUUCCAA	624	AT4456-4457	76.75	0.12	87.58	5.02	
MAPT_1476	1476	UUUUGUCAUCGCUUCCAGUCC	217	GGAAGCGAUGACAAAA	625	AT2522-2523	76.77	1.72	97.25	0.17	
MAPT_3594	3594	UGGCAGCAGUUCCAACCUUCA	218	GUUGGAACUGCUGCCA	626	AT2664-2665	77.02	1.72	83.73	0.56	

MAPT_5435	5435	UUAAAGCUCUAG CUGCACACG	219	GCAGCUAGAG CUUUAA	627	AT2792-2793	77.25	3.84	88.74	0.59	
MAPT_4451	4451	UGUAUAUGUUC AGCUGCUCCA	220	CAGCUGAACA UAUACA	628	AT2716-2717	77.28	1.25	78.69	3.53	
MAPT_5619	5619	UCGUGAAGAAAU GCAGCCGAA	221	CUGCAUUUC UUCACGA	629	AT2810-2811	77.38	5.64	66.83	0.27	
MAPT_2921	2921	UCCUGAGGAAAU GUUGGAUGU	222	CAACAUUUCC UCAGGA	630	AT2634-2635	77.40	2.45	94.69	98.39	
MAPT_4048	4048	UAGGGAACCGAA UCAGAUCAU	223	CUGAUUCGG UUCCCUA	631	AT2690-2691	77.48	5.72	77.49	5.70	
MAPT_6483	6483	UGUAGAUGGGAC ACGCAGGUG	224	GCGUGUCCCA UCUACA	632	AT2876-2877	77.51	0.32	80.16	0.33	
MAPT_2856	2856	UCACCCAUCAAU UUGGAAAGA	225	CCAAAUUGA UGGGUGA	633	AT2616-2617	77.99	1.28	102.85	98.69	
MAPT_4114	4114	UGGCAGAAACAC CUAGGGUCA	226	CUAGGUGUU UCUGCCA	634	AT2694-2695	78.04	0.22	83.06	0.35	
MAPT_1470	1470	UAUCGCUUCCAG UCCCGUCUU	227	GGGACUGGA AGCGAUA	635	AT4160-4161	78.71	1.81	84.18	0.38	
MAPT_2811	2811	UUGAUUUUGAA GUCCCGAGCC	228	GGGACUUCA AAAUCAA	636	AT4352-4353	78.83	0.30	78.96	3.25	
MAPT_6500	6500	UUAUGAAGCUGC AGGUCUGUA	229	ACCUGCAGCU UCAUAA	637	AT2878-2879	79.07	0.56	80.52	0.81	
MAPT_2833	2833	UAAUUUGCUCU UACUCCCAUC	230	GAGUAAGAG CAAAUUA	638	AT4372-4373	79.12	6.50	74.04	2.96	
MAPT_282	282	UUAGUCGACAGA GGCGAGGAC	231	CGCCUCUGUC GACUAA	639	AT4116-4117	79.30	2.35	100.80	13.04	

MAPT_4960	4960	UUUGUGAUGCA GGAGUUGUAA	232	ACUCCUGCAU CACAAA	640	AT2754-2755	79.37	4.12	86.53	7.33	
MAPT_304	304	UUCCUGGUUCAA AGUUCACCU	233	AACUUUGAA CCAGGAA	641	AT4138-4139	79.41	3.81	87.75	1.60	
MAPT_2864	2864	UUACUAGCCCAC CCAUCAAUU	234	AUGGGUGGG CUAGUAA	642	AT4390-4391	79.43	0.84	83.95	2.47	
MAPT_1471	1471	UCAUCGCUUCCA GUCCCGUCU	235	GGACUGGAA GCGAUGA	643	AT4162-4163	80.99	0.97	102.02	1.04	
MAPT_3587	3587	UGUUCCAACCUU CAGAACUCA	236	UCUGAAGGU UGGAACA	644	AT2660-2661	81.02	5.84	85.98	4.54	
MAPT_4537	4537	UAGUCACUCUGG UGAAUCCAA	237	UUCACCAGAG UGACUA	645	AT2726-2727	81.11	1.07	86.03	1.21	
MAPT_2441	2441	UAAGGUCAGCUU GUGGGUUUC	238	CCACAAGCUG ACCUUA	646	AT4280-4281	81.42	0.31	81.86	2.89	
MAPT_3562	3562	UACAGGGUUUCU GUGGAGCAG	239	CCACAGAAAC CCUGUA	647	AT2652-2653	81.74	0.96	93.86	95.59	
MAPT_4354	4354	UGGUGUGGAGGG CUGAUACUA	240	UCAGCCCUCC ACACCA	648	AT2704-2705	81.80	4.70	94.17	4.49	
MAPT_5208	5208	UGGCUUUGGGAA CAGUGUCUC	241	ACUGUUCCCA AAGCCA	649	AT2770-2771	82.29	2.15	101.24	1.06	
MAPT_2389	2389	UUGAUAUUGUC CAGGGACCCA	242	CCCUGGACAA UAUCAA	650	AT4266-4267	82.73	0.06	70.69	1.85	
MAPT_2537	2537	UUUGCUGAGAU GCCGUGGAGA	243	ACGGCAUCUC AGCAAA	651	AT4284-4285	83.47	3.53	82.44	2.63	
MAPT_6482	6482	UUAGAUGGGACA CGCAGGUGA	244	UGCGUGUCCC AUCUAA	652	AT2874-2875	83.96	0.31	91.05	4.54	

MAPT_2922	2922	UGCCUGAGGAAA UGUUGGAUG	245	AACAUUUCC UCAGGCA	653	AT2636-2637	84.76	1.54	87.15	91.20	
MAPT_2770	2770	UGUUAAGUGAU UAACCAAUUA	246	GGUUAAUCA CUUAACA	654	AT4340-4341	84.84	2.47	90.85	11.18	
MAPT_2442	2442	UGAAGGUCAGCU UGUGGGUUU	247	CACAAGCUGA CCUUCA	655	AT4282-4283	85.12	1.03	93.51	1.47	
MAPT_4963	4963	UUUCUUGUGAU GCAGGAGUUG	248	CCUGCAUCAC AAGAAA	656	AT2760-2761	85.18	1.03	92.48	2.46	
MAPT_1472	1472	UUCAUCGCUUCC AGUCCCGUC	249	GACUGGAAGC GAUGAA	657	AT4164-4165	85.26	5.19	73.79	2.70	
MAPT_6296	6296	UGGAGGCAUGAU UGUGGGCUU	250	CACAAUCAUG CCUCCA	658	AT2852-2853	85.28	0.37	68.57	8.02	
MAPT_276	276	UACAGAGGCGAG GACGGGAGA	251	CGUCCUCGCC UCUGUA	659	AT2510-2511	85.34	0.43	96.10	1.71	
MAPT_3663	3663	UAGGCACAAGUC CUUACAAAG	252	UAAGGACUU GUGCCUA	660	AT4416-4417	85.37	0.99	84.89	0.94	
MAPT_2175	2175	UGGACUGGACGU UGCUAAGAU	253	AGCAACGUCC AGUCCA	661	AT4206-4207	85.69	3.00	92.25	2.11	
MAPT_6713	6713	UUAUAUAGACA UUCACAGACA	254	GUGAAUGUC UAUAUAA	662	AT2910-2911	86.18	15.08	68.16	5.74	
MAPT_2807	2807	UUUUGAAGUCCC GAGCCAAAG	255	GCUCGGGACU UCAAAA	663	AT4350-4351	86.32	2.48	86.25	7.90	
MAPT_3581	3581	UACCUUCAGAAC UCAAUAAAA	256	UUGAGUUCU GAAGGUA	664	AT2658-2659	86.69	3.02	86.68	7.47	
MAPT_5890	5890	UCUAUCUAGCCC ACCCAAGGA	257	GGGUGGGCU AGAUAGA	665	AT4448-4449	86.83	3.20	99.95	1.06	

MAPT_2145	2145	UAUUAAUUAUC UGCACCUUCC	258	GUGCAGAUA AUUAAUA	666	AT4186-4187	87.10	2.29	86.02	1.33	
MAPT_4540	4540	UCAUAGUCACUC UGGUGAAUC	259	ACCAGAGUGA CUAUGA	667	AT2730-2731	87.16	3.86	115.90	2.57	
MAPT_2181	2181	UACACUUGGACU GGACGUUGC	260	GUCCAGUCCA AGUGUA	668	AT4212-4213	87.28	1.71	96.36	1.90	
MAPT_308	308	UGCCAUCCUGGU UCAAAGUUC	261	UUGAACCAG GAUGGCA	669	AT4144-4145	87.70	2.55	100.75	3.89	
MAPT_5546	5546	UACAUUUCCUUC UCCUUCUCA	262	AGGAGAAGG AAAUGUA	670	AT2806-2807	87.71	8.35	87.49	8.67	
MAPT_2865	2865	UUUACUAGCCCA CCCAUCAAU	263	UGGGUGGGC UAGUAAA	671	AT4392-4393	87.92	2.89	86.67	12.57	
MAPT_5243	5243	UUGUGCAAGGUC AGCGGGCUG	264	CGCUGACCUU GCACAA	672	AT2778-2779	88.13	0.47	119.92	6.08	
MAPT_2201	2201	UUUGAUAUUAU CCUUUGAGCC	265	AAAGGAUAA UAUCAAA	673	AT4218-4219	88.49	1.13	94.02	2.43	
MAPT_3633	3633	UAGCCCUAAAGU CCCAGGUCU	266	UGGGACUUU AGGGCUA	674	AT4408-4409	89.05	2.90	87.98	3.34	
MAPT_6327	6327	UCGGCUUAGAGG GAAGGAUGC	267	CUUCCCUCUA AGCCGA	675	AT2860-2861	89.17	2.72	98.81	3.75	
MAPT_513	513	UUGGAGUGCUCU UAGCAUCAG	268	GCUAAGAGCA CUCCAA	676	AT4156-4157	89.17	4.91	88.88	0.25	
MAPT_3631	3631	UCCCUAAAGUCC CAGGUCUGC	269	CCUGGGACUU UAGGGA	677	AT4404-4405	89.50	3.38	92.42	2.67	
MAPT_2177	2177	UUUGGACUGGAC GUUGCUAAG	270	CAACGUCCAG UCCAAA	678	AT4208-4209	89.57	6.94	98.61	1.20	

MAPT_3677	3677	UGGACGUCUCCC AAGAGGCAC	271	UCUUGGGAG ACGUCCA	679	AT2676-2677	90.02	0.06	85.34	4.76	
MAPT_5312	5312	UGCUGAGUUUCU UUAGGCAGC	272	CUAAAGAAA CUCAGCA	680	AT2786-2787	90.15	4.26	133.95	5.89	
MAPT_2866	2866	UAUUACUAGCCC ACCCAUCAA	273	GGGUGGGCU AGUAAUA	681	AT4394-4395	90.38	0.25	85.04	1.59	
MAPT_3632	3632	UGCCCUAAAGUC CCAGGUCUG	274	CUGGGACUU UAGGGCA	682	AT4406-4407	90.42	2.21	92.14	5.53	
MAPT_2143	2143	UUAAUUAUCUG CACCUUCCCG	275	AGGUGCAGA UAAUUAA	683	AT4184-4185	91.00	3.78	93.92	0.18	
MAPT_2920	2920	UCUGAGGAAAUG UUGGAUGUG	276	CCAACAUUUC CUCAGA	684	AT2632-2633	91.13	3.44	136.28	149.69	
MAPT_2193	2193	UAUCCUUUGAGC CACACUUGG	277	UGUGGCUCA AAGGAUA	685	AT4216-4217	91.24	3.24	80.91	3.60	
MAPT_2190	2190	UCUUUGAGCCAC ACUUGGACU	278	AAGUGUGGC UCAAAGA	686	AT2544-2545	91.29	8.99	100.98	5.24	
MAPT_2199	2199	UGAUAUUAUCC UUUGAGCCAC	279	UCAAAGGAU AAUAUCA	687	AT2548-2549	91.51	6.77	113.22	3.69	
MAPT_4914	4914	UUCGGGCUAUGA CCAGAGAGA	280	CUGGUCAUA GCCCGAA	688	AT2750-2751	91.92	4.12	115.51	6.38	
MAPT_2162	2162	UCUAAGAUCCAG CUUCUUAUU	281	GAAGCUGGA UCUUAGA	689	AT4198-4199	91.93	3.18	111.42	0.52	
MAPT_2176	2176	UUGGACUGGACG UUGCUAAGA	282	GCAACGUCCA GUCCAA	690	AT2540-2541	92.52	6.69	95.16	4.73	
MAPT_6315	6315	UAAGGAUGCCAA GGUCUUAGG	283	GACCUUGGCA UCCUUA	691	AT2856-2857	92.68	1.04	102.54	0.20	

MAPT_2186	2186	UGAGCCACACUUGGACUGGAC	284	GUCCAAGUGUGGCUCA	692	AT4214-4215	92.76	1.33	92.07	4.24	
MAPT_2169	2169	UGACGUUGCUAAGAUCCAGCU	285	GAUCUUAGCAACGUCA	693	AT4200-4201	93.03	0.81	100.21	5.88	
MAPT_2160	2160	UAAGAUCCAGCUUCUUAUUAA	286	AAGAAGCUGGAUCUUA	694	AT4194-4195	93.14	3.00	101.55	2.39	
MAPT_2148	2148	UCUUAUUAAUUAUCUGCACCU	287	CAGAUAAUUAAUAAGA	695	AT4188-4189	93.27	2.94	91.90	3.58	
MAPT_3658	3658	UCAAGUCCUUACAAAGAGAAC	288	CUUUGUAAGGACUUGA	696	AT2672-2673	93.29	0.97	94.04	4.65	
MAPT_2858	2858	UCCCACCCAUCAAUUUGGAAA	289	AAAUUGAUGGGUGGGA	697	AT2620-2621	93.35	4.32	113.72	111.65	
MAPT_2806	2806	UUUGAAGUCCCGAGCCAAAGC	290	GGCUCGGGACUUCAAA	698	AT4348-4349	93.41	2.64	90.63	2.36	
MAPT_2256	2256	UGCUCAGGUCAACUGGUUUGU	291	CCAGUUGACCUGAGCA	699	AT2562-2563	93.51	2.49	128.36	123.18	
MAPT_2172	2172	UCUGGACGUUGCUAAGAUCCA	292	CUUAGCAACGUCCAGA	700	AT4204-4205	93.56	5.15	97.66	2.05	
MAPT_6091	6091	UAAAAGGGUUACGAGGCAGUU	293	CCUCGUAACCCUUUUA	701	AT2840-2841	93.60	1.90	89.99	2.17	
MAPT_2857	2857	UCCACCCAUCAAUUUGGAAAG	294	CAAAUUGAUGGGUGGA	702	AT2618-2619	93.68	0.80	103.67	100.85	
MAPT_2229	2229	UUUGCACACUGCCGCCUCCCG	295	GGCGGCAGUGUGCAAA	703	AT2550-2551	93.86	2.83	112.22	18.37	
MAPT_2245	2245	UCUGGUUUGUAGACUAUUUGC	296	UAGUCUACAAACCAGA	704	AT2560-2561	94.27	5.40	108.43	103.67	

MAPT_5528	5528	UCAGAUCCCUUC AACUUAGGA	297	AGUUGAAGG GAUCUGA	705	AT2802-2803	94.33	6.33	83.82	6.42	
MAPT_2178	2178	UCUUGGACUGGA CGUUGCUAA	298	AACGUCCAGU CCAAGA	706	AT4210-4211	94.39	1.72	97.27	6.28	
MAPT_2161	2161	UUAAGAUCCAGC UUCUUAUUA	299	AGAAGCUGG AUCUUAA	707	AT4196-4197	94.46	0.92	108.24	3.97	
MAPT_3628	3628	UUAAAGUCCCAG GUCUGCAAA	300	AGACCUGGGA CUUUAA	708	AT4400-4401	94.51	0.16	97.04	5.53	
MAPT_3665	3665	UAGAGGCACAAG UCCUUACAA	301	AGGACUUGU GCCUCUA	709	AT4420-4421	95.34	3.73	101.21	4.71	
MAPT_3659	3659	UACAAGUCCUUA CAAAGAGAA	302	UUUGUAAGG ACUUGUA	710	AT2674-2675	95.39	2.94	91.90	0.27	
MAPT_6297	6297	UGGGAGGCAUGA UUGUGGGCU	303	ACAAUCAUGC CUCCCA	711	AT2854-2855	95.44	6.09	83.27	1.18	
MAPT_4735	4735	UGCUGGUCUCUG UUGGGUCCC	304	CCAACAGAGA CCAGCA	712	AT2748-2749	95.61	10.51	89.55	1.10	
MAPT_2195	2195	UUUAUCCUUUG AGCCACACUU	305	UGGCUCAAA GGAUAAA	713	AT2546-2547	95.68	1.76	106.88	7.28	
MAPT_3638	3638	UUGGUUAGCCCU AAAGUCCCA	306	CUUUAGGGC UAACCAA	714	AT4412-4413	95.97	1.40	101.10	7.35	
MAPT_2387	2387	UAUAUUGUCCAG GGACCCAAU	307	GUCCCUGGAC AAUAUA	715	AT4264-4265	96.21	0.82	72.81	0.43	
MAPT_2151	2151	UCUUCUUAUUA AUUAUCUGCA	308	AUAAUUAAU AAGAAGA	716	AT4190-4191	96.29	0.18	99.42	2.17	
MAPT_5142	5142	UAGAGCAGAUCC AGGACAGGC	309	UCCUGGAUC UGCUCUA	717	AT2766-2767	96.33	8.67	87.34	3.54	

MAPT_6352	6352	UGUGAGAGGUGG CACAGAGGU	310	UGUGCCACCU CUCACA	718	AT2862-2863	96.93	2.75	90.31	3.75	
MAPT_2027	2027	UUUGGCGGAAGA CGGCGACUU	311	GCCGUCUUCC GCCAAA	719	AT2530-2531	97.21	1.52	96.40	0.95	
MAPT_6110	6110	UAAAUGUGGUU GAAAUCAUGA	312	AUUUCAACC ACAUUUA	720	AT2844-2845	97.29	2.26	90.60	0.94	
MAPT_2239	2239	UUGUAGACUAU UUGCACACUG	313	UGCAAAUAG UCUACAA	721	AT4224-4225	97.30	1.84	95.29	1.65	
MAPT_2094	2094	UGGAGCCGAUCU UGGACUUGA	314	UCCAAGAUCG GCUCCA	722	AT4178-4179	97.33	8.65	88.21	1.71	
MAPT_5497	5497	UACUCAGCGAAC GGCAGGGAG	315	UGCCGUUCGC UGAGUA	723	AT2796-2797	97.38	5.90	85.21	5.92	
MAPT_4395	4395	UGGAAAAGAACC AUUUCCAAG	316	AAAUGGUUC UUUUCCA	724	AT2712-2713	97.78	2.69	112.89	2.00	
MAPT_6295	6295	UGAGGCAUGAUU GUGGGCUUA	317	CCACAAUCAU GCCUCA	725	AT2850-2851	99.52	11.63	102.56	6.07	
MAPT_3630	3630	UCCUAAAGUCCC AGGUCUGCA	318	ACCUGGGACU UUAGGA	726	AT4402-4403	99.64	2.11	111.82	4.98	
MAPT_5145	5145	UUCUAGAGCAGA UCCAGGACA	319	UGGAUCUGC UCUAGAA	727	AT2768-2769	99.87	2.77	104.48	3.55	
MAPT_6266	6266	UAAAGAGGGCAG CAGGCCAAA	320	CCUGCUGCCC UCUUUA	728	AT2846-2847	99.98	5.24	96.97	4.29	
MAPT_5282	5282	UAAAGGCGGCUU CCCUUUUCU	321	AGGGAAGCCG CCUUUA	729	AT2784-2785	100.02	6.71	142.11	11.98	
MAPT_2932	2932	UAAAAGGAAUU GCCUGAGGAA	322	CAGGCAAUUC CUUUUA	730	AT2640-2641	100.05	3.19	89.36	89.00	

MAPT_2439	2439	UGGUCAGCUUGUGGGUUUCAA	323	ACCCACAAGCUGACCA	731	AT4276-4277	100.12	8.55	92.92	0.53	
MAPT_3646	3646	UAAGAGAACUGGUUAGCCCUA	324	CUAACCAGUUCUCUUA	732	AT2670-2671	100.31	0.09	83.99	0.12	
MAPT_3603	3603	UCAAAAUCAUGGCAGCAGUUC	325	GCUGCCAUGAUUUUGA	733	AT2666-2667	100.40	2.57	99.84	1.35	
MAPT_3635	3635	UUUAGCCCUAAAGUCCCAGGU	326	GGACUUUAGGGCUAAA	734	AT4410-4411	100.42	0.94	98.66	0.41	
MAPT_2154	2154	UCAGCUUCUUAUUAAUUAUCU	327	AUUAAUAAGAAGCUGA	735	AT4192-4193	100.56	0.75	105.11	3.73	
MAPT_3661	3661	UGCACAAGUCCUUACAAAGAG	328	UGUAAGGACUUGUGCA	736	AT4414-4415	100.58	1.45	88.48	0.18	
MAPT_2170	2170	UGGACGUUGCUAAGAUCCAGC	329	AUCUUAGCAACGUCCA	737	AT4202-4203	100.81	5.17	104.11	4.02	
MAPT_2212	2212	UCCGGGACGUGUUUGAUAUUA	330	UCAAACACGUCCCGGA	738	AT4220-4221	100.93	2.03	94.72	1.62	
MAPT_2392	2392	UGGGUGAUAUUGUCCAGGGAC	331	UGGACAAUAUCACCCA	739	AT4268-4269	101.32	9.91	96.03	3.74	
MAPT_2332	2332	UCAGAUUUUACUUCCACCUGG	332	UGGAAGUAAAAUCUGA	740	AT2570-2571	101.52	5.97	116.31	112.63	
MAPT_2230	2230	UUUUGCACACUGCCGCCUCCC	333	GCGGCAGUGUGCAAAA	741	AT4222-4223	101.57	6.31	97.04	2.32	
MAPT_4060	4060	UGGAGGAGGAGACAGGGAACC	334	CCUGUCUCCUCCUCCA	742	AT2692-2693	101.79	5.52	92.10	0.69	
MAPT_3664	3664	UGAGGCACAAGUCCUUACAAA	335	AAGGACUUGUGCCUCA	743	AT4418-4419	102.18	2.90	91.27	0.11	

MAPT_6717	6717	UACACUAUAUAG ACAUUCACA	336	AUGUCUAUA UAGUGUA	744	AT2914-2915	102.28	10.07	72.14	1.21	
MAPT_3854	3854	UGACAUUGUGAC GUGUGAUGA	337	ACACGUCACA AUGUCA	745	AT2680-2681	102.75	1.73	91.80	0.33	
MAPT_2144	2144	UUUAAUUAUCU GCACCUUCCC	338	GGUGCAGAU AAUUAAA	746	AT2534-2535	102.94	2.80	103.06	1.28	
MAPT_272	272	UAGGCGAGGACG GGAGAGGAC	339	CUCCCGUCCU CGCCUA	747	AT2508-2509	103.01	0.66	104.80	3.94	
MAPT_2914	2914	UAAAUGUUGGA UGUGGCCAUG	340	CCACAUCCAA CAUUUA	748	AT2628-2629	103.20	5.36	93.82	95.05	
MAPT_2067	2067	UCAGGUCUGGCA UGGGCACGG	341	CCCAUGCCAG ACCUGA	749	AT4174-4175	103.49	9.07	101.71	4.12	
MAPT_4360	4360	UUUGUCGGGUG UGGAGGGCUG	342	CUCCACACCC GACAAA	750	AT2708-2709	103.53	3.00	110.04	3.73	
MAPT_6412	6412	UGAGGAGGGUGA AGCGAGUGA	343	CGCUUCACCC UCCUCA	751	AT2866-2867	103.67	2.03	97.41	1.02	
MAPT_512	512	UGGAGUGCUCUU AGCAUCAGA	344	UGCUAAGAG CACUCCA	752	AT2516-2517	103.85	2.70	106.15	2.35	
MAPT_4002	4002	UGAUGAGUGGA ACUGAGAGUG	345	UCAGUUCCAC UCAUCA	753	AT2684-2685	103.87	0.50	100.01	4.56	
MAPT_3666	3666	UAAGAGGCACAA GUCCUUACA	346	GGACUUGUG CCUCUUA	754	AT4422-4423	104.49	0.92	96.07	3.76	
MAPT_2296	2296	UGAUGGAUGUU GCCUAAUGAG	347	UAGGCAACA UCCAUCA	755	AT4240-4241	104.50	9.26	91.63	4.08	
MAPT_5242	5242	UGUGCAAGGUCA GCGGGCUGA	348	CCGCUGACCU UGCACA	756	AT2776-2777	104.75	1.83	90.17	3.47	

MAPT_2393	2393	UUGGGUGAUAU UGUCCAGGGA	349	GGACAAUAU CACCCAA	757	AT4270-4271	104.82	7.15	106.58	0.02	
MAPT_2009	2009	UUUGGGUGGAG UACGGACCAC	350	CCGUACUCCA CCCAAA	758	AT2528-2529	104.92	2.15	101.61	5.11	
MAPT_4298	4298	UGAGGUUGGCAG CUACAAGCU	351	GUAGCUGCCA ACCUCA	759	AT2698-2699	105.11	2.49	107.00	1.50	
MAPT_2265	2265	UGGUCACCUUGC UCAGGUCAA	352	CUGAGCAAGG UGACCA	760	AT2564-2565	105.44	1.50	117.24	117.98	
MAPT_2238	2238	UGUAGACUAUU UGCACACUGC	353	GUGCAAAUA GUCUACA	761	AT2558-2559	105.52	4.04	111.24	117.03	
MAPT_2283	2283	UUAAUGAGCCAC ACUUGGAGG	354	AAGUGUGGC UCAUUAA	762	AT2566-2567	105.58	5.39	112.00	108.01	
MAPT_5050	5050	UUUGGAGAGGA ACCCAGUCUG	355	UGGGUUCCUC UCCAAA	763	AT2762-2763	105.63	0.11	106.57	1.55	
MAPT_2233	2233	UCUAUUUGCACA CUGCCGCCU	356	GCAGUGUGCA AAUAGA	764	AT2552-2553	106.35	0.22	102.99	101.01	
MAPT_6714	6714	UCUAUAUAGACA UUCACAGAC	357	UGAAUGUCU AUAUAGA	765	AT2912-2913	106.42	2.07	70.36	0.05	
MAPT_5346	5346	UCCAAACCAGAA GUGGCAGAA	358	CCACUUCUGG UUUGGA	766	AT2788-2789	106.62	2.01	115.10	6.84	
MAPT_5120	5120	UUUCAUCCCAAU CCCUGCUGU	359	AGGGAUUGG GAUGAAA	767	AT2764-2765	107.13	0.98	97.86	4.42	
MAPT_2298	2298	UAUGAUGGAUG UUGCCUAAUG	360	GGCAACAUCC AUCAUA	768	AT2568-2569	107.28	1.19	105.93	104.51	
MAPT_2147	2147	UUUAUUAAUUA UCUGCACCUU	361	GCAGAUAAU UAAUAAA	769	AT2536-2537	107.63	4.96	94.85	0.22	

MAPT_1452	1452	UUUUGCUUUUA CUGACCAUGC	362	GUCAGUAAA AGCAAAA	770	AT2518-2519	107.74	2.87	95.89	1.15	
MAPT_442	442	UGAGAUUCUUU CAGGCCAGCG	363	GCCUGAAAGA AUCUCA	771	AT4154-4155	107.76	0.54	95.28	1.92	
MAPT_5365	5365	UGGGUUGCCUUU AACUGUACC	364	AGUUAAAGG CAACCCA	772	AT2790-2791	107.85	3.68	111.30	0.19	
MAPT_6361	6361	UGGAGCCAGUGU GAGAGGUGG	365	UCUCACACUG GCUCCA	773	AT2864-2865	108.07	2.77	89.15	3.61	
MAPT_257	257	UAGGACAGCGGA GGAGGAGAA	366	CUCCUCCGCU GUCCUA	774	AT2504-2505	108.80	1.66	101.16	7.74	
MAPT_4302	4302	UCUGGGAGGUUG GCAGCUACA	367	CUGCCAACCU CCCAGA	775	AT2700-2701	109.25	1.76	109.60	8.31	
MAPT_2137	2137	UUCUGCACCUUC CCGCCUCCC	368	GCGGGAAGG UGCAGAA	776	AT4180-4181	109.26	9.80	96.34	3.57	
MAPT_4356	4356	UCGGGUGUGGAG GGCUGAUAC	369	AGCCCUCCAC ACCCGA	777	AT2706-2707	110.12	5.81	106.58	2.22	
MAPT_260	260	UGAGAGGACAGC GGAGGAGGA	370	CUCCGCUGUC CUCUCA	778	AT2506-2507	111.42	2.14	104.41	2.50	
MAPT_2236	2236	UAGACUAUUUGC ACACUGCCG	371	GUGUGCAAA UAGUCUA	779	AT2554-2555	111.71	3.62	101.62	99.57	
MAPT_2237	2237	UUAGACUAUUU GCACACUGCC	372	UGUGCAAAU AGUCUAA	780	AT2556-2557	112.35	4.18	103.98	103.88	
MAPT_2034	2034	UGCGGCUCUUGG CGGAAGACG	373	UCCGCCAAGA GCCGCA	781	AT2532-2533	112.56	10.85	104.93	0.00	
MAPT_3552	3552	UUGUGGAGCAGA GGGAAGCCC	374	UCCCUCUGCU CCACAA	782	AT2650-2651	112.78	3.81	109.96	106.37	

MAPT_4364	4364	UCCCUUUGUCGGGUGUGGAGG	375	ACACCCGACAAAGGGA	783	AT2710-2711	112.96	6.87	121.64	1.78	
MAPT_2140	2140	UUUAUCUGCACCUUCCCGCCU	376	GGAAGGUGCAGAUAAA	784	AT4182-4183	113.84	0.53	88.43	5.02	
MAPT_4303	4303	UUCUGGGAGGUUGGCAGCUAC	377	UGCCAACCUCCCAGAA	785	AT2702-2703	114.70	2.56	115.43	5.66	
MAPT_3619	3619	UAGGUCUGCAAAGUGGCCAAA	378	CCACUUUGCAGACCUA	786	AT2668-2669	115.55	3.06	99.69	0.98	
MAPT_4021	4021	UGUGGUGAGGGUCCCAGUUGG	379	UGGGACCCUCACCACA	787	AT2688-2689	115.73	8.31	107.47	2.06	
MAPT_2173	2173	UACUGGACGUUGCUAAGAUCC	380	UUAGCAACGUCCAGUA	788	AT2538-2539	116.09	9.91	98.57	5.93	
MAPT_5512	5512	UAGGAGAAUUGCUGGGACUCA	381	CCCAGCAAUUCUCCUA	789	AT2800-2801	116.13	4.32	105.73	3.28	
MAPT_3591	3591	UAGCAGUUCCAACCUUCAGAA	382	AAGGUUGGAACUGCUA	790	AT2662-2663	119.17	0.10	98.18	2.40	
MAPT_215	215	UGAAGGUGGGCGGUGGCAGCG	383	CCACCGCCCACCUUCA	791	AT2502-2503	120.29	2.44	103.83	6.58	
MAPT_178	178	UGGAGCUGGUGGGUGGCGGUG	384	CCACCCACCAGCUCCA	792	AT2500-2501	120.97	1.93	103.20	5.64	
MAPT_5258	5258	UGCAGCAGAUGGAGUUUGUGC	385	AACUCCAUCUGCUGCA	793	AT2782-2783	121.91	6.16	121.40	7.24	
MAPT_2394	2394	UGUGGGUGAUAUUGUCCAGGG	386	GACAAUAUCACCCACA	794	AT4272-4273	122.69	15.77	136.15	2.24	
MAPT_3768	3768	UAGUGGCCGUGGGAAGGACAG	387	CUUCCCACGGCCACUA	795	AT2678-2679	123.50	2.27	102.47	6.43	

MAPT_5231	5231	UGCGGGCUGAGG UGCUCUGGU	388	AGCACCUCAG CCGCA	796	AT2774-2775	124.21	3.29	114.94	2.89	
MAPT_5256	5256	UAGCAGAUGGAG UUUGUGCAA	389	CAAACUCCAU CUGCUA	797	AT2780-2781	124.51	8.64	141.77	14.29	
MAPT_1799	1799	UGGUGUCUUUG GAGCGGGCGG	390	CGCUCCAAAG ACACCA	798	AT2524-2525	125.98	3.03	107.99	0.11	
MAPT_2388	2388	UGAUAUUGUCCA GGGACCCAA	391	UCCCUGGACA AUAUCA	799	AT2574-2575	129.01	4.07	105.90	109.93	
MAPT_2549	2549	UGUGGAGGAGAC AUUGCUGAG	392	CAAUGUCUCC UCCACA	800	AT2586-2587	129.67	11.19	103.65	106.39	
MAPT_3875	3875	UGUGGUGAGGCU GGGAAUUCG	393	UCCCAGCCUC ACCACA	801	AT2682-2683	129.85	1.08	106.17	5.44	
MAPT_2065	2065	UGGUCUGGCAUG GGCACGGGG	394	UGCCCAUGCC AGACCA	802	AT4172-4173	130.79	15.54	122.54	0.81	
MAPT_6294	6294	UAGGCAUGAUUG UGGGCUUAG	395	CCCACAAUCA UGCCUA	803	AT2848-2849	131.86	7.42	105.77	0.56	
MAPT_218	218	UGCAGAAGGUGG GCGGUGGCA	396	CCGCCCACCU UCUGCA	804	AT4114-4115	132.69	0.92	123.78	19.17	
MAPT_2461	2461	UUGGCUUUGGCG UUCUCGCGG	397	AGAACGCCAA AGCCAA	805	AT2584-2585	132.70	3.13	96.47	91.35	
MAPT_5860	5860	UGCAGGUGGGAG AAGUGAGGG	398	ACUUCUCCCA CCUGCA	806	AT2816-2817	133.56	5.44	88.10	1.81	
MAPT_5499	5499	UGGACUCAGCGA ACGGCAGGG	399	CCGUUCGCUG AGUCCA	807	AT2798-2799	143.81	3.31	118.25	11.83	
MAPT_6639	6639	UAGAAAUCAUGG GACUUGCAA	400	AGUCCCAUGA UUUCUA	808	AT2894-2895	147.89	0.56	77.14	1.40	

MAPT_177	177	UGAGCUGGUGGG UGGCGGUGA	401	GCCACCCACC AGCUCA	809	AT4112-4113	148.50	16.73	111.18	1.25	
MAPT_2415	2415	UUUUAUUUCCU CCGCCAGGGA	402	GGCGGAGGAA AUAAAA	810	AT2582-2583	148.94	0.46	123.87	123.56	
MAPT_2188	2188	UUUGAGCCACAC UUGGACUGG	403	CCAAGUGUGG CUCAAA	811	AT2542-2543	157.79	12.85	96.72	2.32	
MAPT_4006	4006	UGUUGGAUGAG UGGAACUGAG	404	UUCCACUCAU CCAACA	812	AT2686-2687	164.82	4.97	105.90	1.35	
MAPT_1802	1802	UGGUGGUGUCU UUGGAGCGGG	405	UCCAAAGACA CCACCA	813	AT2526-2527	179.60	3.42	112.98	5.36	
MAPT_2916	2916	UGGAAAUGUUG GAUGUGGCCA	406	ACAUCCAACA UUUCCA	814	AT2630-2631	208.64	4.16	119.86	126.03	
MAPT_2391	2391	UGGUGAUAUUG UCCAGGGACC	407	CUGGACAAU AUCACCA	815	AT2578-2579	279.32	16.92	114.06	123.49	
MAPT_3565	3565	UAAAACAGGGUU UCUGUGGAG	408	CAGAAACCCU GUUUUA	816	AT2654-2655			84.10	78.85	

Example 2. *In Vivo* Screening

[0211] *In vivo* screening was performed using 12 week old hMAPT transgenic mice. Briefly, PBS or divalent siRNA was administered via bilateral stereotactic ICV injection at a dose of 1 nmol, 2 nmol or 5 nmol in a total volume of 5 uL. One week after compound administration, animals were euthanized, perfused, and the brain was sliced into 1mm thick cortical slices. Biopsy punches (1-2mm diameter) were taken of the relevant brain regions (Striatum = Cpu, hippocampus = HP, temporal cortex = tCTx) and were snap frozen. Tissue punches were homogenized in Trizol (Invitrogen) using a Qiagen TissueLyser and total RNA was isolated the RNeasy kit (Qiagen). Quantitative reverse transcriptase polymerase change reaction (QRT-PCR) was performed to assess target (human MAPT) gene expression relative to housekeeping (mouse ATP5B) gene expression using TaqMan primer/probes and Fast Advanced master mix (Thermo). Data (Table 3A) are presented as % MAPT target knockdown (N=8 animals, 4 male, 4 female, 2 technical replicates each) relative to PBS treated control animals, where 100% represents complete target knockdown and 0% represents no target knockdown. Note: m = 2'Ome; f = 2'F; # = phosphorothioate; -DIO = DIO oligo linker; V = vinyl phosphonate.

[0212] Tau protein knockdown (Table 3B) is quantified by fluorescent ELISA (abcam 229394). Biological samples are lysed using tissue lysis buffer (CST Cell Lysis Buffer #9803) and bead-beater homogenization on a Qiagen Tissuelyser II. The ELISA is performed using the tissue lysates in accordance to the manufacturer's instructions. The ELISA utilizes an anti-tag coated immunoassay plate to bind to a conjugated capture antibody which in turn binds to the analyte. An HRP conjugated detection antibody is used in conjunction with a substrate to generate the fluorescent signal which is read on a fluorescent plate reader. In Tables 3A and 3B, below, 100% represents complete target knockdown and 0% represents no target knockdown.

Table 3A. In Vivo Screening (mRNA Knockdown)

						% MAPT Knock-Down									
						Cpu		**HP**		**tCTx**		**TH**		**Medulla**	
Pos.	antisense sequence	SEQ ID NO.	sense sequence	SEQ ID NO.	*In vivo* duplex ID#	5 nmol	1 nmol	5 nmol	1 nmol	5 nmol	1 nmol	5 nmol	1 nmol	5 nmol	1 nmol
MAPT_2687	5'-VP(mU)#(fC)#(mA)(fC)(fA)(fC)(mU)(fC)(mU)(fC)(mU)(fC)(mA)(fU)(mU)(fC)#(mU)#(mC)#(mU)#(mC)#(mC)	832	(mG)#(mA)#(mA)(fU)(mG)(fA)(mG)(fA)(mG)(fA)(mG)(mU)(mG)(fU)#(mG)#(mA)-DIO	847	AT4692-4693	24.9	15.6	49.9	1.0	44.7	22.1	42.7	-29.8	22.4	7.1
MAPT_286	5'-VP(mU)#(fC)#(mU)(fG)(fA)(fU)(mA)(fG)(mU)(fC)(mG)(fA)(mC)(fA)(mG)(fA)#(mG)#(mG)#(mC)#(mG)#(mA)	833	(mU)#(mC)#(mU)(fG)(mU)(fC)(mG)(fA)(mC)(fU)(mA)(mU)(mC)(fA)#(mG)#(mA)-DIO	848	AT4688-4689	42.7	21.1	52.0	8.1	50.0	-19.8	53.6	-6.0	41.7	19.5
						Cpu		**HP**		**tCTx**		**TH**		**Medulla**	
Pos.	antisense sequence		sense sequence		*In vivo* duplex ID#	5 nmol	2 nmol	5 nmol	2 nmol	5 nmol	2 nmol	5 nmol	2 nmol	5 nmol	2 nmol
MAPT_2679	5'-VP(mU)#(fC)#(mU)(fC)(fA)(fU)(mU)(fC)(mU)(fC)(mU)(fC)(mC)(fU)(mC)(fU)#(mC)#(mC)#(mA)#(mC)#(mA)	834	(mA)#(mG)#(mA)(fG)(mG)(fA)(mG)(fA)(mG)(fA)(mA)(mU)(mG)(fA)#(mG)#(mA)-DIO	849	AT4694-4695	37.2	30.7	47.3	44.0	22.1	27.6	27.9	37.5	35.2	30.5

MAPT_356	5'-VP(mU)#(fU)#(mA)(fC)(fG)(fU)(mC)(fC)(mC)(fA)(mG)(fC)(mG)(fU)(mG)(fA)#(mU)#(mC)#(mU)#(mC)	835	(mU)#(mC)#(mA)(fC)(mG)(fC)(mU)(fG)(mG)(fG)(mA)(mC)(mG)(fU)#(mA)#(mA)-DIO	850	AT4690-4691	42.8	35.1	62.0	48.5	25.6	23.3	39.9	31.4	43.5	19.5
MAPT_2334	5'-VP(mU)#(fC)#(mU)(fC)(fA)(fG)(mA)(fU)(mU)(fU)(mU)(fA)(mC)(fU)(mU)(fC)#(mC)#(mA)#(mC)#(mU)	836	(mG)#(mA)#(mA)(fG)(mU)(fA)(mA)(fU)(A)(mA)(fU)(mC)(mU)(mG)(fA)#(mG)#(mA)-DIO	851	AT4684-4685	38.2	32.6	46.9	45.2	22.9	15.0	11.8	23.1	25.0	8.8
MAPT_2817	5'-VP(mU)#(fC)#(mA)(fU)(fC)(fA)(mC)(fU)(mG)(fA)(mU)(fU)(mU)(fU)(mG)(fA)#(mG)#(mU)#(mC)#(mC)	837	(mU)#(mC)#(mA)(fA)(mA)(fA)(mU)(fC)(mA)(fG)(mU)(mG)(mA)(fU)#(mG)#(mA)-DIO	852	AT4686-4687	23.2	20.8	37.3	17.5	10.0	3.5	2.4	24.5	22.8	5.7
MAPT_2327	5'-VP(mU)#(fU)#(mU)(fU)(fA)(fC)(mU)(fU)(mC)(fC)(mA)(fC)(mC)(fU)(mG)(fG)#(mC)#(mC)#(mA)#(mC)#(mC)	838	(mC)#(mC)#(mA)(fG)(mG)(fU)(mG)(fG)(mA)(fA)(mG)(mU)(mA)(fA)#(mA)#(mA)-DIO	853	AT4696-4697	37.6	2.0	52.3	11.1	25.0	-10.2	40.8	-41.3	18.6	0.3
MAPT_2689	5'-VP(mU)#(fU)#(mC)(fC)(fA)(fC)(mA)(fC)(mU)(fC)(mU)(fC)(mU)(fC)(mA)(fU)#(mU)	839	(mA)#(mU)#(mG)(fA)(mG)(fA)(mG)(fA)(mG)(fU)(mG)(mU)(mG)(fG)#(m	854	AT4700-4701	34.0	16.5	60.6	23.3	33.7	-14.0	25.7	-72.9	17.1	11.2

	#(mC)#(mU)#(mC)#(mU)		A)#(mA)-DIO										
MAPT_2681	5'-VP(mU)#(fC)#(mU)(fC)(fU)(fC)(mA)(fU)(mU)(fC)(mU)(fC)(mU)(fC)(mC)(fU)#(mC)#(mU)#(mC)#(mC)#(mA)	840	(mA)#(mG)#(mG)(fA)(mG)(fA)(mG)(fA)(mA)(fU)(mG)(mA)(mG)(fA)#(mG)#(mA)-DIO	855	AT4698-4699	35.8	18.0	57.7	37.6	18.4	-15.7	43.1	-28.2	28.5	2.0
MAPT_2851	5'-VP(mU)#(fA)#(mU)(fC)(fA)(fA)(mU)(fU)(mU)(fG)(mG)(fA)(mA)(fA)(mG)(fA)#(mU)#(mG)#(mA)#(mA)#(mA)	841	(mU)#(mC)#(mU)(fU)(mU)(fC)(mC)(fA)(mA)(fA)(mU)(mU)(mG)(fA)#(mU)#(mA)-DIO	856	AT4702-4703	6.9	9.8	9.0	25.0	-10.8	-20.0	-17.9	-93.0	-10.0	-1.5
MAPT_2330	5'-VP(mU)#(fG)#(mA)(fU)(fU)(fU)(mU)(fA)(mC)(fU)(mU)(fC)(mC)(fA)(mC)(fC)#(mU)#(mG)#(mG)#(mC)#(mC)	842	(mG)#(mG)#(mU)(fG)(mG)(fA)(mA)(fG)(mU)(fA)(mA)(mA)(mA)(fU)#(mC)#(mA)-DIO	857	AT4704-4705	41.0	39.7	55.8	33.4	43.7	-40.9	41.0	-23.0	26.5	7.8
MAPT_2686	5'-VP(mU)#(fA)#(mC)(fA)(fC)(fU)(mC)(fU)(mC)(fA)(mU)(fU)(mC)(fU)#(mC)#(mU)#(mC)#(mC)#(mU)	843	(mA)#(mG)#(mA)(fA)(mU)(fG)(mA)(fG)(mA)(mG)(mU)(fG)#(mU)#(mA)-DIO	858	AT4706-4707	33.0	32.6	47.3	50.7	14.7	9.3	38.3	-70.1	21.2	10.4
MAPT_2690	5'-VP(mU)#(fU)#(mU)(fC)(fC)(fA)(mC)(fA)(mC)(fU)	844	(mU)#(mG)#(mA)(fG)(mA)(fG)(mU)(fG)(mU)(fG	859	AT4708-4709	51.9	41.7	67.6	64.2	48.2	36.9	66.3	42.7	43.3	32.9

	(mC)(fU)(mC)(fU)(mC)(fA)#(mU)#(mU)#(mC)#(mU)#(mC)		)(mU)(mG)(mG)(fA)#(mA)#(mA)-DIO										
MAPT_2814	5'-VP(mU)#(fC)#(mA)(fC)(fU)(fG)(mA)(fU)(mU)(fU)(mU)(fG)(mA)(fA)(mG)(fU)#(mC)#(mC)#(mG)#(mA)	845	(mA)#(mC)#(mU)(fU)(mC)(fA)(mA)(fA)(mA)(fU)(mC)(mA)(mG)(fU)#(mG)#(mA)-DIO	860	AT4710-4711	34.9	29.9	32.1	25.3	0.5	9.8	41.0	-11.2	14.9	8.6
MAPT_2841	5'-VP(mU)#(fA)#(mA)(fA)(fG)(fG)(fA)(mU)(fG)(mA)(fA)(mA)(fU)(mU)(fU)(mU)(mG)(fC)#(mU)#(mC)#(mU)#(mA)	846	(mG)#(mC)#(mA)(fA)(mA)(fU)(mU)(fU)(mC)(fA)(mU)(mC)(mU)(fU)#(mU)#(mA)-DIO	861	AT4712-4713	37.6	30.6	33.1	34.6	22.1	20.3	34.4	2.9	34.0	19.3

Table 3B *In Vivo* Screening (Protein Knockdown)

						% MAPT Protein Knock-Down									
						Cpu		HP		tCTx		TH		Medulla	
Pos.	**antisense sequence**	**SEQ ID NO.**	**sense sequence**	**SEQ ID NO.**	***In vivo* duplex ID#**	**5 nmol**	**1 nmol**	**5 nmol**	**1 nmol**	**5 nmol**	**1 nmol**	**5 nmol**	**1 nmol**	**5 nmol**	**1 nmol**
MAPT_2687	5'-VP(mU)#(fC)#(mA)(fC)(fA)(fC)(mU)(fC)(mU)(fC)(mU)(fC)(mA)(fU)(mU)(fC)#(mU)#(mC)#(mU)#(mC)#(mC)	832	(mG)#(mA)#(mA)(fU)(mG)(fA)(mG)(fA)(mG)(fA)(mG)(mU)(mG)(fU)#(mG)#(mA)-DIO	847	AT4692-4693	36	9	47	28	26	10	38	6	38	20
MAPT_286	5'-VP(mU)#(fC)#(mU)(fG)(fA)(fU)(mA)(fG)(mU)(fC)(mG)(fA)(mC)(fA)(mG)(fA)#(mG)#(mG)#(mC)#(mG)#(mA)	833	(mU)#(mC)#(mU)(fG)(mU)(fC)(mG)(fA)(mC)(fU)(mA)(mU)(mC)(fA)#(mG)#(mA)-DIO	848	AT4688-4689	41	0	60	7	50	0	47	27	63	25

Example 3. Durability of MAPT knockdown *in vivo*

Objective

[0213] This Example describes the results of a series of experiments undertaken to determine the durability of MAPT silencing with a di-branched siRNA molecule *in vivo*.

Materials and Methods

In vivo administration of di-siRNA

[0214] A siRNA molecule of the disclosure was synthesized as a di-branched siRNA molecule having the structure of Formula XVII. The sense strand had the sequence of SEQ ID NO. 409 and a pattern of chemical modifications defined by the broad structure of Formula III and the specific structure of Formula S1. The antisense strand had the sequence of SEQ ID NO. 1 and a pattern of chemical modifications defined by the broad structure of Formula II and the specific structure of Formula A2. The antisense strand further included a 5' vinyl phosphonate moiety of Formula XI.

[0215] *In vivo* durability was assessed in 12-week-old hMAPT transgenic mice using similar methods as described in Example 2. Briefly, PBS or the di-branched siRNA molecule described above was administered via bilateral stereotactic ICV injection at a dose of 30 nmol in a total volume of 10 μL.

[0216] One month, two months, three months, or four months after compound administration, animals were euthanized, perfused, and the brain was sliced into 1 mm thick cortical slices. Biopsy punches (1-2 mm diameter) were taken of the relevant brain regions (frontal cortex = fCTx, striatum = Cpu, thalamus = Thal, temporal cortex = tCTx, hippocampus = HP, midbrain = Mb, pons = Pons, medulla = Med, cerebellum = CB, cervical spinal cord = SC-C, thoracic spinal cord = SC-T, and lumbar spinal cord = SC-L) and snap frozen.

RNA quantification analysis

[0217] mRNA quantification was performed as described in Example 2. Data are presented as % MAPT target knockdown (N=8 animals, 4 male, 4 female, 2 technical replicates each), with each siRNA treatment group normalized to time-matched PBS control animals. Results are shown in Figures 1A-C.

Protein quantification analysis

[0218] Protein quantification was performed as described in Example 2. Data are presented as % MAPT target knockdown (N=8 animals, 4 male, 4 female, 2 technical replicates each), with each siRNA treatment group normalized to time-matched PBS control animals. Results are shown in Figures 2A-B.

Statistical assessment

[0219] Statistical significance between treatment with di-siRNA and PBS control in each brain region at each time point was determined using two-tailed Mann-Whitney test. ***=$p<0.001$, **=$p<0.01$, *=$p<0.05$.

Results

[0220] The results in this example demonstrate that a siRNA molecule of the disclosure, with a sense strand having SEQ ID NO. 409 and an antisense strand having SEQ ID NO. 1 successfully reduced MAPT gene and protein expression *in vivo* for up to four months post-treatment.

WHAT IS CLAIMED IS:

1. A small interfering RNA (siRNA) molecule comprising an antisense strand and sense strand having complementarity to the antisense strand, wherein the antisense strand is from 10 to 30 nucleotides in length and has complementarity sufficient to hybridize to a region within a microtubule-associated protein tau (*MAPT*) mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816, wherein the antisense strand has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of SEQ ID NOs: 1-408.

2. The siRNA molecule of claim 1, wherein the antisense strand comprises at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

3. The siRNA molecule of claim 1 or 2, wherein the antisense strand comprises from 15 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816, optionally wherein the antisense strand comprises 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

4. The siRNA molecule of any one of claims 1-3, wherein the antisense strand comprises 3 or fewer nucleotide mismatches relative to a region of 21 contiguous nucleobases of the *MAPT* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

5. The siRNA molecule of any one of claims 1-4, wherein the region of the *MAPT* mRNA transcript has the nucleic acid sequence of any one of SEQ ID NOs: 817-831.

6. The siRNA molecule of claim 5, wherein the region of the *MAPT* mRNA transcript has the nucleic acid sequence of any one of SEQ ID NOs: 817-821, 823-825, and 827-830.

7. The siRNA molecule of any one of claims 1-6, wherein the antisense strand has a nucleic acid sequence that is at least 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-408.

8. The siRNA molecule of any one of claims 1-7, wherein the sense strand has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of SEQ ID NOs: 409-816, optionally wherein the sense strand has a nucleic acid sequence that is at least 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid sequence of any one of SEQ ID NOs: 409-816.

9. The siRNA molecule of any one of claims 1-8, wherein the antisense strand comprises:

(a) a structure represented by Formula I, wherein Formula I is, in the 5'-to-3' direction:

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C'\text{-}P^1)_k\text{-}C'$$

Formula I;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$;
each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;
each D is a 2'-F ribonucleoside;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7; and
k is an integer from 1 to 7,

optionally wherein the antisense strand comprises a structure represented by Formula A1, wherein Formula A1 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(b) a structure represented by Formula II, wherein Formula II is, in the 5'-to-3' direction:

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C\text{-}P^1)_k\text{-}C'$$

Formula II;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$;
each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;
each D is a 2'-F ribonucleoside;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7; and
k is an integer from 1 to 7,

optionally wherein the antisense strand comprises a structure represented by Formula A2, wherein Formula A2 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-A-S-A

Formula A2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(c) a structure represented by Formula IV, wherein Formula IV is, in the 5'-to-3' direction:

$$A\text{-}(A')_j\text{-}C\text{-}P^2\text{-}B\text{-}(C\text{-}P^1)_k\text{-}C'$$

Formula IV;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
B is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D\text{-}P^1$;
each C is a 2'-O-Me ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;
each D is a 2'-F ribonucleoside;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7; and
k is an integer from 1 to 7,

optionally wherein the antisense strand comprises a structure represented by Formula A3, wherein Formula A3 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B-S-A-S-A-S-A

Formula A3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage; or

(d) a structure represented by Formula VI, wherein Formula VI is, in the 5'-to-3' direction:

$$A\text{-}B_j\text{-}E\text{-}B_k\text{-}E\text{-}F\text{-}G_l\text{-}D\text{-}P^1\text{-}C'$$

Formula VI;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each B is represented by the formula $C\text{-}P^2$;

each C is a 2'-O-Me ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;
each D is a 2'-F ribonucleoside;
each E is represented by the formula D-P^2-C-P^2;
F is represented by the formula D-P^1-C-P^1;
each G is represented by the formula C-P^1;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7;
k is an integer from 1 to 7; and
l is an integer from 1 to 7,

optionally wherein the antisense strand comprises a structure represented by Formula A4, wherein Formula A4 is, in the 5'-to-3' direction:

A-S-B-S-A-O-A-O-A-O-B-O-A-O-A-O-A-O-A-O-A-O-A-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

10. The siRNA molecule of any one of claims 1-9, wherein the sense strand comprises:

(a) a structure represented by Formula III, wherein Formula III is, in the 5'-to-3' direction:

$E\text{-}(A')_m\text{-}F$

Formula III;

wherein E is represented by the formula $(C\text{-}P^1)_2$;
F is represented by the formula $(C\text{-}P^2)_3$-D-P^1-C-P^1-C, $(C\text{-}P^2)_3$-D-P^2-C-P^2-C, $(C\text{-}P^2)_3$-D-P^1-C-P^1-D, or $(C\text{-}P^2)_3$-D-P^2-C-P^2-D;
A', C, D, P^1, and P^2 are as defined in Formula II; and
m is an integer from 1 to 7,

optionally wherein:

(i) the sense strand comprises a structure represented by Formula S1, wherein Formula S1 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-A

Formula S1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(ii) the sense strand comprises a structure represented by Formula S2, wherein Formula S2 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-A

Formula S2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(iii) the sense strand comprises a structure represented by Formula S3, wherein Formula S3 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-B

Formula S3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage; or

(iv) the sense strand comprises a structure represented by Formula S4, wherein Formula S4 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-B

Formula S4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(b) a structure represented by Formula V, wherein Formula V is, in the 5'-to-3' direction:

$$E\text{-}(A')_m\text{-}C\text{-}P^2\text{-}F$$

Formula V;

wherein E is represented by the formula $(C\text{-}P^1)_2$;
F is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$;
A', C, D, P^1 and P^2 are as defined in Formula IV; and
m is an integer from 1 to 7,

optionally wherein:

(i) the sense strand comprises a structure represented by Formula S5, wherein Formula S5 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A

Formula S5;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(ii) the sense strand comprises a structure represented by Formula S6, wherein Formula S6 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A

Formula S6;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(iii) the sense strand comprises a structure represented by Formula S7, wherein Formula S7 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B

Formula S7;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage; or

(iv) the sense strand comprises a structure represented by Formula S8, wherein Formula S8 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B

Formula S8;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage; or

(c) a structure represented by Formula VII, wherein Formula VII is, in the 5'-to-3' direction:

$H\text{-}B_m\text{-}I_n\text{-}A'\text{-}B_o\text{-}H\text{-}C$

Formula VII;

wherein A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
each H is represented by the formula $(C\text{-}P^1)_2$;
each I is represented by the formula $(D\text{-}P^2)$;
B, C, D, P^1 and P^2 are as defined in Formula VI;
m is an integer from 1 to 7;
n is an integer from 1 to 7; and
o is an integer from 1 to 7,

optionally wherein the sense strand comprises a structure represented by Formula S9, wherein Formula S9 is, in the 5'-to-3' direction:

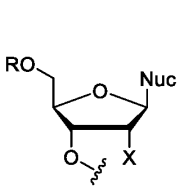
A-S-A-S-A-O-A-O-A-O-B-O-B-O-B-O-A-O-B-O-A-O-A-O-A-O-A-S-A-S-A

Formula S9;

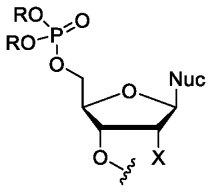
wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

11. The siRNA molecule of any one of claims 1-10, wherein the antisense strand further comprises a 5' phosphorus stabilizing moiety at the 5' end of the antisense strand and/or the sense strand further comprises a 5' phosphorus stabilizing moiety at the 5' end of the sense strand.

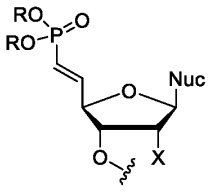
12. The siRNA molecule of claim 11, wherein each 5' phosphorus stabilizing moiety is, independently, represented by any one of Formulas IX-XVI:



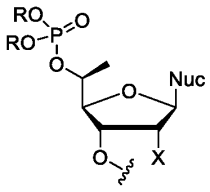
Formula IX



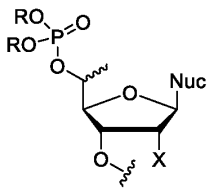
Formula X



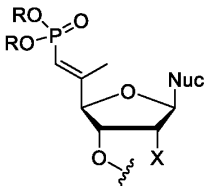
Formula XI



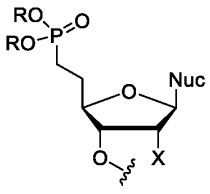
Formula XII



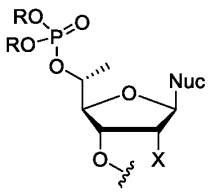
Formula XIII



Formula XIV



Formula XV

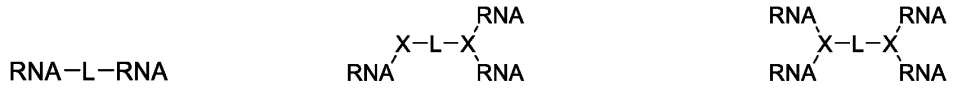


Formula XVI

wherein Nuc represents a nucleobase selected from the group consisting of adenine, uracil, guanine, thymine, and cytosine, and R represents an optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, phenyl, benzyl, hydroxy, or hydrogen.

13. The siRNA molecule of any one of claims 1-12, wherein the siRNA molecule is a branched siRNA molecule.

14. The siRNA molecule of claim 13, wherein the branched siRNA molecule is a di-branched siRNA molecule, optionally wherein the di-branched siRNA molecule is represented by any one of Formulas XVII-XIX:



Formula XVII; **Formula XVIII**; **Formula XIX**;

wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

15. An siRNA molecule comprising:

a) a sense strand comprising the sequence (mG)#(mA)#(mA)(fU)(mG)(fA)(mG)(fA)(mG)(fA)(mG)(mU)(mG)(fU)#(mG)#(mA)-DIO (SEQ ID NO: 847) and an antisense strand comprising the sequence V(mU)#(fC)#(mA)(fC)(fA)(fC)(mU)(fC)(mU)(fC)(mU)(fC)(mA)(fU)(mU)(fC)#(mU)#(mC)#(mU)#(mC)#(mC) (SEQ ID NO: 832);

b) a sense strand comprising the sequence (mU)#(mC)#(mU)(fG)(mU)(fC)(mG)(fA)(mC)(fU)(mA)(mU)(mC)(fA)#(mG)#(mA)-DIO (SEQ ID NO: 848) and an antisense strand comprising the sequence V(mU)#(fC)#(mU)(fG)(fA)(fU)(mA)(fG)(mU)(fC)(mG)(fA)(mC)(fA)(mG)(fA)#(mG)#(mG)#(mC)#(mG)#(mA) (SEQ ID NO: 833);

c) a sense strand comprising the sequence (mA)#(mG)#(mA)(fG)(mG)(fA)(mG)(fA)(mG)(fA)(mA)(mU)(mG)(fA)#(mG)#(mA)-DIO (SEQ ID NO: 849) and an antisense strand comprising the sequence V(mU)#(fC)#(mU)(fC)(fA)(fU)(mU)(fC)(mU)(fC)(mU)(fC)(mC)(fU)(mC)(fU)#(mC)#(mC)#(mA)#(mC)#(mA) (SEQ ID NO: 834);

d) a sense strand comprising the sequence (mU)#(mC)#(mA)(fC)(mG)(fC)(mU)(fG)(mG)(fG)(mA)(mC)(mG)(fU)#(mA)#(mA)-DIO (SEQ ID NO: 850) and an antisense strand comprising the sequence V(mU)#(fU)#(mA)(fC)(fG)(fU)(mC)(fC)(mC)(fA)(mG)(fC)(mG)(fU)(mG)(fA)#(mU)#(mC)#(mU)#(mU)#(mC) (SEQ ID NO: 835);

e) a sense strand comprising the sequence (mG)#(mA)#(mA)(fG)(mU)(fA)(mA)(fA)(mA)(fU)(mC)(mU)(mG)(fA)#(mG)#(mA)-DIO (SEQ ID NO: 851) and an antisense strand comprising the sequence V(mU)#(fC)#(mU)(fC)(fA)(fG)(mA)(fU)(mU)(fU)(mU)(fA)(mC)(fU)(mU)(fC)#(mC)#(mA)#(mC)#(mC)#(mU) (SEQ ID NO: 836);

f) a sense strand comprising the sequence (mU)#(mC)#(mA)(fA)(mA)(fA)(mU)(fC)(mA)(fG)(mU)(mG)(mA)(fU)#(mG)#(mA)-DIO (SEQ ID NO: 852) and an antisense strand comprising the sequence V(mU)#(fC)#(mA)(fU)(fC)(fA)(mC)(fU)(mG)(fA)(mU)(fU)(mU)(fU)(mG)(fA)#(mA)#(mG)#(mU)#(mC)#(mC) (SEQ ID NO: 837);

g) a sense strand comprising the sequence (mC)#(mC)#(mA)(fG)(mG)(fU)(mG)(fG)(mA)(fA)(mG)(mU)(mA)(fA)#(mA)#(mA)-DIO (SEQ ID NO: 853) and an antisense strand comprising the sequence V(mU)#(fU)#(mU)(fU)(fA)(fC)(mU)(fU)(mC)(fC)(mA)(fC)(mC)(fU)(mG)(fG)#(mC)#(mC)#(mA)#(mC)#(mC) (SEQ ID NO: 838);

h) a sense strand comprising the sequence (mA)#(mU)#(mG)(fA)(mG)(fA)(mG)(fA)(mG)(fU)(mG)(mU)(mG)(fG)#(mA)#(mA)-DIO (SEQ ID NO: 854) and an antisense strand comprising the sequence V(mU)#(fU)#(mC)(fC)(fA)(fC)(mA)(fC)(mU)(fC)(mU)(fC)(mU)(fC)(mA)(fU)#(mU)#(mC)#(mU)#(mC)#(mU) (SEQ ID NO: 839);

i) a sense strand comprising the sequence (mA)#(mG)#(mG)(fA)(mG)(fA)(mG)(fA)(mA)(fU)(mG)(mA)(mG)(fA)#(mG)#(mA)-DIO (SEQ ID NO: 855) and an antisense strand comprising the sequence V(mU)#(fC)#(mU)(fC)(fU)(fC)(mA)(fU)(mU)(fC)(mU)(fC)(mU)(fC)(mC)(fU)#(mC)#(mU)#(mC)#(mC)#(mA) (SEQ ID NO: 840);

j) a sense strand comprising the sequence (mU)#(mC)#(mU)(fU)(mU)(fC)(mC)(fA)(mA)(fA)(mU)(mU)(mG)(fA)#(mU)#(mA)-DIO (SEQ ID NO: 856) and an antisense strand comprising the sequence V(mU)#(fA)#(mU)(fC)(fA)(fA)(mU)(fU)(mU)(fG)(mG)(fA)(mA)(fA)(mG)(fA)#(mU)#(mG)#(mA)#(mA)#(mA) (SEQ ID NO: 841);

k) a sense strand comprising the sequence (mG)#(mG)#(mU)(fG)(mG)(fA)(mA)(fG)(mU)

(fA)(mA)(mA)(mA)(fU)#(mC)#(mA)-DIO (SEQ ID NO: 857) and an antisense strand comprising the sequence V(mU)#(fG)#(mA)(fU)(fU)(fU)(mU)(fA)(mC)(fU)(mU)(fC)(mC) (fA)(mC)(fC)#(mU)#(mG)#(mG)#(mC)#(mC) (SEQ ID NO: 842);

l) a sense strand comprising the sequence (mA)#(mG)#(mA)(fA)(mU)(fG)(mA)(fG) (mA)(fG)(mA)(mG)(mU)(fG)#(mU)#(mA)-DIO (SEQ ID NO: 858) and an antisense strand comprising the sequence V(mU)#(fA)#(mC)(fA)(fC)(fU)(mC)(fU)(mC)(fU)(mC)(fA)(mU) (fU)(mC)(fU)#(mC)#(mU)#(mC)#(mC)#(mU) (SEQ ID NO: 843);

m) a sense strand comprising the sequence (mU)#(mG)#(mA)(fG)(mA)(fG)(mA)(fG) (mU)(fG)(mU)(mG)(mG)(fA)#(mA)#(mA)-DIO (SEQ ID NO: 859) and an antisense strand comprising the sequence V(mU)#(fU)#(mU)(fC)(fC)(fA)(mC)(fA)(mC)(fU)(mC)(fU)(mC)(fU) (mC)(fA)#(mU)#(mU)#(mC)#(mU)#(mC) (SEQ ID NO: 844);

n) a sense strand comprising the sequence (mA)#(mC)#(mU)(fU)(mC)(fA)(mA)(fA) (mA)(fU)(mC)(mA)(mG)(fU)#(mG)#(mA)-DIO (SEQ ID NO: 860) and an antisense strand comprising the sequence VP(mU)#(fC)#(mA)(fC)(fU)(fG)(mA)(fU)(mU)(fU)(mU)(fG)(mA)(fA) (mG)(fU)#(mC)#(mC)#(mC)#(mG)#(mA) (SEQ ID NO: 845); or

o) a sense strand comprising the sequence (mG)#(mC)#(mA)(fA)(mA)(fU)(mU) (fU)(mC)(fA)(mU)(mC)(mU)(fU)#(mU)#(mA)-DIO (SEQ ID NO: 861) and an antisense strand comprising the sequence VP(mU)#(fA)#(mA)(fA)(fG)(fA)(mU)(fG)(mA)(fA)(mA)(fU)(mU) (fU)(mG)(fC)#(mU)#(mC)#(mU)#(mU)#(mA) (SEQ ID NO: 846),

wherein m represents a 2'-O-Me ribonucleoside, f represents a 2'-F ribonucleoside, # represents a phosphorothioate internucleoside linkage, -DIO represents a divalent oligonucleotide (DIO) linker; and V represents a vinyl phosphonate.

16. A pharmaceutical composition comprising the siRNA molecule of any one of claims 1-15 and a pharmaceutically acceptable excipient, carrier, or diluent.

17. A method of treating a tauopathy in a human subject in need thereof, the method comprising administering a therapeutically effective amount of the siRNA molecule of any one of claims 1-15 or the pharmaceutical composition of claim 16 to the subject.

18. The method of claim 17, wherein the tauopathy is Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, or corticobasal degeneration.

19. The method of claim 17 or 18, wherein the siRNA molecule or the pharmaceutical composition is administered to the subject by way of intracerebroventricular, intrastriatal, intraparenchymal, or intrathecal injection.

20. A kit comprising the siRNA molecule of any one of claims 1-15, or the pharmaceutical composition of claim 16, and a package insert, wherein the package insert instructs a user of the kit to perform the method of any one of claims 17-19.