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(71) Applicant: **BIORCHESTRA CO., LTD.** [KR/KR];  
2F-216, Venture-dong, KRIBB, 125, Gwahak-ro, Yuseong-  
gu, Daejeon 34141 (KR).

(72) Inventors: **RYU, Jin-Hyeob**; c/o BIORCHESTRA CO.,  
LTD., 2F-216, Venture-dong, KRIBB, 125, Gwahak-ro,  
Yuseong-gu, Daejeon 34141 (KR). **PARK, Young Jin**;  
c/o BIORCHESTRA CO., LTD., 2F-216, Venture-dong,  
KRIBB, 125, Gwahak-ro, Yuseong-gu, Daejeon 34141  
(KR). **PARK, Suhyeong**; c/o BIORCHESTRA CO., LTD.,  
2F-216, Venture-dong, KRIBB, 125, Gwahak-ro, Yuseong-  
gu, Daejeon 34141 (KR). **LIM, Yu Na**; c/o BIORCHES-  
TRA CO., LTD., 2F-216, Venture-dong, KRIBB, 125, Gwa-  
hak-ro, Yuseong-gu, Daejeon 34141 (KR). **KIM, Insun**;  
c/o BIORCHESTRA CO., LTD., 2F-216, Venture-dong,  
KRIBB, 125, Gwahak-ro, Yuseong-gu, Daejeon 34141  
(KR). **KWON, Mincheol**; c/o BIORCHESTRA CO., LTD.,  
2F-216, Venture-dong, KRIBB, 125, Gwahak-ro, Yuseong-  
gu, Daejeon 34141 (KR). **KIM, Jihye**; c/o BIORCHES-  
TRA CO., LTD., 2F-216, Venture-dong, KRIBB, 125, Gwa-  
hak-ro, Yuseong-gu, Daejeon 34141 (KR).

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(54) Title: MICROTUBULE-ASSOCIATED PROTEIN TAU TARGETING SIRNAS AND USES THEREOF

(57) Abstract: The present disclosure relates to siRNA, which target MAPT transcript in a cell, leading to reduced expression of MAPT protein. Reduction of MAPT protein expression is beneficial for the treatment of certain medical disorders, e.g., a tauopathy.



# MICROTUBULE-ASSOCIATED PROTEIN TAU TARGETING SIRNAS AND USES THEREOF

## CROSS REFERENCE TO EARLIER FILED APPLICATION

**[0001]** This Application claims the priority benefit of U.S. Provisional Application No. 63/493,244, filed March 30, 2023. The entire disclosure of the above-referenced application is incorporated herein by reference.

## REFERENCE TO ELECTRONICALLY FILED SEQUENCE LISTING

**[0002]** The content of the electronically submitted sequence listing (Name: 4366\_074PC01\_SequenceListing\_ST26.xml; Size: 120,705 bytes; and Date of Creation: March 29, 2024) is herein incorporated by reference in its entirety.

## FIELD OF THE DISCLOSURE

**[0003]** The present disclosure relates to oligonucleotides, *e.g.*, siRNAs, that target a Microtubule-associated protein tau (*MAPT*) transcript in a cell, leading to modified expression of Microtubule-associated protein tau (*MAPT*) protein, thereby treating a disease or disorder related to *MAPT* gene/protein expression.

## BACKGROUND OF THE DISCLOSURE

**[0004]** Microtubule-associated protein tau (*MAPT*) is a small soluble protein that is expressed in many cell types. It is predominantly localized within the presynaptic terminals of neurons. While the precise function has yet to be fully elucidated, *MAPT* has been suggested to play an important role in the regulation of synaptic transmission. Due to *MAPT*'s role in the regulation of synaptic transmission, alterations of *MAPT* expression and/or function can disrupt critical biological processes. Such disruptions have been thought to contribute to tauopathies, which are neurodegenerative diseases characterized by abnormal accumulation of *MAPT* protein aggregates within the brain.

**[0005]** Tauopathies, such as behavioral variant frontotemporal dementia, are highly prevalent neurodegenerative conditions, especially in the elderly. Dementia currently affects more than 55 million people worldwide and as of 2017, more than 5 million Americans had been

diagnosed with dementia. In 2017, the average annual cost of care for a patient with dementia was \$89,000. As the population ages the number of people living with the disease will increase placing an even greater burden on the healthcare system and the families of the patients. The treatment options for this disease are scant, and there are no small molecule treatments for this disease on market. The current potential best treatment for the disease, Lecanemab (currently pending before the FDA), is linked to increased brain bleeding and swelling, with potentially deadly contraindications that limit its usefulness. More cost effective and robust treatment options are necessary to properly handle this worsening health crisis.

## BRIEF SUMMARY OF THE DISCLOSURE

**[0006]** The present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are capable of hybridizing to a nucleic acid sequence within an Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises:

- i. 5'-AACGUCCAGUCCAAGUGUGGC-3' (SEQ ID NO: 1) (sense strand) or  
5'-GCCACACUUGGACUGGACGTT-3' (SEQ ID NO: 2) (antisense strand);
- ii. 5'-AGCAACGUCCAGUCCAAG-3' (SEQ ID NO: 3) (sense strand) or  
5'-CUUGGACUGGACGUUGCU-3' (SEQ ID NO: 4) (antisense strand);
- iii. 5'-AAGGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 5) (sense strand) or  
5'-CUUAUUAUUAUCUGCACCTT-3' (SEQ ID NO: 6) (antisense strand);
- iv. 5'-UGAGAACCUGAAGCACCAG-3' (SEQ ID NO: 7) (sense strand) or  
5'-CUGGUGCUUCAGGUUCUCA-3' (SEQ ID NO: 8) (antisense strand);
- v. 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or  
5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand);
- vi. 5'-AAUUAUAAGAAGCUGGAUCU-3' (SEQ ID NO: 11) (sense strand) or  
5'-AGAUCCAGCUUCUUAUUAATT-3' (SEQ ID NO: 12) (antisense strand);
- vii. 5'-GAGCCCAAGAAGGUGGCAG-3' (SEQ ID NO: 13) (sense strand) or  
5'-CUGCCACCUUCUUGGGCUC-3' (SEQ ID NO: 14) (antisense strand);
- viii. 5'-ACCCGGGAGCCCAAGAAG-3' (SEQ ID NO: 15) (sense strand) or  
5'-CUUCUUGGGCUCCCGGGU-3' (SEQ ID NO: 16) (antisense strand);
- ix. 5'-AGAAGCUGGAUCUAGCAA-3' (SEQ ID NO: 17) (sense strand) or

- 5'-UUGC UAAGAUCCAGCUUCU-3' (SEQ ID NO: 18) (antisense strand);
- x. 5'-AAGGAUAAUAUCAAACACGUC-3' (SEQ ID NO: 19) (sense strand) or  
5'-GACGUGUUUGAUUAUUAUCCTT-3' (SEQ ID NO: 20) (antisense strand);
- xi. 5'-AUAAUAUCAAACACGUCCC-3' (SEQ ID NO: 21) (sense strand) or  
5'-GGGACGUGUUUGAUUAUUAU-3' (SEQ ID NO: 22) (antisense strand);
- xii. 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or  
5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand);
- xiii. 5'-AAUAUCACCCACGUCCCUGG-3' (SEQ ID NO: 25) (sense strand) or  
5'-CCAGGGACGUGGGUGAUATT-3' (SEQ ID NO: 26) (antisense strand);
- xiv. 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or  
5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);
- xv. 5'-CCAAAGCCAAGACAGACCA-3' (SEQ ID NO: 29) (sense strand) or  
5'-UGGUCUGUCUUGGCUUUGG-3' (SEQ ID NO: 30) (antisense strand);
- xvi. 5'-AAGCAGGGUUUGUGAUCAG-3' (SEQ ID NO: 31) (sense strand) or  
5'-CUGAUCACAAACCCUGCTT-3' (SEQ ID NO: 32) (antisense strand);
- xvii. 5'-CUCGGGACUUCAAAAUCAG-3' (SEQ ID NO: 33) (sense strand) or  
5'-CUGAUUUUGAAGUCCCGAG-3' (SEQ ID NO: 34) (antisense strand);
- xviii. 5'-AGGGCAGCCUGUGGGAGAA-3' (SEQ ID NO: 35) (sense strand) or  
5'-UUCUCCCACAGGCUGCCCU-3' (SEQ ID NO: 36) (antisense strand); or
- xix. 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or  
5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).

**[0007]** The present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are capable of hybridizing to a nucleic acid sequence within an Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises:

- i. 5'-AAGCUGGAUCUUAGCAACGUC-3' (SEQ ID NO: 37) (sense strand) or  
5'-GACGUUGCUAAGAUCCAGCTT-3' (SEQ ID NO: 38) (antisense strand);
- ii. 5'-AGUGUGCAAUAGUCUACAA-3' (SEQ ID NO: 39) (sense strand) or  
5'-UUGUAGACUAUUUGCACACU-3' (SEQ ID NO: 40) (antisense strand);
- iii. 5'-AAGGACAGAGUCCAGUCGAAG-3' (SEQ ID NO: 41) (sense strand) or  
5'-CUUCGACUGGACUCUGUCCTT-3' (SEQ ID NO: 42) (antisense strand);

- iv. 5'-AAGAUUGAAACCCACAAGC-3' (SEQ ID NO: 43) (sense strand) or  
5'-GCUUGUGGGUUUCAUUCTT-3' (SEQ ID NO: 44) (antisense strand);
- v. 5'-GAAACCCACAAGCUGACCU-3' (SEQ ID NO: 45) (sense strand) or  
5'-AGGUCAGCUUGUGGGUUUC-3' (SEQ ID NO: 46) (antisense strand);
- vi. 5'-AAUAUCAAACACGUCCCCGGA-3' (SEQ ID NO: 47) (sense strand) or  
5'-UCCCCGGGACGUGUUUGAUATT-3' (SEQ ID NO: 48) (antisense strand);
- vii. 5'-AUCAAACACGUCCCCGGGAG-3' (SEQ ID NO: 49) (sense strand) or  
5'-CUCCCCGGGACGUGUUUGAU-3' (SEQ ID NO: 50) (antisense strand);
- viii. 5'-AACACGUCCCCGGGAGGCGGCA-3' (SEQ ID NO: 51) (sense strand) or  
5'-UGCCGCCUCCCCGGGACGUGTT-3' (SEQ ID NO: 52) (antisense strand);
- ix. 5'-ACGUCCCCGGGAGGCGGCAG-3' (SEQ ID NO: 53) (sense strand) or  
5'-CUGCCGCCUCCCCGGGACGU-3' (SEQ ID NO: 54) (antisense strand); or
- x. 5'-UCCCCGGGAGGCGGCAGUGU-3' (SEQ ID NO: 55) (sense strand) or  
5'-ACACUGCCGCCUCCCCGGA-3' (SEQ ID NO: 56) (antisense strand).

**[0008]** In some aspects, the present disclosure provides an oligonucleotide wherein the contiguous nucleotide sequence is complementary to the nucleic acid sequence.

**[0009]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AACGUCCAGUCCAAGUGUGGC-3' (SEQ ID NO: 1) (sense strand) or 5'- GCCACACUUGGACUGGACGTT-3' (SEQ ID NO: 2) (antisense strand).

**[0010]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AGCAACGUCCAGUCCAAG-3' (SEQ ID NO: 3) (sense strand) or 5'- CUUGGACUGGACGUUGCU-3' (SEQ ID NO: 4).

**[0011]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AAGGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 5) (sense strand) or 5'- CUUAUUAUUAUCUGCACCTT -3' (SEQ ID NO: 6) (antisense strand).

[0012] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGAGAACCUGAAGCACCAG-3' (SEQ ID NO: 7) (sense strand) or 5'-CUGGUGCUUCAGGUUCUCA-3' (SEQ ID NO: 8) (antisense strand).

[0013] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand).

[0014] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AAUUAUAAGAAGCUGGAUCU-3' (SEQ ID NO: 11) (sense strand) or 5'-AGAUCCAGCUUCUUAUUAATT-3' (SEQ ID NO: 12) (antisense strand).

[0015] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GAGCCCAAGAAGGUGGCAG-3' (SEQ ID NO: 13) (sense strand) or 5'-CUGCCACCUUCUUGGGCUC-3' (SEQ ID NO: 14) (antisense strand).

[0016] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-ACCCGGGAGCCCAAGAAG-3' (SEQ ID NO: 15) (sense strand) or 5'-CUUCUUGGGCUCCCGGGU-3' (SEQ ID NO: 16) (antisense strand).

[0017] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGAAGCUGGAUCUAGCAA-3' (SEQ ID NO: 17) (sense strand) or 5'-UUGCUAAGAUCAGCUUCU-3' (SEQ ID NO: 18) (antisense strand).

[0018] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a

nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AAGGAUAAUAUCAAACACGUC-3' (SEQ ID NO: 19) (sense strand) or 5'- GACGUGUUUGAUUAUUAUCCTT-3' (SEQ ID NO: 20) (antisense strand).

**[0019]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AUAAUAUCAAACACGUCCC-3' (SEQ ID NO: 21) (sense strand) or 5'- GGGACGUGUUUGAUUAUUAU-3' (SEQ ID NO: 22) (antisense strand).

**[0020]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'- UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand).

**[0021]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AAUAUCACCCACGUCCCUGG-3' (SEQ ID NO: 25) (sense strand) or 5'- CCAGGGACGUGGGUGAUATT-3' (SEQ ID NO: 26) (antisense strand).

**[0022]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'- UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand).

**[0023]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- CCAAAGCCAAGACAGACCA-3' (SEQ ID NO: 29) (sense strand) or 5'- UGGUCUGUCUUGGCUUUGG-3' (SEQ ID NO: 30) (antisense strand).

**[0024]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the

contiguous nucleotide sequence comprises: 5'- AAGCAGGGUUUGUGAUCAG-3' (SEQ ID NO: 31) (sense strand) or 5'- CUGAUCACAAACCCUGCTT-3' (SEQ ID NO: 32) (antisense strand).

**[0025]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- CUCGGGACUUCAAAAUCAG-3' (SEQ ID NO: 33) (sense strand) or 5'- CUGAUUUUGAAGUCCCGAG-3' (SEQ ID NO: 34) (antisense strand).

**[0026]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AGGGCAGCCUGUGGGAGAA-3' (SEQ ID NO: 35) (sense strand) or 5'- UUCUCCCACAGGCUGCCCU-3' (SEQ ID NO: 36) (antisense strand).

**[0027]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AAGCUGGAUCUUAGCAACGUC-3' (SEQ ID NO: 37) (sense strand) or 5'- GACGUUGCUAAGAUCAGCTT-3' (SEQ ID NO: 38) (antisense strand).

**[0028]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AGUGUGCAAUAGUCUACAA-3' (SEQ ID NO: 39) (sense strand) or 5'- UUGUAGACUAAUUGCACACU-3' (SEQ ID NO: 40) (antisense strand).

**[0029]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AAGGACAGAGUCCAGUCGAAG-3' (SEQ ID NO: 41) (sense strand) or 5'- CUUCGACUGGACUCUGUCCTT-3' (SEQ ID NO: 42) (antisense strand).

**[0030]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AAGAUUGAAACCCACAAGC-3' (SEQ ID NO: 43) (sense strand) or 5'- GCUUGUGGGUUUCAUUCTT-3' (SEQ ID NO: 44) (antisense strand).

[0031] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GAAACCCACAAGCUGACCU-3' (SEQ ID NO: 45) (sense strand) or 5'-AGGUCAGCUUGUGGGUUUC-3' (SEQ ID NO: 46) (antisense strand).

[0032] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AAUAUCAAACACGUCCCGGGA-3' (SEQ ID NO: 47) (sense strand) or 5'-UCCCGGGACGUGUUUGAUATT-3' (SEQ ID NO: 48) (antisense strand).

[0033] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AUCAAACACGUCCCGGGAG-3' (SEQ ID NO: 49) (sense strand) or 5'-CUCCCGGGACGUGUUUGAU-3' (SEQ ID NO: 50) (antisense strand).

[0034] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AACACGUCCCGGGAGGCGGCA-3' (SEQ ID NO: 51) (sense strand) or 5'-UGCCGCCUCCCGGGACGUGTT-3' (SEQ ID NO: 52) (antisense strand).

[0035] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-ACGUCCCGGGAGGCGGCAG-3' (SEQ ID NO: 53) (sense strand) or 5'-CUGCCGCCUCCCGGGACGU-3' (SEQ ID NO: 54) (antisense strand).

[0036] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UCCCGGGAGGCGGCAGUGU-3' (SEQ ID NO: 55) (sense strand) or 5'-ACACUGCCGCCUCCCGGGA-3' (SEQ ID NO: 56) (antisense strand).

[0037] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a

nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).

**[0038]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotide from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

**[0039]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0040]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0041]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0042]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

**[0043]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0044]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein the nucleotides in the sense strand and/or the nucleotides in the antisense strand are linked by a phosphodiester bond, a phosphothioate bond, or any combination thereof.

**[0045]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0046]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

**[0047]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0048]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0049]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0050]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the

contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

**[0051]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotide from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0052]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0053]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense nucleotides, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0054]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the

contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

**[0055]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0056]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0057]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0058]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to

3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

**[0059]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0060]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0061]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0062]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is

RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand is 2'-OMe.

**[0063]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0064]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0065]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0066]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' F at the sugar position.

**[0067]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0068]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0069]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0070]** In some aspects, the oligonucleotide in the present disclosure is double stranded and comprises:

- i. 5'-AACGUCCAGUCCAAGUGUGGC-3' (SEQ ID NO: 1) (sense strand) and/or 5'-GCCACACUUGGACUGGACGTT-3' (SEQ ID NO: 2) (antisense strand);
- ii. 5'-AGCAACGUCCAGUCCAAG-3' (SEQ ID NO: 3) (sense strand) and/or 5'-CUUGGACUGGACGUUGCU-3' (SEQ ID NO: 4) (antisense strand);
- iii. 5'-AAGGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 5) (sense strand) and/or 5'-CUUAUUAUUAUCUGCACCTT-3' (SEQ ID NO: 6) (antisense strand);

- iv. 5'-UGAGAACCUGAAGCACCAG -3' (SEQ ID NO: 7) (sense strand) and/or  
5'-CUGGUGCUUCAGGUUCUCA-3' (SEQ ID NO: 8) (antisense strand);
- v. 5'-AGCGGCUACAGCAGCCCCG -3' (SEQ ID NO: 9) (sense strand) and/or  
5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand);
- vi. 5'-AAUUAUAAGAAGCUGGAUCU-3' (SEQ ID NO: 11) (sense strand) and/or  
5'-AGAUC CAGCUUCUUAUUAATT-3' (SEQ ID NO: 12) (antisense strand);
- vii. 5'-GAGCCCAAGAAGGUGGCAG-3' (SEQ ID NO: 13) (sense strand) and/or  
5'-CUGCCACCUUCUUGGGCUC-3' (SEQ ID NO: 14) (antisense strand);
- viii. 5'-ACCCGGGAGCCCAAGAAG-3' (SEQ ID NO: 15) (sense strand) and/or  
5'-CUUCUUGGGCUC CCGGGU-3' (SEQ ID NO: 16) (antisense strand);
- ix. 5'-AGAAGCUGGAUCUAGCAA-3' (SEQ ID NO: 17) (sense strand) and/or  
5'-UUGC UAAGAUC CAGCUUCU-3' (SEQ ID NO: 18) (antisense strand);
- x. 5'-AAGGAUAAUAUCAAACACGUC-3' (SEQ ID NO: 19) (sense strand) and/or  
5'-GACGUGUUUGAUUAUUAUCCTT-3' (SEQ ID NO: 20) (antisense strand);
- xi. 5'-AUAAUAUCAAACACGUCCC-3' (SEQ ID NO: 21) (sense strand) and/or  
5'-GGGACGUGUUUGAUUAUUAU-3' (SEQ ID NO: 22) (antisense strand);
- xii. 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and/or  
5'-JUCCACCUGGCCACCUCU-3' (SEQ ID NO: 24) (antisense strand);
- xiii. 5'-AAUAUCACCCACGUCCCUGG-3' (SEQ ID NO: 25) (sense strand) and/or  
5'-CCAGGGACGUGGGUGAUATT-3' (SEQ ID NO: 26) (antisense strand);
- xiv. 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and/or  
5'-UUUUACUUC CACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);
- xv. 5'-CCAAAGCCAAGACAGACCA-3' (SEQ ID NO: 29) (sense strand) and/or  
5'-UGGUCUGUCUUGGCUUUGG-3' (SEQ ID NO: 30) (antisense strand);
- xvi. 5'-AAGCAGGGUUUGUGAUCAG-3' (SEQ ID NO: 31) (sense strand) and/or  
5'-CUGAUCACAAACCCUGCTT-3' (SEQ ID NO: 32) (antisense strand);
- xvii. 5'-CUCGGGACUUCAAAAUCAG-3' (SEQ ID NO: 33) (sense strand) and/or  
5'-CUGAUUUUGAAGUCCCGAG-3' (SEQ ID NO: 34) (antisense strand);
- xviii. 5'-AGGGCAGCCUGUGGGAGAA-3' (SEQ ID NO: 35) (sense strand) and/or  
5'-UUCUCCCACAGGCUGCCCU-3' (SEQ ID NO: 36) (antisense strand); or
- xix. 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and/or

5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).

**[0071]** In some aspects, the oligonucleotide in the present disclosure is double stranded and comprises:

- i. 5'-AAGCUGGAUCUUAGCAACGUC-3' (SEQ ID NO: 37) (sense strand) and/or  
5'-GACGUUGCUAAGAUCAGCTT-3' (SEQ ID NO: 38) (antisense strand);
- ii. 5'-AGUGUGCAAUAGUCUACAA-3' (SEQ ID NO: 39) (sense strand) and/or  
5'-UUGUAGACUAUUUGCACACU-3' (SEQ ID NO: 40) (antisense strand);
- iii. 5'-AAGGACAGAGUCCAGUCGAAG-3' (SEQ ID NO: 41) (sense strand) and/or  
5'-CUUCGACUGGACUCUGUCCTT-3' (SEQ ID NO: 42) (antisense strand);
- iv. 5'-AAGAUUGAAACCCACAAGC-3' (SEQ ID NO: 43) (sense strand) and/or  
5'-GCUUGUGGGUUUCAUUCTT-3' (SEQ ID NO: 44) (antisense strand);
- v. 5'-GAAACCCACAAGCUGACCU-3' (SEQ ID NO: 45) (sense strand) and/or  
5'-AGGUCAGCUUGUGGGUUUC-3' (SEQ ID NO: 46) (antisense strand);
- vi. 5'-AAUAUCAAACACGUCCCCGGA-3' (SEQ ID NO: 47) (sense strand) and/or  
5'-UCCCCGGGACGUGUUUGAUATT-3' (SEQ ID NO: 48) (antisense strand);
- vii. 5'-AUCAAACACGUCCCCGGGAG-3' (SEQ ID NO: 49) (sense strand) and/or  
5'-CUCCCCGGGACGUGUUUGAU-3' (SEQ ID NO: 50) (antisense strand);
- viii. 5'-AACACGUCCCCGGGAGGCGGCA-3' (SEQ ID NO: 51) (sense strand) and/or  
5'-UGCCGCCUCCCCGGGACGUGTT-3' (SEQ ID NO: 52) (antisense strand);
- ix. 5'-ACGUCCCCGGGAGGCGGCAG-3' (SEQ ID NO: 53) (sense strand) and/or  
5'-CUGCCGCCUCCCCGGGACGU-3' (SEQ ID NO: 54) (antisense strand); or
- x. 5'-UCCCCGGGAGGCGGCAGUGU-3' (SEQ ID NO: 55) (sense strand) and/or  
5'-ACACUGCCGCCUCCCCGGA-3' (SEQ ID NO: 56) (antisense strand).

**[0072]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AACGUCCAGUCCAAGUGUGGC-3' (SEQ ID NO: 1) (sense strand) and 5'-GCCACACUUGGACUGGACGTT-3' (SEQ ID NO: 2) (antisense strand).

**[0073]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGCAACGUCCAGUCCAAG-3' (SEQ ID NO: 3) (sense strand) and 5'-CUUGGACUGGACGUUGC-3' (SEQ ID NO: 4) (antisense strand).

**[0074]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AAGGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 5) (sense strand) and 5'-CUUAUUAUUUAUCUGCACCTT-3' (SEQ ID NO: 6) (antisense strand).

**[0075]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-UGAGAACCUGAAGCACCAG-3' (SEQ ID NO: 7) (sense strand) and 5'-CUGGUGCUUCAGGUUCUCA-3' (SEQ ID NO: 8) (antisense strand).

**[0076]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand).

**[0077]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AAUUAUAAGAAGCUGGAUCU-3' (SEQ ID NO: 11) (sense strand) and 5'-AGAUCAGCUUCUUAUUAATT-3' (SEQ ID NO: 12) (antisense strand).

**[0078]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-GAGCCCAAGAAGGUGGCAG-3' (SEQ ID NO: 13) (sense strand) and 5'-CUGCCACCUUCUUGGGCUC-3' (SEQ ID NO: 14) (antisense strand).

**[0079]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-ACCCGGGAGCCCAAGAAG-3' (SEQ ID NO: 15) (sense strand) and 5'-CUUCUUGGGCUCCCGGGU-3' (SEQ ID NO: 16) (antisense strand).

**[0080]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGAAGCUGGAUCUUAGCAA-3' (SEQ ID NO: 17) (sense strand) and 5'-UUGCUAAGAUCAGCUUCU-3' (SEQ ID NO: 18) (antisense strand).

**[0081]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AAGGAUAAUAUCAAACACGUC-3' (SEQ ID NO: 19) (sense strand) and 5'-GACGUGUUUGAUUAUUCCTT-3' (SEQ ID NO: 20) (antisense strand).

**[0082]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AUAAUAUCAAACACGUCCC-3' (SEQ ID NO: 21) (sense strand) and 5'-GGGACGUGUUUGAUUAUUAU-3' (SEQ ID NO: 22) (antisense strand).

**[0083]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand).

**[0084]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AAUAUCACCCACGUCCUGG-3' (SEQ ID NO: 25) (sense strand) and 5'-CCAGGGACGUGGGUGAUATT-3' (SEQ ID NO: 26) (antisense strand).

**[0085]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUUCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand).

**[0086]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-CCAAAGCCAAGACAGACCA-3' (SEQ ID NO: 29) (sense strand) and 5'-UGGUCUGUCUUGGCUUUGG-3' (SEQ ID NO: 30) (antisense strand).

**[0087]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AAGCAGGGUUUGUGAUCAG-3' (SEQ ID NO: 31) (sense strand) and 5'-CUGAUCACAAACCCUGCTT-3' (SEQ ID NO: 32) (antisense strand).

**[0088]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-CUCGGGACUUCAAAAUCAG-3' (SEQ ID NO: 33) (sense strand) and 5'-CUGAUUUUGAAGUCCCGAG-3' (SEQ ID NO: 34) (antisense strand).

**[0089]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGGGCAGCCUGUGGGAGAA-3' (SEQ ID NO: 35) (sense strand) and 5'-UUCUCCCACAGGCUGCCCU-3' (SEQ ID NO: 36) (antisense strand).

**[0090]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AAGCUGGAUCUUAGCAACGUC-3' (SEQ ID NO: 37) (sense strand) and 5'-GACGUUGCUAAGAUCAGCTT-3' (SEQ ID NO: 38) (antisense strand).

**[0091]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGUGUGCAAUAGUCUACAA-3' (SEQ ID NO: 39) (sense strand) and 5'-UUGUAGACUAUUUGCACACU-3' (SEQ ID NO: 40) (antisense strand).

**[0092]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AAGGACAGAGUCCAGUCGAAG-3' (SEQ ID NO: 41) (sense strand) and 5'-CUUCGACUGGACUCUGUCCTT-3' (SEQ ID NO: 42) (antisense strand).

**[0093]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AAGAUUGAAACCCACAAGC-3' (SEQ ID NO: 43) (sense strand) and 5'-GCUUGUGGGUUUCAAUCTT-3' (SEQ ID NO: 44) (antisense strand).

**[0094]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-GAAACCCACAAGCUGACCU-3' (SEQ ID NO: 45) (sense strand) and 5'-AGGUCAGCUUGUGGGUUUC-3' (SEQ ID NO: 46) (antisense strand).

**[0095]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AAUAUCAAACACGUCCCGGGA-3' (SEQ ID NO: 47) (sense strand) and 5'-UCCCGGGACGUGUUUGAUATT-3' (SEQ ID NO: 48) (antisense strand).

**[0096]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AUCAAACACGUCCCGGGAG-3' (SEQ ID NO: 49) (sense strand) and 5'-CUCCCGGGACGUGUUUGAU-3' (SEQ ID NO: 50) (antisense strand).

**[0097]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AACACGUCCCGGGAGGCGGCA-3' (SEQ ID NO: 51) (sense strand) and 5'-UGCCGCCUCCCGGGACGUGTT-3' (SEQ ID NO: 52) (antisense strand).

**[0098]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-ACGUCCCGGGAGGCGGCAG-3' (SEQ ID NO: 53) (sense strand) and 5'-CUGCCGCCUCCCGGGACGU-3' (SEQ ID NO: 54) (antisense strand).

**[0099]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-UCCCGGGAGGCGGCAGUGU-3' (SEQ ID NO: 55) (sense strand) and 5'-ACACUGCCGCCUCCCGGGA-3' (SEQ ID NO: 56) (antisense strand).

**[0100]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).

**[0101]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotide from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

**[0102]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the

antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0103]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0104]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0105]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

**[0106]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0107]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein the nucleotides in the sense strand and/or the nucleotides in the antisense strand are linked by a phosphodiester bond, a phosphothioate bond, or any combination thereof.

**[0108]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the

antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0109]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

**[0110]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0111]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0112]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0113]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

**[0114]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-

CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotide from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0115]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0116]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense nucleotides, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0117]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

**[0118]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0119]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein at least one of the

backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0120]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0121]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

**[0122]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0123]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0124]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0125]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-

UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand is 2'-OMe.

**[0126]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0127]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0128]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0129]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' F at the sugar position.

**[0130]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0131]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-

UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0132]** In some aspects, the oligonucleotide in the present disclosure comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0133]** In some aspects, the oligonucleotide of the present disclosure is capable of inhibiting the expression of the human *MAPT* transcript in a cell which is expressing the human *MAPT* transcript. In some aspects, the oligonucleotide of the present disclosure is capable of inhibiting the expression of the monkey *MAPT* transcript in a cell which is expressing the monkey *MAPT* transcript.

**[0134]** In some aspects, the sense and antisense strands in the oligonucleotide forms an RNA duplex are covalently linked by a single-stranded hairpin. In some aspects, the oligonucleotide comprises non-nucleotide materials. In some aspects, the oligonucleotide further comprises an addition, deletion, substitution, or alteration of one or more nucleotides.

**[0135]** In some aspects, the present disclosure provides oligonucleotides wherein the sense and antisense RNA strands are stabilized against nuclease degradation.

**[0136]** In some aspects, the present disclosure provides an oligonucleotide that also comprises a 3' overhang of 1 to 6 nucleotides or about 2 nucleotides.

**[0137]** In some aspects, the present disclosure provides an oligonucleotide that also comprises a 3' overhang of 1 to 6 nucleotides or about 2 nucleotides with a sequence of: GCCACACUUGGACUGGACGTT (SEQ ID NO: 2), CUUAUUAUUAUCUGCACCTT (SEQ ID NO: 6), AGAUCCAGCUUCUUAUUAATT (SEQ ID NO: 12), GACGUUGCUAAGAUCAGCTT (SEQ ID NO: 38), GACGUGUUUGAUUAUUAUCCTT (SEQ ID NO: 20), CCAGGGACGUGGGUGAUATT (SEQ ID NO: 26), CUUCGACUGGACUCUGUCCTT (SEQ ID NO: 42), GCUUGUGGGUUUCAUUCTT (SEQ ID NO: 44), CUGAUCACAAACCCUGCTT (SEQ ID NO: 32), UCCCGGGACGUGUUUGAUATT (SEQ ID NO: 48), or UGCCGCCUCCCGGGACGUGTT (SEQ ID NO: 52).

[0138] In some aspects, the sense RNA strand in the oligonucleotide comprises a first 3' overhang, and the antisense RNA strand in the oligonucleotide comprises a second 3' overhang. In some aspects, the first and second 3' overhangs in the oligonucleotide separately comprise from 1 to about 6 nucleotides. In some aspects, the first 3' overhang in the oligonucleotide comprises a dinucleotide and the second 3' overhang comprises a dinucleotide.

[0139] In some aspects, the present disclosure provides an oligonucleotide where the dinucleotide comprising the first and second 3' overhangs is dithymidylic acid (TT) or diuridylic acid (uu).

[0140] In some aspects, the present disclosure provides an oligonucleotide wherein the 3' overhang is stabilized against nuclease degradation.

[0141] In some aspects, the present disclosure provides an oligonucleotide that comprises at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten nucleoside analogues.

[0142] In some aspects, the present disclosure provides an oligonucleotide wherein the nucleoside analogue or analogues are one or more sugar modified nucleosides selected from the group consisting of Locked Nucleic Acid (LNA); 2'-O-alkyl-RNA; 2'-amino-DNA; 2'-fluoro-DNA; arabino nucleic acid (ANA); 2'-fluoro-ANA, hexitol nucleic acid (HNA), intercalating nucleic acid (INA), constrained ethyl nucleoside (cEt), 2'-O-methyl nucleic acid (2'-OMe), 2'-O-methoxyethyl nucleic acid (2'-MOE), and any combination thereof.

[0143] In some aspects, the present disclosure provides an oligonucleotide wherein the nucleoside analogue or analogues comprise a bicyclic sugar. In some aspects, the bicyclic sugar comprises cEt, 2',4'-constrained 2'-O-methoxyethyl (cMOE), LNA,  $\alpha$ -L-LNA,  $\beta$ -D-LNA, 2'-O,4'-C-ethylene-bridged nucleic acids (ENA), amino-LNA, oxy-LNA, or thio-LNA.

[0144] In some aspects, the present disclosure provides an oligonucleotide wherein the nucleoside analogue or analogues comprise an LNA. In some aspects, the oligonucleotide comprises 5'-methylcytosine, pseudouridine, or 5-methoxyuridine. In some aspects, the oligonucleotide comprises one or more 5' methyl cytosine nucleobases.

[0145] In some aspects, the present disclosure provides an oligonucleotide which reduces expression of *MAPT* mRNA in a cell by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% compared to a cell not exposed to the oligonucleotide.

[0146] In some aspects, the present disclosure provides an oligonucleotide which reduces expression of *MAPT* protein in a cell by at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% compared to a cell not exposed to the oligonucleotide.

[0147] In some aspects, the present disclosure provides an oligonucleotide which comprises an internucleoside linkage selected from: a phosphodiester linkage, a phosphotriester linkage, a methylphosphonate linkage, a phosphoramidate linkage, a phosphorothioate linkage, and combinations thereof. In some aspects, the internucleoside linkage comprises one or more stereo-defined, modified phosphate linkages.

[0148] In some aspects, the present disclosure provides a conjugate comprising oligonucleotides wherein the oligonucleotide is covalently attached to at least one non-nucleotide or non-polynucleotide moiety.

[0149] In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide wherein the non-nucleotide or non-polynucleotide moiety comprises a protein, a fatty acid chain, a sugar residue, a glycoprotein, a polymer, or any combinations thereof.

[0150] In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide wherein the non-nucleotide or non-polynucleotide moiety comprises a cholesteryl moiety, a vinyl phosphonate moiety, or any combination thereof.

[0151] In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-GGUGCAGAUAAUUAAG-3' (SEQ ID NO: 64) (sense strand) and/or

5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand),

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position,

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position, wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond, and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0152]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and/or

5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand),

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position,

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position, wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond, and

wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strands.

**[0153]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and/or

5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand),

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and

wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0154]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and/or

5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand),

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and

wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0155]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and

5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand),

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and

wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0156]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and

5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand),

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position; wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0157]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and

5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand),

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position; wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotide from 5' to 3' of the antisense strand comprise 2'-F at the sugar position; wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense nucleotides, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0158]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and  
 5'-CGGGGCUAGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand),  
 wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;  
 wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotide from 5' to 3' of the antisense strand comprise 2'-F at the sugar position;  
 wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense nucleotides, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0159]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the nucleic acid sequence comprises, consists essentially of, or consists of:

5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and  
 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand),  
 wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position;  
 wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0160]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and  
 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand),

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position; wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0161]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and

5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand),

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0162]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and

5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand),

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0163]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and

5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand is 2'-OMe; wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0164]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and

5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand is 2'-OMe; wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester

bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0165]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and

5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand is 2'-OMe; wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand and a vinyl phosphonate moiety is linked to the antisense strand.

**[0166]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and

5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' F at the sugar position; wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprises 2' OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprises 2' F at the sugar position; wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

[0167] In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and

5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' F at the sugar position; wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprises 2' OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprises 2' F at the sugar position; wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

[0168] In some aspects, the present disclosure provides a composition comprising an oligonucleotide or conjugate and a pharmaceutically acceptable carrier and/or a therapeutic agent. In some aspects, the therapeutic agent is a Microtubule-associated protein tau antagonist. In some aspects, the Microtubule-associated protein tau antagonist is an anti-Microtubule-associated protein tau antibody or fragment thereof.

[0169] In some aspects, the present disclosure provides an oligonucleotide, a conjugate, or a composition as a kit with instructions for use.

[0170] In some aspects, the present disclosure provides a method of inhibiting or reducing *MAPT* protein expression in a cell, the method comprising administering an oligonucleotide, a conjugate, or a composition to a cell expressing *MAPT* protein, wherein the *MAPT* protein expression in the cell is inhibited or reduced after the administration.

[0171] In some aspects, the present disclosure provides a method in which the oligonucleotide inhibits or reduces expression of *MAPT* mRNA in the cell after the administration.

[0172] In some aspects, the present disclosure provides a method wherein the expression of *MAPT* mRNA is reduced by at least about 20%, at least about 30%, at least about 40%, at least

about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% after the administration compared to a cell not exposed to the oligonucleotide.

**[0173]** In some aspects, the oligonucleotide reduces expression of *MAPT* protein in the cell after the administration by at least about 60%, at least about 70%, at least about 80%, or at least about 90% compared to a cell not exposed to the oligonucleotide.

**[0174]** In some aspects, the present disclosure provides methods of inhibiting or reducing *MAPT* protein expression in a cell where the cell is a neuron.

**[0175]** In some aspects, the present disclosure provides a method for treating a tauopathy in a subject in need thereof, comprising administering an effective amount of an oligonucleotide, a conjugate, or a composition to the subject. In some aspects, the present disclosure provides methods of treating tauopathy in a subject wherein the tauopathy is selected from the group consisting of behavioral variant frontotemporal dementia, primary progressive aphasia, corticobasal syndrome, Richardson's syndrome, Pick's disease, Parkinsonism linked to chromosome 17, Primary age related tauopathy, Tangle-predominant dementia, Corticobasal degeneration, Progressive supranuclear palsy, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, globular glial tauopathy, Argyrophilic grain disease, Aging-related tau astrogliopathy, and any combinations thereof. In some aspects, the present disclosure provides methods of treating tauopathy in a subject that is human. In some aspects, the present disclosure provides a method of treating tauopathy in a subject, wherein the oligonucleotide, the conjugate, or the composition is administered orally, parenterally, intrathecally, intra-cerebroventricularly, pulmonarily, topically, or intraventricularly.

## BRIEF DESCRIPTION OF FIGURES

**[0176]** **FIG. 1A** shows Western blot analyses of tau protein expression level after *MAPT* siRNA (100 nM) transfection for 48 h in differentiated SH-SY5Y. The table below the Western blot shows the % inhibition of the total tau protein. siMAPT 1, 2, 4, 5, 6, 8, 10, 11, 12, 14, 15, 21, 22, and 23 effectively reduces the tau protein level. The beta ( $\beta$ )-actin protein expression was used as a control. **FIG. 1B** shows relative mRNA expression levels of tau after *MAPT* siRNA (100 nM) transfection in Tau-WT (3R2N and 4R2N) transfected SH-SY5Y cells and relative mRNA expression level of *MAPT* isoform (4R2N) after *MAPT* siRNA (100 nM) transfection in Tau-MUT (L266V, 4R2N isoform) transfected SH-SY5Y cells. siMAPT 5, 6, 8, 9, 10, 12, 14, 15, 21, and 22 effectively reduces wild type tau mRNA. siMAPT 1 and 17 effectively reduces Tau-MUT (L266V). siMAPT 3, 11, and 23 effectively reduces both wild type tau and tau-

MUT. All data are mean  $\pm$  SD. \*\* $P < 0.01$ , and \*\*\*\* $P < 0.0001$  compared to the control (Con). ### $P < 0.05$ , ### $P < 0.01$ , #### $P < 0.001$ , and ##### $P < 0.0001$  compared to the transfection control.

[0177] **FIG. 2A** shows Western blot analyses of tau protein expression levels following different concentration of *MAPT* siRNA (No.5) transfection for 48 h in SH-SY5Y. Beta ( $\beta$ )-actin protein expression was used as a control. A graph of the % expression is shown, with its IC<sub>50</sub>. The % tau protein expression is shown in the table for 1nM, 5nM, 10nM, 50nM, 100nM, 250nM, 500nM, and 1000nM of siRNA no. 5. **FIG. 2B** shows Western blot analyses of tau protein expression levels following different concentration of *MAPT* siRNA (No.10) transfection for 48 h in SH-SY5Y. Beta ( $\beta$ )-actin protein expression was used as a control. A graph of the % expression is shown, with its IC<sub>50</sub>. The % tau protein expression is shown in the table for 10nM, 100nM, and 1000nM of siRNA no. 10. **FIGs. 2C and 2D** show relative mRNA expression levels of total tau following different concentration of *MAPT* siRNA (No.5) transfection (**FIG. 2C**) and siRNA (No.10) transfection (**FIG. 2D**) for 48 h in Tau-WT (3R1N, 3R2N, 4R1N, and 4R3N) transfected SH-SY5Y cells. **FIGs. 2E and 2F** show relative mRNA expression levels of *MAPT* isoform (4R2N) after *MAPT* siRNA (No.5) transfection (**FIG. 2E**) and siRNA (No.10) transfection (**FIG. 2F**) for 48h in Tau-MUT (L226V, 4R2N isoform) transfected SH-SY5Y cells respectively.

[0178] **FIGs. 3A through 3F** show relative mRNA expression levels of wild-type Tau, and 3R0N, 4R2N, and 4R1N Tau isoforms following different concentration of *MAPT* siRNA for 48 h in Tau-MUT ((L266V, 4R2N) and (P301S, 4R1N)) and Tau-WT (3R1N, 3R2N, 4R1N, 4R2N) and Tau-WT (3R0N) transfected SH-SY5Y cells. **FIGs. 3A through 3F** correspond to siRNA No.1 (**FIG. 3A**), siRNA No.17 (**FIG. 3B**), siRNA No.20 (**FIG. 3C**), siRNA No.23 (**FIG. 3D**), siRNA No.3 (**FIG. 3E**), and siRNA No.11 (**FIG. 3F**) respectively.

[0179] **FIG. 4A** shows a schematic illustration of the experimental schedule. Mice were subjected to behavior test for 3days after ICV injection of A $\beta$ Os (2  $\mu$ g) (4-weeks). BIOK-*Mapt* siRNA (2  $\mu$ g) was ICV injected 2-week post to A $\beta$ Os. **FIG. 4B** shows the results of a Y-maze test with vehicle control (Con), A $\beta$ Os, and A $\beta$ Os + *Mapt* siRNA (No.17) (left bar, middle bar, and right bar, respectively) (9-week-old, mice, n=5 mice per group) for assessment of spatial working memory. **FIG. 4C** shows the results of a Y-maze test with vehicle control, A $\beta$ Os and A $\beta$ Os + *Mapt* siRNA (No.11) (left bar, middle bar, and right bar, respectively) for assessment of spatial working memory. **FIGs. 4D through 4F** show quantification of Western blot analyses of total tau (**FIG. 4D**), p-tau (pT181) (**FIG. 4E**), and p-tau (pS202) (**FIG. 4F**) expression levels in protein tissue lysates from hippocampal tissue of A $\beta$ Os ICV injected mice following *Mapt* siRNA (No.17) ICV injection (n=5 mice) respectively. **FIGs. 4D through 4F** show the results of this test with bars

representing vehicle control (Con), A $\beta$ Os, and A $\beta$ Os + *Mapt* siRNA (No.17) (left bar, middle bar, and right bar, respectively) conditions. FIG. 4G shows a summary of the quantified average Tau inhibition % for FIG. 4D through 4F. FIGS. 4H through 4J show quantifications of Western blot analyses of total tau (FIG. 4H), p-tau (pT181) (FIG. 4I), and p-tau (pS202) (FIG. 4J) expression levels in protein tissue lysates from hippocampal tissue of A $\beta$ Os ICV injected mice following *Mapt* siRNA (No.11) ICV injection (n=5 mice) respectively. FIGS. 4H through 4J show the results of this test with bars representing vehicle control (Con), A $\beta$ Os, and A $\beta$ Os + *Mapt* siRNA (No.11) (left bar, middle bar, and right bar, respectively) conditions. FIG. 4K shows a summary of the quantified average Tau inhibition % for FIGS. 4H through 4J. All data are mean  $\pm$  SD. \*\*P < 0.01 compared to the control (Con). #P < 0.05 and ##P < 0.01 compared to the A $\beta$ Os control.

[0180] FIGS. 5A through 5D show quantifications of Western blot analyses of total tau (t-tau) and hyperphosphorylated tau (p-tau) protein expression levels in each brain tissue such as hippocampus (FIG. 5A), prefrontal cortex (FIG. 5B), entorhinal cortex (FIG. 5C), and striatum (FIG. 5D) following ICV injection of B1OK-*Mapt* siRNA in P301S transgenic mice respectively. ICV injection of B1OK-*Mapt* siRNA was performed a total of 3 times at 2-week intervals for 6-week, and brain tissue dissected 6-week after the first injection of B1OK-*Mapt* siRNA in P301S transgenic mice. FIG. 5E shows the results of a Y-maze test with vehicle control and *Mapt* siRNA (Nos. 20, 11, 17) in P301S transgenic mice for assessment of spatial working memory (26-week-old, mice, n=4 mice per group). All data are mean  $\pm$  SD. \*P < 0.05, \*\*P < 0.01, and \*\*\*P < 0.001 compared to the vehicle control (Con).

[0181] FIG. 6 shows siMAPT sense and antisense sequences, their sequence ID Nos, and their target exons.

[0182] FIG. 7 shows the *MAPT* mRNA sequence.

[0183] FIG. 8 shows the *MAPT* isoform mRNA sequences for 4R2N, 4R1N, 4R0N, 3R2N, 3R1N, and 3R0N.

[0184] FIGS. 9A through 9I show the sense strand and antisense strand for #3\*\_M1/M1/siMAPT-3\*-On\_chol (FIG. 9A), #5\_M2/M2/siMAPT-5-On\_chol (FIG. 9B), #14\_M3/M3/siMAPT-14-On\_chol (FIG. 9C), #17\_M4/M4/siMAPT-17-On\_chol (FIG. 9D), #3\*\_M5/M5/siMAPT-3\*-Am\_chol (FIG. 9E), #5\_M6/M6/siMAPT-5-Am\_chol (FIG. 9F), #14\_M7/M7/siMAPT-14-Am\_chol (FIG. 9G), #17\_M8/M8/siMAPT-17-Am\_chol (FIG. 9H), and #17\_M9/M9/siMAPT-17-On\_chol\_vinyl (FIG. 9I). Also shown is a cholesteryl and vinyl phosphonate moiety.

[0185] **FIGs. 10A through 10C** show the relative expression of mTau MAPT RNA following administration with siRNA #1 in the hippocampus (**FIG. 10A**), entorhinal cortex (**FIG. 10B**), and prefrontal cortex (**FIG. 10C**) (sub brain regions) of C57BL/6N Mice at 7, 21, and 28 days compared to a control group. A table showing the inhibition percent at 7, 21, and 28 days is also shown for **FIGs. 10A through 10C**. All data are mean  $\pm$  SD. Significance was set at \*\*\*\* $P < 0.0001$  compared to the WT (Vehicle) group. Significance was determined using a one-way ANOVA and post-hoc tukey's test.

[0186] **FIGs. 10D through 10F** show the relative expression of mTau MAPT RNA following administration with siRNA #17 in the hippocampus (**FIG. 10D**), entorhinal cortex (**FIG. 10E**), and prefrontal cortex (**FIG. 10F**) (sub brain regions) of C57BL/6N Mice at 7, 21, and 28 days compared to a control group. A table showing the inhibition percent at 7, 21, and 28 days is also shown for **FIGs. 10D through 10F**. All data are mean  $\pm$  SD. Significance was set at \*\*\*\* $P < 0.0001$  compared to the WT (Vehicle) group. Significance was determined using a one-way ANOVA and post-hoc tukey's test.

[0187] **FIGs. 11A through 11C** show the relative expression of huTau MAPT RNA following administration with siRNA #1 in the hippocampus (**FIG. 11A**), entorhinal cortex (**FIG. 11B**), and prefrontal cortex (**FIG. 11C**) (sub brain regions) of PS19 Mice at 7, 21, and 28 days compared to a control group. A table showing the inhibition percent at 7, 21, and 28 days is also shown for **FIGs. 11A through 11C**. All data are mean  $\pm$  SD. Significance was set at \*\*\*\* $P < 0.0001$  compared to the WT (Vehicle) group. Significance was determined using a one-way ANOVA and post-hoc tukey's test.

[0188] **FIGs. 11D through 11F** show the relative expression of huTau MAPT RNA following administration with siRNA #17 in the hippocampus (**FIG. 11D**), entorhinal cortex (**FIG. 11E**), and prefrontal cortex (**FIG. 11F**) (sub brain regions) of PS19 Mice at 7, 21, and 28 days compared to a control group. A table showing the inhibition percent at 7, 21, and 28 days is also shown for **FIGs. 11D through 11F**. All data are mean  $\pm$  SD. Significance was set at \*\*\*\* $P < 0.0001$  compared to the WT (Vehicle) group. Significance was determined using a one-way ANOVA and post-hoc tukey's test.

[0189] **FIG. 12A** shows the schematic illustration of the experimental schedule for BDDS-MAPT siRNA efficacy test in PS19 mice. ICV injections took place on weeks 22, 25, 28, 31, 34, and 37. Administration of the nest building test occurred on weeks 26, 32, and 38. Administration of open field test occurred on weeks 27 and 33. Administration of the elevated plus maze test occurred on weeks 27, and 36. Administration of the Y-maze test occurred on week 39. Mice were

sacrificed, tissue was harvested, and the brain was fixed at 40 weeks. **FIGs. 12B** through **12E** show western blot analysis of human tau (**FIG. 12B**), p-tau (pT181) (**FIG. 12C**), p-tau (Ser 404) (**FIG. 12D**), and p-tau (Ser 396) (**FIG. 12E**) expression levels in protein tissue lysates from tissue of PS19 ICV injected mice following MAPT siRNA #1 or #17 administration compared to WT and PS19 vehicle administration. All data are mean  $\pm$  SD. Significance was set at \*\*\*\*P < 0.0001 compared to the WT (Vehicle) group. Significance was set at #####P < 0.0001 compared to the PS19 (Vehicle) group. Significance was set at †P < 0.05, ††P < 0.01 and ††††P < 0.0001 for indicated comparisons. Significance was determined using a one-way ANOVA and post-hoc tukey's test.

**[0190]** **FIG. 13A** shows immunohistochemistry (IHC) images of AT8 (Ser202/Thr205) in the hippocampus of wild-type (WT), PS19, PS19 + MAPT siRNA #1, and PS19 + MAPT siRNA #17 administered mice at 10 months of age. **FIG. 13B** shows a summary of the relative intensity of AT8 (Ser202/Thr205) in the hippocampus of wild-type (WT), PS19, PS19 + MAPT siRNA #1, and PS19 + MAPT siRNA #17 administered mice at 10 months of age. **FIG. 13C** shows immunohistochemistry (IHC) images of AT8 (Ser202/Thr205) in the entorhinal cortex of wild-type (WT), PS19, PS19 + MAPT siRNA #1, and PS19 + MAPT siRNA #17 administered mice at 10 months of age. **FIG. 13D** shows a summary of the relative intensity of AT8 (Ser202/Thr205) in the entorhinal cortex of wild-type (WT), PS19, PS19 + MAPT siRNA #1, and PS19 + MAPT siRNA #17 administered mice at 10 months of age. AT8 is contrasted against black background. Scale bar = 250 $\mu$ m. All data are mean  $\pm$  SD. Significance was set at \*\*P < 0.01 and \*\*\*\*P < 0.0001 compared to the WT (Vehicle) group. Significance was set at #####P < 0.0001 compared to the PS19 (Vehicle) group. Significance was determined using a one-way ANOVA and post-hoc tukey's test.

**[0191]** **FIG. 14A** shows the nest building score (measured using Deacon's nesting score) for vehicle, PS19, PS19 + MAPT siRNA #1, and PS19 + MAPT siRNA #17 administered mice. **FIG. 14B** shows the untorn nestlet weight for vehicle, PS19, PS19 + MAPT siRNA #1, and PS19 + MAPT siRNA #17 administered mice. **FIG. 14C** shows the time in open arms for vehicle, PS19, PS19 + MAPT siRNA #1, and PS19 + MAPT siRNA #17 administered mice for the elevated plus maze test. **FIG. 14D** shows the time in closed arms for vehicle, PS19, PS19 + MAPT siRNA #1, and PS19 + MAPT siRNA #17 administered mice for the elevated plus maze test. All data are mean  $\pm$  SD. Significance was set at \*\*P < 0.01 and \*\*\*\*P < 0.0001 compared to the WT (Vehicle) group. Significance was set at #P < 0.05 and #####P < 0.0001 compared to the PS19 (Vehicle) group. Significance was determined using a one-way ANOVA and post-hoc tukey's test.

[0192] **FIG. 15A** and **15B** show the results of an open field test for vehicle, PS19, PS19 + MAPT siRNA #1, and PS19 + MAPT siRNA #17 administered mice. Ambulatory distance is indicated on the left chart, and resting time is indicated of the right chart of **FIG. 15A**. Rearing behavior (vertical activity) is shown on **FIG. 15B**. **FIG. 15C** shows the results of a spatial working memory test for vehicle, PS19, PS19 + MAPT siRNA #1, and PS19 + MAPT siRNA #17 administered mice as determined by the Y-maze test. All data are mean  $\pm$  SD. Significance was set at  $**P < 0.01$  and  $****P < 0.0001$  compared to the WT (Vehicle) group. Significance was set at  $\#P < 0.05$ ,  $\##P < 0.01$ ,  $\###P < 0.001$  and  $####P < 0.0001$  compared to the PS19 (Vehicle) group. Significance was determined using a one-way ANOVA and post-hoc tukey's test.

[0193] **FIG. 16** shows relative tau mRNA expression levels after naked MAPT siRNA (siRNA #3\*, siRNA #5, siRNA#14 and siRNA #17) and modified siRNA (M1, M2, M3, M4, M5, M6, M7, M8 and M9) transfection for 48 h in HMC3 (Human microglia) (n=3). In **FIG. 16** each modified siRNA (M1, M2, M3, M4, M5, M6, M7, M8 and M9) was transfected twice with a 5-fold dilution between the two (10 nM and 50 nM). In **FIG. 16** each naked siRNA (siRNA #3\*, siRNA #5, siRNA#14 and siRNA #17) was transfected at a concentration of 50 nM. All data are mean  $\pm$  SEM. Significance was set at  $***P < 0.001$  and  $****P < 0.0001$  compared to the control (Con). Significance was determined using a one-way ANOVA and post-hoc tukey's test.

## DETAILED DESCRIPTION OF DISCLOSURE

### I. Definitions

[0194] It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "a nucleotide sequence," is understood to represent one or more nucleotide sequences. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

[0195] Furthermore, "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0196] It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0197] It is understood that the terms "MAPT siRNA No.," "siRNA No.," "siMAPT No.," "MAPT siRNA #," "siRNA #," and "siMAPT #" are used interchangeably in the present disclosure. It is understood that the terms "MAPT siRNA" and "siMAPT" are used interchangeably in the present disclosure.

[0198] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0199] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, nucleotide sequences are written left to right in 5' to 3' orientation. Amino acid sequences are written left to right in amino to carboxy orientation. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

[0200] The term "about" is used herein to mean approximately, roughly, around, or in the regions of. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" can modify a numerical value above and below the stated value by a variance of, *e.g.*, 10 percent, up or down (higher or lower). For example, if it is stated that "the siRNA reduces expression of *MAPT* protein in a cell following administration of the siRNA by at least about 60%," it is implied that the *MAPT* levels are reduced by a range of 50% to 70%.

[0201] "G," "C," "A," "T," and "U" each generally stand for a naturally-occurring nucleotide that contains guanine, cytosine, adenine, thymine, and uracil as a base, respectively. However, it will be understood that the term "nucleotide" can refer to an alternative nucleotide, as further detailed below, or a surrogate replacement moiety. The skilled person is well aware that guanine, cytosine, adenine, thymine, and uracil can be replaced by other moieties without

substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base can base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine can be replaced in the nucleotide sequences of dsRNA featured herein by a nucleotide containing, for example, inosine. In another example, adenine and cytosine anywhere in the oligonucleotide can be replaced with guanine and uracil, respectively to form G-U Wobble base pairing with the target mRNA. Sequences containing such replacement moieties are suitable for the compositions and methods featured herein.

**[0202]** In some aspects, the nucleobase moiety is modified by changing the purine or pyrimidine into a modified purine or pyrimidine, such as substituted purine or substituted pyrimidine, such as an “alternative nucleobase” selected from isocytosine, pseudoisocytosine, 5-methyl cytosine, 5-thiozolo-cytosine, 5-propynyl-cytosine, 5-propynyl-uridine, 5-bromouridine 5-thiazolo-uridine, 2-thio-uridine, pseudouridine, 1-methylpseudouridine, 5-methoxyuridine, 2'-thio-thymine, inosine, diaminopurine, 6-aminopurine, 2-aminopurine, 2,6-diaminopurine, and 2-chloro-6-aminopurine.

**[0203]** The nucleobase moieties can be indicated by the letter code for each corresponding nucleobase, e.g. A, T, G, C, or U, wherein each letter can include alternative nucleobases of equivalent function.

**[0204]** A “sugar” or “sugar moiety,” includes naturally occurring sugars having a furanose ring. A sugar also includes an “alternative sugar,” defined as a structure that is capable of replacing the furanose ring of a nucleoside. In some aspects, alternative sugars are non-furanose (or 4'-substituted furanose) rings or ring systems or open systems. Such structures include simple changes relative to the natural furanose ring, such as a six-membered ring, or can be more complicated as is the case with the non-ring system used in peptide nucleic acid. Alternative sugars can include sugar surrogates wherein the furanose ring has been replaced with another ring system such as, for example, a morpholino or hexitol ring system. Sugar moieties useful in the preparation of oligonucleotides having motifs include, without limitation,  $\beta$ -D-ribose,  $\beta$ -D-2'-deoxyribose, substituted sugars (such as 2', 5' and bis substituted sugars), 4'-S-sugars (such as 4'-S-ribose, 4'-S-2'-deoxyribose and 4'-S-2'-substituted ribose), bicyclic alternative sugars (such as the 2'-O—CH<sub>2</sub>-4' or 2'-O—(CH<sub>2</sub>)<sub>2</sub>-4' bridged ribose derived bicyclic sugars) and sugar surrogates (such as when the ribose ring has been replaced with a morpholino or a hexitol ring system). The type of heterocyclic base and internucleoside linkage used at each position is variable and is not a factor

in determining the motif. In most nucleosides having an alternative sugar moiety, the heterocyclic nucleobase is generally maintained to permit hybridization.

**[0205]** The term "nucleotide" as used herein, refers to a glycoside comprising a sugar moiety, a base moiety and a covalently linked group (linkage group), such as a phosphate or phosphorothioate internucleotide linkage group, and covers both naturally occurring nucleotides, such as DNA or RNA, and non-naturally occurring nucleotides comprising modified sugar and/or base, which are also referred to as "nucleotide analogs" herein. Herein, a single nucleotide (unit) can also be referred to as a monomer or nucleic acid unit. In certain aspects, the term "nucleotide analogs" refers to nucleotides having modified sugar moieties. Non-limiting examples of the nucleotides having modified sugar moieties (*e.g.*, LNA) are disclosed elsewhere herein. In other aspects, the term "nucleotide analogs" refers to nucleotides having modified nucleobase moieties. The nucleotides having modified nucleobase moieties include, but are not limited to, 5-methylcytosine, isocytosine, pseudoisocytosine, 5-bromouracil, 5-propynyluracil, 6-aminopurine, 2-aminopurine, inosine, diaminopurine, and 2-chloro-6-aminopurine.

**[0206]** The term "nucleoside" as used herein is used to refer to a glycoside comprising a sugar moiety and a base moiety, which can be covalently linked by the internucleotide linkages between the nucleosides of the siRNA. In the field of biotechnology, the term "nucleoside" is often used to refer to a nucleic acid monomer or unit. In the context of an ASO, the term "nucleoside" can refer to the base alone, *i.e.*, a nucleobase sequence comprising cytosine (DNA and RNA), guanine (DNA and RNA), adenine (DNA and RNA), thymine (DNA) and uracil (RNA), in which the presence of the sugar backbone and internucleotide linkages are implicit. Likewise, particularly in the case of oligonucleotides where one or more of the internucleotide linkage groups are modified, the term "nucleotide" can refer to a "nucleoside." For example the term "nucleotide" can be used, even when specifying the presence or nature of the linkages between the nucleosides.

**[0207]** The term "alternative nucleoside" refers to a nucleoside having an alternative sugar or an alternative nucleobase, such as those described herein.

**[0208]** An "alternative nucleotide," as used herein, refers to a nucleotide having an alternative nucleoside or an alternative sugar, and an internucleoside linkage, which can include alternative nucleoside linkages.

**[0209]** The terms "oligonucleotide" and "polynucleotide," as used herein, are defined as it is generally understood by the skilled person as a molecule comprising two or more covalently linked nucleosides. Such covalently bound nucleosides can be referred to as nucleic acid molecules or oligomers. Oligonucleotides are commonly made in the laboratory by solid-phase chemical

synthesis followed by purification. When referring to a sequence of the oligonucleotide, reference is made to the sequence or order of nucleobase moieties, or modifications thereof, of the covalently linked nucleotides or nucleosides. The oligonucleotide can be man-made. For example, the oligonucleotide can be chemically synthesized and be purified or isolated. The oligonucleotides can comprise one or more alternative nucleosides or nucleotides (*e.g.*, including those described herein). It is also understood that oligonucleotide includes compositions lacking a sugar moiety or nucleobase but is still capable of forming a pairing with or hybridizing to a target sequence. "Oligonucleotide" refers to a short polynucleotide (*e.g.*, of 100 or fewer linked nucleosides).

**[0210]** As used herein, the term "strand" refers to an oligonucleotide comprising a chain of linked nucleosides. A "strand comprising a nucleobase sequence" refers to an oligonucleotide comprising a chain of linked nucleosides that is described by the sequence referred to using the standard nucleobase nomenclature.

**[0211]** The term "antisense," as used herein, refers to a nucleic acid comprising an oligonucleotide or polynucleotide that is sufficiently complementary to all or a portion of a gene, primary transcript, or processed mRNA, so as to interfere with expression of the endogenous gene (*e.g.*, SCNA). "Complementary" polynucleotides are those that are capable of base pairing according to the standard Watson-Crick complementarity rules. Specifically, purines will base pair with pyrimidines to form a combination of guanine paired with cytosine (G:C) and adenine paired with either thymine (A:T) in the case of DNA, or adenine paired with uracil (A:U) in the case of RNA. It is understood that two polynucleotides can hybridize to each other even if they are not completely complementary to each other, provided that each has at least one region that is substantially complementary to the other.

**[0212]** The terms "antisense strand" and "guide strand" refer to the strand of a dsRNA that includes a region that is substantially complementary to a target sequence, *e.g.*, an *MAPT* mRNA.

**[0213]** The terms "sense strand" and "passenger strand," as used herein, refer to the strand of a dsRNA that includes a region that is substantially complementary to a region of the antisense strand as that term is defined herein.

**[0214]** The term "dsRNA" refers to an agent that includes a sense strand and antisense strand that contains linked nucleosides as that term is defined herein. dsRNA includes, for example, siRNAs and shRNAs, which mediate the targeted cleavage of an RNA transcript via an RNA-induced silencing complex (RISC) pathway. dsRNA directs the sequence-specific degradation of mRNA through a process known as RNA interference (RNAi). The dsRNA reduces the expression of *MAPT* in a cell, *e.g.*, a cell within a subject, such as a mammalian subject. In

general, the majority of linked nucleosides of each strand of a dsRNA are ribonucleosides, but as described in detail herein, each or both strands can include one or more non-ribonucleosides, *e.g.*, deoxyribonucleosides and/or alternative nucleosides.

**[0215]** The terms “siRNA” and “short interfering RNA” (also known as “small interfering RNA”) refer to an RNA agent, such as a double-stranded agent, of about 10-50 nucleotides in length, the strands optionally having overhanging ends comprising, for example 1, 2, or 3 overhanging linked nucleosides, which is capable of directing or mediating RNA interference. Naturally-occurring siRNAs are generated from longer dsRNA molecules (*e.g.*, >25 linked nucleosides in length) by a cell's RNAi machinery (*e.g.*, Dicer or a homolog thereof).

**[0216]** The terms “shRNA” and “short hairpin RNA,” as used herein, refer to an RNA agent having a stem-loop structure, comprising at least two regions of complementary sequence, the degree of complementarity and orientation of the regions being sufficient such that base pairing occurs between the regions, at least two of the regions being joined by a loop region which results from a lack of base pairing between nucleobases within the loop region.

**[0217]** The term “nucleic acids” or “nucleotides” is intended to encompass plural nucleic acids. In some aspects, the term “nucleic acids” or “nucleotides” refers to a target sequence, *e.g.*, pre-mRNAs, mRNAs, or DNAs *in vivo* or *in vitro*. When the term refers to the nucleic acids or nucleotides in a target sequence, the nucleic acids or nucleotides can be naturally occurring sequences within a cell. In other aspects, “nucleic acids” or “nucleotides” refer to a sequence in the siRNAs of the disclosure. When the term refers to a sequence in the siRNAs, the nucleic acids or nucleotides are not naturally occurring, *i.e.*, chemically synthesized, enzymatically produced, recombinantly produced, or any combination thereof. In one aspect, the nucleic acids or nucleotides in the siRNAs are produced synthetically or recombinantly, but are not a naturally occurring sequence or a fragment thereof. In another aspect, the nucleic acids or nucleotides in the siRNAs are not naturally occurring because they contain at least one nucleotide analog that is not naturally occurring in nature. The term “nucleic acid” or “nucleoside” refers to a single nucleic acid segment, *e.g.*, a DNA, an RNA, or an analog thereof, present in a polynucleotide. “Nucleic acid” or “nucleoside” includes naturally occurring nucleic acids or non-naturally occurring nucleic acids. In some aspects, the terms “nucleotide”, “unit” and “monomer” are used interchangeably. It will be recognized that when referring to a sequence of nucleotides or monomers, what is referred to is the sequence of bases, such as A, T, G, C or U, and analogs thereof.

**[0218]** The term “nucleotide length” as used herein means the total number of the nucleotides (monomers) in a given sequence. For example, the sequence of

CUUAUUAUUUAUCUGCACC (SEQ ID NO: 65) has 19 nucleotides; thus the nucleotide length of the sequence is 19. The term "nucleotide length" is therefore used herein interchangeably with "nucleotide number."

**[0219]** As one of ordinary skill in the art would recognize, the 5' terminal nucleotide of an oligonucleotide does not comprise a 5' internucleotide linkage group, although it can comprise a 5' terminal group.

**[0220]** As used herein, the term "nucleoside overhang" refers to at least one unpaired nucleobase that protrudes from the duplex structure of a dsRNA. For example, when a 3'-end of one strand of a dsRNA extends beyond the 5'-end of the other strand, or vice versa, there is a nucleoside overhang. A dsRNA can comprise an overhang of at least one nucleoside; alternatively, the overhang can comprise at least two nucleosides, at least three nucleosides, at least four nucleosides, at least five nucleosides or more. A nucleoside overhang can comprise or consist of an alternative nucleoside, including a deoxynucleotide/nucleoside. A nucleoside overhang can comprise or consist of one or more phosphorothioates bonds. The overhang(s) can be on the sense strand, the antisense strand, or any combination thereof. Furthermore, the nucleoside(s) of an overhang can be present on the 5'-end, 3'-end or both ends of either an antisense or sense strand of a dsRNA. In some aspects, the overhang includes a self-complementary portion such that the overhang is capable of forming a hairpin structure that is stable under physiological conditions.

**[0221]** The terms "blunt" and "blunt ended" mean that there are no unpaired nucleobases at a given terminal end of a dsRNA, i.e., no nucleoside overhang. One or both ends of a dsRNA can be blunt. Where both ends of a dsRNA are blunt, the dsRNA is said to be blunt ended. To be clear, a "blunt ended" dsRNA is a dsRNA that is blunt at both ends, i.e., no nucleoside overhang at either end of the molecule. Most often, such a molecule will be double stranded over its entire length. As used herein, the term "cleavage region" refers to a region that is located immediately adjacent to the cleavage site. The cleavage site is the site on the target at which cleavage occurs. In some aspects, the cleavage region comprises three bases on either end of, and immediately adjacent to, the cleavage site. In some aspects, the cleavage region comprises two bases on either end of, and immediately adjacent to, the cleavage site. In some aspects, the cleavage site specifically occurs at the site bound by nucleosides 10 and 11 of the antisense strand, and the cleavage region comprises nucleosides 11, 12, and 13.

**[0222]** As used herein, a "coding region" or "coding sequence" is a portion of polynucleotide which consists of codons translatable into amino acids. Although a "stop codon"

(TAG, TGA, or TAA) is typically not translated into an amino acid, it can be considered to be part of a coding region, but any flanking sequences, for example promoters, ribosome binding sites, transcriptional terminators, introns, untranslated regions ("UTRs"), and the like, are not part of a coding region. The boundaries of a coding region are typically determined by a start codon at the 5' terminus, encoding the amino terminus of the resultant polypeptide, and a translation stop codon at the 3' terminus, encoding the carboxyl terminus of the resulting polypeptide.

**[0223]** The term "non-coding region" as used herein means a nucleotide sequence that is not a coding region. Examples of non-coding regions include, but are not limited to, promoters, ribosome binding sites, transcriptional terminators, introns, untranslated regions ("UTRs"), non-coding exons and the like. Some of the exons can be wholly or part of the 5' untranslated region (5' UTR) or the 3' untranslated region (3' UTR) of each transcript. The untranslated regions are important for efficient translation of the transcript and for controlling the rate of translation and half-life of the transcript.

**[0224]** The term "region" when used in the context of a nucleotide sequence refers to a section of that sequence. For example, the phrase "region within a nucleotide sequence" or "region within the complement of a nucleotide sequence" refers to a sequence shorter than the nucleotide sequence, but longer than at least 10 nucleotides located within the particular nucleotide sequence or the complement of the nucleotides sequence, respectively. The term "sub-sequence" or "subsequence" can also refer to a region of a nucleotide sequence.

**[0225]** The term "downstream," when referring to a nucleotide sequence, means that a nucleic acid or a nucleotide sequence is located 3' to a reference nucleotide sequence. In certain aspects, downstream nucleotide sequences relate to sequences that follow the starting point of transcription. For example, the translation initiation codon of a gene is located downstream of the start site of transcription.

**[0226]** The term "upstream" refers to a nucleotide sequence that is located 5' to a reference nucleotide sequence.

**[0227]** Unless otherwise indicated, the sequences provided herein are listed from 5' end (left) to 3' end (right).

**[0228]** As used herein, the term "regulatory region" refers to nucleotide sequences located upstream (5' non-coding sequences), within, or downstream (3' non-coding sequences) of a coding region, and which influence the transcription, RNA processing, stability, or translation of the associated coding region. Regulatory regions can include promoters, translation leader sequences, introns, polyadenylation recognition sequences, RNA processing sites, effector binding sites,

UTRs, and stem-loop structures. If a coding region is intended for expression in a eukaryotic cell, a polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence.

**[0229]** The term "transcript" as used herein can refer to a primary transcript that is synthesized by transcription of DNA and becomes a messenger RNA (mRNA) after processing, *i.e.*, a precursor messenger RNA (pre-mRNA), and the processed mRNA itself. The term "transcript" can be interchangeably used with "pre-mRNA" and "mRNA." After DNA strands are transcribed to primary transcripts, the newly synthesized primary transcripts are modified in several ways to be converted to their mature, functional forms such as mRNA, tRNA, rRNA, lncRNA, miRNA and others. Thus, the term "transcript" can include exons, introns, 5' UTRs, and 3' UTRs.

**[0230]** The term "expression" as used herein refers to a process by which a polynucleotide produces a gene product, for example, a RNA or a polypeptide. It includes, without limitation, transcription of the polynucleotide into messenger RNA (mRNA) and the translation of an mRNA into a polypeptide. Expression produces a "gene product." As used herein, a gene product can be either a nucleic acid, *e.g.*, a messenger RNA produced by transcription of a gene, or a polypeptide which is translated from a transcript. Gene products described herein further include nucleic acids with post transcriptional modifications, *e.g.*, polyadenylation or splicing, or polypeptides with post translational modifications, *e.g.*, methylation, glycosylation, the addition of lipids, association with other protein subunits, or proteolytic cleavage.

**[0231]** The terms "identical" or percent "identity" in the context of two or more nucleic acids refer to two or more sequences that are the same or have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned (introducing gaps, if necessary) for maximum correspondence, not considering any conservative amino acid substitutions as part of the sequence identity. The percent identity can be measured using sequence comparison software or algorithms or by visual inspection. Various algorithms and software are known in the art that can be used to obtain alignments of amino acid or nucleotide sequences.

**[0232]** One such non-limiting example of a sequence alignment algorithm is the algorithm described in Karlin *et al.*, 1990, *Proc. Natl. Acad. Sci.*, 87:2264-2268, as modified in Karlin *et al.*, 1993, *Proc. Natl. Acad. Sci.*, 90:5873-5877, and incorporated into the NBLAST and XBLAST programs (Altschul *et al.*, 1991, *Nucleic Acids Res.*, 25:3389-3402). In certain aspects, Gapped BLAST can be used as described in Altschul *et al.*, 1997, *Nucleic Acids Res.* 25:3389-3402. BLAST-2, WU-BLAST-2 (Altschul *et al.*, 1996, *Methods in Enzymology*, 266:460-480), ALIGN,

ALIGN-2 (Genentech, South San Francisco, California) or Megalign (DNASTAR) are additional publicly available software programs that can be used to align sequences. In certain aspects, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (*e.g.*, using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 90 and a length weight of 1, 2, 3, 4, 5, or 6). In certain alternative aspects, the GAP program in the GCG software package, which incorporates the algorithm of Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) can be used to determine the percent identity between two amino acid sequences (*e.g.*, using either a BLOSUM 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5). Alternatively, in certain aspects, the percent identity between nucleotide or amino acid sequences is determined using the algorithm of Myers and Miller (CABIOS, 4:11-17 (1989)). For example, the percent identity can be determined using the ALIGN program (version 2.0) and using a PAM120 with residue table, a gap length penalty of 12 and a gap penalty of 4. One skilled in the art can determine appropriate parameters for maximal alignment by particular alignment software. In certain aspects, the default parameters of the alignment software are used.

**[0233]** In certain aspects, the percentage identity "X" of a first nucleotide sequence to a second nucleotide sequence is calculated as  $100 \times (Y/Z)$ , where Y is the number of amino acid residues scored as identical matches in the alignment of the first and second sequences (as aligned by visual inspection or a particular sequence alignment program) and Z is the total number of residues in the second sequence. If the length of a first sequence is longer than the second sequence, the percent identity of the first sequence to the second sequence will be higher than the percent identity of the second sequence to the first sequence.

**[0234]** Different regions within a single polynucleotide target sequence that align with a polynucleotide reference sequence can each have their own percent sequence identity. It is noted that the percent sequence identity value is rounded to the nearest tenth. For example, 80.11, 80.12, 80.13, and 80.14 are rounded down to 80.1, while 80.15, 80.16, 80.17, 80.18, and 80.19 are rounded up to 80.2. It also is noted that the length value will always be an integer.

**[0235]** As used herein, the terms "homologous" and "homology" are interchangeable with the terms "identity" and "identical."

**[0236]** The term "naturally occurring variant thereof" refers to variants of the *MAPT* polypeptide sequence or *MAPT* nucleic acid sequence (*e.g.*, transcript) which exist naturally within the defined taxonomic group, such as mammalian, such as mouse, monkey, and human. Typically, when referring to "naturally occurring variants" of a polynucleotide the term also can encompass

any allelic variant of the *MAPT*-encoding genomic DNA which is found at Chromosomal position 17q21.31 by chromosomal translocation or duplication, and the RNA, such as mRNA derived therefrom. "Naturally occurring variants" can also include variants derived from alternative splicing of the *MAPT* mRNA. When referenced to a specific polypeptide sequence, *e.g.*, the term also includes naturally occurring forms of the protein, which can therefore be processed, *e.g.*, by co- or post-translational modifications, such as signal peptide cleavage, proteolytic cleavage, glycosylation, etc.

**[0237]** In determining the degree of "complementarity" between siRNAs of the disclosure (or regions thereof) and the target region of the nucleic acid which encodes mammalian *MAPT* protein (*e.g.*, the *MAPT* gene), such as those disclosed herein, the degree of "complementarity" (also, "homology" or "identity") is expressed as the percentage identity (or percentage homology) between the sequence of the siRNA (or region thereof) and the sequence of the target region (or the reverse complement of the target region) that best aligns therewith. The percentage is calculated by counting the number of aligned bases that are identical between the two sequences, dividing by the total number of contiguous monomers in the siRNA, and multiplying by 100. In such a comparison, if gaps exist, it is preferable that such gaps are merely mismatches rather than areas where the number of monomers within the gap differs between the siRNA of the disclosure and the target region.

**[0238]** The term "complement" as used herein indicates a sequence that is complementary to a reference sequence. It is well known that complementarity is the base principle of DNA replication and transcription as it is a property shared between two DNA or RNA sequences, such that when they are aligned antiparallel to each other, the nucleotide bases at each position in the sequences will be complementary, much like looking in the mirror and seeing the reverse of things. Therefore, for example, the complement of a sequence of 5'"ATGC"3' can be written as 3'"TACG"5' or 5'"GCAT"3'. The terms "reverse complement", "reverse complementary" and "reverse complementarity" as used herein are interchangeable with the terms "complement", "complementary" and "complementarity."

**[0239]** The terms "corresponding to" and "corresponds to," when referencing two separate nucleic acid or nucleotide sequences can be used to clarify regions of the sequences that correspond or are similar to each other based on homology and/or functionality, although the nucleotides of the specific sequences can be numbered differently. For example, different isoforms of a gene transcript can have similar or conserved portions of nucleotide sequences whose numbering can differ in the respective isoforms based on alternative splicing and/or other modifications. In

addition, it is recognized that different numbering systems can be employed when characterizing a nucleic acid or nucleotide sequence (*e.g.*, a gene transcript and whether to begin numbering the sequence from the translation start codon or to include the 5'UTR). Further, it is recognized that the nucleic acid or nucleotide sequence of different variants of a gene or gene transcript can vary. As used herein, however, the regions of the variants that share nucleic acid or nucleotide sequence homology and/or functionality are deemed to "correspond" to one another. For example, a nucleotide sequence of a *MAPT* transcript corresponding to nucleotides X to Y of SEQ ID NO: 57 ("reference sequence") refers to an *MAPT* transcript sequence (*e.g.*, *MAPT* pre-mRNA or mRNA) that has an identical sequence or a similar sequence to nucleotides X to Y of SEQ ID NO: 57. A person of ordinary skill in the art can identify the corresponding X and Y residues in the *MAPT* transcript sequence by aligning the *MAPT* transcript sequence with SEQ ID NO: 57.

**[0240]** The terms "corresponding nucleotide analog" and "corresponding nucleotide" are intended to indicate that the nucleobase in the nucleotide analog and the naturally occurring nucleotide have the same pairing, or hybridizing, ability. For example, when the 2-deoxyribose unit of the nucleotide is linked to an adenine, the "corresponding nucleotide analog" contains a pentose unit (different from 2-deoxyribose) linked to an adenine.

**[0241]** "Potency" is normally expressed as an  $IC_{50}$  or  $EC_{50}$  value, in  $\mu M$ , nM or pM unless otherwise stated. Potency can also be expressed in terms of percent inhibition.  $IC_{50}$  is the median inhibitory concentration of a therapeutic molecule.  $EC_{50}$  is the median effective concentration of a therapeutic molecule relative to a vehicle or control (*e.g.*, saline). In functional assays,  $IC_{50}$  is the concentration of a therapeutic molecule that reduces a biological response, *e.g.*, transcription of mRNA or protein expression, by 50% of the biological response that is achieved by the therapeutic molecule. In functional assays,  $EC_{50}$  is the concentration of a therapeutic molecule that produces 50% of the biological response, *e.g.*, transcription of mRNA or protein expression.  $IC_{50}$  or  $EC_{50}$  can be calculated by any number of means known in the art.

**[0242]** By "subject" or "individual" or "animal" or "patient" or "mammal," is meant any subject, particularly a mammalian subject, for whom diagnosis, prognosis, or therapy is desired. Mammalian subjects include humans, domestic animals, farm animals, sports animals, and zoo animals including, *e.g.*, humans, non-human primates, dogs, cats, guinea pigs, rabbits, rats, mice, horses, cattle, bears, and so on.

**[0243]** The term "pharmaceutical composition" refers to a preparation which is in such form as to permit the biological activity of the active ingredient to be effective, and which contains

no additional components which are unacceptably toxic to a subject to which the composition would be administered. Such composition can be sterile.

**[0244]** An "effective amount" of an siRNA as disclosed herein is an amount sufficient to carry out a specifically stated purpose. An "effective amount" can be determined empirically and in a routine manner, in relation to the stated purpose.

**[0245]** Terms such as "treating" or "treatment" or "to treat" or "alleviating" or "to alleviate" refer to both (1) therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder and (2) prophylactic or preventative measures that prevent and/or slow the development of a targeted pathologic condition or disorder. Thus, those in need of treatment include those already with the disorder; those prone to have the disorder; and those in whom the disorder is to be prevented. In certain aspects, a subject is successfully "treated" for a disease or condition disclosed elsewhere herein according to the methods provided herein if the patient shows, *e.g.*, total, partial, or transient alleviation or elimination of symptoms associated with the disease or disorder.

**[0246]** The term "*MAPT* protein" refers to, as way of example not limitation, wild-type *MAPT* protein, *MAPT* protein variants, *MAPT* isoforms (3R-, 4R-, 0N3R, 3R0N, 1N3R, 3R1N, 2N3R, 3R2N, 0N4R, 4R0N, 1N4R, 4R1N, 2N4R, 4R2N), or any combination thereof. *MAPT* isoforms can be defined by the amount of N regions and R regions they contain, so *e.g.*, 0N3R and 3R0N are equivalent to each other, this is also true for 1N3R and 3R1N, 2N3R and 3R2N, 0N4R and 4R0N, 1N4R and 4R1N, and 2N4R and 4R2N.

## II. Oligonucleotides

**[0247]** The present disclosure employs specific oligonucleotides (*e.g.*, siRNAs) for use in modulating the function of nucleic acid molecules encoding mammalian Microtubule-associated protein tau, such as the *MAPT* nucleic acid, *e.g.*, *MAPT* transcript, including *MAPT* pre-mRNA, and *MAPT* mRNA, or naturally occurring variants of such nucleic acid molecules encoding mammalian Microtubule-associated protein tau. The oligonucleotides (*e.g.*, siRNAs) that are capable of modulating the *MAPT* nucleic acid can bind to and modulate the expression of human *MAPT*, mouse *MAPT*, monkey *MAPT*, or any combination thereof. In some aspects, the oligonucleotides (*e.g.*, siRNAs) are capable of modulating one or more *MAPT* isoform 3R-, *MAPT* isoform 4R-, *MAPT* isoform 0N3R, *MAPT* isoform 1N3R, *MAPT* isoform 2N3R, *MAPT* isoform 0N4R, *MAPT* isoform 1N4R, *MAPT* isoform 2N4R, or any combination thereof. In some aspects,

the oligonucleotides (*e.g.*, siRNAs) that are capable of modulating the *MAPT* nucleic acid binds to human *MAPT*, mouse *MAPT*, and monkey *MAPT*.

**[0248]** The siRNA comprises a contiguous nucleotide sequence of from about 10 to about 30, such as 10–20, 16–20, or 15–25 nucleotides in length.

**[0249]** In various aspects, the siRNA of the disclosure comprises RNA (units). In some aspects, the siRNA comprises one or more DNA units. In one aspect, the siRNA according to the disclosure is a linear molecule or is synthesized as a linear molecule. In various aspects, the siRNA of the disclosure can consist entirely of the contiguous nucleotide region. Thus, in some aspects the siRNA is not substantially self-complementary.

**[0250]** In one aspect, the siRNA of the disclosure can be in the form of any pharmaceutically acceptable salts. The term "pharmaceutically acceptable salts" as used herein refers to derivatives of the siRNA of the disclosure wherein the siRNA is modified (*e.g.*, addition of a cation) by making salts thereof. Such salts retain the desired biological activity of the siRNAs without imparting undesired toxicological effects. In some aspects, the siRNA of the disclosure is in the form of a sodium salt. In other aspects, the siRNA is in the form of a potassium salt.

## II.A. The Target

**[0251]** In some aspects, the siRNA of the disclosure is capable of down-regulating (*e.g.*, reducing or removing) expression of the *MAPT* mRNA or protein. In this regard, the siRNA of the disclosure can affect indirect inhibition of *MAPT* protein through the reduction in *MAPT* mRNA levels, typically in a mammalian cell, such as a human cell, such as a neuronal cell. In particular, the present disclosure is directed to siRNAs that target one or more regions of the *MAPT* pre-mRNA.

**[0252]** Synonyms of *MAPT* are known and include TAU, TAU\_HUMAN, MSTD, PPND, DDPAC, MAPTL, MTBT1, MTBT2, tau-40, FTDP-17, PPP1R103, FLJ31424, MGC138549, Neurofibrillary tangle protein, Tau-derived paired helical filament hexapeptide, protein phosphatase 1, regulatory subunit 103, G protein beta1/gamma2 subunit-interacting factor 1, Paired helical filament-tau, PHF-tau, and Tau-PHF6. The mRNA sequence for Homo sapiens microtubule associated protein tau (*MAPT*), transcript variant 1, can be found under publicly available Accession Number NM\_016835.5, and the reference sequence for Homo sapiens microtubule associated protein tau (*MAPT*) can be found under publicly available Accession Number NG\_007398.2. The sequence for *MAPT* protein can be found under publicly available Accession Numbers: P10636 (primary accession) and, P18518, Q14799, Q15549, Q15550,

Q15551, Q1RMF6, Q53YB1, Q5CZI7, Q5XWF0, Q6QT54, Q9UDJ3, Q9UMH0, and Q9UQ96 (secondary accessions), each of which is incorporated by reference herein in its entirety. Natural variants of the *MAPT* gene product are known. For example, natural variants of *MAPT* protein can contain one or more amino acid substitutions. Therefore, the siRNAs of the present disclosure can be designed to reduce or inhibit expression of the natural variants of the *MAPT* protein.

**[0253]** Mutations in *MAPT* are known to cause one or more pathological conditions. The siRNAs of the disclosure can be used to reduce or inhibit the expression of a SNP or alternatively spliced *MAPT* transcript containing one or more mutations and consequently reduce the formation of a mutated *MAPT* protein. Examples of *MAPT* protein mutants include, but are not limited to a *MAPT* protein comprising one or more mutations selected from: A2S, P4T, R5C, R5L, R5H, E9K, M11L, G16V, T17M, L20F, G21V, R23S, G27E, T30K, T30I, G55R, D34Y, G37V, A41T, P59L, P78A, G86S, A91T, A91V, T95M, A103G, A74G, A45G, G78S, G49S, G107S, G107D, G78D, G49D, G107V, G49V, G78V, I108V, I79V, I50V, S113T, S55T, S84T, E115D, E57D, E86D, E117K, E59K, E88K, A60G, A89G, A118G, A143S, R155H, E183K, P126S, P201S, F136fs, F211fs, P140S, P215S, T178S, T253S, E179fs, E254fs, R182C, R257C, P202L, P277L, A206S, A281S, G208fs, G283fs, G213R, G288R, R222C, I260T, R297C, R222S, R297S, V224G, V299G, D225N, D300N, Q230R, Q305R, A250T, A325T, E262D, E337D, S273P, S348P, E278D, E353D, S282L, S357L, D285N, D360N, V289A, V364A, A297G, A372G, A297V, A372V, V311M, V386M, K313N, K388N, S318L, S393L, R338Q, R413Q, K366Q, K441Q, V368I, V443I, R370W, R445W, R452H, R97H, R126H, R377H, R68H, S71N, S100N, S129N, S380N, S455N, K130E, K101E, K381E, K456E, K72E, D459N, D133N, D104N, D75N, D384N, D138N, D389N, D109N, D80N, D464N, R398C, R473C, L410F, L485F, G418D, G493D, S427F, S502F, V431M, V506M, Y441H, Y516H, S447P, S522P, R448\*, R523\*, G461A, G470A, G86A, G115A, G144A, G536A, G115E, G144E, G470E, G461E, G86E, G536E, I151T, I468T, I122T, I93T, I477T, I543T, I122M, I151M, I468M, I477M, I543M, I93M, A152T, A469T, A123T, A94T, A478T, A544T, P551L, P476L, P130L, P101L, P159L, P485L, Q165R, Q491R, Q136R, Q107R, Q557R, Q482R, N109S, N138S, N167S, N484S, N493S, N559S, A139T, A485T, A494T, A110T, A560T, A168T, I171T, I488T, I113T, I142T, I497T, I563T, P176L, P502L, P118L, P147L, P493L, P568L, A495T, A178T, A120T, A149T, A504T, A570T, A503V, P512S, P513A, D135fs, D528fs, D510fs, D585fs, D164fs, D193fs, D519fs, G509R, G134R, G192R, G163R, G527R, G518R, G584R, G138S, G167S, G196S, G513S, G522S, G531S, G588S, G143S, G172S, G536S, G201S, G527S, G593S, G518S, G149S, G178S, G207S, G524S, G533S, G542S, G599S, R601C, R535C, R544C, R209C, R526C, R151C, R180C, R535L, R151L, R601L, R180L, R209L, R526L, R544L, R526H,

R209H, R151H, R180H, R544H, R535H, R601H, R546C, R153C, R182C, R211C, R537C, R603C, R528C, R537H, R603H, R211H, R153H, R528H, R546H, R182H, T154N, T183N, T212N, T529N, T538N, T547N, T604N, P155L, P184L, P213L, P530L, P539L, P548L, P605L, P161S, P190S, P554S, P219S, P536S, P545S, P611S, T162P, T555P, T191P, T537P, T220P, T546P, T612P, R547W, R556W, R221W, R538W, R163W, R192W, R613W, R163Q, R547Q, R192Q, R221Q, R538Q, R556Q, R613Q, A556T, A239T, A574T, A181T, A210T, A565T, A631T, R559C, R242C, R568C, R577C, R634C, R213C, R184C, V190M, V219M, V248M, V565M, V574M, V583M, V640M, K257T, K574T, K199T, K228T, K592T, K583T, K649T, I577V, I202V, I231V, I260V, I595V, I586V, I652V, G261S, G578S, G203S, G587S, G232S, G596S, G653S, L266V, L583V, L237V, L601V, L208V, L592V, L658V, Q586L, Q604L, Q211L, Q240L, Q269L, Q661L, Q595L, P212L, P241L, P270L, P587L, P605L, P596L, P662L, G272V, G589V, G243V, G607V, G214V, G598V, G664V, S2I, P22L, I25T, V65A, A112D, A123V, V592L, V217L, V246L, V275L, V610L, V667L, N279K, N221K, N250K, N596K, N614K, N671K, K598del, K616del, K223del, K252del, K281del, K673del, V229I, V258I, V287I, V604I, V622I, V679I, N613del, N296del, N238del, N267del, N631del, N688del, N613H, N267H, N296D, N296H, N238H, N631H, N688H, V242I, V271I, V300I, V617I, V635I, V692I, P301S, P301L, P301T, P243S, P272S, P618S, P636S, P693S, P243L, P272L, P618L, P636L, P693L, G303V, G620V, G274V, G638V, G245V, G695V, S247I, S276I, S305I, S622I, S640I, S697I, S305N, S247N, S276N, S622N, S640N, S697N, V278F, V626F, V220F, V249F, V251F, V701F, V280F, V309F, V604F, V644F, L632R, L286R, L315R, L315A, L650R, L255R, L257R, L284R, S285R, L226R, Δ296N, L610R, L707R, K317M, K317N, K634M, K259M, K288M, K228M, K257M, K652M, K286M, K612M, K709M, S320F, S320Y, S637F, S291F, S655F, S231F, S260F, S262F, S289F, S615F, S712F, G244\*, G304\*, G275\*, G302\*, G650\*, G725\*, G273\*, G333\*, G628\*, G668\*, G273R, Δ280K, G652S, G246S, G277S, G275S, G304S, G306S, G670S, G335S, G630S, G727S, G652V, G277V, G306V, G275V, G304V, G670V, G246V, G335V, G630V, N410H, G727V, Q653R, Q276R, Q671R, Q307R, Q247R, Q336R, Q278R, Q305R, Q631R, Q728R, Q247H, Q276H, Q336H, Q653H, Q278H, Q307H, Q305H, Q671H, Q631H, Q728H, V337M, V654M, V306M, V308M, V279M, V248M, V277M, V672M, V632M, V729M, E342V, E659V, E282V, E677V, E253V, E313V, E284V, E311V, E637V, E734V, Q351R, Q668R, Q322R, Q686R, Q262R, Q293R, Q291R, Q320R, Q646R, Q743R, S352L, S669L, S263L, S292L, S321L, S323L, S294L, S687L, S647L, S744L, S267T, S296T, S298T, S325T, S327T, S356T, S651T, S673T, S691T, S748T, H362Y, H679Y, H331Y, H697Y, H302Y, H304Y, H273Y, H333Y, H657Y, H754Y, V680I, V363I, V332I, V305I, V698I, V303I, V274I, V334I, V658I,

V755I, P304T, P306T, P332S, G335A, P335T, P275T, P681T, P699T, P333T, P364T, P364S, G336R, P659T, P756T, K369I, K686I, K309I, K280I, K311I, K338I, K340I, K704I, K664I, K761I, L316V, E372G, L376V, L318V, L345V, L347V, L711V, L287V, L693V, L671V, L768V, G706R, G300R, G358R, G360R, G329R, G331R, G724R, G684R, G781R, G389R, G706R, G358R, G360R, G300R, G329R, G331R, G724R, G684R, G781R, A330T, A332T, A359T, A707T, A685T, A782T, A301T, A390T, A361T, A725T, I709V, I727V, I361V, I303V, I332V, I363V, I334V, I392V, I687V, I784V, R406W, R723W, R375W, R317W, R346W, R741W, R348W, R377W, R701W, R798W, G357S, G415S, G384S, G750S, G326S, G355S, G732S, G386S, G710S, G807S, D358N, D387N, D713N, D418N, D360N, D753N, D810N, D329N, D389N, D735N, Q741K, Q364K, Q366K, Q395K, Q759K, Q335K, Q424K, Q393K, Q719K, Q816K, A368T, A395T, A426T, A818T, A721T, A337T, A366T, A397T, A743T, A761T, T744M, T367M, T427M, T338M, T369M, T396M, T398M, T762M, T722M, T819M, Q350R, Q379R, Q381R, Q408R, Q410R, Q439R, Q734R, Q756R, Q774R, Q831R, G351A, G380A, G382A, G409A, G411A, G440A, G735A, G757A, G775A, G832A, I1085T, I1084T, P1010L, P1009L, and any combination thereof. Examples of *MAPT* protein mutants include, but are not limited to a *MAPT* protein comprising one or more mutations selected from: L266V and P301S, and any combination thereof. The siRNA of the disclosure can be designed to reduce or inhibit expression of any mutants of *MAPT* proteins.

**[0254]** Alternative exon splicing of the *MAPT* gene transcript can produce six common isoforms of the *MAPT* protein, which include 0N4R, 1N4R, 2N4R, 0N3R, 1N3R, and 2N3R (also represented by 4R- and 3R-). Neurodegenerative conditions are associated with over- and under-expression of these isoforms, with specific neurodegenerative conditions being associated with specific isoforms. In a healthy brain, the ratio of the 4R- isoform to the 3R- isoform is about 50/50.

**[0255]** An example of a target nucleic acid sequence of the siRNAs is *MAPT* mRNA. In some aspects, the "target nucleic acid" comprises an exon region of an *MAPT* protein-encoding nucleic acids or naturally occurring variants thereof, and RNA nucleic acids derived therefrom. In some aspects, for example when used in research or diagnostics the "target nucleic acid" can be a cDNA or a synthetic oligonucleotide derived from the above DNA or RNA nucleic acid targets. The mRNA encoding *MAPT* protein is shown as SEQ ID NO: 57. See FIG 7. The *MAPT* mRNA sequences of the six most common *MAPT* isoforms are shown as SEQ ID NOs: 58-63. The amino acid sequence for *MAPT* protein can be found under publicly available Accession Number P10636. Specifically 0N3R can be found under P10636-2, 0N4R can be found under P10636-6, 1N3R can be found under P10636-4, 1N4R can be found under P10636-7 (, 2N3R can be found under

P10636-5, and 2N4R can be found under P10636-8. FIG. 8 shows the mRNA sequences for the 3R0N (SEQ ID NO: 58), 4R0N (SEQ ID NO: 59), 3R1N (SEQ ID NO: 60), 4R1N (SEQ ID NO: 61), 3R2N (SEQ ID NO: 62), and 4R2N (SEQ ID NO: 63) *MAPT* isoforms.

**[0256]** In certain aspects, the ASO of the disclosure is capable of hybridizing to the target nucleic acid (*e.g.*, *MAPT* transcript) under physiological condition, *i.e.*, *in vivo* condition. In some aspects, the ASO of the disclosure is capable of hybridizing to the target nucleic acid (*e.g.*, *MAPT* transcript) *in vitro*. In some aspects, the ASO of the disclosure is capable of hybridizing to the target nucleic acid (*e.g.*, *MAPT* transcript) *in vitro* under stringent conditions. Stringency conditions for hybridization *in vitro* are dependent on, *inter alia*, productive cell uptake, RNA accessibility, temperature, free energy of association, salt concentration, and time (*see, e.g.*, Stanley T Crooks, *Antisense Drug Technology: Principles, Strategies and Applications*, 2<sup>nd</sup> Edition, CRC Press (2007)). Generally, conditions of high to moderate stringency are used for *in vitro* hybridization to enable hybridization between substantially similar nucleic acids, but not between dissimilar nucleic acids. An example of stringent hybridization conditions include hybridization in 5X saline-sodium citrate (SSC) buffer (0.75 M sodium chloride/0.075 M sodium citrate) for 1 hour at 40° C, followed by washing the sample 10 times in 1X SSC at 40° C and 5 times in 1X SSC buffer at room temperature. *In vivo* hybridization conditions consist of intracellular conditions (*e.g.*, physiological pH and intracellular ionic conditions) that govern the hybridization of antisense oligonucleotides with target sequences. *In vivo* conditions can be mimicked *in vitro* by relatively low stringency conditions. For example, hybridization can be carried out *in vitro* in 2X SSC (0.3 M sodium chloride/0.03 M sodium citrate), 0.1% SDS at 37° C. A wash solution containing 4X SSC, 0.1% SDS can be used at 37° C, with a final wash in 1X SSC at 45° C.

## II.B. Oligonucleotide Sequences

**[0257]** The oligonucleotides, *e.g.*, siRNA, of the disclosure comprise a specific contiguous nucleotide sequence which corresponds to the complement of a region of *MAPT* transcript, *e.g.*, a nucleotide sequence corresponding to SEQ ID NO: 57. In some aspects, the disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are capable of hybridizing to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises:

- i. 5'-AACGUCCAGUCCAAGUGUGGC-3' (SEQ ID NO: 1) (sense strand) or  
5'-GCCACACUUGGACUGGACGTT-3' (SEQ ID NO: 2) (antisense strand);

- ii. 5'-AGCAACGUCCAGUCCAAG-3' (SEQ ID NO: 3) (sense strand) or  
5'-CUUGGACUGGACGUUGCU-3' (SEQ ID NO: 4) (antisense strand);
- iii. 5'-AAGGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 5) (sense strand) or  
5'-CUUAUUAUUAUCUGCACCTT-3' (SEQ ID NO: 6) (antisense strand);
- iv. 5'-UGAGAACCUGAAGCACCAG-3' (SEQ ID NO: 7) (sense strand) or  
5'-CUGGUGCUUCAGGUUCUCA-3' (SEQ ID NO: 8) (antisense strand);
- v. 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or  
5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand);
- vi. 5'-AAUUAUAAGAAGCUGGAUCU-3' (SEQ ID NO: 11) (sense strand) or  
5'-AGAUC CAGCUUCUUAUUAATT-3' (SEQ ID NO: 12) (antisense strand);
- vii. 5'-GAGCCCAAGAAGGUGGCAG-3' (SEQ ID NO: 13) (sense strand) or  
5'-CUGCCACCUUCUUGGGCUC-3' (SEQ ID NO: 14) (antisense strand);
- viii. 5'-ACCCGGGAGCCCAAGAAG-3' (SEQ ID NO: 15) (sense strand) or  
5'-CUUCUUGGGCUC CCGGGU-3' (SEQ ID NO: 16) (antisense strand);
- ix. 5'-AGAAGCUGGAUCUAGCAA-3' (SEQ ID NO: 17) (sense strand) or  
5'-UUGC UAAGAUC CAGCUUCU-3' (SEQ ID NO: 18) (antisense strand);
- x. 5'-AAGGAUAAUAUCAACACGUC-3' (SEQ ID NO: 19) (sense strand) or  
5'-GACGUGUUUGAUUUAUCC TT-3' (SEQ ID NO: 20) (antisense strand);
- xi. 5'-AUAAUAUCAACACGUCCC-3' (SEQ ID NO: 21) (sense strand) or  
5'-GGGACGUGUUUGAUUUAU-3' (SEQ ID NO: 22) (antisense strand);
- xii. 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or  
5'-UUCCACCUGGCCACCUCU-3' (SEQ ID NO: 24) (antisense strand);
- xiii. 5'-AAUAUCACCCACGUCCCUGG-3' (SEQ ID NO: 25) (sense strand) or  
5'-CCAGGGACGUGGGUGAUATT-3' (SEQ ID NO: 26) (antisense strand);
- xiv. 5'-UGGCCAGGUGGAAGUAAA-3' (SEQ ID NO: 27) (sense strand) or  
5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);
- xv. 5'-CCAAAGCCAAGACAGACCA-3' (SEQ ID NO: 29) (sense strand) or  
5'-UGGUCUGUCUUGGCUUUGG-3' (SEQ ID NO: 30) (antisense strand);
- xvi. 5'-AAGCAGGGUUUGUGAUCAG-3' (SEQ ID NO: 31) (sense strand) or  
5'-CUGAUCACAAACCCUGCTT-3' (SEQ ID NO: 32) (antisense strand); or
- xvii. 5'-CUCGGGACUCAA AAUCAG-3' (SEQ ID NO: 33) (sense strand) or

5'-CUGAUUUUGAAGUCCCGAG-3' (SEQ ID NO: 34) (antisense strand).

**[0258]** In some aspects, the disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are capable of hybridizing to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises:

- i. 5'-AGGGCAGCCUGUGGGAGAA-3' (SEQ ID NO: 35) (sense strand) or  
5'-UUCUCCCACAGGCUGCCCU-3' (SEQ ID NO: 36) (antisense strand); or
- ii. 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or  
5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).

**[0259]** The oligonucleotides, *e.g.*, siRNA, of the disclosure comprise a specific contiguous nucleotide sequence which corresponds to the complement of a region of *MAPT* transcript, *e.g.*, a nucleotide sequence corresponding to SEQ ID NO: 57. In some aspects, the disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are capable of hybridizing to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises:

- i. 5'-AAGCUGGAUCUUAGCAACGUC-3' (SEQ ID NO: 37) (sense strand) or  
5'-GACGUUGCUAAGAUCAGCTT-3' (SEQ ID NO: 38) (antisense strand);
- ii. 5'-AGUGUGCAAAUAGUCUACAA-3' (SEQ ID NO: 39) (sense strand) or  
5'-UUGUAGACUAUUUGCACACU-3' (SEQ ID NO: 40) (antisense strand);
- iii. 5'-AAGGACAGAGUCCAGUCGAAG-3' (SEQ ID NO: 41) (sense strand) or  
5'-CUUCGACUGGACUCUGUCCTT-3' (SEQ ID NO: 42) (antisense strand);
- iv. 5'-AAGAUUGAAACCCACAAGC-3' (SEQ ID NO: 43) (sense strand) or  
5'-GCUUGUGGGUUUCAUUCTT-3' (SEQ ID NO: 44) (antisense strand);
- v. 5'-GAAACCCACAAGCUGACCU-3' (SEQ ID NO: 45) (sense strand) or  
5'-AGGUCAGCUUGUGGGUUUC-3' (SEQ ID NO: 46) (antisense strand);
- vi. 5'-AAUAUCAAACACGUCCCGGGA-3' (SEQ ID NO: 47) (sense strand) or  
5'-UCCCGGGACGUGUUUGAUATT-3' (SEQ ID NO: 48) (antisense strand);
- vii. 5'-AUCAAACACGUCCCGGGAG-3' (SEQ ID NO: 49) (sense strand) or  
5'-CUCCCGGGACGUGUUUGAU-3' (SEQ ID NO: 50) (antisense strand);
- viii. 5'-AACACGUCCCGGGAGGCGGCA-3' (SEQ ID NO: 51) (sense strand) or  
5'-UGCCGCCUCCCGGGACGUGTT-3' (SEQ ID NO: 52) (antisense strand);

- ix. 5'-ACGUCCCCGGGAGGCGGCAG-3' (SEQ ID NO: 53) (sense strand) or  
5'-CUGCCGCCUCCCCGGGACGU-3' (SEQ ID NO: 54) (antisense strand);
- x. 5'-UCCCCGGGAGGCGGCAGUGU-3' (SEQ ID NO: 55) (sense strand) or  
5'-ACACUGCCGCCUCCCCGGGA-3' (SEQ ID NO: 56) (antisense strand).

**[0260]** In some aspects, the contiguous nucleotide sequence is complementary to the nucleic acid sequence.

**[0261]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AACGUCCAGUCCAAGUGUGGC-3' (SEQ ID NO: 1) (sense strand) or 5'- GCCACACUUGGACUGGACGTT-3' (SEQ ID NO: 2) (antisense strand).

**[0262]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AGCAACGUCCAGUCCAAG-3' (SEQ ID NO: 3) (sense strand) or 5'- CUUGGACUGGACGUUGCU-3' (SEQ ID NO: 4) (antisense strand).

**[0263]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AAGGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 5) (sense strand) or 5'- CUUAUUAUUAUCUGCACCTT -3' (SEQ ID NO: 6) (antisense strand).

**[0264]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- UGAGAACCUGAAGCACCAG -3' (SEQ ID NO: 7) (sense strand) or 5'- CUGGUGCUUCAGGUUCUCA-3' (SEQ ID NO: 8) (antisense strand).

**[0265]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'- AGCGGCUACAGCAGCCCCG -3' (SEQ ID NO: 9) (sense strand) or 5'- CGGGGUCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand).

**[0266]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AAUUAUAAGAAGCUGGAUCU-3' (SEQ ID NO: 11) (sense strand) or 5'-AGAUCCAGCUUCUUAUUAATT-3' (SEQ ID NO: 12) (antisense strand).

**[0267]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GAGCCCAAGAAGGUGGCAG-3' (SEQ ID NO: 13) (sense strand) or 5'-CUGCCACCUUCUUGGGCUC-3' (SEQ ID NO: 14) (antisense strand).

**[0268]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-ACCCGGGAGCCCAAGAAG-3' (SEQ ID NO: 15) (sense strand) or 5'-CUUCUUGGGCUCCCGGGU-3' (SEQ ID NO: 16) (antisense strand).

**[0269]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGAAGCUGGAUCUAGCAA-3' (SEQ ID NO: 17) (sense strand) or 5'-UUGCUAAGAUAUCCAGCUUCU-3' (SEQ ID NO: 18) (antisense strand).

**[0270]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AAGGAUAAUAUCAAACACGUC-3' (SEQ ID NO: 19) (sense strand) or 5'-GACGUGUUUGAUUAUUCCTT-3' (SEQ ID NO: 20) (antisense strand).

**[0271]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AUAAUAUCAAACACGUCCC-3' (SEQ ID NO: 21) (sense strand) or 5'-GGGACGUGUUUGAUUAUUAU-3' (SEQ ID NO: 22) (antisense strand).

**[0272]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a

nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand).

[0273] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AAUAUCACCCACGUCCCUGG-3' (SEQ ID NO: 25) (sense strand) or 5'-CCAGGGACGUGGGUGAUATT-3' (SEQ ID NO: 26) (antisense strand).

[0274] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand).

[0275] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-CCAAAGCCAAGACAGACCA-3' (SEQ ID NO: 29) (sense strand) or 5'-UGGUCUGUCUUGGCUUUGG-3' (SEQ ID NO: 30) (antisense strand).

[0276] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AAGCAGGGUUUGUGAUCAG-3' (SEQ ID NO: 31) (sense strand) or 5'-CUGAUCACAAACCUGCTT-3' (SEQ ID NO: 32) (antisense strand).

[0277] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-CUCGGGACUUCAAAAUCAG-3' (SEQ ID NO: 33) (sense strand) or 5'-CUGAUUUUGAAGUCCCGAG-3' (SEQ ID NO: 34) (antisense strand).

[0278] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the

contiguous nucleotide sequence comprises: 5'-AGGGCAGCCUGUGGGAGAA-3' (SEQ ID NO: 35) (sense strand) or 5'-UUCUCCCACAGGCUGCCCU-3' (SEQ ID NO: 36) (antisense strand).

**[0279]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AAGCUGGAUCUUAGCAACGUC-3' (SEQ ID NO: 37) (sense strand) or 5'-GACGUUGCUAAGAUCAGCTT-3' (SEQ ID NO: 38) (antisense strand).

**[0280]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGUGUGCAAUAGUCUACAA-3' (SEQ ID NO: 39) (sense strand) or 5'-UUGUAGACUAAUUGCACACU-3' (SEQ ID NO: 40) (antisense strand).

**[0281]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AAGGACAGAGUCCAGUCGAAG-3' (SEQ ID NO: 41) (sense strand) or 5'-CUUCGACUGGACUCUGUCCTT-3' (SEQ ID NO: 42) (antisense strand).

**[0282]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AAGAUUGAAACCCACAAGC-3' (SEQ ID NO: 43) (sense strand) or 5'-GCUUGUGGGUUUCAAUCTT-3' (SEQ ID NO: 44) (antisense strand).

**[0283]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GAAACCCACAAGCUGACCU-3' (SEQ ID NO: 45) (sense strand) or 5'-AGGUCAGCUUGUGGGUUUC-3' (SEQ ID NO: 46) (antisense strand).

**[0284]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AAUAUCAAACACGUCCGGGA-3' (SEQ ID NO: 47) (sense strand) or 5'-UCCCGGGACGUGUUUGAUATT-3' (SEQ ID NO: 48) (antisense strand).

[0285] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AUCAAACACGUCCCGGGAG-3' (SEQ ID NO: 49) (sense strand) or 5'-CUCCCGGGACGUGUUUGAU-3' (SEQ ID NO: 50) (antisense strand).

[0286] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AACACGUCCCGGGAGGCGGCA-3' (SEQ ID NO: 51) (sense strand) or 5'-UGCCGCCUCCCGGGACGUGTT-3' (SEQ ID NO: 52) (antisense strand).

[0287] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-ACGUCCCGGGAGGCGGCAG-3' (SEQ ID NO: 53) (sense strand) or 5'-CUGCCGCCUCCCGGGACGU-3' (SEQ ID NO: 54) (antisense strand).

[0288] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UCCCGGGAGGCGGCAGUGU-3' (SEQ ID NO: 55) (sense strand) or 5'-ACACUGCCGCCUCCCGGGA-3' (SEQ ID NO: 56) (antisense strand).

[0289] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).

[0290] In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is

RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

**[0291]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0292]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0293]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0294]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

**[0295]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUAAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0296]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUAAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein the nucleotides in the sense strand and/or the nucleotides in the antisense strand are linked by a phosphodiester bond, a phosphothioate bond, or any combination thereof.

**[0297]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-GGUGCAGAUAAUUAAG-3' (SEQ ID NO: 64) (sense strand) or 5'-CUUAUAAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0298]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

**[0299]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0300]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0301]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); and wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0302]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

**[0303]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a

nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0304]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0305]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense nucleotides, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0306]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

**[0307]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a

nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0308]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0309]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0310]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

**[0311]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein

the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0312]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0313]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0314]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand is 2'-OMe.

**[0315]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein

the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0316]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0317]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0318]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' F at the sugar position.

**[0319]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0320]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0321]** In some aspects, the present disclosure provides an oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) or 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0322]** In some aspects, the oligonucleotide, e.g. siRNA, is double stranded and comprises:

- i. 5'-AACGUCCAGUCCAAGUGUGGC-3' (SEQ ID NO: 1) (sense strand) and/or 5'-GCCACACUUGGACUGGACGTT-3' (SEQ ID NO: 2) (antisense strand);
- ii. 5'-AGCAACGUCCAGUCCAAG-3' (SEQ ID NO: 3) (sense strand) and/or 5'-CUUGGACUGGACGUUGCU-3' (SEQ ID NO: 4) (antisense strand);
- iii. 5'-AAGGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 5) (sense strand) and/or 5'-CUUAUUAUUAUCUGCACCTT-3' (SEQ ID NO: 6) (antisense strand);
- iv. 5'-UGAGAACCUGAAGCACCAG-3' (SEQ ID NO: 7) (sense strand) and/or 5'-CUGGUGCUUCAGGUUCUCA-3' (SEQ ID NO: 8) (antisense strand);
- v. 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and/or 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand);
- vi. 5'-AAUUAUAAGAAGCUGGAUCU-3' (SEQ ID NO: 11) (sense strand) and/or 5'-AGAUCAGCUUCUUAUUAATT-3' (SEQ ID NO: 12) (antisense strand);
- vii. 5'-GAGCCCAAGAAGGUGGCAG-3' (SEQ ID NO: 13) (sense strand) and/or 5'-CUGCCACCUUCUUGGGCUC-3' (SEQ ID NO: 14) (antisense strand);
- viii. 5'-ACCCGGGAGCCCAAGAAG-3' (SEQ ID NO: 15) (sense strand) and/or

- 5'-CUUCUUGGGCUCCCGGGU-3' (SEQ ID NO: 16) (antisense strand);
- ix. 5'-AGAAGCUGGAUCUUAGCAA-3' (SEQ ID NO: 17) (sense strand) and/or  
5'-UUGCUAAGAUAUCCAGCUUCU-3' (SEQ ID NO: 18) (antisense strand);
- x. 5'-AAGGAUAAUAUCAAACACGUC-3' (SEQ ID NO: 19) (sense strand) and/or  
5'-GACGUGUUUGAUUUAUCC'TT-3' (SEQ ID NO: 20) (antisense strand);
- xi. 5'-AUAAUAUCAAACACGUCCC-3' (SEQ ID NO: 21) (sense strand) and/or  
5'-GGGACGUGUUUGAUUUAU-3' (SEQ ID NO: 22) (antisense strand);
- xii. 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and/or  
5'-UUCCACCUGGCCACCUCU-3' (SEQ ID NO: 24) (antisense strand);
- xiii. 5'-AAUAUCACCCACGUCCCUGG-3' (SEQ ID NO: 25) (sense strand) and/or  
5'-CCAGGGACGUGGGUGAUATT-3' (SEQ ID NO: 26) (antisense strand);
- xiv. 5'-UGGCCAGGUGGAAGUAAA-3' (SEQ ID NO: 27) (sense strand) and/or  
5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);
- xv. 5'-CCAAAGCCAAGACAGACCA-3' (SEQ ID NO: 29) (sense strand) and/or  
5'-UGGUCUGUCUUGGCUUUGG-3' (SEQ ID NO: 30) (antisense strand);
- xvi. 5'-AAGCAGGGUUUGUGAUCAG-3' (SEQ ID NO: 31) (sense strand) and/or  
5'-CUGAUCACAAACCCUGCTT-3' (SEQ ID NO: 32) (antisense strand); or
- xvii. 5'-CUCGGGACUUCAAAUCAG-3' (SEQ ID NO: 33) (sense strand) and/or  
5'-CUGAUUUUGAAGUCCCGAG-3' (SEQ ID NO: 34) (antisense strand).

**[0323]** In some aspects, the oligonucleotide, e.g. siRNA, is double stranded and comprises:

- i. 5'-AGGGCAGCCUGUGGGAGAA-3' (SEQ ID NO: 35) (sense strand) and/or  
5'-UUCUCCCACAGGCUGCCCU-3' (SEQ ID NO: 36) (antisense strand) or
- ii. 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and/or  
5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).

**[0324]** In some aspects, the oligonucleotide, e.g. siRNA, is double stranded and comprises:

- i. 5'-AAGCUGGAUCUUAGCAACGUC-3' (SEQ ID NO: 37) (sense strand) and/or  
5'-GACGUUGCUAAGAUAUCCAGCTT-3' (SEQ ID NO: 38) (antisense strand);
- ii. 5'-AGUGUGCAAAUAGUCUACAA-3' (SEQ ID NO: 39) (sense strand) and/or  
5'-UUGUAGACUAAUUGCACACU-3' (SEQ ID NO: 40) (antisense strand);
- iii. 5'-AAGGACAGAGUCCAGUCGAAG-3' (SEQ ID NO: 41) (sense strand) and/or  
5'-CUUCGACUGGACUCUGUCCTT-3' (SEQ ID NO: 42) (antisense strand);

- iv. 5'-AAGAUUGAAACCCACAAGC-3' (SEQ ID NO: 43) (sense strand) and/or  
5'-GCUUGUGGGUUUCAUUCTT-3' (SEQ ID NO: 44) (antisense strand);
- v. 5'-GAAACCCACAAGCUGACCU-3' (SEQ ID NO: 45) (sense strand) and/or  
5'-AGGUCAGCUUGUGGGUUUC-3' (SEQ ID NO: 46) (antisense strand);
- vi. 5'-AAUAUCAAACACGUCCCCGGA-3' (SEQ ID NO: 47) (sense strand) and/or  
5'-UCCCCGGGACGUGUUUGAUATT-3' (SEQ ID NO: 48) (antisense strand);
- vii. 5'-AUCAAACACGUCCCCGGGAG-3' (SEQ ID NO: 49) (sense strand) and/or  
5'-CUCCCCGGGACGUGUUUGAU-3' (SEQ ID NO: 50) (antisense strand);
- viii. 5'-AACACGUCCCCGGGAGGCGGCA-3' (SEQ ID NO: 51) (sense strand) and/or  
5'-UGCCGCCUCCCCGGGACGUGTT-3' (SEQ ID NO: 52) (antisense strand);
- ix. 5'-ACGUCCCCGGGAGGCGGCAG-3' (SEQ ID NO: 53) (sense strand) and/or  
5'-CUGCCGCCUCCCCGGGACGU-3' (SEQ ID NO: 54) (antisense strand); or
- x. 5'-UCCCCGGGAGGCGGCAGUGU-3' (SEQ ID NO: 55) (sense strand) and/or  
5'-ACACUGCCGCCUCCCCGGA-3' (SEQ ID NO: 56) (antisense strand).

**[0325]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AACGUCCAGUCCAAGUGUGGC-3' (SEQ ID NO: 1) (sense strand) and 5'-GCCACACUUGGACUGGACGTT-3' (SEQ ID NO: 2) (antisense strand).

**[0326]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGCAACGUCCAGUCCAAG-3' (SEQ ID NO: 3) (sense strand) and 5'-CUUGGACUGGACGUUGCU-3' (SEQ ID NO: 4) (antisense strand).

**[0327]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AAGGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 5) (sense strand) and 5'-CUUAUUAUUAUCUGCACCTT-3' (SEQ ID NO: 6) (antisense strand).

**[0328]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-UGAGAACCUGAAGCACCCAG-3' (SEQ ID NO: 7) (sense strand) and 5'-CUGGUGCUUCAGGUUCUCA-3' (SEQ ID NO: 8) (antisense strand).

**[0329]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand).

[0330] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AAUUAUAAGAAGCUGGAUCU-3' (SEQ ID NO: 11) (sense strand) and 5'-AGAUCAGCUUCUUAUUAATT-3' (SEQ ID NO: 12) (antisense strand).

[0331] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-GAGCCCAAGAAGGUGGCAG-3' (SEQ ID NO: 13) (sense strand) and 5'-CUGCCACCUUCUUGGGCUC-3' (SEQ ID NO: 14) (antisense strand).

[0332] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-ACCCGGGAGCCCAAGAAG-3' (SEQ ID NO: 15) (sense strand) and 5'-CUUCUUGGGCUCCCGGGU-3' (SEQ ID NO: 16) (antisense strand).

[0333] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGAAGCUGGAUCUUAGCAA-3' (SEQ ID NO: 17) (sense strand) and 5'-UUGCUAAGAUCAGCUUCU-3' (SEQ ID NO: 18) (antisense strand).

[0334] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AAGGAUAAUAUCAAACACGUC-3' (SEQ ID NO: 19) (sense strand) and 5'-GACGUGUUUGAUUAUUCCTT-3' (SEQ ID NO: 20) (antisense strand).

[0335] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AUAAUAUCAAACACGUCCC-3' (SEQ ID NO: 21) (sense strand) and 5'-GGGACGUGUUUGAUUAUUAU-3' (SEQ ID NO: 22) (antisense strand).

[0336] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand).

[0337] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AAUAUCACCCACGUCCCUGG-3' (SEQ ID NO: 25) (sense strand) and 5'-CCAGGGACGUGGGUGAUATT-3' (SEQ ID NO: 26) (antisense strand).

[0338] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand).

[0339] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-CCAAAGCCAAGACAGACCA-3' (SEQ ID NO: 29) (sense strand) and 5'-UGGUCUGUCUUGGCUUUGG-3' (SEQ ID NO: 30) (antisense strand).

[0340] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AAGCAGGGUUUGUGAUCAG-3' (SEQ ID NO: 31) (sense strand) and 5'-CUGAUCACAAACCCUGCTT-3' (SEQ ID NO: 32) (antisense strand).

[0341] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-CUCGGGACUUCAAAAUCAG-3' (SEQ ID NO: 33) (sense strand) and 5'-CUGAUUUUGAAGUCCCGAG-3' (SEQ ID NO: 34) (antisense strand).

[0342] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGGGCAGCCUGUGGGAGAA-3' (SEQ ID NO: 35) (sense strand) and 5'-UUCUCCACAGGCUGCCCU-3' (SEQ ID NO: 36) (antisense strand).

[0343] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AAGCUGGAUCUUAGCAACGUC-3' (SEQ ID NO: 37) (sense strand) and 5'-GACGUUGCUAAGAUCAGCTT-3' (SEQ ID NO: 38) (antisense strand).

[0344] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGUGUGCAAUAGUCUACAA-3' (SEQ ID NO: 39) (sense strand) and 5'-UUGUAGACUAUUUGCACACU-3' (SEQ ID NO: 40) (antisense strand).

[0345] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AAGGACAGAGUCCAGUCGAAG-3' (SEQ ID NO: 41) (sense strand) and 5'-CUUCGACUGGACUCUGUCCTT-3' (SEQ ID NO: 42) (antisense strand).

[0346] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AAGAUUGAAACCCACAAGC-3' (SEQ ID NO: 43) (sense strand) and 5'-GCUUGUGGGUUUCAAUCTT-3' (SEQ ID NO: 44) (antisense strand).

[0347] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-GAAACCCACAAGCUGACCU-3' (SEQ ID NO: 45) (sense strand) and 5'-AGGUCAGCUUGUGGGUUUC-3' (SEQ ID NO: 46) (antisense strand).

[0348] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AAUAUCAAACACGUCCCGGGA-3' (SEQ ID NO: 47) (sense strand) and 5'-UCCCGGGACGUGUUUGAUATT-3' (SEQ ID NO: 48) (antisense strand).

[0349] In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AUCAAACACGUCCCGGGAG-3' (SEQ ID NO: 49) (sense strand) and 5'-CUCCCGGGACGUGUUUGAU-3' (SEQ ID NO: 50) (antisense strand).

**[0350]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AACACGUCCCCGGGAGGCGGCA-3' (SEQ ID NO: 51) (sense strand) and 5'-UGCCGCCUCCCCGGGACGUGTT-3' (SEQ ID NO: 52) (antisense strand).

**[0351]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-ACGUCCCCGGGAGGCGGCAG-3' (SEQ ID NO: 53) (sense strand) and 5'-CUGCCGCCUCCCCGGGACGU-3' (SEQ ID NO: 54) (antisense strand).

**[0352]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-UCCCCGGGAGGCGGCAGUGU-3' (SEQ ID NO: 55) (sense strand) and 5'-ACACUGCCGCCUCCCCGGGA-3' (SEQ ID NO: 56) (antisense strand).

**[0353]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).

**[0354]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

**[0355]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0356]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0357]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-

CUUAUUAUUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0358]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

**[0359]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0360]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein the nucleotides in the sense strand and/or the nucleotides in the antisense strand are linked by a phosphodiester bond, a phosphothioate bond, or any combination thereof.

**[0361]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and 5'-CUUAUUAUUUAUCUGCACC -3' (SEQ ID NO: 65) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0362]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

**[0363]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0364]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0365]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0366]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

**[0367]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0368]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0369]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense nucleotides, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0370]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

**[0371]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0372]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0373]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0374]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand

comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

**[0375]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0376]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0377]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0378]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand is 2'-OMe.

**[0379]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

**[0380]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUUCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0381]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUUCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

**[0382]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUUCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' F at the sugar position.

**[0383]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUUCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

**[0384]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUUCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

**[0385]** In some aspects, the oligonucleotide, *e.g.*, siRNA, comprises: 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and 5'-UUUUACUUCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand); wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are

linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

**[0386]** In some aspects, siRNA Nos. 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14, 15, 17, 20, 21, 22, and 23 reduced the expression level of total tau protein. In some aspects siRNA Nos. 1, 2, 4, 5, 6, 8, 10, 11, 12, 14, 15, 21, 22, and 23 effectively reduced the expression level of total tau protein.

**[0387]** In some aspects, siRNA Nos. 7, 13, 16, 17, 20, 25, 26, 27, and 28 failed to reduce the expression level of total tau protein.

**[0388]** In some aspects, siRNA Nos. 1 and 17 effectively reduced the expression level of mutant *MAPT* (L266V).

**[0389]** In some aspects, siRNA Nos. 3, 11, and 23 effectively reduced the expression level of wild-type & mutant *MAPT*.

**[0390]** In some aspects, siRNA Nos. 5, 6, 8, 9, 10, 12, 14, 15, 21, and 22 effectively reduced expression levels of wild-type *MAPT* (4R2N).

**[0391]** In some aspects, siRNA Nos. 1 and 17 effectively reduced the expression level of 4R- *MAPT* isoforms.

**[0392]** In some aspects, siRNA Nos. 20 and 23 effectively reduced the expression level of wild-type, 4R-, and 3R- *MAPT* isoforms.

**[0393]** In some aspects, siRNA Nos. 3 and 11 effectively reduced the expression level of wild-type and 4R- *MAPT* isoforms.

**[0394]** In some aspects, siRNA No. 5 effectively reduced the expression level of wild-type and 3R- *MAPT* isoforms.

**[0395]** In some aspects, siRNA Nos. 1, 2, 4, 5, 6, 8, 10, 11, 12, 14, 15, 21, 22 and 23 effectively reduced the expression level of total tau protein and will be effective for diseases characterized by the aggregation and deposition of tau. (*e.g.*, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis).

**[0396]** In some aspects, siRNA Nos. 1 and 17 specifically reduced 4R-tau isoforms thus, will provide therapeutic effects in treating 4R-tauopathies (*e.g.*, Progressive supranuclear palsy, Corticobasal degeneration, Globular glial tauopathy, Argyrophilic grain disease, and Aging-related tau astrogliopathy).

**[0397]** In some aspects, siRNA Nos. 20 and 23 reduced all forms of tau, thus will provide therapeutic effects in treating (3R-)+(4R-) tauopathies (*e.g.*, Primary age related tauopathy, Tangle-predominant dementia, Frontotemporal dementia, and parkinsonism linked to chromosome 17)

[0398] In some aspects, siRNA Nos. 3 and 11 reduced wild-type (except 3R-tau isoforms) and 4R-tau isoforms, thus will provide therapeutic effects in treating 3R/4R imbalance tauopathies induced by abnormally increased 4R-tau isoforms.

[0399] In some aspects, siRNA No. 17 efficiently reduced tau hyperphosphorylation and restored recognition decline in P301S transgenic mice.

[0400] In some aspects, siRNA Nos. 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14, 15, 17, 20, 21, 22, and 23 exhibited knockdown effects.

[0401] In some aspects siRNA Nos. 7, 13, 16, 18, 19, 24, 25, 26, 27, and 28 did not exhibit knockdown effects.

[0402] In some aspects, the disclosure provides an siRNA which comprises a contiguous nucleotide sequence of a total of from 10-30 nucleotides, such as 10-15 nucleotides, 10-20 nucleotides, or 10-25 nucleotides in length wherein the contiguous nucleotide sequence has at least about 85%, at least about 90%, at least about 95%, at least about 98%, or at least about 99% sequence identity to a region within the complement of a mammalian *MAPT* transcript, such as SEQ ID NO: 57 or SEQ ID NOS: 58-63.

[0403] In some aspects, the siRNAs of the disclosure bind to the target nucleic acid sequence (*e.g.*, *MAPT* transcript) and are capable of inhibiting or reducing expression of the *MAPT* transcript by at least about 10%, at least about 20% , at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% in a tissue (*e.g.*, a brain region) of a mouse expressing a human *MAPT* gene (*e.g.*, P301L) compared to the control.

[0404] In some aspects, the siRNAs are capable of reducing expression of *MAPT* protein by at least about 10%, at least about 20% , at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% in a tissue (*e.g.*, a brain region) of a mouse expressing a human *MAPT* gene (*e.g.*, P301L) compared to the control.

[0405] In some aspects, the siRNA of the disclosure bind to the target nucleic acid sequence (*e.g.*, *MAPT* transcript) and are capable of inhibiting or reducing expression of the *MAPT* transcript by at least about 10%, at least about 20% , at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% in a tissue (*e.g.*, a brain region) of a cyno expressing the wild-type *MAPT* gene when administered *in vivo* compared to the control.

**[0406]** In some aspects, the siRNAs are capable of reducing expression of *MAPT* protein by at least about 10%, at least about 20% , at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% in a tissue (*e.g.*, a brain region) of a cyno expressing the wild-type *MAPT* gene when administered *in vivo* compared to the control.

**[0407]** In certain aspects, the siRNAs of the disclosure bind to the *MAPT* transcript and inhibit or reduce expression of the *MAPT* mRNA by at least about 10% or about 20% compared to the normal (*i.e.* control) expression level in the cell, *e.g.*, at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90% or about 95% compared to the normal expression level (such as the expression level in the absence of the siRNA(s) or conjugate(s)) in the cell. In certain aspects, the siRNA reduces expression of *MAPT* protein in a cell following administration of the siRNA by at least 60%, at least 70%, at least 80%, or at least 90% compared to a cell not exposed to the siRNA (*i.e.*, control). In some aspects, the siRNA reduces expression of *MAPT* protein in a cell following administration of the siRNA by at least about 60%, at least about 70%, at least about 80%, or at least about 90% compared to a cell not exposed to the siRNA (*i.e.*, control).

**[0408]** In certain aspects, the siRNA of the disclosure has at least one property selected from: (1) reduces expression of *MAPT* mRNA in a cell, *e.g.*, HeLa cell, compared to a control cell that has not been exposed to the siRNA; (2) does not significantly reduce calcium oscillations in a cell; (3) does not significantly reduce tubulin intensity in a cell; (4) reduces expression of Microtubule-associated protein tau protein in a cell; and (5) any combinations thereof compared to a control cell that has not been exposed to the siRNA.

**[0409]** In some aspects, the siRNA can tolerate 1, 2, 3, or 4 (or more) mismatches, when hybridizing to the target sequence and still sufficiently bind to the target to show the desired effect, *i.e.*, down-regulation of the target mRNA and/or protein. Mismatches can, for example, be compensated by increased length of the siRNA nucleotide sequence and/or an increased number of nucleotide analogs, which are disclosed elsewhere herein.

**[0410]** In some aspects, the siRNA of the disclosure comprises no more than 3 mismatches when hybridizing to the target sequence. In other aspects, the contiguous nucleotide sequence comprises no more than 2 mismatches when hybridizing to the target sequence. In other aspects, the contiguous nucleotide sequence comprises no more than 1 mismatch when hybridizing to the target sequence.

[0411] However, it is recognized that, in some aspects, the nucleotide sequence of the ASO can comprise additional 5' or 3' nucleotides, such as, independently, 1, 2, 3, 4 or 5 additional nucleotides 5' and/or 3', which are non-complementary to the target sequence. In this respect the siRNA of the disclosure, can, in some aspects, comprise a contiguous nucleotide sequence which is flanked 5' and/or 3' by additional nucleotides. In some aspects the additional 5' and/or 3' nucleotides are naturally occurring nucleotides, such as DNA or RNA.

## II.C. siRNA Length

[0412] The siRNAs can comprise a contiguous nucleotide sequence of a total of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 contiguous nucleotides in length.

[0413] In some aspects, the siRNAs comprise a contiguous nucleotide sequence of a total of about 10–22, such as 10–21 or 12–18, such as 13–17 or 12–16, such as 13, 14, 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides in length.

[0414] In some aspects, the siRNAs comprise a contiguous nucleotide sequence of a total of 16, 17, 18, 19, or 20 (16 to 20) contiguous nucleotides in length. In some aspects, the siRNA comprises a sense strand and an antisense strand, each of the strands comprises 19 contiguous nucleotides in length.

[0415] In some aspects, the siRNA according to the disclosure consists of no more than 22 nucleotides, such as no more than 21 or 20 nucleotides, such as no more than 18 nucleotides, such as 15, 16 or 17 nucleotides. In some aspects the siRNA of the disclosure comprises less than 22 nucleotides. It should be understood that when a range is given for an siRNA, or contiguous nucleotide sequence length, the range includes the lower and upper lengths provided in the range, for example from (or between) 10–30, includes both 10 and 30.

## II.D. Nucleosides and Nucleoside analogs

[0416] In one aspect of the disclosure, the siRNAs comprise one or more non-naturally occurring nucleotide analogs. "Nucleotide analogs" or "nucleotide analogues" as used herein are variants of natural nucleotides, such as DNA or RNA nucleotides, by virtue of modifications in the sugar and/or base moieties. Analogs could in principle be merely "silent" or "equivalent" to the natural nucleotides in the context of the oligonucleotide, *i.e.* have no functional effect on the way the oligonucleotide works to inhibit target gene expression. Such "equivalent" analogs can nevertheless be useful if, for example, they are easier or cheaper to manufacture, or are more stable

to storage or manufacturing conditions, or represent a tag or label. In some aspects, however, the analogs will have a functional effect on the way in which the siRNA works to inhibit expression; for example by producing increased binding affinity to the target and/or increased resistance to intracellular nucleases and/or increased ease of transport into the cell. Specific examples of nucleoside analogs are described by *e.g.* Freier & Altmann; *Nucl. Acid Res.*, 1997, 25, 4429-4443 and Uhlmann; *Curr. Opinion in Drug Development*, 2000, 3(2), 293-213, and in Scheme 1.

**[0417]** In some aspects, the oligonucleotide comprises a sense strand comprising 5' RMRRMMRRRRRRMRMMMMRM3', wherein R is RNA and M is 2'-OMe and/or an antisense strand comprising 5' RRMRRRRRRRRRRMRRRRRR3', wherein R is RNA and M is 2'-OMe. In some aspects, the oligonucleotide comprises a 5' methyl cytosine.

**[0418]** In some aspects, the oligonucleotide comprises a sense strand comprising 5' MMMMMMFMMFFMMMMMMMM3', wherein M is 2'-OMe and F is 2'-F and/or an antisense strand comprising 5' MMFMFMFMFMFMFMFMFM3', wherein M is 2'-OMe and F is 2'-F. In some aspects, the oligonucleotide comprises a 5' methyl cytosine.

#### II.D.1. Nucleobase

**[0419]** The term nucleobase includes the purine (*e.g.*, adenine and guanine) and pyrimidine (*e.g.*, uracil, thymine and cytosine) moiety present in nucleosides and nucleotides which form hydrogen bonds in nucleic acid hybridization. In the context of the present disclosure the term nucleobase also encompasses modified nucleobases which may differ from naturally occurring nucleobases, but are functional during nucleic acid hybridization. In some aspects the nucleobase moiety is modified by modifying or replacing the nucleobase. In this context "nucleobase" refers to both naturally occurring nucleobases such as adenine, guanine, cytosine, thymine, uracil, xanthine and hypoxanthine, as well as non-naturally occurring variants. Such variants are for example described in Hirao *et al.*, (2012) *Accounts of Chemical Research* vol 45 page 2055 and Bergstrom (2009) *Current Protocols in Nucleic Acid Chemistry Suppl.* 37 1.4.1.

**[0420]** In some aspects the nucleobase moiety is modified by changing the purine or pyrimidine into a modified purine or pyrimidine, such as substituted purine or substituted pyrimidine, such as a nucleobase selected from isocytosine, pseudoisocytosine, 5-methyl cytosine, 5-thiozolo-cytosine, 5-propynyl-cytosine, 5-propynyl-uracil, 5-bromouracil 5-thiazolo-uracil, 2-thio-uracil, 2'thio-thymine, inosine, diaminopurine, 6-aminopurine, 2-aminopurine, 2,6-diaminopurine and 2-chloro-6-aminopurine.

[0421] The nucleobase moieties may be indicated by the letter code for each corresponding nucleobase, *e.g.*, A, T, G, C or U, wherein each letter may optionally include modified nucleobases of equivalent function. For example, in the exemplified oligonucleotides, the nucleobase moieties are selected from A, T, G, C, and 5-methyl cytosine. Optionally, for LNA gapmers, 5-methyl cytosine LNA nucleosides may be used.

#### II.D.2. Sugar Modification

[0422] The siRNA of the disclosure can comprise one or more nucleosides which have a modified sugar moiety, *i.e.* a modification of the sugar moiety when compared to the ribose sugar moiety found in DNA and RNA. Numerous nucleosides with modification of the ribose sugar moiety have been made, primarily with the aim of improving certain properties of oligonucleotides, such as affinity and/or nuclease resistance.

[0423] Such modifications include those where the ribose ring structure is modified, *e.g.* by replacement with a hexose ring (HNA), or a bicyclic ring, which typically have a biradical bridge between the C2' and C4' carbons on the ribose ring (LNA), or an unlinked ribose ring which typically lacks a bond between the C2' and C3' carbons (*e.g.*, UNA). Other sugar modified nucleosides include, for example, bicyclohexose nucleic acids (WO2011/017521) or tricyclic nucleic acids (WO2013/154798). Modified nucleosides also include nucleosides where the sugar moiety is replaced with a non-sugar moiety, for example in the case of peptide nucleic acids (PNA), or morpholino nucleic acids.

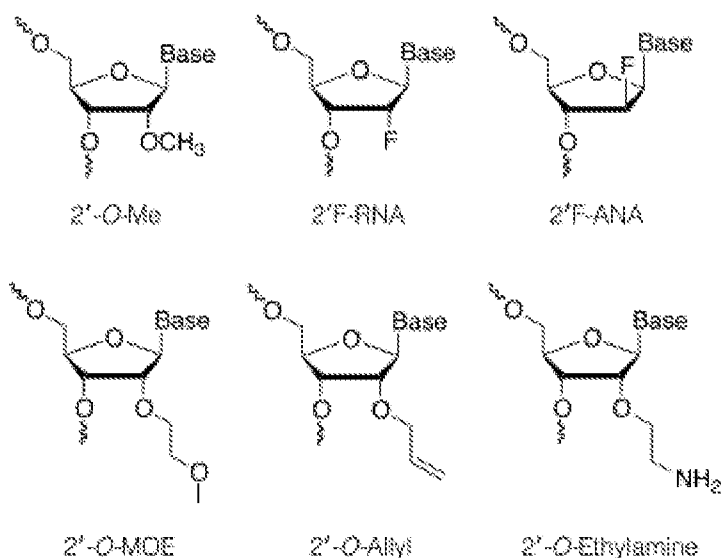
[0424] Sugar modifications also include modifications made via altering the substituent groups on the ribose ring to groups other than hydrogen, or the 2'-OH group naturally found in RNA nucleosides. Substituents may, for example be introduced at the 2', 3', 4' or 5' positions. Nucleosides with modified sugar moieties also include 2' modified nucleosides, such as 2' substituted nucleosides. Indeed, much focus has been spent on developing 2' substituted nucleosides, and numerous 2' substituted nucleosides have been found to have beneficial properties when incorporated into oligonucleotides, such as enhanced nucleoside resistance and enhanced affinity.

[0425] In some aspects, the sugar modification comprises an affinity enhancing sugar modification, *e.g.*, LNA. An affinity enhancing sugar modification increases the binding affinity of the ASOs to the target RNA sequence (*e.g.*, intron1/exon2 junction of *MAPT* mRNA). In some aspects, an siRNA comprising a sugar modification disclosed herein has a binding affinity to a target RNA sequence that is enhanced by at least 5%, at least 10%, at least 20%, at least 30%, at

least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100% compared to a control (*e.g.*, an siRNA without such sugar modification).

#### II.D.2.a 2' modified nucleosides

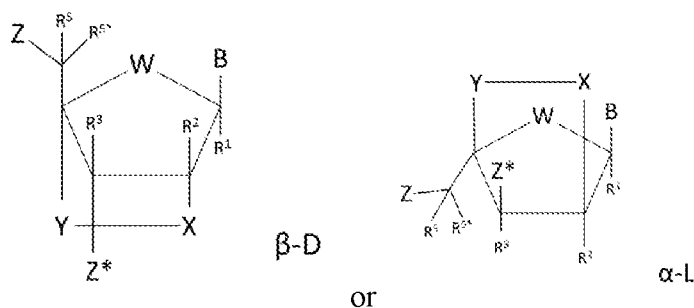
**[0426]** A 2' sugar modified nucleoside is a nucleoside which has a substituent other than H or –OH at the 2' position (2' substituted nucleoside) or comprises a 2' linked biradical, and includes 2' substituted nucleosides and LNA (2' – 4' biradical bridged) nucleosides. For example, the 2' modified sugar may provide enhanced binding affinity and/or increased nuclease resistance to the oligonucleotide. Examples of 2' substituted modified nucleosides are 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA (MOE), 2'-amino-DNA, 2'-Fluoro-RNA, and 2'-F-ANA nucleoside. For further examples, please see *e.g.* Freier & Altmann; Nucl. Acid Res., 1997, 25, 4429-4443 and Uhlmann; Curr. Opinion in Drug Development, 2000, 3(2), 293-213, and Deleavey and Damha, Chemistry and Biology 2012, 19, 937. Below are illustrations of some 2' substituted modified nucleosides.



#### II.D.2.b Locked Nucleic Acid Nucleosides (LNA).

**[0427]** LNA nucleosides are modified nucleosides which comprise a linker group (referred to as a biradical or a bridge) between C2' and C4' of the ribose sugar ring of a nucleotide. These nucleosides are also termed bridged nucleic acid or bicyclic nucleic acid (BNA) in the literature.

**[0428]** In some aspects, the modified nucleoside or the LNA nucleosides of the ASO of the disclosure has a general structure of the formula II or III:



Formula II

Formula III

wherein W is selected from -O-, -S-, -N(R<sup>a</sup>)-, -C(R<sup>a</sup>R<sup>b</sup>)-, such as, in some aspects -O-; B designates a nucleobase or modified nucleobase moiety; Z designates an internucleoside linkage to an adjacent nucleoside, or a 5'-terminal group; Z\* designates an internucleoside linkage to an adjacent nucleoside, or a 3'-terminal group; and X designates a group selected from the group consisting of -C(R<sup>a</sup>R<sup>b</sup>)-, -C(R<sup>a</sup>)=C(R<sup>b</sup>)-, -C(R<sup>a</sup>)=N-, -O-, -Si(R<sup>a</sup>)<sub>2</sub>-, -S-, -SO<sub>2</sub>-, -N(R<sup>a</sup>)-, and >C=Z.

**[0429]** In some aspects, X is selected from the group consisting of: -O-, -S-, NH-, NR<sup>a</sup>R<sup>b</sup>-, -CH<sub>2</sub>-, CR<sup>a</sup>R<sup>b</sup>-, -C(=CH<sub>2</sub>)-, and -C(=CR<sup>a</sup>R<sup>b</sup>)-. In some aspects, X is -O-.

**[0430]** In some aspects, Y designates a group selected from the group consisting of -C(R<sup>a</sup>R<sup>b</sup>)-, -C(R<sup>a</sup>)=C(R<sup>b</sup>)-, -C(R<sup>a</sup>)=N-, -O-, -Si(R<sup>a</sup>)<sub>2</sub>-, -S-, -SO<sub>2</sub>-, -N(R<sup>a</sup>)-, and >C=Z. In some aspects, Y is selected from the group consisting of: -CH<sub>2</sub>-, -C(R<sup>a</sup>R<sup>b</sup>)-, -CH<sub>2</sub>CH<sub>2</sub>-, -C(R<sup>a</sup>R<sup>b</sup>)-C(R<sup>a</sup>R<sup>b</sup>)-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -C(R<sup>a</sup>R<sup>b</sup>)C(R<sup>a</sup>R<sup>b</sup>)C(R<sup>a</sup>R<sup>b</sup>)-, -C(R<sup>a</sup>)=C(R<sup>b</sup>)-, and -C(R<sup>a</sup>)=N-.

**[0431]** In some aspects, Y is selected from the group consisting of: -CH<sub>2</sub>-, -CHR<sup>a</sup>-, -CHCH<sub>3</sub>-, CR<sup>a</sup>R<sup>b</sup>-, and -X-Y- together designate a bivalent linker group (also referred to as a radicle) together designate a bivalent linker group consisting of 1, 2, 3 or 4 groups/atoms selected from the group consisting of -C(R<sup>a</sup>R<sup>b</sup>)-, -C(R<sup>a</sup>)=C(R<sup>b</sup>)-, -C(R<sup>a</sup>)=N-, -O-, -Si(R<sup>a</sup>)<sub>2</sub>-, -S-, -SO<sub>2</sub>-, -N(R<sup>a</sup>)-, and >C=Z.

**[0432]** In some aspects, -X-Y designates a biradical selected from the groups consisting of: -X-CH<sub>2</sub>-, -X-CR<sup>a</sup>R<sup>b</sup>-, -X-CHR<sup>a</sup>-, -X-C(HCH<sub>3</sub>)-, -O-Y-, -O-CH<sub>2</sub>-, -S-CH<sub>2</sub>-, -NH-CH<sub>2</sub>-, -O-CHCH<sub>3</sub>-, -CH<sub>2</sub>-O-CH<sub>2</sub>-, -O-CH(CH<sub>3</sub>CH<sub>3</sub>)-, -O-CH<sub>2</sub>-CH<sub>2</sub>-, OCH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -O-CH<sub>2</sub>OCH<sub>2</sub>-, -O-NCH<sub>2</sub>-, -C(=CH<sub>2</sub>)-CH<sub>2</sub>-, -NR<sup>a</sup>-CH<sub>2</sub>-, N-O-CH<sub>2</sub>-, -S-CR<sup>a</sup>R<sup>b</sup>- and -S-CHR<sup>a</sup>-.

**[0433]** In some aspects -X-Y- designates -O-CH<sub>2</sub>- or -O-CH(CH<sub>3</sub>)-.

**[0434]** In certain aspects, Z is selected from -O-, -S-, and -N(R<sup>a</sup>)-, and R<sup>a</sup> and, when present R<sup>b</sup>, each is independently selected from hydrogen, optionally substituted C<sub>1-6</sub>-alkyl, optionally substituted C<sub>2-6</sub>-alkenyl, optionally substituted C<sub>2-6</sub>-alkynyl, hydroxy, optionally substituted C<sub>1-6</sub>-alkoxy, C<sub>2-6</sub>-alkoxyalkyl, C<sub>2-6</sub>-alkenyloxy, carboxy, C<sub>1-6</sub>-alkoxycarbonyl, C<sub>1-6</sub>-alkylcarbonyl, formyl, aryl, aryloxy-carbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxy-carbonyl,

heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C<sub>1-6</sub>-alkyl)amino, carbamoyl, mono- and di(C<sub>1-6</sub>-alkyl)-amino-carbonyl, amino-C<sub>1-6</sub>-alkyl-aminocarbonyl, mono- and di(C<sub>1-6</sub>-alkyl)amino-C<sub>1-6</sub>-alkyl-aminocarbonyl, C<sub>1-6</sub>-alkyl-carbonylamino, carbamido, C<sub>1-6</sub>-alkanoyloxy, sulphono, C<sub>1-6</sub>-alkylsulphonyloxy, nitro, azido, sulphanyl, C<sub>1-6</sub>-alkylthio, halogen, where aryl and heteroaryl may be optionally substituted and where two geminal substituents R<sup>a</sup> and R<sup>b</sup> together may designate optionally substituted methylene (=CH<sub>2</sub>), wherein for all chiral centers, asymmetric groups may be found in either *R* or *S* orientation.

**[0435]** In some aspects, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> and R<sup>5\*</sup> are independently selected from the group consisting of: hydrogen, optionally substituted C<sub>1-6</sub>-alkyl, optionally substituted C<sub>2-6</sub>-alkenyl, optionally substituted C<sub>2-6</sub>-alkynyl, hydroxy, C<sub>1-6</sub>-alkoxy, C<sub>2-6</sub>-alkoxyalkyl, C<sub>2-6</sub>-alkenyloxy, carboxy, C<sub>1-6</sub>-alkoxycarbonyl, C<sub>1-6</sub>-alkylcarbonyl, formyl, aryl, aryloxy-carbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxy-carbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C<sub>1-6</sub>-alkyl)amino, carbamoyl, mono- and di(C<sub>1-6</sub>-alkyl)-amino-carbonyl, amino-C<sub>1-6</sub>-alkyl-aminocarbonyl, mono- and di(C<sub>1-6</sub>-alkyl)amino-C<sub>1-6</sub>-alkyl-aminocarbonyl, C<sub>1-6</sub>-alkyl-carbonylamino, carbamido, C<sub>1-6</sub>-alkanoyloxy, sulphono, C<sub>1-6</sub>-alkylsulphonyloxy, nitro, azido, sulphanyl, C<sub>1-6</sub>-alkylthio, and halogen, where aryl and heteroaryl may be optionally substituted, and where two geminal substituents together may designate oxo, thioxo, imino, or optionally substituted methylene.

**[0436]** In some aspects R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> and R<sup>5\*</sup> are independently selected from C<sub>1-6</sub> alkyl, such as methyl, and hydrogen.

**[0437]** In some aspects R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> and R<sup>5\*</sup> are all hydrogen.

**[0438]** In some aspects R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, are all hydrogen, and either R<sup>5</sup> and R<sup>5\*</sup> is also hydrogen and the other of R<sup>5</sup> and R<sup>5\*</sup> is other than hydrogen, such as C<sub>1-6</sub> alkyl such as methyl.

**[0439]** In some aspects, R<sup>a</sup> is either hydrogen or methyl. In some aspects, when present, R<sup>b</sup> is either hydrogen or methyl.

**[0440]** In some aspects, one or both of R<sup>a</sup> and R<sup>b</sup> is hydrogen.

**[0441]** In some aspects, one of R<sup>a</sup> and R<sup>b</sup> is hydrogen and the other is other than hydrogen.

**[0442]** In some aspects, one of R<sup>a</sup> and R<sup>b</sup> is methyl and the other is hydrogen.

**[0443]** In some aspects, both of R<sup>a</sup> and R<sup>b</sup> are methyl.

**[0444]** In some aspects, the biradical -X-Y- is -O-CH<sub>2</sub>-, W is O, and all of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> and R<sup>5\*</sup> are all hydrogen. Such LNA nucleosides are disclosed in WO99/014226, WO00/66604, WO98/039352 and WO2004/046160 which are all hereby incorporated by reference, and include what are commonly known as beta-D-oxy LNA and alpha-L-oxy LNA nucleosides.

[0445] In some aspects, the biradical  $-X-Y-$  is  $-S-CH_2-$ , W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. Such thio LNA nucleosides are disclosed in WO99/014226 and WO2004/046160.

[0446] In some aspects, the biradical  $-X-Y-$  is  $-NH-CH_2-$ , W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. Such amino LNA nucleosides are disclosed in WO99/014226 and WO2004/046160.

[0447] In some aspects, the biradical  $-X-Y-$  is  $-O-CH_2-CH_2-$  or  $-O-CH_2-CH_2-CH_2-$ , W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. Such LNA nucleosides are disclosed in WO00/047599 and Morita *et al.*, *Bioorganic & Med.Chem. Lett.* 12 73-76, which are hereby incorporated by reference, and include what are commonly known as 2'-O-4'-C-ethylene bridged nucleic acids (ENA).

[0448] In some aspects, the biradical  $-X-Y-$  is  $-O-CH_2-$ , W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ , and one of  $R^5$  and  $R^{5*}$  are hydrogen, and the other of  $R^5$  and  $R^{5*}$  is other than hydrogen such as  $C_{1-6}$  alkyl, such as methyl. Such 5' substituted LNA nucleosides are disclosed in WO2007/134181.

[0449] In some aspects, the biradical  $-X-Y-$  is  $-O-CR^aR^b-$ , wherein one or both of  $R^a$  and  $R^b$  are other than hydrogen, such as methyl, W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ , and one of  $R^5$  and  $R^{5*}$  are hydrogen, and the other of  $R^5$  and  $R^{5*}$  is other than hydrogen such as  $C_{1-6}$  alkyl, such as methyl. Such bis modified LNA nucleosides are disclosed in WO2010/077578.

[0450] In some aspects, the biradical  $-X-Y-$  designate the bivalent linker group  $-O-CH(CH_2OCH_3)-$  (2' O-methoxyethyl bicyclic nucleic acid - Seth at al., 2010, *J. Org. Chem.* Vol 75(5) pp. 1569-81). In some aspects, the biradical  $-X-Y-$  designate the bivalent linker group  $-O-CH(CH_2CH_3)-$  (2'O-ethyl bicyclic nucleic acid - Seth at al., 2010, *J. Org. Chem.* Vol 75(5) pp. 1569-81). In some aspects, the biradical  $-X-Y-$  is  $-O-CHR^a-$ , W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. Such 6' substituted LNA nucleosides are disclosed in WO10036698 and WO07090071.

[0451] In some aspects, the biradical  $-X-Y-$  is  $-O-CH(CH_2OCH_3)-$ , W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. Such LNA nucleosides are also known as cyclic MOEs in the art (cMOE) and are disclosed in WO07090071.

[0452] In some aspects, the biradical  $-X-Y-$  designates the bivalent linker group  $-O-CH(CH_3)-$  - in either the R- or S- configuration. In some aspects, the biradical  $-X-Y-$  together designate the bivalent linker group  $-O-CH_2-O-CH_2-$  (Seth *et al.*, 2010, *J. Org. Chem.*). In some aspects, the biradical  $-X-Y-$  is  $-O-CH(CH_3)-$ , W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. Such 6' methyl LNA nucleosides are also known as cET nucleosides in the art, and may

be either (S)cET or (R)cET stereoisomers, as disclosed in WO07090071 (beta-D) and WO2010/036698 (alpha-L)).

**[0453]** In some aspects, the biradical  $-X-Y-$  is  $-O-CR^aR^b-$ , wherein in neither  $R^a$  or  $R^b$  is hydrogen, W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. In some aspects,  $R^a$  and  $R^b$  are both methyl. Such 6' di-substituted LNA nucleosides are disclosed in WO 2009006478.

**[0454]** In some aspects, the biradical  $-X-Y-$  is  $-S-CHR^a-$ , W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. Such 6' substituted thio LNA nucleosides are disclosed in WO11156202. In some 6' substituted thio LNA aspects  $R^a$  is methyl.

**[0455]** In some aspects, the biradical  $-X-Y-$  is  $-C(=CH_2)-C(R^aR^b)-$ , such as  $-C(=CH_2)-CH_2-$ , or  $-C(=CH_2)-CH(CH_3)-$  W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. Such vinyl carbo LNA nucleosides are disclosed in WO08154401 and WO09067647.

**[0456]** In some aspects the biradical  $-X-Y-$  is  $-N(-OR^a)-$ , W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. In some aspects  $R^a$  is  $C_{1-6}$  alkyl such as methyl. Such LNA nucleosides are also known as N substituted LNAs and are disclosed in WO2008/150729. In some aspects, the biradical  $-X-Y-$  together designate the bivalent linker group  $-O-NR^a-CH_3-$  (Seth *et al.*, 2010, *J. Org. Chem*). In some aspects the biradical  $-X-Y-$  is  $-N(R^a)-$ , W is O, and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. In some aspects  $R^a$  is  $C_{1-6}$  alkyl such as methyl.

**[0457]** In some aspects, one or both of  $R^5$  and  $R^{5*}$  is hydrogen and, when substituted the other of  $R^5$  and  $R^{5*}$  is  $C_{1-6}$  alkyl such as methyl. In such an aspect,  $R^1$ ,  $R^2$ ,  $R^3$ , may all be hydrogen, and the biradical  $-X-Y-$  may be selected from  $-O-CH_2-$  or  $-O-CH(CR^a)-$ , such as  $-O-CH(CH_3)-$ .

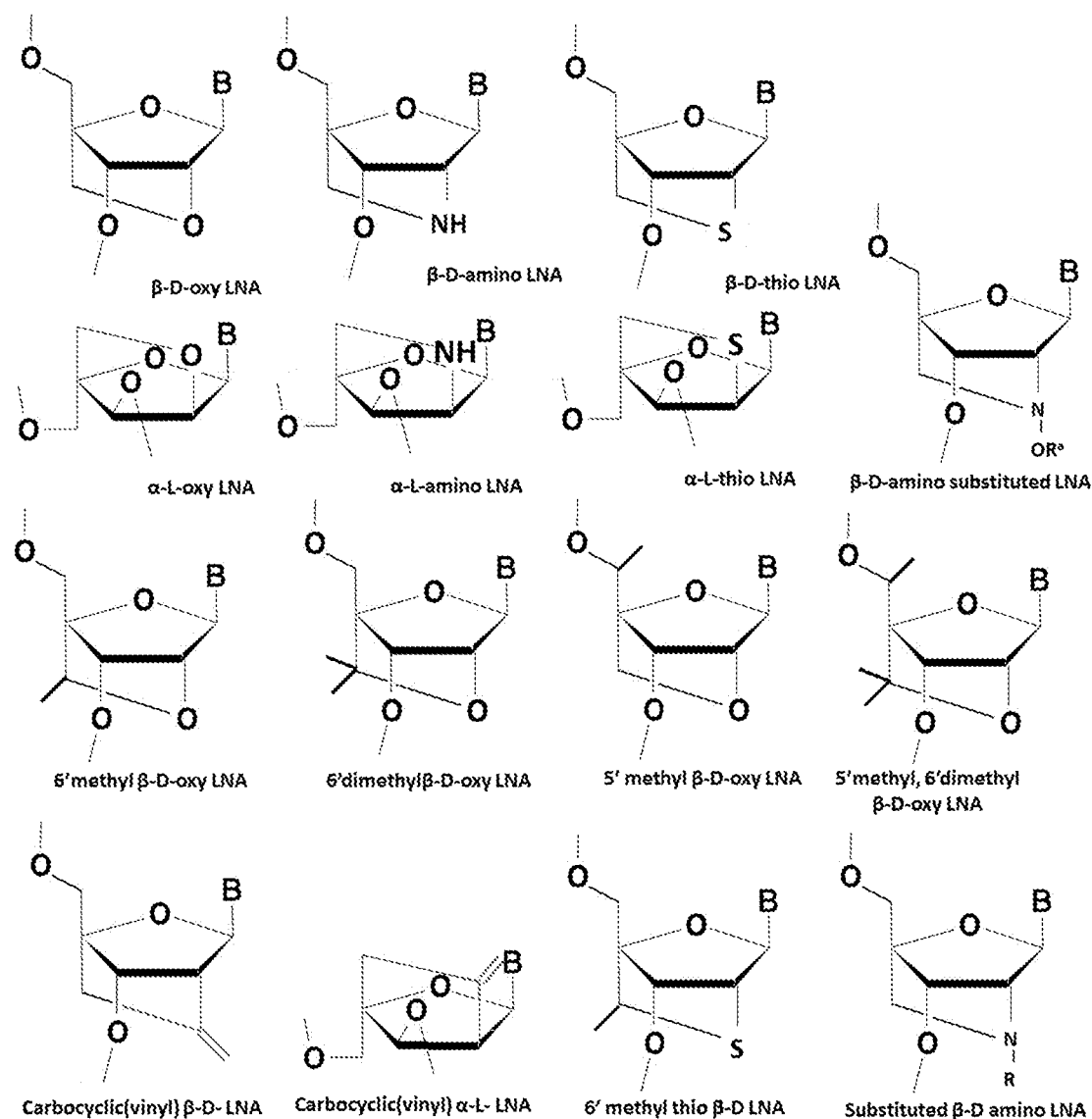
**[0458]** In some aspects, the biradical is  $-CR^aR^b-O-CR^aR^b-$ , such as  $CH_2-O-CH_2-$ , W is O and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. In some aspects  $R^a$  is  $C_{1-6}$  alkyl such as methyl. Such LNA nucleosides are also known as conformationally restricted nucleotides (CRNs) and are disclosed in WO2013036868.

**[0459]** In some aspects, the biradical is  $-O-CR^aR^b-O-CR^aR^b-$ , such as  $O-CH_2-O-CH_2-$ , W is O and all of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $R^{5*}$  are all hydrogen. In some aspects  $R^a$  is  $C_{1-6}$  alkyl such as methyl. Such LNA nucleosides are also known as COC nucleotides and are disclosed in Mitsuoka *et al.*, *Nucleic Acids Research* 2009 37(4), 1225-1238.

**[0460]** It will be recognized than, unless specified, the LNA nucleosides may be in the beta-D or alpha-L stereoisofom.

**[0461]** Certain examples of LNA nucleosides are presented in Scheme 1.

Scheme 1



[0462] As illustrated in the examples, in some aspects of the disclosure the LNA nucleosides in the oligonucleotides are beta-D-oxy-LNA nucleosides.

## II.E. Nuclease mediated degradation

[0463] Nuclease mediated degradation refers to an oligonucleotide capable of mediating degradation of a complementary nucleotide sequence when forming a duplex with such a sequence.

[0464] In some aspects, the oligonucleotide may function via nuclease mediated degradation of the target nucleic acid, where the oligonucleotides of the disclosure are capable of recruiting a nuclease, particularly and endonuclease, preferably endoribonuclease (RNase), such as RNase H. Examples of oligonucleotide designs which operate via nuclease mediated

mechanisms are oligonucleotides which typically comprise a region of at least 5 or 6 DNA nucleosides and are flanked on one side or both sides by affinity enhancing nucleosides, for example gapmers.

#### II.F. RNase H Activity and Recruitment

**[0465]** The RNase H activity of an oligonucleotide refers to its ability to recruit RNase H when in a duplex with a complementary RNA molecule and induce cleavage and subsequent degradation of the complementary RNA molecule. WO01/23613 provides *in vitro* methods for determining RNase H activity, which may be used to determine the ability to recruit RNase H. Typically an oligonucleotide is deemed capable of recruiting RNase H if it, when provided with a complementary target nucleic acid sequence, has an initial rate, as measured in pmol/l/min, of at least 5%, such as at least 10% or more than 20% of the of the initial rate determined when using a oligonucleotide having the same base sequence as the modified oligonucleotide being tested, but containing only DNA monomers, with phosphorothioate linkages between all monomers in the oligonucleotide, and using the methodology provided by Example 91 - 95 of WO01/23613.

**[0466]** In some aspects, an oligonucleotide is deemed essentially incapable of recruiting RNase H if, when provided with the complementary target nucleic acid, the RNase H initial rate, as measured in pmol/l/min, is less than 20%, such as less than 10%, such as less than 5% of the initial rate determined when using a oligonucleotide having the same base sequence as the oligonucleotide being tested, but containing only DNA monomers, with no 2' substitutions, with phosphorothioate linkages between all monomers in the oligonucleotide, and using the methodology provided by Example 91 - 95 of WO01/23613.

#### II.G. Internucleotide Linkages

**[0467]** The monomers of the siRNA described herein are coupled together via linkage groups. Suitably, each monomer is linked to the 3' adjacent monomer via a linkage group.

**[0468]** The person having ordinary skill in the art would understand that, in the context of the present disclosure, the 5' monomer at the end of an siRNA does not comprise a 5' linkage group, although it may or may not comprise a 5' terminal group.

**[0469]** The terms "linkage group" and "internucleotide linkage" are intended to mean a group capable of covalently coupling together two nucleotides. Specific and preferred examples include phosphate groups and phosphorothioate groups.

[0470] The nucleotides of the siRNA of the disclosure or contiguous nucleotides sequence thereof are coupled together via linkage groups. Suitably each nucleotide is linked to the 3' adjacent nucleotide via a linkage group.

[0471] Suitable internucleotide linkages include those listed within WO2007/031091, for example the internucleotide linkages listed on the first paragraph of page 34 of WO2007/031091 (hereby incorporated by reference in its entirety).

[0472] Examples of suitable internucleotide linkages that can be used with the disclosure include phosphodiester linkage, a phosphotriester linkage, a methylphosphonate linkage, a phosphoramidate linkage, a phosphorothioate linkage, and combinations thereof.

[0473] It is, in some aspects, preferred to modify the internucleotide linkage from its normal phosphodiester to one that is more resistant to nuclease attack, such as phosphorothioate or boranophosphate – these two, being cleavable by RNase H, also allow that route of antisense inhibition in reducing the expression of the target gene.

[0474] Suitable sulphur (S) containing internucleotide linkages as provided herein may be preferred. Phosphorothioate internucleotide linkages are also preferred, particularly for the gap region (B) of gapmers. Phosphorothioate linkages can also be used for the flanking regions (A and C, and for linking A or C to D, and within region D, as appropriate).

[0475] Regions A, B and C, can, however, comprise internucleotide linkages other than phosphorothioate, such as phosphodiester linkages, particularly, for instance when the use of nucleotide analogs protects the internucleotide linkages within regions A and C from endonuclease degradation – such as when regions A and C comprise LNA nucleotides.

[0476] The internucleotide linkages in the siRNA can be phosphodiester, phosphorothioate or boranophosphate so as to allow RNase H cleavage of targeted RNA. Phosphorothioate is preferred for improved nuclease resistance and other reasons, such as ease of manufacture. In some aspects, the internucleotide linkages comprise one or more stereo-defined internucleotide linkages (*e.g.*, such as stereo-defined modified phosphate linkages, *e.g.*, phosphodiester, phosphorothioate, or boranophosphate linkages with a defined stereochemical structure). The term "stereo-defined internucleotide linkage" is used interchangeably with "chirally controlled internucleotide linkage" and refers to a internucleotide linkage in which the stereochemical designation of the phosphorus atom is controlled such that a specific amount of  $R_p$  or  $S_p$  of the internucleotide linkage is present within an siRNA strand. The stereochemical designation of a chiral linkage can be defined (controlled) by, for example, asymmetric synthesis. An siRNA having at least one stereo-defined

internucleotide linkage can be called as a stereo-defined siRNA, which includes both a fully stereo-defined siRNA and a partially stereo-defined ASO.

**[0477]** In one aspect of the siRNA of the disclosure, the nucleotides and/or nucleotide analogs are linked to each other by means of phosphorothioate groups.

**[0478]** In some aspects, the oligonucleotide comprises a sense strand comprising 5' RMRRMMRRRRRRMRMMMMRM3', wherein R is RNA and M is 2'-OMe and/or an antisense strand comprising 5' RRMRRRRRRRRRRMRRRRRR3', wherein R is RNA and M is 2'-OMe. In some aspects, the oligonucleotide comprises a phosphothioate bond between the first and second nucleotides and the second and third nucleotides of the sense strand and/or the first and second nucleotides, the second and third nucleotides, the 17<sup>th</sup> and 18<sup>th</sup> nucleotides, and the 18<sup>th</sup> and 19<sup>th</sup> nucleotides of the antisense strand. In some aspects, the oligonucleotide comprises a phosphothioate bond. In some aspects, the oligonucleotide comprises 5' methyl cytosine.

**[0479]** In some aspects, the oligonucleotide comprises a sense strand comprising 5' MMMMMMFMMMMMMMMM3', wherein M is 2'-OMe and F is 2'-F and/or an antisense strand comprising 5' MMFMFMFMFMFMFMFMF3', wherein M is 2'-OMe and F is 2'-F. In some aspects, the oligonucleotide comprises a 5' methyl cytosine. In some aspects, the oligonucleotide comprises a phosphothioate bond between the first and second nucleotides and the second and third nucleotides of the sense strand and/or the first and second nucleotides, the 17<sup>th</sup> and 18<sup>th</sup> nucleotides, and the 18<sup>th</sup> and 19<sup>th</sup> nucleotides of the antisense strand. In some aspects, the oligonucleotide comprises a phosphothioate bond. In some aspects, the oligonucleotide comprises 5' methyl cytosine.

**[0480]** It is recognized that the inclusion of phosphodiester linkages, such as one or two linkages, into an otherwise phosphorothioate siRNA, particularly between or adjacent to nucleotide analog units (typically in region A and/or C) can modify the bioavailability and/or bio-distribution of an ASO – see WO2008/113832, hereby incorporated by reference.

**[0481]** In some aspects, such as the aspects referred to above, where suitable and not specifically indicated, all remaining linkage groups are either phosphodiester or phosphorothioate, or a mixture thereof.

**[0482]** In some aspects all the internucleotide linkage groups are phosphorothioate.

**[0483]** When referring to specific gapmer oligonucleotide sequences, such as those provided herein it will be understood that, in various aspects, when the linkages are phosphorothioate linkages, alternative linkages, such as those disclosed herein can be used, for example phosphate (phosphodiester) linkages can be used, particularly for linkages between

nucleotide analogs, such as LNA, units. Likewise, when referring to specific gapmer oligonucleotide sequences, such as those provided herein, when the C residues are annotated as 5-'methyl modified cytosine, in various aspects, one or more of the Cs present in the siRNA can be unmodified C residues.

## II.H. Conjugates

**[0484]** The term conjugate as used herein refers to an oligonucleotide which is covalently linked to a non-nucleotide moiety (conjugate moiety or region C or third region).

**[0485]** Conjugation of the oligonucleotide of the disclosure to one or more non-nucleotide moieties may improve the pharmacology of the oligonucleotide, e.g. by affecting the activity, cellular distribution, cellular uptake or stability of the oligonucleotide. In some aspects the conjugate moiety modify or enhance the pharmacokinetic properties of the oligonucleotide by improving cellular distribution, bioavailability, metabolism, excretion, permeability, and/or cellular uptake of the oligonucleotide. In particular the conjugate may target the oligonucleotide to a specific organ, tissue or cell type and thereby enhance the effectiveness of the oligonucleotide in that organ, tissue or cell type. At the same time the conjugate may serve to reduce activity of the oligonucleotide in non-target cell types, tissues or organs, *e.g.*, off target activity or activity in non-target cell types, tissues or organs. WO 93/07883 and WO2013/033230 provides suitable conjugate moieties. Further suitable conjugate moieties are those capable of binding to the asialoglycoprotein receptor (ASGPr). In particular tri-valent N-acetylgalactosamine conjugate moieties are suitable for binding to the ASGPr, see for example WO 2014/076196, WO 2014/207232 and WO 2014/179620.

**[0486]** Oligonucleotide conjugates and their synthesis has also been reported in comprehensive reviews by Manoharan in *Antisense Drug Technology, Principles, Strategies, and Applications*, S.T. Crooke, ed., Ch. 16, Marcel Dekker, Inc., 2001 and Manoharan, *Antisense and Nucleic Acid Drug Development*, 2002, 12, 103.

**[0487]** In an aspect, the non-nucleotide moiety (conjugate moiety) is selected from the group consisting of carbohydrates, cell surface receptor ligands, drug substances, hormones, lipophilic substances, polymers, proteins, peptides, toxins (e.g. bacterial toxins), vitamins, viral proteins (e.g. capsids), and combinations thereof.

**[0488]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide wherein the non-nucleotide or non-polynucleotide moiety comprises a protein, a fatty acid chain, a sugar residue, a glycoprotein, a polymer, or any combinations thereof.

**[0489]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide wherein the non-nucleotide or non-polynucleotide moiety comprises a cholesteryl moiety, a vinyl phosphonate moiety, or any combination thereof.

**[0490]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and/or

5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand),

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position,

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position, wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond, and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0491]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and/or

5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand),

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position,

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position, wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond, and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strands.

**[0492]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and/or

5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand),

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0493]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and/or

5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand),

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0494]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGCGGCUACAGCAGCCCCG -3' (SEQ ID NO: 9) (sense strand) and  
 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand),  
 wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position;  
 wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0495]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGCGGCUACAGCAGCCCCG -3' (SEQ ID NO: 9) (sense strand) and  
 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand),  
 wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position;  
 wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0496]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGCGGCUACAGCAGCCCCG -3' (SEQ ID NO: 9) (sense strand) and  
 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand),  
 wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position; wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense nucleotides, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0497]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and

5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand),

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotide from 5' to 3' of the antisense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense nucleotides, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and

wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0498]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and

5'-JUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand),

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0499]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and

5'-JUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand),

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position; wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0500]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and

5'-JUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand),

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position; wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0501]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and

5'-UCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand),

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0502]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and

5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand is 2'-OMe; wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester

bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0503]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and

5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand is 2'-OMe; wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0504]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and

5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand is 2'-OMe; wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position; wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand and a vinyl phosphonate moiety is linked to the antisense strand.

**[0505]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and

5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' F at the sugar position; wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprises 2' OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprises 2' F at the sugar position; wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

**[0506]** In some aspects, the present disclosure provides a conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and

5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' F at the sugar position; wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprises 2' OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprises 2' F at the sugar position; wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the 3' end of the sense strand.

**[0507]** In some aspects, the conjugate comprises an oligonucleotide and a non nucleotide moiety, wherein the oligonucleotide comprises a sense strand comprising 5' RMRRMMRRRRRRMRMMMMRM3', wherein R is RNA and M is 2'-OMe and/or an antisense strand comprising 5' RRMRRRRRRRRRRMRRRRRR3', wherein R is RNA and M is 2'-OMe. In

some aspects, the oligonucleotide comprises a phosphothioate bond between the first and second nucleotides and the second and third nucleotides of the sense strand and/or the first and second nucleotides, the 17<sup>th</sup> and 18<sup>th</sup> nucleotides, and the 18<sup>th</sup> and 19<sup>th</sup> nucleotides of the antisense strand. In some aspects, the oligonucleotide in the conjugate comprises a phosphothiate bond. In some aspects, the oligonucleotide comprises 5' methyl cytosine. In some aspects, the non nucleotide moiety in the conjugate is a cholesteryl moiety linked to the sense or antisense strand. In some aspects, the non nucleotide moiety comprises a vinyl phosphonate moiety.

**[0508]** In some aspects, the conjugate comprises an oligonucleotide and a non nucleotide moiety, wherein the oligonucleotide comprises a sense strand comprising 5' MMMMMMFMMFFMMMMMMM3', wherein M is 2'-OMe and F is 2'-F and/or an antisense strand comprising 5' MMFMFMFMFMFMFMFMFM3', wherein M is 2'-OMe and F is 2'-F. In some aspects, the oligonucleotide comprises a 5' methyl cytosine. In some aspects, the oligonucleotide comprises a phosphothioate bond between the first and second nucleotides and the second and third nucleotides of the sense strand and/or the first and second nucleotides, the 17<sup>th</sup> and 18<sup>th</sup> nucleotides, and the 18<sup>th</sup> and 19<sup>th</sup> nucleotides of the antisense strand. In some aspects, the oligonucleotide in the conjugate comprises a phosphothiate bond. In some aspects, the oligonucleotide in the conjugate comprises 5' methyl cytosine. In some aspects, the non nucleotide moiety in the conjugate is a cholesteryl moiety linked to the sense or antisense strand. In some aspects, the non nucleotide moiety comprises a vinyl phosphonate moiety.

### III. Pharmaceutical Compositions and Administration Routes

**[0509]** The oligonucleotide, *e.g.*, siRNA, of the disclosure can be used in pharmaceutical formulations and compositions. Suitably, such compositions comprise a pharmaceutically acceptable diluent, carrier, salt or adjuvant.

**[0510]** The oligonucleotide, *e.g.*, siRNA, of the disclosure can be included in a unit formulation such as in a pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious side effects in the treated patient. However, in some forms of therapy, serious side effects may be acceptable in terms of ensuring a positive outcome to the therapeutic treatment.

**[0511]** The formulated drug may comprise pharmaceutically acceptable binding agents and adjuvants. Capsules, tablets, or pills can contain for example the following compounds: microcrystalline cellulose, gum or gelatin as binders; starch or lactose as excipients; stearates as lubricants; various sweetening or flavoring agents. For capsules the dosage unit may contain a

liquid carrier like fatty oils. Likewise coatings of sugar or enteric agents may be part of the dosage unit. The oligonucleotide formulations can also be emulsions of the active pharmaceutical ingredients and a lipid forming a micellular emulsion.

**[0512]** The pharmaceutical compositions of the present disclosure can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be (a) oral (b) pulmonary, *e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, (c) topical including epidermal, transdermal, ophthalmic and to mucous membranes including vaginal and rectal delivery; or (d) parenteral including intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, *e.g.*, intrathecal, intra-cerebroventricular, or intraventricular, administration. In one aspect the oligonucleotide, *e.g.*, siRNA, is administered IV, IP, orally, topically or as a bolus injection or administered directly in to the target organ. In another aspect, the oligonucleotide, *e.g.*, siRNA, is administered intrathecal or intra-cerebroventricular as a bolus injection.

**[0513]** Pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, sprays, suppositories, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Examples of topical formulations include those in which the oligonucleotide, *e.g.*, siRNA, of the disclosure are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Compositions and formulations for oral administration include but are not limited to powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitables. Compositions and formulations for parenteral, intrathecal, intra-cerebroventricular, or intraventricular administration can include sterile aqueous solutions which can also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

**[0514]** Pharmaceutical compositions of the present disclosure include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions may be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids. Delivery of drug to the target tissue can be enhanced by carrier-mediated delivery including, but not limited to, cationic liposomes,

cyclodextrins, porphyrin derivatives, branched chain dendrimers, polyethylenimine polymers, nanoparticles and microspheres (Dass CR. *J Pharm Pharmacol* 2002; 54(1):3-27).

**[0515]** The pharmaceutical formulations of the present disclosure, which can conveniently be presented in unit dosage form, can be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

**[0516]** For parenteral, subcutaneous, intradermal or topical administration the formulation can include a sterile diluent, buffers, regulators of tonicity and antibacterials. The active oligonucleotides, *e.g.*, siRNAs, can be prepared with carriers that protect against degradation or immediate elimination from the body, including implants or microcapsules with controlled release properties. For intravenous administration the carriers can be physiological saline or phosphate buffered saline. International Publication No. WO2007/031091 (A2), published March 22, 2007, further provides suitable pharmaceutically acceptable diluent, carrier and adjuvants - which are hereby incorporated by reference.

#### IV. Diagnostics

**[0517]** This disclosure further provides a diagnostic method useful during diagnosis of *MAPT* related diseases, *e.g.*, a tauopathy. Non-limiting examples of tauopathy include, but are not limited to, behavioral variant frontotemporal dementia, primary progressive aphasia, corticobasal syndrome, Richardson's syndrome, Pick's disease, Parkinsonism linked to chromosome 17, Primary age related tauopathy, Tangle-predominant dementia, Corticobasal degeneration, Progressive supranuclear palsy, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Argyrophilic grain disease, Aging-related tau astrogliopathy, and globular glial tauopathy.

**[0518]** The oligonucleotides, *e.g.*, siRNAs, of the disclosure can be used to measure expression of *MAPT* transcript in a tissue or body fluid from an individual and comparing the measured expression level with a standard *MAPT* transcript expression level in normal tissue or body fluid, whereby an increase in the expression level compared to the standard is indicative of a disorder treatable by an oligonucleotide, *e.g.*, siRNA, of the disclosure.

**[0519]** The oligonucleotides, *e.g.*, siRNAs, of the disclosure can be used to assay *MAPT* transcript levels in a biological sample using any methods known to those of skill in the art.

(Touboul *et. al.*, *Anticancer Res.* (2002) 22 (6A): 3349-56; Verjout *et. al.*, *Mutat. Res.* (2000) 640: 127-38); Stowe *et. al.*, *J. Virol. Methods* (1998) 75 (1): 83-91).

**[0520]** By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source of cells potentially expressing *MAPT* transcript. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art.

#### V. Kits comprising ASOs

**[0521]** This disclosure further provides kits that comprise an oligonucleotide, *e.g.*, siRNA, of the disclosure described herein and that can be used to perform the methods described herein. In certain aspects, a kit comprises at least one oligonucleotide, *e.g.*, siRNA, in one or more containers. In some aspects, the kits contain all of the components necessary and/or sufficient to perform a detection assay, including all controls, directions for performing assays, and any necessary software for analysis and presentation of results. One skilled in the art will readily recognize that the disclosed oligonucleotide, *e.g.*, siRNA, can be readily incorporated into one of the established kit formats which are well known in the art.

#### VI. Methods of Using

**[0522]** The oligonucleotides, *e.g.*, siRNAs, of the disclosure can be utilized for therapeutics and prophylaxis.

**[0523]** *MAPT* is a 352-441 amino acid protein preferentially expressed in neurons at pre-synaptic terminals where it is thought to play a role in regulating synaptic transmission. *MAPT* is natively unfolded, but can form a "paperclip" like structure. Preclusion of this structure via post-translational modifications, truncations, and mutations can cause abnormal aggregation of the protein. One mutation that has been extensively studied is P301L. This mutation is associated with misfolding and hyperphosphorylation of the protein leading to the formation of neurofibrillary tangles. These neurofibrillary tangles consist of aggregated, insoluble accumulations of misfolded *MAPT* proteins and are a characteristic feature of some members of a group of neurodegenerative diseases collectively known as tauopathies, notably Dementia and Alzheimer's Disease. Other tauopathies are characterized by Pick bodies, astrocytic plaques, tufted astrocytes, and astrocytic inclusions.

**[0524]** In certain tauopathies, *MAPT* can form pathological aggregates in neurons known as Neurofibrillary Tangles, which are characteristic of both Alzheimer's Disease and Dementia. The present oligonucleotides, *e.g.*, siRNAs, therefore can reduce the number of the *MAPT*

pathological aggregates or prevent formation of the *MAPT* pathological aggregates. In some aspects, the oligonucleotides, *e.g.*, siRNAs, of the disclosure reduce the number of neurofibrillary tangles, Pick bodies, astrocytic plaques, tufted astrocytes, and astrocytic inclusions, or prevent formation of neurofibrillary tangle, Pick bodies, astrocytic plaques, tufted astrocytes, and astrocytic inclusions, . Reports of either undetectable or low levels of *MAPT* mRNA expression in oligodendrocytes suggest that some pathological form of *MAPT* is propagated from neurons, where it is highly expressed, to oligodendrocytes. In certain aspects, the oligonucleotides, *e.g.*, siRNAs, of the disclosure reduce or prevent propagation of *MAPT*, *e.g.*, pathological form of *MAPT*, from neurons.

**[0525]** The oligonucleotides, *e.g.*, siRNAs, can be used in research, *e.g.*, to specifically inhibit the synthesis of *MAPT* protein (typically by degrading or inhibiting the mRNA and thereby prevent protein formation) in cells and experimental animals thereby facilitating functional analysis of the target or an appraisal of its usefulness as a target for therapeutic intervention. Further provided are methods of down-regulating the expression of *MAPT* mRNA and/or *MAPT* protein in cells or tissues comprising contacting the cells or tissues, *in vitro* or *in vivo*, with an effective amount of one or more of the oligonucleotides, *e.g.*, siRNAs, conjugates or compositions of the disclosure.

**[0526]** For therapeutics, an animal or a human, suspected of having a disease or disorder, which can be treated by modulating the expression of *MAPT* transcript and/or *MAPT* protein is treated by administering oligonucleotide, *e.g.*, siRNA, compounds in accordance with this disclosure. Further provided are methods of treating a mammal, such as treating a human, suspected of having or being prone to a disease or condition, associated with expression of *MAPT* transcript and/or *MAPT* protein by administering a therapeutically or prophylactically effective amount of one or more of the oligonucleotides, *e.g.*, siRNAs, or compositions of the disclosure. The oligonucleotide, *e.g.*, siRNA, a conjugate or a pharmaceutical composition according to the disclosure is typically administered in an effective amount. In some aspects, the oligonucleotide, *e.g.*, siRNA, or conjugate of the disclosure is used in therapy.

**[0527]** The disclosure further provides for an oligonucleotide, *e.g.*, siRNA, according to the disclosure, for use in treating one or more of the diseases referred to herein, such as a disease selected from the group consisting of behavioral variant frontotemporal dementia, primary progressive aphasia, corticobasal syndrome, Richardson's syndrome, Pick's disease, Parkinsonism linked to chromosome 17, Primary age related tauopathy, Tangle-predominant dementia, Corticobasal degeneration, Progressive supranuclear palsy, globular glial tauopathy, Alzheimer's

disease, Parkinson's disease, amyotrophic lateral sclerosis, Argrophilic grain disease, Aging-related tau astrogliopathy, and any combinations thereof.

**[0528]** The disclosure further provides for a method for treating tauopathies, the method comprising administering an effective amount of one or more oligonucleotides, *e.g.*, siRNAs, conjugates, or pharmaceutical compositions thereof to an animal in need thereof (such as a patient in need thereof).

**[0529]** In certain aspects, the disease, disorder, or condition is associated with overexpression of *MAPT* gene transcript and/or *MAPT* protein.

**[0530]** The disclosure also provides for methods of inhibiting (*e.g.*, by reducing) the expression of *MAPT* gene transcript and/or *MAPT* protein in a cell or a tissue, the method comprising contacting the cell or tissue, *in vitro* or *in vivo*, with an effective amount of one or more oligonucleotides, *e.g.*, siRNAs, conjugates, or pharmaceutical compositions thereof, of the disclosure to affect degradation of expression of *MAPT* gene transcript thereby reducing *MAPT* protein.

**[0531]** In certain aspects, the oligonucleotides, *e.g.*, siRNAs, are used to reduce the expression of *MAPT* mRNA in one or more sections of brain, *e.g.*, hippocampus, brainstem, striatum, or any combinations thereof. In other aspects, the oligonucleotides, *e.g.*, siRNAs, reduce the expression of *MAPT* mRNA, *e.g.*, in brain stem and/or striatum, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5% compared to the *MAPT* mRNA expression after administration of or exposure to a vehicle (no ASO), at day 3, day 5, day 7, day 10, day 14, day 15, day 20, day 21, or day 25. In some aspects, the expression of *MAPT* mRNA is maintained below 70%, below 60%, below 50%, below 40%, below 30%, below 20%, below 10%, or below 5% compared to the *MAPT* mRNA expression after administration of or exposure to a vehicle (no oligonucleotide) until day 28, day 30, day 32, day 35, day 40, day 42, day 45, day 49, day 50, day 56, day 60, day 63, day 70, or day 75.

**[0532]** In other aspects, the oligonucleotides, *e.g.*, siRNAs, of the present disclosure reduces *MAPT* mRNA and/or *MAPT* protein expression in medulla, caudate putamen, pons cerebellum, lumbar spinal cord, frontal cortex, and/or any combinations thereof.

**[0533]** The disclosure also provides for the use of the oligonucleotide, *e.g.*, siRNA, or conjugate of the disclosure as described for the manufacture of a medicament. The disclosure also provides for a composition comprising the oligonucleotide, *e.g.*, siRNA, or conjugate thereof for use in treating a disorder as referred to herein, or for a method of the treatment of as a disorder as referred to herein. The present disclosure also provides oligonucleotides, *e.g.*, siRNAs, or

conjugates for use in therapy. The present disclosure additionally provides oligonucleotides, *e.g.*, siRNAs, or conjugates for use in the treatment of tauopathies.

**[0534]** The disclosure further provides for a method for inhibiting *MAPT* protein in a cell which is expressing *MAPT* comprising administering an oligonucleotide, *e.g.*, siRNA, or a conjugate according to the disclosure to the cell so as to affect the inhibition of *MAPT* protein in the cell.

**[0535]** The disclosure includes a method of reducing, ameliorating, preventing, or treating neuronal hyperexcitability in a subject in need thereof comprising administering an oligonucleotide, *e.g.*, siRNA, or a conjugate according to the disclosure.

**[0536]** The disclosure also provides for a method for treating a disorder as referred to herein the method comprising administering an oligonucleotide, *e.g.*, siRNA, or a conjugate according to the disclosure as herein described and/or a pharmaceutical composition according to the disclosure to a patient in need thereof.

**[0537]** The oligonucleotides, *e.g.*, siRNAs, and other compositions according to the disclosure can be used for the treatment of conditions associated with over expression or expression of mutated version of *MAPT* protein.

**[0538]** The disclosure provides for the oligonucleotide, *e.g.*, siRNA, or the conjugate according to disclosure, for use as a medicament, such as for the treatment of tauopathies. In some aspects the tauopathy is a disease selected from the group consisting of behavioral variant frontotemporal dementia, primary progressive aphasia, corticobasal syndrome, Richardson's syndrome, Pick's disease, Parkinsonism linked to chromosome 17, Primary age related tauopathy, Tangle-predominant dementia, Corticobasal degeneration, Progressive supranuclear palsy, and globular glial tauopathy, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Argrophilic grain disease, Aging-related tau astrogliopathy, and any combinations thereof.

**[0539]** The disclosure further provides use of an oligonucleotide, *e.g.*, siRNA, of the disclosure in the manufacture of a medicament for the treatment of a disease, disorder or condition as referred to herein. In some aspects, the oligonucleotide, *e.g.*, siRNA, or conjugate of the disclosure is used for the manufacture of a medicament for the treatment of a tauopathy.

**[0540]** Generally stated, one aspect of the disclosure is directed to a method of treating a mammal suffering from or susceptible to conditions associated with abnormal levels of *MAPT* (*i.e.*, a tauopathy), comprising administering to the mammal a therapeutically effective amount of an oligonucleotide, *e.g.*, siRNA, targeted to *MAPT* transcript that comprises one or more LNA units.

The oligonucleotide, *e.g.*, siRNA, a conjugate or a pharmaceutical composition according to the disclosure is typically administered in an effective amount.

[0541] The disease or disorder, as referred to herein, can, in some aspects be associated with a mutation in the *MAPT* gene or a gene whose protein product is associated with or interacts with *MAPT* protein. Therefore, in some aspects, the target *MAPT* is a mutated form or a non human species of the *MAPT* sequence.

[0542] An interesting aspect of the disclosure is directed to the use of an oligonucleotide, *e.g.*, siRNA, (compound) as defined herein or a conjugate as defined herein for the preparation of a medicament for the treatment of a disease, disorder or condition as referred to herein.

[0543] The methods of the disclosure can be employed for treatment or prophylaxis against diseases caused by abnormal levels of *MAPT* protein. In some aspects, diseases caused by abnormal levels of *MAPT* protein are tauopathies. In certain aspects, tauopathies include behavioral variant frontotemporal dementia, primary progressive aphasia, corticobasal syndrome, Richardson's syndrome, Pick's disease, Parkinsonism linked to chromosome 17, Primary age related tauopathy, Tangle-predominant dementia, Corticobasal degeneration, Progressive supranuclear palsy, globular glial tauopathy, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Argyrophilic grain disease, and Aging-related tau astroglipathy.

[0544] Alternatively stated, in some aspects, the disclosure is furthermore directed to a method for treating abnormal levels of *MAPT* protein, the method comprising administering an oligonucleotide, *e.g.*, siRNA, of the disclosure, or a conjugate of the disclosure or a pharmaceutical composition of the disclosure to a patient in need thereof.

[0545] The disclosure also relates to an oligonucleotide, *e.g.*, siRNA, a composition or a conjugate as defined herein for use as a medicament.

[0546] The disclosure further relates to use of a compound, composition, or a conjugate as defined herein for the manufacture of a medicament for the treatment of abnormal levels of *MAPT* protein or expression of mutant forms of *MAPT* protein (such as allelic variants, such as those associated with one of the diseases referred to herein).

[0547] A patient who is in need of treatment is a patient suffering from or likely to suffer from the disease or disorder.

## VII. Vectors and Delivery Systems

[0548] In some aspects, the oligonucleotides, *e.g.*, siRNAs, of the present disclosure can be administered, *e.g.*, to a subject suffering from a disease or condition associated with abnormal

(*e.g.*, increased) inflammasome activity, using any relevant delivery system known in the art. In certain aspects, the delivery system is a vector. Accordingly, in some aspects, the present disclosure provides a vector comprising an oligonucleotide, *e.g.*, siRNA, of the present disclosure.

**[0549]** In some aspects, the vector is viral vector. In some aspects, the viral vector is an adenoviral vector or an adenoassociated viral vector. In certain aspects, the viral vector is an AAV that has a serotype of AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, or any combination thereof. In some aspects, the adenoviral vector is a third generation adenoviral vector. ADEASY™ is by far the most popular method for creating adenoviral vector constructs. The system consists of two types of plasmids: shuttle (or transfer) vectors and adenoviral vectors. The transgene of interest is cloned into the shuttle vector, verified, and linearized with the restriction enzyme PmeI. This construct is then transformed into ADEASIER-1 cells, which are BJ5183 *E. coli* cells containing PADEASY™. PADEASY™ is a ~33Kb adenoviral plasmid containing the adenoviral genes necessary for virus production. The shuttle vector and the adenoviral plasmid have matching left and right homology arms which facilitate homologous recombination of the transgene into the adenoviral plasmid. One can also co-transform standard BJ5183 with supercoiled PADEASY™ and the shuttle vector, but this method results in a higher background of non-recombinant adenoviral plasmids. Recombinant adenoviral plasmids are then verified for size and proper restriction digest patterns to determine that the transgene has been inserted into the adenoviral plasmid, and that other patterns of recombination have not occurred. Once verified, the recombinant plasmid is linearized with PacI to create a linear dsDNA construct flanked by ITRs. 293 or 911 cells are transfected with the linearized construct, and virus can be harvested about 7-10 days later. In addition to this method, other methods for creating adenoviral vector constructs known in the art at the time the present application was filed can be used to practice the methods disclosed herein.

**[0550]** In some aspects, the viral vector is a retroviral vector, *e.g.*, a lentiviral vector (*e.g.*, a third or fourth generation lentiviral vector). Lentiviral vectors are usually created in a transient transfection system in which a cell line is transfected with three separate plasmid expression systems. These include the transfer vector plasmid (portions of the HIV provirus), the packaging plasmid or construct, and a plasmid with the heterologous envelop gene (*env*) of a different virus. The three plasmid components of the vector are put into a packaging cell which is then inserted into the HIV shell. The virus portions of the vector contain insert sequences so that the virus cannot replicate inside the cell system. Current third generation lentiviral vectors encode only three of the

nine HIV-1 proteins (Gag, Pol, Rev), which are expressed from separate plasmids to avoid recombination-mediated generation of a replication-competent virus. In fourth generation lentiviral vectors, the retroviral genome has been further reduced (see, *e.g.*, TAKARA® LENTI-X™ fourth-generation packaging systems).

**[0551]** Any AAV vector known in the art can be used in the methods disclosed herein. The AAV vector can comprise a known vector or can comprise a variant, fragment, or fusion thereof. In some aspects, the AAV vector is selected from the group consisting of AAV type 1 (AAV1), AAV2, AAV3A, AVV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AVV9, AVV10, AVV11, AVV12, AVV13, AAVrh.74, avian AAV, bovine AAV, canine AAV, equine AAV, goat AVV, primate AAV, non-primate AAV, bovine AAV, shrimp AVV, snake AVV, and any combination thereof.

**[0552]** In some aspects, the AAV vector is derived from an AAV vector selected from the group consisting of AAV1, AAV2, AAV3A, AVV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AVV9, AVV10, AVV11, AVV12, AVV13, AAVrh.74, avian AAV, bovine AAV, canine AAV, equine AAV, goat AVV, primate AAV, non-primate AAV, ovine AAV, shrimp AVV, snake AVV, and any combination thereof.

**[0553]** In some aspects, the AAV vector is a chimeric vector derived from at least two AAV vectors selected from the group consisting of AAV1, AAV2, AAV3A, AVV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AVV9, AVV10, AVV11, AVV12, AVV13, AAVrh.74, avian AAV, bovine AAV, canine AAV, equine AAV, goat AVV, primate AAV, non-primate AAV, ovine AAV, shrimp AVV, snake AVV, and any combination thereof.

**[0554]** In certain aspects, the AAV vector comprises regions of at least two different AAV vectors known in the art.

**[0555]** In some aspects, the AAV vector comprises an inverted terminal repeat from a first AAV (*e.g.*, AAV1, AAV2, AAV3A, AVV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AVV9, AVV10, AVV11, AVV12, AVV13, AAVrh.74, avian AAV, bovine AAV, canine AAV, equine AAV, goat AVV, primate AAV, non-primate AAV, ovine AAV, shrimp AVV, snake AVV, or any derivative thereof) and a second inverted terminal repeat from a second AAV (*e.g.*, AAV1, AAV2, AAV3A, AVV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AVV9, AVV10, AVV11, AVV12, AVV13, AAVrh.74, avian AAV, bovine AAV, canine AAV, equine AAV, goat AVV, primate AAV, non-primate AAV, ovine AAV, shrimp AVV, snake AVV, or any derivative thereof).

**[0556]** In some aspects, the AVV vector comprises a portion of an AAV vector selected from the group consisting of AAV1, AAV2, AAV3A, AVV3B, AAV4, AAV5, AAV6, AAV7,

AAV8, AVV9, AVV10, AVV11, AVV12, AVV13, AAVrh.74, avian AAV, bovine AAV, canine AAV, equine AAV, goat AVV, primate AAV, non-primate AAV, ovine AAV, shrimp AVV, snake AVV, and any combination thereof. In some aspects, the AAV vector comprises AAV2.

**[0557]** In some aspects, the AVV vector comprises a splice acceptor site. In some aspects, the AVV vector comprises a promoter. Any promoter known in the art can be used in the AAV vector of the present disclosure. In some aspects, the promoter is an RNA Pol III promoter. In some aspects, the RNA Pol III promoter is selected from the group consisting of the U6 promoter, the H1 promoter, the 7SK promoter, the 5S promoter, the adenovirus 2 (Ad2) VAI promoter, and any combination thereof. In some aspects, the promoter is a cytomegalovirus immediate-early gene (CMV) promoter, an EF1a promoter, an SV40 promoter, a PGK1 promoter, a Ubc promoter, a human beta actin promoter, a CAG promoter, a TRE promoter, a UAS promoter, a Ac5 promoter, a polyhedrin promoter, a CaMKIIa promoter, a GAL1 promoter, a GAL10 promoter, a TEF promoter, a GDS promoter, a ADH1 promoter, a CaMV35S promoter, or a Ubi promoter. In a specific aspect, the promoter comprises the U6 promoter.

**[0558]** In some aspects, the AAV vector comprises a constitutively active promoter (constitutive promoter). In some aspects, the constitutive promoter is selected from the group consisting of hypoxanthine phosphoribosyl transferase (HPRT), adenosine deaminase, pyruvate kinase, beta-actin promoter, cytomegalovirus (CMV), simian virus (*e.g.*, SV40), papilloma virus, adenovirus, human immunodeficiency virus (HIV), Rous sarcoma virus, a retrovirus long terminal repeat (LTR), Murine stem cell virus (MSCV) and the thymidine kinase promoter of herpes simplex virus.

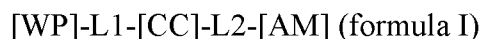
**[0559]** In some aspects, the promoter is an inducible promoter. In some aspects, the inducible promoter is a tissue specific promoter. In certain aspects, the tissue specific promoter drives transcription of the coding region of the AVV vector in a neuron, a glial cell, or in both a neuron and a glial cell.

**[0560]** In some aspects, the AVV vector comprises one or more enhancers. In some aspects, the one or more enhancer are present in the AAV alone or together with a promoter disclosed herein. In some aspects, the AAV vector comprises a 3'UTR poly(A) tail sequence. In some aspects, the 3'UTR poly(A) tail sequence is selected from the group consisting of bGH poly(A), actin poly(A), hemoglobin poly(A), and any combination thereof. In some aspects, the 3'UTR poly(A) tail sequence comprises bGH poly(A).

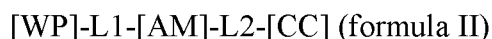
**[0561]** In some aspects, an oligonucleotide, *e.g.*, siRNA, disclosed herein is administered with a delivery agent. Non-limiting examples of delivery agents that can be used include an

exosome, a lipidoid, a liposome, a lipoplex, a lipid nanoparticle, an extracellular vesicle, a synthetic vesicle, a polymeric compound, a peptide, a protein, a cell, a nanoparticle mimic, a nanotube, a micelle, a viral vector, or a conjugate.

**[0562]** Thus, in some aspects, the present disclosure also provides a composition comprising an oligonucleotide, *e.g.*, siRNA, of the present disclosure and a delivery agent. In some aspects, the delivery agent comprises a carrier unit, *e.g.*, that can self-assemble into micelles or be incorporated into micelles. In some aspects, the delivery agent comprises a cationic carrier unit comprising



or



wherein

WP is a water-soluble biopolymer moiety;

CC is a positively charged (*i.e.*, cationic) carrier moiety;

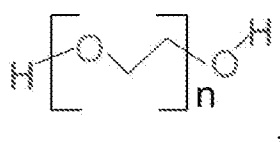
AM is an adjuvant moiety; and,

L1 and L2 are independently optional linkers, and

wherein when mixed with a nucleic acid at an ionic ratio of about 1:1, the cationic carrier unit forms a micelle. Accordingly, in some aspects, the oligonucleotide, *e.g.*, siRNA, and the cationic carrier unit are capable of associating with each other (*e.g.*, via a covalent bond or a non-valent bond) to form a micelle when mixed together.

**[0563]** In some aspects, composition comprising an oligonucleotide, *e.g.*, siRNA, of the present disclosure interacts with the cationic carrier unit via an ionic bond.

**[0564]** In some aspects, the water-soluble biopolymer moiety comprises poly(alkylene glycols), poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharides), poly( $\alpha$ -hydroxy acid), poly(vinyl alcohol), polyglycerol, polyphosphazene, polyoxazolines ("POZ") poly(N-acryloylmorpholine), or any combinations thereof. In some aspects, the water-soluble polymer comprises polyethylene glycol ("PEG"), polyglycerol, or poly(propylene glycol) ("PPG"). In some aspects, the water-soluble biopolymer moiety comprises:



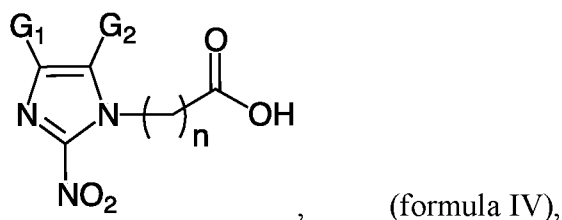
(formula III),

wherein n is 1-1000.

[0565] In some aspects, the n is at least about 110, at least about 111, at least about 112, at least about 113, at least about 114, at least about 115, at least about 116, at least about 117, at least about 118, at least about 119, at least about 120, at least about 121, at least about 122, at least about 123, at least about 124, at least about 125, at least about 126, at least about 127, at least about 128, at least about 129, at least about 130, at least about 131, at least about 132, at least about 133, at least about 134, at least about 135, at least about 136, at least about 137, at least about 138, at least about 139, at least about 140, or at least about 141. In some aspects, the n is about 80 to about 90, about 90 to about 100, about 100 to about 110, about 110 to about 120, about 120 to about 130, about 140 to about 150, about 150 to about 160.

[0566] In some aspects, the water-soluble biopolymer moiety is linear, branched, or dendritic. In some aspects, the cationic carrier moiety comprises one or more basic amino acids. In some aspects, the cationic carrier moiety comprises at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, 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, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, or at least 50 basic amino acids. In some aspects, the cationic carrier moiety comprises about 30 to about 50 basic amino acids. In some aspects, the basic amino acid comprises arginine, lysine, histidine, or any combination thereof. In some aspects, the cationic carrier moiety comprises about 40 lysine monomers.

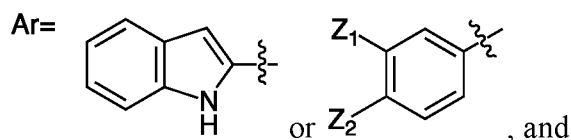
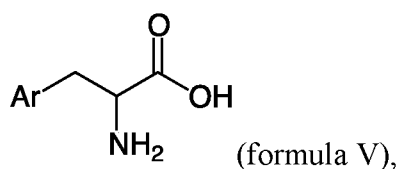
[0567] In some aspects, the adjuvant moiety is capable of modulating an immune response, an inflammatory response, and/or a tissue microenvironment. In some aspects, the adjuvant moiety comprises an imidazole derivative, an amino acid, a vitamin, or any combination thereof. In some aspects, the adjuvant moiety comprises:



wherein each of G1 and G2 is H, an aromatic ring, or 1-10 alkyl, or G1 and G2 together form an aromatic ring, and wherein n is 1-10.

**[0568]** In some aspects, the adjuvant moiety comprises nitroimidazole. In some aspects, the adjuvant moiety comprises metronidazole, tinidazole, nimorazole, dimetridazole, pretomanid, ornidazole, megazol, azanidazole, benznidazole, or any combination thereof. In some aspects, the adjuvant moiety comprises an amino acid.

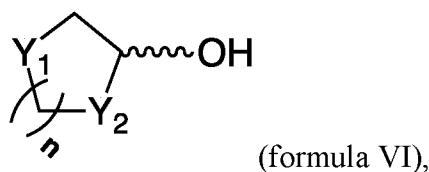
**[0569]** In some aspects, the adjuvant moiety comprises



wherein Ar is

wherein each of Z1 and Z2 is H or OH.

**[0570]** In some aspects, the adjuvant moiety comprises a vitamin. In some aspects, the vitamin comprises a cyclic ring or cyclic hetero atom ring and a carboxyl group or hydroxyl group. In some aspects, the vitamin comprises:



wherein each of Y1 and Y2 is C, N, O, or S, and wherein n is 1 or 2.

**[0571]** In some aspects, the vitamin is selected from the group consisting of vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin B7, vitamin B9, vitamin B12, vitamin C, vitamin D2, vitamin D3, vitamin E, vitamin M, vitamin H, and any combination thereof. In some aspects, the vitamin is vitamin B3.

**[0572]** In some aspects, the adjuvant moiety comprises at least about two, at least about three, at least about four, at least about five, at least about six, at least about seven, at least about eight, at least about nine, at least about ten, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, or at least about 20 vitamin B3. In some aspects, the adjuvant moiety comprises about 10 vitamin B3.

[0573] In some aspects, the composition comprises a water-soluble biopolymer moiety with about 120 to about 130 PEG units, a cationic carrier moiety comprising a poly-lysine with about 30 to about 40 lysines, and an adjuvant moiety with about 5 to about 10 vitamin B3.

[0574] In some aspects, the composition comprises (i) a water-soluble biopolymer moiety with about 100 to about 200 PEG units, (ii) about 30 to about 40 lysines with an amine group (*e.g.*, about 32 lysines), (iii) about 15 to 20 lysines, each having a thiol group (*e.g.*, about 16 lysines, each with a thiol group), and (iv) about 30 to 40 lysines fused to vitamin B3 (*e.g.*, about 32 lysines, each fused to vitamin B3). In some aspects, the composition further comprises a targeting moiety, *e.g.*, a LAT1 targeting ligand, *e.g.*, phenyl alanine, linked to the water soluble polymer. In some aspects, the thiol groups in the composition form disulfide bonds.

[0575] In some aspects, the composition comprises (1) a micelle comprising (i) about 100 to about 200 PEG units, (ii) about 30 to about 40 lysines with an amine group (*e.g.*, about 32 lysines), (iii) about 15 to 20 lysines, each having a thiol group (*e.g.*, about 16 lysines, each with a thiol group), and (iv) about 30 to 40 lysines fused to vitamin B3 (*e.g.*, about 32 lysines, each fused to vitamin B3), and (2) an oligonucleotide, *e.g.*, siRNA, wherein the oligonucleotide, *e.g.*, siRNA, is encapsulated within the micelle. In some aspects, the composition further comprises a targeting moiety, *e.g.*, a LAT1 targeting ligand, *e.g.*, phenyl alanine, linked to the PEG units. In some aspects, the thiol groups in the micelle form disulfide bonds.

[0576] The present disclosure also provides a micelle comprising an oligonucleotide, *e.g.*, siRNA, of the present disclosure, wherein the oligonucleotide, *e.g.*, siRNA, and the delivery agent are associated with each other.

[0577] In some aspects, the association is a covalent bond, a non-covalent bond, or an ionic bond. In some aspects, the positive charge of the cationic carrier moiety of the cationic carrier unit is sufficient to form a micelle when mixed with the oligonucleotide, *e.g.*, siRNA, disclosed herein in a solution, wherein the overall ionic ratio of the positive charges of the cationic carrier moiety of the cationic carrier unit and the negative charges of the oligonucleotide, *e.g.*, siRNA, (or vector comprising the inhibitor) in the solution is about 1: 1.

[0578] In some aspects, the cationic carrier unit is capable of protecting the oligonucleotide, *e.g.*, siRNA, of the present disclosure from enzymatic degradation. See PCT Publication No. WO2020/261227, which is herein incorporated by reference in its entirety.

[0579] The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, transgenic biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such

techniques are explained fully in the literature. See, for example, Sambrook *et al.*, ed. (1989) Molecular Cloning A Laboratory Manual (2nd ed.; Cold Spring Harbor Laboratory Press); Sambrook *et al.*, ed. (1992) Molecular Cloning: A Laboratory Manual, (Cold Springs Harbor Laboratory, NY); D. N. Glover ed., (1985) DNA Cloning, Volumes I and II; Gait, ed. (1984) Oligonucleotide Synthesis; Mullis *et al.* U.S. Pat. No. 4,683,195; Hames and Higgins, eds. (1984) Nucleic Acid Hybridization; Hames and Higgins, eds. (1984) Transcription And Translation; Freshney (1987) Culture Of Animal Cells (Alan R. Liss, Inc.); Immobilized Cells And Enzymes (IRL Press) (1986); Perbal (1984) A Practical Guide To Molecular Cloning; the treatise, Methods In Enzymology (Academic Press, Inc., N.Y.); Miller and Calos eds. (1987) Gene Transfer Vectors For Mammalian Cells, (Cold Spring Harbor Laboratory); Wu *et al.*, eds., Methods In Enzymology, Vols. 154 and 155; Mayer and Walker, eds. (1987) Immunochemical Methods In Cell And Molecular Biology (Academic Press, London); Weir and Blackwell, eds., (1986) Handbook Of Experimental Immunology, Volumes I-IV; Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986); ); Crooke, Antisense drug Technology: Principles, Strategies and Applications, 2<sup>nd</sup> Ed. CRC Press (2007) and in Ausubel *et al.* (1989) Current Protocols in Molecular Biology (John Wiley and Sons, Baltimore, Md.).

**[0580]** All of the references cited above, as well as all references cited herein, are incorporated herein by reference in their entirety.

**[0581]** The following examples are offered by way of illustration and not by way of limitation.

## EXAMPLES

### EXAMPLE 1

**[0582]** Various siRNAs (FIG. 6) at 100nM were transfected into SH-SY5Y cells. Cells were transfected using the reagent *in vivo*-jetPEI<sup>®</sup>-PC (101000171) from polyplus. In order to prepare the cells, neuroblastoma cell line SH-SY5Y was cultured in 1:1 mixture of Ham's F12 and Dulbecco's modified Eagle's medium (DMEM; Hyclone) with 10% fetal bovine serum (FBS; Hyclone) and 1% penicillin/streptomycin (Gibco) for 3-4 days before experimentation and then sub-cultured for differentiation in 12-well culture plates (Corning Costar, Corning, NY, USA) at  $1.5 \times 10^5$  cells/well. A day after plating, the media was removed and replaced with SH-SY5Y media with 3% FBS containing 10  $\mu$ M all-trans-Retinoic acid (ATRA) and cells were then grown for 3 days. Afterwards, the media was replaced with SH-SY5Y media with 3% FBS containing 80 nM

12-O-tetradecanoyl-phorbol-13-acetate (TPA) and cells were grown for an additional 3 days. At the end of the 6 days of differentiation, the media was replaced with SH-SY5Y media with 3% FBS. SH-SY5Y human cells can be differentiated to a more mature neuron-like phenotype that is characterized by neuronal markers.

**[0583]** After transfection of siRNAs in the cells, the cells were incubated for 48 hours. Microtubule associated protein tau protein expression was measured by Western Blot. For the Western blot analysis, cell lysis was performed in a RIPA buffer (iNtRON Biotechnology, Seongnam, Korea) with protease inhibitor cocktail (Roche, Basel, Switzerland), phosphatase inhibitor cocktail 2 (Sigma-Aldrich, P5726), and phosphatase inhibitor cocktail 3 (Sigma-Aldrich, P0044). The mixture was centrifuged at 4 °C for 15 min at 13,000 rpm. The concentration of the supernatant was measured using DC protein assay reagents (Bio-Rad, Hercules, CA, USA). Proteins were then separated in sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride (PVDF) membranes (Millipore, Burlington, MA, USA). The membranes were incubated with the appropriate primary antibodies. Species-specific horseradish peroxidase (HRP)-conjugated secondary antibodies were used to detect the bound antibodies. The protein bands of interest were analyzed using chemiluminescence detection. The antibodies used are as follows:  $\beta$ -actin (sc-47778) from Santa Cruz Biotechnology; Tau monoclonal antibody (TAU-5) (AHB0042), p-Tau (Thr181) (MN1050), and p-Tau (Ser202/Thr205, AT8) (MN1020) from Invitrogen; Tau monoclonal antibody (TAU-46) (4019S) and p-Tau (Ser202) from cell signaling technology.

**[0584]** Signals on western blots were normalized to those of ACTB (Actin Beta). The relative tau protein expression levels between the non-transfection control and the candidate siRNAs (FIG. 6) transfection were compared. Candidate siRNAs exhibiting an inhibitory effect of more than 30% compared to the control were selected for further analysis. Because only endogenous tau levels were measured in the initial screen, the knockdown effect could not be efficiently confirmed. As such, candidate siRNAs exhibiting a 10% or greater knockdown effect in first screening step were re-tested under the condition of tau overexpression. Candidate siRNAs (No. 3, 9, 17, and 20) (FIG. 6) were confirmed to exhibit an efficient inhibitory effect of more than 30% compared to the control. The results are shown in FIG 1A. Table 1 shows the inhibition % effect if each siRNA on total tau protein expression.

Table 1

| Candidate siRNA<br>number | Percent Inhibition<br>of Total Tau Protein | Candidate siRNA<br>number | Percent Inhibition<br>of Total Tau Protein |
|---------------------------|--------------------------------------------|---------------------------|--------------------------------------------|
| 1                         | 42                                         | 15                        | 57                                         |
| 2                         | 61                                         | 16                        | -21                                        |
| 3                         | 17                                         | 17                        | -16                                        |
| 4                         | 59                                         | 18                        | 19                                         |
| 5                         | 71                                         | 19                        | 9                                          |
| 6                         | 58                                         | 20                        | -12                                        |
| 7                         | -12                                        | 21                        | 61                                         |
| 8                         | 45                                         | 22                        | 68                                         |
| 9                         | 17                                         | 23                        | 32                                         |
| 10                        | 68                                         | 24                        | 6                                          |
| 11                        | 62                                         | 25                        | -37                                        |
| 12                        | 65                                         | 26                        | -39                                        |
| 13                        | -17                                        | 27                        | -34                                        |
| 14                        | 66                                         | 28                        | -37                                        |

## Example 2

**[0585]** Various siRNAs (FIG. 6) at 100nM were transfected into SH-SY5Y cells as shown in Example 1. After the transfection, the cells were incubated for 48 hours. Cells were transfected using the reagent *in vivo*-jetPEI®-PC (101000171) from polyplus. Microtubule associated protein tau and its' isoforms mRNA expression was measured.

**[0586]** For mRNA expression level, Quantitative RT-PCR analyses were conducted. Total RNA was isolated using small and large RNA kits (Macherey-Nagel, Allentown, PA, USA) and QIAzol lysis reagent (Qiagen, Hilden, Germany). TOPscript™ RT DryMIX (Enzynomics, Daejeon, Korea) was used to synthesize cDNA for mRNA detection and quantification. The reverse-transcribed product was subjected to qRT-PCR using TOPreal™ qPCR 2 × PreMIX, SYBR Green (Enzynomics), and primers (Table 2) as shown below.

Table 2

| Gene                 | 5'- primer sequence -3'                |
|----------------------|----------------------------------------|
| <i>MAPT</i> exon 1   | GCCAGGAGTTCTGAAGTGATG (SEQ ID NO: 83)  |
| <i>MAPT</i> exon 2   | GAGGACGGATCTGAGGAAACC (SEQ ID NO: 84)  |
| <i>MAPT</i> exon 4/5 | CATGCGAGCTTGGGTCAC (SEQ ID NO: 85)     |
| <i>MAPT</i> exon 9   | CCCAAGTCGCCGTCTTCC (SEQ ID NO: 86)     |
| <i>MAPT</i> exon 10  | ACTTGGA CTGGACGTTGCTA (SEQ ID NO: 87)  |
| <i>MAPT</i> exon 11  | TGGTTTATGATGGATGTTGCCT (SEQ ID NO: 88) |

**[0587]** PCR primers were commercially synthesized (Bioneer, Daejeon, Korea). A 50-cycle amplification was applied for all primers using the CFX96 Real-Time System (Bio-Rad). The normalization was performed using GAPDH as the reference gene.

**[0588]** Total tau gene expression level was detected using primers exon 9 forward and exon 11 reverse after candidate siRNA (100nM) (FIG. 6) transfection in SH-SY5Y cells transfected with Tau-WT (3R2N and 4R2N) (FIG. 8). 4R- tau isoform gene expression level was detected using primers exon 9 forward and exon 10 reverse after candidate siRNA (100nM) transfection in SH-SY5Y cells transfected with Tau-MUT (L266V, 4R2N isoform) (FIG. 8). When the difference in reduction between the total tau gene and the tau isoform expressions was more than 30%, the siRNA was classified as a candidate that effectively reduced either total tau gene or tau isoform expression, depending on which one the siRNA reduced to a greater extent. If the reducing effect for both total tau gene and tau isoform expression was more than 40% and there difference between the two was less than 20%, the siRNA was classified as a group that effectively reduced both types. The results are shown in FIG 1B. Table 3 shows the inhibition % effect of each siRNA on Tau total and Tau isoform mRNA expression.

Table 3

| Candidate siRNA number | Percent Inhibition of Tau total | Percent Inhibition of Tau Isoform | Effectively Reduces            |
|------------------------|---------------------------------|-----------------------------------|--------------------------------|
| 1                      | 38                              | 61                                | MUT MAPT (L266V, 4R2N isoform) |

|    |    |    |                                                          |
|----|----|----|----------------------------------------------------------|
| 3  | 84 | 73 | WT MAPT (3R2N and 4R2N) & MUT MAPT (L266V, 4R2N isoform) |
| 5  | 86 | 24 | WT MAPT (3R2N and 4R2N)                                  |
| 6  | 74 | 36 | WT MAPT (3R2N and 4R2N)                                  |
| 8  | 63 | 14 | WT MAPT (4R2N)                                           |
| 9  | 63 | 21 | WT MAPT (4R2N)                                           |
| 10 | 91 | 38 | WT MAPT (4R2N)                                           |
| 11 | 86 | 73 | WT MAPT (3R2N and 4R2N) & MUT MAPT (L266V, 4R2N isoform) |
| 12 | 67 | 14 | WT MAPT (3R2N and 4R2N)                                  |
| 14 | 40 | 17 | WT MAPT (3R2N and 4R2N)                                  |
| 15 | 74 | 27 | WT MAPT (3R2N and 4R2N)                                  |
| 17 | 40 | 75 | MUT MAPT (L266V, 4R2N isoform)                           |
| 21 | 61 | 2  | WT MAPT (3R2N and 4R2N)                                  |
| 22 | 74 | 6  | WT MAPT (3R2N and 4R2N)                                  |
| 23 | 82 | 66 | WT MAPT (3R2N and 4R2N) & MUT MAPT (L266V, 4R2N isoform) |

FIG. 6 further summarizes the results and shows that: siMAPT Nos. 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14, 15, 17, 20, 21, 22, and 23 had knockdown effects. siMAPT Nos. 7, 13, 16, 18, 19, 24, 25, 26, 27, and 28 did not have knockdown effects. siMAPT Nos. 3, 4, 5, 8, and 9 targeted exon 9. siMAPT Nos. 1, 2, 3, 6, 10, 11, 12, 7, 13, 24, 25, 26, 27, and 28 targeted exon 10. siMAPT Nos. 14 and 13 targeted exon 11. siMAPT Nos. 14, 15, 16, 17, and 18 targeted exon 12. siMAPT Nos. 20, 21, 22, 23, 18 and 19 targeted exon 13. siMAPT No. 3\* was predicted to behave similarly to siMAPT No. 3.

### EXAMPLE 3

**[0589]** In order to show the inhibition of tau protein expression by selected siRNAs, *e.g.*, Nos. 5 and 10, different concentration of BLOK-*MAPT* siRNA (No.5 and No. 10) were transfected in SH-SY5Y. Cells were transfected using the reagent *in vivo*-jetPEI®-PC (101000171) from polyplus. Western blot analysis as shown in Example 1 was performed. FIG. 2A and 2B show that siRNA No. 5 and No. 10 (FIG. 6) are capable of reducing tau protein expression with IC<sub>50</sub> of 2.5 nM and 2.2 nM, respectively.

**[0590]** To show the inhibition of various tau isomers, Tau 3R1N and 3R2N (FIG. 8) were co-transfected for 24 h in SH-SY5Y. Tau 4R1N and 4R2N (FIG. 8) were co-transfected for 48 h. After harvesting each Tau 3R-1N, 2N and Tau 4R-1N, 2N transfected SH-SY5Y cells, reseeding was performed at a 1:1 ratio. Different concentration of BLOK-*MAPT* siRNA (No.5) and siRNA (No.10) (FIG. 6) were transfected for 48 h in Tau-WT transfected SH-SY5Y cells. The relative mRNA expression level of total tau was measured as described in Example2. FIGs. 2C and 2D show the % inhibition level of siRNA No. 5 and No. 10 (FIG. 6), respectively.

**[0591]** Also, to measure relative mRNA expression level of MAPT isoform (4R2N) (FIG. 8). BLOK-*MAPT* siRNA (No.5) and siRNA (No.10) (FIG. 6) were transfected for 48h in Tau-MUT (L226V, 4R2N isoform) (FIG. 8) transfected SH-SY5Y cells. FIGs. 2E and 2F show the percent inhibition of siRNA No. 5 and No. 10 (FIG. 6), respectively. BLOK-*MAPT* siRNA (No.5 and No.10) (FIG. 6) efficiently reduced the Tau-WT (3R1N, 3R2N, 4R1N, 4R2N) (FIG. 8).

### EXAMPLE 4

**[0592]** Wild-type tau proteins were overexpressed in sH-SY5Y cells as described above. Different concentration of BLOK-*MAPT* siRNA were added for 48 h in Tau-WT (3R1N, 3R2N, 4R1N, and 4R2N) (FIG. 8) transfected sH-SY5Y cells. Cells were transfected using the reagent *in vivo*-jetPEI®-PC (101000171) from polyplus. FIGs. 3A to 3F show the knockdown efficacy by siRNA No. 1 (FIG. 3A), siRNA No.17 (FIG. 3B), siRNA No.20 (FIG. 3C), siRNA No.23 (FIG.

3D), siRNA No.3 (FIG. 3E), and siRNA No.11 (FIG. 3F) of wild-type Tau, 3R0N isoform, 4R1N isoform, and 4R2N isoform (FIG. 8).

## EXAMPLE 5

**[0593]** In order to show that MAPT siRNA can restore memory deficit in AD acute mouse model, mice were subjected to behavior test for 3 days after ICV injection of A $\beta$ Os (2  $\mu$ g) (4-weeks). BIOK-*Mapt* siRNA No. 17 (2  $\mu$ g) (FIG. 6) was ICV injected 2-week post to A $\beta$ Os.

**[0594]** A Y-maze was used to evaluate spatial working memory. The assay was conducted in the black plastic arms of a Y-shaped maze. A mouse was placed in the center and was allowed to freely explore the arms for 5 min. The experiment was recorded with EthoVision software 11.5. By analyzing the number of arm entries, the alternation percentage was calculated by dividing the number of three consecutive arm entries (triads) by the number of possible triads  $\times$  100 (Total arm entries - 2).

**[0595]** FIG. 4B shows the result of a Y-maze test with vehicle control, A $\beta$ Os and A $\beta$ Os + BIOK-*Mapt* siRNA (No.17) (FIG. 6) (9-week-old, mice, n=5 mice per group) for assessment of spatial working memory. FIG. 4C shows the result of a Y-maze test with vehicle control, A $\beta$ Os and A $\beta$ Os + BIOK-*Mapt* siRNA (No.11) (FIG. 6) (9-week-old, mice, n=5 mice per group) for assessment of spatial working memory.

**[0596]** To measure the expression levels of total tau (FIG. 4D), p-tau (pT181) (FIG. 4E), and p-tau (pS202) (FIG. 4F), tissue lysates were obtained from hippocampal tissue of A $\beta$ Os ICV injected mice that were administered with BIOK-*Mapt* siRNA (No.17) (FIG. 6) via ICV injection (n=5 mice). FIG. 4G shows that the average Tau inhibition % for FIG. 4D-4F were 23.25%  $\pm$  32.33, 53.61%  $\pm$  10.48, and 51.54%  $\pm$  6.21 respectively. The Western blot analysis shows the expression levels of total tau (FIG. 4H), p-tau (pT181) (FIG. 4I), and p-tau (pS202) (FIG. 4J) in protein tissue lysates from hippocampal tissue of A $\beta$ Os ICV injected mice that were administered with BIOK-*Mapt* siRNA (No.11) (FIG. 6) via ICV injection (n=5 mice). FIG. 4K shows that the average Tau inhibition % for FIG. 4G-4I were 67.37%  $\pm$  17.11, 53.03%  $\pm$  17.37, and 47.64%  $\pm$  9.29 respectively. All data are mean  $\pm$  SD. \*\*P < 0.01 compared to the control (Con). #P < 0.05 and ##P < 0.01 compared to the A $\beta$ Os control.

## EXAMPLE 6

**[0597]** BIOK-*Mapt* siRNA was ICV injected in Tau P301S transgenic mice a total of 3 times at 2-week intervals for 6-week. 6 weeks after the first injection of BIOK-*Mapt* siRNA in

P301S transgenic mice, brain tissue was dissected from the mice. To obtain the brain tissue dissection, after euthanizing the mouse, the brain was extracted from the skull and rinsed in cold PBS to remove excess blood. After rinsing, the brain was cut into two halves, then the posterior parts and olfactory bulb was cut off with a razor blade. After removing the tissue covering the medial surface of the hippocampi, the hippocampi was separated from the cerebral cortex. Subsequently, the remaining internal structures were removed to isolate the cerebral cortex.

**[0598]** FIGs. 5A to 5D shows the Western blot analysis of total tau (t-tau) and hyperphosphorylated tau (p-tau) protein expression levels in each brain tissue such as hippocampus (FIG. 5A), prefrontal cortex (FIG. 5B), entorhinal cortex (FIG. 5C), and striatum (FIG. 5D) following ICV injection of B1OK-*Mapt* siRNA in P301S transgenic mice. FIG. 5E shows a Y-maze test with vehicle control and B1OK-*Mapt* siRNA (Nos. 20, 11, 17) (FIG. 6) in P301S transgenic mice for assessment of spatial working memory (26-week-old, mice, n=4 mice per group). All data are mean  $\pm$  SD. \*P < 0.05, \*\*P < 0.01, and \*\*\*P < 0.001 compared to the vehicle control (Con).

**[0599]** The alternation percentage was decreased in the AD (Alzheimer's disease) acute mouse model compared to the control, but was significantly recovered with exposure to siRNA No. 17. Less recovery was observed after exposure to siRNA No. 11 (FIG. 6). The total number of arm entries was similar across all groups, indicating normal locomotor function of the mice. These results indicate that siRNA No. 17's (FIG. 6) ability to specifically reduce the expression of 4R-*MAPT* isoforms efficiently restores recognition decline in the AD acute mouse model. siRNA No. 17 (FIG. 6) efficiently reduces tau hyperphosphorylation, but not total tau protein expression. siRNA No. 17's (FIG. 6) recovery effect on recognition decline is likely due to its ability to efficiently reduce tau hyperphosphorylation, which is a characteristic of tauopathies, without a similar reduction in total tau protein expression. siRNA No.11 (FIG. 6) also reduces tau hyperphosphorylation, but reduces total tau protein expression at a similar rate. siRNA No. 11 (FIG. 6) did not cause a recovery effect on recognition decline, and this is likely because of the loss of functional tau proteins.

#### EXAMPLE 7: Evaluating the Effectiveness of MAPT siRNA #1 and #17 in Reducing mTau mRNA in Brain Subregions of C57BL/6N Mice

**[0600]** MAPT siRNA #1 is included in the screening group that reduces total tau and it is a representative siRNA that reduces total tau. MAPT siRNA #17 is designed to specifically target

the 4R-tau isoform without loss of function for total tau protein. The 4R-tau isoform is known to be a major cause of tauopathies that induces tau aggregation.

**[0601]** The results of **Example 7** are shown in **FIGs. 10A-10F**. The results show that mTau mRNA is decreased by 50~65%, as measured by qRT-PCR results at 7, 21, and 28 days, in the hippocampus (**FIG. 10A**), entorhinal cortex (**FIG. 10B**), and prefrontal cortex (**FIG. 10C**) (sub brain regions) regions of C57BL/6N mice 4 weeks after a single injection of siRNA #1. The results show that mTau mRNA is decreased by 30~40%, as measured by qRT-PCR results at 7, 21, and 28 days, in the hippocampus (**FIG. 10D**), entorhinal cortex (**FIG. 10E**), and prefrontal cortex (**FIG. 10F**) (sub brain regions) regions of C57BL/6N mice 4 weeks after a single injection of siRNA #17. The results show that siRNA #1 is more effective than siRNA #17 at reducing mTau mRNA levels in the hippocampus, entorhinal cortex, and prefrontal cortex of C57BL/6N mice.

#### EXAMPLE 8: Evaluating the Effectiveness of MAPT siRNA #1 and #17 in Reducing huTau mRNA in Brain Subregions of PS19 Mice

**[0602]** The PS19 (P301S Tg) mouse is a tauopathy pathogenic model that expresses the 1N4R transgene (P301S mutation) of human tau.

**[0603]** PS19 mice (The Jackson Laboratory) overexpressing mutant human MAPT P301S were used for **Examples 8-12**. Genotyping was performed by ear snipping, DNA isolation, and polymerase chain reaction (PCR) with the primers of MAPT. The C57BL/6N mice used in this study were obtained from Koatech. Mice had free access to a regular diet (S-01010; samtako) and purified water. Mice were maintained on a 12/12 h dark/light cycle (lights on at 7:00 a.m.) in a climate-controlled vivarium (22 °C). Before the experiment, mice were handled daily for three days. The daily behavioral observation took place between 10 a.m. and 5 p.m. Mice were habituated to the procedure room for 30 min before the beginning of each behavioral test. All experiments were done blind with aspect to the genotype of mice. Only male mice were used throughout **Examples 8-12**. All experimental procedures were approved and conducted following the Institutional Animal Care and Use Committee (IACUC) guidelines of the Biorchestra.

**[0604]** For **Examples 8-12** mice were anesthetized with Avertin. Mice received a unilateral injection of MAPT siRNA #1 and #17, administered with a Hamilton syringe (26S gauge needle) using the in vivo jet. The stereotaxic injection was delivered into the right lateral ventricle (AP: -0.2 mm, ML: -0.8 mm, DV: -2.5 mm, relative to the bregma) at a rate of 1 µl/min for a total dose

of 2 µg/4µl. After the injection, the needle was left in place for an additional 5 minutes before being slowly retracted.

**[0605]** The results of **Example 8** are shown in **FIGs. 11A-11F**. The results show that huTau mRNA is decreased by 30~40%, as measured by qRT-PCR results at 7, 21, and 28 days, in the hippocampus (**FIG. 11A**), entorhinal cortex (**FIG. 11B**), and prefrontal cortex (**FIG. 11C**) (sub brain regions) regions of PS19 mice 4 weeks after a single injection of siRNA #1. The results show that huTau mRNA is decreased by 60~80%, as measured by qRT-PCR results at 7, 21, and 28 days, in the hippocampus (**FIG. 11D**), entorhinal cortex (**FIG. 11E**), and prefrontal cortex (**FIG. 11F**) (sub brain regions) regions of PS19 mice 4 weeks after a single injection of siRNA #17. The results show that siRNA #17 is more effective than siRNA #1 at reducing huTau mRNA (4R-tau isoform) levels in the hippocampus, entorhinal cortex, and prefrontal cortex of PS19 mice.

#### EXAMPLE 9: MAPT siRNA #1 and #17 Impact on Tau Protein Expressions in PS19 Mice

**[0606]** The reagents used in **Example 9** are as follows: *in vivo*-jetPEI<sup>®</sup>-PC (101000171) from polyplus. The antibodies used in **Example 9** are as follows: β-actin (sc-47778), Tau13 (sc-21796) from Santa Cruz Biotechnology; p-Tau (Thr181) (MN1050) and p-Tau (Ser202/ Thr205, AT8) (MN1020) from Invitrogen; Tau monoclonal antibody p-Tau (Ser396) (9632) from cell signaling technology.

**[0607]** To determine whether the 4R-tau isoform specific targeting strategy affects the therapeutic effect, the pathology alleviation effect was compared after ICV injection of siRNA #1 and siRNA #17 in the PS19 mouse model. To evaluate whether MAPT siRNA #1 and MAPT siRNA #17 reduce phosphorylated tau accumulation and pathological features in tau mutant (P301S) carrying mice, a series of IV injection were performed in the PS19 mouse model. 6-month-old PS19 mice were repeatedly injected with MAPT siRNA at doses of 2 micrograms at intervals of 3 weeks, for a total of 6 ICV injection before being sacrificed at 10 months (40 weeks) of age (**FIG. 12A**). Next, expression level of human tau (Tau-13) and phosphor-tau (Thr181, Ser404 and Ser396) was analyzed using Western blotting using the methodology of **Example 1**.

**[0608]** The results of **Example 9** are shown in **FIGs. 12B-12E**. It was observed that in the hippocampus, there was increased tau protein and phosphorylation in PS19 mice compared to the WT mice (**FIGs. 12B-12E**). MAPT siRNA #17 reversed hyper-phosphorylated tau (tau pathology markers) in aged PS19 mice more effectively than MAPT siRNA #1 (**FIGs. 12B-12E**). MAPT

siRNA #17, which specifically targets against human tau in the 9 months old PS19 tauopathy mouse model, showed a marked decrease and even reversal of tau hyperphosphorylation (Tau-13 (**FIG. 12B**), Thr181 (**FIG. 12C**), Ser404 (**FIG. 12D**), Ser396 (**FIG. 12E**)) pathology across the brain regions despite the age of the PS19 mice. These results show potential therapeutic effect for MAPT siRNA #17 in the later and severe stages of tauopathy and alzheimer's diseases.

#### EXAMPLE 10: MAPT siRNA #1 and #17 Effect on Tau Pathology in the Hippocampus and Entorhinal Cortex of PS19 Mice

**[0609]** After sacrificing the mouse, the brain was extracted from the skull and rinsed in cold phosphate buffer solution (PBS) to remove excess blood. After rinsing, the brain was cut into two halves, then the posterior parts and the olfactory bulb was cut off with a razor blade. The hippocampus was first dissected by making a longitudinal cut along the curvature of the hippocampal formation. For the entorhinal cortex, a lateral cut was made to separate it from the adjoining regions, carefully preserving its structure. The prefrontal cortex dissection involved a frontal sectioning (approximately 2 mm from the anterior tip of the brain).

**[0610]** Brain sections were prepared for free-floating immunohistochemical staining. The sections were blocked with 5% normal donkey serum and then incubated for 48 h at 4 °C with the primary antibody to Mouse Anti-AT-8 (1:200, Thermo Fisher Scientific, MN1020). The sections were then incubated for 2 h at room temperature with a corresponding Donkey Anti-Mouse Alexa fluor 488-conjugated secondary antibody (1:400, Invitrogen, A-21202). The sections were mounted and imaged on a confocal laser scanning microscope. Analysis of cell counting was performed by using ImageJ software.

**[0611]** Tau pathology first deposits at 5-6 months in PS19 mice. To assess whether MAPT siRNA #1 and #17 can prevent or reverse pathological progression, vehicle (n=5) or MAPT siRNA (n=5) was administered at 6 months of age to PS19 mice. An immunohistochemistry (IHC) experiment was performed by immunostaining with the phosphor-tau antibody AT8 in the brain sections of the PS19 mice.

**[0612]** The results of **Example 10** are shown in **FIGs. 13A-13D**. PS19 mice treated with vehicle (Con) showed extensive AT8-positive tau deposition by 10 months of age, particularly in the hippocampus (**FIGs. 13A** and **13B**) and entorhinal cortex (**FIGs. 13C** and **13D**) regions compared to WT mice (where no expression of the AT8 epitope was detected). MAPT siRNA ICV injection at doses of 2 micrograms greatly reduced the amount of AT8 stained tau pathology

deposition in the hippocampus (**FIGs. 13A and 13B**) and entorhinal cortex (**FIGs. 13C and 13D**) regions. However, MAPT siRNA #17 was much better than MAPT siRNA #1 in preventing and suppressing Tau pathology deposition and phosphorylation in aged PS19 mice (**FIGs. 13A-13D**). This result indicates that MAPT siRNA #17 treatment efficiently leads to decrease in abnormal tau accumulation in the hippocampus and entorhinal cortex of PS19 mice.

#### EXAMPLE 11: Efficacy of MAPT siRNA #1 and #17 in Reversing Behavioral Deficits in PS19 Mice Measured by Nest Building and Elevated Plus Maze Tests

**[0613]** The nest building test is used to evaluate murine cognition. The nest building test was performed when the mice were 26, 32 and 38 weeks old. All mice were allocated to a cage with wooden chip bedding without any environmental enrichment items such as cardboard houses or tunnels. Each cage was supplied with exactly 3.0 grams of Nestlet material in the center of the cage. The nest building was scored 24, 48, and 72 hrs later (Table 4), and the remaining Nestlet material was measured. The experimenters were blinded to the groups to prevent bias.

Table 4. Nest building test scoring criteria (Deacon's nesting score criteria)

| Score | Description                                                                                                                                                                                                                                                                                                                                                                          |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1     | Nestlet not noticeably touched (more than 90% intact).                                                                                                                                                                                                                                                                                                                               |
| 2     | Nestlet partially torn (50-90% remaining intact).                                                                                                                                                                                                                                                                                                                                    |
| 3     | Nestlet mostly shredded but often no identifiable nest site: less than 50% of the Nestlet remains intact, but less than 90% is within a quarter of the cage floor area, i.e., the cotton is not gathered into a nest but is spread around the cage. The material may sometimes be in a broadly defined nest area, but the critical definition here is that 50-90% has been shredded. |
| 4     | An identifiable but flat nest: more than 90% of the Nestlet is torn and the material is gathered into a nest within a quarter of the cage floor area, but the nest is flat, with walls higher than mouse body height (of a mouse curled up on its side for less than 50% of its circumference).                                                                                      |
| 5     | A (near) perfect nest: more than 90% of the Nestlet is torn and the nest is a crater, with walls higher than mouse body height for more than 50% of its circumference.                                                                                                                                                                                                               |

**[0614]** The elevated plus maze (EPM) test was conducted at the age of 27 and 36 weeks to test levels of anxiety in PS19 mice. The EPM test consisted of a black acrylic platform, 30 cm in

diameter and 6 cm wide, elevated 50 cm above the ground. The maze was divided into four equal quadrants, two of which were enclosed with black acrylic walls 20 cm in height. There were walls on both the inner and outer sides of the platform to provide the ‘closed’ areas of the maze. The ‘open’ arms had no walls. The maze was surrounded by curtains to prevent any distractions. Videos were taken using a camera that was positioned above the maze. Mouse behavior was analyzed using the EthoVision software.

**[0615]** Typical behavioral deficits caused by tauopathy include decreased nesting activity and reduced anxiety.

**[0616]** The results of **Example 11** are shown in **FIGs. 14A-14D**. In the nest building test (**FIGs. 14A** and **14B**), decreased nesting activity was observed in PS19 mice compared to WT mice as measured by nest building score and untorn nestlet weight. However, this nesting activity was significantly increased following treatment with either MAPT siRNAs #1 or #17 (**FIGs. 14A** and **14B**). In the elevated plus maze test, the PS19 group exhibited reduced anxiety behavior (an indicator of mental deficiency) as indicated by an increased amount of time spent in open arms of the elevated maze, and a lower amount of time spent in closed arms of the elevated maze (**FIGs. 14C** and **14D**). This alteration in anxiety behavior (mental deficiency) was alleviated following treatment with either MAPT siRNA #1 or #17 (**FIGs. 14C** and **14D**). Additionally, MAPT siRNA #17 alleviated cognitive decline and acute behavioral deficits in aged PS19 mice more effectively than MAPT siRNA #1 as measured by the nest building test and the elevated plus maze test.

#### EXAMPLE 12: Therapeutic Effects of MAPT siRNA #1 and #17 on Hyperactivity and Spatial Memory in PS19 Mice Measured by Open Field and Y-Maze Tests

**[0617]** The Y-maze test was used to evaluate spatial working memory and was conducted when the mice were 39 weeks old. The test was conducted in black plastic arms of a Y-shaped maze. A mouse was placed in the center and was allowed to freely explore the arms for 5 min. The experiment was recorded with EthoVision software 11.5. By analyzing the number of arm entries, the alternation percentage was calculated by dividing the number of three consecutive arm entries (triads) by the number of possible triads  $\times 100$  (Total arm entries - 2).

**[0618]** The open field test was conducted when the mice were 27 and 33 weeks old to test the level of hyperactivity in the mice. The mice were brought to the experimental room for at least 1 hr of acclimation to the experimental room conditions prior to testing. Activity chambers (Med Associates Inc, St Albans, VT; 27 x 27 x 20.3 cm) were equipped with infrared beams. Mice were

placed in the center of the chamber and their behavior as recorded for 30 min in 5-minute segments. Quantitative analysis was performed on the following three dependent measures: distance, resting time, and rearing counts. Animals were tested at low-stress conditions where the light was lowered to approximately 10-30 lux of red light.

**[0619]** Typical behavioral impairment caused by tauopathy include distinct hyperactivity and decline of working memory

**[0620]** The results of **Example 12** are shown in **FIGs. 15A-15C**. In the open field test, increased hyperactivity was observed in PS19 mice compared to WT mice as measured by distance traveled, resting time, and rearing count (**FIGs. 15A-15B**). However, this hyperactivity was significantly reduced following treatment with either MAPT siRNA #1 or #17 (**FIGs. 15A-15B**). In the Y-maze test, significant decrease in alternation (%) was observed in the PS19 mice compared to the WT mice (**FIG. 15C**). However, this decrease in alternation (%) was significantly reduced following treatment with either MAPT siRNA #1 or #17 (**FIG. 15C**). Additionally, MAPT siRNA #17 alleviated cognitive decline and acute behavioral deficits in aged PS19 mice more effectively than MAPT siRNA #1 as measured by the Y-maze test and open field test

**EXAMPLE 13: *in vitro* Knockdown Efficacy 48 h after Naked siRNA (siRNA #3\*, siRNA #5, siRNA#14 and siRNA #17) and modified siRNA (M1, M2, M3, M4, M5, M6, M7, M8 and M9) Transfection in the HMC3 Cell Line.**

**[0621]** The previous examples established that specifically targeting the 4R-tau isoform effectively alleviates tau pathology in the PS19 mouse model. To develop RNA therapeutics for tauopathies, MAPT siRNAs #3\*, #5, #14, and #17, which specifically target the 4R-tau isoform, were chemically modified. The chemically modified MAPT siRNAs are shown in **FIGs. 9A-9I**. Specifically, the sense strand and antisense strand for #3\*\_M1/M1/siMAPT-3\*-On\_chol (**FIG. 9A**), #5\_M2/M2/siMAPT-5-On\_chol (**FIG. 9B**), #14\_M3/M3/siMAPT-14-On\_chol (**FIG. 9C**), #17\_M4/M4/siMAPT-17-On\_chol (**FIG. 9D**), #3\*\_M5/M5/siMAPT-3\*-Am\_chol (**FIG. 9E**), #5\_M6/M6/siMAPT-5-Am\_chol (**FIG. 9F**), #14\_M7/M7/siMAPT-14-Am\_chol (**FIG. 9G**), #17\_M8/M8/siMAPT-17-Am\_chol (**FIG. 9H**), and #17\_M9/M9/siMAPT-17-On\_chol\_vinyl (**FIG. 9I**) are shown.

**[0622]** Naked MAPT siRNA (#3\*, #5, #14 and #17) transfection at 50 nM showed a significant reduction (%) of MAPT transcript at 48 h post-transfection in human a cell line (**FIG. 16**). Modified siRNAs M1, M4, M7, M8, and M9 at 10 nM and 50 nM showed the best knockdown

efficacy of the modified MAPT siRNAs, and M7, M8, and M9 showed better knockdown efficacy than naked MAPT siRNAs #3\*, #5, #14 and #17 in the HMC3 cell line (human brain microglia) (**FIG. 16**).

## WHAT IS CLAIMED IS:

1. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are capable of hybridizing to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
  - i. 5'-AACGUCCAGUCCAAGUGUGGC-3' (SEQ ID NO: 1) (sense strand) or  
5'-GCCACACUUGGACUGGACGTT-3' (SEQ ID NO: 2) (antisense strand);
  - ii. 5'-AGCAACGUCCAGUCCAAG-3' (SEQ ID NO: 3) (sense strand) or  
5'-CUUGGACUGGACGUUGCU-3' (SEQ ID NO: 4) (antisense strand);
  - iii. 5'-AAGGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 5) (sense strand) or  
5'-CUUAUUAUUAUCUGCACCTT-3' (SEQ ID NO: 6) (antisense strand);
  - iv. 5'-UGAGAACCUGAAGCACCAG-3' (SEQ ID NO: 7) (sense strand) or  
5'-CUGGUGCUUCAGGUUCUA-3' (SEQ ID NO: 8) (antisense strand);
  - v. 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or  
5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand);
  - vi. 5'-AAUUAUAAGAAGCUGGAUCU-3' (SEQ ID NO: 11) (sense strand) or  
5'-AGAUCAGCUUCUUAUUAATT-3' (SEQ ID NO: 12) (antisense strand);
  - vii. 5'-GAGCCCAAGAAGGUGGCAG-3' (SEQ ID NO: 13) (sense strand) or  
5'-CUGCCACCUUCUUGGGCUC-3' (SEQ ID NO: 14) (antisense strand);
  - viii. 5'-ACCCGGGAGCCCAAGAAG-3' (SEQ ID NO: 15) (sense strand) or  
5'-CUUCUUGGGCUCCCGGGU-3' (SEQ ID NO: 16) (antisense strand);
  - ix. 5'-AGAAGCUGGAUCUAGCAA-3' (SEQ ID NO: 17) (sense strand) or  
5'-UUGCUAAGAUCAGCUUCU-3' (SEQ ID NO: 18) (antisense strand);
  - x. 5'-AAGGAUAAUAUCAAACACGUC-3' (SEQ ID NO: 19) (sense strand) or  
5'-GACGUGUUUGAUUAUUAUCCTT-3' (SEQ ID NO: 20) (antisense strand);
  - xi. 5'-AUAAUAUCAAACACGUCCC-3' (SEQ ID NO: 21) (sense strand) or  
5'-GGGACGUGUUUGAUUAUUAU-3' (SEQ ID NO: 22) (antisense strand);
  - xii. 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or  
5'-JUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand);
  - xiii. 5'-AAUAUCACCCACGUCCCUGG-3' (SEQ ID NO: 25) (sense strand) or  
5'-CCAGGGACGUGGGUGAUATT-3' (SEQ ID NO: 26) (antisense strand);

- xiv. 5'-UGGCCAGGUGGAAGUAAA-3' (SEQ ID NO: 27) (sense strand) or  
5'-UUUUACUCCACCUGGCCAT-3' (SEQ ID NO: 28) (antisense strand);
  - xv. 5'-CCAAAGCCAAGACAGACCA-3' (SEQ ID NO: 29) (sense strand) or  
5'-UGGUCUGUCUUGGCUUUGG-3' (SEQ ID NO: 30) (antisense strand);
  - xvi. 5'-AAGCAGGGUUUGUGAUCAG-3' (SEQ ID NO: 31) (sense strand) or  
5'-CUGAUCACAAACCCUGCTT-3' (SEQ ID NO: 32) (antisense strand);
  - xvii. 5'-CUCGGGACUUCAAAUCAG-3' (SEQ ID NO: 33) (sense strand) or  
5'-CUGAUUUUGAAGUCCCGAGT-3' (SEQ ID NO: 34) (antisense strand);
  - xviii. 5'-AGGGCAGCCUGUGGGAGAA-3' (SEQ ID NO: 35) (sense strand) or  
5'-UUCUCCACAGGCUGCCCU-3' (SEQ ID NO: 36) (antisense strand); or
  - xix. 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or  
5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).
2. The oligonucleotide of claim 1, wherein the contiguous nucleotide sequence is complementary to the nucleic acid sequence.
  3. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
    - a. 5'-AACGUCCAGUCCAAGUGUGGC-3' (SEQ ID NO: 1) (sense strand) or
    - b. 5'-GCCACACUUGGACUGGACGTT-3' (SEQ ID NO: 2) (antisense strand).
  4. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
    - a. 5'-AGCAACGUCCAGUCCAAG-3' (SEQ ID NO: 3) (sense strand) or
    - b. 5'-CUUGGACUGGACGUUGCU-3' (SEQ ID NO: 4) (antisense strand).
  5. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
    - a. 5'-AAGGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 5) (sense strand) or
    - b. 5'-CUUAUUAUUAUCUGCACCTT-3' (SEQ ID NO: 6) (antisense strand).

6. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
  - a. 5'-UGAGAACCUGAAGCACCAG-3' (SEQ ID NO: 7) (sense strand) or
  - b. 5'-CUGGUGCUUCAGGUUCUCA-3' (SEQ ID NO: 8) (antisense strand).
7. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
  - a. 5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) or
  - b. 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand).
8. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
  - a. 5'-AAUUAUAAGAAGCUGGAUCU-3' (SEQ ID NO: 11) (sense strand) or
  - b. 5'-AGAUCCAGCUUCUUAUUAATT-3' (SEQ ID NO: 12) (antisense strand).
9. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
  - a. 5'-GAGCCCAAGAAGGUGGCAG-3' (SEQ ID NO: 13) (sense strand) or
  - b. 5'-CUGCCACCUUCUUGGGCUC-3' (SEQ ID NO: 14) (antisense strand).
10. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
  - a. 5'-ACCCGGGAGCCCAAGAAG-3' (SEQ ID NO: 15) (sense strand) or
  - b. 5'-CUUCUUGGGCUCCCGGU-3' (SEQ ID NO: 16) (antisense strand).
11. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
  - a. 5'-AGAAGCUGGAUCUUAGCAA-3' (SEQ ID NO: 17) (sense strand) or
  - b. 5'-UUGCUAAGAUCAGCUUCU-3' (SEQ ID NO: 18) (antisense strand).

12. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
- 5'-AAGGAUAAUAUCAAACACGUC-3' (SEQ ID NO: 19) (sense strand) or
  - 5'-GACGUGUUUGAUUAUUCCTT-3' (SEQ ID NO: 20) (antisense strand).
13. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
- 5'-AUAAUAUCAAACACGUCCC-3' (SEQ ID NO: 21) (sense strand) or
  - 5'-GGGACGUGUUUGAUUAUUAU-3' (SEQ ID NO: 22) (antisense strand).
14. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
- 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) or
  - 5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand).
15. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
- 5'-AAUAUCACCCACGUCCCUGG-3' (SEQ ID NO: 25) (sense strand) or
  - 5'-CCAGGGACGUGGGUGAUATT-3' (SEQ ID NO: 26) (antisense strand).
16. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
- 5'-UGGCCAGGUGGAAGUAAAAG-3' (SEQ ID NO: 27) (sense strand) or
  - 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand).
17. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
- 5'-CCAAAGCCAAGACAGACCA-3' (SEQ ID NO: 29) (sense strand) or
  - 5'-UGGUCUGUCUUGGCUUUGG-3' (SEQ ID NO: 30) (antisense strand).

18. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
- 5'-AAGCAGGGUUUGUGAUCAGA-3' (SEQ ID NO: 31) (sense strand) or
  - 5'-CUGAUCACAAACCCUGCTT-3' (SEQ ID NO: 32) (antisense strand).
19. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
- 5'-CUCGGGACUUCAAAUCAG-3' (SEQ ID NO: 33) (sense strand) or
  - 5'-CUGAUUUUGAAGUCCCGAG-3' (SEQ ID NO: 34) (antisense strand).
20. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
- 5'-AGGGCAGCCUGUGGGAGAA-3' (SEQ ID NO: 35) (sense strand) or
  - 5'-UUCUCCACAGGCUGCCCU-3' (SEQ ID NO: 36) (antisense strand).
21. An oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises
- 5'-GGUGCAGUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) or
  - 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).
22. The oligonucleotide of claim 1 or 2, which is double stranded and comprises:
- 5'-AACGUCCAGUCCAAGUGUGGC-3' (SEQ ID NO: 1) (sense strand) and  
5'-GCCACACUUGGACUGGACGTT-3' (SEQ ID NO: 2) (antisense strand);
  - 5'-AGCAACGUCCAGUCCAAG-3' (SEQ ID NO: 3) (sense strand) and  
5'-CUUGGACUGGACGUUGCU-3' (SEQ ID NO: 4) (antisense strand);
  - 5'-AAGGUGCAGUAAUUAUAAG-3' (SEQ ID NO: 5) (sense strand) and  
5'-CUUAUUAUUAUCUGCACCTT-3' (SEQ ID NO: 6) (antisense strand);
  - 5'-UGAGAACCUGAAGCACCAG-3' (SEQ ID NO: 7) (sense strand) and  
5'-CUGGUGCUUCAGGUUCUCA-3' (SEQ ID NO: 8) (antisense strand);
  - 5'-AGCGGCUACAGCAGCCCCGG-3' (SEQ ID NO: 9) (sense strand) and

- 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand);
- vi. 5'-AAUUAUAAGAAGCUGGAUCU-3' (SEQ ID NO: 11) (sense strand) and  
5'-AGAUCAGCUUCUUAUUAATT-3' (SEQ ID NO: 12) (antisense strand);
- vii. 5'-GAGCCCAAGAAGGUGGCAG-3' (SEQ ID NO: 13) (sense strand) and  
5'-CUGCCACCUUCUUGGGCUC-3' (SEQ ID NO: 14) (antisense strand);
- viii. 5'-ACCCGGGAGCCCAAGAAG-3' (SEQ ID NO: 15) (sense strand) and  
5'-CUUCUUGGGCUCCCGGGU-3' (SEQ ID NO: 16) (antisense strand);
- ix. 5'-AGAAGCUGGAUCUUAGCAA-3' (SEQ ID NO: 17) (sense strand) and  
5'-UUGCUAAGAUCAGCUUCU-3' (SEQ ID NO: 18) (antisense strand);
- x. 5'-AAGGAUAAUAUCAAACACGUC-3' (SEQ ID NO: 19) (sense strand) and  
5'-GACGUGUUUGAUUAUUAUCCTT-3' (SEQ ID NO: 20) (antisense strand);
- xi. 5'-AUAAUAUCAAACACGUCCC-3' (SEQ ID NO: 21) (sense strand) and  
5'-GGGACGUGUUUGAUUAUUAU-3' (SEQ ID NO: 22) (antisense strand);
- xii. 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and  
5'-JUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand);
- xiii. 5'-AAUAUCACCCACGUCCCUGG-3' (SEQ ID NO: 25) (sense strand) and  
5'-CCAGGGACGUGGGUGAUATT-3' (SEQ ID NO: 26) (antisense strand);
- xiv. 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and  
5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);
- xv. 5'-CCAAAGCCAAGACAGACCA-3' (SEQ ID NO: 29) (sense strand) and  
5'-UGGUCUGUCUUGGCUUUGG-3' (SEQ ID NO: 30) (antisense strand);
- xvi. 5'-AAGCAGGGUUUGUGAUCAG-3' (SEQ ID NO: 31) (sense strand) and  
5'-CUGAUCACAAACCCUGCTT-3' (SEQ ID NO: 32) (antisense strand);
- xvii. 5'-CUCGGGACUUCAAAAUCAG-3' (SEQ ID NO: 33) (sense strand) and  
5'-CUGAUUUUGAAGUCCCGAGT-3' (SEQ ID NO: 34) (antisense strand);
- xviii. 5'-AGGGCAGCCUGUGGGAGAA-3' (SEQ ID NO: 35) (sense strand) and  
5'-UUCUCCACAGGCUGCCCU-3' (SEQ ID NO: 36) (antisense strand); or
- xix. 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and  
5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).
23. The oligonucleotide of claim 22, which comprises:
- a. 5'-AACGUCCAGUCCAAGUGUGGC-3' (SEQ ID NO: 1) (sense strand) and

- b. 5'-GCCACACUUGGACUGGACGTT-3' (SEQ ID NO: 2) (antisense strand).
24. The oligonucleotide of claim 22, which comprises:
- a. 5'-AGCAACGUCCAGUCCAAG-3' (SEQ ID NO: 3) (sense strand) and
- b. 5'-CUUGGACUGGACGUUGCU-3' (SEQ ID NO: 4) (antisense strand).
25. The oligonucleotide of claim 22, which comprises:
- a. 5'-AAGGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 5) (sense strand) and
- b. 5'-CUUAUUAUUAUCUGCACCTT -3' (SEQ ID NO: 6) (antisense strand).
26. The oligonucleotide of claim 22, which comprises:
- a. 5'-UGAGAACCUGAAGCACCAG -3' (SEQ ID NO: 7) (sense strand) and
- b. 5'-CUGGUGCUUCAGGUUCUCA-3' (SEQ ID NO: 8) (antisense strand).
27. The oligonucleotide of claim 22, which comprises:
- a. 5'-AGCGGCUACAGCAGCCCCG -3' (SEQ ID NO: 9) (sense strand) and
- b. 5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand).
28. The oligonucleotide of claim 22, which comprises:
- a. 5'-AAUUAUAAGAAGCUGGAUCU-3' (SEQ ID NO: 11) (sense strand) and
- b. 5'-AGAUCAGCUUCUUAUUAATT-3' (SEQ ID NO: 12) (antisense strand).
29. The oligonucleotide of claim 22, which comprises:
- a. 5'-GAGCCCAAGAAGGUGGCAG-3' (SEQ ID NO: 13) (sense strand) and
- b. 5'-CUGCCACCUUCUUGGGCUC-3' (SEQ ID NO: 14) (antisense strand).
30. The oligonucleotide of claim 22, which comprises:
- a. 5'-ACCCGGGAGCCCAAGAAG-3' (SEQ ID NO: 15) (sense strand) and
- b. 5'-CUUCUUGGGCUCCCGGU-3' (SEQ ID NO: 16) (antisense strand).
31. The oligonucleotide of claim 22, which comprises:
- a. 5'-AGAAGCUGGAUCUUAGCAA-3' (SEQ ID NO: 17) (sense strand) and
- b. 5'-UUGCUAAGAUCAGCUUCU-3' (SEQ ID NO: 18) (antisense strand).
32. The oligonucleotide of claim 22, which comprises:
- a. 5'-AAGGAUAAUAUCAAACACGUC-3' (SEQ ID NO: 19) (sense strand) and
- b. 5'-GACGUGUUUGAUUAUUAUCCTT-3' (SEQ ID NO: 20) (antisense strand).
33. The oligonucleotide of claim 22, which comprises:

- a. 5'-AUAUAUCAAAACACGUCCC-3' (SEQ ID NO: 21) (sense strand) and
  - b. 5'-GGGACGUGUUUGAUUAUUAU-3' (SEQ ID NO: 22) (antisense strand).
34. The oligonucleotide of claim 22, which comprises:
- a. 5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and
  - b. 5'-JUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand).
35. The oligonucleotide of claim 22, which comprises:
- a. 5'-AAUAUCACCCACGUCCCUGG-3' (SEQ ID NO: 25) (sense strand) and
  - b. 5'-CCAGGGACGUGGGUGAUATT-3' (SEQ ID NO: 26) (antisense strand).
36. The oligonucleotide of claim 22, which comprises:
- a. 5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and
  - b. 5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand).
37. The oligonucleotide of claim 22, which comprises:
- a. 5'-CCAAAGCCAAGACAGACCA-3' (SEQ ID NO: 29) (sense strand) and
  - b. 5'-UGGUCUGUCUUGGCUUUGG-3' (SEQ ID NO: 30) (antisense strand).
38. The oligonucleotide of claim 22, which comprises:
- a. 5'-AAGCAGGGUUUGUGAUCAG-3' (SEQ ID NO: 31) (sense strand) and
  - b. 5'-CUGAUCACAAACCCUGCTT-3' (SEQ ID NO: 32) (antisense strand).
39. The oligonucleotide of claim 22, which comprises:
- a. 5'-CUCGGGACUUCAAAAUCAG-3' (SEQ ID NO: 33) (sense strand) and
  - b. 5'-CUGAUUUUGAAGUCCCGAG-3' (SEQ ID NO: 34) (antisense strand).
40. The oligonucleotide of claim 22, which comprises:
- a. 5'-AGGGCAGCCUGUGGGAGAA-3' (SEQ ID NO: 35) (sense strand) and
  - b. 5'-UUCUCCACAGGCUGCCCU-3' (SEQ ID NO: 36) (antisense strand).
41. The oligonucleotide of claim 22, which comprises:
- a. 5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and
  - b. 5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).
42. The oligonucleotide of any one of claims 1 to 41, wherein the oligonucleotide is capable of inhibiting the expression of the human *MAPT* transcript in a cell which is expressing the human *MAPT* transcript.

43. The oligonucleotide of any one of claims 1 to 42, wherein the oligonucleotide is capable of inhibiting the expression of the monkey *MAPT* transcript in a cell which is expressing the monkey *MAPT* transcript.
44. The oligonucleotide of any one of claims 1 to 43, wherein the sense and antisense strands form an RNA duplex are covalently linked by a single-stranded hairpin.
45. The oligonucleotide of any one of claims 1 to 44, wherein the oligonucleotide further comprises non-nucleotide material.
46. The oligonucleotide of claim 1 or 2, wherein the oligonucleotide further comprises an addition, deletion, substitution or alteration of one or more nucleotides.
47. The oligonucleotide of any one of claims 1 to 46, wherein the sense and antisense strands are stabilized against nuclease degradation.
48. The oligonucleotide of any one of claims 1 to 47, further comprising a 3' overhang.
49. The oligonucleotide of claim 48, wherein the 3' overhang comprises from 1 to about 6 nucleotides.
50. The oligonucleotide of claim 48, wherein the 3' overhang comprises about 2 nucleotides.
51. The oligonucleotide of any one of claims 1 to 50, wherein the sense strand comprises a first 3' overhang, and the antisense strand comprises a second 3' overhang.
52. The oligonucleotide of claim 51, wherein the first and second 3' overhangs separately comprise from 1 to about 6 nucleotides.
53. The oligonucleotide of claim 52, wherein the first 3' overhang comprises a dinucleotide and the second 3' overhang comprises a dinucleotide.
54. The oligonucleotide of claim 53, where the dinucleotide comprising the first and second 3' overhangs is dithymidylic acid (TT) or diuridylic acid (uu).
55. The oligonucleotide of any one of claims 48 to 54, wherein the 3' overhang is stabilized against nuclease degradation.
56. The oligonucleotide of any one of claims 1 to 55, which comprises at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten nucleoside analogues.

57. The oligonucleotide of claim 56, wherein the nucleoside analogue or analogues are one or more sugar modified nucleosides selected from the group consisting of Locked Nucleic Acid (LNA); 2'-O-alkyl-RNA; 2'-amino-DNA; 2'-fluoro-DNA (2'-F); arabino nucleic acid (ANA); 2'-fluoro-ANA, hexitol nucleic acid (HNA), intercalating nucleic acid (INA), constrained ethyl nucleoside (cEt), 2'-O-methyl nucleic acid (2'-OMe), 2'-O-methoxyethyl nucleic acid (2'-MOE), and any combination thereof.
58. The oligonucleotide of claim 56 or 57, wherein the nucleoside analogue or analogues comprise a bicyclic sugar.
59. The oligonucleotide of claim 58, wherein the bicyclic sugar comprises cEt, 2',4'-constrained 2'-O-methoxyethyl (cMOE), LNA,  $\alpha$ -L-LNA,  $\beta$ -D-LNA, 2'-O,4'-C-ethylene-bridged nucleic acids (ENA), amino-LNA, oxy-LNA, or thio-LNA.
60. The oligonucleotide of any one of claims 56 to 59, wherein the nucleoside analogue or analogues comprise an LNA.
61. The oligonucleotide of any one of claims 1 to 60, wherein the oligonucleotide comprises 5'-methylcytosine, pseudouridine, or 5-methoxyuridine.
62. The oligonucleotide of any one of claims 1 to 61, wherein the oligonucleotide comprises one or more 5' methyl cytosine nucleobases.
63. The oligonucleotide of any one of claims 1 to 62, which reduces expression of *MAPT* mRNA in a cell by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% compared to a cell not exposed to the oligonucleotide.
64. The oligonucleotide of any one of claims 1 to 63, which reduces expression of *MAPT* protein in a cell by at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% compared to a cell not exposed to the oligonucleotide.
65. The oligonucleotide of any one of claims 1 to 64, which comprises an internucleoside linkage selected from: a phosphodiester linkage, a phosphotriester linkage, a methylphosphonate linkage, a phosphoramidate linkage, a phosphorothioate linkage, and combinations thereof.
66. The oligonucleotide of claim 65, wherein the internucleoside linkage comprises one or more stereo-defined, modified phosphate linkages.

67. The oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are capable of hybridizing to a nucleic acid sequence within a Microtubule-associated protein tau (*MAPT*) transcript, wherein the contiguous nucleotide sequence comprises

5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and/or

5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand).

68. The oligonucleotide of claim 67, wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotide from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

69. The oligonucleotide of claim 67 or 68, wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

70. The oligonucleotide of any one of claims 67 to 69, wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

71. The oligonucleotide of any one of claims 67 to 69, wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

72. The oligonucleotide of claim 67, wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

73. The oligonucleotide of claim 67 or 72, wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

74. The oligonucleotide of any one of claims 67, 72, and 73, wherein the nucleotides in the sense strand and/or the nucleotides in the antisense strand are linked by a phosphodiester bond, a phosphothioate bond, or any combination thereof.

75. The oligonucleotide of any one of claims 67, 72, 73, and 74, wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the

antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

76. The oligonucleotide of claim 27, wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

77. The oligonucleotide of claim 27 or 76, wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

78. The oligonucleotide of claim 76 or 77, wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

79. The oligonucleotide of any one of claims 76 to 78, wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

80. The oligonucleotide of claim 27, wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

81. The oligonucleotide of claim 27 or 80, wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotide from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

82. The oligonucleotide of claim 27, 80, and 81, wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

83. The oligonucleotide of any one of claims 27, 80, 81, and 82, wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense nucleotides, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand

are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

84. The oligonucleotide of claim 34, wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position.

85. The oligonucleotide of claim 34 or 84, wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.

86. The oligonucleotide of any one of claims 34, 84, and 85, wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

87. The oligonucleotide of any one of claims 34, 84, and 85, wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.

88. The oligonucleotide of claim 34, wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position.

89. The oligonucleotide of claim 34 or 88, wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.

90. The oligonucleotide of any one of claims 34, 88, and 89, wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.

91. The oligonucleotide of any one of claims 34, 88, 89, and 90, wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

92. The oligonucleotide of claim 36, wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand is 2'-OMe.
93. The oligonucleotide of claim 36 or 92, wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position.
94. The oligonucleotide of any one of claims 36, 92, and 93, wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.
95. The oligonucleotide of any one of claims 36, 92, and 93, wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond.
96. The oligonucleotide of claim 36, wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' F at the sugar position.
97. The oligonucleotide of claim 36 or 96, wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position.
98. The oligonucleotide of any one of claims 36, 96, and 97, wherein at least one of the backbone of the sense and/or antisense strands is linked to a phosphodiester bond, a phosphothioate bond, or a combination thereof.
99. The oligonucleotide of any one of claims 36, 96, 97, and 98, wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds.

100. A conjugate comprising the oligonucleotide of any one of claims 1 to 99, wherein the oligonucleotide is covalently attached to at least one non-nucleotide or non-polynucleotide moiety to the sense strand and/or the antisense strand.

101. The conjugate of claim 100, wherein the non-nucleotide or non-polynucleotide moiety comprises a protein, a fatty acid chain, a sugar residue, a glycoprotein, a polymer, or any combinations thereof.

102. The conjugate of claim 100, wherein the non-nucleotide or non-polynucleotide moiety comprises a cholesteryl moiety, a vinyl phosphonate moiety, or any combination thereof.

103. A conjugate comprising an oligonucleotide and a non-nucleotide moiety, comprises, consists essentially of, or consists of:

5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and/or

5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand),

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotide from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position,

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position,

wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond, and

wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

104. The conjugate of claim 103, wherein the cholesteryl moiety is linked to the 3' end of the sense strand.

105. A conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-GGUGCAGAUAAUUAUAAG-3' (SEQ ID NO: 64) (sense strand) and/or

5'-CUUAUUAUUAUCUGCACC-3' (SEQ ID NO: 65) (antisense strand),

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and

wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

106. The conjugate of claim 105, wherein the cholesteryl moiety is linked to the 3' end of the sense strand.

107. A conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and

5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand),

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position;

wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and

wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

108. The conjugate of claim 107, wherein the cholesteryl moiety is linked to the 3' end of the sense strand.

109. A conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGCGGCUACAGCAGCCCCG-3' (SEQ ID NO: 9) (sense strand) and

5'-CGGGGCUGCUGUAGCCGCU-3' (SEQ ID NO: 10) (antisense strand),  
 wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;  
 wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotide from 5' to 3' of the antisense strand comprise 2'-F at the sugar position;  
 wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense nucleotides, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds;  
 wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

110. The conjugate of claim 109, wherein the cholesteryl moiety is linked to the 3' end of the sense strand.

111. A conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and

5'-UUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand),

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position;

wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and

wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

112. The conjugate of claim 111, wherein the cholesteryl moiety is linked to the 3' end of the sense strand.

113. A conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-AGGAGGUGGCCAGGUGGAA-3' (SEQ ID NO: 23) (sense strand) and

5'-JUCCACCUGGCCACCUCCU-3' (SEQ ID NO: 24) (antisense strand),

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprise 2'-F at the sugar position;

wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and

wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

114. The conjugate of claim 113, wherein the cholesteryl moiety is linked to the 3' end of the sense strand.

115. A conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and

5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 13<sup>th</sup>, and 18<sup>th</sup> nucleotides from 5' to 3' of the sense strand is RNA and the 2<sup>nd</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand is 2'-OMe;

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand is RNA and the 7<sup>th</sup> and 17<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprise 2'-OMe at the sugar position;

wherein each of the backbone of the sense and antisense strands is linked by a phosphodiester bond; and

wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

116. The conjugate of claim 115, wherein the cholesteryl moiety is linked to the 3' end of the sense strand.

117. The conjugate of claim 115, wherein the cholesteryl moiety is linked to the 3' end of the sense strand and a vinyl phosphonate moiety is linked to the antisense strand.

118. A conjugate comprising an oligonucleotide and a non-nucleotide moiety, wherein the oligonucleotide comprises, consists essentially of, or consists of:

5'-UGGCCAGGUGGAAGUAAAA-3' (SEQ ID NO: 27) (sense strand) and

5'-UUUUACUCCACCUGGCCA-3' (SEQ ID NO: 28) (antisense strand);

wherein the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>, 16<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' OMe at the sugar position and the 7<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, and 11<sup>th</sup> nucleotides from 5' to 3' of the sense strand comprises 2' F at the sugar position.

wherein the 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup>, 15<sup>th</sup>, 17<sup>th</sup>, 18<sup>th</sup>, and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprises 2' OMe at the sugar position and the 2<sup>nd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 14<sup>th</sup>, and 16<sup>th</sup> nucleotides from 5' to 3' of the antisense strand comprises 2' F at the sugar position.

wherein the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the sense strand, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> nucleotides from 5' to 3' of the antisense strand, and the 17<sup>th</sup>, 18<sup>th</sup> and 19<sup>th</sup> nucleotides from 5' to 3' of the antisense strand are linked by phosphorothioate bonds, and every other nucleotide of the sense and antisense strands are linked by phosphodiester bonds; and

wherein the non-nucleotide moiety comprises a cholesteryl moiety linked to the sense or antisense strand.

119. The conjugate of claim 118, wherein the cholesteryl moiety is linked to the 3' end of the sense strand.

120. A pharmaceutical composition comprising the oligonucleotide of any one claims 1 to 99 or the conjugate of any one of claims 100 to 119 and a pharmaceutically acceptable carrier.

121. The composition of claim 120, which further comprises a therapeutic agent.

122. The composition of claim 121, wherein the therapeutic agent is an *MAPT* antagonist.

123. The composition of claim 122, wherein the *MAPT* antagonist is an anti-*MAPT* antibody or fragment thereof.

124. A kit comprising the oligonucleotide of any one claims 1 to 99, the conjugate of any one of claims 100 to 119, or the composition of any one of claims 120 to 123, and instructions for use.

125. A diagnostic kit comprising the oligonucleotide of any one claims 1 to 99, the conjugate of any use of claims 100 to 119, or the composition of any one of claims 120 to 123, and instructions for use.

126. A method of inhibiting or reducing *MAPT* protein expression in a cell, the method comprising administering the oligonucleotide of any one claims 1 to 99, the conjugate of any one of claims 100-119, or the composition of any one of claims 120 to 123 to the cell expressing *MAPT* protein, wherein the *MAPT* protein expression in the cell is inhibited or reduced after the administration.

127. The method of claim 126 wherein the *MAPT* protein is wild-type, a *MAPT* protein variant, a *MAPT* isoform, or any combination thereof.

128. The method of claim 127, wherein the *MAPT* isoform comprises 3R-, 4R-, 0N4R, 1N4R, 2N4R, 0N3R, 1N3R, 2N3R and any combinations thereof.

129. The method of claim 126, wherein the oligonucleotide inhibits or reduces expression of *MAPT* mRNA in the cell after the administration.

130. The method of claim 126 to 129, wherein the expression of *MAPT* mRNA is reduced by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% after the administration compared to a cell not exposed to the oligonucleotide.

131. The method of any one of claims 126 to 129, wherein the oligonucleotide reduces expression of *MAPT* protein in the cell after the administration by at least about 60%, at least about 70%, at least about 80%, or at least about 90% compared to a cell not exposed to the oligonucleotide.

132. The method of any one of claims 126 to 131, wherein the cell is a neuron.

133. A method for treating a tauopathy in a subject in need thereof, comprising administering an effective amount of the oligonucleotide of any one claims 1 to 99, the conjugate of any one of claims 100-119, or the composition of any one of claims 120 to 123 to the subject.

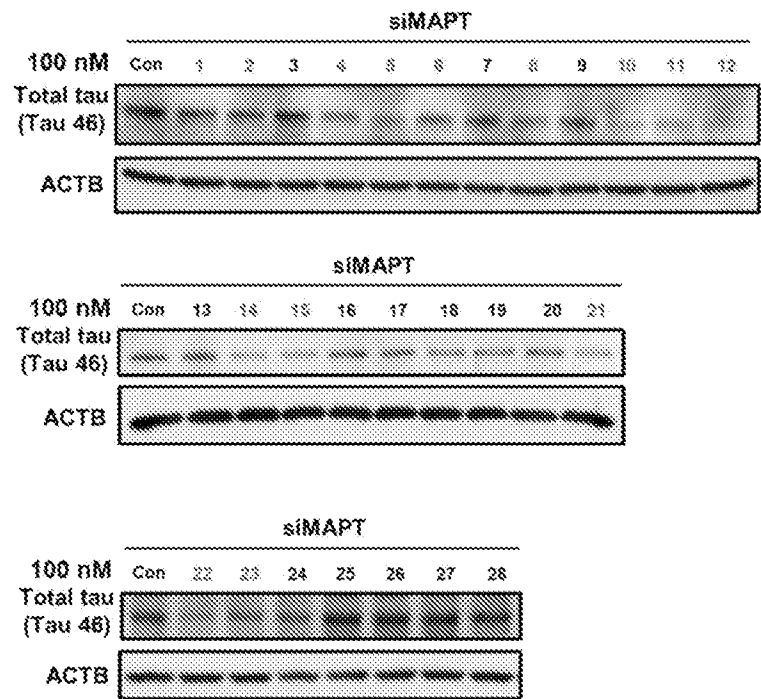
134. The method of claim 133, wherein the tauopathy is selected from the group consisting of behavioral variant frontotemporal dementia, primary progressive aphasia, corticobasal syndrome, Richardson's syndrome, Pick's disease, Parkinsonism linked to chromosome 17, Primary age related tauopathy, Tangle-predominant dementia, Corticobasal degeneration, Progressive

supranuclear palsy, globular glial tauopathy, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Argyrophilic grain disease, Aging-related tau astroglialopathy, and any combinations thereof.

135. The method of claim 133 or 134, wherein the subject is a human.

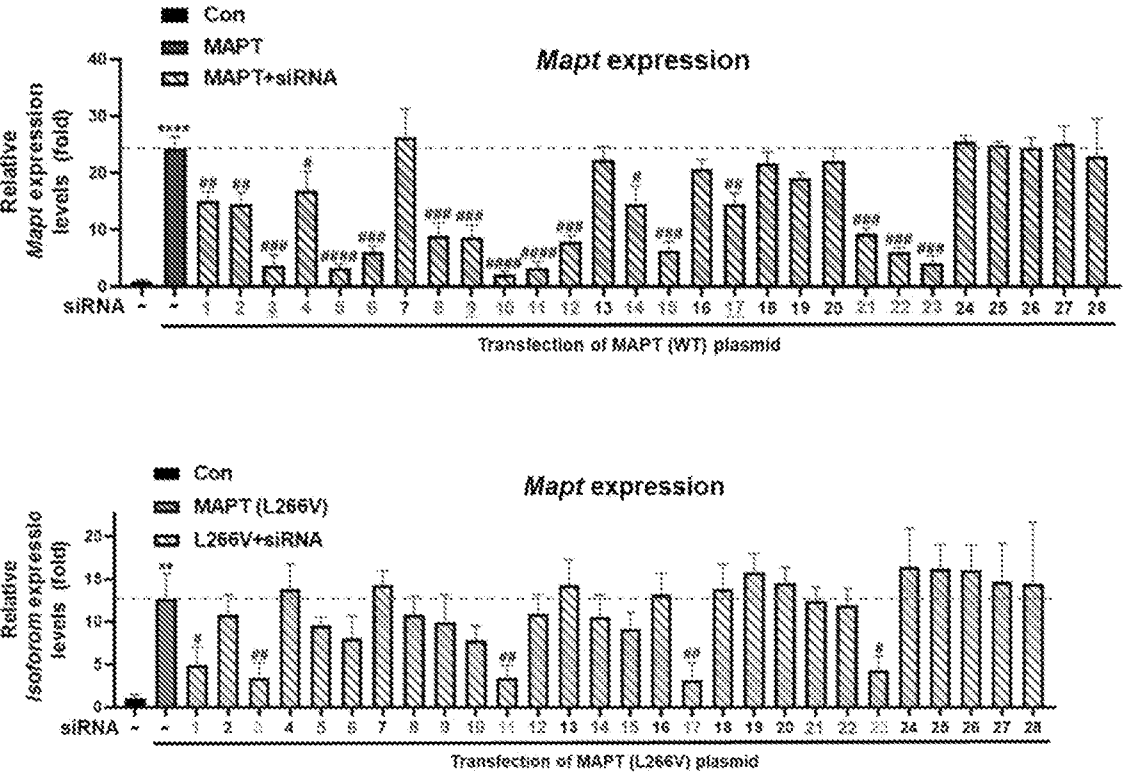
136. The method of any one of claims 133 to 135, wherein the oligonucleotide, the conjugate, or the composition is administered orally, parenterally, intrathecally, intra-cerebroventricularly, pulmonarily, topically, or intraventricularly.

FIG. 1A



| Candidate siRNA (No.) | Inhibition (%) | Candidate siRNA (No.) | Inhibition (%) |
|-----------------------|----------------|-----------------------|----------------|
| 1                     | 42 %           | 15                    | 57 %           |
| 2                     | 81 %           | 16                    | -21 %          |
| 3                     | 17 %           | 17                    | -16 %          |
| 4                     | 58 %           | 18                    | 19 %           |
| 5                     | 71 %           | 19                    | 9 %            |
| 6                     | 58 %           | 20                    | -12 %          |
| 7                     | -12 %          | 21                    | 81 %           |
| 8                     | 45 %           | 22                    | 88 %           |
| 9                     | 17 %           | 23                    | 32 %           |
| 10                    | 68 %           | 24                    | 6 %            |
| 11                    | 62 %           | 25                    | -37 %          |
| 12                    | 65 %           | 26                    | -39 %          |
| 13                    | -17 %          | 27                    | -34 %          |
| 14                    | 66 %           | 28                    | -37 %          |

FIG. 1B



✓ **Group**

- \* siRNA 5, 6, 8, 9, 10, 12, 14, 16, 21, and 22 effectively reduce WT MAPT (4R2N)
- \* siRNA 1 and 17 effectively reduce MUT MAPT (L266V)
- \* siRNA 3, 11, and 23 effectively reduce WT & MUT MAPT

| Candidate siRNA (No.) | Inhibition (%) |               |   |
|-----------------------|----------------|---------------|---|
|                       | Tau (total)    | Tau (isoform) |   |
| 1                     | 38 %           | 61 %          | ✓ |
| 3                     | 84 %           | 73 %          |   |
| 5                     | 86 %           | 24 %          | ✓ |
| 6                     | 74 %           | 36 %          |   |
| 8                     | 63 %           | 14 %          |   |
| 9                     | 63 %           | 21 %          |   |
| 10                    | 91 %           | 38 %          | ✓ |
| 11                    | 86 %           | 73 %          | ✓ |
| 12                    | 67 %           | 14 %          |   |
| 14                    | 40 %           | 17 %          |   |
| 15                    | 74 %           | 27 %          |   |
| 17                    | 40 %           | 75 %          | ✓ |
| 21                    | 61 %           | 2 %           |   |
| 22                    | 74 %           | 6 %           |   |
| 23                    | 82 %           | 66 %          | ✓ |

FIG. 2A

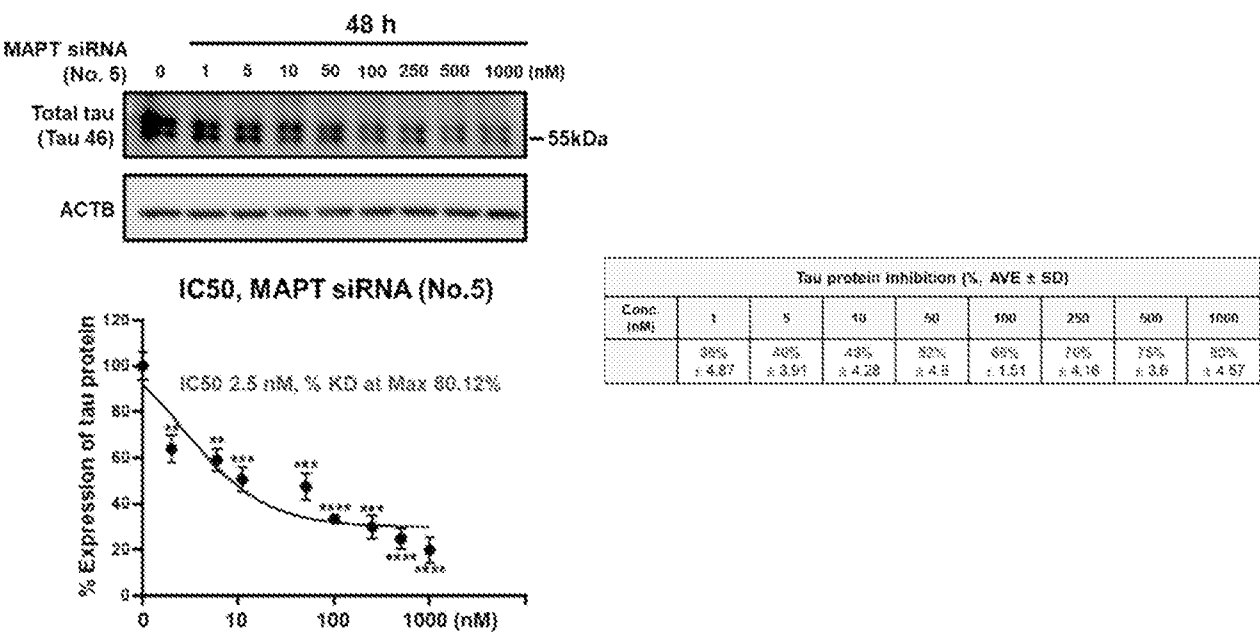


FIG. 2B

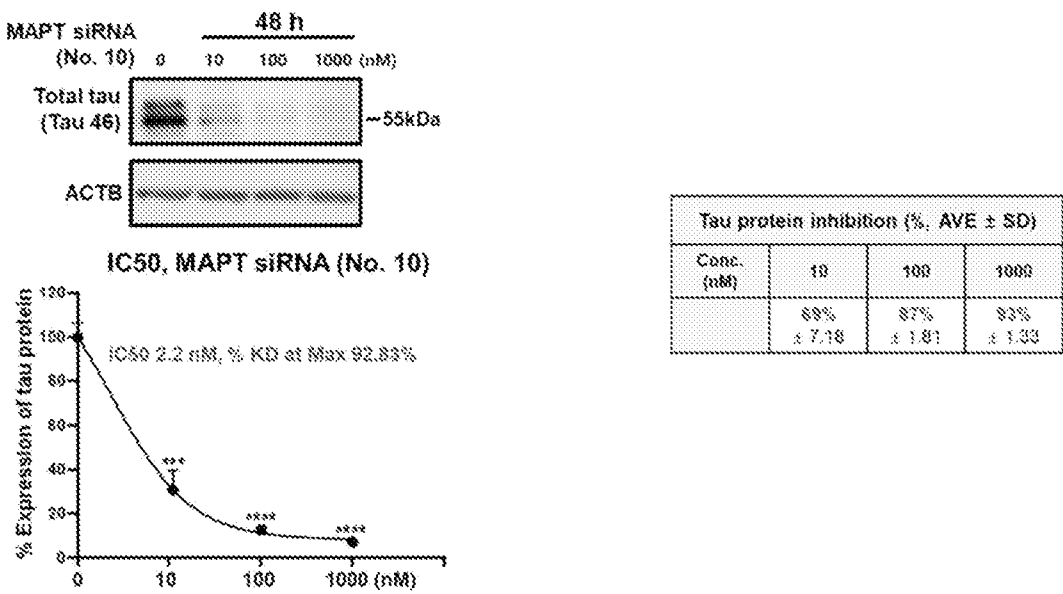


FIG. 2C

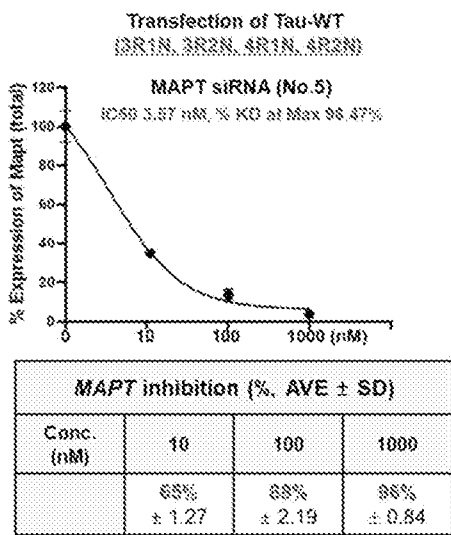


FIG. 2D

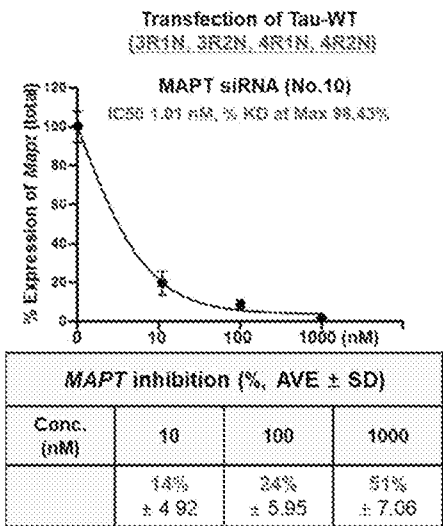


FIG. 2E

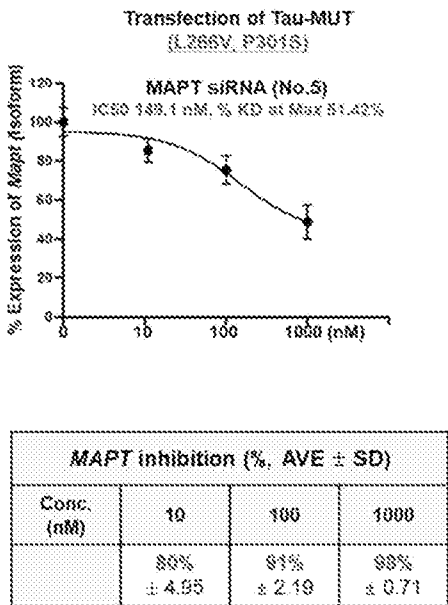


FIG. 2F

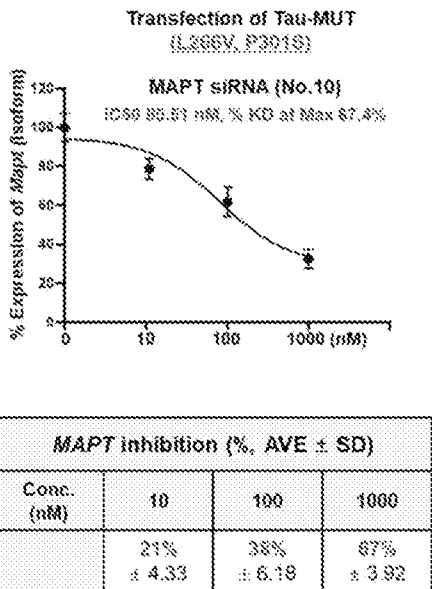
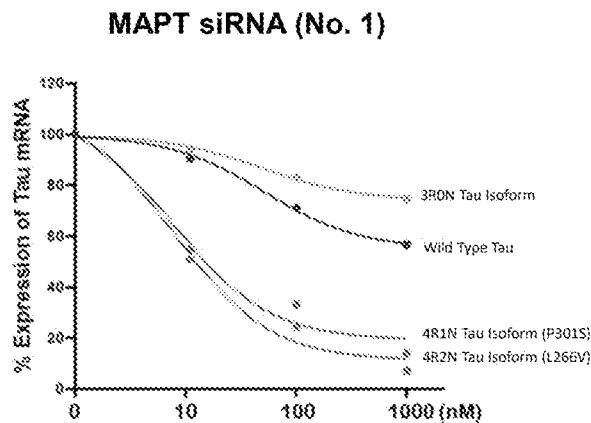
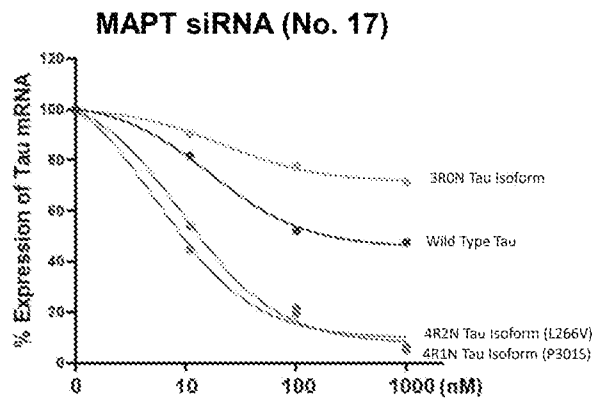


FIG. 3A



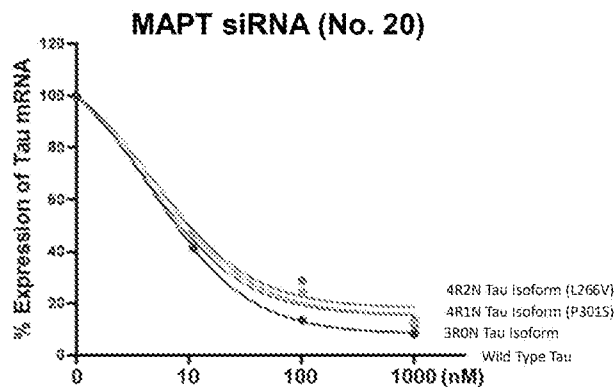
WT Tau form: IC50 1560 nM, % KD at Max 43.25%  
3R0N isoform: % KD at Max 25.14%  
4R2N isoform: IC50 16.82 nM, % KD at Max 82.36%  
4R1N isoform: IC50 27.34 nM, % KD at Max 88.78%

FIG. 3B



WT Tau form: IC50 396.4 nM, % KD at Max 52.22%  
3R0N isoform: % KD at Max 28.62%  
4R2N isoform: IC50 12.22 nM, % KD at Max 94.83%  
4R1N isoform: IC50 16.13 nM, % KD at Max 93.86%

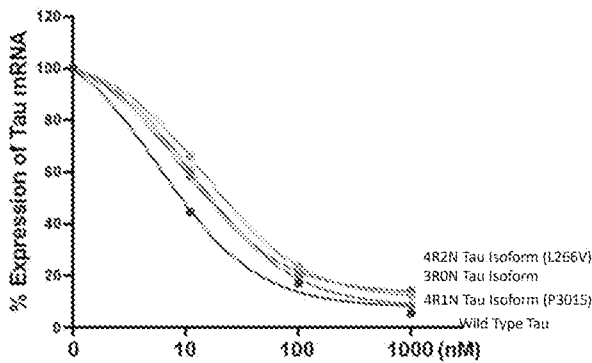
FIG. 3C



WT Tau form: IC50 9.24 nM, % KD at Max 91.72%  
3R0N isoform: IC50 15.22 nM, % KD at Max 87.41%  
4R2N isoform: IC50 18.3 nM, % KD at Max 86.38%  
4R1N isoform: IC50 13.28 nM, % KD at Max 88.32%

FIG. 3D

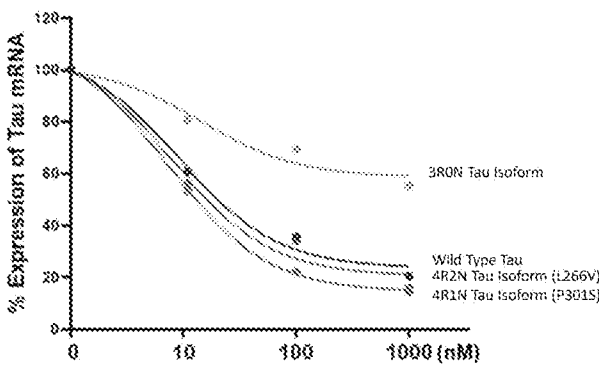
MAPT siRNA (No. 23)



WT Tau form: IC50 11.04 nM, % KD at Max 94.33%  
3R0N isoform: IC50 27.18 nM, % KD at Max 87.52%  
4R2N isoform: IC50 20.6 nM, % KD at Max 85.71%  
4R1N isoform: IC50 19.92 nM, % KD at Max 91.31%

FIG. 3E

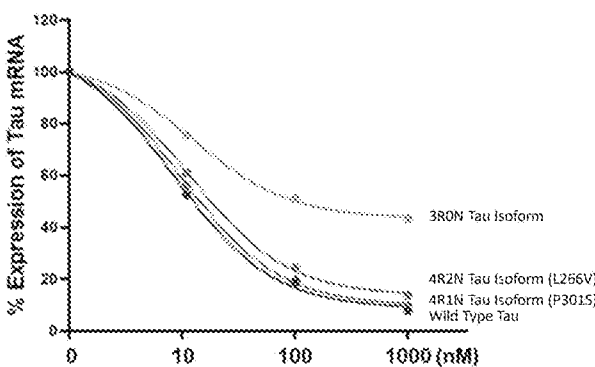
MAPT siRNA (No. 3)



WT Tau form: IC50 40.37 nM, % KD at Max 79.59%  
3R0N isoform: IC50 1470 nM, % KD at Max 44.62%  
4R2N isoform: IC50 30.4 nM, % KD at Max 84.04%  
4R1N isoform: IC50 18.28 nM, % KD at Max 88.48%

FIG. 3F

MAPT siRNA (No. 11)



WT Tau form: IC50 15.33 nM, % KD at Max 92.11%  
3R0N isoform: IC50 263.6 nM, % KD at Max 56.58%  
4R2N isoform: IC50 17.95 nM, % KD at Max 90.34%  
4R1N isoform: IC50 24.53 nM, % KD at Max 88.23%

FIG. 4A

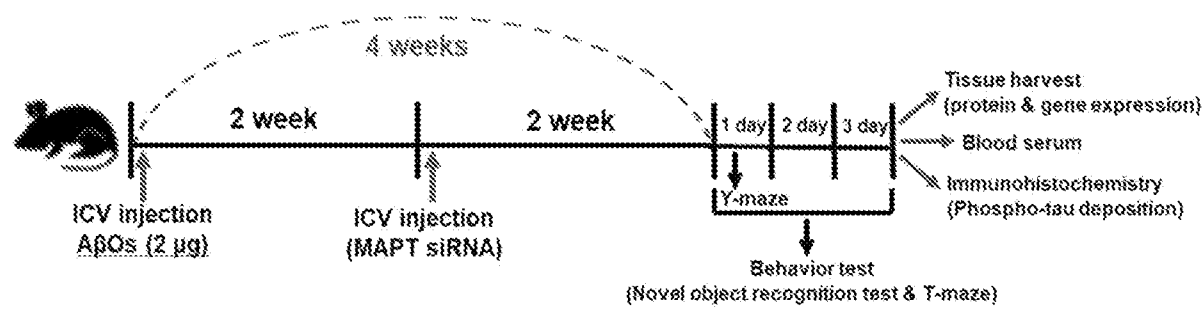


FIG. 4B

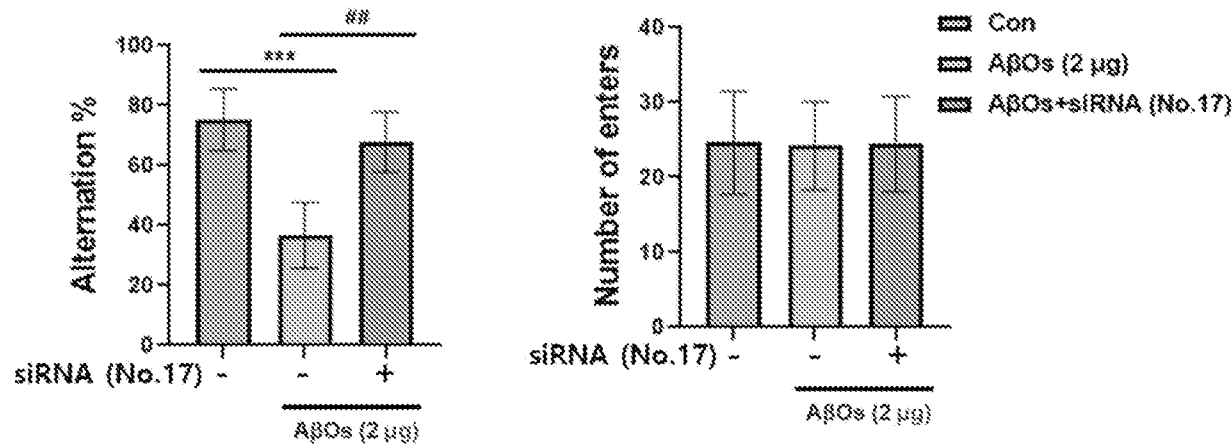


FIG. 4C

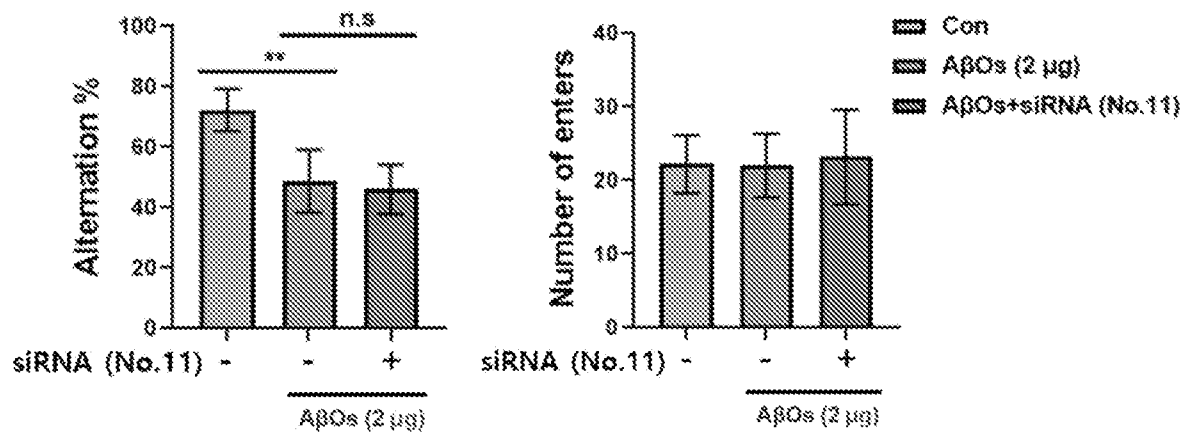


FIG. 4D      FIG. 4E      FIG. 4F

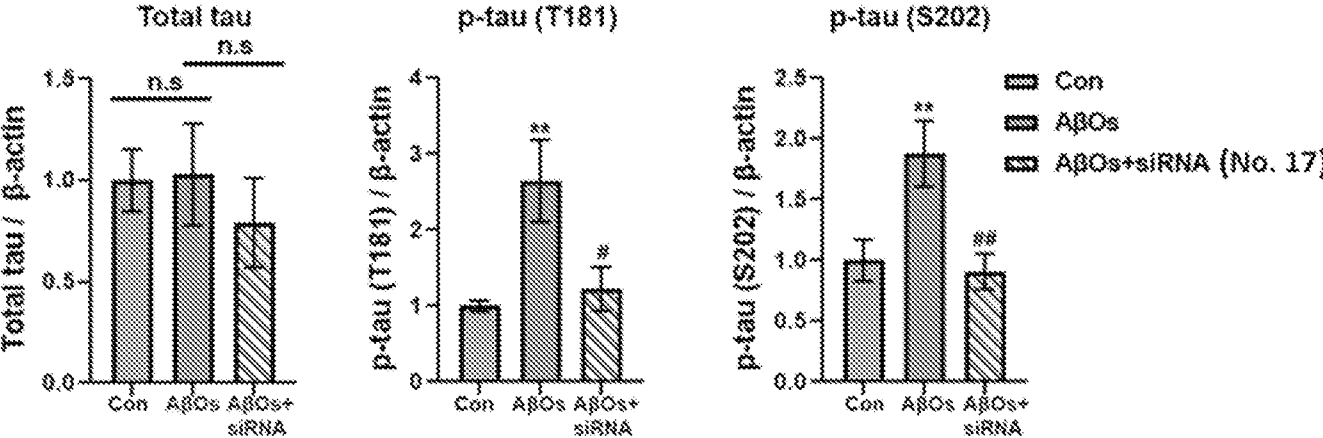


FIG. 4G

| Tau inhibition (% AVE $\pm$ SD) |                       |                       |                      |
|---------------------------------|-----------------------|-----------------------|----------------------|
| Type                            | Total tau             | p-tau (T181)          | P-tau (S202)         |
|                                 | 23.25%<br>$\pm$ 32.33 | 53.61%<br>$\pm$ 10.48 | 51.54%<br>$\pm$ 6.21 |

FIG. 4H      FIG. 4I      FIG. 4J

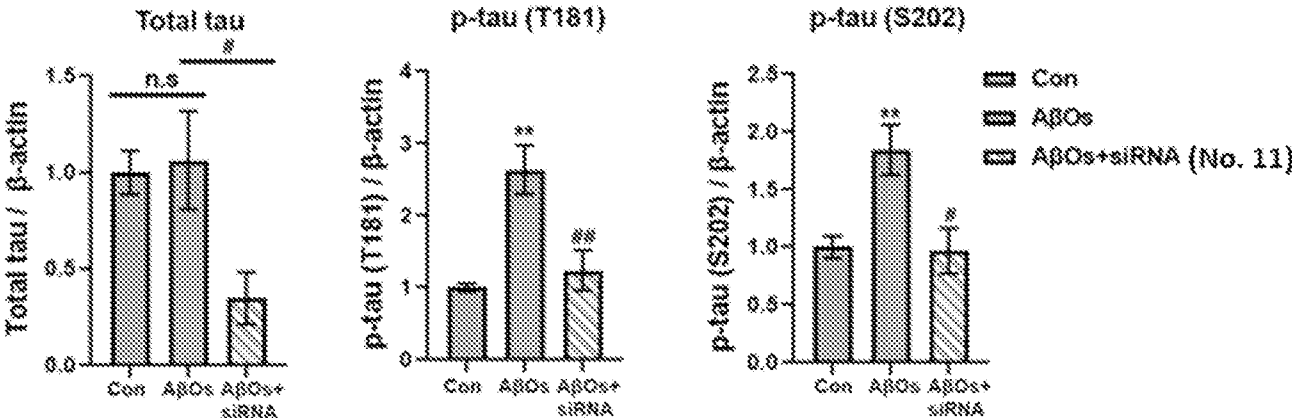
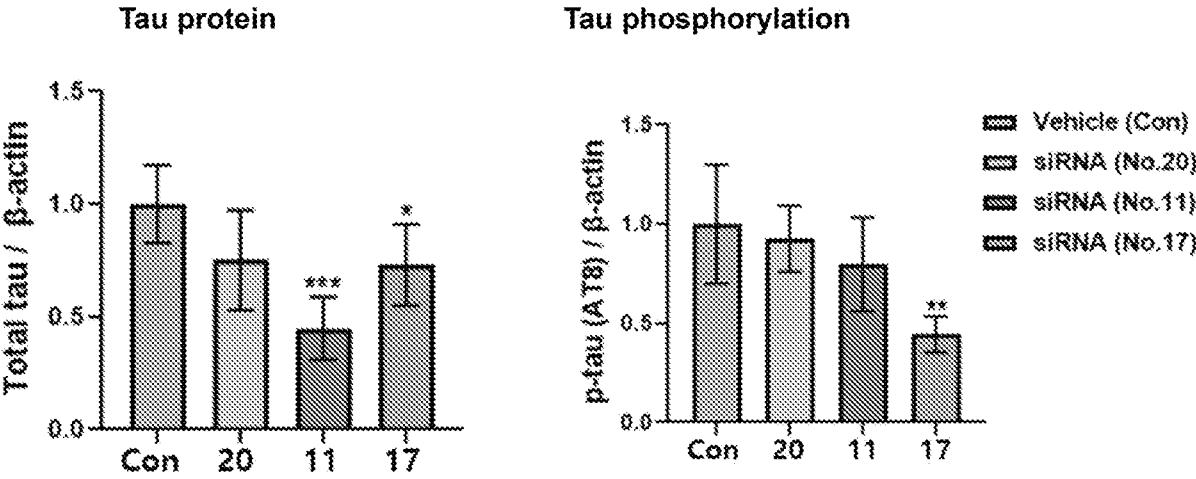


FIG. 4K

| Tau inhibition (% AVE $\pm$ SD) |                       |                       |                      |
|---------------------------------|-----------------------|-----------------------|----------------------|
| Type                            | Total tau             | p-tau (T181)          | P-tau (S202)         |
|                                 | 67.37%<br>$\pm$ 17.11 | 53.03%<br>$\pm$ 17.37 | 47.64%<br>$\pm$ 9.29 |

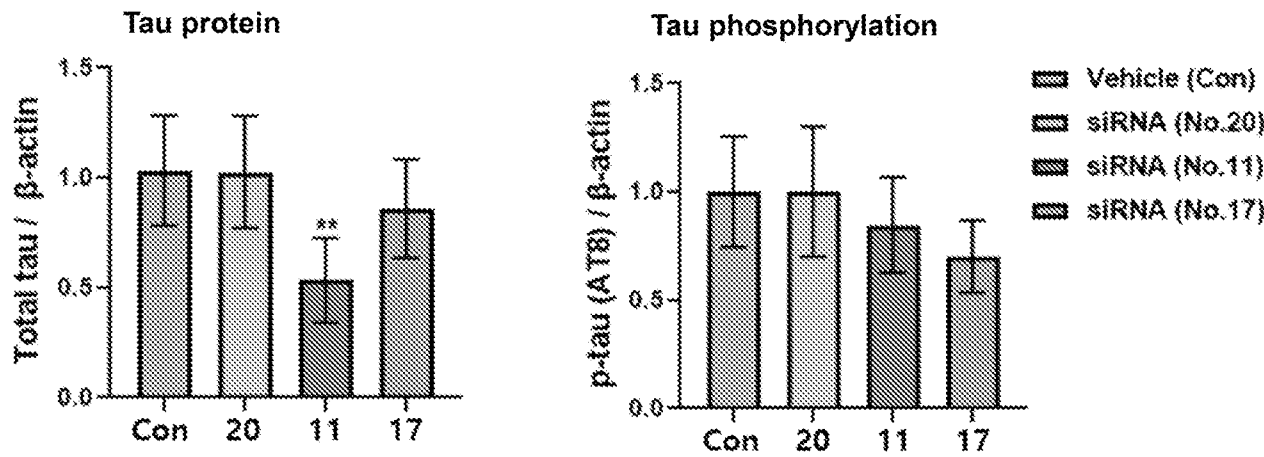
# FIG. 5A

## Hippocampus (P301S)



# FIG. 5B

## Prefrontal cortex (P301S)



# FIG. 5C

## Entorhinal cortex (P301S)

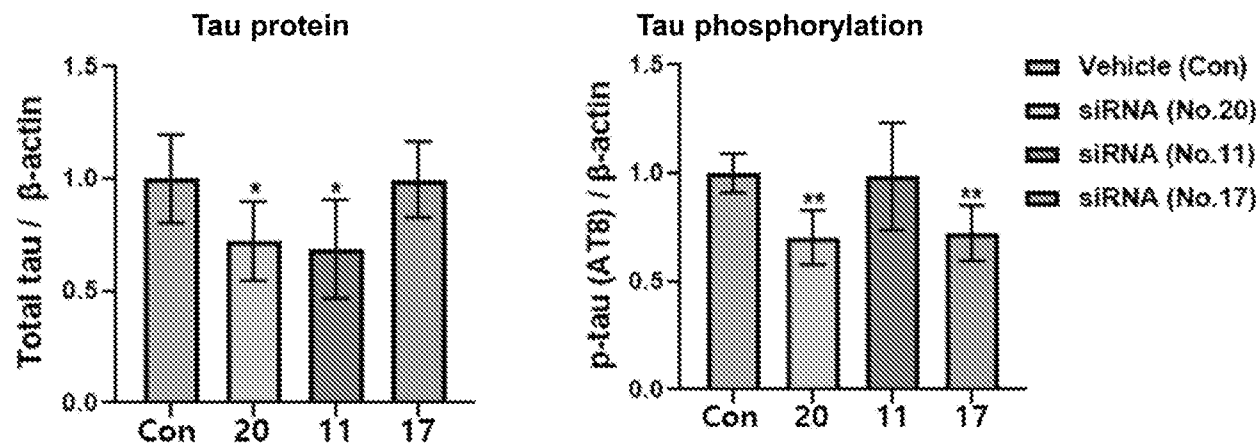


FIG. 5D

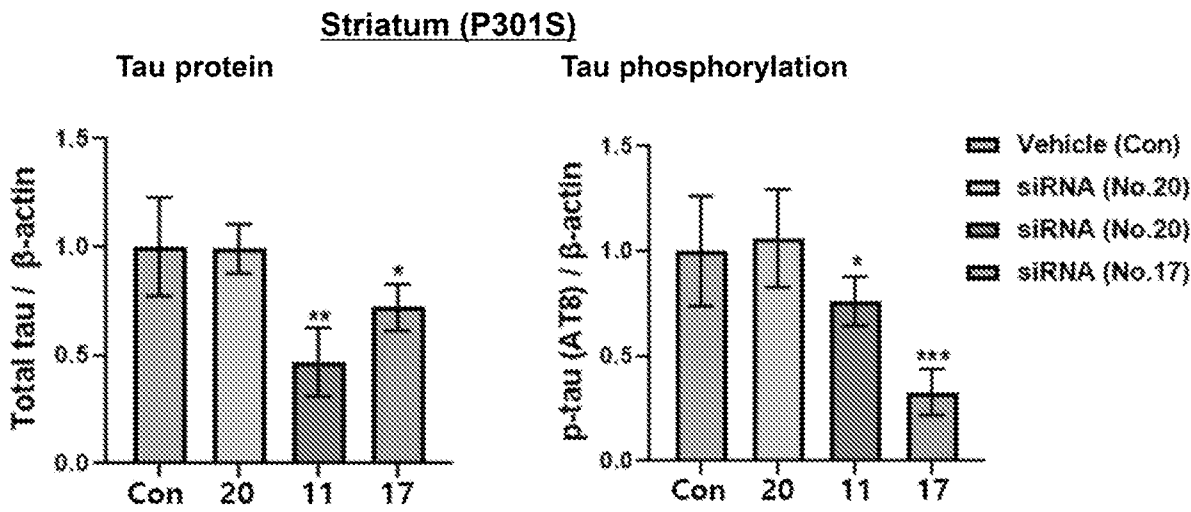


FIG. 5E

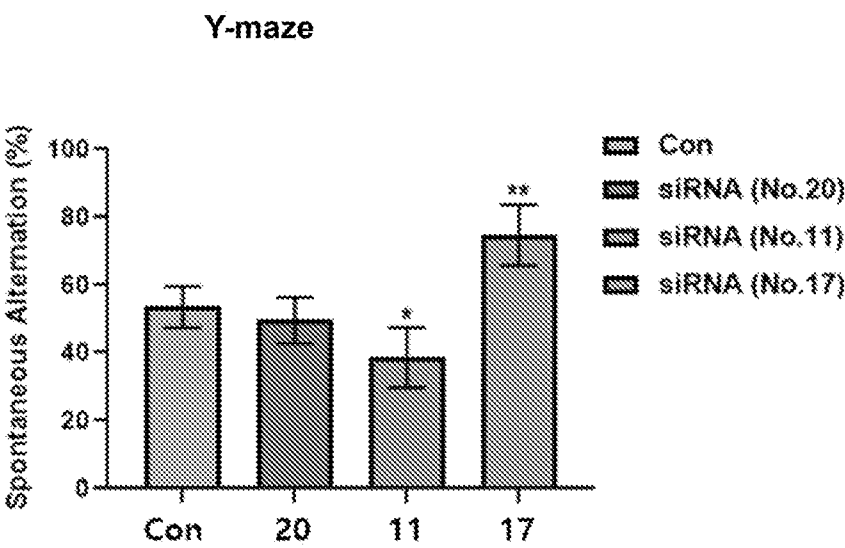


FIG. 6

BIOK-MAPT siRNA Sequences  
Sequences with knockdown effects

| #         | Sense SEQUENCE (5' --> 3') | Sequence ID # | AntiSense SEQUENCE (5' --> 3') | Sequence ID # | Target Exon |
|-----------|----------------------------|---------------|--------------------------------|---------------|-------------|
| siMAPT-1  | AACGUCCAGUCCAAGUGUGGC      | 1             | GCCACACUUGGACUGGACGTT          | 2             | 10          |
| siMAPT-2  | AGCAACGUCCAGUCCAAG         | 3             | CUUGGACUGGACGUUGCU             | 4             | 10          |
| siMAPT-3  | AAGGUGCAGAUAAUUAUAAG       | 5             | CUUAUUAUAUUCUGCACCTT           | 6             | 9~10        |
| siMAPT-4  | UGAGAACCUGAAGCACCAG        | 7             | CUGGUGCUUCAGGUUCUCA            | 8             | 9           |
| siMAPT-5  | AGCGGCUACAGCAGCCCCG        | 9             | CGGGGCGUGCUGUAGCCGCU           | 10            | 9           |
| siMAPT-6  | AAUUAUAAGAAGCUGGAUCU       | 11            | AGAUCAGCUUCUUAUUAATT           | 12            | 10          |
| siMAPT-8  | GAGCCCAAGAAGGUGGCAG        | 13            | CUGCCACCUUCUUGGGCUC            | 14            | 9           |
| siMAPT-9  | ACCCGGGAGCCCAAGAAG         | 15            | CUUCUUGGGCUCCCGGGU             | 16            | 9           |
| siMAPT-10 | AGAAAGCUGGAUCUUAGCAA       | 17            | UUGCUAAGAUCAGCUUCU             | 18            | 10          |
| siMAPT-11 | AAGGAUAAUAUCAAACACGUC      | 19            | GACGUGUUUGAUAAUUCCTT           | 20            | 10          |
| siMAPT-12 | AUAAUAUCAAACACGUCCC        | 21            | GGGACGUGUUUGAUUUUAU            | 22            | 10          |
| siMAPT-14 | AGGAGGUGGCCAGGUGGAA        | 23            | UUCCACCUGGCCACCUCCU            | 24            | 11~12       |
| siMAPT-15 | AAUAUCACCCACGUCCCUGG       | 25            | CCAGGGACGUGGGUGAUATT           | 26            | 12          |
| siMAPT-17 | UGGCCAGGUGGAAGUAAAA        | 27            | UUUUACUCCACCUGGCCA             | 28            | 12          |
| siMAPT-20 | CCAAAGCCAAGACAGACCA        | 29            | UGGUCUGUCUUGGCUUUGG            | 30            | 13          |
| siMAPT-21 | AAGCAGGGUUUGUGAUCAG        | 31            | CUGAUCACAAACCCUGCTT            | 32            | 13          |
| siMAPT-22 | CUCCGGACUUCAAAAUCAG        | 33            | CUGAUUUUGAAGUCCCGAG            | 34            | 13          |
| siMAPT-23 | AGGGCAGCCUGUGGGAGAA        | 35            | UUCUCCACAGGCUGCCCU             | 36            | 13          |
| siMAPT-3* | GGUGCAGAUAAUUAUAAG         | 64            | CUUAUUAUAUUCUGCACC             | 65            | 9~10        |

Sequences without knockdown effects

| #         | Sense SEQUENCE (5' --> 3') | Sequence ID # | AntiSense SEQUENCE (5' --> 3') | Sequence ID # | Target Exon |
|-----------|----------------------------|---------------|--------------------------------|---------------|-------------|
| siMAPT-7  | AAGCUGGAUCUUAGCAACGUC      | 37            | GACGUUGCUAAGAUCACGCTT          | 38            | 10          |
| siMAPT-13 | AGUGUGCAAUAGUCUACAA        | 39            | UUGUAGACUAUUUGCACACU           | 40            | 10~11       |
| siMAPT-16 | AAGGACAGAGUCCAGUUGAAG      | 41            | CUUCGACUGGACUCUGUCCTT          | 42            | 12          |
| siMAPT-18 | AAGAUUGAAACCCACAAGC        | 43            | GCUUGUGGGUUUCAAUCTT            | 44            | 12~13       |
| siMAPT-19 | GAAACCCACAAGCUGACCU        | 45            | AGGUCAGCUUGUGGGUUUC            | 46            | 13          |
| siMAPT-24 | AAUAUCAAAACAGUCCCGGGA      | 47            | UCCCGGGACGUGUUUGAUATT          | 48            | 10          |
| siMAPT-25 | AUCAACACGUCCCGGGAG         | 49            | CUCCCGGGACGUGUUUGAU            | 50            | 10          |
| siMAPT-26 | AACACGUCCCGGGAGGCGGCA      | 51            | UGCCGCCUCCCGGGACGUGTT          | 52            | 10          |
| siMAPT-27 | ACGUCCCGGGAGGCGGCAG        | 53            | CUGCCGCCUCCCGGGACGU            | 54            | 10          |
| siMAPT-28 | UCCCGGGAGGCGGCAGUGU        | 55            | ACACUGCCGCCUCCCGGGA            | 56            | 10          |

# FIG. 7

## MAPT mRNA Sequence

GCAGTACCGCCACCCACAGCTCCGGCACCAACAGCAGCGCCGCTGCCACCGCCACCTTCTGCGCGCCGCCACACAGCCACCTTCTC  
CTCTCCCGCTGTCTCTCCCGTCTCGCTCTGTGACTATCAGGTGAACCTTGAACCAAGGATGGCTGAGCCCGGCCAGGAGTTTGAAGT  
GATGGAAGATCAGCTGGGACGTACGGGTGGGGGACAGGAAAGATCAGGGGGGTACACCATGCACCAAGACCAAGAGGGTGACAC  
GGACCGTGGCCGTGAAGAATCTCCCTGTCAGACCCCCACTGAGGACGGATCTGAGGAACCGGGCTTGAACCTCTGATGCTAAGAGC  
ACTCCAACAGCGGAAGATGTGACAGCACCTTAGTGGATGAGGGAGCTCCCGGCAAGCAGGCTGCCGCGCAGCCCCACACGGAGATC  
CCAGAAGGAACACAGCTGAAGAAGCAGGCATTGGAGACACCCCCAGCCTGGAAGACGAAGCTGCTGGTACAGTGAACCAAGCTGC  
ATGGTCAGTAAAGCAAGACGGGACTGGAAGCGATGACAAAAAAGCCAAAGGGGGCTGATGGTAAACGAAGATCGCCACACCGCG  
GGGAGCAGCCCCCTCAGGCCAGAAGGGCCAGGCCAACGCCACCAGGATTCCAGCAAAAAACCCCGCCGCTCCAAAGACACCACCCAG  
CTCTGGTGAACCTCCAAATCAGGGGATCGCAGCGGTACAGAGCCCGGGCTCCCAAGGCACCTCCCGGCAGCCGCTCCCGCACCCCG  
TCCCTTCCACCCCAACCCCGGGAGCCCAAGAAGTGGCAGTGGTCCGTACTCCACCCAAGTCCCGCTCTTCCGCCAAGAGCCGCT  
GCAGACAGCCCCGTGCCCATGCCAGACCTGAAGAATGTCAAGTCCAAGATCGGCTCCACTGAGAACCCTGAAGCACACCGGGAGGC  
GGGAAGGTGCAGATAATTAATAAGAAGCTGGATCTTAGCAACGTCCAGTCCAAGTGTGGCTCAAAGGATAATATCAAAACACGTCCCGG  
GAGGCGGAGTGTGCAATAGTCTACAAACAGTTGACCTGAGCAAGGTGACCTCCAAGTGTGGCTCATTAGGCAACATCCATCATATA  
ACCAAGAGGTGGCCAGGTGGGAAGTAAATCTGAGAAGCTTGAATTCAGGACACAGATCCAGTCCGAAAGATGGGTCCTGGACAATATC  
ACCCACGTCCCTGGCGGAGGAAATAAAAGATTGAACCCACAAGCTGACCTTCCGCGAGAAGCCAAAGCCAAGACAGACCACGGG  
GCGGAGATCGTGTACAAAGTCCGCAAGTGGTGTCTGGGGACACGTCTCCACGGCATCTCAGCAATGTCTCTCCACCGGCAGCATCGACAT  
GGTAGACTCGCCCCAGCTCGCCACGCTAGCTGACGAGGTGTCTGCTTCCCTTCCGCAAGCAGGGTTTGTGATCAGGCCCTCGGGCGGT  
AATAATTGTGGAGAGGAGAGAATGAGAGAGTGTGAAAAAAGAAATATGACCCGCGCCCGCCCTCTGCCCCAGCTGCTCTCTG  
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GTGGAGCCACAGGCAGACGATGTCAACCTTGTGTAGTGTGACGGGGTGGGGTGGGGCGGGAGGCCACGGGGAGGCCGAGGCAG  
GGGCTGGGCAGAGGGGAGAGGACACAAGAAAGTGGGAGTGGGAGAGGAAAGCCACGTGCTGGAGAGTAGACATCCCTCTCTTGGC  
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GTGCCACCTCTGCAGGGCAGCCTGTGGGAGAAAGGACAGCGGTTAAAGAGAGAAGGCAAGCTGGCAGGAGGGTGGCAGTCTGTGGA  
TGACCTCTTAGAAAAGACTGACCTTGATGTCTTGAGAGCGCTGGCTTCTCTCCCTCCCTGCAGGGTGAAGGGCTGCTGTGAGGG  
CTTCCCTCTGCTCCACAGAAACCTGTGTTTATTTAGTGTCTGAAGTTGGAAGTGTGCTGCTATGATTTTGGCCACTTTGCAGACCTGGGACT  
TTAGGGCTAACCAAGTCTCTTTGTAAAGGACTTGTGCTCTTGGGAGACGTCCACCCGTTTCCAAAGCTTGGGCCACTGGCATCTCTGGAGT  
GTGTGGGGTCTGGGAGGCAGGTCCCGAGCCCTGTGCTTCCCAAGGCACTGCAGTCAACCCGTCTGCGCCGCTGTGCTGTTGTCTG  
CCGTGAGAGCCCAATCACTGCTATACCCCTCATCACAGCTTCAAGTGTCCGGAATTCAGCCCTCAACACCTCTCAGTAATGACC  
CTGGTGTGGTTCAGGAGGTACTACTCCATCTGAGGGTGAATTAAGGGAAGGCAAGTCCAGGCACAAAGAGTGGGACCCAGCCTC  
TCACCTCTCAGTTCACCTCATCCAACCTGGGACCTTCAACACGAATCTCATGATCTGATTCGGTTCCTCTCTCTCCCTCACAGATG  
TGAGCCAGGCCACTGCTCAGCTGTGACCTTAGGTGTCTGTGCTTGTGACATGGAGAGAGCCCTTCCCTGAGAAAGGCTGGCCCT  
TCCTGTGCTGAGCCACAGCAGCAGGTGGGTGTCTTGGTGTGACGTGTGGCACCAGGATGGAAGGGCAAGGCACCCAGGCGAGGCC  
CACAGTCCCGCTGTCCCTCACTTGCACCTTAGCTTGTAGCTGCCAACCTTCCAGACAGCCAGCCCGTGTCTCAGCTCCACATGCATAG  
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GAAAGGCTTCTCTCAGCAGCTGGGACCAACAGAGACCAGCTTCTAGCAGCTAAGGAGGCCGTTTCAAGCTGTGACGAAGGCTGAAGCA  
CAGGATTAGGACTGAAGCGATGATGTCCCTTCCCTACTTCCCTTGGGGCTCCCTGTGTGACAGGCACAGACTAGGTCTTGTGGCTGGT  
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TAGTTCATTTAAATGACTTCAGTGGTGAAGTGTCTGTTGCTATTTGCTGTGCTATGGGGGGAGGGGGAGGAATGTGTAA  
GATAGTTAAATGGGCAAGGGAGATCTGGGGTGCAGCACTTAAATGCTCGTAACCCCTTTTCATGATTTCAACCAATTTGCTAGA  
GGGAGGGAGCAGCCACGGAGTTAGAGGCCCTTGGGGTCTTCTTTTCCACTGACAGGCTTCCAGGCAGCTGGCTAGTTTCACTCCCT  
CCCAGCCAGGTGCAGGCGTAGGAATATGGACATCTGGTGTCTTGGCTGTGCTCCCTCTTTCAGGGGTCTTAAGCCACAATCATGCT  
CCCTAAGACCTTGGCAGCTTCCCTCTAAGCCGTGGCAGCTCTGTGCCACCTCTCACACTGGCTCCAGACACAGCCCTGTGCTTTGG  
AGCTGAGATCAGTCTTCCCTTCCATCTTGTTCCTCAAGTTCAGGACAGGAGTGGGGGAGGGGAGAGGTGATCAGCTGCTG  
TCCCATCTACAGACTGCAGCTTCAATAAACTTCTGATTTCTTCACTTGTGAAAGGGTTACCTTGGGCACTGGCTAGAGCCTCACC  
TCCTAATAGACTTAGCCCCATGAGTTTGCCATGTGTGAGCAGGACTATTTCTGGCACTTGCAAGTCCCATGATTTCTTCGGTAAATCTGAG  
GGTGGGGGAGGGACATGAATATCTTAGCTTAGCTTTCTGTCTGTGAATGCTATATAGTGTATTGTGTGTTTAAACAATGATTTAC  
ACTGACTGTGCTGAAGAAGTGAATTTGGAATAAAGTTATTAATGATTAATA

# FIG. 8

## MAPT Isoform mRNA Sequences

### 4R2N MAPT

ATGGCTGAGCCCCGCCAGGAGTTGGAAGTGATGGAA  
TACACGCTGGGACGTACGGGTTGGGGGACAGGAAAGATC  
AGGGGGGCTACACCATGTCACCAAGAGGGTGAC  
ACGGACGCTGGCTGAAAGAATCTCCCTGCAGACCCC  
CACTGAGGACGGATCTGAGGAACCGGCTCTGAAACCT  
CTGATGCTAAGAGCACTCCAACAGCGGAAGATGTGACA  
GCACCCCTTAGTGGATGAGGGAGCTCCCGCAAGCAGGC  
TGGCGCGCAGCCCCACACGGAGATCCAGAAAGGAACCA  
CAGCTGAAGAAGCAGGCAATTGGAGACACCCCCAGCTG  
GAAGACGAAGCTGCTGGTCACTGACCCAAAGCTCGCAT  
GGTCAGTAAAGCAAAAGCAGGGACTGGAAAGGATGAC  
AAAAAAGCCAAGGGGGCTGATGGTAAACGAAGATCGC  
CACACCGCGGGAGCAGCCCCCTCCAGGCCAGAAGGGC  
CAGGCCAACGCCACAGGATCCAGCAAAACCCCGGCC  
CGCTCCAAAGACACACCCAGCTCTGGTGAACCTCCAA  
AATCAGGGGATCGAGGGCTACAGGAGCCCGGCTCC  
CCAGGCACCTCCCGGACCGCTCCCGCACCCCGTCCCT  
TCCAAACCCACCCCGGAGGCCAAGAAGGTGGCAG  
TGGTCCGTACTCCACCAAGTCCGCGTCTTCCCGCAAGA  
GCGGCTCTGACAGAGCCCGCTGCCATGCCAGACCTG  
AAGATGTCAAGTCCAGATCGGCTCAATAGCAACCT  
GAAGCACCAGCGGGAGCGGGGAAGGTGCAGATAATTA  
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CAGTGTGCAATAGTCTACAAACCACTGTGACCTGAGCA  
AGGTGACCTCAAGTGTGGCTCAATAGGCAACATCCATC  
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GTCTCTGGACAAATATCACCCAGTCCCTGGCGGAGGAA  
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### 3R2N MAPT

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GCAGACCCCACTGAGGACGGATCTGAGGACCAACCG  
GCTCTGAAACCTCTGATGCTAAGAGCACTCCAACAG  
CGGAAGATGTGACAGCACCTTAGTGGATGAGGGAG  
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AGATCCCAAGAAAGCAACAGCTGGAAGAAGCAGGC  
ATTGGAGACACCCCAAGCTTGGAAAGCAGAGCTGCT  
GGTCACTGACCCAAAGCTGCTGCTCAGTAAAGC  
AAAGACGGGACTGGAAGCGATGACAATAAAGCCAA  
GGGGGCTGATGGTAAACCAAGATCGCCACACCGCG  
GGGAGCAGCCCCCTCCAGGCCAGAAGGGCCAGGCCA  
ACGCCACAGGAATCCAGCAAAACCCCGCGCGCTC  
CAAGACACACCCAGCTCTGGTGAACCTCCAAAT  
CAGGGGATCGCAGCGGCTACAGCAGCCCGGCTCCC  
CAGGCACCTCCCGGACGCCGTCCCGCACCCCGTCCC  
TTCCAACCCCAACCCCGGGAGGCCAAGAAGGTGG  
CAGTGGTGGTACTCCACCAAGTGGCGGTCTCTCCB  
CCAAGAGCCGCTGACAGACAGCCCCCGTCCCATC  
CAGACCTGAAGAATGTCAAGTCCAAAGATGGCTCCA  
CTGAGAACCTGAAGCACACCGCGGAGGGCGGAAG  
GTGCAAAATAGTCTACAAACCAAGTTCAGTGAAGCAAG  
GTGACCTCCAAGTGTGGCTCATTAAGGCAACATCCATC  
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GAGGAAATAAAGATGTGAACCCCAAGCTGACCT  
TCCCGGAGAACGCGCAAGGCAAGACAGACACAGGG  
GCGGAGATGCTGTACAAGTCCCGAGTGGTGTCTGGG  
GACACGTCTCCACGGCACTCAGCAATGTCTCTCCA  
CCGGCAGCATCGACATGGTAGACTCGCCCAAGCTCG  
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AGCAGGTTTGTGA

### 4R1N MAPT

ATGGCTGAGCCCCGCCAGGAGTTGGAAGTGATGGAA  
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GATCAGGGGGGCTACACCATGTCACCAAGAGCAAGAG  
GGTGACACGGAGGCTGGCTGAAAGAATCTCCCTGC  
AGACCCCACTGAGGACGGATCTGAGGAACCGGGCT  
CTGAAACCTCTGATGCTAAGAGCACTCCAACAGCGGA  
AGCTGAAGAAGCAGGCAATTGGAGACACCCCAAGCT  
GGAAAGCAGAGCTGCTGGTCACTGACCCAAAGCTCG  
CATGGTCACTGAAAGCAAGACCGGACTGGAAGCGA  
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CAAGAAGGTGGCAGTGGTCCGTACTCCACCAAGTC  
GCCGTCTTCCCGCAAGAGCGCGCTGACAGCAGCCCTC  
GTGCCATGCTCCAGACTGGAAGATGTCAAGTCCAAAG  
TGCGCTTCCACTGAGAACCTGGAAGCACCAGCGGGAG  
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ATCAAAACACGTCGCCGGAGCGGCACTGTGCAATA  
GTCTACAAACCAAGTGTGACTGAGCAAGGTGACCTCCA  
AGTGTGGCTCATTAAGGCAACATCCATCAATAACAGG  
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AGATGGAACCCACAGCTGACCTTCCCGGAGGAAGC  
CAAAAGCCAAAGACAGCACCGGGCGGAGATCGTGT  
ACAAGTCCGCAAGTGGTGTCTGGGGACAGCTTCCACG  
GCATCTCAGCAATGTCTCTCCACCGGCAGCATCGAC  
ATGGTAGACTCGCCCCAGCTGCCACGCTAGCTGAGC  
AGGTGTCTGCTCTCTTGGCCAAGCAGGTTTGTGA

### 3R1N MAPT

ATGGCTGAGCCCCGCCAGGAGTTGGAAGTGATGGAA  
GATCACGCTGGGACGTACGGGTTGGGGGACAGGAA  
AGATCAGGGGGGCTACACCATGTCACCAAGAGCAAGA  
GGGTGACACGGAGGCTGGCTGAAAGAATCTCCCTGC  
AGACCCCACTGAGGACGGATCTGAGGAACCGGGCT  
CTGAAACCTCTGATGCTAAGAGCACTCCAACAGCGGA  
AGCTGAAGAAGCAGGCAATTGGAGACACCCCAAGCT  
GGAAAGCAGAGCTGCTGGTCACTGACCCAAAGCTCG  
CATGGTCACTGAAAGCAAGACCGGACTGGAAGCGA  
TGACAAAAAAGCCAAGGGGGCTGATGGTAAACGA  
GATCGCCACACCGCGGGAGCAGCCCCCTCCAGGCCA  
GAAGGGCCAGGCCAACGCCACCAAGATTCAGCAAA  
AACCCCGCCCGCTCCAAGAGCACACCCAGCTCTGGT  
GAACCTCCAAATCAGGGGATCGCAGCGGCTACAGC  
AGCCCGGGCTCCAGAGCACTCCCGGACAGCGCTCC  
GCACCCCGTCCCTTCCAACCCCAACCCCGGAGCC  
CAAGAAGGTGGCAGTGGTCCGTACTCCACCAAGTC  
GCCGTCTTCCGCCAAGAGCGCGCTGACAGACAGCCCTC  
GTGCCATGCTCCAGACTGGAAGATGTCAAGTCCAAAG  
TGGGCTCCACTGAGAACCCTGAAGCACCAGCGGGAG  
GCGGGGAAGGTGCAAGATGTCTACAAACCAAGTGAACCT  
GAGCAAGGTGACCTCCAAGTGTGGCTCATTAAGCAAC  
ATCCATCAATAACCAAGGAGGTGGCCAGGTGGAAGTAA  
AATCTGGAAGGCTGACTTCAAGGACAGAGTCCAGTC  
GAAGATTTGGTCCCTGGACAATATCACCCAGTCTCT  
GGCGGAGGAATAAAGATTGAACCCCAAGCTG  
ACCTTCCCGGAGAACGCCAAAGCAAGACAGACCC  
GCGGGGAGAGTCTGTACAAGTCCCGAGTGGTGTCTG  
GGGACAGCTCTCCACGGGATCTCAGCAATGTCTCTC  
CACCGGACAGTCCAGATGTGATGACTCGCCCAAGCTC  
GCCACGCTAGCTGACGAAGGTGTCTGGCTCCCTGGCCA  
AGCAGGTTTGTGA

### 4R0N MAPT

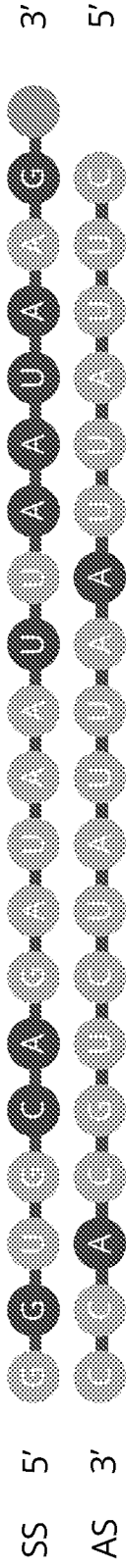
ATGGCTGAGCCCCGCCAGGAGTTGGAAGTGATGGAA  
AGATCACGCTGGGACGTACGGGTTGGGGGACAGGAA  
AAGATCAGGGGGGCTACACCATGTCACCAAGAGCAAGA  
GAGGGTGACACGGAGGCTGGCTGAAAGCTGAAG  
AAGCAGGCAATTGAGACACCCCAAGCTTGAAGAC  
GAAGCTGCTGGTCACTGACCCAAAGCTCGCATGGT  
CAGTAAAGCAAGACCGGACTGGAAAGCGATGAC  
AAAAAAGCCAAGGGGGCTGATGGTAAACGAAGAT  
CGCCACACCCCGGGAGCAGCCCTCCAGGCCAGA  
AGGGCCAGGCCAACGCCACCAAGATTCAGCAAAA  
ACCCCGCCCGCTCCAAGAGCACACCCAGCTCTGG  
TGAACCTCCAAATCAGGGGATCGCAGCGGCTTACA  
GCAGCCCGGCTCCCGAGGCACTCCCGGACGCCGT  
TCCCGCACCCCGTCCCTTCCAACCCCAACCCCGG  
GAGCCCAAGAAGTGGCAGTGGTCCGTACTCCAC  
CAAGTCCCGCTCTCCGCAAGAGCCCGCTGAGCA  
CAGGCCCGCTGCCCCATCGGACACTGGAAGATGTCT  
AAGTCCAAAGCTGGCTCCACTGAGAACCCTGAAGCA  
CCAGCCCGGAGGGGGAGGTGCGAGATATTAATA  
AGAAGCTGGATCTAGCAACGCTCAGTCCAAAGTGT  
GGCTCAAGAGATAATCAACACAGCTCCCGGAGG  
CGGCAGTGTGCAATAGTCTACAAACCAAGTTCAGC  
TGAGCAAGGTGACCTCCAAAGTGTGGCTCATTAAGC  
AACATCATATACAAACCAAGGAGGTGGCCAGGTGGA  
AGTAAATCTGAGAAGCTTGACTTCAAGGACAGAG  
TCCAGTCCGAAGATGGGTCCCTGGACAATATCACCC  
ACGTCCTTGGCGGAGGAAATAAAGATTTGAACCC  
CACAAGGTGACCTTCCCGGAGAACGCCAAAGGCCAA  
GACAGACCAAGCGGGAGAGTGTCTGACAAAGTGGC  
CAGTGGTGTCTGGGACACGCTCTCAACGGCACTCT  
AGCAATGTCTCTCCACCGGCAGCATCGACATGGTA  
GACTCGCCCGAGCTCGCCACGCTAGCTGACGAGGT  
GTCTGGCTCCCTGGCCAAGCAGGTTTGTGA

### 3R0N MAPT

ATGGCTGAGCCCCGCCAGGAGTTGGAAGTGATGGAA  
AGATCACGCTGGGACGTACGGGTTGGGGGACAGGAA  
AAGATCAGGGGGGCTACACCATGTCACCAAGAGCAAGA  
GAGGGTGACACGGAGGCTGGCTGAAAGCTGAAG  
AAGCAGGCAATTGAGACACCCCAAGCTTGAAGAC  
GAAGCTGCTGGTCACTGACCCAAAGCTCGCATGGT  
CAGTAAAGCAAGACCGGACTGGAAGCGATGAC  
AAAAAAGCCAAGGGGGCTGATGGTAAACGAAGAT  
CGCCACACCCCGGGAGCAGCCCCCTCCAGGCCAGA  
AGGGCCAGGCCAACGCCACCAAGATTCAGCAAAA  
ACCCCGCCCGCTCCAAGAGCACACCCAGCTCTGG  
TGAACCTCCAAATCAGGGGATCGCAGCGGCTTACA  
GCAGCCCGGCTCCCGAGGCACTCCCGGACGCCGT  
TCCCGCACCCCGTCCCTTCCAACCCCAACCCCGG  
GAGCCCAAGAAGGTGGCAGTGGTCCGTACTCCAC  
CAAGTCCCGCTCTCCGCAAGAGCGGCTGAGCA  
CAGCCCGGCTGCCCCATGCCAGACTGGAAGATGTCT  
AAGTCCAAGATGGCTCCACTGAGAACCCTGAAGCA  
CCAGCCCGGAGGGGGAGGTGCAAGATGCTTACAA  
AACCAAGTGTGACTTGAAGCAAGGTGACCTCAAGTGT  
GGCTCATTAAGGCAACATCTCATATAAAGCAGGAGGT  
GGCCAGGTGGAAGTAAATCTGAGAAGCTTGACTT  
CAAGGACAGAGTCCAGTCCGAAGATTTGGTCCCTGG  
ACAATATCACCCAGCTCCCTGGCGGAGGAAATAA  
AAGATGAAACCCCAAGCTGACCTTCCCGGAGAA  
CGCCAAAGCCAGACAGACCCAGGGCGGAGATCT  
GTGTACAAGTGGTGTCTGAGGAGTGTCTGAGGACAGCT  
TCCACGGCACTCAGCAATGTCTCTCCACCGGCAG  
CATGCAAGTGTGAGACTGCCCCAGCTCGCCACGCT  
AGCTGACGAGGTGTCTGGCTCCCTGGCCAAGCAGG  
GTTTGTGA

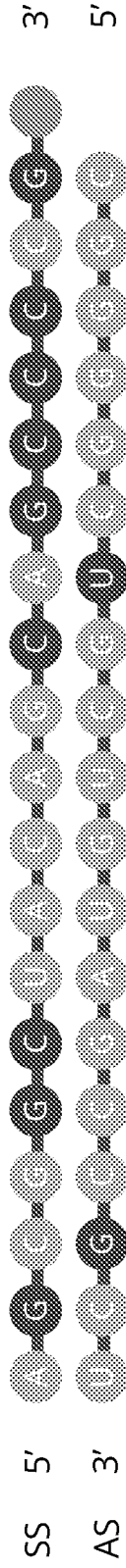
**FIG. 9A**

#3\*\_M1/M1  
siMAPT-3\*-On\_chol



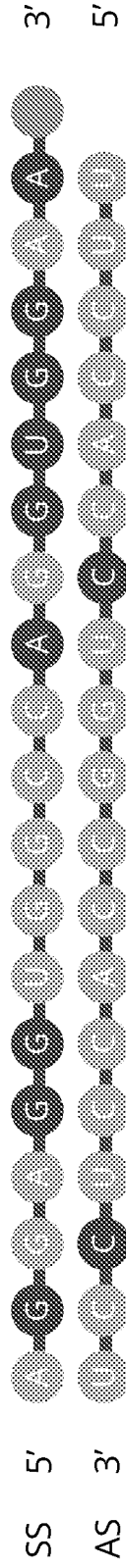
**FIG. 9B**

#5\_M2/M2  
siMAPT-5-On\_chol



**FIG. 9C**

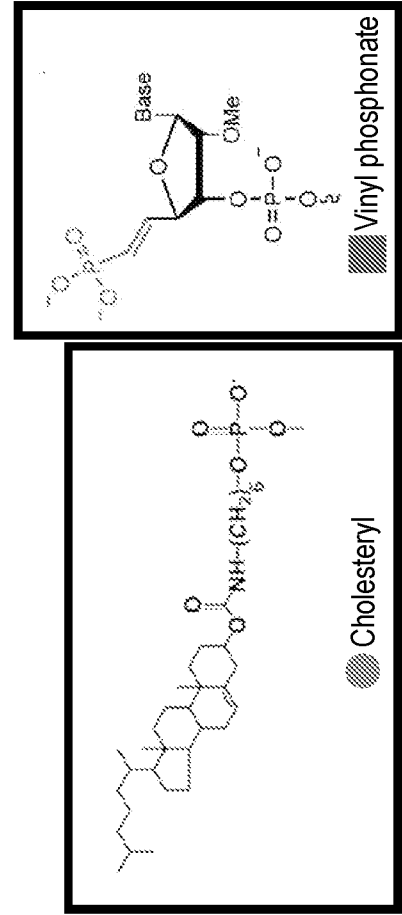
#14\_M3/M3  
siMAPT-14-On\_chol



\*  Phosphorothioate  Phosphodiester

2025

RNA 2'-F 2'-OMe



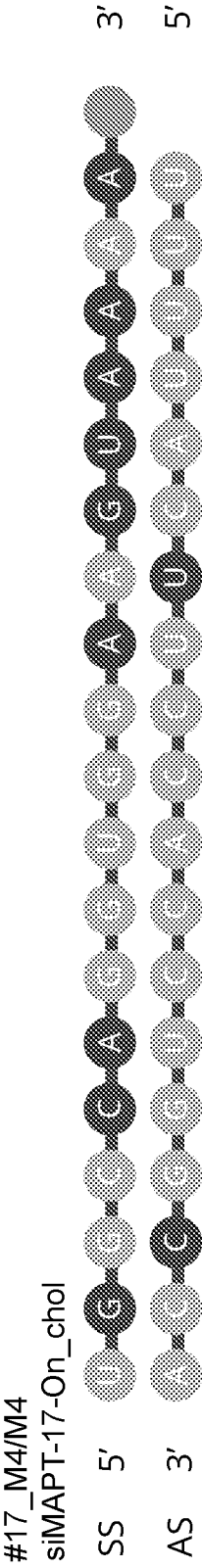


FIG. 9D

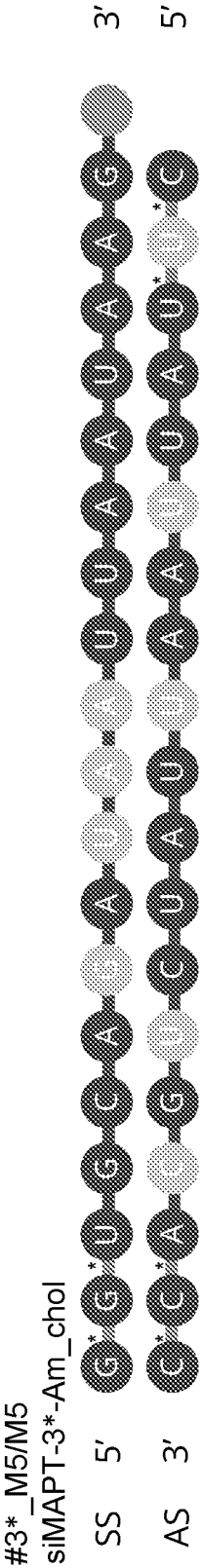


FIG. 9E

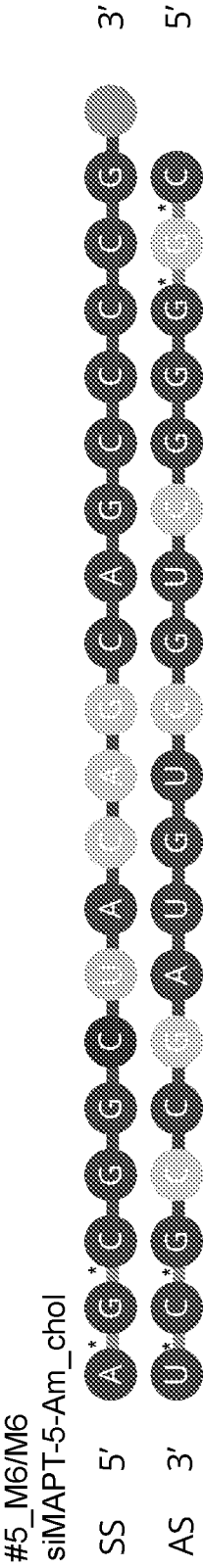
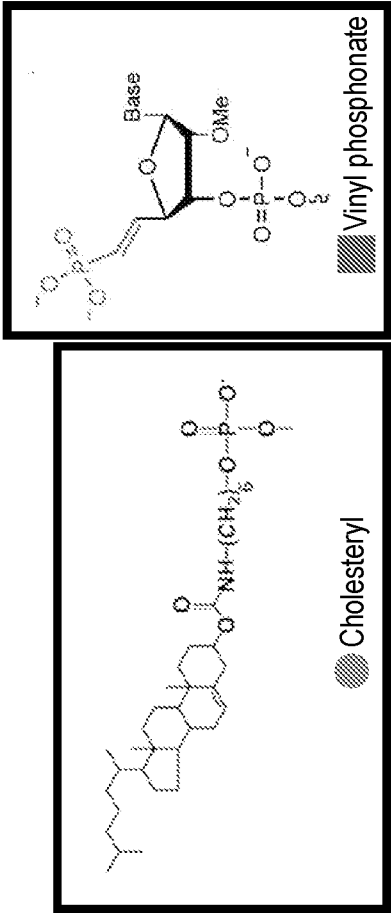


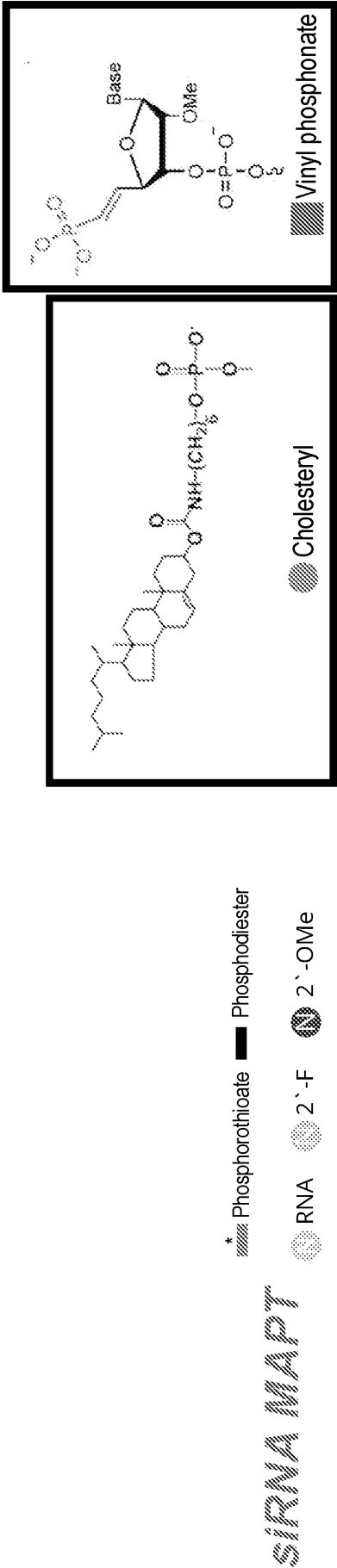
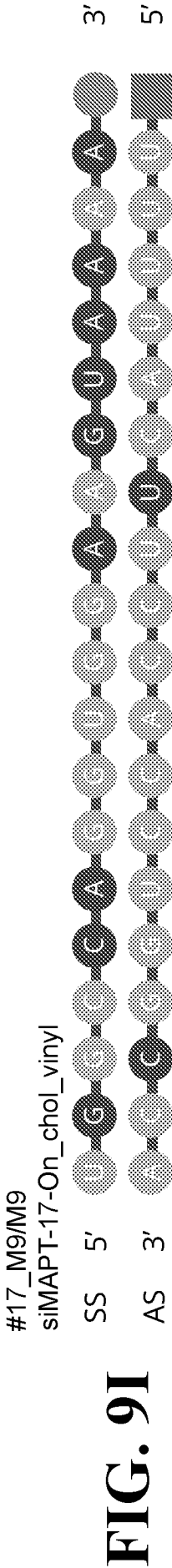
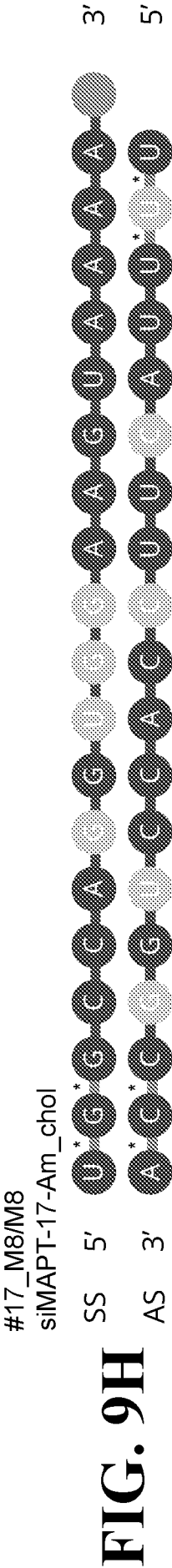
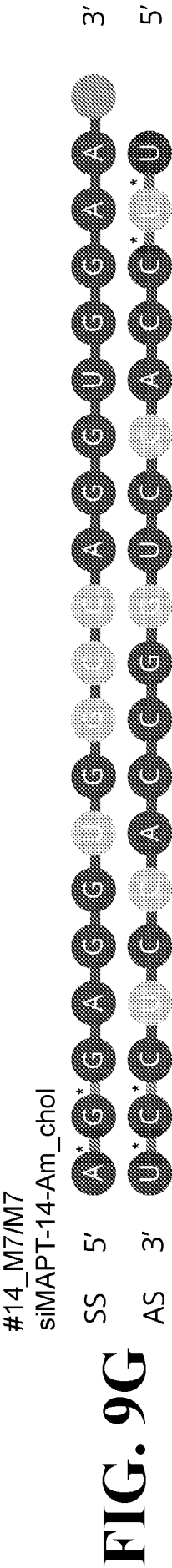
FIG. 9F

**siRNA MAPT**

\* Phosphorothioate    Phosphodiester

RNA    2'-F    2'-OMe





*mTau MAPT expression in sub-brain region of C57BL/6N Mice (SINNA #1)*

All data are mean  $\pm$  SEM. \*\*\*\*P < 0.0001 compared to the WT (Vehicle) group. One-way ANOVA and post-hoc tukey's test.

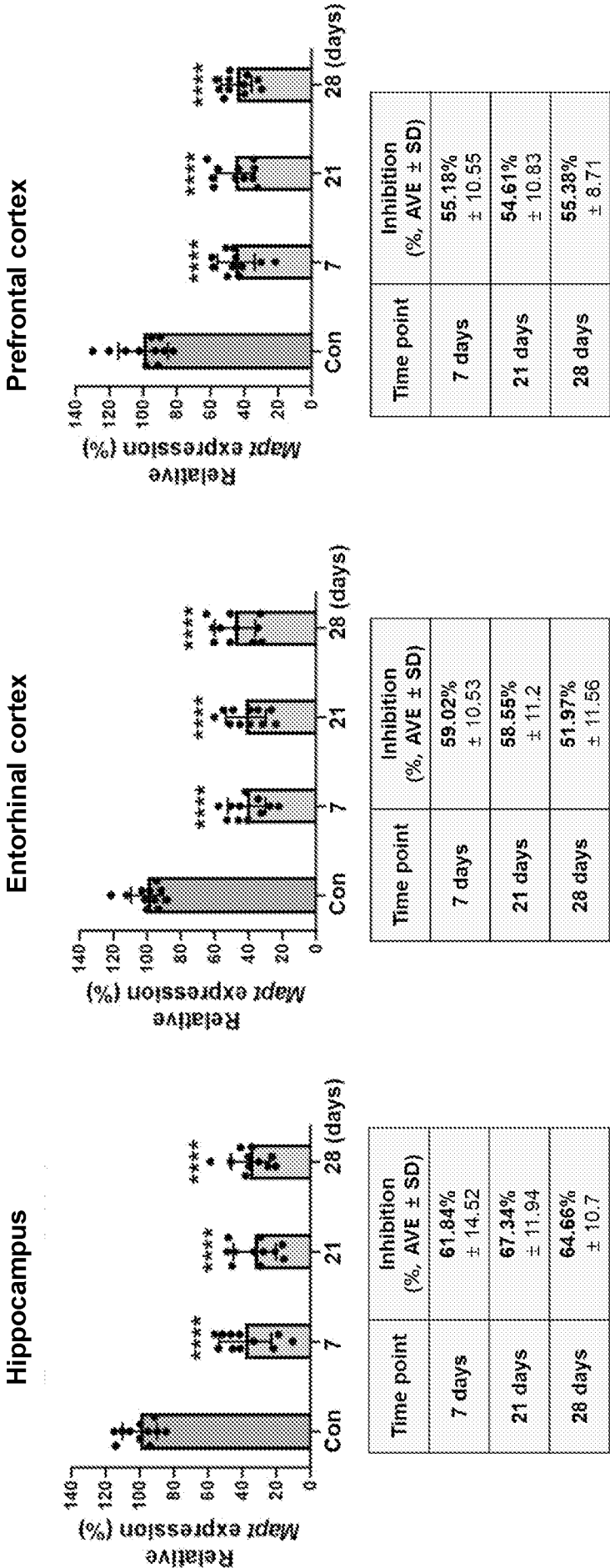


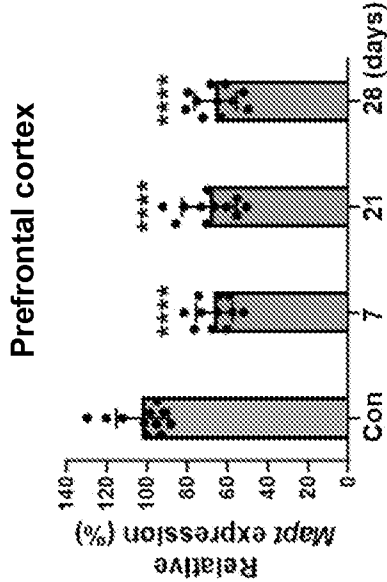
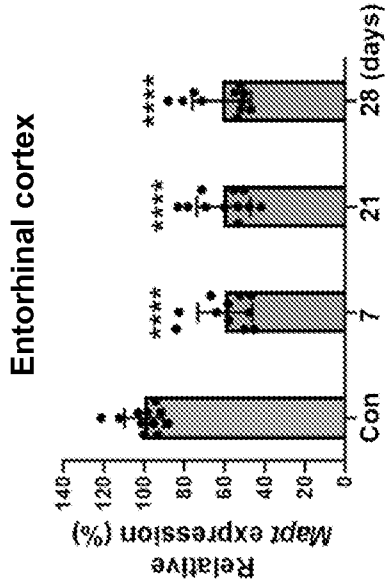
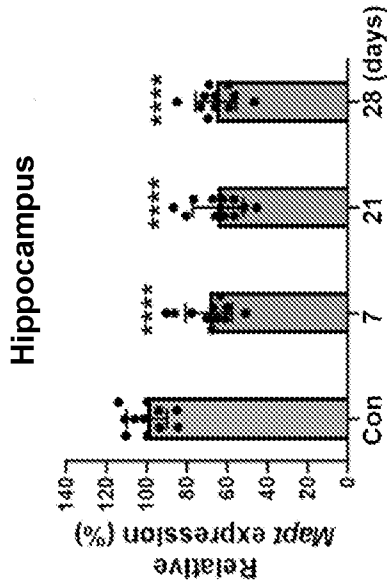
FIG. 10A

FIG. 10B

FIG. 10C

***mTau MAPT expression in sub-brain region of C57BL/6N Mice (siRNA #17)***

All data are mean  $\pm$  SEM. \*\*\*\*P < 0.0001 compared to the WT (Vehicle) group. One-way ANOVA and post-hoc tukey's test.



| Time point | Inhibition<br>(%, AVE $\pm$ SD) |
|------------|---------------------------------|
| 7 days     | 30.87%<br>$\pm$ 11.15           |
| 21 days    | 35.39%<br>$\pm$ 12.08           |
| 28 days    | 34.39%<br>$\pm$ 9.66            |

| Time point | Inhibition<br>(%, AVE $\pm$ SD) |
|------------|---------------------------------|
| 7 days     | 40.36%<br>$\pm$ 13.01           |
| 21 days    | 39.6%<br>$\pm$ 12.68            |
| 28 days    | 38.54%<br>$\pm$ 13.84           |

| Time point | Inhibition<br>(%, AVE $\pm$ SD) |
|------------|---------------------------------|
| 7 days     | 33.44%<br>$\pm$ 8.62            |
| 21 days    | 30.82%<br>$\pm$ 12.81           |
| 28 days    | 34.09%<br>$\pm$ 9.97            |

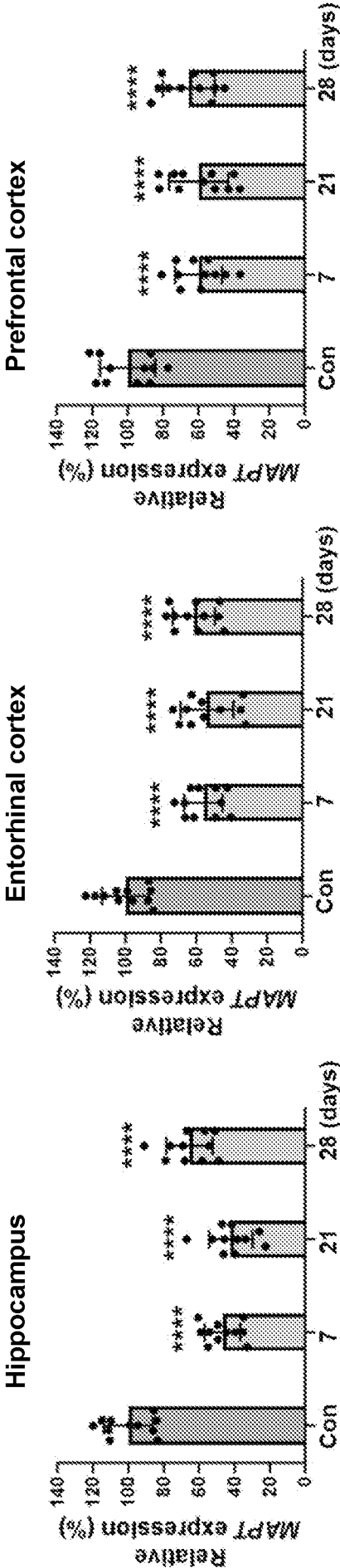
**FIG. 10D**

**FIG. 10E**

**FIG. 10F**

**huTau MAPT expression in sub-brain region of PS19 Mice (SIN#1)**

All data are mean ± SEM. \*\*\*\*P < 0.0001 compared to the PS19 (Vehicle) group. One-way ANOVA and post-hoc tukey's test.



| Time point | Inhibition (%<br>, AVE ± SD) |
|------------|------------------------------|
| 7 days     | 40.06%<br>± 12.62            |
| 21 days    | 40.1%<br>± 15.85             |
| 28 days    | 34.55%<br>± 14.01            |

FIG. 11A

| Time point | Inhibition (%<br>, AVE ± SD) |
|------------|------------------------------|
| 7 days     | 53.15%<br>± 9.54             |
| 21 days    | 57.99%<br>± 11.7             |
| 28 days    | 34.57%<br>± 12.48            |

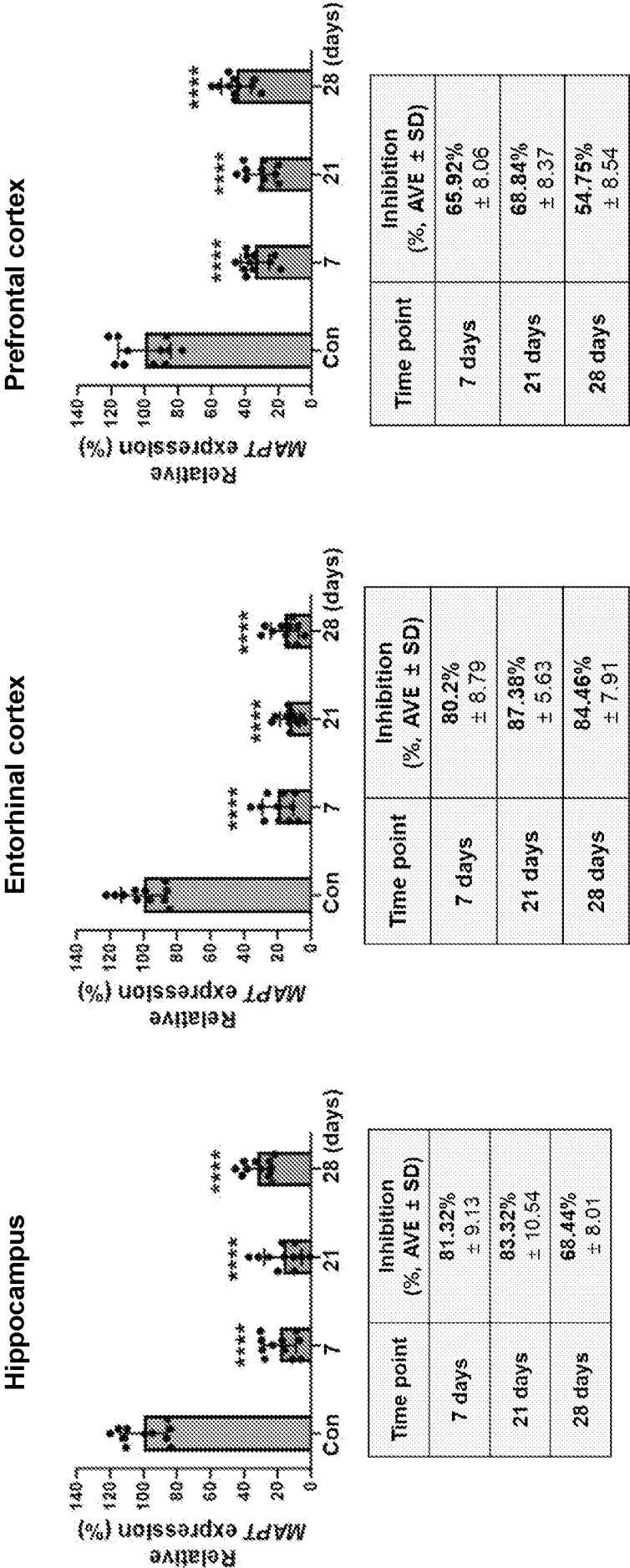
FIG. 11B

| Time point | Inhibition (%<br>, AVE ± SD) |
|------------|------------------------------|
| 7 days     | 44.09%<br>± 10.36            |
| 21 days    | 46.05%<br>± 14.25            |
| 28 days    | 38.6%<br>± 11.39             |

FIG. 11C

**huTau MAPT expression in sub-brain region of PS19 Mice (*siRNA* #17)**

All data are mean  $\pm$  SEM. \*\*\*\*P < 0.0001 compared to the PS19 (Vehicle) group. One-way ANOVA and post-hoc tukey's test.

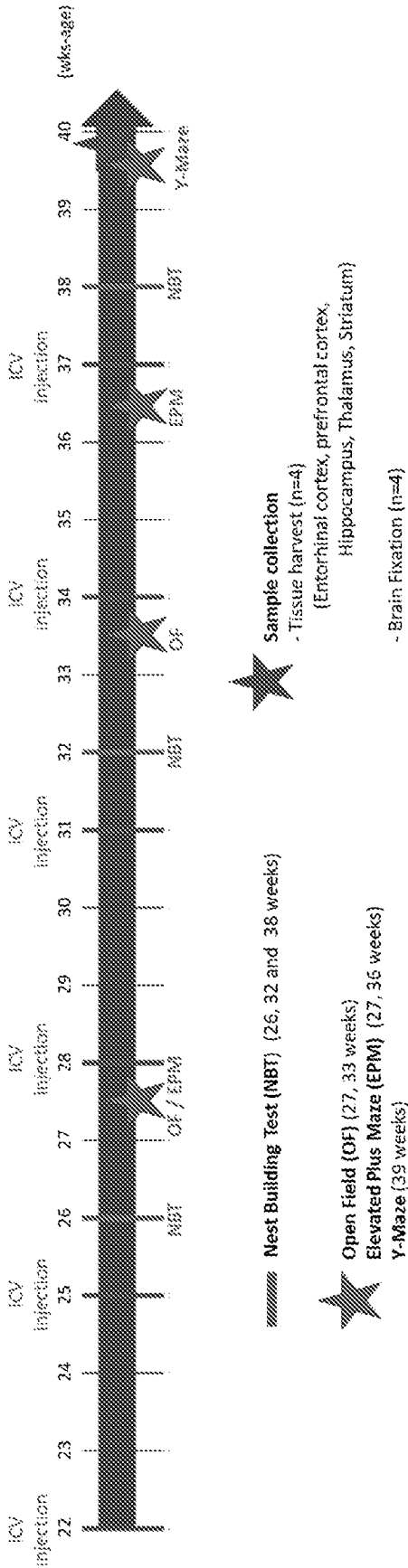


**FIG. 11D**

**FIG. 11E**

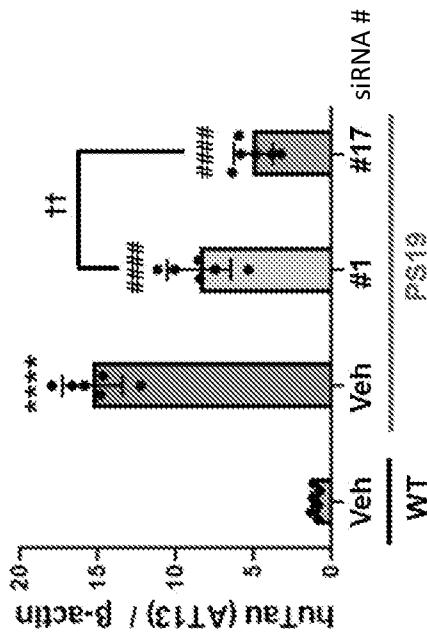
**FIG. 11F**

**Schematic illustration of the experimental schedule for BDDS-MAPT ASO efficacy test in PS19 mice**



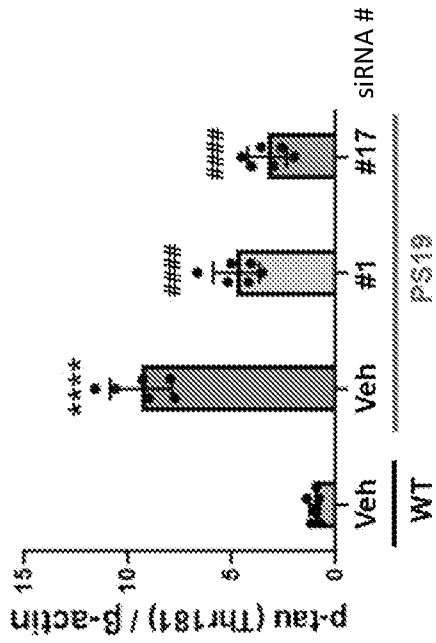
**FIG. 12A**

### Human Tau (Tau13)



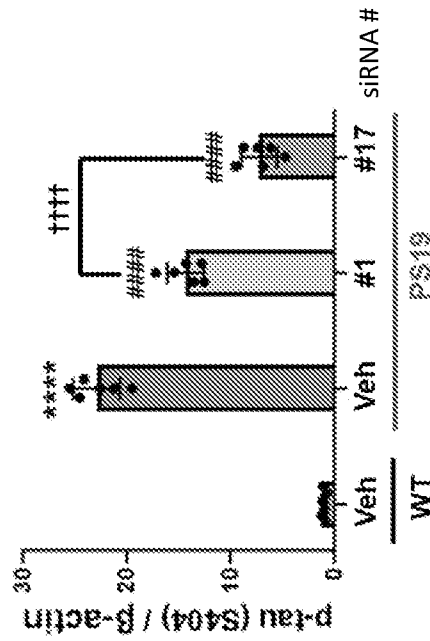
**FIG. 12B**

**P-Tau (Thr 181)**



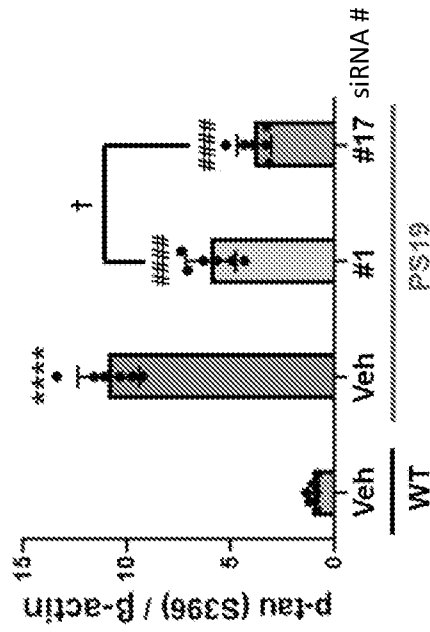
**FIG. 12C**

**P-Tau (Ser 404)**



**FIG. 12D**

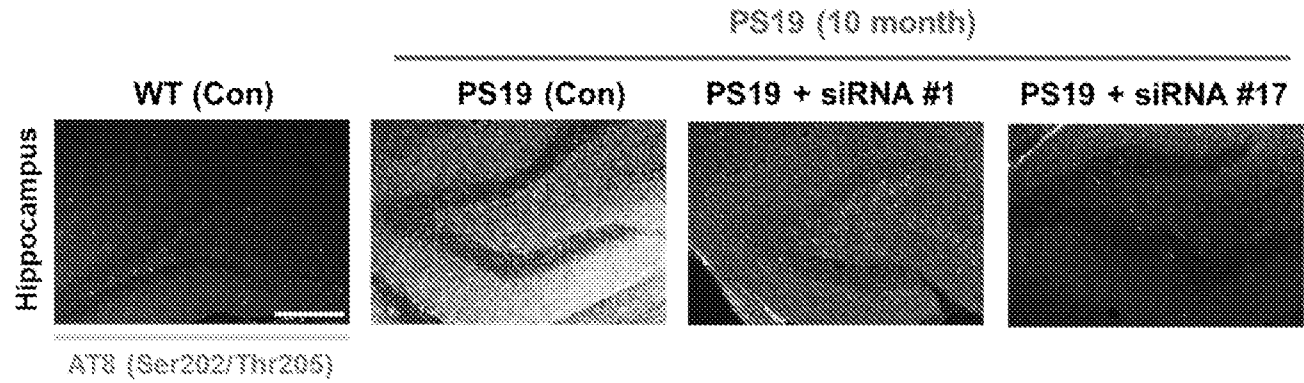
**P-Tau (Ser 396)**



**FIG. 12E**

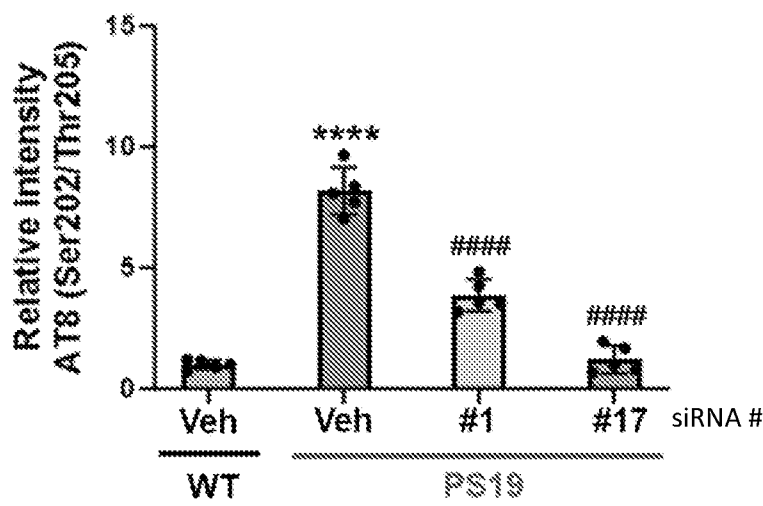
All data are mean  $\pm$  SEM. \*\*\*\*p < 0.0001 compared to the WT (Vehicle) group. ###p < 0.0001 compared to the PS19 (Vehicle) group. +p < 0.05, ++p < 0.01 and +++p < 0.0001 for indicated comparisons. One-way ANOVA and post-hoc tukey's test.

***Immunohistochemistry in hippocampus obtained from PS19 mice***



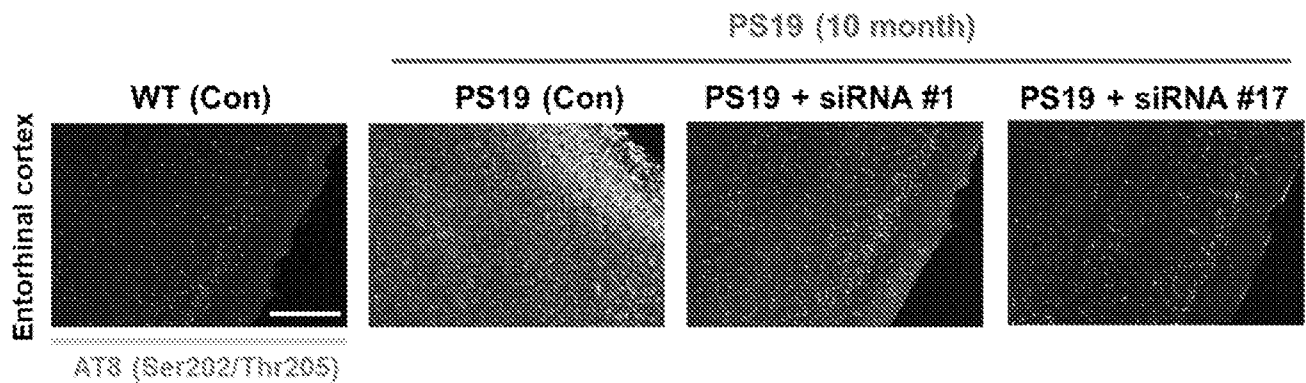
All data are mean  $\pm$  SEM. \*\*P < 0.01 and \*\*\*\*P < 0.0001 compared to the WT (Vehicle) group. ####P < 0.0001 compared to the PS19 (Vehicle) group; One-way ANOVA and post-hoc tukey's test.

**FIG. 13A**



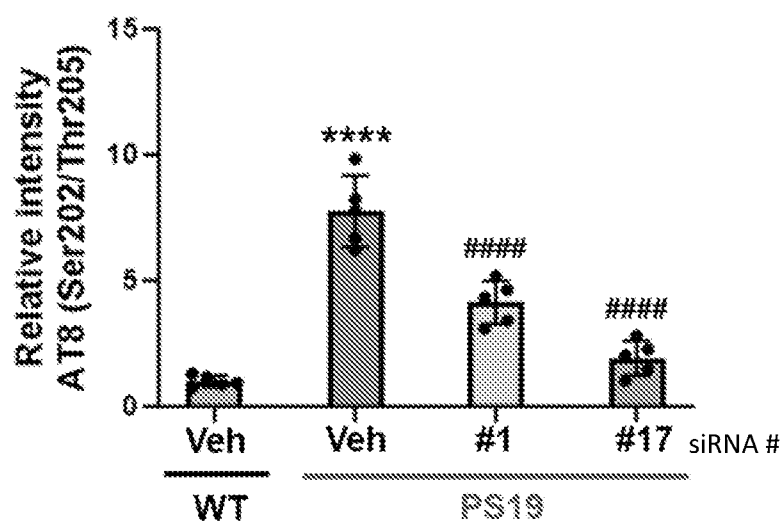
**FIG. 13B**

## ***Immunohistochemistry in Entorhinal obtained from PS19 mice***



All data are mean  $\pm$  SEM. \*\* $P < 0.01$  and \*\*\*\* $P < 0.0001$  compared to the WT (Vehicle) group. #### $P < 0.0001$  compared to the PS19 (Vehicle) group; One-way ANOVA and post-hoc tukey's test.

**FIG. 13C**



**FIG. 13D**

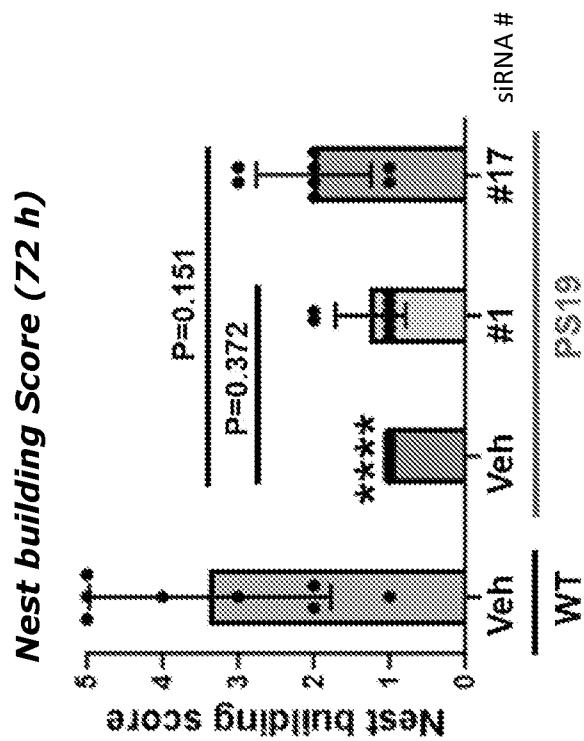
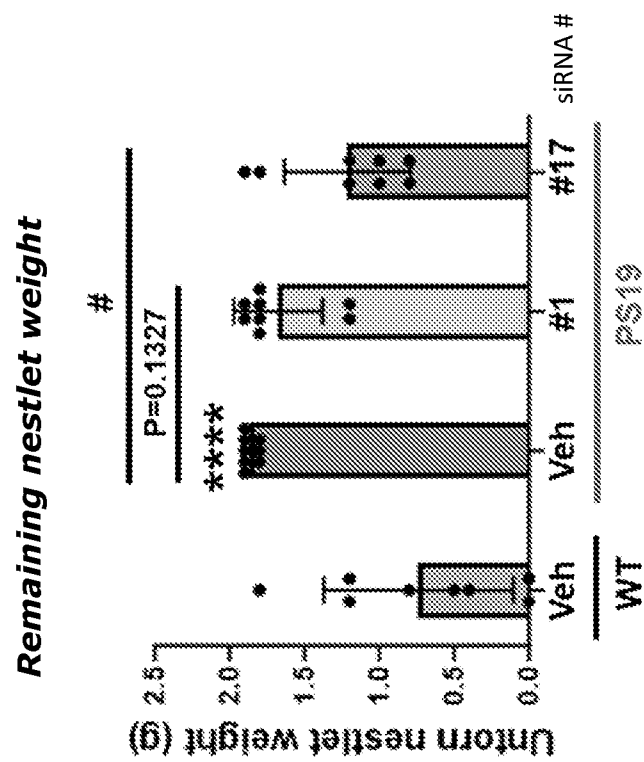


FIG. 14A

All data are mean  $\pm$  SEM. \*\* $P < 0.01$  and \*\*\*\* $P < 0.0001$  compared to the WT (Vehicle) group. #  $P < 0.05$  and ### $P < 0.0001$  compared to the PS19 (Vehicle) group; One-way ANOVA and post-hoc tukey's test.



**FIG. 14B**

All data are mean  $\pm$  SEM. \*\*P < 0.01 and \*\*\*\*P < 0.0001 compared to the WT (Vehicle) group. #P < 0.05 and ###P < 0.0001 compared to the PS19 (Vehicle) group; One-way ANOVA and post-hoc tukey's test.

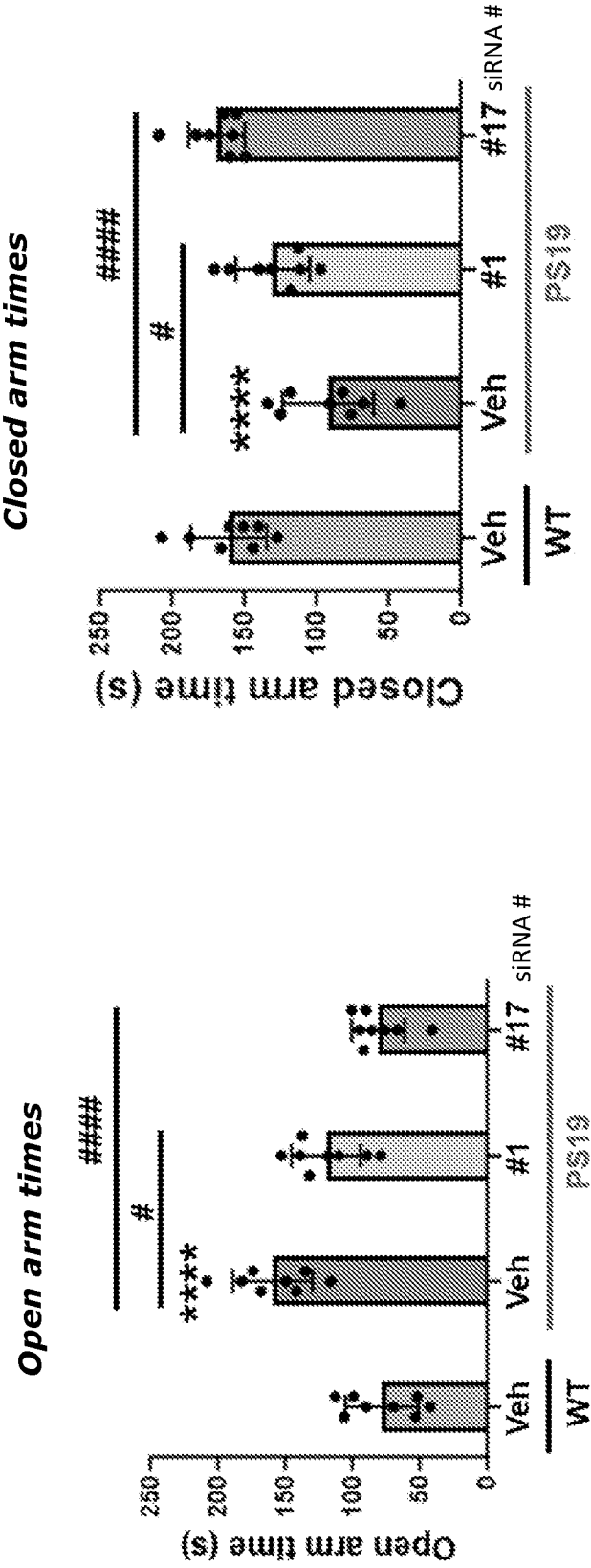


FIG. 14C

FIG. 14D

All data are mean  $\pm$  SEM. \*\* $P < 0.01$  and \*\*\*\* $P < 0.0001$  compared to the WT (Vehicle) group. #  $P < 0.05$  and ###  $P < 0.0001$  compared to the PS19 (Vehicle) group; One-way ANOVA and post-hoc tukey's test.

## Open field test (33 weeks)

### Dysregulated hyperactive phenotype:

Increase of locomotor activity, stereotypic movements and vertical exploration

### Ambulatory distance and resting time (hyperactivity)

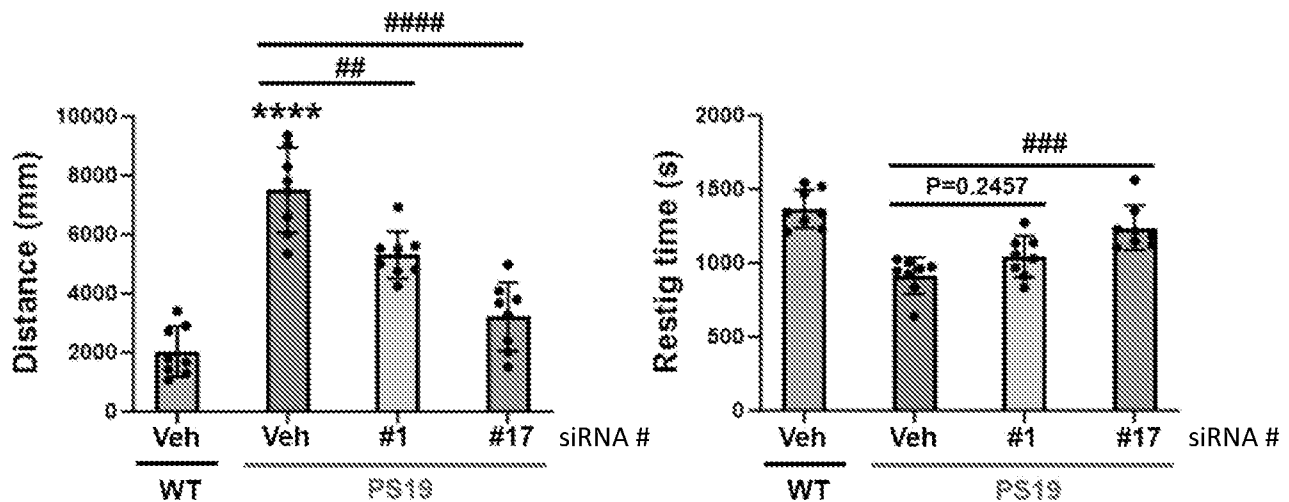


FIG. 15A

### Mania-like rearing behavior (Vertical activity)

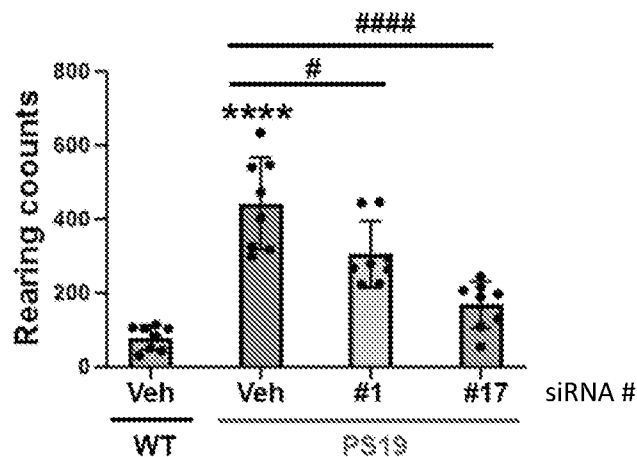
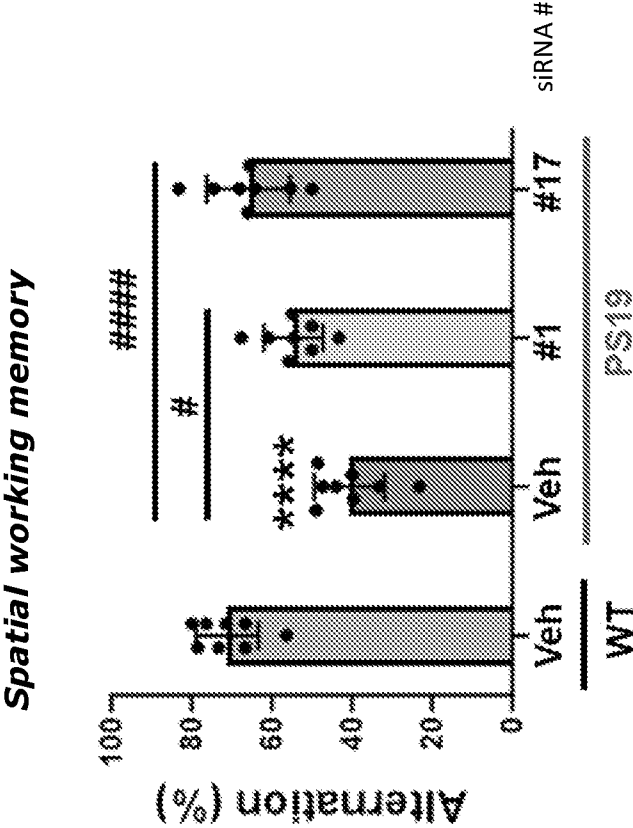


FIG. 15B

All data are mean  $\pm$  SEM. \*\* $P < 0.01$  and \*\*\*\* $P < 0.0001$  compared to the WT (Vehicle) group. # $P < 0.05$ , ## $P < 0.01$ , ### $P < 0.001$  and #### $P < 0.0001$  compared to the PS19 (Vehicle) group; One-way ANOVA and post-hoc tukey's test.



**FIG. 15C**

All data are mean  $\pm$  SEM. \*\* $P < 0.01$  and \*\*\*\* $P < 0.0001$  compared to the WT (Vehicle) group. # $P < 0.05$ , ## $P < 0.01$ , ### $P < 0.001$  and #### $P < 0.0001$  compared to the PS19 (Vehicle) group; One-way ANOVA and post-hoc tukey's test.

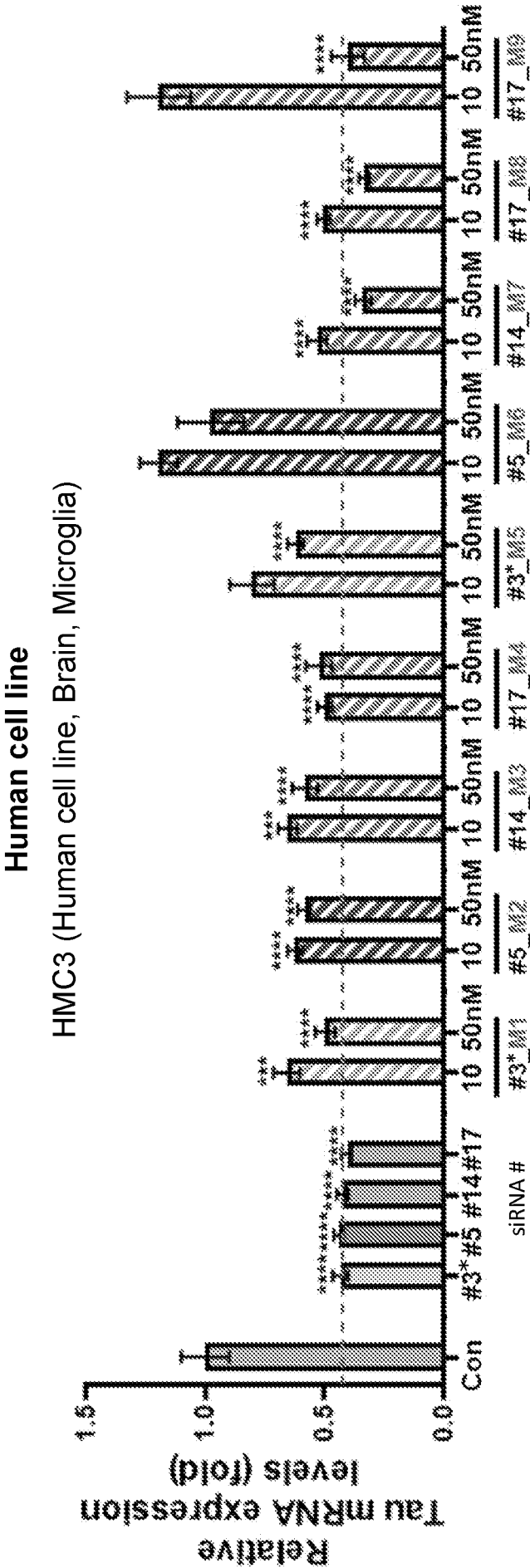


FIG. 16

All data are mean  $\pm$  SEM. \*\* $p < 0.01$ , \*\*\* $p < 0.001$  and \*\*\*\* $p < 0.0001$  compared to the Control (Con) group. One-way ANOVA and post-hoc tukey's test.