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MODULATING TAU EXPRESSION**(71) Applicant: **Ionis Pharmaceuticals, Inc.**, Carlsbad,
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C12N 2310/31 (2013.01); **C12N 2310/32**
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(57)

ABSTRACT

Disclosed are methods for modulating splicing of Tau mRNA in an animal with Tau antisense compounds. Also disclosed herein are methods for reducing expression of Tau mRNA and protein in an animal with Tau antisense compounds. Such compounds and methods are useful to treat, prevent, or ameliorate neurodegenerative diseases in an individual in need thereof. Examples of neurodegenerative diseases that can be treated, prevented, and ameliorated with the administration Tau antisense oligonucleotides include Alzheimer's Disease, Frontotemporal Dementia (FTD), FTDP-17, Progressive Supranuclear Palsy, Chronic Traumatic Encephalopathy, Epilepsy, and Dravet's Syndrome.

Specification includes a Sequence Listing.

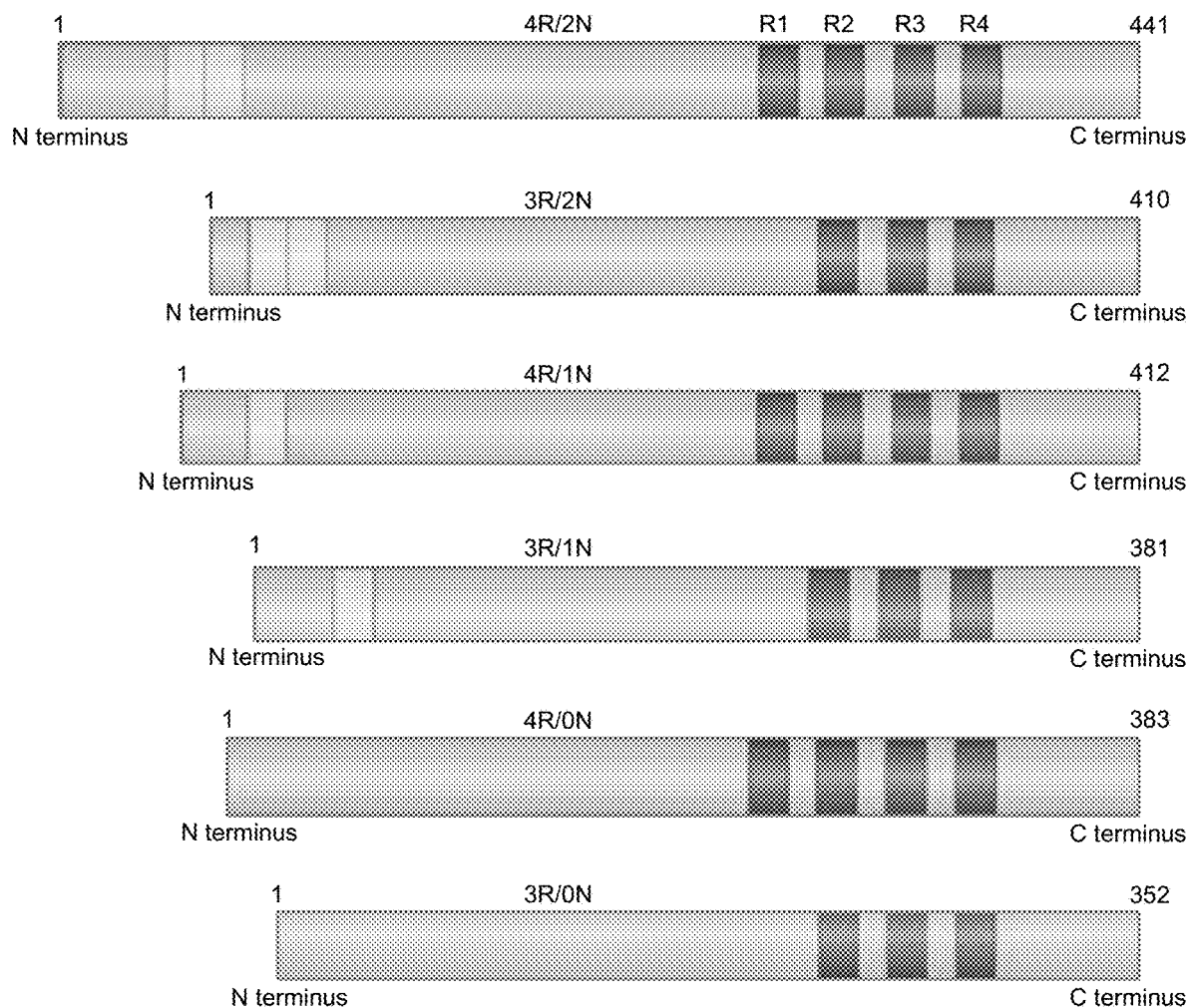


FIG. 1

COMPOSITIONS AND METHODS FOR MODULATING TAU EXPRESSION

SEQUENCE LISTING

[0001] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0220USC2SEQ_ST25.txt created Sep. 21, 2021, which is approximately 228 KB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

BACKGROUND

1. Field

[0002] Disclosed herein are compositions and methods related to the fields of antisense compounds biochemistry, molecular biology, and medicine. Embodiments described herein relate to compounds, compositions, and methods for treating, preventing, or ameliorating neurodegenerative diseases, including tauopathies, Alzheimer's Disease, Frontotemporal Dementia (FTD), FTDP-17, Progressive Supranuclear Palsy (PSP), Chronic Traumatic Encephalopathy (CTE), Corticobasal Ganglionic Degeneration (CBD), Epilepsy, and Dravet's Syndrome by inhibiting expression of Tau or modulating the splicing of Tau in a cell and/or in an animal.

2. Description

[0003] The primary function of Tau is to bind to and stabilize microtubules, which are important structural components of the cytoskeleton involved in mitosis, cytokinesis, and vesicular transport. Tau is found in multiple tissues, but is particularly abundant in axons of neurons. In humans, there are six isoforms of Tau that are generated by alternative splicing of exons 2, 3, and 10. Splicing of exons 2 and 3 at the N-terminus of the protein leads to inclusion of zero, one, or two 29 amino acid acidic domains and is termed 0N, 1N, or 2N Tau respectively. The influence of these domains on Tau function is not fully clear, though may play a role in interactions with the plasma membrane. Inclusion of exon 10 at the C-terminus leads to inclusion of the microtubule binding domain encoded by exon 10. Since there are 3 microtubule binding domains elsewhere in Tau, this Tau isoform (with exon 10 included) is termed 4R Tau, where 'R' refers to the number of repeats of microtubule binding domains. Tau without exon 10 is termed 3R Tau. Since more microtubule binding domains (4R compared with 3R) increases the binding to microtubules, 4R Tau presumably significantly increases microtubule binding and assembly. The ratio of 3R/4R Tau is developmentally regulated, with fetal tissues expressing exclusively 3R Tau and adult human tissues expressing approximately equal levels of 3R/4R Tau. Deviations from the normal ratio of 3R/4R Tau are characteristic of neurodegenerative FTD Tauopathies. It is not known how changing the 3R/4R Tau ratio at a later stage in the adult animal will affect Tau pathogenesis.

[0004] Serine-threonine directed phosphorylation regulates the microtubule binding ability of Tau. Hyperphosphorylation promotes detachment of Tau from microtubules. Other post translational modifications of Tau have been described; however the significance of these is unclear. Phosphorylation of Tau is also developmentally regulated

with higher phosphorylation in fetal tissues and much lower phosphorylation in the adult. One characteristic of neurodegenerative disorders is aberrantly increased Tau phosphorylation.

[0005] The microtubule network is involved in many important processes within the cell including structural integrity needed for maintaining morphology of cells and operating transport machinery. Since binding of Tau to microtubules stabilizes microtubules, Tau is likely to be a key mediator of some of these processes and disruption of normal Tau in neurodegenerative diseases may disrupt some of these key cellular processes.

[0006] One of the early indicators that Tau may be important in neurodegenerative syndromes was the recognition that Tau is a key component of neurofibrillary inclusions in Alzheimer's disease. In fact, neurofibrillary inclusions are aggregates of hyperphosphorylated Tau protein. Along with amyloid beta containing plaques, neurofibrillary inclusions are a hallmark of Alzheimer's disease and correlate significantly with cognitive impairment. 95% of Tau accumulations in AD are found in neuronal processes and is termed neuritic dystrophy. The process(es) whereby this microtubule associated protein becomes disengaged from microtubules and forms accumulations of proteins and how this relates to neuronal toxicity is not well understood.

[0007] Neuronal Tau inclusions are a pathological characteristic of not only Alzheimer's disease, but also a subset of Frontotemporal dementia (FTD), PSP, and CBD. The link between Tau and neurodegeneration was solidified by the discovery that mutations in the Tau gene cause a subset of FTD. These genetic data have also highlighted the importance of the 3R:4R ratio of Tau. Many of the Tau mutations that cause FTD lead to a change in Tau splicing which leads to preferential inclusion of exon 10, and thus to increased 4R Tau. The overall Tau levels are normal. Whether the Tau isoform change or the amino acid change or both cause neurodegeneration remains unknown. Recent data suggest that PSP may also be associated with an increased 4R:3R Tau ratio and thus may be amenable to a similar splicing strategy.

[0008] To help understand the influence of Tau ratios on neurodegeneration, a mouse model based on one of the splicing Tau mutations (N279K) has been generated using a minigene that includes the Tau promoter and the flanking intronic sequences of exon 10. As in humans, these mice demonstrate increased levels of 4R Tau compared with transgenics expressing WT Tau and develop behavioral and motor abnormalities as well as accumulations of aggregated Tau in the brain and spinal cord.

[0009] The protein "Tau" has been associated with multiple diseases of the brain including Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal ganglionic degeneration, dementia pugilistica, parkinsonism linked to chromosome, LYTIC-BODIG disease, tangle-predominant dementia, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, Pick's disease, argyrophilic grain disease, corticobasal degeneration or frontotemporal lobar degeneration and others. Tau-associated disorders such as AD are the most common cause of dementia in the elderly. AD affects an estimated 15 million people worldwide and 40% of the population above 85 years of age. AD is

characterized by two pathological hallmarks: Tau neurofibrillary inclusions (NFT) and amyloid- β (A β) plaques.

[0010] In seizure disorders, the brain's electrical activity is periodically disturbed, resulting in some degree of temporary brain dysfunction. Normal brain function requires an orderly, organized, coordinated discharge of electrical impulses. Electrical impulses enable the brain to communicate with the spinal cord, nerves, and muscles as well as within itself. Seizures may result when the brain's electrical activity is disrupted. There are two basic types of seizures; epileptic and nonepileptic. Epileptic seizures have no apparent cause or trigger and occur repeatedly. Nonepileptic seizures are triggered or provoked by a disorder or another condition that irritates the brain. Certain mental disorders can cause seizure symptoms referred to as psychogenic nonepileptic seizures.

[0011] Alzheimer's Disease (AD) is known to be a clinical risk factor for late onset seizures. Multiple AD mouse models recapitulate this increased seizure susceptibility. Within the last 5 years, many of these AD models have been studied in the setting of mouse tau knockout (tau-/-). Increased seizure susceptibility was ameliorated in these amyloid-depositing tau knockout lines. Further, tau-/- alone interestingly appeared to be protective against chemically induced seizures.

[0012] Anticonvulsants represent the common treatment regime for seizures. However, anticonvulsants are ineffective in a significant percent of people with a seizure disorder and for these individuals, surgery is the only option. Amidst the lack of available treatments for seizure disorders and neurodegenerative diseases, certain methods of the present embodiments provide methods for treating, preventing or ameliorating a seizure disorder and neurodegenerative diseases by inhibiting expression of Tau or modulating the splicing of Tau in an animal.

SUMMARY

[0013] Provided herein are methods for modulating splicing of Tau mRNA in cells, tissues, and animals. Also provided herein are methods for modulating the expression product of a Tau mRNA in cells, tissues, and animals.

[0014] In certain embodiments, modulation can occur in a cell or tissue. In certain embodiments, the cell or tissue is in an animal. In certain embodiments, the animal is human. In certain embodiments, Tau mRNA levels are reduced. In certain embodiments, Tau protein levels are reduced. In certain embodiments, splicing of Tau mRNA is modulated. In certain embodiments, the expression product of a Tau mRNA is modulated. In certain embodiments, exclusion of Tau exon 10 is promoted. In certain embodiments, expression of the 4R isoform of Tau RNA or protein is reduced. In certain embodiments, expression of the 3R isoform of Tau RNA or protein is increased. In certain embodiments, expression of the 4R isoform of Tau RNA or protein is reduced and expression of the 3R isoform of Tau RNA or protein is increased. In certain embodiments, hyperphosphorylated Tau is reduced. Such reduction and modulation can occur in a time-dependent manner or in a dose-dependent manner.

[0015] Several embodiments are drawn to methods of reducing or decreasing one or more symptoms of a tau-associated disorder. In certain embodiments, the symptom is a seizure. In certain embodiments, the tau-associated disorder or neurodegenerative disorder is Alzheimer's disease,

frontotemporal dementia, progressive supranuclear palsy, corticobasal ganglionic degeneration, dementia pugilistica, parkinsonism linked to chromosome, Lytico-Bodig disease, tangle-predominant dementia, ganglioglioma, gangliocytoma, meningioangiomatosis, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, Pick's disease, argyrophilic grain disease, corticobasal degeneration or frontotemporal lobar degeneration. Certain embodiments are drawn to a method of decreasing seizures in a subject with a high 4R:3R tau isoform ratio. In certain embodiments, the methods comprise administering an antisense agent to the subject, wherein the agent decreases expression of tau or decreases the 4R:3R tau ratio in the central nervous system of the subject.

[0016] Also provided are methods useful for preventing, treating, and ameliorating diseases, disorders, and conditions associated with Tau. In certain embodiments, such diseases, disorders, and conditions associated with Tau are neurodegenerative diseases. In certain embodiments, the neurodegenerative disease is any of Alzheimer's Disease, Fronto-temporal Dementia (FTD), FTDP-17, Progressive Supranuclear Palsy, Chronic Traumatic Encephalopathy, Epilepsy, or Dravet's Syndrome. In certain embodiments, one or more symptoms of a neurodegenerative disease is ameliorated, prevented, or delayed (progression slowed). In certain embodiments, the symptom is memory loss, anxiety, or loss of motor function. In certain embodiments, neurodegenerative function is improved. In certain embodiments, neurofibrillary inclusions are reduced.

[0017] Such diseases, disorders, and conditions can have one or more risk factors, causes, or outcomes in common. Certain risk factors and causes for development of a neurodegenerative disease include genetic predisposition and older age.

[0018] In certain embodiments, methods of treatment include administering a Tau antisense compound to an individual in need thereof. The antisense compound may inhibit expression of Tau or modulate splicing of Tau. In certain embodiments, the antisense compound is a single-stranded antisense oligonucleotide. In certain embodiments, the single-stranded antisense oligonucleotide is complementary to a Tau nucleic acid.

[0019] In certain embodiments, the present invention provides compounds comprising oligonucleotides. In certain embodiments, such oligonucleotides are complementary to a Tau transcript. In certain such embodiments, oligonucleotides are complementary to a target region of the Tau transcript comprising exon 10. In certain such embodiments, oligonucleotides are complementary to a target region of the Tau transcript comprising an intron adjacent to exon 10. In certain such embodiments, oligonucleotides are complementary to a target region of the Tau transcript comprising an intron adjacent to exon 10 and downstream of exon 10. In certain such embodiments, oligonucleotides are complementary to a target region of the Tau transcript comprising an intron adjacent to exon 10 and upstream of exon 10. In certain embodiments, the Tau transcript comprises an exonic splice silencer for exon 10. In certain embodiments, oligonucleotides inhibit inclusion of exon 10. In certain embodiments, oligonucleotides promote skipping of exon 10. In certain such embodiments, 3R Tau mRNA is increased. In certain such embodiments, Tau mRNA with exon 10 mRNA is decreased. In certain embodiments, the 4R isoform of the

Tau protein is decreased. In certain embodiments, the 3R isoform of the Tau protein is increased.

[0020] In certain embodiments, including, but not limited to any of the above numbered embodiments, the Tau transcript is in a human. In certain embodiments, including, but not limited to any of the above numbered embodiments, the Tau transcript is in a mouse.

[0021] The present disclosure provides the following non-limiting numbered embodiments:

[0022] Embodiment 1. A compound comprising a modified oligonucleotide consisting of 8 to 30 linked nucleosides and having a nucleobase sequence comprising a complementary region comprising at least 8 contiguous nucleobases complementary to a target region of equal length of a Tau transcript.

[0023] Embodiment 2. The compound of embodiment 1, wherein the complementary region of the modified oligonucleotide is 100% complementary to the target region.

[0024] Embodiment 3. The compound of embodiment 1 or 2, wherein the complementary region of the nucleobase sequence of the modified oligonucleotide comprises at least 10 contiguous nucleobases.

[0025] Embodiment 4. The compound of embodiment 1 or 2, wherein the complementary region of the nucleobase sequence of the modified oligonucleotide comprises at least 15 contiguous nucleobases.

[0026] Embodiment 5. The compound of embodiment 1 or 2, wherein the complementary region of the nucleobase sequence of the modified oligonucleotide comprises at least 18 contiguous nucleobases.

[0027] Embodiment 6. The compound of any of embodiments 1-5, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal-length region of the Tau transcript, as measured over the entire length of the oligonucleotide.

[0028] Embodiment 7. The compound of any of embodiments 1-5, wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to an equal-length region of the Tau transcript, as measured over the entire length of the oligonucleotide.

[0029] Embodiment 8. The compound of any of embodiments 1-5, wherein the nucleobase sequence of the modified oligonucleotide is 100% complementary to an equal-length region of the Tau transcript, as measured over the entire length of the oligonucleotide.

[0030] Embodiment 9. The compound of any of embodiments 1-8, wherein the target region is within exon 10 of the Tau transcript.

[0031] Embodiment 10. The compound of any of embodiments 1-8, wherein the target region is within intron 9 of the Tau transcript.

[0032] Embodiment 11. The compound of any of embodiments 1-8, wherein the target region is within intron 10 of the Tau transcript.

[0033] Embodiment 12. The compound of any of embodiments 1-8, wherein the target region comprises a portion of intron 9 and a portion of exon 10.

[0034] Embodiment 13. The compound of any of embodiments 1-8, wherein the target region comprises a portion of exon 10 and a portion of intron 10.

[0035] Embodiment 14. The compound of any of embodiments 1-8, wherein the target region comprises a portion of exon 10 and a portion of the intron at the 5'-end of exon 10.

[0036] Embodiment 15. The compound of any of embodiments 1-8, wherein the target region comprises a portion of exon 10 and a portion of the intron at the 3'-end of exon 10.

[0037] Embodiment 16. The compound of any of embodiments 1-15, wherein the target region is within nucleobase 121708 and nucleobase 122044 of SEQ ID NO: 1.

[0038] Embodiment 17. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121796 and nucleobase 122044 of SEQ ID NO: 1.

[0039] Embodiment 18. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121796 and nucleobase 121885 of SEQ ID NO: 1.

[0040] Embodiment 19. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121873 and nucleobase 121898 of SEQ ID NO: 1.

[0041] Embodiment 20. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121869 and nucleobase 121943 of SEQ ID NO: 1.

[0042] Embodiment 21. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 122020 and nucleobase 122044 of SEQ ID NO: 1.

[0043] Embodiment 22. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121881 and nucleobase 121898 of SEQ ID NO: 1.

[0044] Embodiment 23. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121880 and nucleobase 121897 of SEQ ID NO: 1.

[0045] Embodiment 24. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121879 and nucleobase 121896 of SEQ ID NO: 1.

[0046] Embodiment 25. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121878 and nucleobase 121895 of SEQ ID NO: 1.

[0047] Embodiment 26. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121877 and nucleobase 121894 of SEQ ID NO: 1.

[0048] Embodiment 27. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121876 and nucleobase 121893 of SEQ ID NO: 1.

[0049] Embodiment 28. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121875 and nucleobase 121892 of SEQ ID NO: 1.

[0050] Embodiment 29. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121874 and nucleobase 121891 of SEQ ID NO: 1.

[0051] Embodiment 30. The compound of any of embodiments 1-9, wherein the target region is within nucleobase 121873 and nucleobase 121890 of SEQ ID NO: 1.

[0052] Embodiment 31. The compound of any of embodiments 1-15, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 8-200.

[0053] Embodiment 32. The compound of any of embodiments 1-15, wherein the nucleobase sequence of the modified oligonucleotide consists of the nucleobase sequence of any of SEQ ID NOs: 8-200.

[0054] Embodiment 33. The compound of any of embodiments 1-15, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 33, 34, 147, 148, 149, 150, 151, 152, or 153.

[0055] Embodiment 34. The compound of any of embodiments 1-15, wherein the nucleobase sequence of the

- modified oligonucleotide consists of the nucleobase sequence of any of SEQ ID NOs: 33, 34, 147, 148, 149, 150, 151, 152, or 153.
- [0056] Embodiment 35. The compound of any of embodiments 1-15, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 31, 33, 34, 35, 36, 37, 45, 72, 79, 82, 83, 97, 106, 107, 112, 113, 130, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 157, 158, 160, or 200.
- [0057] Embodiment 36. The compound of any of embodiments 1-15, wherein the nucleobase sequence of the modified oligonucleotide consists of the nucleobase sequence of any of SEQ ID NOs: 31, 33, 34, 35, 36, 37, 45, 72, 79, 82, 83, 97, 106, 107, 112, 113, 130, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 157, 158, 160, or 200.
- [0058] Embodiment 37. The compound of any of embodiments 1-36, wherein the modified oligonucleotide comprises at least one modified nucleoside.
- [0059] Embodiment 38. The compound of embodiment 37, wherein at least one modified nucleoside comprises a modified sugar moiety.
- [0060] Embodiment 39. The compound of embodiment 37, wherein at least one modified sugar moiety is a 2'-substituted sugar moiety.
- [0061] Embodiment 40. The compound of embodiment 39, wherein the 2'-substituent of at least one 2'-substituted sugar moiety is selected from among: 2'-OMe, 2'-F, and 2'-MOE.
- [0062] Embodiment 41. The compound of embodiment 39, wherein the 2'-substituent of at least one 2'-substituted sugar moiety is a 2'-MOE.
- [0063] Embodiment 42. The compound of any of embodiments 37-38, wherein at least one modified sugar moiety is a bicyclic sugar moiety.
- [0064] Embodiment 43. The compound of embodiment 42, wherein at least one bicyclic sugar moiety is LNA or cEt.
- [0065] Embodiment 44. The compound of any of embodiments 37-43, wherein at least one sugar moiety is a sugar surrogate.
- [0066] Embodiment 45. The compound of embodiment 44, wherein at least one sugar surrogate is a morpholino.
- [0067] Embodiment 46. The compound of embodiment 44, wherein at least one sugar surrogate is a modified morpholino.
- [0068] Embodiment 47. The compound of any of embodiments 1-46, wherein the modified oligonucleotide comprises at least 5 modified nucleosides, each independently comprising a modified sugar moiety.
- [0069] Embodiment 48. The compound of embodiment 47, wherein the modified oligonucleotide comprises at least 10 modified nucleosides, each independently comprising a modified sugar moiety.
- [0070] Embodiment 49. The compound of embodiment 47, wherein the modified oligonucleotide comprises at least 15 modified nucleosides, each independently comprising a modified sugar moiety.
- [0071] Embodiment 50. The compound of embodiment 47, wherein each nucleoside of the modified oligonucleotide is a modified nucleoside and each independently comprises a modified sugar moiety, wherein the modified sugar moieties of each modified nucleosides are each the same as one another.
- [0072] Embodiment 51. The compound of embodiment 47, wherein each nucleoside of the modified oligonucleotide is a modified nucleoside, each independently comprising a modified sugar moiety.
- [0073] Embodiment 52. The compound of any of embodiments 1-51, wherein the modified oligonucleotide comprises at least two modified nucleosides comprising modified sugar moieties that are the same as one another.
- [0074] Embodiment 53. The compound of any of embodiments 1-52, wherein the modified oligonucleotide comprises at least two modified nucleosides comprising modified sugar moieties that are different from one another.
- [0075] Embodiment 54. The compound of any of embodiments 1-53, wherein the modified oligonucleotide comprises a modified region comprising at least 5 contiguous modified nucleosides.
- [0076] Embodiment 55. The compound of embodiment 54, wherein the modified oligonucleotide comprises a modified region comprising at least 10 contiguous modified nucleosides.
- [0077] Embodiment 56. The compound of embodiment 54, wherein the modified oligonucleotide comprises a modified region comprising at least 15 contiguous modified nucleosides.
- [0078] Embodiment 57. The compound of embodiment 54, wherein the modified oligonucleotide comprises a modified region comprising at least 18 contiguous modified nucleosides.
- [0079] Embodiment 58. The compound of embodiment 54, wherein the modified oligonucleotide comprises a modified region comprising at least 20 contiguous modified nucleosides.
- [0080] Embodiment 59. The compound of any of embodiments 53-58, wherein each modified nucleoside of the modified region has a modified sugar moiety independently selected from among: 2'-F, 2'-OMe, 2'-MOE, cEt, LNA, morpholino, and modified morpholino.
- [0081] Embodiment 60. The compound of any of embodiments 54-59, wherein the modified nucleosides of the modified region each comprise the same modification as one another.
- [0082] Embodiment 61. The compound of embodiment 60, wherein the modified nucleosides of the modified region each comprise the same 2'-substituted sugar moiety.
- [0083] Embodiment 62. The compound of embodiment 61, wherein the 2'-substituted sugar moiety of the modified nucleosides of the region of modified nucleosides is selected from 2'-F, 2'-OMe, and 2'-MOE.
- [0084] Embodiment 63. The compound of embodiment 61, wherein the 2'-substituted sugar moiety of the modified nucleosides of the region of modified nucleosides is 2'-MOE.
- [0085] Embodiment 64. The compound of embodiment 59, wherein the modified nucleosides of the region of modified nucleosides each comprise the same bicyclic sugar moiety.
- [0086] Embodiment 65. The compound of embodiment 64, wherein the bicyclic sugar moiety of the modified nucleosides of the region of modified nucleosides is selected from LNA and cEt.

- [0124] Embodiment 103. The compound of any of embodiments 1-99, wherein the compound decreases expression Tau protein comprising amino acids encoded from exon 10 mRNA.
- [0125] Embodiment 104. The compound of any of embodiments 1-8 or 30-103, having a nucleobase sequence comprising any of the sequences as set forth in SEQ ID NOs. 8-200.
- [0126] Embodiment 105. The compound of any of embodiments 1-8 or 30-103, having a nucleobase sequence comprising any of the sequences as set forth in SEQ ID NOs. 33, 34, 147, 148, 149, 150, 151, 152, or 153.
- [0127] Embodiment 106. The compound of any of embodiments 1-8 or 30-103, having a nucleobase sequence consisting of any of the sequences as set forth in SEQ ID NOs. 8-200.
- [0128] Embodiment 107. The compound of any of embodiments 1-8 or 30-103, having a nucleobase sequence consisting of any of the sequences as set forth in SEQ ID NOs. 33, 34, 147, 148, 149, 150, 151, 152, or 153.
- [0129] Embodiment 108. A double stranded compound comprising the compound of any of embodiments 1-107.
- [0130] Embodiment 109. A compound consisting of ISIS 670011.
- [0131] Embodiment 110. A compound consisting of ISIS 670012.
- [0132] Embodiment 111. A compound consisting of ISIS 670013.
- [0133] Embodiment 112. A compound consisting of ISIS 670014.
- [0134] Embodiment 113. A compound consisting of ISIS 670015.
- [0135] Embodiment 114. A compound consisting of ISIS 670016.
- [0136] Embodiment 115. A compound consisting of ISIS 670017.
- [0137] Embodiment 116. A compound consisting of ISIS 670018.
- [0138] Embodiment 117. A compound consisting of ISIS 670019.
- [0139] Embodiment 118. A compound consisting of ISIS 670020.
- [0140] Embodiment 119. A compound consisting of ISIS 670021.
- [0141] Embodiment 120. A compound consisting of ISIS 670022.
- [0142] Embodiment 121. A compound consisting of ISIS 670023.
- [0143] Embodiment 122. A compound consisting of ISIS 670024.
- [0144] Embodiment 123. A compound consisting of ISIS 670025.
- [0145] Embodiment 124. A compound consisting of ISIS 670026.
- [0146] Embodiment 125. A compound consisting of ISIS 670027.
- [0147] Embodiment 126. A compound consisting of ISIS 670028.
- [0148] Embodiment 127. A compound consisting of ISIS 678329.
- [0149] Embodiment 128. A compound consisting of ISIS 678330.
- [0150] Embodiment 129. A compound consisting of ISIS 678331.
- [0151] Embodiment 130. A compound consisting of ISIS 678332.
- [0152] Embodiment 131. A compound consisting of ISIS 678333.
- [0153] Embodiment 132. A compound consisting of ISIS 678334.
- [0154] Embodiment 133. A compound consisting of ISIS 693840.
- [0155] Embodiment 134. A compound consisting of ISIS 693841.
- [0156] Embodiment 135. A compound consisting of ISIS 693842.
- [0157] Embodiment 136. A compound consisting of ISIS 693843.
- [0158] Embodiment 137. A compound consisting of ISIS 693844.
- [0159] Embodiment 138. A compound consisting of ISIS 693845.
- [0160] Embodiment 139. A compound consisting of ISIS 693846.
- [0161] Embodiment 140. A compound consisting of ISIS 693847.
- [0162] Embodiment 141. A compound consisting of ISIS 693848.
- [0163] Embodiment 142. A compound consisting of ISIS 693849.
- [0164] Embodiment 143. A compound consisting of ISIS 549577.
- [0165] Embodiment 144. A compound consisting of ISIS 549580.
- [0166] Embodiment 145. A compound consisting of ISIS 549581.
- [0167] Embodiment 146. A compound consisting of ISIS 549582.
- [0168] Embodiment 147. A compound consisting of ISIS 549583.
- [0169] Embodiment 148. A compound consisting of ISIS 549584.
- [0170] Embodiment 149. A compound consisting of ISIS 549585.
- [0171] Embodiment 150. A compound consisting of ISIS 549586.
- [0172] Embodiment 151. A compound consisting of ISIS 617341.
- [0173] Embodiment 152. A compound consisting of ISIS 617351.
- [0174] Embodiment 153. A compound consisting of ISIS 617352.
- [0175] Embodiment 154. A compound consisting of ISIS 617353.
- [0176] Embodiment 155. A compound consisting of ISIS 617358.
- [0177] Embodiment 156. A compound consisting of ISIS 617360.
- [0178] Embodiment 157. A compound consisting of ISIS 617361.
- [0179] Embodiment 158. A compound consisting of ISIS 617362.
- [0180] Embodiment 159. A method of modulating splicing of a Tau transcript in a cell comprising contacting the cell with a compound according to any of embodiments 1-158.

- [0181] Embodiment 160. The method of embodiment 158, wherein the cell is in vitro.
- [0182] Embodiment 161. The method of embodiment 158, wherein the cell is in an animal.
- [0183] Embodiment 162. A method of modulating the expression of Tau protein in a cell, comprising contacting the cell with a compound according to any of embodiments 1-158.
- [0184] Embodiment 163. The method of embodiment 162, wherein expression of the 4R isoform of Tau protein is decreased.
- [0185] Embodiment 164. The method of embodiment 162, wherein expression of the 3R isoform of Tau protein is increased.
- [0186] Embodiment 165. The method of any of embodiments 162 to 164, wherein the cell is in vitro.
- [0187] Embodiment 166. The method of any of embodiments 162 to 164, wherein the cell is in an animal.
- [0188] Embodiment 167. A method of reducing or ameliorating one or more symptoms associated with a tau-associated disorder, comprising contacting a cell with a compound according to any of embodiments 1-158.
- [0189] Embodiment 168. The method of embodiment 167, wherein the symptom is seizure.
- [0190] Embodiment 169. The method of any of embodiments 167-168, wherein the cell is in an animal.
- [0191] Embodiment 170. A pharmaceutical composition comprising a compound according to any of embodiments 1-158 and a pharmaceutically acceptable carrier or diluent.
- [0192] Embodiment 171. The pharmaceutical composition of embodiment 170, wherein the pharmaceutically acceptable carrier or diluent is sterile saline.
- [0193] Embodiment 172. A method comprising administering the pharmaceutical composition of embodiments 170 or 171 to an animal.
- [0194] Embodiment 173. The method of embodiment 172, wherein the administration is by injection.
- [0195] Embodiment 174. The method of embodiment 172 or 173, wherein the administration is systemic.
- [0196] Embodiment 175. The method of embodiment 172 or 173, wherein the administration is to the CNS.
- [0197] Embodiment 176. The method of any of embodiments 172-175, wherein the animal has one or more symptoms associated with one or more tau-associated disorders.
- [0198] Embodiment 177. The method of embodiment 176, wherein the administration results in amelioration of one or more symptoms associated with one or more tau-associated disorders.
- [0199] Embodiment 178. The method of any of embodiments 172-175, wherein the animal has one or more symptoms associated with Alzheimer's disease.
- [0200] Embodiment 179. The method of embodiment 178, wherein the administration results in amelioration of one or more symptoms associated with Alzheimer's disease.
- [0201] Embodiment 180. The method of any of embodiments 172-179, wherein the animal is a mouse.
- [0202] Embodiment 181. The method of any of embodiments 172-179, wherein the animal is a human.
- [0203] Embodiment 182. Use of the compound of any of embodiments 1 to 158 or the composition of embodiments 170-171 for the preparation of a medicament for use in the treatment of a tau-associated disorder.
- [0204] Embodiment 183. Use of the compound of any of embodiments 1 to 158 or the composition of embodiments 170-171 for the preparation of a medicament for use in the amelioration of one or more symptoms associated a tau-associated disorder.
- [0205] Embodiment 184. The compound, composition, or method of any of embodiments 1-183, wherein the nucleobase sequence does not consist of the nucleobase sequence as set forth in SEQ ID NO: 45, 66, 68, 69, or 200.
- [0206] Embodiment 185. The compound, composition, or method of any of embodiments 1-183, wherein the nucleobase sequence does not consist of the nucleobase sequence CCAGCTTCTTATTAATTATC or TAA-GATCCAGCTTCTTATTA.
- [0207] Embodiment 186. The compound, composition, or method of any of embodiments 1-183, wherein the target region is not within nucleobase 121828 and nucleobase 121847 of SEQ ID NO: 1.
- [0208] Embodiment 187. The compound, composition, or method of any of embodiments 1-183, wherein the target region is not within nucleobase 121834 and nucleobase 121853 of SEQ ID NO: 1.
- [0209] Embodiment 188. The compound, composition, or method of any of embodiments 1-183, wherein the target region is not within nucleobase 121840 and nucleobase 121859 of SEQ ID NO: 1.
- [0210] Embodiment 189. The compound, composition, or method of any of embodiments 1-183, wherein the target region is not within nucleobase 121924 and nucleobase 121941 of SEQ ID NO: 1.
- [0211] Embodiment 190. The compound, composition, or method of any of embodiments 1-183, wherein the target region is not within nucleobase 121012 and nucleobase 121029 of SEQ ID NO: 1.
- [0212] Embodiment 191. The compound, composition, or method of any of embodiments 1-183, wherein the target region is not within nucleobase 121020 and nucleobase 121037 of SEQ ID NO: 1.
- [0213] Embodiment 192. The compound, composition, or method of any of embodiments 1-183, wherein the target region is not within nucleobase 121024 and nucleobase 121041 of SEQ ID NO: 1.

BRIEF DESCRIPTION OF THE FIGURES

[0214] FIG. 1 depicts a graphical representation of Tau isoforms. The isoforms can differ from each other in the number of tubulin-binding domains (three or four repeats located in the C-terminal half of the protein) and are referred to as 3R or 4R Tau isoforms, respectively. They can also differ in the presence or absence of either one or two 29-amino-acid-long, highly acidic inserts at the N-terminal portion of the protein (the projection domain). Between the projection domain and the microtubule-binding domain lies a basic proline-rich region.

DETAILED DESCRIPTION

[0215] Unless specific definitions are provided, the nomenclature used in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for chemical

synthesis, and chemical analysis. Certain such techniques and procedures may be found for example in “Carbohydrate Modifications in Antisense Research” Edited by Sangvi and Cook, American Chemical Society, Washington D.C., 1994; “Remington’s Pharmaceutical Sciences,” Mack Publishing Co., Easton, Pa., 21st edition, 2005; and “Antisense Drug Technology, Principles, Strategies, and Applications” Edited by Stanley T. Crooke, CRC Press, Boca Raton, Fla.; and Sambrook et al., “Molecular Cloning, A Laboratory Manual,” 2nd Edition, Cold Spring Harbor Laboratory Press, 1989, which are hereby incorporated by reference for any purpose. Where permitted, all patents, applications, published applications and other publications and other data referred to throughout in the disclosure are incorporated by reference herein in their entirety.

[0216] Unless otherwise indicated, the following terms have the following meanings:

[0217] As used herein, “nucleoside” means a compound comprising a nucleobase moiety and a sugar moiety. Nucleosides include, but are not limited to, naturally occurring nucleosides (as found in DNA and RNA) and modified nucleosides. Nucleosides may be linked to a phosphate moiety.

[0218] As used herein, “chemical modification” means a chemical difference in a compound when compared to a naturally occurring counterpart. In reference to an oligonucleotide, chemical modification does not include differences only in nucleobase sequence. Chemical modifications of oligonucleotides include nucleoside modifications (including sugar moiety modifications and nucleobase modifications) and internucleoside linkage modifications.

[0219] As used herein, “furanosyl” means a structure comprising a 5-membered ring comprising four carbon atoms and one oxygen atom.

[0220] As used herein, “naturally occurring sugar moiety” means a ribofuranosyl as found in naturally occurring RNA or a deoxyribofuranosyl as found in naturally occurring DNA.

[0221] As used herein, “sugar moiety” means a naturally occurring sugar moiety or a modified sugar moiety of a nucleoside.

[0222] As used herein, “modified sugar moiety” means a substituted sugar moiety, a bicyclic or tricyclic sugar moiety, or a sugar surrogate.

[0223] As used herein, “substituted sugar moiety” means a furanosyl comprising at least one substituent group that differs from that of a naturally occurring sugar moiety. Substituted sugar moieties include, but are not limited to furanosyls comprising substituents at the 2'-position, the 3'-position, the 5'-position and/or the 4'-position.

[0224] As used herein, “2'-substituted sugar moiety” means a furanosyl comprising a substituent at the 2'-position other than H or OH. Unless otherwise indicated, a 2'-substituted sugar moiety is not a bicyclic sugar moiety (i.e., the 2'-substituent of a 2'-substituted sugar moiety does not form a bridge to another atom of the furanosyl ring).

[0225] As used herein, “MOE” means $-\text{OCH}_2\text{CH}_2\text{OCH}_3$.

[0226] As used herein, “bicyclic sugar moiety” means a modified sugar moiety comprising a 4 to 7 membered ring (including but not limited to a furanosyl) comprising a bridge connecting two atoms of the 4 to 7 membered ring to form a second ring, resulting in a bicyclic structure. In certain embodiments, the 4 to 7 membered ring is a sugar

ring. In certain embodiments the 4 to 7 membered ring is a furanosyl. In certain such embodiments, the bridge connects the 2'-carbon and the 4'-carbon of the furanosyl.

[0227] As used herein the term “sugar surrogate” means a structure that does not comprise a furanosyl and that is capable of replacing the naturally occurring sugar moiety of a nucleoside, such that the resulting nucleoside is capable of (1) incorporation into an oligonucleotide and (2) hybridization to a complementary nucleoside. Such structures include rings comprising a different number of atoms than furanosyl (e.g., 4, 6, or 7-membered rings); replacement of the oxygen of a furanosyl with a non-oxygen atom (e.g., carbon, sulfur, or nitrogen); or both a change in the number of atoms and a replacement of the oxygen. Such structures may also comprise substitutions corresponding to those described for substituted sugar moieties (e.g., 6-membered carbocyclic bicyclic sugar surrogates optionally comprising additional substituents). Sugar surrogates also include more complex sugar replacements (e.g., the non-ring systems of peptide nucleic acid). Sugar surrogates include without limitation morpholino, modified morpholinos, cyclohexenyls and cyclohexitols.

[0228] As used herein, “nucleotide” means a nucleoside further comprising a phosphate linking group. As used herein, “linked nucleosides” may or may not be linked by phosphate linkages and thus includes, but is not limited to “linked nucleotides.” As used herein, “linked nucleosides” are nucleosides that are connected in a continuous sequence (i.e. no additional nucleosides are present between those that are linked).

[0229] As used herein, “nucleobase” means a group of atoms that can be linked to a sugar moiety to create a nucleoside that is capable of incorporation into an oligonucleotide, and wherein the group of atoms is capable of bonding with a complementary naturally occurring nucleobase of another oligonucleotide or nucleic acid. Nucleobases may be naturally occurring or may be modified.

[0230] As used herein, “heterocyclic base” or “heterocyclic nucleobase” means a nucleobase comprising a heterocyclic structure.

[0231] As used herein the terms, “unmodified nucleobase” or “naturally occurring nucleobase” means the naturally occurring heterocyclic nucleobases of RNA or DNA: the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) (including 5-methyl C), and uracil (U).

[0232] As used herein, “modified nucleobase” means any nucleobase that is not a naturally occurring nucleobase.

[0233] As used herein, “modified nucleoside” means a nucleoside comprising at least one chemical modification compared to naturally occurring RNA or DNA nucleosides. Modified nucleosides comprise a modified sugar moiety and/or a modified nucleobase.

[0234] As used herein, “bicyclic nucleoside” or “BNA” means a nucleoside comprising a bicyclic sugar moiety.

[0235] As used herein, “constrained ethyl nucleoside” or “cEt” means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH(CH₃)—O-2'bridge.

[0236] As used herein, “locked nucleic acid nucleoside” or “LNA” means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH₂—O-2'bridge.

[0237] As used herein, “2'-substituted nucleoside” means a nucleoside comprising a substituent at the 2'-position other

than H or OH. Unless otherwise indicated, a 2'-substituted nucleoside is not a bicyclic nucleoside.

[0238] As used herein, "2'-deoxynucleoside" means a nucleoside comprising 2'-H furanosyl sugar moiety, as found in naturally occurring deoxyribonucleosides (DNA). In certain embodiments, a 2'-deoxynucleoside may comprise a modified nucleobase or may comprise an RNA nucleobase (e.g., uracil).

[0239] As used herein, "oligonucleotide" means a compound comprising a plurality of linked nucleosides. In certain embodiments, an oligonucleotide comprises one or more unmodified ribonucleosides (RNA) and/or unmodified deoxyribonucleosides (DNA) and/or one or more modified nucleosides.

[0240] As used herein "oligonucleoside" means an oligonucleotide in which none of the internucleoside linkages contains a phosphorus atom. As used herein, oligonucleotides include oligonucleosides.

[0241] As used herein, "modified oligonucleotide" means an oligonucleotide comprising at least one modified nucleoside and/or at least one modified internucleoside linkage.

[0242] As used herein "internucleoside linkage" means a covalent linkage between adjacent nucleosides in an oligonucleotide.

[0243] As used herein "naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

[0244] As used herein, "modified internucleoside linkage" means any internucleoside linkage other than a naturally occurring internucleoside linkage.

[0245] As used herein, "oligomeric compound" means a polymeric structure comprising two or more sub-structures. In certain embodiments, an oligomeric compound comprises an oligonucleotide. In certain embodiments, an oligomeric compound comprises one or more conjugate groups and/or terminal groups. In certain embodiments, an oligomeric compound consists of an oligonucleotide.

[0246] As used herein, "terminal group" means one or more atom attached to either, or both, the 3' end or the 5' end of an oligonucleotide. In certain embodiments a terminal group is a conjugate group. In certain embodiments, a terminal group comprises one or more terminal group nucleosides.

[0247] As used herein, "conjugate" means an atom or group of atoms bound to an oligonucleotide or oligomeric compound. In general, conjugate groups modify one or more properties of the compound to which they are attached, including, but not limited to pharmacodynamic, pharmacokinetic, binding, absorption, cellular distribution, cellular uptake, charge and/or clearance properties.

[0248] As used herein, "conjugate linking group" means any atom or group of atoms used to attach a conjugate to an oligonucleotide or oligomeric compound.

[0249] As used herein, "antisense compound" means a compound comprising or consisting of an oligonucleotide at least a portion of which is complementary to a target nucleic acid to which it is capable of hybridizing, resulting in at least one antisense activity.

[0250] As used herein, "antisense activity" means any detectable and/or measurable change attributable to the hybridization of an antisense compound to its target nucleic acid.

[0251] As used herein, "detecting" or "measuring" means that a test or assay for detecting or measuring is performed. Such detection and/or measuring may result in a value of

zero. Thus, if a test for detection or measuring results in a finding of no activity (activity of zero), the step of detecting or measuring the activity has nevertheless been performed.

[0252] As used herein, "detectable and/or measureable activity" means a statistically significant activity that is not zero.

[0253] As used herein, "essentially unchanged" means little or no change in a particular parameter, particularly relative to another parameter which changes much more. In certain embodiments, a parameter is essentially unchanged when it changes less than 5%. In certain embodiments, a parameter is essentially unchanged if it changes less than two-fold while another parameter changes at least ten-fold. For example, in certain embodiments, an antisense activity is a change in the amount of a target nucleic acid. In certain such embodiments, the amount of a non-target nucleic acid is essentially unchanged if it changes much less than the target nucleic acid does, but the change need not be zero.

[0254] As used herein, "expression" means the process by which a gene ultimately results in a protein. Expression includes, but is not limited to, transcription, post-transcriptional modification (e.g., splicing, polyadenylation, addition of 5'-cap), and translation.

[0255] As used herein, "target nucleic acid" means a nucleic acid molecule to which an antisense compound hybridizes.

[0256] As used herein, "mRNA" means an RNA molecule that encodes a protein.

[0257] As used herein, "pre-mRNA" means an RNA transcript that has not been fully processed into mRNA. Pre-mRNA includes one or more intron.

[0258] As used herein, "transcript" means an RNA molecule transcribed from DNA. Transcripts include, but are not limited to mRNA, pre-mRNA, and partially processed RNA.

[0259] As used herein, "Tau transcript" means a transcript transcribed from a Tau gene. In certain embodiments, a Tau transcript is represented by GENBANK Accession No NT_010783.15, truncated from nucleotides 9240000 to 9381000 (SEQ ID NO: 1), or a variant thereof.

[0260] As used herein, "Tau gene" means a gene that encodes a Tau protein and any Tau protein isoforms. In certain embodiments, Tau protein isoforms include the 3R isoform and the 4R isoform.

[0261] As used herein, "3R" means a Tau transcript that includes does not include exon 10.

[0262] As used herein, "3R Tau isoform" means a Tau protein isoform that does not include amino acids encoded from exon 10.

[0263] As used herein, "4R" means a Tau transcript that includes exon 10.

[0264] As used herein, "4R Tau isoform" means a Tau protein isoform that includes amino acids encoded from exon 10.

[0265] As used herein, "Tau-associated disease" means any neurological or neurodegenerative disease associated with Tau. Non-limiting examples of Tau-associated disorders include Alzheimer's disease, progressive supranuclear palsy, dementia pugilistica, frontotemporal dementia, parkinsonism linked to chromosome, Lytico-Bodig disease, tangle-predominant dementia, ganglioglioma, gangliocytoma, meningioangiomatosis, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, Pick's disease, corticobasal ganglionic degeneration, argyrophilic grain disease, supra-

nuclear palsy, corticobasal degeneration, frontotemporal dementia, or frontotemporal lobar degeneration.

[0266] As used herein, “Tauopathy” means disorders characterized by a build-up of Tau protein in the brain.

[0267] As used herein, “Tau-specific inhibitor” includes but is not limited to a “antisense compound” targeted to Tau.

[0268] As used herein, “targeting” or “targeted to” means the association of an antisense compound to a particular target nucleic acid molecule or a particular region of a target nucleic acid molecule. An antisense compound targets a target nucleic acid if it is sufficiently complementary to the target nucleic acid to allow hybridization under physiological conditions.

[0269] As used herein, “nucleobase complementarity” or “complementarity” when in reference to nucleobases means a nucleobase that is capable of base pairing with another nucleobase. For example, in DNA, adenine (A) is complementary to thymine (T). For example, in RNA, adenine (A) is complementary to uracil (U). In certain embodiments, complementary nucleobase means a nucleobase of an antisense compound that is capable of base pairing with a nucleobase of its target nucleic acid. For example, if a nucleobase at a certain position of an antisense compound is capable of hydrogen bonding with a nucleobase at a certain position of a target nucleic acid, then the position of hydrogen bonding between the oligonucleotide and the target nucleic acid is considered to be complementary at that nucleobase pair. Nucleobases comprising certain modifications may maintain the ability to pair with a counterpart nucleobase and thus, are still capable of nucleobase complementarity.

[0270] As used herein, “non-complementary” in reference to nucleobases means a pair of nucleobases that do not form hydrogen bonds with one another.

[0271] As used herein, “complementary” in reference to oligomeric compounds (e.g., linked nucleosides, oligonucleotides, or nucleic acids) means the capacity of such oligomeric compounds or regions thereof to hybridize to another oligomeric compound or region thereof through nucleobase complementarity under stringent conditions. Complementary oligomeric compounds need not have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. In certain embodiments, complementary oligomeric compounds or regions are complementary at 70% of the nucleobases (70% complementary). In certain embodiments, complementary oligomeric compounds or regions are 80% complementary. In certain embodiments, complementary oligomeric compounds or regions are 90% complementary. In certain embodiments, complementary oligomeric compounds or regions are 95% complementary. In certain embodiments, complementary oligomeric compounds or regions are 100% complementary.

[0272] As used herein, “hybridization” means the pairing of complementary oligomeric compounds (e.g., an antisense compound and its target nucleic acid). While not limited to a particular mechanism, the most common mechanism of pairing involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleobases.

[0273] As used herein, “specifically hybridizes” means the ability of an oligomeric compound to hybridize to one nucleic acid site with greater affinity than it hybridizes to

another nucleic acid site. In certain embodiments, an antisense oligonucleotide specifically hybridizes to more than one target site.

[0274] As used herein, “percent complementarity” means the percentage of nucleobases of an oligomeric compound that are complementary to an equal-length portion of a target nucleic acid. Percent complementarity is calculated by dividing the number of nucleobases of the oligomeric compound that are complementary to nucleobases at corresponding positions in the target nucleic acid by the total length of the oligomeric compound.

[0275] As used herein, “percent identity” means the number of nucleobases in a first nucleic acid that are the same type (independent of chemical modification) as nucleobases at corresponding positions in a second nucleic acid, divided by the total number of nucleobases in the first nucleic acid.

[0276] As used herein, “modulation” means a change of amount or quality of a molecule, function, or activity when compared to the amount or quality of a molecule, function, or activity prior to modulation. For example, modulation includes the change, either an increase (stimulation or induction) or a decrease (inhibition or reduction) in gene expression. As a further example, modulation of expression can include a change in splice site selection of pre-mRNA processing, resulting in a change in the absolute or relative amount of a particular splice-variant compared to the amount in the absence of modulation.

[0277] As used herein, “motif” means a pattern of chemical modifications in an oligomeric compound or a region thereof. Motifs may be defined by modifications at certain nucleosides and/or at certain linking groups of an oligomeric compound.

[0278] As used herein, “nucleoside motif” means a pattern of nucleoside modifications in an oligomeric compound or a region thereof. The linkages of such an oligomeric compound may be modified or unmodified. Unless otherwise indicated, motifs herein describing only nucleosides are intended to be nucleoside motifs. Thus, in such instances, the linkages are not limited.

[0279] As used herein, “sugar motif” means a pattern of sugar modifications in an oligomeric compound or a region thereof.

[0280] As used herein, “linkage motif” means a pattern of linkage modifications in an oligomeric compound or region thereof. The nucleosides of such an oligomeric compound may be modified or unmodified. Unless otherwise indicated, motifs herein describing only linkages are intended to be linkage motifs. Thus, in such instances, the nucleosides are not limited.

[0281] As used herein, “nucleobase modification motif” means a pattern of modifications to nucleobases along an oligonucleotide. Unless otherwise indicated, a nucleobase modification motif is independent of the nucleobase sequence.

[0282] As used herein, “sequence motif” means a pattern of nucleobases arranged along an oligonucleotide or portion thereof. Unless otherwise indicated, a sequence motif is independent of chemical modifications and thus may have any combination of chemical modifications, including no chemical modifications.

[0283] As used herein, “type of modification” in reference to a nucleoside or a nucleoside of a “type” means the chemical modification of a nucleoside and includes modified and unmodified nucleosides. Accordingly, unless otherwise

indicated, a “nucleoside having a modification of a first type” may be an unmodified nucleoside.

[0284] As used herein, “differently modified” mean chemical modifications or chemical substituents that are different from one another, including absence of modifications. Thus, for example, a MOE nucleoside and an unmodified DNA nucleoside are “differently modified,” even though the DNA nucleoside is unmodified. Likewise, DNA and RNA are “differently modified,” even though both are naturally-occurring unmodified nucleosides. Nucleosides that are the same but for comprising different nucleobases are not differently modified. For example, a nucleoside comprising a 2'-OMe modified sugar and an unmodified adenine nucleobase and a nucleoside comprising a 2'-OMe modified sugar and an unmodified thymine nucleobase are not differently modified.

[0285] As used herein, “the same type of modifications” refers to modifications that are the same as one another, including absence of modifications. Thus, for example, two unmodified DNA nucleoside have “the same type of modification,” even though the DNA nucleoside is unmodified. Such nucleosides having the same type modification may comprise different nucleobases.

[0286] As used herein, “pharmaceutically acceptable carrier or diluent” means any substance suitable for use in administering to an animal. In certain embodiments, a pharmaceutically acceptable carrier or diluent is sterile saline. In certain embodiments, such sterile saline is pharmaceutical grade saline.

[0287] As used herein, “substituent” and “substituent group,” means an atom or group that replaces the atom or group of a named parent compound. For example a substituent of a modified nucleoside is any atom or group that differs from the atom or group found in a naturally occurring nucleoside (e.g., a modified 2'-substituent is any atom or group at the 2'-position of a nucleoside other than H or OH). Substituent groups can be protected or unprotected. In certain embodiments, compounds of the present invention have substituents at one or at more than one position of the parent compound. Substituents may also be further substituted with other substituent groups and may be attached directly or via a linking group such as an alkyl or hydrocarbyl group to a parent compound.

[0288] Likewise, as used herein, “substituent” in reference to a chemical functional group means an atom or group of atoms differs from the atom or a group of atoms normally present in the named functional group. In certain embodiments, a substituent replaces a hydrogen atom of the functional group (e.g., in certain embodiments, the substituent of a substituted methyl group is an atom or group other than hydrogen which replaces one of the hydrogen atoms of an unsubstituted methyl group). Unless otherwise indicated, groups amenable for use as substituents include without limitation, halogen, hydroxyl, alkyl, alkenyl, alkynyl, acyl ($-\text{C}(\text{O})\text{R}_{aa}$), carboxyl ($-\text{C}(\text{O})\text{O}-\text{R}_{aa}$), aliphatic groups, alicyclic groups, alkoxy, substituted oxy ($-\text{O}-\text{R}_{aa}$), aryl, aralkyl, heterocyclic radical, heteroaryl, heteroarylalkyl, amino ($-\text{N}(\text{R}_{bb})(\text{R}_{cc})$), imino ($=\text{NR}_{bb}$), amido ($-\text{C}(\text{O})\text{N}(\text{R}_{bb})(\text{R}_{cc})$ or $-\text{N}(\text{R}_{bb})\text{C}(\text{O})\text{R}_{aa}$), azido ($-\text{N}_3$), nitro ($-\text{NO}_2$), cyano ($-\text{CN}$), carbamido ($-\text{OC}(\text{O})\text{N}(\text{R}_{bb})(\text{R}_{cc})$ or $-\text{N}(\text{R}_{bb})\text{C}(\text{O})\text{OR}_{aa}$), ureido ($-\text{N}(\text{R}_{bb})\text{C}(\text{O})\text{N}(\text{R}_{bb})(\text{R}_{cc})$), thioureido ($-\text{N}(\text{R}_{bb})\text{C}(\text{S})\text{N}(\text{R}_{bb})-\text{R}_{cc}$), guanidinyl ($-\text{N}(\text{R}_{bb})\text{C}(=\text{NR}_{bb})\text{N}(\text{R}_{bb})(\text{R}_{cc})$), amidinyl ($-\text{C}(=\text{NR}_{bb})\text{N}(\text{R}_{bb})(\text{R}_{cc})$ or $-\text{N}(\text{R}_{bb})\text{C}(=\text{NR}_{bb})(\text{R}_{aa})$), thiol

($-\text{SR}_{bb}$), sulfinyl ($-\text{S}(\text{O})\text{R}_{bb}$), sulfonyl ($-\text{S}(\text{O})_2\text{R}_{bb}$) and sulfonimidoyl ($-\text{S}(\text{O})_2\text{N}(\text{R}_{bb})(\text{R}_{cc})$ or $-\text{N}(\text{R}_{bb})\text{S}(\text{O})_2\text{R}_{bb}$). Wherein each R_{aa} , R_{bb} and R_{cc} is, independently, H, an optionally linked chemical functional group or a further substituent group with a preferred list including without limitation, alkyl, alkenyl, alkynyl, aliphatic, alkoxy, acyl, aryl, aralkyl, heteroaryl, alicyclic, heterocyclic and heteroarylalkyl. Selected substituents within the compounds described herein are present to a recursive degree.

[0289] As used herein, “alkyl,” as used herein, means a saturated straight or branched hydrocarbon radical containing up to twenty four carbon atoms. Examples of alkyl groups include without limitation, methyl, ethyl, propyl, butyl, isopropyl, n-hexyl, octyl, decyl, dodecyl and the like. Alkyl groups typically include from 1 to about 24 carbon atoms, more typically from 1 to about 12 carbon atoms (C1-C12 alkyl) with from 1 to about 6 carbon atoms being more preferred.

[0290] As used herein, “alkenyl,” means a straight or branched hydrocarbon chain radical containing up to twenty four carbon atoms and having at least one carbon-carbon double bond. Examples of alkenyl groups include without limitation, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, dienes such as 1,3-butadiene and the like. Alkenyl groups typically include from 2 to about 24 carbon atoms, more typically from 2 to about 12 carbon atoms with from 2 to about 6 carbon atoms being more preferred. Alkenyl groups as used herein may optionally include one or more further substituent groups.

[0291] As used herein, “alkynyl,” means a straight or branched hydrocarbon radical containing up to twenty four carbon atoms and having at least one carbon-carbon triple bond. Examples of alkynyl groups include, without limitation, ethynyl, 1-propynyl, 1-butyne, and the like. Alkynyl groups typically include from 2 to about 24 carbon atoms, more typically from 2 to about 12 carbon atoms with from 2 to about 6 carbon atoms being more preferred. Alkynyl groups as used herein may optionally include one or more further substituent groups.

[0292] As used herein, “acyl,” means a radical formed by removal of a hydroxyl group from an organic acid and has the general Formula $-\text{C}(\text{O})-\text{X}$ where X is typically aliphatic, alicyclic or aromatic. Examples include aliphatic carbonyls, aromatic carbonyls, aliphatic sulfonyls, aromatic sulfinyls, aliphatic sulfinyls, aromatic phosphates, aliphatic phosphates and the like. Acyl groups as used herein may optionally include further substituent groups.

[0293] As used herein, “alicyclic” means a cyclic ring system wherein the ring is aliphatic. The ring system can comprise one or more rings wherein at least one ring is aliphatic. Preferred alicyclics include rings having from about 5 to about 9 carbon atoms in the ring. Alicyclic as used herein may optionally include further substituent groups.

[0294] As used herein, “aliphatic” means a straight or branched hydrocarbon radical containing up to twenty four carbon atoms wherein the saturation between any two carbon atoms is a single, double or triple bond. An aliphatic group preferably contains from 1 to about 24 carbon atoms, more typically from 1 to about 12 carbon atoms with from 1 to about 6 carbon atoms being more preferred. The straight or branched chain of an aliphatic group may be interrupted with one or more heteroatoms that include nitrogen, oxygen, sulfur and phosphorus. Such aliphatic groups interrupted by heteroatoms include without limitation, polyalkoxys, such

as polyalkylene glycols, polyamines, and polyimines. Aliphatic groups as used herein may optionally include further substituent groups.

[0295] As used herein, “alkoxy” means a radical formed between an alkyl group and an oxygen atom wherein the oxygen atom is used to attach the alkoxy group to a parent molecule. Examples of alkoxy groups include without limitation, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxo, neopentoxo, n-hexoxo and the like. Alkoxy groups as used herein may optionally include further substituent groups.

[0296] As used herein, “aminoalkyl” means an amino substituted C_1 - C_{12} alkyl radical. The alkyl portion of the radical forms a covalent bond with a parent molecule. The amino group can be located at any position and the aminoalkyl group can be substituted with a further substituent group at the alkyl and/or amino portions.

[0297] As used herein, “aralkyl” and “arylalkyl” mean an aromatic group that is covalently linked to a C_1 - C_{12} alkyl radical. The alkyl radical portion of the resulting aralkyl (or arylalkyl) group forms a covalent bond with a parent molecule. Examples include without limitation, benzyl, phenethyl and the like. Aralkyl groups as used herein may optionally include further substituent groups attached to the alkyl, the aryl or both groups that form the radical group.

[0298] As used herein, “aryl” and “aromatic” mean a mono- or polycyclic carbocyclic ring system radicals having one or more aromatic rings. Examples of aryl groups include without limitation, phenyl, naphthyl, tetrahydronaphthyl, indanyl, idenyl and the like. Preferred aryl ring systems have from about 5 to about 20 carbon atoms in one or more rings. Aryl groups as used herein may optionally include further substituent groups.

[0299] As used herein, “halo” and “halogen,” mean an atom selected from fluorine, chlorine, bromine and iodine.

[0300] As used herein, “heteroaryl,” and “heteroaromatic,” mean a radical comprising a mono- or poly-cyclic aromatic ring, ring system or fused ring system wherein at least one of the rings is aromatic and includes one or more heteroatoms. Heteroaryl is also meant to include fused ring systems including systems where one or more of the fused rings contain no heteroatoms. Heteroaryl groups typically include one ring atom selected from sulfur, nitrogen or oxygen. Examples of heteroaryl groups include without limitation, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl and the like. Heteroaryl radicals can be attached to a parent molecule directly or through a linking moiety such as an aliphatic group or hetero atom. Heteroaryl groups as used herein may optionally include further substituent groups.

Oligomeric Compounds

[0301] In certain embodiments, the present invention provides oligomeric compounds. In certain embodiments, such oligomeric compounds comprise oligonucleotides optionally comprising one or more conjugate and/or terminal groups. In certain embodiments, an oligomeric compound consists of an oligonucleotide. In certain embodiments, oligonucleotides comprise one or more chemical modifications. Such chemical modifications include modifications one or more nucleoside (including modifications to the sugar

moiety and/or the nucleobase) and/or modifications to one or more internucleoside linkage.

[0302] Certain Sugar Moieties

[0303] In certain embodiments, oligomeric compounds of the invention comprise one or more modified nucleosides comprising a modified sugar moiety. Such oligomeric compounds comprising one or more sugar-modified nucleosides may have desirable properties, such as enhanced nuclease stability or increased binding affinity with a target nucleic acid relative to oligomeric compounds comprising only nucleosides comprising naturally occurring sugar moieties. In certain embodiments, modified sugar moieties are substituted sugar moieties. In certain embodiments, modified sugar moieties are bicyclic or tricyclic sugar moieties. In certain embodiments, modified sugar moieties are sugar surrogates. Such sugar surrogates may comprise one or more substitutions corresponding to those of substituted sugar moieties.

[0304] In certain embodiments, modified sugar moieties are substituted sugar moieties comprising one or more substituent, including but not limited to substituents at the 2' and/or 5' positions. Examples of sugar substituents suitable for the 2'-position, include, but are not limited to: 2'-F, 2'-OCH₃ (“OMe” or “O-methyl”), and 2'-O(CH₂)₂OCH₃ (“MOE”). In certain embodiments, sugar substituents at the 2' position is selected from allyl, amino, azido, thio, O-allyl, O- C_1 - C_{10} alkyl, O- C_1 - C_{10} substituted alkyl; O- C_1 - C_{10} alkoxy; O- C_1 - C_{10} substituted alkoxy, OCF₃, O(CH₂)₂SCH₃, O(CH₂)₂-O-N(R_m)(R_n), and O-CH₂-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H or substituted or unsubstituted C_1 - C_{10} alkyl. Examples of sugar substituents at the 5'-position, include, but are not limited to: 5'-methyl (R or S); 5'-vinyl, and 5'-methoxy.

[0305] In certain embodiments, substituted sugars comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties (see, e.g., PCT International Application WO 2008/101157, for additional 5', 2'-bis substituted sugar moieties and nucleosides).

[0306] Nucleosides comprising 2'-substituted sugar moieties are referred to as 2'-substituted nucleosides. In certain embodiments, a 2'-substituted nucleoside comprises a 2'-substituent group selected from halo, allyl, amino, azido, O- C_1 - C_{10} alkoxy; O- C_1 - C_{10} substituted alkoxy, SH, CN, OCN, CF₃, OCF₃, O-alkyl, S-alkyl, N(R_m)-alkyl; O-alkenyl, S-alkenyl, or N(R_m)-alkenyl; O-alkynyl, S-alkynyl, N(R_m)-alkynyl; O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, O(CH₂)₂SCH₃, O-(CH₂)₂-O-N(R_m)(R_n) or O-CH₂-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H, an amino protecting group or substituted or unsubstituted C_1 - C_{10} alkyl. These 2'-substituent groups can be further substituted with one or more substituent groups independently selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO₂), thiol, thioalkoxy (S-alkyl), halogen, alkyl, aryl, alkenyl and alkynyl.

[0307] In certain embodiments, a 2'-substituted nucleoside comprises a 2'-substituent group selected from F, NH₂, N₃, OCF₃, O-CH₃, O(CH₂)₃NH₂, CH₂-CH=CH₂, O-CH₂-CH=CH₂, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O-(CH₂)₂-O-N(R_m)(R_n), O(CH₂)₂O(CH₂)₂N(CH₃)₂, and N-substituted acetamide (O-CH₂-C(=O)-N(R_m))

(R_m) where each R_m and R_n is, independently, H, an amino protecting group or substituted or unsubstituted C_1 - C_{10} alkyl.

[0308] In certain embodiments, a 2'-substituted nucleoside comprises a sugar moiety comprising a 2'-substituent group selected from F, OCF_3 , $O-CH_3$, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O-(CH_2)_2-O-N(CH_3)_2$, $-O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and $O-CH_2-C(=O)-N(H)CH_3$.

[0309] In certain embodiments, a 2'-substituted nucleoside comprises a sugar moiety comprising a 2'-substituent group selected from F, $O-CH_3$, and $OCH_2CH_2OCH_3$.

[0310] Certain modified sugar moieties comprise a bridging sugar substituent that forms a second ring resulting in a bicyclic sugar moiety. In certain such embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and the 2' furanose ring atoms. Examples of such 4' to 2' sugar substituents, include, but are not limited to: $-[C(R_a)(R_b)]_n-$, $-[C(R_a)(R_b)]_n-O-$, $-C(R_aR_b)-N(R)-O-$ or, $-C(R_aR_b)-O-N(R)-$; 4'-(CH_2)₂-2', 4'-(CH_2)-O-2' (LNA); 4'-(CH_2)-S-2'; 4'-(CH_2)₂-O-2' (ENA); 4'-CH(CH_3)-O-2' (cEt) and 4'-CH(CH_2OCH_3)-O-2', and analogs thereof (see, e.g., U.S. Pat. No. 7,399,845, issued on Jul. 15, 2008); 4'-C(CH_3)(CH_3)-O-2' and analogs thereof, (see, e.g., WO2009/006478, published Jan. 8, 2009); 4'-CH₂-N(OCH_3)-2' and analogs thereof (see, e.g., WO2008/150729, published Dec. 11, 2008); 4'-CH₂-O-N(CH_3)-2' (see, e.g., US2004/0171570, published Sep. 2, 2004); 4'-CH₂-O-N(R)-2', and 4'-CH₂-N(R)-O-2', wherein each R is, independently, H, a protecting group, or C_1 - C_{12} alkyl; 4'-CH₂-N(R)-O-2', wherein R is H, C_1 - C_{12} alkyl, or a protecting group (see, U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008); 4'-CH₂-C(H)(CH_3)-2' (see, e.g., Chattopadhyaya, et al., J. Org. Chem., 2009, 74, 118-134); and 4'-CH₂-C($=CH_2$)-2' and analogs thereof (see, published PCT International Application WO 2008/154401, published on Dec. 8, 2008).

[0311] In certain embodiments, such 4' to 2' bridges independently comprise from 1 to 4 linked groups independently selected from $-[C(R_a)(R_b)]_n-$, $-C(R_a)=C(R_b)-$, $-C(R_a)=N-$, $-C(=NR_a)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-Si(R_a)_2-$, $-S(=O)_x-$, and $-N(R_a)-$;

[0312] wherein:

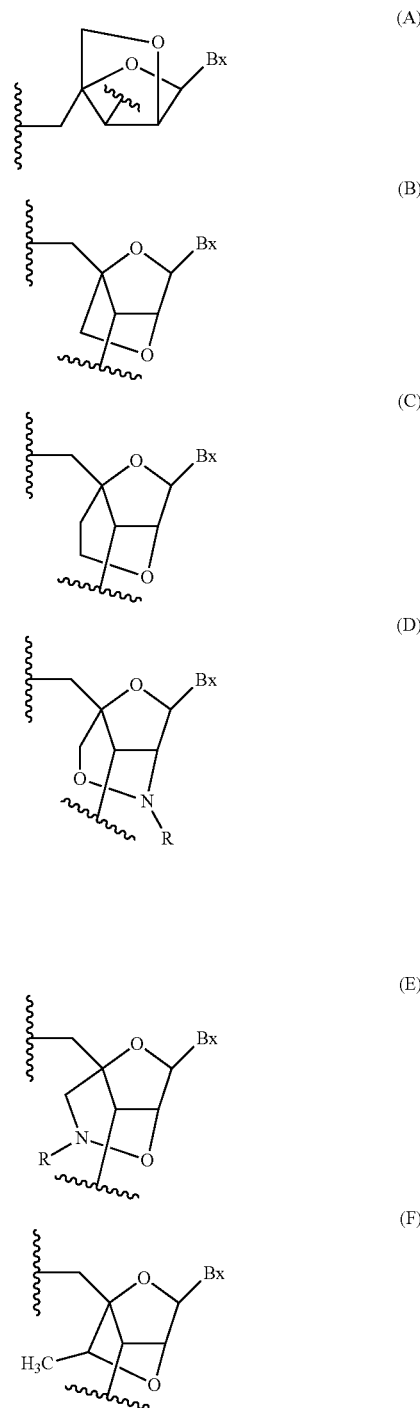
[0313] x is 0, 1, or 2;

[0314] n is 1, 2, 3, or 4;

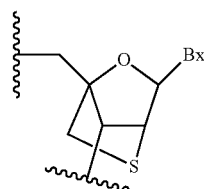
[0315] each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5 - C_7 alicyclic radical, substituted C_5 - C_7 alicyclic radical, halogen, OJ_1 , NJ_1J_2 , SJ_1 , N_3 , $COOJ_1$, acyl ($C(=O)-H$), substituted acyl, CN, sulfonyl ($S(=O)_2-J_1$), or sulfoxyl ($S(=O)-J_1$); and each J_1 and J_2 is, independently, H, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, acyl ($C(=O)-H$), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1 - C_{12} aminoalkyl, substituted C_1 - C_{12} aminoalkyl, or a protecting group.

[0316] Nucleosides comprising bicyclic sugar moieties are referred to as bicyclic nucleosides or BNAs. Bicyclic nucleosides include, but are not limited to, (A) α -L-Methyleneoxy (4'-CH₂-O-2') BNA, (B) β -D-Methyleneoxy (4'-CH₂-O-2') BNA (also referred to as locked nucleic acid or

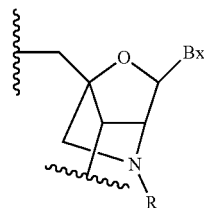
LNA), (C) Ethyleneoxy (4'-(CH_2)₂-O-2') BNA, (D) Aminoxy (4'-CH₂-O-N(R)-2') BNA, (E) Oxyamino (4'-CH₂-N(R)-O-2') BNA, (F) Methyl(methyleneoxy) (4'-CH(CH_3)-O-2') BNA (also referred to as constrained ethyl or cEt), (G) methylene-thio (4'-CH₂-S-2') BNA, (H) methylene-amino (4'-CH₂-N(R)-2') BNA, (I) methyl carbocyclic (4'-CH₂-CH(CH_3)-2') BNA, and (J) propylene carbocyclic (4'-(CH_2)₃-2') BNA as depicted below.



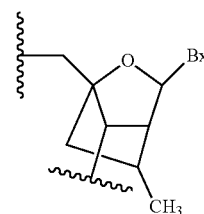
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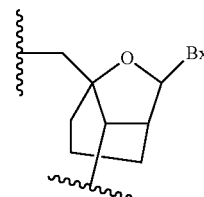
(G)



(H)



(I)



(J)

wherein Bx is a nucleobase moiety and R is, independently, H, a protecting group, or C₁-C₁₂ alkyl.

[0317] Additional bicyclic sugar moieties are known in the art, for example: Singh et al., *Chem. Commun.*, 1998, 4, 455-456; Koshkin et al., *Tetrahedron*, 1998, 54, 3607-3630; Wahlestedt et al., *Proc. Natl. Acad. Sci. U.S.A.*, 2000, 97, 5633-5638; Kumar et al., *Bioorg. Med. Chem. Lett.*, 1998, 8, 2219-2222; Singh et al., *J. Org. Chem.*, 1998, 63, 10035-10039; Srivastava et al., *J. Am. Chem. Soc.*, 129(26) 8362-8379 (Jul. 4, 2007); Elayadi et al., *Curr. Opinion Inven. Drugs*, 2001, 2, 558-561; Braasch et al., *Chem. Biol.*, 2001, 8, 1-7; Orum et al., *Curr. Opinion Mol. Ther.*, 2001, 3, 239-243; U.S. Pat. Nos. 7,053,207, 6,268,490, 6,770,748, 6,794,499, 7,034,133, 6,525,191, 6,670,461, and 7,399,845; WO 2004/106356, WO 1994/14226, WO 2005/021570, and WO 2007/134181; U.S. Patent Publication Nos. US2004/0171570, US2007/0287831, and US2008/0039618; U.S. patent application Ser. Nos. 12/129,154, 60/989,574, 61/026,995, 61/026,998, 61/056,564, 61/086,231, 61/097,787, and 61/099,844; and PCT International Applications Nos. PCT/US2008/064591, PCT/US2008/066154, and PCT/US2008/068922.

[0318] In certain embodiments, bicyclic sugar moieties and nucleosides incorporating such bicyclic sugar moieties are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the α -L configuration or in the β -D configuration. Previously, α -L-methyleneoxy (4'-CH₂-O-2') bicyclic

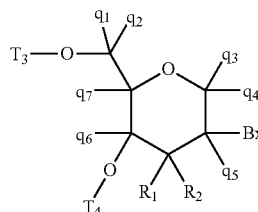
nucleosides have been incorporated into antisense oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research*, 2003, 21, 6365-6372).

[0319] In certain embodiments, substituted sugar moieties comprise one or more non-bridging sugar substituent and one or more bridging sugar substituent (e.g., 5'-substituted and 4'-2' bridged sugars). (see, PCT International Application WO 2007/134181, published on Nov. 22, 2007, wherein LNA is substituted with, for example, a 5'-methyl or a 5'-vinyl group).

[0320] In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the naturally occurring sugar is substituted, e.g., with a sulfur, carbon or nitrogen atom. In certain such embodiments, such modified sugar moiety also comprises bridging and/or non-bridging substituents as described above. For example, certain sugar surrogates comprise a 4'-sulfur atom and a substitution at the 2'-position (see, e.g., published U.S. Patent Application US2005/0130923, published on Jun. 16, 2005) and/or the 5' position. By way of additional example, carbocyclic bicyclic nucleosides having a 4'-2' bridge have been described (see, e.g., Freier et al., *Nucleic Acids Research*, 1997, 25(22), 4429-4443 and Albaek et al., *J. Org. Chem.*, 2006, 71, 7731-7740).

[0321] In certain embodiments, sugar surrogates comprise rings having other than 5-atoms. For example, in certain embodiments, a sugar surrogate comprises a six-membered tetrahydropyran. Such tetrahydropyrans may be further modified or substituted. Nucleosides comprising such modified tetrahydropyrans include, but are not limited to, hexitol nucleic acid (HNA), anitol nucleic acid (ANA), manitol nucleic acid (MNA) (see Leumann, C J. *Bioorg. & Med. Chem.* (2002) 10:841-854), fluoro HNA (F-HNA), and those compounds having Formula VII:

VII



wherein independently for each of said at least one tetrahydropyran nucleoside analog of Formula VII:

[0322] Bx is a nucleobase moiety;

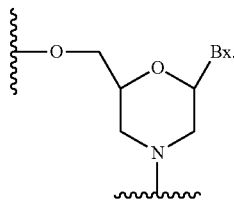
[0323] T₃ and T₄ are each, independently, an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound or one of T₃ and T₄ is an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound and the other of T₃ and T₄ is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group; q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each, independently, H, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl, or substituted C₂-C₆ alkynyl; and

[0324] each of R₁ and R₂ is independently selected from among: hydrogen, halogen, substituted or unsubstituted alkoxy, NJ₁J₂, SJ₁, N₃, OC(=X)J₁, OC(=X)NJ₁J₂, NJ₃C(=X)NJ₁J₂, and CN, wherein X is O, S or NJ₁, and each J₁, J₂, and J₃ is, independently, H or C₁-C₆ alkyl.

[0325] In certain embodiments, the modified THP nucleosides of Formula VII are provided wherein q_1 , q_2 , q_3 , q_4 , q_5 , q_6 and q_7 are each H. In certain embodiments, at least one of q_1 , q_2 , q_3 , q_4 , q_5 , q_6 and q_7 is other than H. In certain embodiments, at least one of q_1 , q_2 , q_3 , q_4 , q_5 , q_6 and q_7 is methyl. In certain embodiments, THP nucleosides of Formula VII are provided wherein one of R_1 and R_2 is F. In certain embodiments, R_1 is fluoro and R_2 is H, R_1 is methoxy and R_2 is H, and R_1 is methoxyethoxy and R_2 is H.

[0326] Many other bicyclic and tricyclic sugar and sugar surrogate ring systems are known in the art that can be used to modify nucleosides (see, e.g., review article: Leumann, J. C., *Bioorganic & Medicinal Chemistry*, 2002, 10, 841-854).

[0327] In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example nucleosides comprising morpholino sugar moieties and their use in oligomeric compounds has been reported (see for example: Braasch et al., *Biochemistry*, 2002, 41, 4503-4510; and U.S. Pat. Nos. 5,698,685; 5,166,315; 5,185,444; and 5,034,506). As used here, the term “morpholino” means a sugar surrogate having the following structure:



In certain embodiments, morpholinos may be modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are referred to herein as “modified morpholinos.”

[0328] Combinations of modifications are also provided without limitation, such as 2'-F-5'-methyl substituted nucleosides (see PCT International Application WO 2008/101157 Published on Aug. 21, 2008 for other disclosed 5', 2'-bis substituted nucleosides) and replacement of the ribosyl ring oxygen atom with S and further substitution at the 2'-position (see published U.S. Patent Application US2005-0130923, published on Jun. 16, 2005) or alternatively 5'-substitution of a bicyclic nucleic acid (see PCT International Application WO 2007/134181, published on Nov. 22, 2007 wherein a 4'-CH₂—O-2' bicyclic nucleoside is further substituted at the 5' position with a 5'-methyl or a 5'-vinyl group). The synthesis and preparation of carbocyclic bicyclic nucleosides along with their oligomerization and biochemical studies have also been described (see, e.g., Srivastava et al., *J. Am. Chem. Soc.* 2007, 129(26), 8362-8379).

[0329] Certain Nucleobases

[0330] In certain embodiments, nucleosides of the present invention comprise one or more unmodified nucleobases. In certain embodiments, nucleosides of the present invention comprise one or more modified nucleobases.

[0331] In certain embodiments, modified nucleobases are selected from: universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases as defined herein. 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil; 5-propynylcytosine;

5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl CH₃) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine, 3-deazaguanine and 3-deazaadenine, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases as defined herein. Further modified nucleobases include tricyclic pyrimidines such as phenoxazine cytidine ([5,4-b][1,4]benzoxazin-2(3H)-one), phenothiazine cytidine (1H-pyrimido[5,4-b][1,4]benzothiazin-2(3H)-one), G-clamps such as a substituted phenoxazine cytidine (e.g. 9-(2-aminoethoxy)-H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), carbazole cytidine (2H-pyrimido[4,5-b]indol-2-one), pyridindole cytidine (H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-one). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, Kroschwitz, J. I., Ed., John Wiley & Sons, 1990, 858-859; those disclosed by Englisch et al., *Angewandte Chemie*, International Edition, 1991, 30, 613; and those disclosed by Sanghvi, Y. S., Chapter 15, *Antisense Research and Applications*, Crooke, S. T. and Lebleu, B., Eds., CRC Press, 1993, 273-288.

[0332] Representative United States patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include without limitation, U.S. Pat. Nos. 3,687,808; 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121; 5,596,091; 5,614,617; 5,645,985; 5,681,941; 5,750,692; 5,763,588; 5,830,653 and 6,005,096, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference in its entirety.

[0333] Certain Internucleoside Linkages

[0334] In certain embodiments, the present invention provides oligomeric compounds comprising linked nucleosides. In such embodiments, nucleosides may be linked together using any internucleoside linkage. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to, phosphodiester (P=O), phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates (P=S). Representative non-phosphorus containing internucleoside linking groups include, but are not limited to, methylenemethylimino (—CH₂—N(CH₃)—O—CH₂—), thiodiester (—O—C(O)—S—), thionocarbamate (—O—C(O)(NH)—S—), siloxane (—O—Si(H)₂—O—), and N,N'-dimethylhydrazine (—CH₂—N(CH₃)—N(CH₃)—). Modified linkages, compared to natural phosphodiester linkages, can be used to alter, typically increase, nuclease resistance of

the oligomeric compound. In certain embodiments, internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or as separate enantiomers. Representative chiral linkages include, but are not limited to, alkylphosphonates and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art.

[0335] The oligonucleotides described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (R) or (S), α or β such as for sugar anomers, or as (D) or (L) such as for amino acids etc. Included in the antisense compounds provided herein are all such possible isomers, as well as their racemic and optically pure forms.

[0336] Neutral internucleoside linkages include without limitation, phosphotriesters, methylphosphonates, MMI (3'-CH₂-N(CH₃)-O-5'), amide-3 (3'-CH₂-C(=O)-N(H)-5'), amide-4 (3'-CH₂-N(H)-C(=O)-5'), formacetal (3'-O-CH₂-O-5'), and thioformacetal (3'-S-CH₂-O-5'). Further neutral internucleoside linkages include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (See for example: *Carbohydrate Modifications in Antisense Research*; Y. S. Sanghvi and P. D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH₂ component parts.

[0337] Certain Motifs

[0338] In certain embodiments, the present invention provides oligomeric compounds comprising oligonucleotides. In certain embodiments, such oligonucleotides comprise one or more chemical modification. In certain embodiments, chemically modified oligonucleotides comprise one or more modified nucleosides. In certain embodiments, chemically modified oligonucleotides comprise one or more modified nucleosides comprising modified sugars. In certain embodiments, chemically modified oligonucleotides comprise one or more modified nucleobases. In certain embodiments, chemically modified oligonucleotides comprise one or more modified internucleoside linkages. In certain embodiments, the chemical modifications (sugar modifications, nucleobase modifications, and/or linkage modifications) define a pattern or motif. In certain embodiments, the patterns of chemical modifications of sugar moieties, internucleoside linkages, and nucleobases are each independent of one another. Thus, an oligonucleotide may be described by its sugar modification motif, internucleoside linkage motif and/or nucleobase modification motif (as used herein, nucleobase modification motif describes the chemical modifications to the nucleobases independent of the sequence of nucleobases).

[0339] Certain Sugar Motifs

[0340] In certain embodiments, oligonucleotides comprise one or more type of modified sugar moieties and/or naturally occurring sugar moieties arranged along an oligonucleotide or region thereof in a defined pattern or sugar modification motif. Such motifs may include any of the sugar modifications discussed herein and/or other known sugar modifications.

[0341] In certain embodiments, the oligonucleotides comprise or consist of a region having a gapmer sugar modification motif, which comprises two external regions or

“wings” and an internal region or “gap.” The three regions of a gapmer motif (the 5'-wing, the gap, and the 3'-wing) form a contiguous sequence of nucleosides wherein at least some of the sugar moieties of the nucleosides of each of the wings differ from at least some of the sugar moieties of the nucleosides of the gap. Specifically, at least the sugar moieties of the nucleosides of each wing that are closest to the gap (the 3'-most nucleoside of the 5'-wing and the 5'-most nucleoside of the 3'-wing) differ from the sugar moiety of the neighboring gap nucleosides, thus defining the boundary between the wings and the gap. In certain embodiments, the sugar moieties within the gap are the same as one another. In certain embodiments, the gap includes one or more nucleoside having a sugar moiety that differs from the sugar moiety of one or more other nucleosides of the gap. In certain embodiments, the sugar modification motifs of the two wings are the same as one another (symmetric gapmer). In certain embodiments, the sugar modification motifs of the 5'-wing differs from the sugar modification motif of the 3'-wing (asymmetric gapmer). In certain embodiments, oligonucleotides comprise 2'-MOE modified nucleosides in the wings and 2'-F modified nucleosides in the gap.

[0342] In certain embodiments, oligonucleotides are fully modified. In certain such embodiments, oligonucleotides are uniformly modified. In certain embodiments, oligonucleotides are uniform 2'-MOE. In certain embodiments, oligonucleotides are uniform 2'-F. In certain embodiments, oligonucleotides are uniform morpholino. In certain embodiments, oligonucleotides are uniform BNA. In certain embodiments, oligonucleotides are uniform LNA. In certain embodiments, oligonucleotides are uniform cEt.

[0343] In certain embodiments, oligonucleotides comprise a uniformly modified region and additional nucleosides that are unmodified or differently modified. In certain embodiments, the uniformly modified region is at least 5, 10, 15, or 20 nucleosides in length. In certain embodiments, the uniform region is a 2'-MOE region. In certain embodiments, the uniform region is a 2'-F region. In certain embodiments, the uniform region is a morpholino region. In certain embodiments, the uniform region is a BNA region. In certain embodiments, the uniform region is a LNA region. In certain embodiments, the uniform region is a cEt region.

[0344] In certain embodiments, the oligonucleotide does not comprise more than 4 contiguous unmodified 2'-deoxynucleosides. In certain circumstances, antisense oligonucleotides comprising more than 4 contiguous 2'-deoxynucleosides activate RNase H, resulting in cleavage of the target RNA. In certain embodiments, such cleavage is avoided by not having more than 4 contiguous 2'-deoxynucleosides, for example, where alteration of splicing and not cleavage of a target RNA is desired.

[0345] Certain Internucleoside Linkage Motifs

[0346] In certain embodiments, oligonucleotides comprise modified internucleoside linkages arranged along the oligonucleotide or region thereof in a defined pattern or modified internucleoside linkage motif. In certain embodiments, internucleoside linkages are arranged in a gapped motif, as described above for sugar modification motif. In such embodiments, the internucleoside linkages in each of two wing regions are different from the internucleoside linkages in the gap region. In certain embodiments the internucleoside linkages in the wings are phosphodiester and the internucleoside linkages in the gap are phosphorothioate. The sugar modification motif is independently selected, so

such oligonucleotides having a gapped internucleoside linkage motif may or may not have a gapped sugar modification motif and if it does have a gapped sugar motif, the wing and gap lengths may or may not be the same.

[0347] In certain embodiments, oligonucleotides comprise a region having an alternating internucleoside linkage motif. In certain embodiments, oligonucleotides of the present invention comprise a region of uniformly modified internucleoside linkages. In certain such embodiments, the oligonucleotide comprises a region that is uniformly linked by phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide is uniformly linked by phosphorothioate. In certain embodiments, each internucleoside linkage of the oligonucleotide is selected from phosphodiester and phosphorothioate. In certain embodiments, each internucleoside linkage of the oligonucleotide is selected from phosphodiester and phosphorothioate and at least one internucleoside linkage is phosphorothioate.

[0348] In certain embodiments, the oligonucleotide comprises at least 6 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 8 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 10 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 6 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 8 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 10 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 12 consecutive phosphorothioate internucleoside linkages. In certain such embodiments, at least one such block is located at the 3' end of the oligonucleotide. In certain such embodiments, at least one such block is located within 3 nucleosides of the 3' end of the oligonucleotide.

[0349] In certain embodiments, compounds and compositions, including modified oligonucleotides, are delivered to the CNS. In certain embodiments, compounds and compositions, including modified oligonucleotides, are delivered to the CNS via intracerebroventricular administration or intracerebroventricular bolus administration. In certain embodiments, one or more modified oligonucleotides may exhibit high potency and high selectivity toward a nucleic acid target, but may possess certain degrees of acute toxicity when delivered into the CNS via intracerebroventricular administration. In certain embodiments, introduction of one or more modifications to the internucleoside linkages of the modified oligonucleotide ameliorates or reduces acute toxicity associated with CNS delivery via intracerebroventricular administration. In certain embodiments, introduction of one or more phosphodiester internucleoside linkages into the modified oligonucleotide ameliorates or reduces acute toxicity associated with CNS delivery via intracerebroventricular administration.

[0350] In certain embodiments, an oligomeric compound has an internucleoside linkage motif selected from the table below, wherein each "N" represents a nucleoside, each subscript "s" represents a phosphorothioate internucleoside linkage, and each subscript "o" represents a phosphodiester internucleoside linkage:

Internucleoside Linkage Motifs
$N_s N_s N_o N_s N_o N_s N_o N_s N_o N_s N_o N_s N$
$N_s N_o N_o N_s N_s N_s N_s N_s N_o N_o N_s N$

[0351] In certain embodiments, the inclusion of 3, 4, 5, 6, 7, 8, or 9 phosphodiester internucleoside linkages into the modified oligonucleotide ameliorates or reduces acute toxicity associated with CNS delivery via intracerebroventricular administration.

[0352] Certain Nucleobase Modification Motifs

[0353] In certain embodiments, oligonucleotides comprise chemical modifications to nucleobases arranged along the oligonucleotide or region thereof in a defined pattern or nucleobases modification motif. In certain such embodiments, nucleobase modifications are arranged in a gapped motif. In certain embodiments, nucleobase modifications are arranged in an alternating motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases is chemically modified.

[0354] In certain embodiments, oligonucleotides comprise a block of modified nucleobases. In certain such embodiments, the block is at the 3'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleotides of the 3'-end of the oligonucleotide. In certain such embodiments, the block is at the 5'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleotides of the 5'-end of the oligonucleotide.

[0355] In certain embodiments, nucleobase modifications are a function of the natural base at a particular position of an oligonucleotide. For example, in certain embodiments each purine or each pyrimidine in an oligonucleotide is modified. In certain embodiments, each adenine is modified. In certain embodiments, each guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each cytosine is modified. In certain embodiments, each uracil is modified.

[0356] In certain embodiments, some, all, or none of the cytosine moieties in an oligonucleotide are 5-methyl cytosine moieties. Herein, 5-methyl cytosine is not a "modified nucleobase." Accordingly, unless otherwise indicated, unmodified nucleobases include both cytosine residues having a 5-methyl and those lacking a 5 methyl. In certain embodiments, the methylation state of all or some cytosine nucleobases is specified.

[0357] Certain Overall Lengths

[0358] In certain embodiments, the present invention provides oligomeric compounds including oligonucleotides of any of a variety of ranges of lengths. In certain embodiments, the invention provides oligomeric compounds or oligonucleotides consisting of X to Y linked nucleosides, where X represents the fewest number of nucleosides in the range and Y represents the largest number of nucleosides in the range. In certain such embodiments, X and Y are each independently selected from 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, and 50; provided that $X < Y$. For example, in certain embodiments, the invention provides oligomeric compounds which comprise oligonucleotides consisting of 8 to 9, 8 to 10, 8 to 11, 8 to 12, 8 to 13, 8 to 14, 8 to 15, 8 to 16, 8 to 17, 8 to 18, 8 to 19, 8 to 20, 8 to 21, 8 to 22, 8 to 23, 8 to 24, 8 to 25, 8 to 26, 8 to 27, 8 to 28, 8 to 29, 8 to 30,

9 to 10, 9 to 11, 9 to 12, 9 to 13, 9 to 14, 9 to 15, 9 to 16, 9 to 17, 9 to 18, 9 to 19, 9 to 20, 9 to 21, 9 to 22, 9 to 23, 9 to 24, 9 to 25, 9 to 26, 9 to 27, 9 to 28, 9 to 29, 9 to 30, 10 to 11, 10 to 12, 10 to 13, 10 to 14, 10 to 15, 10 to 16, 10 to 17, 10 to 18, 10 to 19, 10 to 20, 10 to 21, 10 to 22, 10 to 23, 10 to 24, 10 to 25, 10 to 26, 10 to 27, 10 to 28, 10 to 29, 10 to 30, 11 to 12, 11 to 13, 11 to 14, 11 to 15, 11 to 16, 11 to 17, 11 to 18, 11 to 19, 11 to 20, 11 to 21, 11 to 22, 11 to 23, 11 to 24, 11 to 25, 11 to 26, 11 to 27, 11 to 28, 11 to 29, 11 to 30, 12 to 13, 12 to 14, 12 to 15, 12 to 16, 12 to 17, 12 to 18, 12 to 19, 12 to 20, 12 to 21, 12 to 22, 12 to 23, 12 to 24, 12 to 25, 12 to 26, 12 to 27, 12 to 28, 12 to 29, 12 to 30, 13 to 14, 13 to 15, 13 to 16, 13 to 17, 13 to 18, 13 to 19, 13 to 20, 13 to 21, 13 to 22, 13 to 23, 13 to 24, 13 to 25, 13 to 26, 13 to 27, 13 to 28, 13 to 29, 13 to 30, 14 to 15, 14 to 16, 14 to 17, 14 to 18, 14 to 19, 14 to 20, 14 to 21, 14 to 22, 14 to 23, 14 to 24, 14 to 25, 14 to 26, 14 to 27, 14 to 28, 14 to 29, 14 to 30, 15 to 16, 15 to 17, 15 to 18, 15 to 19, 15 to 20, 15 to 21, 15 to 22, 15 to 23, 15 to 24, 15 to 25, 15 to 26, 15 to 27, 15 to 28, 15 to 29, 15 to 30, 16 to 17, 16 to 18, 16 to 19, 16 to 20, 16 to 21, 16 to 22, 16 to 23, 16 to 24, 16 to 25, 16 to 26, 16 to 27, 16 to 28, 16 to 29, 16 to 30, 17 to 18, 17 to 19, 17 to 20, 17 to 21, 17 to 22, 17 to 23, 17 to 24, 17 to 25, 17 to 26, 17 to 27, 17 to 28, 17 to 29, 17 to 30, 18 to 19, 18 to 20, 18 to 21, 18 to 22, 18 to 23, 18 to 24, 18 to 25, 18 to 26, 18 to 27, 18 to 28, 18 to 29, 18 to 30, 19 to 20, 19 to 21, 19 to 22, 19 to 23, 19 to 24, 19 to 25, 19 to 26, 19 to 27, 19 to 28, 19 to 29, 19 to 30, 20 to 21, 20 to 22, 20 to 23, 20 to 24, 20 to 25, 20 to 26, 20 to 27, 20 to 28, 20 to 29, 20 to 30, 21 to 22, 21 to 23, 21 to 24, 21 to 25, 21 to 26, 21 to 27, 21 to 28, 21 to 29, 21 to 30, 22 to 23, 22 to 24, 22 to 25, 22 to 26, 22 to 27, 22 to 28, 22 to 29, 22 to 30, 23 to 24, 23 to 25, 23 to 26, 23 to 27, 23 to 28, 23 to 29, 23 to 30, 24 to 25, 24 to 26, 24 to 27, 24 to 28, 24 to 29, 24 to 30, 25 to 26, 25 to 27, 25 to 28, 25 to 29, 25 to 30, 26 to 27, 26 to 28, 26 to 29, 26 to 30, 27 to 28, 27 to 29, 27 to 30, 28 to 29, 28 to 30, or 29 to 30 linked nucleosides. In embodiments where the number of nucleosides of an oligomeric compound or oligonucleotide is limited, whether to a range or to a specific number, the oligomeric compound or oligonucleotide may, nonetheless further comprise additional other substituents. For example, an oligonucleotide comprising 8-30 nucleosides excludes oligonucleotides having 31 nucleosides, but, unless otherwise indicated, such an oligonucleotide may further comprise, for example one or more conjugates, terminal groups, or other substituents. In certain embodiments, a gapmer oligonucleotide has any of the above lengths.

[0359] One of skill in the art will appreciate that certain lengths may not be possible for certain motifs. For example: a gapmer having a 5'-wing region consisting of four nucleotides, a gap consisting of at least six nucleotides, and a 3'-wing region consisting of three nucleotides cannot have an overall length less than 13 nucleotides. Thus, one would understand that the lower length limit is 13 and that the limit of 10 in "10-20" has no effect in that embodiment.

[0360] Further, where an oligonucleotide is described by an overall length range and by regions having specified lengths, and where the sum of specified lengths of the regions is less than the upper limit of the overall length range, the oligonucleotide may have additional nucleosides, beyond those of the specified regions, provided that the total number of nucleosides does not exceed the upper limit of the overall length range. For example, an oligonucleotide con-

sisting of 20-25 linked nucleosides comprising a 5'-wing consisting of 5 linked nucleosides; a 3'-wing consisting of 5 linked nucleosides and a central gap consisting of 10 linked nucleosides ($5+5+10=20$) may have up to 5 nucleosides that are not part of the 5'-wing, the 3'-wing, or the gap (before reaching the overall length limitation of 25). Such additional nucleosides may be 5' of the 5'-wing and/or 3' of the 3' wing.

[0361] Certain Oligonucleotides

[0362] In certain embodiments, oligonucleotides of the present invention are characterized by their sugar motif, internucleoside linkage motif, nucleobase modification motif and overall length. In certain embodiments, such parameters are each independent of one another. Thus, each internucleoside linkage of an oligonucleotide having a gapmer sugar motif may be modified or unmodified and may or may not follow the gapmer modification pattern of the sugar modifications. Thus, the internucleoside linkages within the wing regions of a sugar-gapmer may be the same or different from one another and may be the same or different from the internucleoside linkages of the gap region. Likewise, such sugar-gapmer oligonucleotides may comprise one or more modified nucleobase independent of the gapmer pattern of the sugar modifications. Herein if a description of an oligonucleotide or oligomeric compound is silent with respect to one or more parameter, such parameter is not limited. Thus, an oligomeric compound described only as having a gapmer sugar motif without further description may have any length, internucleoside linkage motif, and nucleobase modification motif. Unless otherwise indicated, all chemical modifications are independent of nucleobase sequence.

[0363] Certain Conjugate Groups

[0364] In certain embodiments, oligomeric compounds are modified by attachment of one or more conjugate groups. In general, conjugate groups modify one or more properties of the attached oligomeric compound including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, cellular distribution, cellular uptake, charge and clearance. Conjugate groups are routinely used in the chemical arts and are linked directly or via an optional conjugate linking moiety or conjugate linking group to a parent compound such as an oligomeric compound, such as an oligonucleotide. Conjugate groups includes without limitation, intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, thioethers, polyethers, cholesterol, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins and dyes. Certain conjugate groups have been described previously, for example: cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660, 306-309; Manoharan et al., Bioorg. Med. Chem. Lett., 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, e.g., do-decan-diol or undecyl residues (Saison-Behmoaras et al., EMBO J., 1991, 10, 1111-1118; Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol

chain (Manoharan et al., *Nucleosides & Nucleotides*, 1995, 14, 969-973), or adamantane acetic acid (Manoharan et al., *Tetrahedron Lett.*, 1995, 36, 3651-3654), a palmitoyl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, 1264, 229-237), or an octadecylamine or hexylamino-carbonyl-oxy-cholesterol moiety (Crooke et al., *J. Pharmacol. Exp. Ther.*, 1996, 277, 923-937).

[0365] In certain embodiments, a conjugate group comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fen-bufen, ketoprofen, (S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triodobenzoic acid, flufenamic acid, folic acid, a benzothiadiazide, chlorothiazide, a diazepam, indo-methicin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

[0366] In certain embodiments, conjugate groups are directly attached to oligonucleotides in oligomeric compounds. In certain embodiments, conjugate groups are attached to oligonucleotides by a conjugate linking group. In certain such embodiments, conjugate linking groups, including, but not limited to, bifunctional linking moieties such as those known in the art are amenable to the compounds provided herein. Conjugate linking groups are useful for attachment of conjugate groups, such as chemical stabilizing groups, functional groups, reporter groups and other groups to selective sites in a parent compound such as for example an oligomeric compound. In general a bifunctional linking moiety comprises a hydrocarbyl moiety having two functional groups. One of the functional groups is selected to bind to a parent molecule or compound of interest and the other is selected to bind essentially any selected group such as chemical functional group or a conjugate group. In some embodiments, the conjugate linker comprises a chain structure or an oligomer of repeating units such as ethylene glycol or amino acid units. Examples of functional groups that are routinely used in a bifunctional linking moiety include, but are not limited to, electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In some embodiments, bifunctional linking moieties include amino, hydroxyl, carboxylic acid, thiol, unsaturations (e.g., double or triple bonds), and the like.

[0367] Some nonlimiting examples of conjugate linking moieties include pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminohexanoic acid (AHX or AHA). Other linking groups include, but are not limited to, substituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl or substituted or unsubstituted C_2 - C_{10} alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

[0368] Conjugate groups may be attached to either or both ends of an oligonucleotide (terminal conjugate groups) and/or at any internal position.

[0369] In certain embodiments, conjugate groups are at the 3'-end of an oligonucleotide of an oligomeric compound. In certain embodiments, conjugate groups are near the 3'-end. In certain embodiments, conjugates are attached at the 3'-end of an oligomeric compound, but before one or more terminal group nucleosides. In certain embodiments, conjugate groups are placed within a terminal group.

[0370] In certain embodiments, the present invention provides oligomeric compounds. In certain embodiments, oli-

gomer compounds comprise an oligonucleotide. In certain embodiments, an oligomeric compound comprises an oligonucleotide and one or more conjugate and/or terminal groups. Such conjugate and/or terminal groups may be added to oligonucleotides having any of the chemical motifs discussed above. Thus, for example, an oligomeric compound comprising an oligonucleotide having region of alternating nucleosides may comprise a terminal group.

Antisense Compounds

[0371] In certain embodiments, oligomeric compounds of the present invention are antisense compounds. Such antisense compounds are capable of hybridizing to a target nucleic acid, resulting in at least one antisense activity. In certain embodiments, antisense compounds specifically hybridize to one or more target nucleic acid. In certain embodiments, a specifically hybridizing antisense compound has a nucleobase sequence comprising a region having sufficient complementarity to a target nucleic acid to allow hybridization and result in antisense activity and insufficient complementarity to any non-target so as to avoid non-specific hybridization to any non-target nucleic acid sequences under conditions in which specific hybridization is desired (e.g., under physiological conditions for in vivo or therapeutic uses, and under conditions in which assays are performed in the case of in vitro assays).

[0372] In certain embodiments, the present invention provides antisense compounds comprising oligonucleotides that are fully complementary to the target nucleic acid over the entire length of the oligonucleotide. In certain embodiments, oligonucleotides are 99% complementary to the target nucleic acid. In certain embodiments, oligonucleotides are 95% complementary to the target nucleic acid. In certain embodiments, such oligonucleotides are 90% complementary to the target nucleic acid.

[0373] In certain embodiments, such oligonucleotides are 85% complementary to the target nucleic acid. In certain embodiments, such oligonucleotides are 80% complementary to the target nucleic acid. In certain embodiments, an antisense compound comprises a region that is fully complementary to a target nucleic acid and is at least 80% complementary to the target nucleic acid over the entire length of the oligonucleotide. In certain such embodiments, the region of full complementarity is from 6 to 14 nucleobases in length.

[0374] In certain embodiments antisense compounds and antisense oligonucleotides comprise single-strand compounds. In certain embodiments antisense compounds and antisense oligonucleotides comprise double-strand compounds.

[0375] Certain Modified Oligonucleotides

[0376] In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 31. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 33. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 34. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 35. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 36. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 37. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 45.

[0377] In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 72. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 79. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 82. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 83. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 97. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 106. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 107. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 112. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 113. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 130. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 140.

[0378] In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 141. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 142. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 143. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 144. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 145. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 146. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 147. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 148. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 149.

[0379] In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 150. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 151. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 152. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 153. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 157. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 158. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 160. In certain embodiments, a modified oligonucleotide has the sequence of SEQ ID NO. 200.

[0380] Certain Pathways and Mechanisms Associated with Neurodegenerative Disorders

[0381] In certain embodiments, a neurodegenerative syndrome or disorder may be any neurodegenerative syndrome or disorder associated with Tau. Non limiting examples of a neurodegenerative disorder associated with Tau may include Alzheimer's disease, progressive supranuclear palsy, dementia pugilistica, frontotemporal dementia, parkinsonism linked to chromosome, LYTIC-BODIG disease, tangle-predominant dementia, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, Pick's disease, corticobasal ganglionic degeneration, argyrophilic grain disease, supranuclear palsy, corticobasal degeneration, frontotemporal dementia, or frontotemporal lobar degeneration. In some embodiments, the method of the invention comprises modifying frontotemporal dementia (FTD). In other embodiments, the method of the

invention comprises modifying Alzheimer's disease (AD). In yet other embodiments, the method of the invention comprises modifying progressive supranuclear palsy. In other embodiments, the method of the invention comprises modifying corticobasal ganglionic degeneration.

[0382] In certain embodiments, described herein are compositions and methods of modifying a neurodegenerative syndrome by altering the splicing of a nucleic acid encoding Tau. Tau is a protein found in multiple tissues, but is particularly abundant in axons of neurons. The primary function of Tau is to bind to and stabilize microtubules, which are important structural components of the cytoskeleton involved in mitosis, cytokinesis and vesicular transport. In humans, there are six isoforms of Tau that are generated by alternative splicing of exons 2, 3, and 10. Splicing of exons 2 and 3 at the N-terminus of the protein leads to inclusion of zero, one or two 29 amino acid, acidic domains and is termed 0N, 1N, or 2N Tau respectively. Inclusion of exon 10 at the C-terminus leads to inclusion of the microtubule binding domain encoded by exon 10. Since there are 3 microtubule binding domains elsewhere in Tau, this Tau isoform (with exon 10 included) is termed 4R Tau, where R refers to the number of repeats of microtubule binding domains. (FIG. 1). Tau without exon 10 is termed 3R Tau. In healthy subjects, the ratio of 3R:4R Tau is developmentally regulated, with fetal tissues expressing almost exclusively 3R Tau and adult human tissues expressing approximately equal levels of 3R/4R Tau. Deviations from the normal ratio of 3R/4R Tau are characteristic of neurodegenerative syndromes such as FTD and Tauopathies.

[0383] In certain embodiments, the 4R:3R Tau ratio in the central nervous system of the subject may be normal, low or high. As used herein, a "normal 4R:3R Tau ratio" in the central nervous system signifies a 4R:3R Tau ratio in the central nervous system that is substantially the same as the 4R:3R Tau ratio in the central nervous system of a subject from the same species and of approximately the same age not suffering from a neurodegenerative disease. In certain embodiments, certain antisense oligonucleotide compositions and/or methods decrease the normal 4R:3R Tau ratio in the central nervous system of a subject. In other embodiments, certain antisense oligonucleotide compositions and/or methods decrease a low 4R:3R Tau ratio in the central nervous system of a subject.

[0384] In certain embodiments, certain antisense oligonucleotide compositions and/or methods decrease a high 4R:3R Tau ratio in the central nervous system of a subject. In certain embodiments, certain antisense oligonucleotide compositions and/or methods decrease a high 4R:3R Tau ratio caused by a defect in splicing of the nucleic acid encoding Tau in the subject. Defects in splicing of the nucleic acid encoding Tau in the subject may be caused, for instance, by genetic mutations altering the splicing of the nucleic acid encoding Tau and leading to a high 4R:3R Tau ratio. A mutation may be either a substitution mutation or a deletion mutation which creates a new, aberrant, splice element. Non-limiting examples of genetic mutations that may alter the splicing of the nucleic acid encoding Tau and lead to a high 4R:3R Tau ratio may include N279K, P301S, 280, L284L, N296H, N296N, 296N, P301S, G303V, E10+11, E10+12, E10+13, E+10+14 and E10+16, and E10+19.

[0385] In certain embodiments, administration of an antisense oligonucleotide decreases the 4R:3R Tau ratio in the

central nervous system of a subject by altering the splicing of a nucleic acid encoding Tau.

[0386] In certain embodiments, increasing exclusion of exon 10 of a Tau transcript inhibits one or more tau-associated disorders. In certain embodiments, the tau-associated disorder may be any of Alzheimer's Disease, frontotemporal Dementia (FTD), FTDP-17, Progressive Supranuclear Palsy (PSP), Chronic Traumatic Encephalopathy (CTE), Corticobasal Ganglionic Degeneration (CBD), epilepsy, Dravet's Syndrome, dementia pugilistica, parkinsonism linked to chromosome, LYTICO-BODIG disease, tangle-predominant dementia, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, Pick's disease, argyrophilic grain disease, supranuclear palsy, corticobasal degeneration, or frontotemporal lobar degeneration.

[0387] Certain Target Nucleic Acids and Mechanisms

[0388] In certain embodiments, antisense compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid. In certain embodiments, the target nucleic acid is an endogenous RNA molecule. In certain embodiments, the target nucleic acid is a pre-mRNA. In certain embodiments, the target nucleic acid is a tau transcript. In certain embodiments, the target RNA is a Tau pre-mRNA.

[0389] In certain embodiments, an antisense compound is complementary to a region of Tau pre-mRNA. In certain embodiments, an antisense compound is complementary within a region of Tau pre-mRNA comprising an exon encoding the 4R isoform. In certain embodiments, an antisense compound is complementary to a region of Tau pre-mRNA comprising an intron-exon splice junction. In certain embodiments, an antisense compound is complementary to a region of Tau pre-mRNA comprising the intron-exon splice junction adjacent to exon 10. In certain embodiments, an antisense compound is complementary to a region of Tau pre-mRNA comprising the intron-exon splice junction between intron 9 and exon 10. In certain embodiments, an antisense compound is complementary to a region of Tau pre-mRNA comprising the intron-exon splice junction between exon 10 and intron 10. In certain embodiments, an antisense compound is complementary within a region of Tau pre-mRNA consisting of exon 10.

[0390] In certain embodiments, an antisense compound is complementary within a region of Tau pre-mRNA comprising an exonic splicing silencer within exon 10. In certain embodiments, an antisense compound is complementary within a region of Tau pre-mRNA comprising an exonic splicing enhancer within exon 10.

[0391] In certain embodiments, an antisense compound comprises a modified oligonucleotide consisting of 8 to 30 linked nucleosides and having a nucleobase sequence comprising a complementary region comprising at least 8 contiguous nucleobases complementary to a target region of equal length of a Tau transcript.

[0392] In certain embodiments, the target region is within nucleobase 121708 and nucleobase 122044 of SEQ ID NO: 1. In certain embodiments, the target region is within nucleobase 121796 and nucleobase 122044 of SEQ ID NO: 1. In certain embodiments, the target region is within nucleobase 121796 and nucleobase 121885 of SEQ ID NO: 1. In certain embodiments, the target region is within nucleobase 121873 and nucleobase 121898 of SEQ ID NO: 1. In certain

embodiments, the target region is within nucleobase 121869 and nucleobase 121943 of SEQ ID NO: 1. In certain embodiments, the target region is within nucleobase 122020 and nucleobase 122044 of SEQ ID NO: 1. In certain embodiments, the target region is within nucleobase 121881 and nucleobase 121898 of SEQ ID NO: 1. In certain embodiments, the target region is within nucleobase 121880 and nucleobase 121897 of SEQ ID NO: 1. In certain embodiments, the target region is within nucleobase 121879 and nucleobase 121896 of SEQ ID NO: 1.

[0393] In certain embodiments, the target region is within nucleobase 121878 and nucleobase 121895 of SEQ ID NO: 1. In certain embodiments, the target region is within nucleobase 121877 and nucleobase 121894 of SEQ ID NO: 1. In certain embodiments, the target region is within nucleobase 121876 and nucleobase 121893 of SEQ ID NO: 1. In certain embodiments, the target region is within nucleobase 121875 and nucleobase 121892 of SEQ ID NO: 1. In certain embodiments, the target region is within nucleobase 121874 and nucleobase 121891 of SEQ ID NO: 1. In certain embodiments, the target region is within nucleobase 121873 and nucleobase 121890 of SEQ ID NO: 1.

[0394] In certain embodiments, an antisense oligonucleotide modulates splicing of a pre-mRNA. In certain embodiments, an antisense oligonucleotide modulates splicing a Tau pre-mRNA. In certain embodiments, an antisense oligonucleotide increases the amount of Tau 3R mRNA. In certain embodiments, an antisense oligonucleotide increases the exclusion of exon 10 in Tau mRNA. In certain embodiments, an antisense oligonucleotide decreases the inclusion of exon 10 in Tau mRNA. In certain embodiments, an antisense oligonucleotide increases the amount of 3R Tau mRNA. In certain embodiments, an antisense oligonucleotide decreases the amount of 4R Tau mRNA.

[0395] In certain embodiments it is desirable to alter the splicing of Tau pre-mRNA to exclude exon 10. By altering the splicing of Tau pre-mRNA to exclude exon 10, expression of 3R Tau will increase and expression of 4R Tau will decrease. In certain embodiments it is desirable to alter the splicing of Tau pre-mRNA to decrease expression of 4R Tau.

[0396] In certain embodiments, an antisense oligonucleotide decreases the amount of Tau 3R mRNA. In certain embodiments, an antisense oligonucleotide decreases the exclusion of exon 10 in Tau mRNA. In certain embodiments, an antisense oligonucleotide increases the inclusion of exon 10 in Tau mRNA. In certain embodiments, an antisense oligonucleotide decreases the amount of 3R Tau mRNA. In certain embodiments, an antisense oligonucleotide increases the amount of 4R Tau mRNA. In certain embodiments it is desirable to alter the splicing of Tau pre-mRNA to include exon 10, for example to produce a phenotypic effect in a mouse or animal model.

Certain Pharmaceutical Compositions

[0397] In certain embodiments, the present invention provides pharmaceutical compositions comprising one or more antisense compound. In certain embodiments, such pharmaceutical composition comprises a suitable pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutical composition comprises a sterile saline solution and one or more antisense compound. In certain embodiments, such pharmaceutical composition consists of a sterile saline solution and one or more antisense compound. In certain embodiments, the sterile saline is pharma-

ceutical grade saline. In certain embodiments, a pharmaceutical composition comprises one or more antisense compound and sterile water. In certain embodiments, a pharmaceutical composition consists of one or more antisense compound and sterile water. In certain embodiments, the sterile saline is pharmaceutical grade water. In certain embodiments, a pharmaceutical composition comprises one or more antisense compound and phosphate-buffered saline (PBS). In certain embodiments, a pharmaceutical composition consists of one or more antisense compound and sterile phosphate-buffered saline (PBS). In certain embodiments, the sterile saline is pharmaceutical grade PBS.

[0398] In certain embodiments, antisense compounds may be admixed with pharmaceutically acceptable active and/or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions depend on a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

[0399] Pharmaceutical compositions comprising antisense compounds encompass any pharmaceutically acceptable salts, esters, or salts of such esters. In certain embodiments, pharmaceutical compositions comprising antisense compounds comprise one or more oligonucleotide which, upon administration to an animal, including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of antisense compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts.

[0400] A prodrug can include the incorporation of additional nucleosides at one or both ends of an oligomeric compound which are cleaved by endogenous nucleases within the body, to form the active antisense oligomeric compound.

[0401] Lipid moieties have been used in nucleic acid therapies in a variety of methods. In certain such methods, the nucleic acid is introduced into preformed liposomes or lipoplexes made of mixtures of cationic lipids and neutral lipids. In certain methods, DNA complexes with mono- or poly-cationic lipids are formed without the presence of a neutral lipid. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to a particular cell or tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to fat tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to muscle tissue.

[0402] In certain embodiments, pharmaceutical compositions provided herein comprise one or more modified oligonucleotides and one or more excipients. In certain such embodiments, excipients are selected from water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose and polyvinylpyrrolidone.

[0403] In certain embodiments, a pharmaceutical composition provided herein comprises a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical compositions

including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

[0404] In certain embodiments, a pharmaceutical composition provided herein comprises one or more tissue-specific delivery molecules designed to deliver the one or more pharmaceutical agents of the present invention to specific tissues or cell types. For example, in certain embodiments, pharmaceutical compositions include liposomes coated with a tissue-specific antibody.

[0405] In certain embodiments, a pharmaceutical composition provided herein comprises a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™ and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0406] In certain embodiments, a pharmaceutical composition provided herein is prepared for oral administration. In certain embodiments, pharmaceutical compositions are prepared for buccal administration.

[0407] In certain embodiments, a pharmaceutical composition is prepared for administration by injection (e.g., intravenous, subcutaneous, intramuscular, etc.). In certain of such embodiments, a pharmaceutical composition comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (e.g., ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical compositions for injection are presented in unit dosage form, e.g., in ampoules or in multi-dose containers. Certain pharmaceutical compositions for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, such suspensions may also contain suitable stabilizers or agents that increase the solubility of the pharmaceutical agents to allow for the preparation of highly concentrated solutions.

[0408] In certain embodiments, a pharmaceutical composition is prepared for transmucosal administration. In certain of such embodiments penetrants appropriate to the barrier to

be permeated are used in the formulation. Such penetrants are generally known in the art.

[0409] In certain embodiments, a pharmaceutical composition provided herein comprises an oligonucleotide in a therapeutically effective amount. In certain embodiments, the therapeutically effective amount is sufficient to prevent, alleviate or ameliorate symptoms of a disease or to prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art.

[0410] In certain embodiments, one or more modified oligonucleotide provided herein is formulated as a prodrug. In certain embodiments, upon in vivo administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically more active form of an oligonucleotide. In certain embodiments, prodrugs are useful because they are easier to administer than the corresponding active form. For example, in certain instances, a prodrug may be more bioavailable (e.g., through oral administration) than is the corresponding active form. In certain instances, a prodrug may have improved solubility compared to the corresponding active form. In certain embodiments, prodrugs are less water soluble than the corresponding active form. In certain instances, such prodrugs possess superior transmittal across cell membranes, where water solubility is detrimental to mobility. In certain embodiments, a prodrug is an ester. In certain such embodiments, the ester is metabolically hydrolyzed to carboxylic acid upon administration. In certain instances the carboxylic acid containing compound is the corresponding active form. In certain embodiments, a prodrug comprises a short peptide (polyaminoacid) bound to an acid group. In certain of such embodiments, the peptide is cleaved upon administration to form the corresponding active form.

[0411] In certain embodiments, the present invention provides compositions and methods for reducing the amount or activity of a target nucleic acid in a cell. In certain embodiments, the cell is in an animal. In certain embodiments, the animal is a mammal. In certain embodiments, the animal is a rodent. In certain embodiments, the animal is a primate. In certain embodiments, the animal is a non-human primate. In certain embodiments, the animal is a human.

[0412] In certain embodiments, the present invention provides methods of administering a pharmaceutical composition comprising an oligomeric compound of the present invention to an animal. Suitable administration routes include, but are not limited to, oral, rectal, transmucosal, intestinal, enteral, topical, suppository, through inhalation, intrathecal, intracerebroventricular, intraperitoneal, intranasal, intraocular, intratumoral, and parenteral (e.g., intravenous, intramuscular, intramedullary, and subcutaneous). In certain embodiments, pharmaceutical intrathecal are administered to achieve local rather than systemic exposures. For example, pharmaceutical compositions may be injected directly in the area of desired effect (e.g., into the eyes, ears).

[0413] In certain embodiments, a pharmaceutical composition is administered to an animal having at least one Tau-associated disorder. In certain embodiments, such administration results in reduction in expression of the 4R isoform. In certain embodiments, a pharmaceutical composition is administered to an animal having at least one symptom associated with a Tau-associated disorder. In certain embodiments, such administration results in ameliora-

tion of at least one symptom. In certain embodiments, administration of a pharmaceutical composition to an animal results in a decrease of 4R mRNA in a cell of the animal. In certain embodiments, such administration results in an increase in 3R mRNA. In certain embodiments, such administration results in a decrease in 4R protein and an increase 3R protein. In certain embodiments, a 3R protein is preferred over a 4R protein. In certain embodiments, the administration of certain antisense oligonucleotides delays the onset of one or more Tau-associated disorders. In certain embodiments, the administration of certain antisense oligonucleotides prevents or reduces seizures. In certain embodiments, the administration of certain antisense oligonucleotides causes the amount of 4R protein to decrease in the CNS. In certain embodiments, the administration of certain antisense oligonucleotides rescues cellular phenotype.

Nonlimiting Disclosure and Incorporation by Reference

[0414] While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references, GenBank accession numbers, and the like recited in the present application is incorporated herein by reference in its entirety.

[0415] Although the sequence listing accompanying this filing identifies each sequence as either “RNA” or “DNA” as required, in reality, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as “RNA” or “DNA” to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (2'-OH for the natural 2'-H of DNA) or as an RNA having a modified base (thymine (methylated uracil) for natural uracil of RNA).

[0416] Accordingly, nucleic acid sequences provided herein, including, but not limited to those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to such nucleic acids having modified nucleobases. By way of further example and without limitation, an oligomeric compound having the nucleobase sequence “ATCGATCG” encompasses any oligomeric compounds having such nucleobase sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those having sequence “AUCGAUCG” and those having some DNA bases and some RNA bases such as “AUCGATCG” and oligomeric compounds having other modified or naturally occurring bases, such as “AT^{me}CGAUCG,” wherein ^{me}C indicates a cytosine base comprising a methyl group at the 5-position.

EXAMPLES

Non-Limiting Disclosure and Incorporation by Reference

[0417] While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described

herein and are not intended to limit the same. Each of the references recited in the present application is incorporated herein by reference in its entirety.

Example 1: Effects of Uniform 2'-MOE Modified Oligonucleotides on Human Tau Exon 10

[0418] A series of modified oligonucleotides were designed to target exon 10 of human Tau and were screened for their effects in reducing exon 10 inclusion in vitro. These modified oligonucleotides were designed by shifting 4 nucleotides upstream or downstream (i.e. microwalk) across the target site. They are 18 nucleosides in length, wherein each nucleoside has a 2'-MOE modification. Each internucleoside linkage throughout the modified oligonucleotide are phosphorothioate internucleoside linkages (P=S). All cytosine residues throughout the modified oligonucleotides are 5-methylcytosines.

[0419] “Start site” indicates the 5'-most nucleoside to which the modified oligonucleotide is targeted. “Stop site” indicates the 3'-most nucleoside to which the modified oligonucleotide is targeted. Each modified oligonucleotide listed in the tables below is targeted to SEQ ID NO: 1 (GENBANK Accession No NT_010783.15 truncated from nucleotides 9240000 to 9381000).

[0420] A172 cells were transfected using Lipofectamine2000® with 5 nM concentration of modified oli-

gonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and the mRNA levels of Tau transcripts containing exon 10 were measured by quantitative real-time PCR. Human primer probe set 9_10 or 10_11 was used to measure mRNA levels. Tau exon 10 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent of Tau exon 10 mRNA expression, relative to untreated control levels and is denoted as “% UTC.”

[0421] Human primer probe set 9_10 (forward sequence CACTGAGAACCTGAAGCACC, designated herein as SEQ ID NO: 2; reverse sequence GGACTGGACGTTGCTAAGATC, designated herein as SEQ ID NO: 3; probe sequence TTAAT-TATCTGCACCTTCCCGCCTCC, designated herein as SEQ ID NO: 4).

[0422] Human primer probe set 10_11 (forward sequence GGATAATATCAAACACGTCCCG, designated herein as SEQ ID NO: 5; reverse sequence TGCCTAATGAGC-CACACTTG, designated herein as SEQ ID NO: 6; probe sequence GTCTACAAACCAGTTGACCTGAGC, designated herein as SEQ ID NO: 7).

[0423] As illustrated in Tables 1 and 2, ISIS 549583, 549584, 549585, 549586, 549595, 549571, 549566, 549570, 549587, 549568, 549617, 549567, 549576, 549577, 549580, and 549581 show 70% or greater reduction in human Tau exon 10 inclusion comparing to untreated control.

TABLE 1

Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 using Primer Probe Set 9_10					
ISIS NO	Sequence	% UTC	SEQ ID NO: 1	SEQ ID NO: 1	SEQ ID NO
			Start Site	Stop Site	
549543	CCCGCCTACTTGCTCGCA	130	121708	121725	8
549544	TGGACCCGCTACTTGCT	119	121712	121729	9
549545	ACCCTGGACCCGCTACT	106	121716	121733	10
549546	CATGCGCCACCCCTGGACC	84	121724	121741	11
549547	GTGACATGCGCCACCCCTG	78	121728	121745	12
549548	ATGAGTGACATGCGCCAC	63	121732	121749	13
549549	TTCGATGAGTGACATGCG	70.0	121736	121753	14
549550	CACCTTCGATGAGTGACA	69	121740	121757	15
549551	CCTCCACTTTCGATGAGT	103	121744	121761	16
549552	GACGCCTCCACTTTCGAT	148	121748	121765	17
549553	CAAGGACGCCTCCACTTT	116	121752	121769	18
549554	CTCGCAAGGACGCCTCCA	80	121756	121773	19
549555	CTTGCTCGCAAGGACGCC	102	121760	121777	20
549556	CCTGCTTGCTCGCAAGGA	109	121764	121781	21
549557	CCCGCTGCTTGCTCGCA	100	121768	121785	22
549558	TGGACCCGCTGCTTGCT	111	121772	121789	23
549559	ACCCTGGACCCGCTGCT	108	121776	121793	24
549560	CGCCACCTTGACCCGCC	88	121720	121737	25

TABLE 1-continued

Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 using Primer Probe Set 9_10				
ISIS NO	Sequence	% UTC	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site SEQ ID NO
			121780	121797
549561	GACACGCCACCCTGGACC	83	121784	121801 26
549562	GAGTGACACGCCACCCTG	77	121788	121805 27
549563	GGATGAGTGACACGCCAC	58	121792	121809 28
549564	AAAAGGATGAGTGACACG	49	121796	121813 29
549565	AGAAAAAGGATGAGTGA	35	121800	121817 30
549566	AGCCAGAAAAAGGATGA	21	121804	121821 31
549567	TGGTAGCCAGAAAAAGG	32	121808	121825 32
549583	TTATCCTTTGAGCCACAC	11	121876	121893 33
549584	GATATTATCCTTTGAGCC	11	121880	121897 34
549585	GTTTGATATTATCCTTTG	13	121884	121901 35
549586	ACGTGTTTGATATTATCC	17	121888	121905 36
549587	CGGACGTGTTTGATATT	24	121892	121909 37
549588	CTCCCGGACGTGTTTGA	52	121896	121913 38
549589	CCGCCTCCCGGACGTGT	57	121900	121917 39
549590	ACTGCCGCTCCCGGGAC	84	121904	121921 40
549591	TCACACTGCCGCTCCCG	48	121908	121925 41
549592	GTA CTCACTGCCGCT	30	121912	121929 42
549593	GAAGTACTCACTGCC	35	121916	121933 43
549594	GTGTGAAGGTACTCACAC	63	121920	121937 44
549595	GGACGTGTGAAGGTACTC	20	121924	121941 45
549596	CATGGGACGTGTGAAGGT	125	121928	121945 46
549597	GGCGCATGGGACGTGTGA	216	121932	121949 47
549598	GCACGGCGCATGGGACGT	242	121936	121953 48
549599	CACAGCACGGCGCATGGG	158	121940	121957 49
549600	AAGCCACAGCACGGCGCA	162	121944	121961 50
549601	ATTCAAGCCACAGCACGG	175	121948	121965 51
549602	AATAATTCAAGCCACAGC	164	121952	121969 52
549603	TCCTAATAATTCAAGCCA	200	121956	121973 53
549604	CACTTCCTAATAATTCAA	133	121960	121977 54
549605	ACACCATTCTAATAAT	113	121964	121981 55
549606	ACTCACACCACTTCCTAA	136	121968	121985 56
549608	GTGTACGCACTCACACCA	80.6	121976	121993 57
549609	GCAAGTGTACGCACTCAC	49.9	121980	121997 58
549610	TCTCGCAAGTGTACGCAC	86.5	121984	122001 59

TABLE 1-continued

Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 using Primer Probe Set 9 10					
ISIS NO Sequence	% UTC	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO	
549611 AGTGTCTCGCAAGTGATC	62.4	121988	122005	60	
549612 ATGCAGTGTCTCGCAAGT	46.4	121992	122009	61	
549613 TTCTATGCAGTGTCTCGC	46.6	121996	122013	62	
549614 TTTATTCTATGCAGTGTC	33.2	122000	122017	63	
549615 AGGATTTATTCTATGCAG	34.3	122004	122021	64	
549616 AAGAAGGATTTATTCTAT	46.5	122008	122025	65	
549617 GCCCAAGAAGGATTTATT	29.6	122012	122029	66	
549618 GAGAGCCCAAGAAGGATT	38.6	122016	122033	67	
549619 TCCTGAGAGCCCAAGAAG	36.9	122020	122037	68	
549620 CAGATCCTGAGAGCCCAA	38.3	122024	122041	69	

TABLE 2

Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 using Primer Probe Set 10 11						
ISIS No. Sequence	% UTC	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Mismatches	SEQ ID No.	
549543 CCCGCCTACTTGCTCGCA	128	121725 121768	121708 121785	0 1	8	
549544 TGGACCCGCTACTTGCT	117	121712 121772	121729 121789	0 1	9	
549545 ACCCTGGACCCGCTACT	98	121716 121776	121733 121793	0 1	10	
549546 CATGCGCCACCCTGGACC	78	121724	121741	0	11	
549547 GTGACATGCGCCACCCTG	75	121728	121745	0	12	
549548 ATGAGTGACATGCGCCAC	63	121732	121749	0	13	
549549 TTCGATGAGTGACATGCG	74	121736	121753	0	14	
549550 CACTTTCGATGAGTGACA	76	121740	121757	0	15	
549551 CCTCCACTTTCGATGAGT	107	121744	121761	0	16	
549552 GACGCCTCCACTTTCGAT	137	121748	121765	0	17	
549553 CAAGGACGCCTCCACTTT	108	121692 121752	121709 121769	1 0	18	
549554 CTCGCAAGGACGCCTCCA	71	121696 121756	121713 121773	1 0	19	
549555 CTTGCTCGCAAGGACGCC	108	121700 121760	121717 121777	1 0	20	
549556 CTTGCTTGTCTCGCAAGGA	106	121704 121764	121721 121781	1 0	21	
549557 CCCGCCTGCTTGTCTCGCA	93	121708 121768	121725 121785	1 0	22	

TABLE 2-continued

Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 using Primer Probe Set 10_11						
ISIS No.	Sequence	% UTC	SEQ ID NO: 1		Mismatches	SEQ ID No.
			Start Site	Stop Site		
549558	TGGACCCGCTGCTTGCT	111	121712 121772	121729 121789	1 0	23
549559	ACCCTGGACCCGCTTGCT	100	121716 121776	121733 121793	1 0	24
549560	CGCCACCCTGGACCCGCC	89	121720 121780	121737 121797	0 0	25
549561	GACACGCCACCTGGACC	80	121784	121801	0	26
549562	GAGTGACACGCCACCTG	81	121788	121805	0	27
549563	GGATGAGTGACACGCCAC	54	121792	121809	0	28
549564	AAAAGGATGAGTGACACG	45	121796	121813	0	29
549565	AGAAAAAAGGATGAGTGA	34	121800	121817	0	30
549566	AGCCAGAAAAAAGGATGA	19	121804	121821	0	31
549567	TGGTAGCCAGAAAAAAGG	31	121808	121825	0	32
549568	CCTTTGGTAGCCAGAAAA	23	121812	121829	0	70
549569	TGCACCTTTGGTAGCCAG	53	121816	121833	0	71
549570	TAATTATCTGCACCTTTG	26	121824	121841	0	72
549571	TTCTTAATTATCTGCACC	21	121828	121845	1	73
549572	CTTCTTCTTAATTATCTG	30	121832	121849	1	74
549573	CCAGCTTCTTCTTAATTA	34	121836	121853	1	75
549574	AGATCCAGCTTCTTCTTA	43	121840	121857	1	76
549575	GCTAAGATCCAGCTTCTT	25	121844	121861	0	77
549576	CGTTGCTAAGATCCAGCT	18	121848	121865	0	78
549577	TGGACGTTGCTAAGATCC	16	121852	121869	0	79
549578	GGACTGGACGTTGCTAAG	44	121856	121873	0	80
549579	ACTTGGACTGGACGTTGC	36	121860	121877	0	81
549580	CCACACTTGGACTGGACG	19	121864	121881	0	82
549581	TGAGCCACACTTGGACTG	16	121868	121885	0	83
549595	GGACGTGTGAAGGTACTC	20	121924	121941	0	45

TABLE 2-continued

Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 using Primer Probe Set 10_11						
ISIS No.	Sequence	% UTC	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Mismatches	SEQ ID No.
549596	CATGGGACGTGTGAAGGT	128	121928	121945	0	46
549597	GGCGCATGGGACGTGTGA	199	121932	121949	0	47
549598	GCACGGCGCATGGGACGT	199	121936	121953	0	48
549599	CACAGCACGGCGCATGGG	149	121940	121957	0	49
549600	AAGCCACAGCACGGCGCA	156	121944	121961	0	50
549601	ATTCAAGCCACAGCACGG	166	121948	121965	0	51
549602	AATAATTCAAGCCACAGC	159	121952	121969	0	52
549603	TCCTAATAATTCAAGCCA	179	121956	121973	0	53
549604	CACTTCCTAATAATTCAA	123	121960	121977	0	54
549605	ACACCACCTTCCTAATAAT	113	121964	121981	0	55
549606	ACTCACACCACTTCCTAA	119	121968	121985	0	56
549608	GTGTACGCACTCACACCA	77.2	121976	121993	0	57
549609	GCAAGTGTACGCACTCAC	53.0	121980	121997	0	58
549610	TCTCGCAAGTGTACGCAC	87.4	121984	122001	0	59
549611	AGTGTCTCGCAAGTGTAC	69.2	121988	122005	0	60
549612	ATGCAGTGTCTCGCAAGT	43.3	121992	122009	0	61
549613	TTCTATGCAGTGTCTCGC	41.4	121996	122013	0	62
549614	TTTATTCTATGCAGTGTC	29.2	122000	122017	0	63
549615	AGGATTATTCTATGCAG	30.9	122004	122021	0	64
549616	AAGAAGGATTTATTCTAT	45.8	122008	122025	0	65
549617	GCCCAAGAAGGATTTATT	31.8	122012	122029	0	66
549618	GAGAGCCCAAGAAGGATT	41.8	122016	122033	0	67
549619	TCCTGAGAGCCCAAGAAG	41.7	122020	122037	0	68
549620	CAGATCCTGAGAGCCCAA	35.6	122024	122041	0	69

Example 2: Effects of Uniform 2'-MOE Modified
Oligonucleotides on Human Tau Exon 10

[0424] A series of modified oligonucleotides were designed to target exon 10 of human Tau and were screened for their effects in reducing exon 10 inclusion in vitro. These modified oligonucleotides were designed by shifting 1 nucleotide upstream or downstream (i.e. microwalk) across the target site. They are 18 nucleosides in length, wherein each nucleoside has a 2'-MOE modification. Each internucleoside linkage throughout the modified oligonucleotide are phosphorothioate internucleoside linkages (P=S). All cytosine residues throughout the modified oligonucleotides are 5-methylcytosines.

[0425] “Start site” indicates the 5'-most nucleoside to which the modified oligonucleotide is targeted. “Stop site” indicates the 3'-most nucleoside to which the modified

oligonucleotide is targeted. Each modified oligonucleotide listed in the tables below is targeted to SEQ ID NO: 1 (GENBANK Accession No NT_010783.15 truncated from nucleotides 9240000 to 9381000).

[0426] A172 cells were transfected using Lipofectamine2000® with 5 nM concentration of modified oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and the mRNA levels of Tau transcripts containing exon 10 were measured by quantitative real-time PCR. Human Tau primer probe set 10_11 or 9_10 R_s was used to measure mRNA levels. Tau exon 10 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent of Tau exon 10 mRNA expression, relative to untreated control levels and is denoted as “% UTC.”

[0427] Human primer probe set 10_11 (forward sequence GGATAATATCAAACACGTCCCG, designated herein as SEQ ID NO: 5; reverse sequence TGCCTAATGAGC-

CACACTTG, designated herein as SEQ ID NO: 6; probe sequence GTCTACAAACCAGTTGACCTGAGC, designated herein as SEQ ID NO: 7).

[0428] Human Tau primer probe set 9_10 R_s (forward sequence CACTGAGAACCTGAAGCACC, designated

herein as SEQ ID NO: 2; reverse sequence GGACGTTGCTAAGATCCAGCT, designated herein as SEQ ID NO: 3; probe sequence TTAAT-TATCTGCACCTTCCCGCCTCC, designated herein as SEQ ID NO: 4).

TABLE 3

Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 using Human Tau primer probe set 10_11					
ISIS NO	Sequence	% UTC	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO
549564	AAAAGGATGAGTGACACG	43	121796	121813	29
617296	AAAAAGGATGAGTGACAC	38	121797	121814	84
617297	AAAAAAGGATGAGTGACA	40	121798	121815	85
617298	GAAAAAAGGATGAGTGAC	39	121799	121816	86
549565	AGAAAAAAGGATGAGTGA	45	121800	121817	30
617299	CAGAAAAAAGGATGAGTG	39	121801	121818	87
617300	CCAGAAAAAAGGATGAGT	34	121802	121819	88
617301	GCCAGAAAAAAGGATGAG	34	121803	121820	89
549566	AGCCAGAAAAAAGGATGA	21	121804	121821	31
617302	TAGCCAGAAAAAAGGATG	26	121805	121822	90
617303	GTAGCCAGAAAAAAGGAT	27	121806	121823	91
617304	GGTAGCCAGAAAAAAGGA	32	121807	121824	92
549567	TGGTAGCCAGAAAAAAGG	39	121808	121825	32
617305	TTGGTAGCCAGAAAAAAG	34	121809	121826	93
617306	TTTGGTAGCCAGAAAAAA	49	121810	121827	94
617307	CTTGGTAGCCAGAAAAAA	37	121811	121828	95
549568	CCTTGGTAGCCAGAAAAA	27	121812	121829	70
617308	ACCTTGGTAGCCAGAAA	31	121813	121830	96
617309	CACCTTGGTAGCCAGAA	23	121814	121831	97
617310	GCACCTTGGTAGCCAGA	59	121815	121832	98
549569	TGCACCTTGGTAGCCAG	59	121816	121833	71
617311	CTGCACCTTGGTAGCCA	59	121817	121834	99
617312	TCTGCACCTTGGTAGCC	58	121818	121835	100
617313	ATCTGCACCTTGGTAGC	53	121819	121836	101
415866	TATCTGCACCTTGGTAG	41	121820	121837	102
617314	TTATCTGCACCTTGGTA	36	121821	121838	103
617315	ATTATCTGCACCTTGGT	31	121822	121839	104
617316	AATTATCTGCACCTTGG	38	121823	121840	105
549570	TAATTATCTGCACCTTG	21	121824	121841	72
617317	TTAATTATCTGCACCTTT	23	121825	121842	106
617318	ATTAATTATCTGCACCTT	25	121826	121843	107
617319	TATTAATTATCTGCACCT	27	121827	121844	108

TABLE 3-continued

Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 using Human Tau primer probe set 10_11					
ISIS NO	Sequence	% UTC	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO
617320	TTATTAATTATCTGCACC	27	121828	121845	109
617321	CTTATTAATTATCTGCAC	26	121829	121846	110
617322	TCTTATTAATTATCTGCA	25	121830	121847	111
617323	TTCTTATTAATTATCTGC	25	121831	121848	112
617324	CTTCTTATTAATTATCTG	25	121832	121849	113
617325	GCTTCTTATTAATTATCT	26	121833	121850	114
617326	AGCTTCTTATTAATTATC	32	121834	121851	115
617327	CAGCTTCTTATTAATTAT	31	121835	121852	116
617328	CCAGCTTCTTATTAATTA	29	121836	121853	117
617329	TCCAGCTTCTTATTAATT	35	121837	121854	118
617330	ATCCAGCTTCTTATTAAT	29	121838	121855	119
617331	GATCCAGCTTCTTATTAA	33	121839	121856	120
617332	AGATCCAGCTTCTTATTA	33	121840	121857	121
617333	AAGATCCAGCTTCTTAT	37	121841	121858	122
617334	TAAGATCCAGCTTCTTAT	42	121842	121859	123
617335	CTAAGATCCAGCTTCTTA	34	121843	121860	124
549575	GCTAAGATCCAGCTTCTT	29	121844	121861	77
617336	TGCTAAGATCCAGCTTCT	42	121845	121862	125
617337	TTGCTAAGATCCAGCTTC	36	121846	121863	126
617338	GTTGCTAAGATCCAGCTT	35	121847	121864	127
549576	CGTTGCTAAGATCCAGCT	26	121848	121865	78
617339	ACGTTGCTAAGATCCAGC	25	121849	121866	128
617340	GACGTTGCTAAGATCCAG	30	121850	121867	129
617341	GGACGTTGCTAAGATCCA	24	121851	121868	130
549577	TGGACGTTGCTAAGATCC	25	121852	121869	79
617342	CTGGACGTTGCTAAGATC	27	121853	121870	131
617343	ACTGGACGTTGCTAAGAT	29	121854	121871	132
617344	GACTGGACGTTGCTAAGA	34	121855	121872	133
549578	GGACTGGACGTTGCTAAG	40	121856	121873	80
617345	TGGACTGGACGTTGCTAA	51	121857	121874	134
617346	TTGGACTGGACGTTGCTA	43	121858	121875	135
617347	CTTGGACTGGACGTTGCT	38	121859	121876	136
549579	ACTTGGACTGGACGTTGC	34	121860	121877	81
617348	CACCTGGACTGGACGTTG	39	121861	121878	137
617349	ACACTGGACTGGACGTT	30	121862	121879	138

TABLE 3-continued

Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 using Human Tau primer probe set 10_11				
ISIS NO Sequence	% UTC	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO
617350 CACACTTGGACTGGACGT	32	121863	121880	139
549580 CCACACTTGGACTGGACG	27	121864	121881	82
617351 GCCACACTTGGACTGGAC	23	121865	121882	140
617352 AGCCACACTTGGACTGGA	23	121866	121883	141
617353 GAGCCACACTTGGACTGG	26	121867	121884	142
549581 TGAGCCACACTTGGACTG	24	121868	121885	83

TABLE 4

Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 using Human Tau primer probe set 9_10 R5				
ISIS NO Sequence	% UTC	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO
617354 TTGAGCCACACTTGGACT	21	121869	121886	143
617355 TTTGAGCCACACTTGGAC	22	121870	121887	144
617356 CTTTGTGAGCCACACTTGA	16	121871	121888	145
549582 CCTTTGAGCCACACTTGG	14	121872	121889	146
617357 TCCTTTGAGCCACACTTG	17	121873	121890	147
617358 ATCCTTTGAGCCACACTT	17	121874	121891	148
617359 TATCCTTTGAGCCACACT	19	121875	121892	149
549583 TTATCCTTTGAGCCACAC	20	121876	121893	33
617360 ATTATCCTTTGAGCCACA	21	121877	121894	150
617361 TATTATCCTTTGAGCCAC	15	121878	121895	151
617362 ATATTATCCTTTGAGCCA	16	121879	121896	152
549584 GATATTATCCTTTGAGCC	17	121880	121897	34
565989 TGATATTATCCTTTGAGC	17	121881	121898	153
565990 TTGATATTATCCTTTGAG	20	121882	121899	154
565991 TTTGATATTATCCTTTGA	28	121883	121900	155
549585 GTTTGATATTATCCTTTG	22	121884	121901	35
617363 TGTTTGATATTATCCTTT	25	121885	121902	156
617364 GTGTTTGATATTATCCTT	22	121886	121903	157
617365 CGTGTTTGATATTATCCT	20	121887	121904	158
549586 ACGTGTTTGATATTATCC	21	121888	121905	36
617366 GACGTGTTTGATATTATC	24	121889	121906	159
617367 GGACGTGTTTGATATTAT	16	121890	121907	160
617368 GGGACGTGTTTGATATTA	33	121891	121908	161
549587 CGGGACGTGTTTGATATT	20	121892	121909	37

TABLE 4-continued

Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 using Human Tau primer probe set 9_10 R5					
ISIS NO	Sequence	% UTC	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO
617369	CCGGGACGTGTTTGATAT	25	121893	121910	162
617370	CCCGGGACGTGTTTGATA	43	121894	121911	163
617371	TCCCGGGACGTGTTTGAT	52	121895	121912	164
549588	CTCCCGGGACGTGTTTGA	53	121896	121913	38
549590	ACTGCCGCCTCCCGGGAC	48	121904	121921	40
617372	CACTGCCGCCTCCCGGGA	71	121905	121922	165
617373	ACACTGCCGCCTCCCGGG	60	121906	121923	166
617374	CACACTGCCGCCTCCCGG	40	121907	121924	167
549591	TCACACTGCCGCCTCCCG	47	121908	121925	41
617375	CTCACACTGCCGCCTCCC	33	121909	121926	168
617376	ACTCACACTGCCGCCTCC	34	121910	121927	169
617377	TACTCACACTGCCGCCTC	34	121911	121928	170
549592	GTA CTCACTGCCGCCT	31	121912	121929	42
617378	GGTACTCACACTGCCGCC	29	121913	121930	171
617379	AGGTACTCACACTGCCGC	34	121914	121931	172
617380	AAGGTACTCACACTGCCG	43	121915	121932	173
549593	GAAGGTACTCACACTGCC	33	121916	121933	43
617381	TGAAGGTACTCACACTGC	28	121917	121934	174
617382	GTGAAGGTACTCACACTG	41	121918	121935	175
617383	TGTGAAGGTACTCACACT	43	121919	121936	176
549594	GTGTGAAGGTACTCACAC	68	121920	121937	44
617384	CGTGTGAAGGTACTCACA	35	121921	121938	177
617385	ACGTGTGAAGGTACTCAC	34	121922	121939	178
617386	GACGTGTGAAGGTACTCA	29	121923	121940	179
549595	GGACGTGTGAAGGTACTC	26	121924	121941	45
617387	GGGACGTGTGAAGGTACT	36	121925	121942	180
617388	TGGGACGTGTGAAGGTAC	36	121926	121943	181
617389	ATGGGACGTGTGAAGGTA	94	121927	121944	182
549596	CATGGGACGTGTGAAGGT	141	121928	121945	46
617390	GCATGGGACGTGTGAAGG	297	121929	121946	183
510184	CGCATGGGACGTGTGAAG	295	121930	121947	184
617391	GCGCATGGGACGTGTGAA	274	121931	121948	185
549597	GGCGCATGGGACGTGTGA	284	121932	121949	47
510185	CGGCGCATGGGACGTGTG	276	121933	121950	186
617392	ACGGCGCATGGGACGTGT	304	121934	121951	187
510186	CACGGCGCATGGGACGTG	268	121935	121952	188

TABLE 4-continued

Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 using Human Tau primer probe set 9_10 R5					
ISIS NO	Sequence	% UTC	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO
549598	GCACGGCGCATGGGACGT	305	121936	121953	48
617393	AGCACGGCGCATGGGACG	237	121937	121954	189
510187	CAGCACGGCGCATGGGAC	144	121938	121955	190
617394	ACAGCACGGCGCATGGGA	170	121939	121956	191
549599	CACAGCACGGCGCATGGG	183	121940	121957	49
549619	TCCTGAGAGCCCAAGAAG	42	122020	122037	68
617395	ATCCTGAGAGCCCAAGAA	38	122021	122038	192
617396	GATCCTGAGAGCCCAAGA	44	122022	122039	193
617397	AGATCCTGAGAGCCCAAG	35	122023	122040	194
549620	CAGATCCTGAGAGCCCAA	35	122024	122041	69
617398	CCAGATCCTGAGAGCCCA	39	122025	122042	195
617399	GCCAGATCCTGAGAGCCC	47	122026	122043	196
617400	AGCCAGATCCTGAGAGCC	38	122027	122044	197

Example 3: Inhibitory Effect of Uniform 2'-MOE Modified Oligonucleotides on Human Tau Exon 10

[0429] Several modified oligonucleotides from Tables 3 and 4 were selected and further evaluated for their effects on inhibiting human Tau exon 10 expression in vitro. ISIS 549595 was included in the study for comparison.

[0430] “Start site” indicates the 5'-most nucleoside to which the modified oligonucleotide is targeted. “Stop site” indicates the 3'-most nucleoside to which the modified oligonucleotide is targeted. Each modified oligonucleotide listed in the tables below is targeted to SEQ ID NO: 1 (GENBANK Accession No NT_010783.15 truncated from nucleotides 9240000 to 9381000).

[0431] A172 cells were transfected using Lipofectamine2000® with 0, 0.1, 0.3, 1, 3, 10, or 30 nM concentration of modified oligonucleotide as specified in the table below. After a treatment period of approximately 24

hours, RNA was isolated from the cells and the mRNA levels of Tau transcripts containing exon 10 were measured by quantitative real-time PCR. Human Tau primer probe set 9_10 R₅ was used to measure mRNA levels, except for ISIS 549581. Human Tau primer probe set 10_11 was used for this oligonucleotide. Human Tau exon 10 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®.

[0432] The half maximal inhibitory concentration (IC₅₀) of each oligonucleotide is presented in the table below and was calculated by plotting the concentrations of oligonucleotides used versus the percent inhibition of human Tau exon 10 mRNA expression achieved at each concentration, and noting the concentration of oligonucleotide at which 50% inhibition of human Tau exon 10 mRNA expression was achieved compared to the control. Results are presented below.

TABLE 5

Inhibitory effect of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 expression					
ISIS NO	Sequence	IC ₅₀ (nM)	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO
549581	TGAGCCACACTTGGACTG	1.20	121868	121885	83
617354	TTGAGCCACACTTGGACT	1.39	121869	121886	143
617355	TTTGAGCCACACTTGGAC	1.08	121870	121887	144
617356	CTTTGAGCCACACTTGGGA	0.74	121871	121888	145
549582	CCTTTGAGCCACACTTGG	0.49	121872	121889	146

TABLE 5-continued

Inhibitory effect of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 expression				
ISIS NO	Sequence	IC ₅₀ (nM)	SEQ ID	
			NO: 1 Start Site	SEQ ID NO: 1 Stop Site
617357	TCCTTTGAGCCACACTTG	0.64	121873	121890
617358	ATCCTTTGAGCCACACTT	0.44	121874	121891
617359	TATCCTTTGAGCCACACT	0.54	121875	121892
549583	TTATCCTTTGAGCCACAC	0.37	121876	121893
617360	ATTATCCTTTGAGCCACA	0.39	121877	121894
617361	TATTATCCTTTGAGCCAC	0.38	121878	121895
549595	GGACGTGTGAAGGTACTC	0.97	121924	121941

Example 4: Inhibitory Effect of Uniform 2'-MOE Modified Oligonucleotides on Human Tau Exon 10

[0433] Several modified oligonucleotides from Table 4 were selected and further evaluated for their effects on inhibiting human Tau exon 10 expression in vitro. ISIS 549595 was included in the study for comparison.

[0434] “Start site” indicates the 5'-most nucleoside to which the modified oligonucleotide is targeted. “Stop site” indicates the 3'-most nucleoside to which the modified oligonucleotide is targeted. Each modified oligonucleotide listed in the tables below is targeted to SEQ ID NO: 1 (GENBANK Accession No NT_010783.15 truncated from nucleotides 9240000 to 9381000).

[0435] A172 cells were transfected using Lipofectamine2000® with 0, 0.1, 0.3, 1, 3, 10, or 30 nM concentration of modified oligonucleotide as specified in the table below. After a treatment period of approximately 24 hours, RNA was isolated from the cells and the mRNA levels of Tau transcripts containing exon 10 were measured by quantitative real-time PCR. Human Tau primer probe set 9_10 R_s was used to measure mRNA levels. Human Tau exon 10 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®.

[0436] The IC₅₀ of each oligonucleotide was calculated in the same manner as illustrated in Example 3 and the results are presented below.

TABLE 6

Inhibitory effect of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 expression				
ISIS NO	Sequence	IC ₅₀ (nM)	SEQ ID	
			NO: 1 Start Site	SEQ ID NO: 1 Stop Site
617362	ATATTATCCTTTGAGCCA	0.27	121879	121896
549584	GATATTATCCTTTGAGCC	0.40	121880	121897
565989	TGATATTATCCTTTGAGC	0.58	121881	121898
565990	TTGATATTATCCTTTGAG	1.23	121882	121899
549585	GTTTGATATTATCCTTTG	0.71	121884	121901
617364	GTGTTTGATATTATCCTT	0.61	121886	121903
617365	CGTGTTTGATATTATCCT	0.74	121887	121904
549586	ACGTGTTTGATATTATCC	0.93	121888	121905
617367	GGACGTGTTTGATATTAT	0.64	121890	121907
549587	CGGGACGTGTTTGATATT	0.97	121892	121909
549620	CAGATCCTGAGAGCCCAA	3.46	122024	122041
549595	GGACGTGTGAAGGTACTC	1.25	121924	121941

Example 5: Inhibitory Effect of Uniform 2'-MOE Modified Oligonucleotides on Human Tau Exon 10

[0437] Several modified oligonucleotides from Tables 3 and 4 were selected and further evaluated for their effects on inhibiting human Tau exon 10 expression in vitro. ISIS 549595 was included in the study for comparison.

[0438] “Start site” indicates the 5'-most nucleoside to which the modified oligonucleotide is targeted. “Stop site” indicates the 3'-most nucleoside to which the modified oligonucleotide is targeted. Each modified oligonucleotide listed in the tables below is targeted to SEQ ID NO: 1 (GENBANK Accession No NT_010783.15 truncated from nucleotides 9240000 to 9381000).

[0439] A172 cells were transfected using Lipofectamine2000® with 0, 0.1, 0.3, 1, 3, 10, or 30 nM concentrations of modified oligonucleotide as specified in the table below. After a treatment period of approximately 24 hours, RNA was isolated from the cells and the mRNA levels of Tau transcripts containing exon 10 were measured by quantitative real-time PCR. Human Tau primer probe set 10_11 was used to measure mRNA levels, except for ISIS 549595. Human Tau primer probe set 9_10 R₅ was used for this oligonucleotide. Human Tau exon 10 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®.

[0440] The IC₅₀ of each oligonucleotide was calculated in the same manner as illustrated in Example 3 and the results are presented below.

[0442] “Start site” indicates the 5'-most nucleoside to which the modified oligonucleotide is targeted. “Stop site” indicates the 3'-most nucleoside to which the modified oligonucleotide is targeted. Each modified oligonucleotide listed in the tables below is targeted to SEQ ID NO: 1 (GENBANK Accession No NT_010783.15 truncated from nucleotides 9240000 to 9381000).

[0443] ISIS 617782 is 21 nucleosides in length, wherein each nucleoside has a 2'-OCH₃ modification and is denoted as the subscript “m”. Each internucleoside linkage throughout the modified oligonucleotide are phosphorothioate internucleoside linkages (P=S).

[0444] ISIS 617781 is 18 nucleosides in length, wherein each nucleoside has a 2'-OCH₃ modification and is denoted as the subscript “m”. Each internucleoside linkage throughout the modified oligonucleotide are phosphorothioate internucleoside linkages (P=S).

[0445] ISIS 415833 is 20 nucleosides in length, wherein each nucleoside has a 2'-MOE modification. Each internucleoside linkage throughout the modified oligonucleotide are phosphorothioate internucleoside linkages (P=S). All cytosine residues throughout the modified oligonucleotides are 5-methylcytosines.

[0446] A172 cells were transfected using Lipofectamine2000® with 0, 0.1, 0.3, 1, 3, 10, or 30 nM concentration of modified oligonucleotide as specified in the table below. After a treatment period of approximately 24 hours, RNA was isolated from the cells and the mRNA

TABLE 7					
Inhibitory effect of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 expression					
ISIS NO	Sequence	IC ₅₀ (nM)	SEQ ID		
			NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO
549566	AGCCAGAAAAAGGATGA	1.00	121804	121821	31
617309	CACCTTTGGTAGCCAGAA	1.11	121814	121831	97
549570	TAATTATCTGCACCTTTG	1.39	121824	121841	72
617317	TTAATTATCTGCACCTTT	1.26	121825	121842	106
617318	ATTAATTATCTGCACCTT	1.21	121826	121843	107
617323	TTCTTATTAATTATCTGC	0.96	121831	121848	112
617324	CTTCTTATTAATTATCTG	1.06	121832	121849	113
617341	GGACGTTGCTAAGATCCA	0.82	121851	121868	130
549577	TGGACGTTGCTAAGATCC	0.87	121852	121869	79
617351	GCCACACTGGGACTGGAC	0.91	121865	121882	140
617352	AGCCACACTGGGACTGGA	0.79	121866	121883	141
549595	GGACGTGTGAAGGTACTC	0.73	121924	121941	45

Example 6: Inhibitory Effect of Uniform 2'-MOE Modified Oligonucleotides on Human Tau Exon 10

[0441] Several modified oligonucleotides from Tables 1 and 4 were selected and further evaluated for their effect on inhibiting human Tau exon 10 expression in vitro. ISIS 617782, 617781, and 415833 were included in the study for comparison.

levels of Tau transcripts containing exon 10 were measured by quantitative real-time PCR. Human Tau primer probe set 9_10 R₅ was used to measure mRNA levels, except for ISIS 617781 and 415883. Human Tau primer probe set 10_11 was used for these two oligonucleotides. Human Tau exon 10 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®.

[0447] The IC₅₀ of each oligonucleotide was calculated in the same manner as illustrated in Example 3 and the results are presented below.

TABLE 8

Inhibitory effect of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 expression					
ISIS NO	Sequence	IC ₅₀ (nM)	SEQ ID		
			NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO
617357	TCCTTTGAGCCACACTTG	0.48	121873	121890	147
617358	ATCCTTTGAGCCACACTT	0.34	121874	121891	148
617359	TATCCTTTGAGCCACACT	0.41	121875	121892	149
549583	TTATCCTTTGAGCCACAC	0.27	121876	121893	33
617360	ATTATCCTTTGAGCCACA	0.33	121877	121894	150
617361	TATTATCCTTTGAGCCAC	0.24	121878	121895	151
617362	ATATTATCCTTTGAGCCA	0.27	121879	121896	152
549584	GATATTATCCTTTGAGCC	0.19	121880	121897	34
565989	TGATATTATCCTTTGAGC	0.39	121881	121898	153
617782	U _m G _m A _m A _m G _m G _m U _m A _m C _m U _m C _m A _m C _m A _m C _m U _m G _m C _m C _m G _m C _m	4.33	121914	121934	198
617781	U _m A _m U _m C _m U _m G _m C _m A _m C _m C _m U _m U _m U _m G _m G _m U _m A _m G _m	20.25	121820	121837	199
415883	TCTTATTAATTATCTGCACC	0.65	121828	121847	200

Example 7: Modified Oligonucleotides Targeting Exon 10 of Human Tau

[0448] A series of modified oligonucleotides were designed to target exon 10 of human Tau. “Start site” indicates the 5'-most nucleoside to which the modified oligonucleotide is targeted. “Stop site” indicates the 3'-most nucleoside to which the modified oligonucleotide is targeted. Each modified oligonucleotide listed in the tables below is targeted to SEQ ID NO: 1 (GENBANK Accession No NT_010783.15 truncated from nucleotides 9240000 to 9381000).

[0449] In the table below, “^mC” indicates 5-methylcytosine, subscript “e” indicates 2'-O-methoxyethyl, subscript “f” indicates 2'-deoxyfluoro, subscript “d” indicates 2'-deoxy, subscript “p” indicates a peptide nucleic acid monomer, subscript “s” indicates a phosphorothioate internucleoside linkage, subscript “o” indicates a phosphodiester internucleoside linkage, “P-” indicates an O-linker at the 5'-end (PNA Bio, Thousand Oaks, Calif.), “—N” indicates a 3'-end carboxy amide.

TABLE 9

Modified oligonucleotides targeting human Tau				
ISIS NO	Sequence	SEQ ID NO:		
		1 Start Site	1 Stop Site	SEQ ID NO
549607	A _{es} ^m C _{es} G _{es} ^m C _{es} A _{es} ^m C _{es} T _{es} ^m C _{es} A _{es} ^m C _{es} A _{es} ^m C _{es} A _{es} ^m C _{es} T _{es} T _{es} ^m C _e	121972	121989	201
565985	^m C _{es} G _{es} ^m C _{es} ^m C _{es} T _{es} A _{es} ^m C _{es} T _{es} T _{es} G _{es} ^m C _{es} T _{es} ^m C _{es} G _{es} ^m C _{es} A _{es} A _{es} G _e	121706	121723	202
565986	G _{es} A _{es} ^m C _{es} ^m C _{es} ^m C _{es} G _{es} ^m C _{es} T _{es} A _{es} ^m C _{es} T _{es} T _{es} G _{es} ^m C _{es} T _{es} ^m C _{es} G _e	121710	121727	203
565987	G _{es} A _{es} ^m C _{es} ^m C _{es} ^m C _{es} G _{es} ^m C _{es} T _{es} T _{es} G _{es} ^m C _{es} T _{es} T _{es} G _{es} ^m C _{es} T _{es} ^m C _{es} G _e	121770	121787	204
565988	^m C _{es} ^m C _{es} T _{es} G _{es} G _{es} A _{es} ^m C _{es} ^m C _{es} ^m C _{es} G _{es} ^m C _{es} T _{es} G _{es} ^m C _{es} T _{es} T _{es} G _e	121774	121791	205

TABLE 9-continued

Modified oligonucleotides targeting human Tau				
ISIS NO	Sequence	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO
566007	$mC_{es}G_{es}C_{fs}C_{fs}U_{fs}A_{fs}C_{fs}U_{fs}U_{fs}G_{fs}C_{fs}U_{fs}C_{fs}G_{fs}C_{fs}A_{fs}$ $A_{es}G_e$	121706	121723	206
566012	$mC_{es}mC_{es}U_{fs}G_{fs}G_{fs}A_{fs}C_{fs}C_{fs}G_{fs}C_{fs}C_{fs}U_{fs}G_{fs}C_{fs}U_{fs}$ $T_{es}G_e$	121774	121791	207
566013	$T_{es}G_{es}A_{fs}U_{fs}A_{fs}U_{fs}U_{fs}A_{fs}U_{fs}C_{fs}C_{fs}U_{fs}U_{fs}G_{fs}A_{fs}G_{es}$ mC_e	121881	121898	208
566014	$T_{es}T_{es}G_{fs}A_{fs}U_{fs}A_{fs}U_{fs}U_{fs}A_{fs}U_{fs}C_{fs}C_{fs}U_{fs}U_{fs}G_{fs}A_{es}$ G_e	121882	121899	209
566015	$T_{es}T_{es}U_{fs}G_{fs}A_{fs}U_{fs}A_{fs}U_{fs}U_{fs}A_{fs}U_{fs}C_{fs}C_{fs}U_{fs}$ $U_{fs}U_{fs}G_{es}A_e$	121883	121900	210
566016	$mC_{es}A_{es}C_{fs}U_{fs}U_{fs}C_{fs}C_{fs}U_{fs}A_{fs}A_{fs}U_{fs}A_{fs}A_{fs}$ $U_{fs}U_{fs}C_{fs}A_{es}A_e$	121960	121977	211
566017	$A_{es}mC_{es}A_{fs}C_{fs}C_{fs}A_{fs}C_{fs}U_{fs}U_{fs}C_{fs}C_{fs}U_{fs}A_{fs}A_{fs}$ $U_{fs}A_{fs}A_{es}T_e$	121964	121981	212
566018	$A_{es}mC_{es}U_{fs}C_{fs}A_{fs}C_{fs}A_{fs}C_{fs}C_{fs}A_{fs}C_{fs}U_{fs}U_{fs}C_{fs}$ $C_{fs}U_{fs}A_{es}A_e$	121968	121985	213
568409	$mC_{es}mC_{es}C_{fs}G_{fs}C_{fs}C_{fs}U_{fs}A_{fs}C_{fs}U_{fs}U_{fs}G_{fs}C_{fs}$ $U_{fs}C_{fs}G_{fs}mC_{es}A_e$	121708	121725	214
568410	$G_{es}A_{es}C_{fs}C_{fs}C_{fs}G_{fs}C_{fs}C_{fs}U_{fs}A_{fs}C_{fs}U_{fs}U_{fs}G_{fs}$ $C_{fs}U_{fs}mC_{es}G_e$	121710	121727	215
568411	$G_{es}A_{es}C_{fs}C_{fs}C_{fs}G_{fs}C_{fs}C_{fs}U_{fs}G_{fs}C_{fs}U_{fs}U_{fs}G_{fs}$ $C_{fs}U_{fs}mC_{es}G_e$	121770	121787	216
568412	$T_{es}G_{es}G_{fs}A_{fs}C_{fs}C_{fs}C_{fs}G_{fs}C_{fs}C_{fs}U_{fs}G_{fs}C_{fs}U_{fs}$ $U_{fs}G_{fs}mC_{es}T_e$	121772	121789	217
624464	$U_{ms}C_{ms}U_{ms}U_{ms}A_{ms}U_{ms}U_{ms}A_{ms}A_{ms}U_{ms}U_{ms}$ $A_{ms}U_{ms}C_{ms}U_{ms}G_{ms}C_{ms}A_{ms}C_{ms}C_m$	121828	121847	218
624465	$T_{ks}mC_{ds}T_{ds}T_{ks}A_{ds}T_{ds}T_{ks}A_{ds}A_{ds}T_{ks}T_{ds}A_{ds}T_{ks}$ $mC_{ds}T_{ds}G_{ks}mC_{ds}A_{ds}mC_{ks}mC_k$	121828	121847	200
624466	$T_{ks}mC_{es}T_{es}T_{ks}A_{es}T_{es}T_{ks}A_{es}A_{es}T_{ks}T_{es}A_{es}T_{ks}$ $mC_{es}T_{es}G_{ks}mC_{es}A_{es}mC_{ks}mC_k$	121828	121847	200
624467	$T_{ks}mC_{es}T_{es}T_{ko}A_{es}T_{es}T_{ko}A_{es}A_{es}T_{ko}T_{es}A_{es}T_{ko}$ $mC_{es}T_{es}G_{ko}mC_{es}A_{es}mC_{ks}mC_k$	121828	121847	200
624468	$T_{ks}mC_{ds}T_{ds}T_{ko}A_{ds}T_{ds}T_{ko}A_{ds}A_{ds}T_{ko}T_{ds}A_{ds}T_{ko}$ $mC_{ds}T_{ds}G_{ko}mC_{ds}A_{ds}mC_{ks}mC_k$	121828	121847	200
626881	$P-T_P C_P T_P T_P A_P T_P A_P A_P T_P T_P A_P T_P C_P T_P G_P$ $C_P A_P C_P C_P-N$	121828	121847	200
670011	$G_{es}G_{es}A_{eo}mC_{es}G_{eo}T_{es}T_{eo}G_{es}mC_{eo}T_{es}A_{eo}A_{es}$ $G_{eo}A_{es}T_{eo}mC_{es}mC_{es}A_e$	121851	121868	130
670012	$mC_{es}mC_{es}T_{eo}T_{es}T_{eo}G_{es}A_{eo}G_{es}mC_{eo}mC_{es}A_{eo}mC_{es}$ $A_{eo}mC_{es}T_{eo}T_{es}G_{es}G_e$	121872	121889	146
670013	$A_{es}T_{es}mC_{eo}mC_{es}T_{eo}T_{es}T_{eo}G_{es}A_{eo}G_{es}mC_{eo}mC_{es}$ $A_{eo}mC_{es}A_{eo}mC_{es}T_{es}T_e$	121874	121891	148
670014	$T_{es}T_{es}A_{eo}T_{es}mC_{eo}mC_{es}T_{eo}T_{es}T_{eo}G_{es}A_{eo}G_{es}$ $mC_{eo}mC_{es}A_{eo}mC_{es}A_{es}mC_e$	121876	121893	33
670015	$A_{es}T_{es}T_{eo}A_{es}T_{eo}mC_{es}mC_{eo}T_{es}T_{eo}T_{es}G_{eo}A_{es}G_{eo}$ $mC_{es}mC_{eo}A_{es}mC_{es}A_e$	121877	121894	150
670016	$T_{es}A_{es}T_{eo}T_{es}A_{eo}T_{es}mC_{eo}mC_{es}T_{eo}T_{es}T_{eo}G_{es}A_{eo}$ $G_{es}mC_{eo}mC_{es}A_{es}mC_e$	121878	121895	151

TABLE 9-continued

Modified oligonucleotides targeting human Tau						
ISIS NO	Sequence	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO		
670017	A _{es} T _{es} A _{eo} T _{es} T _{eo} A _{es} T _{eo} ^m C _{es} ^m C _{eo} T _{es} T _{eo} T _{es} G _{eo} A _{es} G _{eo} ^m C _{es} ^m C _{es} A _e	121879	121896	152		
670018	G _{es} A _{es} T _{eo} A _{es} T _{eo} T _{es} A _{eo} T _{es} ^m C _{eo} ^m C _{es} T _{eo} T _{es} T _{eo} G _{es} A _{eo} G _{es} ^m C _{es} ^m C _e	121880	121897	34		
670019	G _{es} T _{es} T _{eo} T _{es} G _{eo} A _{es} T _{eo} A _{es} T _{eo} T _{es} A _{eo} T _{es} ^m C _{eo} ^m C _{es} T _{eo} T _{es} T _{es} G _e	121884	121901	35		
670020	G _{es} G _{eo} A _{eo} ^m C _{eo} G _{es} T _{es} T _{es} G _{es} ^m C _{es} T _{es} A _{es} A _{es} G _{eo} A _{eo} T _{eo} ^m C _{es} ^m C _{es} A _e	121851	121868	130		
670021	^m C _{es} ^m C _{eo} T _{eo} T _{eo} T _{es} G _{es} A _{es} G _{es} ^m C _{es} ^m C _{es} A _{es} ^m C _{es} A _{eo} ^m C _{eo} T _{eo} T _{es} G _{es} G _e	121872	121889	146		
670022	A _{es} T _{eo} ^m C _{eo} ^m C _{eo} T _{es} T _{es} T _{es} G _{es} A _{es} G _{es} ^m C _{es} ^m C _{es} A _{eo} ^m C _{eo} A _{eo} ^m C _{es} T _{es} T _e	121874	121891	148		
670023	T _{es} T _{eo} A _{eo} T _{eo} ^m C _{es} ^m C _{es} T _{es} T _{es} T _{es} G _{es} A _{es} G _{es} ^m C _{eo} ^m C _{eo} A _{eo} ^m C _{es} A _{es} ^m C _e	121876	121893	33		
670024	A _{es} T _{eo} T _{eo} A _{eo} T _{es} ^m C _{es} ^m C _{es} T _{es} T _{es} T _{es} G _{es} A _{es} G _{eo} ^m C _{eo} ^m C _{eo} A _{es} ^m C _{es} A _e	121877	121894	150		
670025	T _{es} A _{eo} T _{eo} T _{eo} A _{es} T _{es} ^m C _{es} ^m C _{es} T _{es} T _{es} T _{es} G _{es} A _{eo} G _{eo} ^m C _{eo} ^m C _{es} A _{es} ^m C _e	121878	121895	151		
670026	A _{es} T _{eo} A _{eo} T _{eo} T _{es} A _{es} T _{es} ^m C _{es} ^m C _{es} T _{es} T _{es} T _{es} G _{eo} A _{eo} G _{eo} ^m C _{es} ^m C _{es} A _e	121879	121896	152		
670027	G _{es} A _{eo} T _{eo} A _{eo} T _{es} T _{es} A _{es} T _{es} ^m C _{es} ^m C _{es} T _{es} T _{es} T _{eo} G _{eo} A _{eo} G _{es} ^m C _{es} ^m C _e	121880	121897	34		
670028	G _{es} T _{eo} T _{eo} T _{eo} G _{es} A _{es} T _{es} A _{es} T _{es} T _{es} A _{es} T _{es} ^m C _{eo} ^m C _{eo} T _{eo} T _{es} T _{es} G _e	121884	121901	35		
678329	G _{es} ^m C _{es} ^m C _{eo} A _{es} ^m C _{eo} A _{es} ^m C _{eo} T _{es} T _{eo} G _{es} G _{eo} A _{es} ^m C _{eo} T _{es} G _{eo} G _{es} A _{es} ^m C _e	121865	121882	140		
678330	A _{es} G _{es} ^m C _{eo} ^m C _{es} A _{eo} ^m C _{es} A _{eo} ^m C _{es} T _{eo} T _{es} G _{eo} G _{es} A _{eo} ^m C _{es} T _{eo} G _{es} G _{es} A _e	121866	121883	141		
678331	T _{es} G _{es} A _{eo} G _{es} ^m C _{eo} ^m C _{es} A _{eo} ^m C _{es} A _{eo} ^m C _{es} T _{eo} T _{es} G _{eo} G _{es} A _{eo} ^m C _{es} T _{es} G _e	121868	121885	83		
678332	G _{es} ^m C _{eo} ^m C _{eo} A _{eo} ^m C _{es} A _{es} ^m C _{es} T _{es} T _{es} G _{es} G _{es} A _{es} ^m C _{eo} T _{eo} G _{eo} G _{es} A _{es} ^m C _e	121865	121882	140		
678333	A _{es} G _{eo} ^m C _{eo} ^m C _{eo} A _{es} ^m C _{es} A _{es} ^m C _{es} T _{es} T _{es} G _{es} G _{es} A _{eo} ^m C _{eo} T _{eo} G _{es} G _{es} A _e	121866	121883	141		
678334	T _{es} G _{eo} A _{eo} G _{eo} ^m C _{es} ^m C _{es} A _{es} ^m C _{es} A _{es} ^m C _{es} T _{es} T _{es} G _{eo} G _{eo} A _{eo} ^m C _{es} T _{es} G _e	121868	121885	83		
693840	T _{es} G _{es} G _{eo} A _{es} ^m C _{eo} G _{es} T _{eo} T _{es} G _{eo} ^m C _{es} T _{eo} A _{es} A _{eo} G _{es} A _{eo} T _{es} ^m C _{es} ^m C _e	121852	121869	79		
693841	^m C _{es} ^m C _{es} A _{eo} ^m C _{es} A _{eo} ^m C _{es} T _{eo} T _{es} G _{eo} G _{es} A _{eo} ^m C _{es} T _{eo} G _{es} G _{eo} A _{es} ^m C _{es} G _e	121864	121881	82		
693842	A _{es} ^m C _{es} G _{eo} T _{es} G _{eo} T _{es} T _{eo} T _{es} G _{eo} A _{es} T _{eo} A _{es} T _{eo} T _{es} A _{eo} T _{es} ^m C _{es} ^m C _e	121888	121905	36		
693843	G _{es} G _{es} A _{eo} ^m C _{es} G _{eo} T _{es} G _{eo} T _{es} G _{eo} A _{es} A _{eo} G _{es} G _{eo} T _{es} A _{eo} ^m C _{es} T _{es} ^m C _e	121924	121941	45		
693844	G _{es} A _{es} G _{eo} ^m C _{es} ^m C _{eo} A _{es} ^m C _{eo} A _{es} ^m C _{eo} T _{es} T _{eo} G _{es} G _{eo} A _{es} ^m C _{eo} T _{es} G _{es} G _e	121867	121884	142		
693845	T _{es} G _{eo} G _{eo} A _{eo} ^m C _{es} G _{es} T _{es} T _{es} G _{es} ^m C _{es} T _{es} A _{es} A _{eo} G _{eo} A _{eo} T _{es} ^m C _{es} ^m C _e	121852	121869	79		

TABLE 9-continued

Modified oligonucleotides targeting human Tau				
ISIS NO	Sequence	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	SEQ ID NO
693846	$^{m}C_{es}^{m}C_{eo}A_{eo}^{m}C_{eo}A_{es}^{m}C_{es}T_{es}T_{es}G_{es}G_{es}A_{es}^{m}C_{es}$ $T_{eo}G_{eo}G_{eo}A_{es}^{m}C_{es}G_e$	121864	121881	82
693847	$A_{es}^{m}C_{eo}G_{eo}T_{eo}G_{es}T_{es}T_{es}T_{es}G_{es}A_{es}T_{es}A_{es}T_{eo}$ $T_{eo}A_{eo}T_{es}^{m}C_{es}^{m}C_e$	121888	121905	36
693848	$G_{es}G_{eo}A_{eo}^{m}C_{eo}G_{es}T_{es}G_{es}T_{es}G_{es}A_{es}A_{es}G_{es}G_{eo}$ $T_{eo}A_{eo}^{m}C_{es}T_{es}^{m}C_e$	121924	121941	45
693849	$G_{es}A_{eo}G_{eo}^{m}C_{eo}^{m}C_{es}A_{es}^{m}C_{es}A_{es}^{m}C_{es}T_{es}T_{es}G_{es}$ $G_{eo}A_{eo}^{m}C_{eo}T_{es}G_{es}G_e$	121867	121884	142

Example 8: In Vivo Analysis of Oligonucleotides
Targeting Human Tau Exon 10

[0450] Sprague Dawley rats were separated into groups of 3 rats for the experiment presented in Table 11 and into groups of 2 or 4 rats for the experiment presented in Table 12. Each rat in each group of rats was administered a single 3 mg intrathecal (IT) dose of an oligonucleotide selected from Table 3, 4, or 9. At various time points after injection from 3 hours to 8 weeks, the movement of 7 different parts of the body was evaluated for each rat. The 7 body parts are (1) the rat's tail; (2) the rat's posterior posture; (3) the rat's hind limbs; (4) the rat's hind paws; (5) the rat's forepaws; (6) the rat's anterior posture; and (7) the rat's head. For each of the 7 different body parts, each rat was given a sub-score of 0 if the body part was moving or 1 if the body part was paralyzed. After each of the 7 body parts were evaluated, the sub-scores were summed for each rat and then averaged for each group. For example, if a rat's tail, head, and all other evaluated body parts were moving 3 hours after the 3 mg IT dose, it would get a summed score of 0. If another rat was not moving its tail 3 hours after the 3 mg IT dose but all other evaluated body parts were moving, it would receive a score of 1. Saline treated rats generally receive a score of 0. A score of at the top end of the range would be suggestive of toxicity. Results are presented as the average score for each treatment group in Tables 11 and 12.

TABLE 11-continued

3 mg IT bolus in vivo study				
ISIS No.	Score 3 hours after injection	Score 2 weeks after injection	Score 8 weeks after injection	SEQ ID NO.
670013	0.3	2.3	2.3	148
670022	2.0	2.3	3.0	148
617358	3.7	0.0	1.3	148
670014	0.0	0.0	0.0	33
670023	2.0	1.0	0.3	33
549583	2.3	0.0	0.0	33
670015	1.0	2.0	0.7	150
670024	1.0	0.7	0.0	150
617360	5.3	0.0	1.0	150
670025	0.3	5.3	5.3	151
670016	2.3	1.3	1.7	151
617361	3.0	0.0	0.3	151
670017	0.0	1.7	1.3	152
670026	1.0	3.7	3.3	152
617362	4.7	3.7	2.7	152
670018	0.3	0.3	0.3	34
670027	1.0	0.7	0.7	34
549584	5.0	2.7	3.7	34
670028	2.0	0.0	0.0	35
670019	3.0	0.0	0.0	35
549585	4.7	5.3	7.0	35

TABLE 11

3 mg IT bolus in vivo study				
ISIS No.	Score 3 hours after injection	Score 2 weeks after injection	Score 8 weeks after injection	SEQ ID NO.
670020	1.0	2.7	2.7	130
670011	2.3	2.3	2.3	130
617341	3.0	0.0	0.0	130
678329	2.3	0.0	0.0	140
678332	3.0	0.0	1.3	140
617351	7.0	0.0	4.0	140
678330	2.7	2.3	3.0	141
678333	2.7	2.3	2.3	141
617352	7.0	0.0	2.0	141
678331	3.0	0.0	0.0	83
678334	4.3	2.3	2.3	83
549581	7.0	0.0	0.3	83
670012	2.7	0.0	0.0	146
670021	3.0	0.0	1.0	146
549582	4.3	0.0	0.0	146

TABLE 12

3 mg IT bolus in vivo study			
ISIS No.	No. of rats in treatment group	Score 3 hours after injection	SEQ ID NO.
549577	4	3.3	79
693840	4	1.8	79
693845	4	0.0	79
549580	4	7.0	82
693841	4	1.8	82
693846	4	2.5	82
617353	4	7.0	142
693844	2	3.5	142
693849	4	5.0	142
549582	4	4.3	146
549586	4	5.0	36
693847	2	1.0	36
549595	4	6.5	45
693843	2	2.0	45
693848	2	7.0	45

Example 9: Inhibitory Effect In Vivo of a Modified
Oligonucleotide Targeting Human Tau Exon 10

[0451] B6.Cg-Mapttm1(EGFP)Klt Tg(MAPT)8cPdav/J mice (The Jackson Laboratory) express the 3R and 4R isoforms of human Tau. The effect of oligonucleotides selected from Table 3, 4, or 8 on shifting of the 4R isoform to 3R isoform was assessed in this mouse model.

[0452] Groups of four B6.Cg-Mapttm1(EGFP)Klt Tg(MAPT)8cPdav/J mice (3-4 months of age) were administered 500 µg of oligonucleotide via an intracerebroventricular (ICV) bolus injection. A control group of four mice was similarly treated with PBS. Two weeks after the dose, animals were sacrificed and RNA was extracted from the cerebral cortex, hippocampus, and/or spinal cord. mRNA expression of the 4R isoform and total human Tau were analyzed by qRT-PCR. The 4R isoform was analyzed using primer probe set hTau 9_10 junction (forward sequence 5'-CACTGAGAACCTGAAGCACC-3', SEQ ID NO: 219; reverse sequence 5'-GTTGCTAAGATCCAGCTTCTT-3', SEQ ID NO: 220; probe sequence 5'-TTAAT-TATCTGCACCTTCCCGCCTCC-3', SEQ ID NO: 221) or primer probe set hTau 10_11 junction (forward sequence 5'-AATATCAAACACGTCCCGGGAG-3', SEQ ID NO: 222; reverse sequence 5'-TGCCTAATGAGCCACACTTG-3', SEQ ID NO: 223; probe sequence 5'-GTCTA-CAAACCAGTTGACCTGAGC-3', SEQ ID NO: 224). Total Tau was analyzed using primer probe set RTS104 (forward sequence 5'-AAGATTGGGTCCCTGGACAAT-3', SEQ ID NO: 225; reverse sequence 5'-AGCTTGTTGGTTCAATCTTTTATT-3', SEQ ID NO: 226; probe sequence 5'-CACC-CACGTCCCTGGCGGA-3', SEQ ID NO: 227). The ratio of 4R isoform to total Tau mRNA levels was normalized to mouse GAPDH levels, which were analyzed using primer probe set mGapdh_LTS00102 (forward sequence 5'-GGCAAATCAACGGCACAGT-3', SEQ ID NO: 228; reverse sequence 5'-GGGTCTCGCTCCTGGAAGAT-3', SEQ ID NO: 229; probe sequence 5'-AAGGCCGAGAATGGGAAGCTTGTCATC-3', SEQ ID NO: 230). The results are presented in Tables 13-15 as the average ratio of 4R isoform to total Tau mRNA normalized to GAPDH levels for each treatment group divided by the average ratio for the PBS group. "ND" indicates no data.

[0453] Inflammation was also assessed by performing RT-PCT to determine the expression levels of AIF1 in the cortex, hippocampus, and/or spinal cord. After normalization of all samples to GAPDH, the average AIF1 value for each treatment group was divided by the average AIF1 value for the PBS control group. The results are presented in Tables 13-15.

TABLE 13

Effect of modified oligonucleotides on Tau exon 10 skipping in transgenic mice							
ISIS NO.	4R cortex	4R hippo	4R spinal cord	AIF1 cortex	AIF1 hippo	AIF1 spinal cord	SEQ ID NO.
415883	0.50	0.46	0.56	1.35	1.27	1.44	200
549566	0.54	0.54	0.66	1.09	1.13	1.46	31
549570	0.58	0.60	0.64	1.17	1.16	1.39	72
549577	0.25	0.30	0.38	2.92	3.27	4.39	79
549581	0.25	ND	ND	1.04	1.07	1.40	83

TABLE 13-continued

Effect of modified oligonucleotides on Tau exon 10 skipping in transgenic mice							
ISIS NO.	4R cortex	4R hippo	4R spinal cord	AIF1 cortex	AIF1 hippo	AIF1 spinal cord	SEQ ID NO.
549582	0.07	0.10	0.12	0.89	0.95	1.15	146
549583	0.25	0.26	0.25	0.97	0.94	1.09	33
617309	0.36	0.36	0.51	1.06	1.06	1.09	97

TABLE 14

Effect of modified oligonucleotides on Tau exon 10 skipping in transgenic mice					
ISIS NO.	4R cortex	4R hippo	4R spinal cord	AIF1 spinal cord	SEQ ID NO.
549582	0.21	0.21	0.23	0.97	146
549584	0.32	0.28	0.28	1.12	34
549585	0.30	0.27	0.30	1.05	35
565989	0.36	0.32	0.36	1.03	153
565990	0.50	0.46	0.53	0.97	154
617341	0.25	0.28	0.28	1.16	130
617351	0.13	0.18	0.14	1.01	140
617352	0.09	0.13	0.09	1.06	141
617354	0.31	ND	ND	1.21	143
617355	0.43	0.50	0.37	1.18	144
617356	0.30	0.40	0.49	0.98	145
617357	0.33	0.33	0.27	1.31	147
617358	0.27	0.27	0.34	1.12	148
617359	0.32	0.32	0.37	0.95	149
617360	0.21	0.19	0.29	1.19	150
617361	0.26	0.21	0.37	1.04	151
617362	0.26	0.27	0.34	0.90	152
617364	0.39	0.33	0.43	1.09	157

TABLE 15

Effect of modified oligonucleotides on Tau exon 10 skipping in transgenic mice						
ISIS NO.	4R cortex	4R hippo	4R spinal cord	AIF1 cortex	AIF1 spinal cord	SEQ ID NO.
549582	0.26	0.34	0.29	0.74	1.03	146
549586	0.25	0.43	0.38	0.97	0.98	36
549587	0.39	0.47	0.46	0.96	1.17	37
549595	0.27	0.39	0.39	0.84	0.92	45
617317	0.62	0.83	0.53	0.88	1.05	106
617318	0.57	0.69	0.49	0.94	1.06	107
617323	0.60	0.82	0.49	0.92	1.10	112
617324	0.72	0.88	0.49	0.70	1.03	113
617365	0.31	0.42	0.27	0.79	0.87	158
617367	0.39	0.46	0.35	0.90	1.29	160

Example 10: Effect In Vivo of Mixed Backbone
Oligonucleotides on Human Tau Exon 10 Skipping

[0454] Groups of four B6.Cg-Mapttm1(EGFP)Klt Tg(MAPT)8cPdav/J mice (see Example 9) were administered 125 µg of an oligonucleotide selected from Table 3, 4, or 9 or PBS via ICV bolus injection. Two weeks after the dose, animals were sacrificed and RNA was extracted from the cerebral cortex and/or hippocampus and analyzed as described in Example 9. The results are presented in Tables 16 and 17 as the average ratio of the 4R isoform to total Tau mRNA normalized to PBS for each treatment group.

[0455] Expression of allograft inflammatory factor (AIF1) was tested as a measure of inflammation by performing RT-PCT to determine the expression levels of AIF1 in the cortex and spinal cord. After normalization of all samples to GAPDH, the average AIF1 value for each treatment group was divided by the average AIF1 value for the PBS control group. The results are presented in Tables 16 and 17.

TABLE 16

Effect of modified oligonucleotides on Tau exon 10 skipping in transgenic mice				
ISIS NO.	4R Cortex	AIF1 cortex	AIF1 spinal cord	SEQ ID NO.
549582	0.42	1.0	0.9	146
549583	0.71	0.9	1.2	33
617341	0.64	1.0	0.9	130
617361	0.63	1.1	1.1	151
670011	0.78	1.0	1.0	130
670012	0.47	0.9	1.1	146
670013	0.63	1.0	0.9	148
670014	0.90	0.9	1.0	33
670015	0.70	0.9	0.9	150
670018	0.75	1.0	1.0	34
670019	0.58	1.1	1.0	35
670020	0.67	0.9	0.9	130
670023	0.87	1.0	1.0	33
670024	0.60	1.0	1.1	150
670025	0.72	1.1	0.9	151
670027	0.79	1.0	0.9	34
670028	0.66	1.1	1.0	35
678329	0.13	1.0	1.0	140
678330	0.51	0.9	0.9	141
678331	1.12	0.9	1.0	83
678332	0.27	0.9	1.0	140

TABLE 16-continued

Effect of modified oligonucleotides on Tau exon 10 skipping in transgenic mice				
ISIS NO.	4R Cortex	AIF1 cortex	AIF1 spinal cord	SEQ ID NO.
678333	0.56	0.9	0.9	141
678334	1.10	0.9	1.2	83

TABLE 17

Effect of modified oligonucleotides on Tau exon 10 skipping in transgenic mice				
ISIS No.	4R Cortex	AIF1 cortex	AIF1 spinal cord	SEQ ID NO.
549577	0.56	1.4	1.6	79
549580	0.52	0.9	1.2	82
549582	0.27	0.9	1.0	146
549586	0.90	1.1	1.3	36
549595	0.90	1.0	1.4	45
617353	1.35	1.0	1.3	142
693840	0.80	0.9	1.2	79
693841	0.91	1.1	1.1	82
693842	1.20	1.0	0.8	36
693843	1.31	1.0	1.6	45
693844	2.22	1.1	1.6	142
693845	0.86	1.0	1.4	79
693846	0.84	1.0	1.4	82
693847	0.89	1.0	1.8	36
693848	0.76	0.9	1.9	45
693849	2.08	0.8	1.8	142

SEQUENCE LISTING

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gtactcacac tgccgcct

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gaaggtactc acactgcc 18

<210> SEQ ID NO 44
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gtgtgaaggt actcacac 18

<210> SEQ ID NO 45
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ggacgtgtga aggtactc 18

<210> SEQ ID NO 46
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<400> SEQUENCE: 46

catgggacgt gtgaaggt 18

<210> SEQ ID NO 47
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<212> TYPE: DNA
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ggcgcacgtg acgtgtga 18

<210> SEQ ID NO 48
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gcacggcgca tgggacgt 18

<210> SEQ ID NO 49
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cacagcacgg cgcatggg 18

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aagccacagc acggcgca 18

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attcaagcca cagcacgg 18

<210> SEQ ID NO 52
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<400> SEQUENCE: 52

aataattcaa gccacagc 18

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tcctaataat tcaagcca 18

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cacttcctaa taattcaa 18

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acaccacttc ctaataat

18

<210> SEQ ID NO 56

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<223> OTHER INFORMATION: Synthetic oligonucleotide

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actcacacca cttcctaa

18

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gtgtacgcac tcacacca

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gcaagtgtac gcactcac

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tctcgcaagt gtacgcac

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agtggtctgc aagtgtac

18

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<223> OTHER INFORMATION: Synthetic oligonucleotide

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atgcagtgtc tcgcaagt

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ttctatgcag tgtctcgc 18

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tttattctat gcagtgtc 18

<210> SEQ ID NO 64
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aggattttatt ctatgcag 18

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aagaaggatt tattctat 18

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gccaagaag gatttatt 18

<210> SEQ ID NO 67
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gagagcccaa gaaggatt 18

<210> SEQ ID NO 68
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<400> SEQUENCE: 68

tcctgagagc ccaagaag 18

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cagatcctga gagcccaa 18

<210> SEQ ID NO 70
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<400> SEQUENCE: 70

cctttggtag ccagaaaa 18

<210> SEQ ID NO 71
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<220> FEATURE:
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<400> SEQUENCE: 71

tgcacctttg gtagccag 18

<210> SEQ ID NO 72
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<400> SEQUENCE: 72

taattatctg cacctttg 18

<210> SEQ ID NO 73
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<400> SEQUENCE: 73

ttcttaatta tctgcacc 18

<210> SEQ ID NO 74
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 74

cttcttctta attatctg

18

<210> SEQ ID NO 75

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 75

ccagcttctt cttaatta

18

<210> SEQ ID NO 76

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<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 76

agatccagct tcttctta

18

<210> SEQ ID NO 77

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<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 77

gctaagatcc agcttctt

18

<210> SEQ ID NO 78

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<212> TYPE: DNA

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 78

cggtgctaag atccagct

18

<210> SEQ ID NO 79

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<212> TYPE: DNA

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<400> SEQUENCE: 79

tggacgttgc taagatcc

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<210> SEQ ID NO 80

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<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 80

ggactggacg ttgctaag

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<210> SEQ ID NO 81
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 81

acttggactg gacgttgc 18

<210> SEQ ID NO 82
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 82

ccacacttgg actggacg 18

<210> SEQ ID NO 83
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 83

tgagccacac ttggactg 18

<210> SEQ ID NO 84
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 84

aaaaaggatg agtgacac 18

<210> SEQ ID NO 85
<211> LENGTH: 18
<212> TYPE: DNA
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<400> SEQUENCE: 85

aaaaaaggat gagtgaca 18

<210> SEQ ID NO 86
<211> LENGTH: 18
<212> TYPE: DNA
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<400> SEQUENCE: 86

gaaaaaagga tgagtgc 18

<210> SEQ ID NO 87
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<400> SEQUENCE: 87

cagaaaaaag gatgagtg 18

<210> SEQ ID NO 88
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<400> SEQUENCE: 88

ccagaaaaaa ggatgagt 18

<210> SEQ ID NO 89
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 89

gccagaaaaa aggatgag 18

<210> SEQ ID NO 90
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 90

tagccagaaa aaaggatg 18

<210> SEQ ID NO 91
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<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 91

gtagccagaa aaaaggat 18

<210> SEQ ID NO 92
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 92

ggtagccaga aaaaagga 18

<210> SEQ ID NO 93
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 93

ttggtagcca gaaaaaag 18

<210> SEQ ID NO 94

<211> LENGTH: 18

<212> TYPE: DNA

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 94

tttgtagcc agaaaaaa 18

<210> SEQ ID NO 95

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<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 95

ctttgtagc cagaaaaa 18

<210> SEQ ID NO 96

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 96

acctttgta gccagaaa 18

<210> SEQ ID NO 97

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 97

cacctttggt agccagaa 18

<210> SEQ ID NO 98

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<212> TYPE: DNA

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<400> SEQUENCE: 98

gcaccttgg tagccaga 18

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<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 99

ctgcaccttt ggtagcca 18

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<210> SEQ ID NO 100
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 100

tctgcacctt tggtagcc 18

<210> SEQ ID NO 101
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 101

atctgcacct ttggtagc 18

<210> SEQ ID NO 102
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 102

tatctgcacc tttggtag 18

<210> SEQ ID NO 103
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 103

ttatctgcac ctttggtgta 18

<210> SEQ ID NO 104
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 104

attatctgca cctttggt 18

<210> SEQ ID NO 105
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 105

aattatctgc acctttgg 18

<210> SEQ ID NO 106
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 106

ttaattatct gcaccttt 18

<210> SEQ ID NO 107
<211> LENGTH: 18
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 107

attaattatc tgcacctt 18

<210> SEQ ID NO 108
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 108

tattaattat ctgcacct 18

<210> SEQ ID NO 109
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 109

ttattaatta tctgcacc 18

<210> SEQ ID NO 110
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 110

cttattaatt atctgcac 18

<210> SEQ ID NO 111
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 111

tcttattaat tatctgca 18

<210> SEQ ID NO 112
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 112

ttcttattaa ttatctgc

18

<210> SEQ ID NO 113

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 113

cttcttatta attatctg

18

<210> SEQ ID NO 114

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 114

gcttcttatt aattatct

18

<210> SEQ ID NO 115

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

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agcttcttat taattatc

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<210> SEQ ID NO 116

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cagcttctta ttaattat

18

<210> SEQ ID NO 117

<211> LENGTH: 18

<212> TYPE: DNA

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<223> OTHER INFORMATION: Synthetic oligonucleotide

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ccagcttctt attaatta

18

<210> SEQ ID NO 118

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 118

tccagcttct tattaatt

18

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<210> SEQ ID NO 119
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 119

atccagcttc ttattaat 18

<210> SEQ ID NO 120
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 120

gatccagctt cttattaa 18

<210> SEQ ID NO 121
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 121

agatccagct tcttatta 18

<210> SEQ ID NO 122
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 122

aagatccagc ttcttatt 18

<210> SEQ ID NO 123
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 123

taagatccag cttcttat 18

<210> SEQ ID NO 124
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 124

ctaagatcca gcttctta 18

<210> SEQ ID NO 125
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 125

tgctaagatc cagcttct 18

<210> SEQ ID NO 126
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 126

ttgctaagat ccagcttc 18

<210> SEQ ID NO 127
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 127

gttgctaaga tccagctt 18

<210> SEQ ID NO 128
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 128

acgttgctaa gatccagc 18

<210> SEQ ID NO 129
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 129

gacgttgcta agatccag 18

<210> SEQ ID NO 130
<211> LENGTH: 18
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 130

ggacgttgct aagatcca 18

<210> SEQ ID NO 131
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<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 131

ctggacgttg ctaagatc

18

<210> SEQ ID NO 132

<211> LENGTH: 18

<212> TYPE: DNA

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actggacgtt gctaagat

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<212> TYPE: DNA

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<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 133

gactggacgt tgctaaga

18

<210> SEQ ID NO 134

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 134

tggactggac gttgctaa

18

<210> SEQ ID NO 135

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<212> TYPE: DNA

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 135

ttggactgga cgttgcta

18

<210> SEQ ID NO 136

<211> LENGTH: 18

<212> TYPE: DNA

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 136

cttggactgg acgttgct

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<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 137

cacttggact ggacgttg

18

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<210> SEQ ID NO 138
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 138

acacttggac tggacgtt 18

<210> SEQ ID NO 139
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 139

cacacttgga ctggacgt 18

<210> SEQ ID NO 140
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 140

gccacacttg gactggac 18

<210> SEQ ID NO 141
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 141

agccacactt ggactgga 18

<210> SEQ ID NO 142
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 142

gagccacact tggactgg 18

<210> SEQ ID NO 143
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<400> SEQUENCE: 143

ttgagccaca cttggact 18

<210> SEQ ID NO 144
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
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<400> SEQUENCE: 144

tttgagccac acttgac 18

<210> SEQ ID NO 145
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<400> SEQUENCE: 145

ctttgagcca cacttga 18

<210> SEQ ID NO 146
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 146

cctttgagcc acacttg 18

<210> SEQ ID NO 147
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 147

tcctttgagc cacacttg 18

<210> SEQ ID NO 148
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 148

atcctttgag ccacactt 18

<210> SEQ ID NO 149
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 149

tatcctttga gccacact 18

<210> SEQ ID NO 150
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 150

attatccttt gagccaca

18

<210> SEQ ID NO 151

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 151

tattatcctt tgagccac

18

<210> SEQ ID NO 152

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 152

atattatcct ttgagcca

18

<210> SEQ ID NO 153

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 153

tgatattatc ctttgagc

18

<210> SEQ ID NO 154

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 154

ttgatattat cctttgag

18

<210> SEQ ID NO 155

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 155

tttgatatta tcctttga

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<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 156

tgtttgatat tacccttt

18

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<400> SEQUENCE: 157

gtgtttgata ttatcctt 18

<210> SEQ ID NO 158
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<400> SEQUENCE: 158

cgtgtttgat attatcct 18

<210> SEQ ID NO 159
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<220> FEATURE:
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<400> SEQUENCE: 159

gacgtgttg atattatc 18

<210> SEQ ID NO 160
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 160

ggacgtgtt gatattat 18

<210> SEQ ID NO 161
<211> LENGTH: 18
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 161

gggacgtgtt tgatatta 18

<210> SEQ ID NO 162
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 162

ccgggacgtg tttgatat 18

<210> SEQ ID NO 163
<211> LENGTH: 18

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 163

cccgggacgt gtttgata 18

<210> SEQ ID NO 164
<211> LENGTH: 18
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 164

tcccgggacg tgtttgat 18

<210> SEQ ID NO 165
<211> LENGTH: 18
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 165

cactgccgcc tcccggga 18

<210> SEQ ID NO 166
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 166

acactgccgc ctcccggg 18

<210> SEQ ID NO 167
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 167

cacactgccg cctcccgg 18

<210> SEQ ID NO 168
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 168

ctcacactgc cgctccc 18

<210> SEQ ID NO 169
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 169

actcacactg ccgcctcc

18

<210> SEQ ID NO 170

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 170

tactcacact gccgcctc

18

<210> SEQ ID NO 171

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<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 171

ggtactcaca ctgccgcc

18

<210> SEQ ID NO 172

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 172

aggtactcac actgccgc

18

<210> SEQ ID NO 173

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 173

aaggtactca cactgccg

18

<210> SEQ ID NO 174

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 174

tgaaggtact cacactgc

18

<210> SEQ ID NO 175

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 175

gtgaaggtac tcacactg

18

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<210> SEQ ID NO 176
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 176

tgtgaaggta ctcacact 18

<210> SEQ ID NO 177
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 177

cgtgtgaagg tactcaca 18

<210> SEQ ID NO 178
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 178

acgtgtgaag gtactcac 18

<210> SEQ ID NO 179
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 179

gacgtgtgaa ggtactca 18

<210> SEQ ID NO 180
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 180

gggacgtgtg aaggtact 18

<210> SEQ ID NO 181
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 181

tgggacgtgt gaaggtac 18

<210> SEQ ID NO 182
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 182

atgggacgtg tgaaggtg 18

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 183

gcacgggacg tgtgaagg 18

<210> SEQ ID NO 184
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 184

cgcacgggac gtgtgaag 18

<210> SEQ ID NO 185
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 185

gcgcacggga cgtgtgaa 18

<210> SEQ ID NO 186
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 186

cggcacatgg gacgtgtg 18

<210> SEQ ID NO 187
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 187

acggcgcacg ggacgtgt 18

<210> SEQ ID NO 188
<211> LENGTH: 18
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 188

cacggcgcat gggacgtg

18

<210> SEQ ID NO 189

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 189

agcacggcgc atgggacg

18

<210> SEQ ID NO 190

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 190

cagcacggcg catgggac

18

<210> SEQ ID NO 191

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 191

acagcacggc gcatggga

18

<210> SEQ ID NO 192

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 192

atcctgagag cccaagaa

18

<210> SEQ ID NO 193

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 193

gatcctgaga gccaaga

18

<210> SEQ ID NO 194

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 194

agatcctgag agccaag

18

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<210> SEQ ID NO 195
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 195

ccagatcctg agagccca 18

<210> SEQ ID NO 196
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 196

gccagatcct gagagccc 18

<210> SEQ ID NO 197
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 197

agccagatcc tgagagcc 18

<210> SEQ ID NO 198
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 198

ugaagguacu cacacugccg c 21

<210> SEQ ID NO 199
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 199

uaucugcacc uuugguag 18

<210> SEQ ID NO 200
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 200

tcttattaat tatctgcacc 20

<210> SEQ ID NO 201
<211> LENGTH: 18

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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 201

acgcactcac accacttc 18

<210> SEQ ID NO 202
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<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 202

cgctacttg ctgcaag 18

<210> SEQ ID NO 203
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 203

gaccgccta cttgctcg 18

<210> SEQ ID NO 204
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 204

gaccgcctg cttgctcg 18

<210> SEQ ID NO 205
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 205

cctggaccg cctgcttg 18

<210> SEQ ID NO 206
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 206

cgccuacuug cucgcaag 18

<210> SEQ ID NO 207
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: bases at these positions are DNA

<400> SEQUENCE: 207

ccuggaccgcg ccugcutg 18

<210> SEQ ID NO 208
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: bases at these positions are DNA

<400> SEQUENCE: 208

tgauauuauuc cuuugagc 18

<210> SEQ ID NO 209
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<220> FEATURE:
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<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: bases at these positions are DNA

<400> SEQUENCE: 209

ttgauauuuau ccuuugag 18

<210> SEQ ID NO 210
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: bases at these positions are DNA

<400> SEQUENCE: 210

ttugauauua uccuuuga 18

<210> SEQ ID NO 211
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<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 211

cacuuccuaa uaauucaa 18

<210> SEQ ID NO 212
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: bases at these positions are DNA

<400> SEQUENCE: 212

acaccacuuc cuaauaat 18

<210> SEQ ID NO 213
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<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 213

acucacacca cuuccuaa 18

<210> SEQ ID NO 214
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 214

cccgccuacu ugcucgca 18

<210> SEQ ID NO 215
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 215

gaccgcgcuu cuugcucg 18

<210> SEQ ID NO 216
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 216

gaccgcgcuu cuugcucg 18

<210> SEQ ID NO 217
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: bases at these positions are DNA
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: bases at these positions are DNA

<400> SEQUENCE: 217

tggaccgcgc ugcuuugt 18

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<210> SEQ ID NO 218
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<212> TYPE: RNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 218

ucuuauuaau uaucugcacc 20

<210> SEQ ID NO 219
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 219

cactgagaac ctgaagcacc 20

<210> SEQ ID NO 220
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 220

gttgctaaga tccagcttct t 21

<210> SEQ ID NO 221
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Probe

<400> SEQUENCE: 221

ttaattatct gcaccttccc gcctcc 26

<210> SEQ ID NO 222
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 222

aatatcaaac acgtcccggg ag 22

<210> SEQ ID NO 223
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 223

tgccaatga gccacacttg 20

<210> SEQ ID NO 224
<211> LENGTH: 24

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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Probe

<400> SEQUENCE: 224

gtctacaaac cagttgacct gagc 24

<210> SEQ ID NO 225
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 225

aagattgggt ccctggacaa t 21

<210> SEQ ID NO 226
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 226

agcttggtggg tttcaatctt ttatt 26

<210> SEQ ID NO 227
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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Probe

<400> SEQUENCE: 227

caccacgctc cctggcgga 19

<210> SEQ ID NO 228
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 228

ggcaaattca acggcacagt 20

<210> SEQ ID NO 229
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 229

gggtctcgct cctggaagat 20

<210> SEQ ID NO 230
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Probe

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<400> SEQUENCE: 230

aaggccgaga atgggaagct tgtcatc

27

<210> SEQ ID NO 231

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 231

ccagcttctt attaattatc

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<210> SEQ ID NO 232

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<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 232

taagatccag cttcttatta

20

1. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of any of SEQ ID NOs: 8-200.

2. The compound of claim 1, wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

3. The compound of claim 1, wherein the nucleobase sequence of the modified oligonucleotide is 100% complementary to SEQ ID NO: 1.

4. The compound of claim 2, wherein the modified oligonucleotide consists of 16 to 22 linked nucleosides.

5. The compound of claim 2, wherein at least one nucleoside of the modified oligonucleotide comprises a modified sugar moiety.

6. The compound of claim 5, wherein the modified sugar moiety is a 2'-substituted sugar moiety.

7. The compound of claim 6, wherein the 2'-substituted sugar moiety is selected from: a 2'-OMe sugar moiety, a 2'-F sugar moiety, and a 2'-MOE sugar moiety.

8. The compound of claim 5, wherein the modified sugar moiety is a bicyclic sugar moiety.

9. The compound of claim 8, wherein the bicyclic sugar moiety is a LNA sugar moiety or a cEt sugar moiety.

10. The compound of claim 5, wherein the modified sugar moiety is a sugar surrogate.

11. The compound of claim 10, wherein the sugar surrogate is a morpholino.

12. The compound of claim 5, wherein at least one nucleoside of the modified oligonucleotide comprises a naturally occurring sugar moiety.

13. The compound of claim 2, wherein each nucleoside of the modified oligonucleotide comprises a modified sugar moiety.

14. The compound of claim 13, wherein the modified sugar moiety is a 2'-substituted sugar moiety.

15. The compound of claim 14, wherein the 2'-substituted sugar moiety is selected from: a 2' OMe sugar moiety, a 2'-F sugar moiety, and 2' MOE a 2'-OCH₂CH₂OCH₃ sugar moiety.

16. The compound of claim 13, wherein the modified sugar moiety is a bicyclic sugar moiety.

17. The compound of claim 16, wherein the bicyclic sugar moiety is a LNA sugar moiety or a cEt sugar moiety.

18. The compound of claim 13 wherein the modified sugar moiety is a sugar surrogate.

19. The compound of claim 18, wherein the sugar surrogate is a morpholino.

20. The compound of claim 5, wherein at least one nucleobase of the modified oligonucleotide is a modified nucleobase.

21. The compound of claim 20, wherein the modified nucleobase is a 5-methylcytosine.

22. The compound of claim 2, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

23. The compound of claim 22, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

24. The compound of claim 23, wherein the modified oligonucleotide comprises at least one naturally occurring internucleoside linkage.

25. The compound of claim 2, wherein each internucleoside linkage is a modified internucleoside linkage.

26. The compound of claim 25, wherein each modified internucleoside linkage is a phosphorothioate internucleoside linkage.

27. The compound of claim 5, comprising the modified oligonucleotide linked to a conjugate group.

28. A single-stranded modified oligonucleotide consisting of 18 linked nucleosides and having a nucleobase sequence comprising 18 contiguous nucleobases of any of SEQ ID NOs: 8-200, wherein each nucleoside of the modified oligonucleotide

gonucleotide comprises a 2'-substituted sugar moiety and each internucleoside linkage is a phosphorothioate internucleoside linkage or a phosphodiester internucleoside linkage.

29. The single-stranded modified oligonucleotide of claim **28**, wherein the 2'-substituted sugar moiety is 2'-OMe sugar moiety.

30. The single-stranded modified oligonucleotide of claim **29**, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

31. A pharmaceutical composition comprising a single-stranded modified oligonucleotide according to claim **28** and a pharmaceutically acceptable carrier or diluent.

32. The pharmaceutical composition of claim **31**, wherein the single-stranded modified oligonucleotide is a salt.

33. The pharmaceutical composition of claim **32**, wherein the salt is a sodium salt.

34. A method of reducing or ameliorating one or more symptoms associated with a tau-associated disorder, comprising contacting a cell with the single-stranded modified oligonucleotide of claim **28**.

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