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ABSTRACT

Disclosed herein are methods for reducing expression of Tau mRNA and protein in an animal with Tau antisense compounds. Also disclosed are methods for modulating splicing of Tau mRNA in an animal with Tau antisense compounds. Such 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, Fronto-temporal Dementia (FTD), FTDP-17, Progressive Supranuclear Palsy, Chronic Traumatic Encephalopathy, Epilepsy, and Dravet's Syndrome.

COMPOSITIONS AND METHODS FOR MODULATING TAU EXPRESSION FOR REDUCING SEIZURE AND MODIFYING A NEURODEGENERATIVE SYNDROME

SEQUENCE LISTING

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0210WOSEQ.txt created March 14, 2013, which is approximately 434 KB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD

Provided are methods for treating, preventing, or ameliorating neurodegenerative diseases, including tauopathies, Alzheimer's Disease, Fronto-temporal 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 an animal. Certain embodiments are directed to methods, compounds and compositions for treating, preventing or ameliorating a seizure disorder by inhibiting expression of Tau or modulating the splicing of Tau in an animal.

BACKGROUND

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.

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.

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.

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.

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.

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.

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, 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 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 (Aβ) plaques.

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 orprovoked by a disorder or another condition that irritates the brain. Certain mental disorders can cause seizure symptoms referred to as psychogenic nonepileptic seizures.

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.

Anticonvulsants represent the common treatment regime for seizues. 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

Provided herein are methods for modulating levels of Tau mRNA and protein in cells, tissues, and

animals. Also 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.

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.

Several embodiments are drawn to methods of reducing or decreasing seizures in a subject. In certain embodiments, methods are provided for reducing the risk for seizure in a subject. In certain embodiments, the seizures are related to neurodegenerative disorders. In certain embodiments, the neurodegenerative disorder is a tau-associated disorder. 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.

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.

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.

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.

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

Embodiment 1. A method of reducing seizures or risk of seizures in an animal comprising administering a Tau-specific inhibitor to the subject, wherein incidence of seizures or severity of seizures is reduced.

Embodiment 2. The method of embodiment 1, wherein the animal is a human.

Embodiment 3. The method of embodiments 1-2, wherein the Tau-specific inhibitor is an antisense compound.

Embodiment 4. A method comprising administering a Tau antisense compound to an animal for treating a Tau associated disease and thereby ameliorating at least one symptom of the Tau associated disease.

Embodiment 5. A method comprising:

identifying an animal having a Tau associated disease; and

administering a Tau antisense compound and thereby ameliorating at least one symptom of the Tau associated disease.

Embodiment 6. The method of embodiments 4-5, wherein the animal is a human.

Embodiment 7. The method of embodiments 4-6, wherein the symptom is any one of incidence of seizures, seizure severity, presence of neurofibrillary inclusions, loss of memory, loss of cognition, decreased motor function, or bradykinesia.

Embodiment 8. The method of embodiments 4-8, wherein the Tau associated disease is a neurodegenerative disease.

Embodiment 9. The method of embodiment 8, wherein the neurodegenerative disease is selected from among Alzheimer's Disease, Fronto-temporal Dementia (FTD), FTDP-17, Progressive Supranuclear Palsy, Chronic Traumatic Encephalopathy, Epilepsy, and Dravet's Syndrome.

Embodiment 10. The method of embodiments 3-9, wherein the antisense compound comprises a single-stranded antisense oligonucleotide complementary to a Tau nucleic acid.

Embodiment 11. The method of embodiments 1-10, wherein expression of Tau RNA or expression of Tau protein is reduced.

Embodiment 12. The method of embodiments 1-10, wherein expression of the 4R isoform of Tau RNA or expression of the 4R isoform of Tau protein is reduced.

Embodiment 13. The method of embodiments 1-10, wherein expression of the 3R isoform of

Tau RNA or expression of the 3R isoform of Tau protein is increased.

Embodiment 14. The method of embodiments 1-10, wherein expression of the 4R isoform of Tau RNA is reduced and expression of the 3R isoform of Tau RNA is increased.

Embodiment 15. The method of embodiments 1-10, wherein expression of the 4R isoform of Tau protein is reduced and expression of the 3R isoform of Tau protein is increased.

Embodiment 16. The method of embodiments 10-15, wherein the single-stranded antisense oligonucleotide comprises at least one modification.

Embodiment 17. The method of embodiment 10-16, wherein the single-stranded antisense oligonucleotide is specifically hybridizable to a human Tau nucleic acid.

Embodiment 18. The method of embodiments 10-17, wherein the single-stranded antisense oligonucleotide is at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% complementary to an equal length portion of a human Tau nucleic acid.

Embodiment 19. The method of embodiments 10-18, wherein the single-stranded antisense oligonucleotide is 100% complementary to a human Tau nucleic acid.

Embodiment 20. The method of embodiments 16-19, wherein the single-stranded antisense oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 21. The method of embodiment 20, wherein each internucleoside linkage of the single-stranded antisense oligonucleotide is a modified internucleoside linkage.

Embodiment 22. The method of embodiments 20-21, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 23. The method of embodiments 16-22, comprising at least one modified nucleoside.

Embodiment 24. The method of embodiments 16-23, wherein the single-stranded antisense oligonucleotide comprises at least one modified nucleoside having a modified sugar.

Embodiment 25. The method of embodiment 24, wherein the single-stranded antisense oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar.

Embodiment 26. The method of embodiment 25, wherein the bicyclic sugar comprises a 4' to 2' bridge selected from among: 4'-(CH2)n-O-2', wherein n is 1 or 2; and 4'-CH2-O-CH2-2'.

Embodiment 27. The method of embodiment 25, wherein the bicyclic sugar comprises a 4'-CH(CH3)-O-2' bridge.

Embodiment 28. The method of embodiment 24, wherein the at least one modified nucleoside having a modified sugar comprises a non-bicyclic 2'-modified sugar moiety.

Embodiment 29. The method of embodiment 28, wherein the 2'-modified sugar moiety comprises a 2'-O-methoxyethyl group.

Embodiment 30. The method of embodiment 28, wherein the 2'-modified sugar moiety

comprises a 2'-O-methyl group.

Embodiment 31. The method of embodiment 24, wherein the at least one modified nucleoside having a modified sugar comprises a sugar surrogate.

Embodiment 32. The method of embodiment 31, wherein the sugar surrogate is a morpholino.

Embodiment 33. The method of embodiment 31, wherein the sugar surrogate is a peptide nucleic acid.

Embodiment 34. The method of embodiments 23-33, wherein each nucleoside is modified.

Embodiment 35. The method of embodiments 10-34, wherein the single-stranded antisense oligonucleotide comprises at least one modified nucleobase.

Embodiment 36. The method of embodiment 35, wherein the modified nucleobase is a 5'-methylcytosine.

Embodiment 37. The method of embodiment 16-35, wherein the single-stranded antisense oligonucleotide comprises:

a gap segment consisting of linked deoxynucleosides;

a 5' wing segment consisting of linked nucleosides;

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

Embodiment 38. The method of embodiment 37, wherein the single-stranded antisense oligonucleotide comprises:

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides;

a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned immediately adjacent and between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; and wherein each internucleoside linkage is a phosphorothioate linkage.

Embodiment 39. The method of embodiments 10-37, wherein the single-stranded antisense oligonucleotide consists of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 linked nucleosides.

Embodiment 40. The method of any preceding embodiment, wherein the administering is parenteral administration.

Embodiment 41. The method of embodiment 40, wherein the parenteral administration is any of injection or infusion.

Embodiment 42. The method of embodiments 40-41, wherein the parenteral administration is any of intrathecal administration or intracerebroventricular administration.

Embodiment 43. A method comprising administering a Tau antisense compound to an animal

for treating a Tau associated disease and thereby reducing neurofibrillary inclusions.

Embodiment 44. A method comprising administering a Tau antisense compound to an animal for treating a Tau associated disease and thereby improving neurological function.

Embodiment 45. A method comprising:

identifying an animal having a Tau associated disease; and

administering a Tau antisense compound and thereby reducing neurofibrillary inclusions.

Embodiment 46. A method comprising:

identifying an animal having a Tau associated disease; and

administering a Tau antisense compound and thereby improving neurological function.

Embodiment 47. The method of embodiments 43-46, wherein the animal is a human.

Embodiment 48. The method of embodiments 43-47, wherein the antisense compound comprises a single-stranded antisense oligonucleotide complementary to a Tau nucleic acid.

Embodiment 49. The method of embodiments 43-48, wherein the Tau associated disease is a neurodegenerative disease.

Embodiment 50. The method of embodiment 49, wherein the neurodegenerative disease is selected from among Alzheimer's Disease, Fronto-temporal Dementia (FTD), FTDP-17, Progressive Supranuclear Palsy, Chronic Traumatic Encephalopathy, Epilepsy, and Dravet's Syndrome.

Embodiment 51. The method of embodiments 43-50, wherein the expression of Tau RNA or expression of Tau protein is reduced.

Embodiment 52. The method of embodiments 43-50, wherein expression of the 4R isoform of Tau RNA or expression of the 4R isoform of Tau protein is reduced.

Embodiment 53. The method of embodiments 43-50, wherein expression of the 3R isoform of Tau RNA or expression of the 3R isoform of Tau protein is increased.

Embodiment 54. The method of embodiments 43-50, wherein expression of the 4R isoform of Tau RNA is reduced and expression of the 3R isoform of Tau RNA is increased.

Embodiment 55. The method of embodiments 43-50, wherein expression of the 4R isoform of Tau protein is reduced and expression of the 3R isoform of Tau protein is increased.

Embodiment 56. The method of embodiments 48-55, wherein the single-stranded antisense oligonucleotide comprises at least one modification.

Embodiment 57. The method of embodiment 48-56, wherein the single-stranded antisense oligonucleotide is specifically hybridizable to a human Tau nucleic acid.

Embodiment 58. The method of embodiments 48-57, wherein the single-stranded antisense oligonucleotide is at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% complementary to an equal length portion of a human Tau nucleic acid.

Embodiment 59. The method of embodiments 48-58, wherein the single-stranded antisense

oligonucleotide is 100% complementary to a human Tau nucleic acid.

Embodiment 60. The method of embodiments 56-59, wherein the single-stranded antisense oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 61. The method of embodiment 60, wherein each internucleoside linkage of the single-stranded antisense oligonucleotide is a modified internucleoside linkage.

Embodiment 62. The method of embodiments 60-61, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 63. The method of embodiments 56-62, comprising at least one modified nucleoside.

Embodiment 64. The method of embodiments 56-63, wherein the single-stranded antisense oligonucleotide comprises at least one modified nucleoside having a modified sugar.

Embodiment 65. The method of embodiment 64, wherein the single-stranded antisense oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar.

Embodiment 66. The method of embodiment 65, wherein the bicyclic sugar comprises a 4' to 2' bridge selected from among: 4'-(CH2)n-O-2', wherein n is 1 or 2; and 4'-CH2-O-CH2-2'.

Embodiment 67. The method of embodiment 65, wherein the bicyclic sugar comprises a 4'-CH(CH3)-O-2' bridge.

Embodiment 68. The method of embodiment 64, wherein the at least one modified nucleoside having a modified sugar comprises a non-bicyclic 2'-modified sugar moiety.

Embodiment 69. The method of embodiment 68, wherein the 2'-modified sugar moiety comprises a 2'-O-methoxyethyl group.

Embodiment 70. The method of embodiment 68, wherein the 2'-modified sugar moiety comprises a 2'-O-methyl group.

Embodiment 71. The method of embodiment 64, wherein the at least one modified nucleoside having a modified sugar comprises a sugar surrogate.

Embodiment 72. The method of embodiment 71, wherein the sugar surrogate is a morpholino.

Embodiment 73. The method of embodiment 71, wherein the sugar surrogate is a peptide nucleic acid.

Embodiment 74. The method of embodiments 63-73, wherein each nucleoside is modified.

Embodiment 75. The method of embodiments 48-74, wherein the single-stranded antisense oligonucleotide comprises at least one modified nucleobase.

Embodiment 76. The method of embodiment 75, wherein the modified nucleobase is a 5'-methylcytosine.

Embodiment 77. The method of embodiment 56-75, wherein the single-stranded antisense oligonucleotide comprises:

a gap segment consisting of linked deoxynucleosides;

a 5' wing segment consisting of linked nucleosides;

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

Embodiment 78. The method of embodiment 77, wherein the single-stranded antisense oligonucleotide comprises:

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides;

a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned immediately adjacent and between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; and wherein each internucleoside linkage is a phosphorothioate linkage.

Embodiment 79. The method of embodiments 48-77, wherein the single-stranded antisense oligonucleotide consists of 15, 16, 17, 18, or 19 linked nucleosides.

Embodiment 80. The method of embodiments 48-78, wherein the single-stranded antisense oligonucleotide consists of 20 linked nucleosides.

Embodiment 81. The method of embodiments 48-77, wherein the single-stranded antisense oligonucleotide consists of 21, 22, 23, 24, or 25 linked nucleosides.

Embodiment 82. The method of embodiments 43-82 preceding embodiment, wherein the administering is parenteral administration.

Embodiment 83. The method of embodiment 82, wherein the parenteral administration is any of injection or infusion.

Embodiment 84. The method of embodiments 82-83, wherein the parenteral administration is any of intrathecal administration or intracerebroventricular administration.

Embodiment 85. The method of embodiments 43-84, wherein at least one symptom of a Tau associated disease is ameliorated.

Embodiment 86. The method of embodiments 43-85, wherein at least one symptom of a Tau associated disease is prevented.

Embodiment 87. The method of embodiments 43-86, wherein progression of at least one symptom of a Tau associated disease is slowed.

Embodiment 88. The method of embodiments 85-87, wherein the at least one symptom is any of memory loss, anxiety, loss of motor function, incidence of seizures, severity of seizures, and excitotoxicity.

Embodiment 89. A method of decreasing seizures in a subject with a high 4R:3R tau isoform ratio, the method comprising administering an antisense oligonucleotide to the subject, wherein the method

decreases the 4R:3R tau ratio in the central nervous system of the subject.

Embodiment 90. The method of embodiment 89, wherein the high 4R:3R tau isoform ratio in the subject is caused by a splicing defect.

Embodiment 91. The method of embodiment 89, further comprising decreasing the accumulation of aggregated tau in the brain and spinal cord of the subject.

Embodiment 92. The method of embodiment 89, wherein the antisense oligonucleotide is an o methyl oligonucleotide.

Embodiment 93. The method of embodiment 89, wherein the oligonucleotide is administered using a single bolus administration.

Embodiment 94. The method of embodiment 89, wherein the oligonucleotide is administered using a pump.

Embodiment 95. The method of embodiment 89, wherein the total amount of tau in the central nervous system is not changed.

Embodiment 96. A method of modifying a neurodegenerative syndrome in a subject with a high 4R:3R tau isoform ratio, the method comprising administering an antisense oligonucleotide to the central nervous system of the subject, wherein the antisense oligonucleotide decreases the high 4R:3R tau ratio in the central nervous system of the subject.

Embodiment 97. The method of embodiment 89, wherein the high 4R:3R tau isoform ratio in the subject is caused by a splicing defect.

Embodiment 98. The method of embodiment 89, wherein the neurodegenerative syndrome is a neurodegenerative syndrome associated with tau.

Embodiment 99. The method of embodiment 91, wherein the neurodegenerative syndrome neurodegenerative syndrome associated with tau is associated with tau multimerization.

Embodiment 100. The method of embodiment 89, wherein the neurodegenerative syndrome is 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 degeneration, argyrophilic grain disease, supranuclear palsy, corticobasal degeneration, frontotemporal dementia, or frontotemporal lobar degeneration.

Embodiment 101. The method of embodiment 89, wherein the neurodegenerative syndrome is Alzheimer's disease, progressive supranuclear palsy, corticobasal degeneration, or frontotemporal dementia.

Embodiment 102. The method of embodiment 89, wherein modifying a neurodegenerative disease improves the behavioral phenotype of the subject.

Embodiment 103. The method of embodiment 95, wherein the behavioral phenotype of the subject is seizures.

Embodiment 104. The method of embodiment 89, wherein modifying a neurodegenerative disease slows the progression of neurodegenerative disease development in the subject.

Embodiment 105. The method of embodiment 89, wherein modifying a neurodegenerative disease decreases the accumulation of aggregated tau in the brain and spinal cord of the subject.

Embodiment 106. The method of embodiment 89, wherein the antisense oligonucleotide is an o methyl oligonucleotide.

Embodiment 107. The method of embodiment 89, wherein the oligonucleotide is administered using a single bolus administration.

Embodiment 108. The method of embodiment 89, wherein the oligonucleotide is administered using a pump.

Embodiment 109. The method of embodiment 89, wherein the abnormal 4R:3R tau ratio in the central nervous system is decreased without decreasing the total amount of tau in the central nervous system.

Embodiment 110. The method of embodiment 89, wherein the antisense oligo alters the splicing of a nucleic acid encoding tau.

Embodiment 111. A method of reducing seizures or risk of seizures in a subject comprising administering tau-specific inhibitor to the subject, wherein seizures or risk of seizures in the subject is reduced.

Embodiment 112. The method of embodiment 111, wherein the tau-specific inhibitor is a transcriptional inhibitor.

Embodiment 113. The method of embodiment 112, wherein the transcriptional inhibitor is an oligonucleotide.

Embodiment 114. The method of embodiment 113, wherein the oligonucleotide comprises a nucleobase sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, 99% or at least 100% complementary to an equal length portion of a nucleic acid encoding Tau such as any one of SEQ ID NOs: 1-10.

Embodiment 115. The method of embodiment 113 or 114, wherein the oligonucleotide is a modified oligonucleotide.

Embodiment 116. The method of embodiment 113 or 114, wherein the oligonucleotide is an antisense oligonucleotide.

Embodiment 117. The method of any of embodiment 113-115, wherein the oligonucleotide is a single-stranded oligonucleotide.

Embodiment 118. The method of any of embodiments 113-116, wherein the oligonucleotide consists of 12 to 30 linked nucleosides.

Embodiment 119. The method of any of embodiments 113-118, wherein oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 120. The method of any of embodiments 119, wherein the modified

internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 121. The method of any of embodiments11 9, wherein each modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 122. The method of any of embodiments 113-121, wherein the oligonucleotide comprises at least one modified sugar moiety.

Embodiment 123. The method of embodiment 122, wherein the modified sugar moiety is a bicyclic sugar moiety.

Embodiment 124. The method of embodiment 122, wherein the modified sugar moiety is a 2' substituted sugar moiety.

Embodiment 125. The method of embodiment 124, wherein the 2' substituted sugar moiety is selected from among: 2'- O-methoxyethyl (2'-MOE), 2'-OMe, or 2'-Fl.

Embodiment 126. The method of any of embodiments 113-124, wherein the oligonucleotide comprises at least one modified nucleobase.

Embodiment 127. The method of embodiment 126, wherein the modified nucleobase is a 5-methylcytosine.

Embodiment 128. The method of any of embodiment 113-126, wherein the oligonucleotide is a chimeric oligonucleotide.

Embodiment 129. The method of any of embodiments 113-127, wherein the oligonucleotide comprises: (i) a gap segment consisting of linked deoxynucleosides; (ii) a 5' wing segment consisting of linked nucleosides; (iii) a 3' wing segment consisting of linked nucleosides, wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

Embodiment 130. The method of embodiment 128, wherein the oligonucleotide comprises: (i) a gap segment consisting of ten linked deoxynucleosides; (ii) a 5' wing segment consisting of five linked nucleosides; (iii) a 3' wing segment consisting of five linked nucleosides, wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; and wherein each internucleoside linkage is a phosphorothioate linkage.

Embodiment 131. The method of embodiment 111-130, wherein the inhibitor is administered to the CNS of the subject.

Embodiment 132. The method of embodiment 131, wherein the inhibitor is administered by intrathecal or intracerebral vascular administration.

Embodiment 133. The method of embodiment 131 or 132, wherein the administration is by bolus or infusion.

Embodiment 134. The method of any of embodiments 131-133, wherein the administration is by

a pump.

Embodiment 135. A method of reducing seizures or the risk of seizures in a subject comprising administering a tau splice modulating agent to the subject, wherein the seizures or risk of seizures in the subject is reduced.

Embodiment 136. A method of reducing seizures or the risk of seizures in a subject comprising administering an oligonucleotide consists of 12 to 30 linked nucleosides, wherein the oligonucleotide comprises a nucleobase sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, 99% or at least 100% complementary to an equal length portion of a nucleic acid encoding Tau such as any one of SEQ ID NOs:1-10 and, wherein the seizures or risk of seizures in the subject is reduced.

Embodiment 137. The method of embodiment 135, wherein the tau splice modulating agent is an oligonucleotide.

Embodiment 138. The method of embodiment 136-137, wherein the oligonucleotide comprises at least one modified nucleoside.

Embodiment 139. The method of embodiment 138, wherein at least one modified nucleoside comprises a modified sugar moiety.

Embodiment 140. The method of embodiment 139, wherein at least one modified sugar moiety is a 2'-substituted sugar moiety.

Embodiment 141. The method of embodiment 140, wherein the 2'-substituten of at least one 2'-substituted sugar moiety is selected from among: 2'-OMe, 2'-F, and 2'-MOE.

Embodiment 142. The method of embodiment 140, wherein the 2'-substiuent of at least one 2'-substituted sugar moiety is a 2'-MOE.

Embodiment 143. The method of embodiments 139, wherein at least one modified sugar moiety is a bicyclic sugar moiety.

Embodiment 144. The method of embodiment 143, wherein at least one bicyclic sugar moiety is LNA or cEt.

Embodiment 145. The method of embodiment 139, wherein at least one modified sugar moiety is a sugar surrogate.

Embodiment 146. The method of embodiment 145, wherein at least one sugar surrogate is a morpholino.

Embodiment 147. The method of embodiment 145, wherein at least one sugar surrogate is a modified morpholino.

Embodiment 148. The method of embodiments 136-147, wherein the oligonucleotide comprises at least 5 modified nucleosides, each independently comprising a modified sugar moiety.

Embodiment 149. The method of embodiments 136-148, wherein the oligonucleotide comprises at least 10 modified nucleosides, each independently comprising a modified sugar moiety.

Embodiment 150. The method of embodiments 136-499, wherein the oligonucleotide comprises at least 15 modified nucleosides, each independently comprising a modified sugar moiety.

Embodiment 151. The method of embodiments 136-150, wherein each nucleoside of the oligonucleotide is a modified nucleoside, each independently comprising a modified sugar moiety

Embodiment 152. The method of embodiments 136-141, wherein the oligonucleotide comprises at least two modified nucleosides comprising modified sugar moieties that are the same as one another.

Embodiment 153. The method of embodiments 136-147, wherein the oligonucleotide comprises at least two modified nucleosides comprising modified sugar moieties that are different from one another.

Embodiment 154. The method of embodiments 136-147, wherein the oligonucleotide comprises a modified region of at least 5 contiguous modified nucleosides.

Embodiment 155. The method of embodiments 136-147, wherein the oligonucleotide comprises a modified region of at least 10 contiguous modified nucleosides.

Embodiment 156. The method of embodiments 136-147, wherein the oligonucleotide comprises a modified region of at least 15 contiguous modified nucleosides.

Embodiment 157. The method of embodiments 136-147, wherein the oligonucleotide comprises a modified region of at least 20 contiguous modified nucleosides.

Embodiment 158. The method of embodiments 154-157, 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.

Embodiment 159. The method of embodiments 154-158, wherein the modified nucleosides of the modified region each comprise the same modification as one another.

Embodiment 160. The method of embodiment 159, wherein the modified nucleosides of the modified region each comprise the same 2'-substituted sugar moiety.

Embodiment 161. The method of embodiment 160, 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.

Embodiment 162. The method of embodiment 160, wherein the 2'-substituted sugar moiety of the modified nucleosides of the region of modified nucleosides is 2'-MOE.

Embodiment 163. The method of embodiment 159, wherein the modified nucleosides of the region of modified nucleosides each comprise the same bicyclic sugar moiety.

Embodiment 164. The method of embodiment 163, wherein the bicyclic sugar moiety of the modified nucleosides of the region of modified nucleosides is selected from LNA and cEt.

Embodiment 165. The method of embodiment 159, wherein the modified nucleosides of the region of modified nucleosides each comprises a sugar surrogate.

Embodiment 166. The method of embodiment 165, wherein the sugar surrogate of the modified nucleosides of the region of modified nucleosides is a morpholino.

Embodiment 167. The method of embodiment 165, wherein the sugar surrogate of the modified nucleosides of the region of modified nucleosides is a modified morpholino.

Embodiment 168. The method of embodiments 136-167, wherein the oligonucleotide comprises no more than 4 contiguous naturally occurring nucleosides.

Embodiment 169. The method of embodiments 136-167, wherein each nucleoside of the oligonucleotide is a modified nucleoside.

Embodiment 170. The method of embodiment 169, wherein each modified nucleoside comprises a modified sugar moiety.

Embodiment 171. The method of embodiment 170, wherein the modified nucleosides of the modified oligonucleotide comprise the same modification as one another.

Embodiment 172. The method of embodiment 171, wherein the modified nucleosides of the modified oligonucleotide each comprise the same 2'-substituted sugar moiety.

Embodiment 173. The method of embodiment 172, wherein the 2'-substituted sugar moiety of the modified oligonucleotide is selected from 2'-F, 2'-OMe, and 2'-MOE.

Embodiment 174. The method of embodiment 172, wherein the 2'-substituted sugar moiety of the modified oligonucleotide is 2'-MOE.

Embodiment 175. The method of embodiment 171, wherein the modified nucleosides of the oligonucleotide each comprise the same bicyclic sugar moiety.

Embodiment 176. The method of embodiment 175, wherein the bicyclic sugar moiety is selected from LNA and cEt.

Embodiment 177. The method of embodiment 169, wherein the modified nucleosides of the oligonucleotide each comprises a sugar surrogate.

Embodiment 178. The method of embodiment 177, wherein the sugar surrogate is a morpholino.

Embodiment 179. The method of embodiment 178, wherein the sugar surrogate is a modified morpholino.

Embodiment 180. The method of embodiments 136-179, wherein the oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 181. The method of embodiments 136-180, wherein each internucleoside linkage is a modified internucleoside linkage.

Embodiment 182. The method of embodiments 178-181, the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 183. The method of embodiments 136-149, wherein each internucleoside linkage is a modified internucleoside linkage and wherein each internucleoside linkage comprises the same modification.

Embodiment 184. The method of embodiment 183, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 185. The method of embodiment 135-184, wherein the subject has a high 4R-3R tau isoform ratio.

Embodiment 186. The method of embodiments 135-185, wherein 4R:3R tau ratio is reduced in the central nervous system of the subject.

Embodiment 187. The method of embodiments 185, wherein the high 4R:3R tau isoform ratio in the subject is caused by a splicing defect.

Embodiment 188. The method of embodiments 135-187, wherein the total amount of tau in the central nervous system is not changed.

Embodiment 189. The method of embodiments 111-188, wherein the agent, inhibitor or oligonucleotide is administered to the CNS of the subject.

Embodiment 190. The method of embodiment 189, wherein the inhibitor is administered by intrathecal or intracerebral vascular administration.

Embodiment 191. The method of embodiments 189-190, wherein the administration is by bolus or infusion.

Embodiment 192. The method of embodiments 189-191, wherein the oligonucleotide is administered using a pump.

Embodiment 193. The method of embodiments 111-192, wherein the subject has a tau-associated disease.

Embodiment 194. The method of embodiment 193, wherein the tau-associated disease is selected from among: Alzheimer's disease, progressive supranuclear palsy, dementia pugilistica, frontotemporal dementia, parkinsonism linked to chromosome, LyticoBodig disease, tangle-predominant dementia, ganglioglioma, gangliocytoma, meningioangiomatosis, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, HaliervordenSpatz disease, Pick's disease, corticobasal degeneration, argyrophilic grain disease, supranuclear palsy, corticobasal degeneration, frontotemporal dementia, or frontotemporal lobar degeneration.

Embodiment 195. The method of embodiments 111-194 wherein the subject has a seizure disorder.

Embodiment 196. The method of embodiment 195, wherein the seizure disorder is selected from among:epilepsy, meningitis, brain strokes, injury-associated seizures, brain injury, juvenile myoclonic epilepsy, infantile spasms, reflex epilepsy, and febrile seizures.

Embodiment 197. The method of embodiments 111-196 wherein the subject has a neurological disorder.

Embodiment 198. The method of any of the preceding embodiments, wherein the antisense oligonucleotide has the nucleobase sequence of SEQ ID NO: 12.

Embodiment 199. The method of any of the preceding embodiments, wherein the antisense

oligonucleotide has the nucleobase sequence of SEQ ID NO: 13.

Embodiment 200. The method of any of the preceding embodiments, wherein the antisense oligonucleotide has the nucleobase sequence of SEQ ID NO: 14.

Embodiment 201. The method of any of the preceding embodiments, wherein the antisense oligonucleotide has the nucleobase sequence of SEQ ID NO: 15.

Embodiment 202. The method of any of the preceding embodiments, wherein the antisense oligonucleotide has the nucleobase sequence of SEQ ID NO: 16.

Embodiment 203. The method of any of the preceding embodiments, wherein the antisense oligonucleotide has the nucleobase sequence of SEQ ID NO: 17.

Embodiment 204. The method of any of the preceding embodiments, wherein the antisense oligonucleotide has the nucleobase sequence of SEQ ID NO: 18.

Embodiment 205. An antisense oligonucleotide comprising 20 linked modified nucleosides and having the sequence of SEQ ID NO: 12, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

Embodiment 206. An antisense oligonucleotide comprising 20 linked modified nucleosides and having the sequence of SEQ ID NO: 13, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

Embodiment 207. An antisense oligonucleotide comprising 20 linked modified nucleosides and having the sequence of SEQ ID NO: 14, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

Embodiment 208. An antisense oligonucleotide comprising 18 linked modified nucleosides and having the sequence of SEQ ID NO: 15, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

Embodiment 209. An antisense oligonucleotide comprising 18 linked modified nucleosides and having the sequence of SEQ ID NO: 16, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

Embodiment 210. An antisense oligonucleotide comprising 18 linked modified nucleosides and having the sequence of SEQ ID NO: 17, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

Embodiment 211. An antisense oligonucleotide comprising 18 linked modified nucleosides and having the sequence of SEQ ID NO: 18, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

BRIEF DESCRIPTION OF THE FIGURES

Figure 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.

Figure 2 depicts a diagram describing delivery of antisense oligonucleotides. Under anesthesia (inhaled isoflourane/oxygen mixture), a small hole is drilled in skull through which a catheter is placed in the lateral ventricle. The catheter is connected via plastic tubing to an osmotic pump (Alzet pump) which is embedded in a subcutaneous pocket on the back of the animal. Oligos are delivered continuously via this method. Changing the pump can be done easily by removing the osmotic pump without disturbing the indwelling catheter.

Figure 3 depicts two plots showing mouse tau mRNA levels are decreased by mouse tau antisense oligos in vitro. (A) 80 antisense oligonucleotides, 120 nM, against mouse tau were transfected by cytofectin into cultured B16-F10 (murine melanoma cells). Each bar represents tau mRNA levels 48 hours after transfection with a different antisense oligonucleotide measured in triplicate cultures compared with untransfected cells (UTC, 100%). (B) Mouse tau mRNA 48 hours after transfection. Antisense oligos against mouse tau that demonstrated decreased levels of mouse tau in the initial screen (part A) were tested in cultured B16-F10 (murine melanoma cells line) cells transfected by cytofectin with increasing antisense oligos to mouse tau (1-10) or two scrambled oligonucleotide controls, (11, 12). Nine of 10 oligos showed an appropriate dose response in this subsequent screen. Untransfected cells = 100%. These oligos are excellent candidates for in vivo testing of mouse tau knockdown.

Figure 4 depicts two plots and a Western blot showing antisense oligos decrease mouse tau levels in the brain. (A) Saline, control scrambled oligo , or 50 μg of antisense oligos directed against mouse tau were injected into the hippocampus by stereotactic injection. Mice were euthanized after one week and brain parenchyma was examined for mouse tau mRNA levels by QPCR. GAPDH mRNA was used to normalize samples. All three oligos used in this paradigm decreased mouse tau by >75%. Individual antisense oligos were labeled 1-5. Oligos 1 and 3 were not tested in this paradigm. (N=5 Avg+/- SD). (B, C) Since oligo Tau5 worked well in the intraparenchymal (hippocampal) injection in (A), Tau5 was further tested by infusing this oligo into the right lateral ventricle for 1 month, at 100 μg/day via an osmotic pump connected to a catheter in the right lateral ventricle. Mice were euthanized after 1 month and right temporal parietal cortex was examined for mouse tau mRNA levels (N=4, Avg +/- SD), (B) and mouse tau protein levels (C). Protein data from three saline animals and 4 Tau5 treated animals are shown. Tau protein levels are clearly reduced. GAPDH was used a loading control and shows no change.

Figure 5 depicts a plot representing the relative brain tau levels after infusion of 25, 50 and 100μg of the knockdown oligo.

Figure 6 depicts a plot representing the relative brain tau levels 0, 4 and 12 weeks after infusion of the knockdown oligo.

Figure 7 depicts (A) the experimental setup and tissue collection, (B) a plot representing the total endogenous mouse tau mRNA levels 24, 48 and 72 hours after administration of the oligo, and (C) a Western blot of total endogenous mouse tau protein levels and GAPDH levels up to one month after administration of the oligo.

Figure 8 depicts a plot representing the relative brain 4R tau levels after a one month intraventricular infusion of the splicing oligo.

Figure 9 depicts two plots showing tau splicing oligos decrease 4R tau. Oligos designed to specifically decrease 4R tau levels (50μg) or saline were injected into the hippocampus by stereotactic injection into htau mice that express full length human tau. Mice were euthanized after one week and brain parenchyma was examined for human 4R tau mRNA (A) and for human tau 3R tau mRNA (B) by QPCR. GAPDH mRNA was used to normalize samples. (N=4 for saline, and 2 for each oligo, Avg+/-range).

Figure 10 depicts RT-PCR and Western blot results of a one month intraventricular infusion with a splicing oligo. 100ng of starting RNA was used for the RT-PCR. A=Adult mouse with no pump. 20μg protein was loaded for the Western blots. F= E18 fetal rat whole brain homogenate. 4R Tau antibody (RD4) was used at a 1:500 dilution. 3R Tau antibody (RD3) was used at a 1:500 dilution. GAPDH antibody was used at a 1:10,000 dilution.

Figure 11 depicts two plots of (A) seizure severity in mTau+/+, mTau+/-, and mTau-/- mice, and (B) percentage of mice with various stages of seizures in mTau+/+, mTau+/-, and mTau-/- mice.

Figure 12 depicts two plots of (A) seizure severity in mice treated with a knockdown oligo or a splicing oligo, and (B) percentage of mice treated with a knockdown oligo or a splicing oligo with various stages of seizures.

Figure 13 depicts a plot showing the average weight gain by a N279K mouse treated with vehicle, a scrambled oligonucleotide, a human tau knockdown oligonucleotide, a human tau splicing oligonucleotide and nonTg saline.

Figure 14 depicts a graph showing the relative mouse tau levels in different brain regions with vehicle or a knockdown oligo.

Figure 15 depicts a graph showing the relative human tau levels in P301S mice treated with four different antisense oligos.

Figure 16 depicts a graph showing the relative mouse tau levels in P301S mice treated with four different antisense oligos.

Figure 17 depicts a graph showing the relative GFAP expression in P301S mice treated with four different antisense oligos.

Figure 18 depicts a picture (A) and a graph (B) showing tau splicing in N279K mice over time.

Figure 19 depicts hTau splicing oligo screening in N279K mice.

Figure 20 depicts a picture (A) and a graph (B) showing ASO screen for Tau splicing in N279K mice. ICV infusion 60 micrograms/day for 28 days. Mice were sacrificed on the 29th day, and the cortex tissue around the cannula was collected.

Figure 21 depicts graphs showing N279K baseline behavioral deficits.

Figure 22 depicts graphs showing Morris water navigation at different timepoints.

Figure 23 depicts a graph showing N279K average weight gain after 1 month with various antisense treatments.

Figure 24 depicts a graph showing N279K average weight gain after 1 and 2 months with various antisense treatments.

Figure 25 provides a graphical representation of the percentage of cells stained with the antibody AT8 as a measure of hyperphosphorylated Tau in the P301S transgenic mouse model.

Figure 26 provides a graphical representation of the percentage of cells stained with the antibody AT8 as a measure of hyperphosphorylated Tau in the N279K transgenic mouse model.

Figure 27 provides a diagram of each CNS section used for mRNA and protein analysis in Example 6 (Example set 3).

Figure 28 provides a bar graph showing seizure severity.

Figure 29 provides a bar graph showing Tau mRNA (A) and Tau protein (B) levels.

Figure 30 provides a scatter plot showing seizure severity plotted against Tau levels. (A) shows Tau protein levels in PBS, ISIS 141923-treated, and Tau5-treated groups. (B) shows the correlation of Tau protein levels with seizure score in a linear regression plot.

DETAILED DESCRIPTION

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of "or" means "and/or" unless stated otherwise. Additionally, as used herein, the use of "and" means "and/or" unless stated otherwise. Furthermore, the use of the term "including" as well as other forms, such as "includes" and "included", is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit, unless specifically stated otherwise.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. Where permitted, all documents, or portions of documents, cited in this disclosure, including, but not limited to, patents, patent applications, published patent applications, articles, books, treatises, and GENBANK Accession Numbers and associated sequence information obtainable through

databases such as National Center for Biotechnology Information (NCBI) and other data referred to throughout in the disclosure herein are hereby expressly incorporated by reference for the portions of the document discussed herein, as well as in their entirety.

Treatment of neurodegenerative syndrome and seizures

A method of modifying neurodegenerative disease has been developed. Using the methods of the invention, it is now possible to alter the ratio of tau isoforms associated with multiple diseases of the brain. Advantageously, the invention provides a method of bypassing the blood brain barrier to specifically target the generation of certain tau isoforms in the central nervous system, may be administered for an extended period of time using proven technology, and has been demonstrated to provide widespread distribution of therapy throughout the brain and spinal cord where it is most efficient.

I. Method

The present invention provides a method of modifying a neurodegenerative syndrome in a subject by administering an antisense oligonucleotide to the central nervous system. Generally speaking, the antisense oligonucleotide alters splicing of the nucleic acid encoding tau and decreases the abnormal 4R:3R tau ratio in the central nervous system of the subject.

(a) subject

According to the invention, the subject may be any subject that expresses 3R and 4R isoforms of tau. In some embodiments, a subject is a rodent, a human, a livestock animal, a companion animal, or a zoological animal. In one embodiment, the subject may be a rodent, e.g. a mouse, a rat, a guinea pig, etc. In another embodiment, the subject may be a livestock animal. Non-limiting examples of suitable livestock animals may include pigs, cows, horses, goats, sheep, llamas and alpacas. In still another embodiment, the subject may be a companion animal. Non-limiting examples of companion animals may include pets such as dogs, cats, rabbits, and birds. In yet another embodiment, the subject may be a zoological animal. As used herein, a "zoological animal" refers to an animal that may be found in a zoo. Such animals may include non-human primates, large cats, wolves, and bears. In an exemplary embodiment, the subject may be a human.

The subject may be suffering from a neurodegenerative syndrome or may be at risk of developing a neurodegenerative syndrome. In some embodiments, the subject may be suffering from a neurodegenerative syndrome. In other embodiments, the subject may be at risk of developing a neurodegenerative syndrome. Neurodegenerative syndromes are as described further below.

(b) neurodegenerative syndrome

The method of the invention comprises modifying a neurodegenerative syndrome. In some embodiments, a neurodegenerative syndrome may be any neurodegenerative syndrome 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, 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, 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 corticobasalganglionic degeneration.

As used herein, the term "modifying a neurodegenerative syndrome" may refer to curing the neurodegenerative syndrome, slowing the course of development of the syndrome, reversing the course of the syndrome, or improving the behavioral phenotype of a subject having a neurodegenerative syndrome. In some embodiments, the method of the invention modifies a neurodegenerative syndrome by curing the neurodegenerative syndrome. In other embodiments, the method of the invention modifies a neurodegenerative syndrome by slowing the progression of the syndrome.

In yet other embodiments, the method of the invention modifies a neurodegenerative syndrome by improving the behavioral phenotype of a subject having a neurodegenerative syndrome. For instance, the symptoms for subjects suffering from Alzheimer's disease may be the mild early symptoms associated with the neurodegenerative syndrome such as mild forgetfulness of recent events, activities, the names of familiar people or things, and the inability to solve simple math problems. The symptoms may also be the moderate symptoms associated with the neurodegenerative syndrome such as forgetting how to do simple tasks such as grooming, speaking, understanding, reading, or writing. Alternatively, the symptoms may be the severe symptoms associated with the neurodegenerative syndrome such as becoming anxious or aggressive, and wandering away from home. Subjects with AD may also have an increased risk of seizures. The symptoms for subjects suffering from progressive supranuclear palsy may include loss of balance, lunging forward when mobilizing, fast walking, bumping into objects or people, falls, changes in personality, general slowing of movement, visual symptoms, dementia (typically including loss of inhibition and ability to organize information), slurring of speech, difficulty swallowing, and difficulty moving the eyes, particularly in the vertical direction, poor eyelid function, contracture of the facial muscles, a backward tilt of the head with stiffening of the neck muscles, sleep disruption, urinary incontinence and constipation. The symptoms for subjects suffering from FTD may include personality changes, cognitive impairment, and motor symptoms. The symptoms for subjects suffering from corticobasalganglionic degeneration are similar to symptoms in patients suffering from FTD and Parkinson's disease and may include shaking, rigidity, slowness of movement and difficulty with walking and gait, cognitive and behavioural problems, dementia, sensory, sleep and emotional problems. In preferred embodiments, the method of the invention modifies a neurodegenerative syndrome by decreasing the risk of seizures.

(c) differential splicing in tau

The invention describes a method 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 mictrotubule 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. (Figure 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 tauopathies. In essence, the method decreases the 4R:3R tau ratio in the central nervous system of the subject.

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 some embodiments, the method decreases the normal 4R:3R tau ratio in the central nervous system of a subject. In other embodiments, the method decreases an low 4R:3R tau ratio in the central nervous system of a subject.

In preferred embodiments, the method decreases a high 4R:3R tau ratio in the central nervous system of a subject. In exemplary embodiments, the method decreases 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.

(d) antisense oligonucleotide

A method of the invention decreases the 4R:3R tau ratio in the central nervous system of a subject by altering the splicing of a nucleic acid encoding tau using an antisense oligonucleotide. An antisense oligonucleotide is a single stranded ribonucleic acid or deoxyribonucleic acid complementary to a chosen sequence. Antisense oligonucleotides may target a specific, complementary, coding or non-coding, nucleic

acid. Depending on the antisense oligonucleotide used, the binding of the oligonucleotide to its target nucleic acid sequence may or may not activate RNAse H. In some embodiments, the antisense oligonucleotide activates RNAse H, which degrades the target nucleic acid. In preferred embodiments, the antisense oligonucleotide does not activate RNAse H. In an exemplary embodiment, the antisense oligonucleotide of the invention is complementary to the nucleic acid sequence encoding tau, does not activate RNAse H, and disrupts the splicing of the nucleic acid encoding tau to reduce the 4R:3R tau ratio.

Methods of making antisense oligonucleotides which do not activate RNase H are known in the art. See, e.g., U.S. Pat. No. 5,149,797 incorporated herein by reference. Such antisense oligonucleotides may contain one or more structural modification which sterically hinders or prevents binding of RNase H to a duplex molecule comprising the oligonucleotide, but does not substantially hinder or disrupt duplex formation. Antisense oligonucleotides that do not activate RNAse H may include oligonucleotides wherein at least one, two or more of the internucleotide bridging phosphate residues are modified phosphates, such as methyl phosphonates, methyl phosphonothioates, phosphoromorpholidates, phosphoropiperazidates and phosphoramidates. For instance, every other one of the internucleotide bridging phosphate residues may be a modified phosphate, contain a 2' loweralkyl moiety (e.g., C1-C4, linear or branched, saturated or unsaturated alkyl, such as methyl, ethyl, ethenyl, propyl, 1-propenyl, 2-propenyl, and isopropyl) or a combination thereof. In preferred embodiments, the antisense oligonucleotide of the invention that does not activate RNAse H, and disrupts the splicing of the nucleic acid encoding tau to reduce the 4R:3R tau ratio is a 2'-O-(2-methoxyethyl) (MOE)-modified antisense oligonucleotide.

Other methods of modifying an oligonucleotide to hinder binding of RNAse H may be found in P. Furdon et al., Nucleic Acids Res. 17, 9193-9204 (1989); S. Agrawal et al., Proc. Natl. Acad. Sci. USA 87, 1401-1405 (1990); C. Baker et al., Nucleic Acids Res. 18, 3537-3543 (1990); B. Sproat et al., Nucleic Acids Res. 17, 3373-3386 (1989); R. Walder and J. Walder, Proc. Natl. Acad. Sci. USA 85, 5011-5015 (1988) the disclosures of all of which are incorporated herein, in their entirety, by reference.

The antisense oligonucleotide of the invention may be a deoxyribonucleotide oligonucleotide or a ribonucleotide oligonucleotide. The antisense oligonucleotide may be any length provided it binds selectively to the intended location. In general, the antisense oligonucleotide may be from 8, 10 or 12 nucleotides in length up to 20, 30, or 50 nucleotides in length.

The antisense oligonucleotide of the invention may disrupt the splicing of the nucleic acid encoding tau to reduce the 4R:3R tau ratio. The splicing process is a series of reactions, mediated by splicing factors, which is carried out on RNA after transcription but before translation, in which the intron(s) are removed, and the exons joined together sequentially so that the protein may be translated. Each intron is defined by a 5' splice site, a 3' splice site, and a branch point situated there between. An antisense oligonucleotide may block these splice elements when the oligonucleotide either fully or partially overlaps the element, or binds to the pre-mRNA at a position sufficiently close to the element to disrupt the binding and function of the splicing

factors which would ordinarily mediate the particular splicing reaction which occurs at that element. The antisense oligonucleotide may block a variety of different splice elements to carry out the instant invention. For instance, the antisense oligonucleotide may block a mutated element, a cryptic element, or a native element; it may block a 5' splice site, a 3' splice site, or a branch point.

The term "antisense oligonucleotide" includes the physiologically and pharmaceutically acceptable salts thereof: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto. Examples of such salts are (a) salts formed with cations such as sodium, potassium, NH4+, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine.

(e) administration

Antisense oligonucleotides of the invention may be administered to a subject by several different means. For instance, oligonucleotides may generally be administered parenteraly, intraperitoneally, intravascularly, or intrapulmonarily in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. In a preferred embodiment, the oligonucleotide may be administered parenterally. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrathecal, or intrasternal injection, or infusion techniques. Formulation of pharmaceutical compositions is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa. (1975), and Liberman, H. A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y. (1980).

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, and polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Delivery methods are preferably those that are effective to circumvent the blood-brain barrier and are effective to deliver agents to the central nervous system. For example, delivery methods may include the use of

nanoparticles. The particles may be of any suitable structure, such as unilamellar or plurilamellar, so long as the antisense oligonucleotide is contained therein. Positively charged lipids such as N-[1-(2,3-dioleoyloxi)propyl]-N, N,N-trimethyl¬amoniummethylsulfate, or "DOTAP," are particularly preferred for such particles and vesicles. The preparation of such lipid particles is well known in the art. See, e.g., U.S. Pat. Nos. 4,880,635 to Janoff et al.; 4,906,477 to Kurono et al.; 4,911,928 to Wallach; 4,917,951 to Wallach; 4,920,016 to Allen et al.; 4,921,757 to Wheatley et al.; etc.

In one preferred embodiment, the oligonucleotide may be administered in a bolus directly into the central nervous system. The oligonucleotides may be administered to the subject in a bolus once, or multiple times. In some preferred embodiments, the oligonucleotides may be administered once. In other preferred embodiments, the oligonucleotides may be administered multiple times. When administered multiple times, the oligonucleotides may be administered at regular intervals or at intervals that may vary during the treatment of a subject. In some embodiments, the oligonucleotides may be administered multiple times at intervals that may vary during the treatment of a subject. In some embodiments, the oligonucleotides may be administered multiple times at regular intervals.

In another preferred embodiment, the oligonucleotide may be administered by continuous infusion into the central nervous system. Non-limiting examples of methods that may be used to deliver the oligonucleotide into the central nervous system by continuous infusion may include pumps, wafers, gels, foams and fibrin clots. In a preferred embodiment, the oligonucleotide may be delivered into the central nervous system by continuous infusion using an osmotic pump. An osmotic minipump contains a high-osmolality chamber that surrounds a flexible, yet impermeable, reservoir filled with the targeted delivery composition-containing vehicle. Subsequent to the subcutaneous implantation of this minipump, extracellular fluid enters through an outer semi-permeable membrane into the high-osmolality chamber, thereby compressing the reservoir to release the targeted delivery composition at a controlled, pre-determined rate. The targeted delivery composition, released from the pump, may be directed via a catheter to a stereotaxically placed cannula for infusion into the cerebroventricular space. In an exemplary embodiment, the oligonucleotide may be delivered into the central nervous system by continuous infusion using a pump as described in the Examples.

One of skill in the art will recognize that the amount and concentration of the composition administered to a subject will depend in part on the subject, the reason for the administration, and the method of administration. In some embodiments, when the oligonucleotide is administered in a bolus into the central nervous system, the oligonucleotide may be administered to the subject in an amount of about 0.1, 0.2, 0.3, 0.4, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 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, 50 mg/kg or more.

In other embodiments, when the oligonucleotide is administered by continuous infusion using a pump into the central nervous system, the oligonucleotide may be administered to the subject in an amount of about

0.1, 0.2, 0.3, 0.4, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 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, 50 mg/kg or more. In some embodiments, the oligonucleotide may be administered by continuous infusion for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 178, 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, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 days or longer. In one embodiment, the oligonucleotide may be administered by continuous infusion for 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 days or longer. In another embodiment, the oligonucleotide may be administered by continuous infusion for 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65 days or longer. In yet another embodiment, the oligonucleotide may be administered by continuous infusion for 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95 days or longer. Longer continuous infusions of the antisense oligonucleotide may also be envisioned using existing pump technology as is known in the art.

Definitions

Unless specific definitions are provided, the nomenclature utilized 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.

Unless otherwise indicated, the following terms have the following meanings:

"2'-O-methoxyethyl" (also 2'-MOE and 2'-$O(CH_2)_2$-OCH_3 and MOE) refers to an O-methoxy-ethyl modification at the 2' position of a furanosyl ring. A 2'-O-methoxyethyl modified sugar is a modified sugar.

"2'-MOE nucleoside" (also 2'-O-methoxyethyl nucleoside) means a nucleoside comprising a 2'-MOE modified sugar moiety.

"2'-substituted nucleoside" means a nucleoside comprising a substituent at the 2'-position of the furanosyl ring other than H or OH. In certain embodiments, 2' substituted nucleosides include nucleosides with bicyclic sugar modifications.

"3' target site" refers to the nucleotide of a target nucleic acid which is complementary to the 3'-most nucleotide of a particular antisense compound.

"5' target site" refers to the nucleotide of a target nucleic acid which is complementary to the 5'-most nucleotide of a particular antisense compound.

"5-methylcytosine" means a cytosine modified with a methyl group attached to the 5 position. A 5-methylcytosine is a modified nucleobase.

"About" means within ±7% of a value. For example, if it is stated, "the compounds affected at least about 70% inhibition of Tau", it is implied that the Tau levels are inhibited within a range of 63% and 77%.

"Acceptable safety profile" means a pattern of side effects that is within clinically acceptable limits.

"Active pharmaceutical agent" means the substance or substances in a pharmaceutical composition that provide a therapeutic benefit when administered to an individual. For example, in certain embodiments an antisense oligonucleotide targeted to Tau is an active pharmaceutical agent.

"Active target region" means a target region to which one or more active antisense compounds is targeted. "Active antisense compounds" means antisense compounds that reduce target nucleic acid levels or protein levels.

"Administered concomitantly" refers to the co-administration of two agents in any manner in which the pharmacological effects of both are manifest in the patient at the same time. Concomitant administration does not require that both agents be administered in a single pharmaceutical composition, in the same dosage form, or by the same route of administration. The effects of both agents need not manifest themselves at the same time. The effects need only be overlapping for a period of time and need not be coextensive.

"Administering" means providing a pharmaceutical agent to an individual, and includes, but is not limited to administering by a medical professional and self-administering.

"Agent" means an active substance that can provide a therapeutic benefit when administered to an animal. "First Agent" means a therapeutic compound described herein. For example, a first agent can be an antisense oligonucleotide targeting Tau. "Second agent" means a second therapeutic compound described herein (e.g. a second antisense oligonucleotide targeting Tau) and/or a non- Tau therapeutic compound.

"Amelioration" or "ameliorate" or "ameliorating" refers to a lessening of at least one indicator, sign, or symptom of a disease, disorder, or condition. The severity of indicators may be determined by subjective or objective measures, which are known to those skilled in the art.

"Animal" refers to a human or non-human animal, including, but not limited to, mice, rats, rabbits, dogs, cats, pigs, and non-human primates, including, but not limited to, monkeys and chimpanzees.

"Antibody" refers to a molecule characterized by reacting specifically with an antigen in some way, where the antibody and the antigen are each defined in terms of the other. Antibody may refer to a complete antibody molecule or any fragment or region thereof, such as the heavy chain, the light chain, F_{ab} region, and F_c region.

"Antisense activity" means any detectable or measurable activity attributable to the hybridization of an antisense compound to its target nucleic acid. In certain embodiments, antisense activity is a decrease in the amount or expression of a target nucleic acid or protein encoded by such target nucleic acid.

"Antisense compound" means an oligomeric compound that is is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding. Examples of antisense compounds include single-stranded

and double-stranded compounds, such as, antisense oligonucleotides, siRNAs, shRNAs, ssRNAs, and occupancy-based compounds.

"Antisense inhibition" means reduction of target nucleic acid levels or target protein levels in the presence of an antisense compound complementary to a target nucleic acid compared to target nucleic acid levels or target protein levels in the absence of the antisense compound.

"Antisense mechanisms" are all those mechanisms involving hybridization of a compound with target nucleic acid, wherein the outcome or effect of the hybridization is either target degradation or target occupancy with concomitant stalling of the cellular machinery involving, for example, transcription or splicing. Antisense mechanisms include, without limitation, RNase H mediated antisense; RNAi mechanisms, which utilize the RISC pathway and include, without limitation, siRNA, ssRNA, and microRNA mechanisms; and occupancy based mechanisms, including, without limitation uniform modified olionucleotides. Certain antisense compounds may act through more than one such mechanism and/or through additional mechanisms.

"Antisense oligonucleotide" (also "oligo") means a single-stranded oligonucleotide having a nucleobase sequence that permits hybridization to a corresponding region or segment of a target nucleic acid.

"Base complementarity" refers to the capacity for the precise base pairing of nucleobases of an antisense oligonucleotide with corresponding nucleobases in a target nucleic acid (i.e., hybridization), and is mediated by Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen binding between corresponding nucleobases.

"Bicyclic sugar" means a furanosyl ring modified by the bridging of two atoms. A bicyclic sugar is a modified sugar.

"Bicyclic nucleoside" (also BNA) means a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4'-carbon and the 2'-carbon on the sugar ring.

"Cap structure" or "terminal cap moiety" means chemical modifications, which have been incorporated at either terminus of an antisense compound.

"cEt" or "constrained ethyl" means a bicyclic nucleoside having a sugar moiety comprising a bridge connecting the 4'-carbon and the 2'-carbon, wherein the bridge has the formula: 4'-$CH(CH_3)$-O-2'.

"Constrained ethyl nucleoside" (also cEt nucleoside) means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-$CH(CH_3)$-O-2' bridge.

"Chemically distinct region" refers to a region of an antisense compound that is in some way chemically different than another region of the same antisense compound. For example, a region having 2'-O-methoxyethyl nucleotides is chemically distinct from a region having nucleotides without 2'-O-methoxyethyl modifications.

"Chimeric antisense compounds" means antisense compounds that have at least 2 chemically distinct regions, each position having a plurality of subunits.

"Co-administration" means administration of two or more pharmaceutical agents to an individual. The two or more pharmaceutical agents may be in a single pharmaceutical composition, or may be in separate pharmaceutical compositions. Each of the two or more pharmaceutical agents may be administered through the same or different routes of administration. Co-administration encompasses administration in parallel or sequentially.

"Complementarity" means the capacity for pairing between nucleobases of a first nucleic acid and a second nucleic acid.

"Comply" means the adherence with a recommended therapy by an individual.

"Comprise," "comprises" and "comprising" will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements.

"Contiguous nucleobases" means nucleobases immediately adjacent to each other.

"Cure" means a method or course that restores health or a prescribed treatment for an illness.

"Deoxyribonucleotide" means a nucleotide having a hydrogen at the 2' position of the sugar portion of the nucleotide. Deoxyribonucleotides may be modified with any of a variety of substituents.

"Designing" or "Designed to" refer to the process of designing an oligomeric compound that specifically hybridizes with a selected nucleic acid molecule.

"Diluent" means an ingredient in a composition that lacks pharmacological activity, but is pharmaceutically necessary or desirable. For example, in drugs that are injected, the diluent may be a liquid, e.g. saline solution.

"Dosage unit" means a form in which a pharmaceutical agent is provided, e.g. pill, tablet, or other dosage unit known in the art.

"Dose" means a specified quantity of a pharmaceutical agent provided in a single administration, or in a specified time period. In certain embodiments, a dose may be administered in two or more boluses, tablets, or injections. For example, in certain embodiments, where subcutaneous administration is desired, the desired dose requires a volume not easily accommodated by a single injection. In such embodiments, two or more injections may be used to achieve the desired dose. In certain embodiments, a dose may be administered in two or more injections to minimize injection site reaction in an individual. In other embodiments, the pharmaceutical agent is administered by infusion over an extended period of time or continuously. Doses may be stated as the amount of pharmaceutical agent per hour, day, week or month.

"Dosing regimen" is a combination of doses designed to achieve one or more desired effects.

"Duration" means the period of time during which an activity or event continues. In certain embodiments, the duration of treatment is the period of time during which doses of a pharmaceutical agent are administered.

"Effective amount" in the context of modulating an activity or of treating or preventing a condition means the administration of that amount of active ingredient to a subject in need of such modulation, treatment or prophylaxis, either in a single dose or as part of a series, that is effective for modulation of that effect, or for treatment or prophylaxis or improvement of that condition. The effective amount will vary depending upon the health and physical condition of the subject to be treated, the taxonomic group of subjects to be treated, the formulation of the composition, the assessment of the medical situation, and other relevant factors.

"Efficacy" means the ability to produce a desired effect.

"Excitotoxicity" the pathological process by which nerve cells are damaged and killed by excessive stimulation by neurotransmitters.

"Expression" includes all the functions by which a gene's coded information is converted into structures present and operating in a cell. Such structures include, but are not limited to the products of transcription and translation.

"Fully complementary" or "100% complementary" means each nucleobase of a first nucleic acid has a complementary nucleobase in a second nucleic acid. In certain embodiments, a first nucleic acid is an antisense compound and a target nucleic acid is a second nucleic acid.

"Fully modified motif" refers to an antisense compound comprising a contiguous sequence of nucleosides wherein essentially each nucleoside is a sugar modified nucleoside having uniform modification.

"Gapmer" means a chimeric antisense compound in which an internal region having a plurality of nucleosides that support RNase H cleavage is positioned between external regions having one or more nucleosides, wherein the nucleosides comprising the internal region are chemically distinct from the nucleoside or nucleosides comprising the external regions. The internal region may be referred to as the "gap" and the external regions may be referred to as the "wings."

"Tau nucleic acid" or 'Tau DNA" means any nucleic acid encoding Tau. For example, in certain embodiments, a Tau nucleic acid includes, without limitation, any viral DNA sequence encoding a Tau genome or portion thereof, any RNA sequence transcribed from a DNA sequence including any mRNA sequence encoding a Tau protein.

"Hybridization" means the annealing of complementary nucleic acid molecules. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense compound and a nucleic acid target. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense oligonucleotide and a nucleic acid target.

"Identifying an animal having a Tau-related disease or disorder" means identifying an animal having been diagnosed with a Tau-related disease or disorder; or, identifying an animal having any symptom of Tau-related disease or disorder including, but not limited to a neurodegenerative disorder associated with Tau.

"Immediately adjacent" means there are no intervening elements between the immediately adjacent elements.

"Individual" means a human or non-human animal selected for treatment or therapy.

"Individual compliance" means adherence to a recommended or prescribed therapy by an individual.

"Induce", "inhibit", "potentiate", "elevate", "increase", "decrease" or the like, e.g., which denote quantitative differences between two states, refer to at least statistically significant differences between the two states. For example, "an amount effective to inhibit the activity or expression of Tau" means that the level of activity or expression of Tau in a treated sample will differ statistically significantly from the level of Tau activity or expression in untreated cells. Such terms are applied to, for example, levels of expression, and levels of activity.

"Inhibiting Tau" means reducing the level or expression of a Tau mRNA, DNA and/or protein . In certain embodiments, Tau is inhibited in the presence of an antisense compound targeting Tau, including an antisense oligonucleotide targeting Tau, as compared to expression of Tau mRNA, DNA and/or protein levels in the absence of a Tau antisense compound, such as an antisense oligonucleotide.

"Inhibiting the expression or activity" refers to a reduction, blockade of the expression or activity and does not necessarily indicate a total elimination of expression or activity.

"Internucleoside linkage" refers to the chemical bond between nucleosides.

"Intraperitoneal administration" means administration through infusion or injection into the peritoneum.

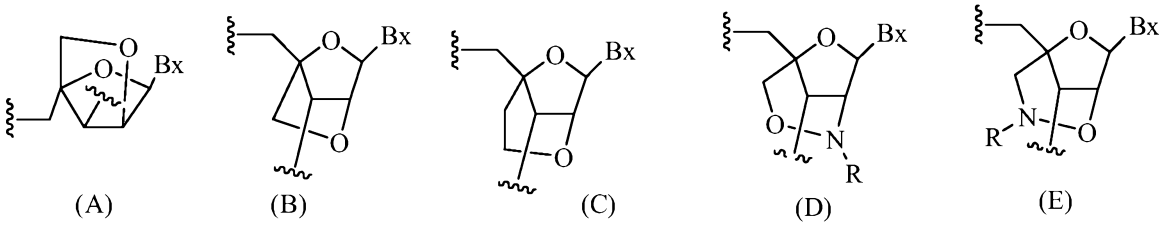
"Intravenous administration" means administration into a vein.

"Lengthened" antisense oligonucleotides are those that have one or more additional nucleosides relative to an antisense oligonucleotide disclosed herein.

"Linked deoxynucleoside" means a nucleic acid base (A, G, C, T, U) substituted by deoxyribose linked by a phosphate ester to form a nucleotide.

"Linked nucleosides" means adjacent nucleosides linked together by an internucleoside linkage.

"Locked nucleic acid" or " LNA" or "LNA nucleosides" means nucleic acid monomers having a bridge connecting two carbon atoms between the 4' and 2'position of the nucleoside sugar unit, thereby forming a bicyclic sugar. Examples of such bicyclic sugar include, but are not limited to A) α-L-Methyleneoxy (4'-CH_2-O-2') LNA , (B) β-D-Methyleneoxy (4'-CH_2-O-2') LNA , (C) Ethyleneoxy (4'-$(CH_2)_2$-O-2') LNA , (D) Aminooxy (4'-CH_2-O-N(R)-2') LNA and (E) Oxyamino (4'-CH_2-N(R)-O-2') LNA, as depicted below.



(A) (B) (C) (D) (E)

As used herein, LNA compounds include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the sugar wherein each of the bridges independently comprises 1 or from 2 to 4 linked groups independently selected from -$[C(R_1)(R_2)]_n$-, -$C(R_1)$=$C(R_2)$-, -$C(R_1)$=N-, -$C(=NR_1)$-,

-C(=O)-, -C(=S)-, -O-, -Si(R_1)$_2$-, -S(=O)$_x$- and -N(R_1)-; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_1 and R_2 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, a heterocycle radical, a 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.

Examples of 4'- 2' bridging groups encompassed within the definition of LNA include, but are not limited to one of formulae: -[C(R_1)(R_2)]$_n$-, -[C(R_1)(R_2)]$_n$-O-, -C(R_1R_2)-N(R_1)-O- or –C(R_1R_2)-O-N(R_1)-. Furthermore, other bridging groups encompassed with the definition of LNA are 4'-CH_2-2', 4'-(CH_2)$_2$-2', 4'-(CH_2)$_3$-2', 4'-CH_2-O-2', 4'-(CH_2)$_2$-O-2', 4'-CH_2-O-N(R_1)-2' and 4'-CH_2-N(R_1)-O-2'- bridges, wherein each R_1 and R_2 is, independently, H, a protecting group or C_1-C_{12} alkyl.

Also included within the definition of LNA according to the invention are LNAs in which the 2'-hydroxyl group of the ribosyl sugar ring is connected to the 4' carbon atom of the sugar ring, thereby forming a methyleneoxy (4'-CH_2-O-2') bridge to form the bicyclic sugar moiety. The bridge can also be a methylene (-CH_2-) group connecting the 2' oxygen atom and the 4' carbon atom, for which the term methyleneoxy (4'-CH_2-O-2') LNA is used. Furthermore; in the case of the bicylic sugar moiety having an ethylene bridging group in this position, the term ethyleneoxy (4'-CH_2CH_2-O-2') LNA is used. α -L- methyleneoxy (4'-CH_2-O-2'), an isomer of methyleneoxy (4'-CH_2-O-2') LNA is also encompassed within the definition of LNA, as used herein.

"Mismatch" or "non-complementary nucleobase" refers to the case when a nucleobase of a first nucleic acid is not capable of pairing with the corresponding nucleobase of a second or target nucleic acid.

"Modified internucleoside linkage" refers to a substitution or any change from a naturally occurring internucleoside bond (i.e. a phosphodiester internucleoside bond).

"Modified nucleobase" means any nucleobase other than adenine, cytosine, guanine, thymidine, or uracil. An "unmodified nucleobase" means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U).

"Modified nucleoside" means a nucleoside having, independently, a modified sugar moiety and/or modified nucleobase.

"Modified nucleotide" means a nucleotide having, independently, a modified sugar moiety, modified internucleoside linkage, or modified nucleobase.

"Modified oligonucleotide" means an oligonucleotide comprising at least one modified internucleoside linkage, a modified sugar, and/or a modified nucleobase.

"Modified sugar" means substitution and/or any change from a natural sugar moiety.

"Monomer" refers to a single unit of an oligomer. Monomers include, but are not limited to, nucleosides and nucleotides, whether naturally occuring or modified.

"Motif" means the pattern of unmodified and modified nucleosides in an antisense compound.

"Natural sugar moiety" means a sugar moiety found in DNA (2'-H) or RNA (2'-OH).

"Naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

"Neurodegenerative disorder" means a chronic progressive neuropathy characterized by selective loss of neurons in motor, sensory, or cognitive systems. Neurodegenerative disorders include, but are not limited to, Tau-associated disorders.

"Neurofibrillary inclusion" means intrneuronal aggregates largely composed of insoluble hyperphosphorylated tau protein. In certain embodiments, neurofibrillary inclusions may be measured through various means including SPECT perfusion imaging, functional MRI, and PET scans. In certain embodiments, reduction of neurofibrillary inclusions may be inferred by improved scores on cognitive exams such as the Mini-Mental State Exam (MMSE) and the Alzheimer's Disease Assessment Scale Cognitive Behavior Section (ADAS-cog).

"Non-complementary nucleobase" refers to a pair of nucleobases that do not form hydrogen bonds with one another or otherwise support hybridization.

"Nucleic acid" refers to molecules composed of monomeric nucleotides. A nucleic acid includes, but is not limited to, ribonucleic acids (RNA), deoxyribonucleic acids (DNA), single-stranded nucleic acids, double-stranded nucleic acids, small interfering ribonucleic acids (siRNA), and microRNAs (miRNA).

"Nucleobase" means a heterocyclic moiety capable of pairing with a base of another nucleic acid.

"Nucleobase complementarity" refers to 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 refers to 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.

"Nucleobase sequence" means the order of contiguous nucleobases independent of any sugar, linkage, and/or nucleobase modification.

"Nucleoside" means a nucleobase linked to a sugar.

"Nucleoside mimetic" includes those structures used to replace the sugar or the sugar and the base and not necessarily the linkage at one or more positions of an oligomeric compound such as for example nucleoside mimetics having morpholino, cyclohexenyl, cyclohexyl, tetrahydropyranyl, bicyclo or tricyclo sugar mimetics, *e.g.*, non furanose sugar units. Nucleotide mimetic includes those structures used to replace the nucleoside and

the linkage at one or more positions of an oligomeric compound such as for example peptide nucleic acids or morpholinos (morpholinos linked by -N(H)-C(=O)-O- or other non-phosphodiester linkage). Sugar surrogate overlaps with the slightly broader term nucleoside mimetic but is intended to indicate replacement of the sugar unit (furanose ring) only. The tetrahydropyranyl rings provided herein are illustrative of an example of a sugar surrogate wherein the furanose sugar group has been replaced with a tetrahydropyranyl ring system. "Mimetic" refers to groups that are substituted for a sugar, a nucleobase, and/ or internucleoside linkage. Generally, a mimetic is used in place of the sugar or sugar-internucleoside linkage combination, and the nucleobase is maintained for hybridization to a selected target.

"Nucleotide" means a nucleoside having a phosphate group covalently linked to the sugar portion of the nucleoside.

"Off-target effect" refers to an unwanted or deleterious biological effect associated with modulation of RNA or protein expression of a gene other than the intended target nucleic acid.

"Oligomeric compound" means a polymer of linked monomeric subunits which is capable of hybridizing to at least a region of a nucleic acid molecule.

"Oligonucleoside" means an oligonucleotide in which the internucleoside linkages do not contain a phosphorus atom.

"Oligonucleotide" (also "oligo") means a polymer of linked nucleosides each of which can be modified or unmodified, independent one from another.

"Parenteral administration" means administration through injection (e.g., bolus injection) or infusion. Parenteral administration includes subcutaneous administration, intravenous administration, intramuscular administration, intraarterial administration, intraperitoneal administration, or intracranial administration, e.g., intrathecal or intracerebroventricular administration.

"Peptide" means a molecule formed by linking at least two amino acids by amide bonds. Without limitation, as used herein, "peptide" refers to polypeptides and proteins.

"Pharmaceutically acceptable carrier" means a medium or diluent that does not interfere with the structure of the oligonucleotide. Certain such carriers enable pharmaceutical compositions to be formulated as, for example, tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspension and lozenges for the oral ingestion by a subject.

"Pharmaceutically acceptable derivative" encompasses pharmaceutically acceptable salts, conjugates, prodrugs or isomers of the compounds described herein.

"Pharmaceutically acceptable salts" means physiologically and pharmaceutically acceptable salts of antisense compounds, i.e., salts that retain the desired biological activity of the parent oligonucleotide and do not impart undesired toxicological effects thereto.

"Pharmaceutical agent" means a substance that provides a therapeutic benefit when administered to an individual. For example, in certain embodiments, an antisense oligonucleotide targeted to Tau is a pharmaceutical agent.

"Pharmaceutical composition" means a mixture of substances suitable for administering to a subject. For example, a pharmaceutical composition may comprise an antisense oligonucleotide and a sterile aqueous solution. In certain embodiments, a pharmaceutical composition shows activity in free uptake assay in certain cell lines.

"Phosphorothioate linkage" means a linkage between nucleosides where the phosphodiester bond is modified by replacing one of the non-bridging oxygen atoms with a sulfur atom. A phosphorothioate linkage is a modified internucleoside linkage.

"Portion" means a defined number of contiguous (i.e., linked) nucleobases of a nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of a target nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of an antisense compound.

"Prevention" or "preventing" refers to delaying or forestalling the onset or development of a condition or disease for a period of time from hours to days, preferably weeks to months.

"Prodrug" means a therapeutic agent that is prepared in an inactive form that is converted to an active form (i.e., drug) within the body or cells thereof by the action of endogenous enzymes or other chemicals and/or conditions.

"Prophylactically effective amount" refers to an amount of a pharmaceutical agent that provides a prophylactic or preventative benefit to an animal.

"Recommended therapy" means a therapeutic regimen recommended by a medical professional for the treatment, amelioration, or prevention of a disease.

"Region" is defined as a portion of the target nucleic acid having at least one identifiable structure, function, or characteristic.

"Ribonucleotide" means a nucleotide having a hydroxy at the 2' position of the sugar portion of the nucleotide. Ribonucleotides may be modified with any of a variety of substituents.

"Salts" mean a physiologically and pharmaceutically acceptable salts of antisense compounds, i.e., salts that retain the desired biological activity of the parent oligonucleotide and do not impart undesired toxicological effects thereto.

"Scrambled oligo" or "scrambled" or "ISIS 141923" is a 5-10-5 MOE gapmer with no known target having the sequence of SEQ ID NO: 11.

"Segments" are defined as smaller or sub-portions of regions within a target nucleic acid.

"Shortened" or "truncated" versions of antisense oligonucleotides Taught herein have one, two or more nucleosides deleted.

"Side effects" means physiological responses attributable to a treatment other than desired effects. In certain embodiments, side effects include, without limitation, injection site reactions, liver function test abnormalities, renal function abnormalities, liver toxicity, renal toxicity, central nervous system abnormalities, and myopathies. For example, increased aminotransferase levels in serum may indicate liver toxicity or liver function abnormality. For example, increased bilirubin may indicate liver toxicity or liver function abnormality.

"Sites," as used herein, are defined as unique nucleobase positions within a target nucleic acid.

"Slows progression" means decrease in the development of the said disease.

"Specifically hybridizable" refers to an antisense compound having a sufficient degree of complementarity between an antisense oligonucleotide and a target nucleic acid to induce a desired effect, while exhibiting minimal or no effects on non-target nucleic acids under conditions in which specific binding is desired, i.e., under physiological conditions in the case of *in vivo* assays and therapeutic treatments.

"Stringent hybridization conditions" or "stringent conditions" refer to conditions under which an oligomeric compound will hybridize to its target sequence, but to a minimal number of other sequences.

"Subcutaneous administration" means administration just below the skin.

"Subject" means a human or non-human animal selected for treatment or therapy.

"Target" refers to a protein, the modulation of which is desired.

"Target gene" refers to a gene encoding a target.

"Targeting" means the process of design and selection of an antisense compound that will specifically hybridize to a target nucleic acid and induce a desired effect.

"Target nucleic acid," "target RNA," "target RNA transcript" and "nucleic acid target" all mean a nucleic acid capable of being targeted by antisense compounds.

"Target region" means a portion of a target nucleic acid to which one or more antisense compounds is targeted.

"Target segment" means the sequence of nucleotides of a target nucleic acid to which an antisense compound is targeted. "5' target site" refers to the 5'-most nucleotide of a target segment. "3' target site" refers to the 3'-most nucleotide of a target segment.

"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, supranuclear palsy, corticobasal degeneration, frontotemporal dementia, or frontotemporal lobar degeneration.

"Tauopathy" means disorders characterized by a build-up of Tau protein in the brain.

"Tau-specific inhibitor" includes but is not limited to a "antisense compound" targeted to Tau.

"Therapeutically effective amount" means an amount of a pharmaceutical agent that provides a therapeutic benefit to an individual.

"Treatment" refers to administering a composition to effect an alteration or improvement of the disease or condition.

"Unmodified" nucleobases mean the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U).

"Unmodified nucleotide" means a nucleotide composed of naturally occuring nucleobases, sugar moieties, and internucleoside linkages. In certain embodiments, an unmodified nucleotide is an RNA nucleotide (i.e. β-D-ribonucleosides) or a DNA nucleotide (i.e. β-D-deoxyribonucleoside).

"Validated target segment" is defined as at least an 8-nucleobase portion (i.e. 8 consecutive nucleobases) of a target region to which an active oligomeric compound is targeted.

"Wing segment" means a plurality of nucleosides modified to impart to an oligonucleotide properties such as enhanced inhibitory activity, increased binding affinity for a target nucleic acid, or resistance to degradation by *in vivo* nucleases.

Certain Embodiments

Certain embodiments provide for methods of administering a Tau antisense compound targeting a Tau nucleic acid for the treatment of a Tau associated disease. In certain embodiments, the Tau nucleic acid is any of the sequences set forth in GENBANK Accession NT_010783.14 truncated from nucleotides 2624000 to 2761000 (incorporated herein as SEQ ID NO: 1); GENBANK Accession No. AK226139.1 (incorporated herein as SEQ ID NO: 2); GENBANK Accession No. NM_001123066.3 (incorporated herein as SEQ ID NO: 3); GENBANK Accession No. NM_001123067.3 (incorporated herein as SEQ ID NO: 4); GENBANK Accession No. NM_001203251.1 (incorporated herein as SEQ ID NO: 5); GENBANK Accession No. NM_001203252.1 (incorporated herein as SEQ ID NO: 6); GENBANK Accession No. NM_005910.5 (incorporated herein as SEQ ID NO: 7); GENBANK Accession No. NM_016834.4 (incorporated herein as SEQ ID NO: 8); GENBANK Accession No. NM_016835.4 (incorporated herein as SEQ ID NO: 9); or GENBANK Accession No. NM_016841.4 (incorporated herein as SEQ ID NO: 10).

A method of treating a Tau associated disease with antiense compounds has been developed. In certain embodiments, neurofibrillary inclusions are reduced. In certain embodiments, neurological function is improved. In certain embodiments, the antisense compounds reduce expression of Tau mRNA and protein. In certain embodiments, the antisense compounds alter the ratio of Tau isoforms. In certain embodiments, the splicing alteration is a decrease in 4R:3R Tau ratio in the central nervous system of the subject. In certain embodiments, the splicing alteration results in a normal 4R:3R Tau ratio. Advantageously, several embodiments provide methods of bypassing the blood brain barrier to specifically target Tau in the central

nervous system, administer for an extended period of time, and achieve widespread distribution of therapy throughout the brain and spinal cord where it is most effective.

Certain embodiments provide methods for the treatment, prevention, or amelioration of diseases, disorders, and conditions associated with Tau in an individual in need thereof. Also contemplated are methods for the preparation of a medicament for the treatment, prevention, or amelioration of a disease, disorder, or condition associated with Tau. Tau associated diseases, disorders, and conditions include neurodegenerative diseases. In certain embodiments, the neurodegenerative disease 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, gangliоglioma, gangliocytoma, meningioangiomatosis, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, Pick's disease, argyrophilic grain disease, supranuclear palsy, corticobasal degeneration, or frontotemporal lobar degeneration.

Described herein are methods comprising administering a Tau antisense compound to an animal for treating a Tau associated disease and thereby reducing neurofibrillary inclusions.

Described herein are methods comprising administering a Tau antisense compound to an animal for treating a Tau associated disease and thereby improving neurological function.

Described herein are methods comprising: (i) identifying an animal having a Tau associated disease; and (ii) administering a Tau antisense compound and thereby reducing neurofibrillary inclusions.

Described herein are methods comprising: (i) identifying an animal having a Tau associated disease; and (ii) administering a Tau antisense compound and thereby improving neurological function.

In certain embodiments, the animal is a human.

In certain embodiments, the antisense compound comprises a single-stranded antisense oligonucleotide complementary to a Tau nucleic acid.

In certain embodiments, the Tau nucleic acid is any of SEQ ID NO: 1-10.

In certain embodiments, the antisense compounds for use in the methods may comprise a single-stranded antisense oligonucleotide comprising a nucleobase sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% complementary to an equal length portion of SEQ ID NOs:1-10. In certain embodiments, the compound may comprise a single-stranded antisense oligonucleotide comprising a nucleobase sequence 100% complementary to an equal length portion of SEQ ID NOs: 1-10.

In certain embodiments, the Tau associated disease is a neurodegenerative disease.

In certain embodiments, the neurodegenerative disease is selected from among Alzheimer's Disease, Fronto-temporal Dementia (FTD), FTDP-17, Progressive Supranuclear Palsy (PSP), Chronic Traumatic Encephalopathy (CTE), Corticobasal Ganglionic Degeneration (CBD), Epilepsy, or Dravet's Syndrome.

In certain embodiments, expression of Tau RNA or expression of Tau protein is reduced.

In certain embodiments, expression of the 4R isoform of Tau RNA or expression of the 4R isoform of Tau protein is reduced.

In certain embodiments, expression of the 3R isoform of Tau RNA or expression of the 3R isoform of Tau protein is increased.

In certain embodiments, expression of the 4R isoform of Tau RNA is reduced and expression of the 3R isoform of Tau RNA is increased.

In certain embodiments, expression of the 4R isoform of Tau protein is reduced and expression of the 3R isoform of Tau protein is increased.

In certain embodiments, the single-stranded antisense oligonucleotide comprises at least one modification.

In certain embodiments, the single-stranded antisense oligonucleotide is specifically hybridizable to a human Tau nucleic acid.

In certain embodiments, the single-stranded antisense oligonucleotide is at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% complementary to an equal length portion of a human Tau nucleic acid.

In certain embodiments, the single-stranded antisense oligonucleotide is 100% complementary to a human Tau nucleic acid.

In certain embodiments, the single-stranded antisense oligonucleotide comprises at least one modified internucleoside linkage.

In certain embodiments, each internucleoside linkage of the single-stranded antisense oligonucleotide is a modified internucleoside linkage.

In certain embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

In certain embodiments, the antisense oligonucleotide comprises at least one modified nucleoside.

In certain embodiments, the single-stranded antisense oligonucleotide comprises at least one modified nucleoside having a modified sugar.

In certain embodiments, the single-stranded antisense oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar.

In certain embodiments, the bicyclic sugar comprises a 4' to 2' bridge selected from among: 4'-(CH2)n-O-2', wherein n is 1 or 2; and 4'-CH2-O-CH2-2'.

In certain embodiments, the bicyclic sugar comprises a 4'-CH(CH3)-O-2' bridge.

In certain embodiments, the at least one modified nucleoside having a modified sugar comprises a non-bicyclic 2'-modified sugar moiety.

In certain embodiments, the 2'-modified sugar moiety comprises a 2'-O-methoxyethyl group.

In certain embodiments, the 2'-modified sugar moiety comprises a 2'-O-methyl group.

In certain embodiments, the at least one modified nucleoside having a modified sugar comprises a sugar surrogate.

In certain embodiments, the sugar surrogate is a morpholino.

In certain embodiments, the sugar surrogate is a peptide nucleic acid.

In certain embodiments, each nucleoside is modified.

In certain embodiments, the single-stranded antisense oligonucleotide comprises at least one modified nucleobase.

In certain embodiments, the modified nucleobase is a 5'-methylcytosine.

In certain embodiments, the single-stranded antisense oligonucleotide comprises:

a gap segment consisting of linked deoxynucleosides;

a 5' wing segment consisting of linked nucleosides;

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

In certain embodiments, the single-stranded antisense oligonucleotide comprises:

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides;

a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned immediately adjacent and between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; and wherein each internucleoside linkage is a phosphorothioate linkage.

In certain embodiments, the single-stranded antisense oligonucleotide consists of 15, 16, 17, 18, or 19 linked nucleosides.

In certain embodiments, the single-stranded antisense oligonucleotide consists of 20 linked nucleosides.

In certain embodiments, the single-stranded antisense oligonucleotide consists of 21, 22, 23, 24, or 25 linked nucleosides.

In certain embodiments, the administering is parenteral administration.

In certain embodimetns, the parenteral administration is any of injection or infusion.

In certain embodiments, the parenteral administration is any of intrathecal administration or intracerebroventricular administration.

In certain embodiments, at least one symptom of a Tau associated disease is ameliorated.

In certain embodiments, at least one symptom of a Tau associated disease is prevented.

In certain embodiments, progression of at least one symptom of a Tau associated disease is slowed.

In certain embodiments, at least one symptom is any of memory loss, anxiety, loss of motor function, incidence of seizures, severity of seizures, and excitotoxicity.

Antisense compounds

Oligomeric compounds include, but are not limited to, oligonucleotides, oligonucleosides, oligonucleotide analogs, oligonucleotide mimetics, antisense compounds, antisense oligonucleotides, and siRNAs. An oligomeric compound may be "antisense" to a target nucleic acid, meaning that is is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding.

In certain embodiments, an antisense compound has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target segment of a target nucleic acid to which it is targeted. In certain such embodiments, an antisense oligonucleotide has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target segment of a target nucleic acid to which it is targeted.

In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 10 to 30 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 12 to 30 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 12 to 22 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 14 to 30 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 14 to 20 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 15 to 30 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 15 to 20 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 16 to 30 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 16 to 20 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 17 to 30 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 17 to 20 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 18 to 30 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 18 to 21 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 18 to 20 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 20 to 30 subunits in length. In other words, such antisense compounds are from 12 to 30 linked subunits, 14 to 30 linked subunits, 14 to 20 subunits, 15 to 30 subunits, 15 to 20 subunits, 16 to 30 subunits, 16 to 20 subunits, 17 to 30 subunits, 17 to 20 subunits, 18 to 30 subunits, 18 to 20 subunits, 18 to 21 subunits, 20 to 30 subunits, or 12 to 22 linked subunits, respectively. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 14 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 16 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 17 subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 18

subunits in length. In certain embodiments, an antisense compound targeted to a Tau nucleic acid is 20 subunits in length. In other embodiments, the antisense compound is 8 to 80, 12 to 50, 13 to 30, 13 to 50, 14 to 30, 14 to 50, 15 to 30, 15 to 50, 16 to 30, 16 to 50, 17 to 30, 17 to 50, 18 to 22, 18 to 24, 18 to 30, 18 to 50, 19 to 22, 19 to 30, 19 to 50, or 20 to 30 linked subunits. In certain such embodiments, the antisense compounds are 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, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 linked subunits in length, or a range defined by any two of the above values. In some embodiments the antisense compound is an antisense oligonucleotide, and the linked subunits are nucleosides.

In certain embodiments, an antisense compound targeted to a Tau nucleic acid is a single stranded ribonucleic acid or deoxyribonucleic acid antisense oligonucleotide. Antisense oligonucleotides may target a specific, complementary, coding or non-coding, nucleic acid. Depending on the antisense oligonucleotide used, the binding of the oligonucleotide to its target nucleic acid sequence may or may not activate RNAse H. In some embodiments, the antisense oligonucleotide activates RNAse H, which degrades the target nucleic acid. The antisense oligonucleotides of several embodiments may be any length provided it binds selectively to the intended location. In general, the antisense oligonucleotide may be from 8, 10 or 12 nucleotides in length up to 20, 30, or 50 nucleotides in length.

In certain embodiments antisense oligonucleotides targeted to a Tau nucleic acid may be shortened or truncated. For example, a single subunit may be deleted from the 5' end (5' truncation), or alternatively from the 3' end (3' truncation). A shortened or truncated antisense compound targeted to a Tau nucleic acid may have two subunits deleted from the 5' end, or alternatively may have two subunits deleted from the 3' end, of the antisense compound. Alternatively, the deleted nucleosides may be dispersed throughout the antisense compound, for example, in an antisense compound having one nucleoside deleted from the 5' end and one nucleoside deleted from the 3' end.

When a single additional subunit is present in a lengthened antisense compound, the additional subunit may be located at the 5' or 3' end of the antisense compound. When two or more additional subunits are present, the added subunits may be adjacent to each other, for example, in an antisense compound having two subunits added to the 5' end (5' addition), or alternatively to the 3' end (3' addition), of the antisense compound. Alternatively, the added subunits may be dispersed throughout the antisense compound, for example, in an antisense compound having one subunit added to the 5' end and one subunit added to the 3' end.

It is possible to increase or decrease the length of an antisense compound, such as an antisense oligonucleotide, and/or introduce mismatch bases without eliminating activity. For example, in Woolf et al. (*Proc. Natl Acad. Sci. USA* 89:7305-7309, 1992), a series of antisense oligonucleotides 13-25

nucleobases in length were tested for their ability to induce cleavage of a target RNA in an oocyte injection model. Antisense oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the antisense oligonucleotides were able to direct specific cleavage of the target mRNA, albeit to a lesser extent than the antisense oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase antisense oligonucleotides, including those with 1 or 3 mismatches.

Gautschi *et al.* (*J. Natl. Cancer Inst.* 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bcl-2 mRNA and having 3 mismatches to the bcl-xL mRNA to reduce the expression of both bcl-2 and bcl-xL *in vitro* and *in vivo*. Furthermore, this oligonucleotide demonstrated potent anti-tumor activity *in vivo*.

Maher and Dolnick (*Nuc. Acid. Res.* 16:3341-3358,1988) tested a series of tandem 14 nucleobase antisense oligonucleotides, and a 28 and 42 nucleobase antisense oligonucleotides comprised of the sequence of two or three of the tandem antisense oligonucleotides, respectively, for their ability to arrest translation of human DHFR in a rabbit reticulocyte assay. Each of the three 14 nucleobase antisense oligonucleotides alone was able to inhibit translation, albeit at a more modest level than the 28 or 42 nucleobase antisense oligonucleotides.

Antisense Compound Motifs

In certain embodiments, antisense compounds targeted to a Tau nucleic acid have chemically modified subunits arranged in patterns, or motifs, to confer to the antisense compounds properties such as enhanced inhibitory activity, increased binding affinity for a target nucleic acid, or resistance to degradation by *in vivo* nucleases.

Chimeric antisense compounds typically contain at least one region modified so as to confer increased resistance to nuclease degradation, increased cellular uptake, increased binding affinity for the target nucleic acid, and/or increased inhibitory activity. A second region of a chimeric antisense compound may optionally serve as a substrate for the cellular endonuclease RNase H, which cleaves the RNA strand of an RNA:DNA duplex.

In certain embodiments, the antisense compounds are uniform sugar-modified oligonucleotides. Antisense compounds having a gapmer motif are considered chimeric antisense compounds. In a gapmer an internal region having a plurality of nucleotides that supports RNaseH cleavage is positioned between external regions having a plurality of nucleotides that are chemically distinct from the nucleosides of the internal region. In the case of an antisense oligonucleotide having a gapmer motif, the gap segment generally serves as the substrate for endonuclease cleavage, while the wing segments comprise modified nucleosides. In certain embodiments, the regions of a gapmer are differentiated by the types of sugar moieties comprising each distinct

region. The types of sugar moieties that are used to differentiate the regions of a gapmer may in some embodiments include β-D-ribonucleosides, β-D-deoxyribonucleosides, 2'-modified nucleosides (such 2'-modified nucleosides may include 2'-MOE and 2'-O-CH_3, among others), and bicyclic sugar modified nucleosides. In certain embodiments, wings may include several modified sugar moieties, including, for example 2'-MOE. In certain embodiments, wings may include several modified and unmodified sugar moieties. In certain embodiments, wings may include various combinations of 2'-MOE nucleosides and 2'-deoxynucleosides.

Each distinct region may comprise uniform sugar moieties, variant, or alternating sugar moieties. The wing-gap-wing motif is frequently described as "X-Y-Z", where "X" represents the length of the 5'-wing, "Y" represents the length of the gap, and "Z" represents the length of the 3'-wing. "X" and "Z" may comprise uniform, variant, or alternating sugar moieties. In certain embodiments, "X" and "Y" may include one or more 2'-deoxynucleosides."Y" may comprise 2'-deoxynucleosides. As used herein, a gapmer described as "X-Y-Z" has a configuration such that the gap is positioned immediately adjacent to each of the 5'-wing and the 3' wing. Thus, no intervening nucleotides exist between the 5'-wing and gap, or the gap and the 3'-wing. Any of the antisense compounds described herein can have a gapmer motif. In certain embodiments, "X" and "Z" are the same; in other embodiments they are different. In certain embodiments, Y is between 8 and 15 nucleosides. X, Y, or Z can be any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, or more nucleosides. Thus, gapmers described herein include, but are not limited to, for example, 5-10-5, 5-10-4, 4-10-4, 4-10-3, 3-10-3, 2-10-2, 5-9-5, 5-9-4, 4-9-5, 5-8-5, 5-8-4, 4-8-5, 5-7-5, 4-7-5, 5-7-4, or 4-7-4.

In certain embodiments, antisense compounds targeted to a Tau nucleic acid possess a 5-8-5 gapmer motif.

In certain embodiments, an antisense compound targeted to a Tau nucleic acid has a gap-narrowed motif. In certain embodiments, a gap-narrowed antisense oligonucleotide targeted to a Tau nucleic acid has a gap segment of 9, 8, 7, or 6 2'-deoxynucleotides positioned immediately adjacent to and between wing segments of 5, 4, 3, 2, or 1 chemically modified nucleosides. In certain embodiments, the chemical modification comprises a bicyclic sugar. In certain embodiments, the bicyclic sugar comprises a 4' to 2' bridge selected from among: 4'-(CH2)n-O-2' bridge, wherein n is 1 or 2; and 4'-CH2-O-CH2-2'. In certain embodiments, the bicyclic sugar is comprises a 4'-CH(CH3)-O-2' bridge. In certain embodiments, the chemical modification comprises a non-bicyclic 2'-modified sugar moiety. In certain embodiments, the non-bicyclic 2'-modified sugar moiety comprises a 2'-O-methylethyl group or a 2'-O-methyl group.

In certain embodiments, an antisense compound targeted to a Tau nucleic acid is uniformly modified. In certain embodiments, the antisense compound comprises 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleosides. In certain embodiments, each nucleoside is chemically modified. In certain embodiments, the chemical modification comprises a non-bicyclic 2'-modified sugar moiety. In certain embodiments, the

2'-modified sugar moiety comprises a 2'-O-methoxyethyl group. In certain embodiments, the 2'-modified sugar moiety comprises a 2'-O-methyl group.

Target Nucleic Acids, Target Regions and Nucleotide Sequences

Nucleotide sequences that encode Tau include, without limitation, the following: GENBANK Accession NT_010783.14 truncated from nucleotides 2624000 to 2761000 (incorporated herein as SEQ ID NO: 1); GENBANK Accession No. AK226139.1 (incorporated herein as SEQ ID NO: 2); GENBANK Accession No. NM_001123066.3 (incorporated herein as SEQ ID NO: 3); GENBANK Accession No. NM_001123067.3 (incorporated herein as SEQ ID NO: 4); GENBANK Accession No. NM_001203251.1 (incorporated herein as SEQ ID NO: 5); GENBANK Accession No. NM_001203252.1 (incorporated herein as SEQ ID NO: 6); GENBANK Accession No. NM_005910.5 (incorporated herein as SEQ ID NO: 7); GENBANK Accession No. NM_016834.4 (incorporated herein as SEQ ID NO: 8); GENBANK Accession No. NM_016835.4 (incorporated herein as SEQ ID NO: 9); or GENBANK Accession No. NM_016841.4 (incorporated herein as SEQ ID NO: 10).

It is understood that the sequence set forth in each SEQ ID NO contained herein is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Antisense compounds described by Isis Number (Isis No) indicate a combination of nucleobase sequence and motif.

In certain embodiments, a target region is a structurally defined region of the target nucleic acid. For example, a target region may encompass a 3' UTR, a 5' UTR, an exon, an intron, an exon/intron junction, a coding region, a translation initiation region, translation termination region, or other defined nucleic acid region. The structurally defined regions for Tau can be obtained by accession number from sequence databases such as NCBI and such information is incorporated herein by reference. In certain embodiments, a target region may encompass the sequence from a 5' target site of one target segment within the target region to a 3' target site of another target segment within the same target region.

Targeting includes determination of at least one target segment to which an antisense compound hybridizes, such that a desired effect occurs. In certain embodiments, the desired effect is a reduction in mRNA target nucleic acid levels. In certain embodiments, the desired effect is reduction of levels of protein encoded by the target nucleic acid or a phenotypic change associated with the target nucleic acid.

A target region may contain one or more target segments. Multiple target segments within a target region may be overlapping. Alternatively, they may be non-overlapping. In certain embodiments, target segments within a target region are separated by no more than about 300 nucleotides. In certain emodiments, target segments within a target region are separated by a number of nucleotides that is, is about, is no more than, is no more than about, 250, 200, 150, 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10 nucleotides on the target nucleic

acid, or is a range defined by any two of the preceeding values. In certain embodiments, target segments within a target region are separated by no more than, or no more than about, 5 nucleotides on the target nucleic acid. In certain embodiments, target segments are contiguous. Contemplated are target regions defined by a range having a starting nucleic acid that is any of the 5' target sites or 3' target sites listed herein.

Suitable target segments may be found within a 5' UTR, a coding region, a 3' UTR, an intron, an exon, or an exon/intron junction. Target segments containing a start codon or a stop codon are also suitable target segments. A suitable target segment may specifcally exclude a certain structurally defined region such as the start codon or stop codon.

The determination of suitable target segments may include a comparison of the sequence of a target nucleic acid to other sequences throughout the genome. For example, the BLAST algorithm may be used to identify regions of similarity amongst different nucleic acids. This comparison can prevent the selection of antisense compound sequences that may hybridize in a non-specific manner to sequences other than a selected target nucleic acid (i.e., non-target or off-target sequences).

There may be variation in activity (e.g., as defined by percent reduction of target nucleic acid levels) of the antisense compounds within an active target region. In certain embodiments, reductions in Tau mRNA levels are indicative of inhibition of Tau expression. Reductions in levels of a Tau protein are also indicative of inhibition of target mRNA expression. In certain embodiments, reductions in the 4R isoform of Tau mRNA levels are indicative of modulation of Tau splicing. Reductions in levels of the 4R isoform of Tau protein are also indicative of modulation of Tau splicing. In certain embodiments, increases in the 3R isoform of Tau mRNA levels are indicative of modulation of Tau splicing. Increases in levels of the 3R isoform of Tau protein are also indicative of modulation of Tau splicing. Reduction in percent of cells staining positive for hyperphosphorylated Tau are indicative of inhibition of Tau expression or modulation of Tau splicing. Improvement in neurological function is indicative of inhibition of Tau expression or modulation of Tau splicing. Improved memory and motor function are indicative of inhibition of Tau expression or modulation of Tau splicing. Reduction of neurofibrillary inclusions is indicative of inhibition of Tau expression or modulation of Tau splicing.

Hybridization

In some embodiments, hybridization occurs between an antisense compound disclosed herein and a Tau nucleic acid. The most common mechanism of hybridization involves hydrogen bonding (e.g., Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding) between complementary nucleobases of the nucleic acid molecules.

Hybridization can occur under varying conditions. Stringent conditions are sequence-dependent and are determined by the nature and composition of the nucleic acid molecules to be hybridized.

Methods of determining whether a sequence is specifically hybridizable to a target nucleic acid are well known in the art. In certain embodiments, the antisense compounds provided herein are specifically hybridizable with a Tau nucleic acid.

Complementarity

An antisense compound and a target nucleic acid are complementary to each other when a sufficient number of nucleobases of the antisense compound can hydrogen bond with the corresponding nucleobases of the target nucleic acid, such that a desired effect will occur (e.g., antisense inhibition of a target nucleic acid, such as a Tau nucleic acid).

Non-complementary nucleobases between an antisense compound and a Tau nucleic acid may be tolerated provided that the antisense compound remains able to specifically hybridize to a target nucleic acid. Moreover, an antisense compound may hybridize over one or more segments of a Tau nucleic acid such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop structure, mismatch or hairpin structure).

In certain embodiments, the antisense compounds provided herein, or a specified portion thereof, are, or are at least, 70%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to a Tau nucleic acid, a target region, target segment, or specified portion thereof. Percent complementarity of an antisense compound with a target nucleic acid can be determined using routine methods.

For example, an antisense compound in which 18 of 20 nucleobases of the antisense compound are complementary to a target region, and would therefore specifically hybridize, would represent 90 percent complementarity. In this example, the remaining noncomplementary nucleobases may be clustered or interspersed with complementary nucleobases and need not be contiguous to each other or to complementary nucleobases. As such, an antisense compound which is 18 nucleobases in length having four noncomplementary nucleobases which are flanked by two regions of complete complementarity with the target nucleic acid would have 77.8% overall complementarity with the target nucleic acid and would thus fall within the scope of the present invention. Percent complementarity of an antisense compound with a region of a target nucleic acid can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST programs known in the art (Altschul *et al.*, *J. Mol. Biol.*, 1990, 215, 403 410; Zhang and Madden, Genome Res., 1997, 7, 649 656). Percent homology, sequence identity or complementarity, can be determined by, for example, the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, Madison Wis.), using default settings, which uses the algorithm of Smith and Waterman (Adv. Appl. Math., 1981, 2, 482 489).

In certain embodiments, the antisense compounds provided herein, or specified portions thereof, are fully complementary (i.e. 100% complementary) to a target nucleic acid, or specified portion thereof. For

example, an antisense compound may be fully complementary to a Tau nucleic acid, or a target region, or a target segment or target sequence thereof. As used herein, "fully complementary" means each nucleobase of an antisense compound is capable of precise base pairing with the corresponding nucleobases of a target nucleic acid. For example, a 20 nucleobase antisense compound is fully complementary to a target sequence that is 400 nucleobases long, so long as there is a corresponding 20 nucleobase portion of the target nucleic acid that is fully complementary to the antisense compound. Fully complementary can also be used in reference to a specified portion of the first and /or the second nucleic acid. For example, a 20 nucleobase portion of a 30 nucleobase antisense compound can be "fully complementary" to a target sequence that is 400 nucleobases long. The 20 nucleobase portion of the 30 nucleobase oligonucleotide is fully complementary to the target sequence if the target sequence has a corresponding 20 nucleobase portion wherein each nucleobase is complementary to the 20 nucleobase portion of the antisense compound. At the same time, the entire 30 nucleobase antisense compound may or may not be fully complementary to the target sequence, depending on whether the remaining 10 nucleobases of the antisense compound are also complementary to the target sequence.

The location of a non-complementary nucleobase may be at the 5' end or 3' end of the antisense compound. Alternatively, the non-complementary nucleobase or nucleobases may be at an internal position of the antisense compound. When two or more non-complementary nucleobases are present, they may be contiguous (i.e. linked) or non-contiguous. In one embodiment, a non-complementary nucleobase is located in the wing segment of a gapmer antisense oligonucleotide.

In certain embodiments, antisense compounds that are, or are up to 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleobases in length comprise no more than 4, no more than 3, no more than 2, or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as a Tau nucleic acid, or specified portion thereof.

In certain embodiments, antisense compounds that are, or are up to 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length comprise no more than 6, no more than 5, no more than 4, no more than 3, no more than 2, or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as a Tau nucleic acid, or specified portion thereof.

The antisense compounds provided also include those which are complementary to a portion of a target nucleic acid. As used herein, "portion" refers to a defined number of contiguous (i.e. linked) nucleobases within a region or segment of a target nucleic acid. A "portion" can also refer to a defined number of contiguous nucleobases of an antisense compound. In certain embodiments, the antisense compounds, are complementary to at least an 8 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 9 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 10 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least

an 11 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 12 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 13 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 14 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 15 nucleobase portion of a target segment. Also contemplated are antisense compounds that are complementary to at least a 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more nucleobase portion of a target segment, or a range defined by any two of these values.

Identity

The antisense compounds provided herein may also have a defined percent identity to a particular nucleotide sequence, SEQ ID NO, or compound represented by a specific Isis number, or portion thereof. As used herein, an antisense compound is identical to the sequence disclosed herein if it has the same nucleobase pairing ability. For example, a RNA which contains uracil in place of thymidine in a disclosed DNA sequence would be considered identical to the DNA sequence since both uracil and thymidine pair with adenine. Shortened and lengthened versions of the antisense compounds described herein as well as compounds having non-identical bases relative to the antisense compounds provided herein also are contemplated. The non-identical bases may be adjacent to each other or dispersed throughout the antisense compound. Percent identity of an antisense compound is calculated according to the number of bases that have identical base pairing relative to the sequence to which it is being compared.

In certain embodiments, the antisense compounds, or portions thereof, are at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to one or more of the antisense compounds or SEQ ID NOs, or a portion thereof, disclosed herein.

In certain embodiments, a portion of the antisense compound is compared to an equal length portion of the target nucleic acid. In certain embodiments, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobase portion is compared to an equal length portion of the target nucleic acid.

In certain embodiments, a portion of the antisense oligonucleotide is compared to an equal length portion of the target nucleic acid. In certain embodiments, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobase portion is compared to an equal length portion of the target nucleic acid.

Modifications

A nucleoside is a base-sugar combination. The nucleobase (also known as base) portion of the nucleoside is normally a heterocyclic base moiety. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to the 2', 3' or 5' hydroxyl moiety of the sugar.

Oligonucleotides are formed through the covalent linkage of adjacent nucleosides to one another, to form a linear polymeric oligonucleotide. Within the oligonucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside linkages of the oligonucleotide.

Modifications to antisense compounds encompass substitutions or changes to internucleoside linkages, sugar moieties, or nucleobases. Modified antisense compounds are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases, or increased inhibitory activity.

Chemically modified nucleosides may also be employed to increase the binding affinity of a shortened or truncated antisense oligonucleotide for its target nucleic acid. Consequently, comparable results can often be obtained with shorter antisense compounds that have such chemically modified nucleosides.

Modified Internucleoside Linkages

The naturally occuring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. Antisense compounds having one or more modified, i.e. non-naturally occurring, internucleoside linkages are often selected over antisense compounds having naturally occurring internucleoside linkages because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the presence of nucleases.

Oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom as well as internucleoside linkages that do not have a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to, phosphodiesters, phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known.

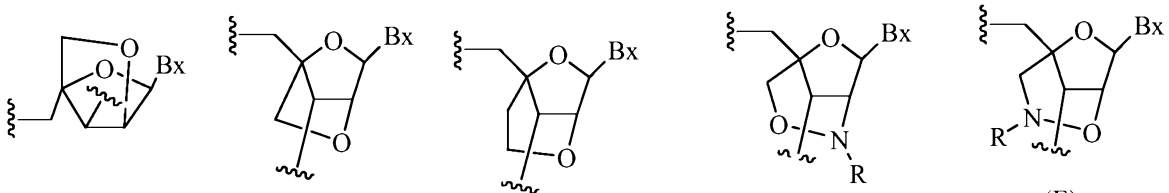
In certain embodiments, antisense compounds targeted to a Tau nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, the modified internucleoside linkages are interspersed throughout the antisense compound. In certain embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage.

Modified Sugar Moieties

Oligomeric compounds provided herein may comprise one or more monomers, including a nucleoside or nucleotide, having a modified sugar moiety. For example, the furanosyl sugar ring of a nucleoside or nucleotide can be modified in a number of ways including, but not limited to, addition of a substituent group and bridging of two non-geminal ring atoms to form a Locked Nucleic Acid (LNA).

In certain embodiments, oligomeric compounds comprise one or more monomers having a bicyclic sugar. In certain embodiments, the monomer is an LNA. In certain such embodiments, LNAs include, but

are not limited to, (A) α-L-Methyleneoxy (4'-CH_2-O-2') LNA , (B) β-D-Methyleneoxy (4'-CH_2-O-2') LNA , (C) Ethyleneoxy (4'-$(CH_2)_2$-O-2') LNA , (D) Aminooxy (4'-CH_2-O-N(R)-2') LNA and (E) Oxyamino (4'-CH_2-N(R)-O-2') LNA, as depicted below.



(A) (B) (C) (D) (E)

In certain embodiments, LNA compounds include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the sugar wherein each of the bridges independently comprises 1 or from 2 to 4 linked groups independently selected from $-[C(R_1)(R_2)]_n-$, $-C(R_1)=C(R_2)-$, $-C(R_1)=N-$, $-C(=NR_1)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-Si(R_1)_2-$, $-S(=O)_x-$ and $-N(R_1)-$;

wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

each R_1 and R_2 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, a heterocycle radical, a 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.

In one embodiment, each of the bridges of the LNA compounds is, independently, $-[C(R_1)(R_2)]_n-$, $-[C(R_1)(R_2)]_n-O-$, $-C(R_1R_2)-N(R_1)-O-$ or $-C(R_1R_2)-O-N(R_1)-$. In another embodiment, each of said bridges is, independently, 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 4'-CH_2-O-N(R_1)-2' and 4'-CH_2-N(R_1)-O-2'- wherein each R_1 is, independently, H, a protecting group or C_1-C_{12} alkyl.

Certain LNA's have been prepared and disclosed in the patent literature as well as in scientific literature (see for example: issued U.S. Patent Nos. 7,053,207; 6,268,490; 6,770,748; 6,794,499; 7,034,133; 6,525,191; 7,696,345; 7,569,575; 7,314,923; 7,217,805; and 7,084,125, hereby incorporated by reference herein in their entirety.

Also provided herein are LNAs in which the 2'-hydroxyl group is connected, to the 4' carbon atom of the ribosyl sugar ring, thereby forming a methyleneoxy (4'-CH_2-O-2') bridge to form the bicyclic sugar moiety (reviewed in Elayadi *et al., Curr. Opinion Invens. Drugs,* 2001, *2*, 558-561; Braasch *et al., Chem. Biol.,* 2001, *8* 1-7; and Orum *et al., Curr. Opinion Mol. Ther.,* 2001, *3*, 239-243; see also U.S. Patent: 6,670,461). Furthermore, the bridge can also be a methylene (-CH_2-) group connecting the 2' oxygen atom to the 4' carbon atom of the sugar ring, for which the term methyleneoxy (4'-CH_2-O-2') LNA is used. In the case of the bicylic sugar moiety having an ethylene bridging group in this position, the term ethyleneoxy (4'-CH_2CH_2-O-2') LNA is used (Singh et al., Chem. Commun., 1998, *4*, 455-456: Morita *et al., Bioorganic Medicinal Chemistry*, 2003, *11*, 2211-2226). Methyleneoxy (4'-CH_2-O-2') LNA and other bicyclic sugar analogs display very high duplex thermal stabilities with complementary DNA and RNA (Tm = +3 to +10 °C), stability towards 3'-exonucleolytic degradation and good solubility properties. Potent and nontoxic antisense oligonucleotides comprising LNAs have been described (Wahlestedt *et al.*, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, *97*, 5633-5638).

An isomer of methyleneoxy (4'-CH_2-O-2') LNA that has also been discussed is α-L- methyleneoxy (4'-CH_2-O-2') LNA which has been shown to have superior stability against a 3'-exonuclease. The α-L-methyleneoxy (4'-CH_2-O-2') LNA's were incorporated into antisense gapmers and chimeras that showed potent antisense activity (Frieden *et al., Nucleic Acids Research,* 2003, *21*, 6365-6372).

The synthesis and preparation of adenine, cytosine, guanine, 5-methyl-cytosine, thymine and uracil LNAs having a methyleneoxy (4'-CH_2-O-2') bridge, along with their oligomerization, and nucleic acid recognition properties have been described (Koshkin *et al., Tetrahedron*, 1998, *54*, 3607-3630). LNAs and preparation thereof are also described in WO 98/39352 and WO 99/14226, incorporated by reference herein.

Analogs of various LNA nucleosides that have 4' to 2' bridging groups such as 4'-CH_2-O-2' (methyleneoxy) and 4'-CH_2-S-2' (methylene-thio), have also been prepared (Kumar *et al., Bioorg. Med. Chem. Lett.*, 1998, *8*, 2219-2222). Preparation of locked nucleoside analogs comprising oligodeoxyribonucleotide duplexes as substrates for nucleic acid polymerases has also been described (Wengel et al., WO 99/14226). Furthermore, synthesis of 2'-amino-LNA, a novel comformationally restricted high-affinity oligonucleotide analog has been described in the art (Singh et al., J. Org. Chem., 1998, 63, 10035-10039). In addition, 2'-amino- and 2'-methylamino-LNA's have been prepared and the thermal stability of their duplexes with complementary RNA and DNA strands has been previously reported.

As used herein, "bicyclic nucleoside" refers to a nucleoside comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic sugar moiety. In certain embodiments, the bridge connects the 2' carbon and another carbon of the sugar ring.

As used herein, "4'-2' bicyclic nucleoside" or "4' to 2' bicyclic nucleoside" refers to a bicyclic nucleoside comprising a furanose ring comprising a bridge connecting the 2' carbon atom and the 4' carbon atom of the sugar ring.

One carbocyclic bicyclic nucleoside having a 4'-$(CH_2)_3$-2' bridge and the alkenyl analog, bridge 4'-CH=CH-CH_2-2', 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). 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).

Many other bicyclic and tricyclic sugar surrogate ring systems are also known in the art that can be used to modify nucleosides for incorporation into antisense compounds as provided herein (*see, e.g.*, review article: Leumann, J. C, *Bioorganic & Medicinal Chemistry*, 2002, *10*, 841-854). Such ring systems can undergo various additional substitutions to further enhance their activity. Such ring systems can undergo various additional substitutions to enhance activity.

As used herein, "2'-modified sugar" means a furanosyl sugar modified at the 2' position. In certain embodiments, such modifications include substituents selected from: a halide, including, but not limited to substituted and unsubstituted alkoxy, substituted and unsubstituted thioalkyl, substituted and unsubstituted amino alkyl, substituted and unsubstituted alkyl, substituted and unsubstituted allyl, and substituted and unsubstituted alkynyl. In certain embodiments, 2' modifications are selected from substituents including, but not limited to: $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, $OCH_2C(=O)N(H)CH_3$, and $O(CH_2)_nON[(CH_2)_nCH_3]_2$, where n and m are from 1 to about 10. Other 2'- substituent groups can also be selected from: C_1-C_{12} alkyl; substituted alkyl; alkenyl; alkynyl; alkaryl; aralkyl; O-alkaryl or O-aralkyl; SH; SCH_3; OCN; Cl; Br; CN; CF_3; OCF_3; $SOCH_3$; SO_2CH_3; ONO_2; NO_2; N_3; NH_2; heterocycloalkyl; heterocycloalkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a reporter group; an intercalator; a group for improving pharmacokinetic properties; and a group for improving the pharmacodynamic properties of an antisense compound, and other substituents having similar properties. In certain embodiments, modifed nucleosides comprise a 2'-MOE side chain (*see, e.g.*, Baker et al., J. Biol. Chem., 1997, 272, 11944-12000). Such 2'-MOE substitution have been described as having improved binding affinity compared to unmodified nucleosides and to other modified nucleosides, such as 2'- *O*-methyl, *O*-propyl, and *O*-aminopropyl. Oligonucleotides having the 2'-MOE substituent also have been shown to be antisense inhibitors of gene expression with promising features for *in vivo* use (*see, e.g.*, Martin, P., *Helv. Chim. Acta*, 1995, *78*, 486-504; Altmann et al., *Chimia*, 1996, *50*, 168-176; Altmann et al., *Biochem. Soc. Trans.*, 1996, *24*, 630-637; and Altmann et al., *Nucleosides Nucleotides*, 1997, *16*, 917-926).

As used herein, "2'-modified nucleoside" or "2'-substituted nucleoside" refers to a nucleoside comprising a sugar comprising a substituent at the 2' position of a furanose ring other than H or OH. 2' modified nucleosides include, but are not limited to, nucleosides with non-bridging 2'substituents, such as allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-$O(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-$N(R_m)(R_n)$, or O-CH_2-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. 2'-modifed nucleosides may further comprise other modifications, for example, at other positions of the sugar and/or at the nucleobase.

As used herein, "2'-F" refers to modification of the 2' position of the furanosyl sugar ring to comprise a fluoro group.

As used herein, "2'-OMe" or "2'-OCH_3" or "2'-O-methyl" each refers to modification at the 2' position of the furanosyl sugar ring to comprise a -OCH_3 group.

As used herein, "oligonucleotide" refers to a compound comprising a plurality of linked nucleosides. In certain embodiments, one or more of the plurality of nucleosides is modified. In certain embodiments, an oligonucleotide comprises one or more ribonucleosides (RNA) and/or deoxyribonucleosides (DNA). Methods for the preparations of modified sugars are well known to those skilled in the art.

In nucleotides having modified sugar moieties, the nucleobase moieties (natural, modified, or a combination thereof) are maintained for hybridization with an appropriate nucleic acid target.

In certain embodiments, antisense compounds comprise one or more nucleosides having modified sugar moieties. In certain embodiments, the modified sugar moiety is 2'-MOE.

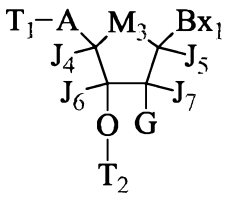
RNAi Compounds

In certain embodiments, antisense compounds are interfering RNA compounds (RNAi), which include double-stranded RNA compounds (also referred to as short-interfering RNA or siRNA) and single-stranded RNAi compounds (or ssRNA). Such compounds work at least in part through the RISC pathway to degrade and/or sequester a target nucleic acid (thus, include microRNA/microRNA-mimic compounds). In certain embodiments, antisense compounds comprise modifications that make them particularly suited for such mechanisms.

i. ssRNA compounds

In certain embodiments, antisense compounds including those particularly suited for use as single-stranded RNAi compounds (ssRNA) comprise a modified 5'-terminal end. In certain such embodiments, the 5'-terminal end comprises a modified phosphate moiety. In certain embodiments, such modified phosphate is stabilized (e.g., resistant to degradation/cleavage compared to unmodified 5'-phosphate). In certain embodiments, such 5'-terminal nucleosides stabilize the 5'-phosphorous moiety. Certain modified 5'-terminal nucleosides may be found in the art, for example in WO/2011/139702.

In certain embodiments, the 5'-nucleoside of an ssRNA compound has Formula IIc:



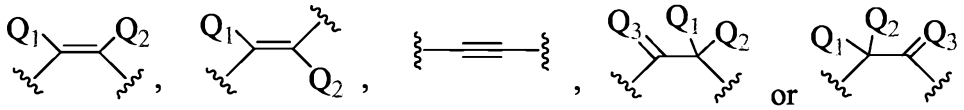
IIc

wherein:

T_1 is an optionally protected phosphorus moiety;

T_2 is an internucleoside linking group linking the compound of Formula IIc to the oligomeric compound;

A has one of the formulas:



Q_1 and Q_2 are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_2-C_6 alkynyl or $N(R_3)(R_4)$;

Q_3 is O, S, $N(R_5)$ or $C(R_6)(R_7)$;

each R_3, R_4 R_5, R_6 and R_7 is, independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl or C_1-C_6 alkoxy;

M_3 is O, S, NR_{14}, $C(R_{15})(R_{16})$, $C(R_{15})(R_{16})C(R_{17})(R_{18})$, $C(R_{15})=C(R_{17})$, $OC(R_{15})(R_{16})$ or $OC(R_{15})(Bx_2)$;

R_{14} is H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

R_{15}, R_{16}, R_{17} and R_{18} are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

Bx_1 is a heterocyclic base moiety;

or if Bx_2 is present then Bx_2 is a heterocyclic base moiety and Bx_1 is H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

J_4, J_5, J_6 and J_7 are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

or J_4 forms a bridge with one of J_5 or J_7 wherein said bridge comprises from 1 to 3 linked biradical groups selected from O, S, NR_{19}, $C(R_{20})(R_{21})$, $C(R_{20})=C(R_{21})$, $C[=C(R_{20})(R_{21})]$ and C(=O) and the other two of J_5, J_6 and J_7 are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

each R_{19}, R_{20} and R_{21} is, independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

G is H, OH, halogen or $O\text{-}[C(R_8)(R_9)]_n\text{-}[(C=O)_m\text{-}X_1]_j\text{-}Z$;

each R_8 and R_9 is, independently, H, halogen, C_1-C_6 alkyl or substituted C_1-C_6 alkyl;

X_1 is O, S or $N(E_1)$;

Z is H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_2-C_6 alkynyl or $N(E_2)(E_3)$;

E_1, E_2 and E_3 are each, independently, H, C_1-C_6 alkyl or substituted C_1-C_6 alkyl;

n is from 1 to about 6;

m is 0 or 1;

j is 0 or 1;

each substituted group comprises one or more optionally protected substituent groups independently selected from halogen, OJ_1, $N(J_1)(J_2)$, $=NJ_1$, SJ_1, N_3, CN, $OC(=X_2)J_1$, $OC(=X_2)N(J_1)(J_2)$ and $C(=X_2)N(J_1)(J_2)$;

X_2 is O, S or NJ_3;

each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl;

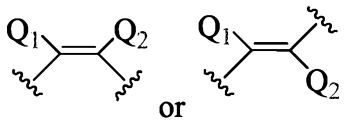
when j is 1 then Z is other than halogen or $N(E_2)(E_3)$; and

wherein said oligomeric compound comprises from 8 to 40 monomeric subunits and is hybridizable to at least a portion of a target nucleic acid.

In certain embodiments, M_3 is O, CH=CH, OCH_2 or $OC(H)(Bx_2)$. In certain embodiments, M_3 is O.

In certain embodiments, J_4, J_5, J_6 and J_7 are each H. In certain embodiments, J_4 forms a bridge with one of J_5 or J_7.

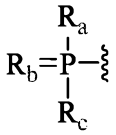
In certain embodiments, A has one of the formulas:



wherein:

Q_1 and Q_2 are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy or substituted C_1-C_6 alkoxy. In certain embodiments, Q_1 and Q_2 are each H. In certain embodiments, Q_1 and Q_2 are each, independently, H or halogen. In certain embodiments, Q_1 and Q_2 is H and the other of Q_1 and Q_2 is F, CH_3 or OCH_3.

In certain embodiments, T_1 has the formula:



wherein:

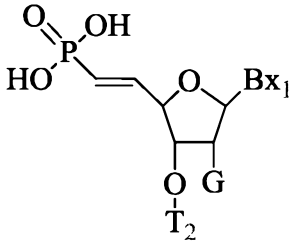
R_a and R_c are each, independently, protected hydroxyl, protected thiol, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, protected amino or substituted amino; and

R_b is O or S. In certain embodiments, R_b is O and R_a and R_c are each, independently, OCH_3, OCH_2CH_3 or $CH(CH_3)_2$.

In certain embodiments, G is halogen, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, $O(CH_2)_2F$, OCH_2CHF_2, OCH_2CF_3, OCH_2-CH=CH_2, $O(CH_2)_2$-OCH_3, $O(CH_2)_2$-SCH_3, $O(CH_2)_2$-OCF_3, $O(CH_2)_3$-$N(R_{10})(R_{11})$, $O(CH_2)_2$-$ON(R_{10})(R_{11})$, $O(CH_2)_2$-$O(CH_2)_2$-$N(R_{10})(R_{11})$, $OCH_2C(=O)$-$N(R_{10})(R_{11})$, $OCH_2C(=O)$-$N(R_{12})$-$(CH_2)_2$-$N(R_{10})(R_{11})$ or $O(CH_2)_2$-$N(R_{12})$-$C(=NR_{13})[N(R_{10})(R_{11})]$ wherein R_{10}, R_{11}, R_{12} and

R_{13} are each, independently, H or C_1-C_6 alkyl. In certain embodiments, G is halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3, $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$ or OCH_2-$N(H)$-$C(=NH)NH_2$. In certain embodiments, G is F, OCH_3 or $O(CH_2)_2$-OCH_3. In certain embodiments, G is $O(CH_2)_2$-OCH_3.

In certain embodiments, the 5'-terminal nucleoside has Formula IIe:



IIe

In certain embodiments, antisense compounds, including those particularly suitable for ssRNA 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.

In certain embodiments, the oligonucleotides comprise or consist of a region having uniform sugar modifications. In certain such embodiments, each nucleoside of the region comprises the same RNA-like sugar modification. In certain embodiments, each nucleoside of the region is a 2'-F nucleoside. In certain embodiments, each nucleoside of the region is a 2'-OMe nucleoside. In certain embodiments, each nucleoside of the region is a 2'-MOE nucleoside. In certain embodiments, each nucleoside of the region is a cEt nucleoside. In certain embodiments, each nucleoside of the region is an LNA nucleoside. In certain embodiments, the uniform region constitutes all or essentially all of the oligonucleotide. In certain embodiments, the region constitutes the entire oligonucleotide except for 1-4 terminal nucleosides.

In certain embodiments, oligonucleotides comprise one or more regions of alternating sugar modifications, wherein the nucleosides alternate between nucleotides having a sugar modification of a first type and nucleotides having a sugar modification of a second type. In certain embodiments, nucleosides of both types are RNA-like nucleosides. In certain embodiments the alternating nucleosides are selected from: 2'-OMe, 2'-F, 2'-MOE, LNA, and cEt. In certain embodiments, the alternating modificatios are 2'-F and 2'-OMe. Such regions may be contiguous or may be interupted by differently modified nucleosides or conjugated nucleosides.

In certain embodiments, the alternating region of alternating modifications each consist of a single nucleoside (i.e., the patern is $(AB)_xA_y$ wheren A is a nucleoside having a sugar modification of a first type and B is a nucleoside having a sugar modification of a second type; x is 1-20 and y is 0 or 1). In certan embodiments, one or more alternating regions in an alternating motif includes more than a single nucleoside of

a type. For example, oligonucleotides may include one or more regions of any of the following nucleoside motifs:

AABBAA;

ABBABB;

AABAAB;

ABBABAABB;

ABABAA;

AABABAB;

ABABAA;

ABBAABBABABAA;

BABBAABBABABAA; or

ABABBAABBABABAA;

wherein A is a nucleoside of a first type and B is a nucleoside of a second type. In certain embodiments, A and B are each selected from 2'-F, 2'-OMe, BNA, and MOE.

In certain embodiments, oligonucleotides having such an alternating motif also comprise a modified 5' terminal nucleoside, such as those of formula IIc or IIe.

In certain embodiments, oligonucleotides comprise a region having a 2-2-3 motif. Such regions comprises the following motif:

$-(A)_2-(B)_x-(A)_2-(C)_y-(A)_3-$

wherein: A is a first type of modifed nucleosde;

B and C, are nucleosides that are differently modified than A, however, B and C may have the same or different modifications as one another;

x and y are from 1 to 15.

In certain embodiments, A is a 2'-OMe modified nucleoside. In certain embodiments, B and C are both 2'-F modified nucleosides. In certain embodiments, A is a 2'-OMe modified nucleoside and B and C are both 2'-F modified nucleosides.

In certain embodiments, oligonucleosides have the following sugar motif:

$5'- (Q)- (AB)_xA_y-(D)_z$

wherein:

Q is a nucleoside comprising a stabilized phosphate moiety. In certain embodiments, Q is a nucleoside having Formula IIc or IIe;

A is a first type of modifed nucleoside;

B is a second type of modified nucleoside;

D is a modified nucleoside comprising a modification different from the nucleoside adjacent to it. Thus, if y is 0, then D must be differently modified than B and if y is 1, then D must be differently modified than A. In certain embodiments, D differs from both A and B.

X is 5-15;

Y is 0 or 1;

Z is 0-4.

In certain embodiments, oligonucleosides have the following sugar motif:

5'- (Q)- $(A)_x$-$(D)_z$

wherein:

Q is a nucleoside comprising a stabilized phosphate moiety. In certain embodiments, Q is a nucleoside having Formula IIc or IIe;

A is a first type of modifed nucleoside;

D is a modified nucleoside comprising a modification different from A.

X is 11-30;

Z is 0-4.

In certain embodiments A, B, C, and D in the above motifs are selected from: 2'-OMe, 2'-F, 2'-MOE, LNA, and cEt. In certain embodiments, D represents terminal nucleosides. In certain embodiments, such terminal nucleosides are not designed to hybridize to the target nucleic acid (though one or more might hybridize by chance). In certiain embodiments, the nucleobase of each D nucleoside is adenine, regardless of the identity of the nucleobase at the corresponding position of the target nucleic acid. In certain embodiments the nucleobase of each D nucleoside is thymine.

In certain embodiments, antisense compounds, including those particularly suited for use as ssRNA comprise modified internucleoside linkages arranged along the oligonucleotide or region thereof in a defined pattern or modified internucleoside linkage motif. In certain embodiments, oligonucleotides comprise a region having an alternating internucleoside linkage motif. In certain embodiments, oligonucleotides 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 internucleoside linkages. 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.

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 one 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.

Oligonucleotides having any of the various sugar motifs described herein, may have any linkage motif. For example, the oligonucleotides, including but not limited to those described above, may have a linkage motif selected from non-limiting the table below:

5' most linkage	Central region	3'-region
PS	Alternating PO/PS	6 PS
PS	Alternating PO/PS	7 PS
PS	Alternating PO/PS	8 PS

ii. siRNA compounds

In certain embodiments, antisense compounds are double-stranded RNAi compounds (siRNA). In such embodiments, one or both strands may comprise any modification motif described above for ssRNA. In certain embodiments, ssRNA compounds may be unmodified RNA. In certain embodiments, siRNA compounds may comprise unmodified RNA nucleosides, but modified internucleoside linkages.

Several embodiments relate to double-stranded compositions wherein each strand comprises a motif defined by the location of one or more modified or unmodified nucleosides. In certain embodiments, compositions are provided comprising a first and a second oligomeric compound that are fully or at least partially hybridized to form a duplex region and further comprising a region that is complementary to and hybridizes to a nucleic acid target. It is suitable that such a composition comprise a first oligomeric compound that is an antisense strand having full or partial complementarity to a nucleic acid target and a second oligomeric compound that is a sense strand having one or more regions of complementarity to and forming at least one duplex region with the first oligomeric compound.

The compositions of several embodiments modulate gene expression by hybridizing to a nucleic acid target resulting in loss of its normal function. In some embodiments, the target nucleic acid is an eRNA. In certain embodiment, the degradation of the targeted eRNA is facilitated by an activated RISC complex that is formed with compositions of the invention.

Several embodiments are directed to double-stranded compositions wherein one of the strands is useful in, for example, influencing the preferential loading of the opposite strand into the RISC (or cleavage)

complex. The compositions are useful for targeting selected nucleic acid molecules and modulating the expression of one or more genes. In some embodiments, the compositions of the present invention hybridize to a portion of a target RNA resulting in loss of normal function of the target RNA.

Certain embodiments are drawn to double-stranded compositions wherein both the strands comprises a hemimer motif, a fully modified motif, a positionally modified motif or an alternating motif. Each strand of the compositions of the present invention can be modified to fulfill a particular role in for example the siRNA pathway. Using a different motif in each strand or the same motif with different chemical modifications in each strand permits targeting the antisense strand for the RISC complex while inhibiting the incorporation of the sense strand. Within this model, each strand can be independently modified such that it is enhanced for its particular role. The antisense strand can be modified at the 5'-end to enhance its role in one region of the RISC while the 3'-end can be modified differentially to enhance its role in a different region of the RISC.

The double-stranded oligonucleotide molecules can be a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The double-stranded oligonucleotide molecules can be assembled from two separate oligonucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary (i.e. each strand comprises nucleotide sequence that is complementary to nucleotide sequence in the other strand; such as where the antisense strand and sense strand form a duplex or double-stranded structure, for example wherein the double-stranded region is about 15 to about 30, e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 base pairs; the antisense strand comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense strand comprises nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof (e.g., about 15 to about 25 or more nucleotides of the double-stranded oligonucleotide molecule are complementary to the target nucleic acid or a portion thereof). Alternatively, the double-stranded oligonucleotide is assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the siRNA are linked by means of a nucleic acid based or non-nucleic acid-based linker(s).

The double-stranded oligonucleotide can be a polynucleotide with a duplex, asymmetric duplex, hairpin or asymmetric hairpin secondary structure, having self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a separate target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The double-stranded oligonucleotide can be a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence

that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof, and wherein the circular polynucleotide can be processed either in vivo or in vitro to generate an active siRNA molecule capable of mediating RNAi.

In certain embodiments, the double-stranded oligonucleotide comprises separate sense and antisense sequences or regions, wherein the sense and antisense regions are covalently linked by nucleotide or non-nucleotide linkers molecules as is known in the art, or are alternately non-covalently linked by ionic interactions, hydrogen bonding, van der waals interactions, hydrophobic interactions, and/or stacking interactions. In certain embodiments, the double-stranded oligonucleotide comprises nucleotide sequence that is complementary to nucleotide sequence of a target gene. In another embodiment, the double-stranded oligonucleotide interacts with nucleotide sequence of a target gene in a manner that causes inhibition of expression of the target gene.

As used herein, double-stranded oligonucleotides need not be limited to those molecules containing only RNA, but further encompasses chemically modified nucleotides and non-nucleotides. In certain embodiments, the short interfering nucleic acid molecules lack 2'-hydroxy (2'-OH) containing nucleotides. In certain embodiments short interfering nucleic acids optionally do not include any ribonucleotides (e.g., nucleotides having a 2'-OH group). Such double-stranded oligonucleotides that do not require the presence of ribonucleotides within the molecule to support RNAi can however have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. Optionally, double-stranded oligonucleotides can comprise ribonucleotides at about 5, 10, 20, 30, 40, or 50% of the nucleotide positions. As used herein, the term siRNA is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi, for example short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering nucleic acid, short interfering modified oligonucleotide, chemically modified siRNA, post-transcriptional gene silencing RNA (ptgsRNA), and others. In addition, as used herein, the term RNAi is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, translational inhibition, or epigenetics. For example, double-stranded oligonucleotides can be used to epigenetically silence genes at both the post-transcriptional level and the pre-transcriptional level. In a non-limiting example, epigenetic regulation of gene expression by siRNA molecules of the invention can result from siRNA mediated modification of chromatin structure or methylation pattern to alter gene expression (see, for example, Verdel et al., 2004, Science, 303, 672-676; Pal-Bhadra et al., 2004, Science, 303, 669-672; Allshire, 2002, Science, 297, 1818-1819; Volpe et al., 2002, Science, 297, 1833-1837; Jenuwein, 2002, Science, 297, 2215-2218; and Hall et al., 2002, Science, 297, 2232-2237).

It is contemplated that compounds and compositions of several embodiments provided herein can target eRNAs by a dsRNA-mediated gene silencing or RNAi mechanism, including, e.g., "hairpin" or stem-loop double-stranded RNA effector molecules in which a single RNA strand with self-complementary sequences is capable of assuming a double-stranded conformation, or duplex dsRNA effector molecules comprising two separate strands of RNA. In various embodiments, the dsRNA consists entirely of ribonucleotides or consists of a mixture of ribonucleotides and deoxynucleotides, such as the RNA/DNA hybrids disclosed, for example, by WO 00/63364, filed Apr. 19, 2000, or U.S. Ser. No. 60/130,377, filed Apr. 21, 1999. The dsRNA or dsRNA effector molecule may be a single molecule with a region of self-complementarity such that nucleotides in one segment of the molecule base pair with nucleotides in another segment of the molecule. In various embodiments, a dsRNA that consists of a single molecule consists entirely of ribonucleotides or includes a region of ribonucleotides that is complementary to a region of deoxyribonucleotides. Alternatively, the dsRNA may include two different strands that have a region of complementarity to each other.

In various embodiments, both strands consist entirely of ribonucleotides, one strand consists entirely of ribonucleotides and one strand consists entirely of deoxyribonucleotides, or one or both strands contain a mixture of ribonucleotides and deoxyribonucleotides. In certain embodiments, the regions of complementarity are at least 70, 80, 90, 95, 98, or 100% complementary to each other and to a target nucleic acid sequence. In certain embodiments, the region of the dsRNA that is present in a double-stranded conformation includes at least 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 50, 75,100, 200, 500, 1000, 2000 or 5000 nucleotides or includes all of the nucleotides in a cDNA or other target nucleic acid sequence being represented in the dsRNA. In some embodiments, the dsRNA does not contain any single stranded regions, such as single stranded ends, or the dsRNA is a hairpin. In other embodiments, the dsRNA has one or more single stranded regions or overhangs. In certain embodiments, RNA/DNA hybrids include a DNA strand or region that is an antisense strand or region (e.g, has at least 70, 80, 90, 95, 98, or 100% complementarity to a target nucleic acid) and an RNA strand or region that is a sense strand or region (e.g, has at least 70, 80, 90, 95, 98, or 100% identity to a target nucleic acid), and vice versa.

In various embodiments, the RNA/DNA hybrid is made in vitro using enzymatic or chemical synthetic methods such as those described herein or those described in WO 00/63364, filed Apr. 19, 2000, or U.S. Ser. No. 60/130,377, filed Apr. 21, 1999. In other embodiments, a DNA strand synthesized in vitro is complexed with an RNA strand made in vivo or in vitro before, after, or concurrent with the transformation of the DNA strand into the cell. In yet other embodiments, the dsRNA is a single circular nucleic acid containing a sense and an antisense region, or the dsRNA includes a circular nucleic acid and either a second circular nucleic acid or a linear nucleic acid (see, for example, WO 00/63364, filed Apr. 19, 2000, or U.S. Ser. No. 60/130,377, filed Apr. 21, 1999.) Exemplary circular nucleic acids include lariat structures in which the free 5'

phosphoryl group of a nucleotide becomes linked to the 2' hydroxyl group of another nucleotide in a loop back fashion.

In other embodiments, the dsRNA includes one or more modified nucleotides in which the 2' position in the sugar contains a halogen (such as fluorine group) or contains an alkoxy group (such as a methoxy group) which increases the half-life of the dsRNA in vitro or in vivo compared to the corresponding dsRNA in which the corresponding 2' position contains a hydrogen or an hydroxyl group. In yet other embodiments, the dsRNA includes one or more linkages between adjacent nucleotides other than a naturally-occurring phosphodiester linkage. Examples of such linkages include phosphoramide, phosphorothioate, and phosphorodithioate linkages. The dsRNAs may also be chemically modified nucleic acid molecules as Taught in U.S. Pat. No. 6,673,661. In other embodiments, the dsRNA contains one or two capped strands, as disclosed, for example, by WO 00/63364, filed Apr. 19, 2000, or U.S. Ser. No. 60/130,377, filed Apr. 21, 1999.

In other embodiments, the dsRNA can be any of the at least partially dsRNA molecules disclosed in WO 00/63364, as well as any of the dsRNA molecules described in U.S. Provisional Application 60/399,998; and U.S. Provisional Application 60/419,532, and PCT/US2003/033466, the teaching of which is hereby incorporated by reference. Any of the dsRNAs may be expressed in vitro or in vivo using the methods described herein or standard methods, such as those described in WO 00/63364.

Occupancy

In certain embodiments, antisense compounds are not expected to result in cleavage or the target nucleic acid via RNase H or to result in cleavage or sequestration through the RISC pathway. In certain such embodiments, antisense activity may result from occupancy, wherein the presence of the hybridized antisense compound disrupts the activity of the target nucleic acid. In certain such embodiments, the antisense compound may be uniformly modified or may comprise a mix of modifications and/or modified and unmodified nucleosides.

In certain embodiments, antisense oligonucleotides do not activate RNAse H. In several aspects, antisense oligonucleotides that do not activate RNAse H are complementary to a nucleic acid sequence encoding Tau and disrupts the splicing of the nucleic acid encoding Tau to reduce the 4R:3R Tau ratio.

The antisense oligonucleotide of several embodiments may disrupt the splicing of the nucleic acid encoding Tau to reduce the 4R:3R Tau ratio. The splicing process is a series of reactions, mediated by splicing factors, which is carried out on RNA after transcription but before translation, in which the intron(s) are removed, and the exons joined together sequentially so that the protein may be translated. Each intron is defined by a 5' splice site, a 3' splice site, and a branch point situated there between. An antisense oligonucleotide may block these splice elements when the oligonucleotide either fully or partially overlaps the element, or binds to the pre-mRNA at a position sufficiently close to the element to disrupt the binding and function of the splicing factors which would ordinarily mediate the particular splicing reaction which occurs at

that element. The antisense oligonucleotide may block a variety of different splice elements to carry out certain embodiments. For instance, the antisense oligonucleotide may block a mutated element, a cryptic element, or a native element; it may block a 5' splice site, a 3' splice site, or a branch point.

Methods of making antisense oligonucleotides which do not activate RNase H are known in the art. See, e.g., U.S. Pat. No. 5,149,797 incorporated herein by reference. Such antisense oligonucleotides may contain one or more structural modification which sterically hinders or prevents binding of RNase H to a duplex molecule comprising the oligonucleotide, but does not substantially hinder or disrupt duplex formation. Antisense oligonucleotides that do not activate RNAse H may include oligonucleotides wherein at least one, two or more of the internucleotide bridging phosphate residues are modified phosphates, such as methyl phosphonates, methyl phosphonothioates, phosphoromorpholidates, phosphoropiperazidates and phosphoramidates. For instance, every other one of the internucleotide bridging phosphate residues may be a modified phosphate, contain a 2' loweralkyl moiety (e.g., C1-C4, linear or branched, saturated or unsaturated alkyl, such as methyl, ethyl, ethenyl, propyl, 1-propenyl, 2-propenyl, and isopropyl) or a combination thereof. In preferred embodiments, the antisense oligonucleotide of the invention that does not activate RNAse H, and disrupts the splicing of the nucleic acid encoding Tau to reduce the 4R:3R Tau ratio is a 2'-O-(2-methoxyethyl) (MOE)-modified antisense oligonucleotide.

Other methods of modifying an oligonucleotide to hinder binding of RNAse H may be found in P. Furdon et al., Nucleic Acids Res. 17, 9193-9204 (1989); S. Agrawal et al., Proc. Natl. Acad. Sci. USA 87, 1401-1405 (1990); C. Baker et al., Nucleic Acids Res. 18, 3537-3543 (1990); B. Sproat et al., Nucleic Acids Res. 17, 3373-3386 (1989); R. Walder and J. Walder, Proc. Natl. Acad. Sci. USA 85,5011-5015 (1988) the disclosures of all of which are incorporated herein, in their entirety, by reference.

Compositions and Methods for Formulating Pharmaceutical Compositions

Antisense oligonucleotides may be admixed with pharmaceutically acceptable active or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

An antisense compound targeted to a Tau nucleic acid can be utilized in pharmaceutical compositions by combining the antisense compound with a suitable pharmaceutically acceptable diluent or carrier. A pharmaceutically acceptable diluent includes phosphate-buffered saline (PBS). PBS is a diluent suitable for use in compositions to be delivered parenterally. Accordingly, in one embodiment, employed in the methods described herein is a pharmaceutical composition comprising an antisense compound targeted to a Tau nucleic acid and a pharmaceutically acceptable diluent. In certain embodiments, the pharmaceutically acceptable diluent is PBS. In certain embodiments, the antisense compound is an antisense oligonucleotide.

Pharmaceutical compositions comprising antisense compounds encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other 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. A prodrug can include the incorporation of additional nucleosides at one or both ends of an antisense compound which are cleaved by endogenous nucleases within the body, to form the active antisense compound.

In certain embodiments, an antisense oligonucleotide can include a physiologically and pharmaceutically acceptable salts thereof: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto. Examples of such salts are (a) salts formed with cations such as sodium, potassium, NH4+, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine.

Administration

Antisense oligonucleotides of certain embodiments may be administered to a subject by several different means. For instance, oligonucleotides may generally be administered parenterally, intraperitoneally, intravascularly, or intrapulmonarily in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. In a preferred embodiment, the oligonucleotide may be administered parenterally.

The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrathecal, or intrasternal injection, or infusion techniques. Formulation of pharmaceutical compositions is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa. (1975), and Liberman, H. A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, NY. (1980).

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water,

Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, and polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Delivery methods are preferably those that are effective to circumvent the blood-brain barrier and are effective to deliver agents to the central nervous system. For example, delivery methods may include the use of nanoparticles. The particles may be of any suitable structure, such as unilamellar or plurilamellar, so long as the antisense oligonucleotide is contained therein.

Positively charged lipids such as N-[1-(2,3-dioleoyloxi)propyl)-N, N,N-trimethyl-amoniummethylsulfate, or "DOTAP," are particularly preferred for such particles and vesicles. The preparation of such lipid particles is well known in the art. See, e.q., U.S. Pat. Nos. 4,880,635 to Janoff et al.; 4,906,477 to Kurono et al.: 4,911,928 to Wallach; 4,917,951 to Wallach; 4,920,016 to Allen et al.: 4,921,757 to Wheatley et al.; etc.

In one embodiment, the compounds provided herein may be administered in a bolus directly into the central nervous system. The compounds provided herein may be administered to the subject in a bolus once, or multiple times. In some preferred embodiments, the compounds provided herein may be administered once. In other preferred embodiments, the compounds provided herein may be administered multiple times. When administered multiple times, the compounds provided herein may be administered at regular intervals or at intervals that may vary during the treatment of a subject. In some embodiments, the compounds provided herein may be administered multiple times at intervals that may vary during the treatment of a subject. In some embodiments, the compounds provided herein may be administered multiple times at regular intervals.

In another preferred embodiment, the compounds provided herein may be administered by continuous infusion into the central nervous system. Non-limiting examples of methods that may be used to deliver the compounds provided herein into the central nervous system by continuous infusion may include pumps, wafers, gels, foams and fibrin clots. In a preferred embodiment, the compounds provided herein may be delivered into the central nervous system by continuous infusion using an osmotic pump. An osmotic mini pump contains a high-osmolality chamber that surrounds a flexible, yet impermeable, reservoir filled with the targeted delivery composition-containing vehicle. Subsequent to the subcutaneous implantation of this minipump, extracellular fluid enters through an outer semi-permeable membrane into the high-osmolality chamber, thereby compressing the reservoir to release the targeted delivery composition at a controlled, pre-determined rate. The targeted delivery composition, released from the pump, may be directed via a catheter to a stereotaxically placed cannula for infusion into the cerebroventricular space. In certain embodiments, the compounds provided herein may be delivered into the central nervous system by continuous

infusion using a pump as described in the Examples.

In another preferred embodiment, the compounds provided herein may be delivered into the central nervous system by intrathecal administration. A catheter may be placed in the intrathecal lumbar space of the animal. The proximal end of the catheter may be attached to a dosing pedestal that may extend through the skin. In further embodiments, the compounds provided herein may be administered as a bolus injection. In other embodiments, the compounds provided herein may be administered as a continuous infusion.

Conjugated Antisense compounds

Antisense compounds may be covalently linked to one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the resulting antisense oligonucleotides. Typical conjugate groups include cholesterol moieties and lipid moieties. Additional conjugate groups include carbohydrates, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes.

Antisense compounds can also be modified to have one or more stabilizing groups that are generally attached to one or both termini of antisense compounds to enhance properties such as, for example, nuclease stability. Included in stabilizing groups are cap structures. These terminal modifications protect the antisense compound having terminal nucleic acid from exonuclease degradation, and can help in delivery and/or localization within a cell. The cap can be present at the 5'-terminus (5'-cap), or at the 3'-terminus (3'-cap), or can be present on both termini. Cap structures are well known in the art and include, for example, inverted deoxy abasic caps. Further 3' and 5'-stabilizing groups that can be used to cap one or both ends of an antisense compound to impart nuclease stability include those disclosed in WO 03/004602 published on January 16, 2003.

Cell culture and antisense compounds treatment

The effects of antisense compounds on the level, activity or expression of Tau nucleic acids can be tested *in vitro* in a variety of cell types. Cell types used for such analyses are available from commerical vendors (*e.g.* American Type Culture Collection, Manassus, VA; Zen-Bio, Inc., Research Triangle Park, NC; Clonetics Corporation, Walkersville, MD) and are cultured according to the vendor's instructions using commercially available reagents (e.g. Invitrogen Life Technologies, Carlsbad, CA). Illustrative cell types include, but are not limited to, SH-SY5Y and A172.

In vitro testing of antisense oligonucleotides

Described herein are methods for treatment of cells with antisense oligonucleotides, which can be modified appropriately for treatment with other antisense compounds.

Cells may be treated with antisense oligonucleotides when the cells reach approximately 60-80% confluency in culture.

One reagent commonly used to introduce antisense oligonucleotides into cultured cells includes the cationic lipid transfection reagent LIPOFECTIN (Invitrogen, Carlsbad, CA). Antisense oligonucleotides may be mixed with LIPOFECTIN in OPTI-MEM 1 (Invitrogen, Carlsbad, CA) to achieve the desired final concentration of antisense oligonucleotide and a LIPOFECTIN concentration that may range from 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

Another reagent used to introduce antisense oligonucleotides into cultured cells includes LIPOFECTAMINE (Invitrogen, Carlsbad, CA). Antisense oligonucleotide is mixed with LIPOFECTAMINE in OPTI-MEM 1 reduced serum medium (Invitrogen, Carlsbad, CA) to achieve the desired concentration of antisense oligonucleotide and a LIPOFECTAMINE concentration that may range from 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

Another technique used to introduce antisense oligonucleotides into cultured cells includes electroporation.

Cells are treated with antisense oligonucleotides by routine methods. Cells may be harvested 16-24 hours after antisense oligonucleotide treatment, at which time RNA or protein levels of target nucleic acids are measured by methods known in the art and described herein. In general, when treatments are performed in multiple replicates, the data are presented as the average of the replicate treatments.

The concentration of antisense oligonucleotide used varies from cell line to cell line. Methods to determine the optimal antisense oligonucleotide concentration for a particular cell line are well known in the art. Antisense oligonucleotides are typically used at concentrations ranging from 1 nM to 300 nM when transfected with LIPOFECTAMINE. Antisense oligonucleotides are used at higher concentrations ranging from 625 to 20,000 nM when transfected using electroporation.

RNA Isolation

RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Methods of RNA isolation are well known in the art. RNA is prepared using methods well known in the art, for example, using the TRIZOL Reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's recommended protocols.

Analysis of inhibition of target levels or expression

Inhibition of levels or expression of a Tau nucleic acid can be assayed in a variety of ways known in the art. For example, target nucleic acid levels can be quantitated by, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), or quantitaive real-time PCR. RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Methods of RNA isolation are well known in the art. Northern blot analysis is also routine in the art. Quantitative real-time PCR can be conveniently accomplished using the

commercially available ABI PRISM 7600, 7700, or 7900 Sequence Detection System, available from PE-Applied Biosystems, Foster City, CA and used according to manufacturer's instructions.

Quantitative Real-Time PCR Analysis of Target RNA Levels

Quantitation of target RNA levels may be accomplished by quantitative real-time PCR using the ABI PRISM 7600, 7700, or 7900 Sequence Detection System (PE-Applied Biosystems, Foster City, CA) according to manufacturer's instructions. Methods of quantitative real-time PCR are well known in the art.

Prior to real-time PCR, the isolated RNA is subjected to a reverse transcriptase (RT) reaction, which produces complementary DNA (cDNA) that is then used as the substrate for the real-time PCR amplification. The RT and real-time PCR reactions are performed sequentially in the same sample well. RT and real-time PCR reagents may be obtained from Invitrogen (Carlsbad, CA). RT real-time-PCR reactions are carried out by methods well known to those skilled in the art.

Gene (or RNA) target quantities obtained by real time PCR are normalized using either the expression level of a gene whose expression is constant, such as cyclophilin A, or by quantifying total RNA using RIBOGREEN (Invitrogen, Inc. Carlsbad, CA). Cyclophilin A expression is quantified by real time PCR, by being run simultaneously with the target, multiplexing, or separately. Total RNA is quantified using RIBOGREEN RNA quantification reagent (Invitrogen, Inc. Eugene, OR). Methods of RNA quantification by RIBOGREEN are Taught in Jones, L.J., et al, (Analytical Biochemistry, 1998, 265, 368-374). A CYTOFLUOR 4000 instrument (PE Applied Biosystems) is used to measure RIBOGREEN fluorescence.

Probes and primers are designed to hybridize to a Tau nucleic acid. Methods for designing real-time PCR probes and primers are well known in the art, and may include the use of software such as PRIMER EXPRESS Software (Applied Biosystems, Foster City, CA).

Quantitative Real-Time PCR Analysis of Target DNA Levels

Quantitation of target DNA levels may be accomplished by quantitative real-time PCR using the ABI PRISM 7600, 7700, or 7900 Sequence Detection System (PE-Applied Biosystems, Foster City, CA) according to manufacturer's instructions. Methods of quantitative real-time PCR are well known in the art.

Gene (or DNA) target quantities obtained by real time PCR are normalized using either the expression level of a gene whose expression is constant, such as cyclophilin A, or by quantifying total DNA using RIBOGREEN (Invitrogen, Inc. Carlsbad, CA). Cyclophilin A expression is quantified by real time PCR, by being run simultaneously with the target, multiplexing, or separately. Total DNA is quantified using RIBOGREEN RNA quantification reagent (Invitrogen, Inc. Eugene, OR). Methods of DNA quantification by RIBOGREEN are Taught in Jones, L.J., et al, (Analytical Biochemistry, 1998, 265, 368-374). A CYTOFLUOR 4000 instrument (PE Applied Biosystems) is used to measure RIBOGREEN fluorescence.

Probes and primers are designed to hybridize to a Tau nucleic acid. Methods for designing real-time PCR probes and primers are well known in the art, and may include the use of software such as PRIMER EXPRESS Software (Applied Biosystems, Foster City, CA).

Analysis of Protein Levels

Antisense inhibition of Tau nucleic acids can be assessed by measuring Tau protein levels. Protein levels of Tau can be evaluated or quantitated in a variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), enzyme-linked immunosorbent assay (ELISA), quantitative protein assays, protein activity assays (for example, caspase activity assays), immunohistochemistry, immunocytochemistry or fluorescence-activated cell sorting (FACS). Antibodies directed to a target can be identified and obtained from a variety of sources, or can be prepared via conventional monoclonal or polyclonal antibody generation methods well known in the art.

In vivo testing of antisense compounds

Antisense compounds, for example, antisense oligonucleotides, are tested in animals to assess their ability to inhibit expression of Tau and produce phenotypic changes. Testing may be performed in non-transgenic animals, or in experimental disease models. For administration to animals, antisense oligonucleotides are formulated in a pharmaceutically acceptable diluent, such as phosphate-buffered saline. Administration includes parenteral routes of administration, such as intraperitoneal, intravenous, subcutaneous, intrathecal, and intracerebroventricular. Calculation of antisense oligonucleotide dosage and dosing frequency is within the abilities of those skilled in the art, and depends upon factors such as route of administration and animal body weight. Following a period of treatment with antisense oligonucleotides, RNA is isolated from brain tissue and changes in Tau nucleic acid expression are measured. Changes in Tau DNA levels are also measured. Changes in Tau protein levels are also measured. Changes in Tau splicing are also measured.

Tau splicing

Certain embodiments provided herein relate to differential splicing in tau. Accordingly, several embodiments provide methods of treating a tau associated disease by lowering tau or 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, 1 N, 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 mictrotubule 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. In healthy subjects, 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 syndromes such as FTD tauopathies. In essence, the method decreases the 4R:3R tau ratio in the central nervous system of the subject.

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 some embodiments, the method decreases the normal 4R:3R tau ratio in the central nervous system of a subject. In other embodiments, the method decreases a low 4R:3R tau ratio in the central nervous system of a subject.

In certain embodiments, the method decreases a high 4R:3R tau ratio in the central nervous system of a subject. In certain embodiments, the method decreases 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, *Ll280,* L284L, N296H, N296N, Ll296N, P301 S, G303V, E10+11, E1 0+12, E1 0+13, E+1 0+14 and E10+16, and E10+19. Certain embodiments relate to a method of decreasing the 4R:3R tau ratio in the central nervous system of a subject by lowering expression of tau or altering the splicing of a nucleic acid encoding tau administering an antisense compound to the subject.

Certain Indications

In certain embodiments, provided herein are methods of treating an individual comprising administering one or more pharmaceutical compositions described herein. In certain embodiments, the individual has a neurodegenerative disease. In certain embodiments, the individual is at risk for developing a neurodegenerative disease, including, but not limited to, Alzheimer's Disease, Fronto-temporal Dementia

(FTD), FTDP-17, Progressive Supranuclear Palsy (PSP), Chronic Traumatic Encephalopathy (CTE), Corticobasal Ganglionic Degeneration (CBD), Epilepsy, and Dravet's Syndrome. In certain embodiments, the individual has been identified as having a Tau associated disease. In certain embodiments, provided herein are methods for prophylactically reducing Tau expression in an individual. In certain embodiments, provided herein are methods for prophylactically modulating Tau splicing in an individual. Certain embodiments include treating an individual in need thereof by administering to an individual a therapeutically effective amount of an antisense compound targeted to a Tau nucleic acid.

In certain embodiments, administration of a therapeutically effective amount of an antisense compound targeted to a Tau nucleic acid is accompanied by monitoring of Tau levels and Tau isoform in an individual, to determine an individual's response to administration of the antisense compound. An individual's response to administration of the antisense compound may be used by a physician to determine the amount and duration of therapeutic intervention.

In certain embodiments, administration of an antisense compound targeted to a Tau nucleic acid results in reduction of Tau expression by at least 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values. In certain embodiments, administration of an antisense compound targeted to a Tau nucleic acid results in reduction of the 4R isoform of Tau expression by at least 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values. In certain embodiments, administration of an antisense compound targeted to a Tau nucleic acid results in reduced memory loss, reduced anxiety, improved motor function in an animal, and/or reduced incidence or severity of seizures. In certain embodiments, administration of a Tau antisense results in reduced memory loss, reduced anxiety, improved motor function; and/or reduced incidence or severity of seizures by at least 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values.

In certain embodiments, pharmaceutical compositions comprising an antisense compound targeted to Tau are used for the preparation of a medicament for treating a patient suffering or susceptible to a neurodegenerative disease including Alzheimer's Disease, Fronto-temporal Dementia (FTD), FTDP-17, Progressive Supranuclear Palsy (PSP), Chronic Traumatic Encephalopathy (CTE), Corticobasal Ganglionic Degeneration (CBD), Epilepsy, and Dravet's Syndrome.

Certain Splicing Compounds

In certain embodiments, splicing compounds are useful for treating neurodegenerative syndromes. In certain embodiments, such splicing compounds promote the exclusion of exon 10, resulting in shifting tau isoform from 4R Tau (which is associated with neurodegenerative syndrome) to 3R Tau. In certain embodiments, such splicing compounds are antisense oligonucleotides wherein each nucleoside comprises a high affinity modification. In certain embodiments, the splicing compound is complementary to a human Tau

genetic sequence. In certain embodiments, the splicing compound is complementary to SEQ ID NO: 1 (GENBANK Accession No. NT_010783.14 truncated from nucleotides 2624000 to 2761000).

Certain splicing compounds are described hereinbelow in the examples and include ISIS 415883, ISIS 415885, ISIS 415887, ISIS 549595, ISIS 549617, ISIS 549619, and ISIS 549620.

ISIS 415883 is 20 nucleobases in length having the sequence (5' to 3') TCTTATTAATTATCTGCACC (SEQ ID NO: 12) and each nucleoside comprises a 2'-MOE modification. Each internucleoside linkage is a phosphorothioate linkage and all cytosine residues are 5-methylcytosines.

ISIS 415885 is 20 nucleobases in length having the sequence (5' to 3') CCAGCTTCTTATTAATTATC (SEQ ID NO: 13) and each nucleoside comprises a 2'-MOE modification. Each internucleoside linkage is a phosphorothioate linkage and all cytosine residues are 5-methylcytosines.

ISIS 415887 is 20 nucleobases in length having the sequence (5' to 3') TAAGATCCAGCTTCTTATTA (SEQ ID NO: 14) and each nucleoside comprises a 2'-MOE modification. Each internucleoside linkage is a phosphorothioate linkage and all cytosine residues are 5-methylcytosines.

ISIS 549595 is 18 nucleobases in length having the sequence (5' to 3') GGACGTGTGAAGGTACTC (SEQ ID NO: 15) and each nucleoside comprises a 2'-MOE modification. Each internucleoside linkage is a phosphorothioate linkage and all cytosine residues are 5-methylcytosines.

ISIS 549617 is 18 nucleobases in length having the sequence (5' to 3') GCCCAAGAAGGATTTATT (SEQ ID NO: 16) and each nucleoside comprises a 2'-MOE modification. Each internucleoside linkage is a phosphorothioate linkage and all cytosine residues are 5-methylcytosines.

ISIS 549619 is 18 nucleobases in length having the sequence (5' to 3') TCCTGAGAGCCCAAGAAG (SEQ ID NO: 17) and each nucleoside comprises a 2'-MOE modification. Each internucleoside linkage is a phosphorothioate linkage and all cytosine residues are 5-methylcytosines.

ISIS 549620 is 18 nucleobases in length having the sequence (5' to 3') CAGATCCTGAGAGCCCAA (SEQ ID NO: 18) and each nucleoside comprises a 2'-MOE modification. Each internucleoside linkage is a phosphorothioate linkage and all cytosine residues are 5-methylcytosines.

Certain Comparator Compounds

In certain embodiments, splicing compounds described herein are compared to certain comparator compounds. In certain embodiments, the splicing compounds described herein perform better than comparator compounds in terms of *in vitro* or *in vivo* efficacy, potency, or tolerability. In certain embodiments, the comparator compound is complementary to a human Tau genetic sequence. In certain embodiments, the splicing compound is complementary to SEQ ID NO: 1 (GENBANK Accession No. NT_010783.14 truncated from nucleotides 2624000 to 2761000).

Certain comparator compounds are described hereinbelow in the examples and include ISIS 617782 and ISIS 617781.

ISIS 617782 is 21 nucleosides in length having the sequence (5' to 3') TGAAGGTACTCACACTGCCGC (SEQ ID NO: 19) and each nucleoside comprises a 2'-OCH_3 modification. Each internucleoside linkage is a phosphorothioate linkage and all cytosine residues are 5-methylcytosines.

ISIS 617781 is 18 nucleosides in length having the sequence (5' to 3') TATCTGCACCTTTGGTAG (SEQ ID NO: 20) and each nucleoside comprises a 2'-OCH_3 modification. Each internucleoside linkage is a phosphorothioate linkage and all cytosine residues are 5-methylcytosines.

As described hereinbelow, ISIS 415883 achieved an IC50 of 0.65 nM in a 6 point dose response curve (0, 0.1, 0.3, 1, 3, 10, or 30 nM) in cultured A172 cells transfected using Lipofectamine2000®, whereas ISIS 617781 achieved an IC50 of 20.25 nM. Human Tau primer probe set 10_11 was used. Thus, ISIS 415883 is more potent than the comparator compound ISIS 617781. See Example 8 hereinbelow.

As described hereinbelow, ISIS 549595, ISIS 549617, ISIS 549619, and ISIS 549620 achieved 20%, 31.8%, 41.7%, and 35.6% (respectively) Tau exon 10 mRNA expression relative to untreated control levels in cultured A172 cells transfected using Lipofectamine2000® with 5 nM oligonucleotide using human Tau primer probe set 10_11. ISIS 617781 achieved 65% Tau exon 10 mRNA expression relative to untreated control levels in cultured A172 cells transfected using Lipofectamine2000® with 10nM oligonucleotide using human Tau primer probe set 10_11. Therefore, ISIS 549595, ISIS 549617, ISIS 549619, and ISIS 549620 are more efficacious than comparator compound ISIS 617781 even when ISIS 617781 is administered at 2x the dose of ISIS 549595, ISIS 549617, ISIS 549619, and ISIS 549620. See Examples 8 and 9 hereinbelow.

As described hereinbelow, ISIS 549595, ISIS 549619, ISIS 549620 achieved 26%, 42%, and 35% (respectively) Tau exon 10 mRNA expression relative to untreated control levels in cultured A172 cells transfected using Lipofectamine2000® with 5 nM oligonucleotide using human Tau primer probe set 9_10 R5. ISIS 617782 achieved 55% Tau exon 10 mRNA expression relative to untreated control levels in cultured A172 cells transfected using Lipofectamine2000® with 3nM and 34% Tau exon 10 mRNA expression relative to untreated control levels in cultured A172 cells transfected using Lipofectamine2000® with 10nM oligonucleotide using human Tau primer probe set 9_10 R5. See Examples 8 and 10 hereinbelow.

EXAMPLE

Non-limiting disclosure and incorporation by reference

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 SET 1

The following examples illustrate various iterations of the invention.

Introduction to Examples 1-7

Accumulation of proteinaceous aggregates is one of the defining hallmarks of neurodegenerative diseases. How these proteins cause disease and how they are subsequently cleared has remained an enigma. Tau, a microtubule binding protein, is one such aggregated protein found in multiple neurodegenerative syndromes including Frontotemporal dementia (FTD), Alzheimer's disease (AD), Progressive Supranuclear Palsy, and Corticobasalganglionic Degeneration. Understanding tau mediated neurodegeneration may lead to important therapeutic strategies for these disorders. Studies in the examples below focus on how to prevent the behavioral effects and pathological abnormalities in mouse models of dementia by decreasing tau levels and by changing the ratio of two different tau isoforms, 3R and 4R tau.

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 clear. Inclusion of exon 10 at the C-terminus leads to inclusion of the microtubule binding domain encoded by exon 10. Since there are 3 mictrotubule 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. (Figure 1). Tau without exon 10 is termed 3R tau. Since more microtubule binding domains (4R compared with 3R) probably increases the binding to microtubules, 4R tau presumably changes the microtubule binding characteristics. 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 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.

Serine-threonine directed phosphorylation regulates the microtubule binding ability of tau. Phosphorylation 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.

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. Given the data suggesting an important role for tau in normal cellular processes, it is surprising that the tau knockout animals do not have an obvious phenotype.

One of the early indicators that tau may be important in neurodegenerative syndromes was the recognition that tau is a key component of neurofibrillary tangles in Alzheimer's disease. Along with amyloid beta containing plaques, neurofibrillary tangles 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. Recent experiments suggest that tau may be a key mediator of amyloid beta induced toxicity. Tau knockout animals are protected from amyloid beta induced toxicity. The animals do develop amyloid beta plaques, but do not develop the behavioral phenotype typical of transgenic amyloid-3 depositing mice. Given the developmental regulation of tau isoforms and the adult onset of AD, it is important to understand whether decreasing levels of tau in the adult animal will provide neuroprotection as suggested by this experiment where tau is deleted developmentally as well as in the adult. Measuring the effect of decreasing levels of tau on neurodegeneration in Alzheimer's mice and FTD model mice is another central question of the examples below. Data from late onset Alzheimer's disease patients suggest that among patients with Alzheimer's disease increased CSF tau may lead to earlier age of onset, implying that tau is not only a component of the pathology of Alzheimer's disease, but may directly influence the course of disease. This reinforces the possibility that decreasing tau levels in patients may slow the course of Alzheimer's disease patients.

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.

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. Very interestingly, additional transgenic lines in which N279K mutation was driven by a CMV promoter were also generated. These CMV-N279K animals have exclusively 4R tau at both fetal and adult stages and do not develop any disease. Therefore it is unlikely that N279K toxicity arises from the N279K amino acid change since CMV-N279K mice have the same mutation. Similarly, expression of increased 4R alone presumably does not cause disease since the CMV-N279K mice express equal levels of 4R tau, but do not develop disease. Rather, these data suggest that tau pathogenesis depends on the shift away from the normal 4R:3R ratio and/or the tau promoter itself. A critical unaddressed question is whether decreasing the 4R:3R ratios in the adult animals will prevent neurodegeneration.

Antisense oligonucleotides are used to achieve tau knockdown and to modulate tau splicing. The inventors have pioneered the use of antisense oligonucleotides in the central nervous system. Although the oligos do not cross the blood brain barrier, this issue is solved by infusing the oligos directly into the cerebral spinal fluid (CSF) that circulates throughout the brain and the spinal cord. Direct CSF infusion of oligos is done using an osmotic pump (Alzet pump) connected via plastic tubing to a catheter implanted in the right lateral ventricle, the space within the brain filled with cerebral spinal fluid (Figure 2). The pump delivers drug at a constant rate into the ventricle. Previous data from the inventors demonstrate a widespread distribution of oligos throughout the brain and spinal cord of both rat and Rhesus monkey, target specificity, and neuroprotection in an animal model of ALS based on expression of mutant SOD1G93A. Surprisingly, the antisense oligos penetrate deeply and evenly into the brain parenchyma targeting all regions of the brain.

Typical antisense oligos are designed to decrease gene expression by activating RNAse H, thus cleaving the target mRNA to which the oligo binds. Oligos may also be designed not to activate RNAse H, but to bind to introns or exon/intron boundaries and promote inclusion or exclusion of a particular exon. This strategy has been successful in mice for SMN, the gene whose absence causes spinal muscular atrophy. A similar strategy to promote exclusion of exon 10 and thus decrease the 4R to 3R tau ratio is described below. Decreasing the abnormal 4R:3R tau ratio may be sufficient to decrease the behavioral deficits and the pathological changes in the tau N279K mice, even though the tau protein sequence remains abnormal.

Example 1. Mouse tau knockdown *in vitro*.

Antisense oligonucleotides that decrease levels of tau mRNA in tissue culture have been identified. 80 antisense oligos designed to decrease mouse tau levels were screened by transfection into a murine cell line (Figure 3A). From these results, 10 antisense oligos were judged to have relative good activity in this assay. These 10 oligos were tested in a dose response curve in a murine cell line (Figure 3B). Nine of 10 oligos were active in this assay, demonstrating >80% decrease in tau mRNA compared with non-transfected controls. Two different scrambled oligos caused 15% knockdown at the highest dose and no effect on tau mRNA levels at lower doses.

Certain active oligos (i.e., oligonucleotides) in this assay, demonstrating >80% decrease in tau mRNA compared with non-transfected controls were taken forward in additional studies.

Example 2. Mouse tau knockdown *in vivo*. (Effect of antisense inhibition of murine Tau by systemic administration in a murine model)

Antisense oligonucleotides from the study described above were selected for testing in vivo. The antisense oligonucleotides were designed as 5-10-5 MOE gapmers, and are 20 nucleosides in length, wherein the central gap segment is comprised of ten 2'-deoxynucleosides and is flanked on both sides (in the 5' and 3' directions) by wings comprising 5 nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment as a 2'-MOE modification. The internucleoside linkages throughout the gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout he gapmer are 5-methylcytosines.

From the above *in vitro* study (Figure 3), 5 oligos were selected to test *in vivo*. First, the oligos were tested by intraperitoneal delivery of 37.5 mg/kg three times per week x 3 weeks. After 3 weeks, a piece of liver and a sample of blood were collected. The blood was used to test for generic toxicity by measuring "liver enzymes", which are proteins found in the liver that are detectable in serum. In the setting of liver toxicity, these enzymes (ALT and AST) are increased. Liver enzymes were changed less than 2 fold indicating that these oligos are not likely to be toxic.

mRNA was isolated from liver and mouse Tau mRNA levels were measured by QPCR using GAPDH as a control. Three of the oligos (#2, 4, 5) decreased tau mRNA levels by about 50%, but there was substantial variability in the results, which is partly attributed to low abundance of tau mRNA in the liver samples (data not shown).

Example: Effect of antisense inhibition of Tau by direct hippocampal administration

As a further test of the oligos, oligos 2, 4, 5 were screened by direct hippocampal injection. Saline, or a scrambled oligo, or 50 μg of antisense oligonucleotide was infused by stereotactic injection into the right hippocampus of a 60 day old non-transgenic mouse. After one week, mice were euthanized and the area surrounding the injection was isolated and used to prepare mRNA. Mouse tau mRNA levels were decreased > 75% in all tau antisense oligo injected hippocampi (Figure 4A).

Example: Effect of antisense inhibition of Tau by intraventricular administration

Since the treatment paradigm for modulating behavior in the transgenic amyloid-3 depositing mice will involve treatment of the entire brain using intraventricular injection of antisense oligonucleotides, the most active antisense oligo (Tau 5, Figure 4A) was next tested by intraventricular injection.

Study 1

Saline or tau #5 was infused into the right lateral ventricle (of 8 week old C57BL6 mice) at 100 μg/day using an indwelling catheter connected to an Alzet osmotic pump buried in a subcutaneous pocket on the back of the animal (as described in Figure 2). After 30 days, animals were euthanized and mRNA was prepared from a section of right frontal cortex. Tau mRNA levels were analyzed by QPCR. Using GAPDH as a normalizer, the knockdown of tau mRNA was about 95% in the animals treated with antisense oligonucleotide (Figure 4B). Tau protein was also clearly decreased by Tau5 antisense oligonucleotide (Figure 4C).

Study 2

Efficacy of lower doses of the Tau5 oligo (i.e., oligonucleotide) was also tested.

The current dose of 100μg/day was tolerated well without any evidence of toxicity. Efficacy of lower doses of the tau5 oligo (i.e., oligonucleotide) were also tested using 25, 50 and 100μg/day with the Alzet pump system. Four to five 8 week old non-transgenic BL6 mice per group were used. The lowest dose tested (25μg/day) was still effective at knocking down relative brain tau levels (Figure5).

Study 3

In addition, the half life of tau5 oligo after intraventricular infusion with the Alzet pump was also tested. Intraventricular infusions using 8 weeks old non-transgenic BL6 mice were as described above, using 3-6 mice per group. Tau5 oligo was infused at 25 and 50μg/day for 1 month. Brains were then collected immediately

after infusion, or 1 month, and 3 months after infusion. Brain tau levels were still significantly lower 12 weeks after infusion (Figure 6).

Example: Duration of action of Tau#5 ASO by intraventricular administration

To further characterize tau knockdown using antisense oligos, tau5 oligo was used to test duration of onset after injection of the oligo into mice (Figure 7). In short, a 50μg hippocampal bolus was injected (1 μl of 50μg/μl solution was infused at 0.2μl/min for 5 minutes) into 12 week old C57BL6 mice, brains were collected at 25 hours, 48 hours, and 72 hours post-injection (+/- 2 hours). Four pieces of brain were collected –Right RNA, Right protein, Left RNA, Left protein (Figure 7A). The right RNA and Right Protein pieces were used for qRT-PCR (Figure 7B) and Western blot analysis (Figure 7C), respectively. Tau mRNA levels significantly drop even after only 24 hours post bolus and continue to drop at 48 and 72 hours (Figure 7B). Tau protein levels do not appear to decrease by the 24 and 48 hour time points by Western blot (Figure 7C), suggesting that there is a lag between the mRNA knockdown and protein knockdown of tau. However, by 72 hours the protein levels begin to decrease such that by 1 week there is a significant decrease in tau protein levels (Figure 7C).

Example 3. Changing human tau splicing.

Saline or splicing oligos (i.e., "splicing oligo 1" also ISIS 415883, "splicing oligo 2" also ISIS 415885, and "splicing oligo 3" also ISIS 415887) which dramatically shifted the tau isoforms from mainly 4R with some 3R tau to mostly 3R tau with some 4R tau in an in vitro study, and designed to specifically decrease 4R tau levels, were infused into the hippocampus by stereotactic injection into htau mice that express full length human tau. Mice were euthanized after one week and brain parenchyma was examined for human 4R tau mRNA and for human 3R tau mRNA by QPCR (Figure 9). The oligos clearly decrease 4R tau levels. They also appear to increase 3R levels. These data demonstrate the oligos are active *in vivo*.

The effect of tau415883 on 4R tau was also tested after intraventricular infusion with the Alzet pump was also tested. Intraventricular infusions using 14 week old non-transgenic BL6 mice were as described above, using 11-12 mice per group. Tau415883 oligo was infused at 50μg/day for 28 days. Relative brain 4R tau levels were significantly lower (Figure 8).

A similar experiment was performed using a month intraventricular infusion (**Figure 10**).

Example 4. PTZ induced seizures.

Example: Effect antisense inhibition of tau on PTZ induced seizures

Seizures were induced and quantified in various mice using pentelenetetrazoll (PTZ). The mice are videotaped for 15 minutes and scored later in a blinded fashion. The final stage reached is recorded. In short, 50mg/kg PTZ was injected ip into mTau-/-, and mTau+/- mice. mTau+/+ mice were used as control. Mice deficient for mTau were more resistant to PTZ induced seizures (Figures 11A and 11B).

Seizures were also induced and measured in mice treated with a tau knockdown oligo or a tau splicing oligos (also ISIS 415883). In short 3 month old C57/BL6 males were dosed for 28 days with 25μg/day of oligo. The pumps were removed, and the animals were allowed to sit for 3 weeks post-pump removal before seizure induction. Seizures were induced using 55mg/kg of PTZ using ip injection. The mice are videotaped for 15 minutes and scored later in a blinded fashion. The results show that the knockdown and the splicing oligos were capable of protecting mice against PTZ induced seizures (Figures 12A and 12B).

Example 5. Effect of knockdown and splicing oligonucleotides on weight gain in N297K mice.

N279K mice treated with vehicle, a scrambled oligonucleotide, a human tau knockdown oligonucleotide, a human tau splicing oligonucleotide (i.e., ISIS 415883) and nonTg saline. The results show that mice treated with the human tau knockdown oligonucleotide, the human tau splicing oligonucleotide and nonTg saline gained significantly more weight than mice treated with vehicle alone (Figure 13).

Example 6. Reversing splicing deficit in N279K Tauopathy mice by decreasing 4R tau levels.

Decreasing 4R tau levels in adult N279K exon 10 mutation mice may improve behavioral and pathological phenotype in these mice. Tau N279K mice are based on one of the tau mutations which causes aberrant splicing of tau, by promoting inclusion of exon 10. Inclusion of exon 10 leads to increased 4R compared with 3R tau, without affecting overall levels of tau. The mice typically develop motor and cognitive behavioral abnormalities at 6 months including deficits on rotarod and on water maze. These deficits are worse at 12 months. As is typical of a variety of tau models, approximately 25% of these animals develop severe motor weakness and die before the rest of the cohort (on average at 45 weeks old). The percentage of animals with this profound motor deficit may be measured in each group and these animals may not be included in other behavioral tests. Brain pathological changes are mild at 6 months and prominent at 1 year. The changes include increased tau and phosphotau staining in neurons and astrocytes, and increased caspase 3 activation. Pathology also included positive Gallyas silver staining in neurons, a stain that detects abnormal filaments such as those composed of aggregated tau as well as Fluorojade B positive staining, indicative of degenerating neuronal cells.

The goal of the treatment is to decrease the 4R:3R ratio in the N279K mice, which is increased by the N279K mutation and which causes preferential inclusion of exon 10. As has been demonstrated *in vivo* (Figure 9), Tau splicing oligos that decrease the inclusion of Exon 10 and thus decrease the 4R:3R tau ratio may be used. Antisense oligos that alter splicing, a control oligo, or saline may be infused into the right lateral ventricle of N279K mice, at 3 months of age. Since pathology starts at 6 months of age, 3 months was chosen to be presymptomatic. The control groups are animals treated with saline alone or a control oligo. Both may be compared to animals treated with an oligo that decreases 4R:3R ratios. Each of the groups may be compared with non-transgenic, untreated mice.

The three groups of N279K mice (saline, oligo control, 4R:3R tau splicing oligo) and a group of non-transgenic mice without pumps may be examined at ages 6 months and 12 months for behavioral analysis. Including the non-transgenic mice in the behavioral studies may document that the N279K mice animals do indeed develop behavioral deficits and help understand to what degree treatment is able to prevent behavioral abnormalities. In terms of the statistical comparisons and treatment effect in the N279K mice, the important comparison may be the saline and oligo control compared to the 4R:3R tau splicing oligo. Mice that develop acute motor weakness (25% expected) may be determined to be dead when they are no longer able to right themselves after being placed on their backs for 30 seconds. There is no primary analysis planned for these animals, though tissues may be retained for any possible future analyses and the number of animals with this phenotype in each group may be scored. In conjunction with the Washington University Behavioral Core, for animals that do not develop overt weakness, radial arm Morris water maze may be analyzed at 6 months and 12 months. Rotarod performance may also be analyzed. At 1 year of age, mice may be euthanized. Just prior to euthanasia, CSF may be collected. Brains may then be collected. The left half of the brain may be fixed with 10% formalin, cyroprotected with sucrose and sectioned for immunocytochemistry of tau, phosphotau, and activated Caspase 3. Gallyas staining and fluorojade staining may also be performed. The right half of the brain may be used for biochemical analyses. Total tau mRNA and protein levels, and 4R:3R ratios may be analyzed.

Given the preliminary data described in the examples above, reversing the splicing deficit in the N279K mice with antisense oligos is likely. Previous data suggest that pathogenesis arises from the change in the ratio of 3R to 4R tau rather than the absolute levels or the missense variant in the 4R containing protein. This is evidenced by tau mice with the N279K minigene construct driven by the CMV promoter. These animals have increased levels of 4R tau both fetally and in the adult animal. However, they do not develop any tau pathology or behavioral abnormalities. Thus it is the tau promoter itself and/or the switch to

increased 4R:3R that appears to be important for disease. These experiments may address an important question regarding whether changing tau ratios in the adult animal may be beneficial.

Example: Effect of antisense oligonucleotide treatment on human tau splicing in N279K tauopathy mice

The effect of ASOs (i.e., antisense oligonucleotides) on tau splicing was tested in vivo. N279K tauopathy mice (Dawson, H.N. et al., Neurosci. 27:9155-9168, 2007) were used in this assay. Tau N279K mice are based on one of the tau mutations which causes aberrant splicing of tau by promoting inclusion of exon 10. Inclusion of exon 10 leads to increased 4R compared to 3R, without affecting overall levels of tau. The effect of ASOs in the splicing of exon 10 and the resulting 4R:3R ratio in these mice was evaluated.

Study 1

Transgenic mice were infused with PBS or 60 μg/day ASO (i.e., ISIS 549595, ISIS 549617, ISIS 549619, and ISIS 549620) for 28 days. Mice were sacrificed on the 29th day, and cortical tissue around the cannula was collected and examined for human 4R tau mRNA and for human 3R tau mRNA by QPCR (Figure 20). Treatment with ASO decreased 4R tau levels and increased 3R levels.

Example 7. Modulating tau levels in mice with Alzheimer's disease-like pathology.

For an amyloid precursor protein (APP) transgenic model the J20 line (Table 1) may be used, which expresses an hAPP minigene with the Swedish (K670M/N671L) and Indiana (V717F) familial Alzheimer's disease (AD) mutations under control of the PDGF promoter. Behavioral deficits in the J20 line Alzheimer's mice typically occur at 4-7 months and include deficits in the Morris water and exploration of a new environment. In addition, about 15% of the animals die early (by 6-8 months) for unclear reasons, but perhaps related to seizures. The death typically occurs in an animal that otherwise appeared well the previous day and is presumably secondary to an acute event. J20 line APP mice with one or both copies of mouse tau deleted are protected from amyloid beta induced toxicity as evidenced by better performance on the Morris water maze, open field exploration, and a normal lifespan in all the animals. Amyloid plaque deposition occurs in only a few J20 animals at 2-4 months, 50% at 6 months, and nearly 100% by 8-10 months. Tau deletion does not affect amyloid plaque levels in the J20 line.

J20 line Alzheimer's mice at age 3 months old may be treated with Tau 5 oligo, an antisense oligonucleotide that clearly decreases mouse tau mRNA and protein (Figure 4). There may be two control groups, one may be treated with saline and another with a scrambled antisense oligonucleotide control. Since

behavioral deficits become apparent between 4 and 7 months of age, and since the J20 line does not have amyloid beta accumulation at 2-4 months, 3 months was chosen as presymptomatic. Treatment may consist of placement of an intraventricular catheter connected to an osmotic pump filled with oligo or saline.

Each litter of animals may be divided into male and female groups. Males and females may then be equally and randomly assigned to a treatment paradigm. Following surgeries, cage cards indicating treatment group may be replaced with animal number assignments such that the technician following the mice may be blinded to the treatment strategy.

The three groups of J20 APP mice (saline, oligo control, antisense oligo against tau) and a group of non-transgenic mice may be examined at ages 6 months and 12 months for cognitive function on water maze, y maze, and the exploration of new environment. Including the non-transgenic mice in the behavioral studies may document that the J20 APP animals do indeed develop behavioral deficits and help understand to what degree treatment is able to prevent behavioral abnormalities. In terms of the statistical comparisons and treatment effect in the J20 APP mice, the important comparison may be the saline and oligo control compared to the antisense oligo against tau. These behavioral studies may be performed in conjunction with the Animal Behavioral Core at Washington University run by Dr. David Wozniak. This core is open to all Washington University investigators, is located within an animal facility, and has a wide array of experience with behavioral measures (hopecenter.wustl.edu/cores/animalBehavior). At one year of age animals may be euthanized. Immediately before euthanasia, cerebral spinal fluid may be drawn. Brains may then be collected. The left half of the brain may be fixed with 10% formalin, cyroprotected with sucrose and sectioned for immunocytochemistry of amyloid beta from the genu of the corpus callosum through the caudal extent of the hippocampus. The percent surface area covered by immunoreactive amyloid beta deposits (percent A13 load) as identified with a rabbit pan A13 antibody may be quantified following stereological principles as described. The right half of the brain may be used for biochemical analyses. It may be confirmed that Amyloid beta levels are not changed, including CSF amyloid beta, and that tau mRNA and protein levels are indeed decreased in the treated animals using tissue homogenate. The J20 APP do recapitulate some aspects of Alzheimer's disease, including amyloid beta deposition and cognitive changes. However, they do not develop tau pathology. Thus tau pathological examinations may not be performed for this set of experiments although tissue may be retained for potential analysis of this or any other measures suggested by future work in the field.

It is expected that decreasing overall tau levels in adult APP transgenic mice may protect the mice from amyloid 13 induced toxicity.

Methods for Examples 1-7.

Screening and identifying effective antisense oligonucleotides.

The overall goal is to identify one or two antisense oligos with potent efficacy and no toxicity that may be used in the subsequent studies. Though this initial work is labor intensive and time consuming, identifying the best oligo in these initial studies will be essential for successfully completing the interesting treatment part of this project using transgenic mice. The antisense oligonucleotides are produced by Isis Pharmaceuticals, Inc. The oligonucletotides used are 20-mer phosphorothioate, 2'-O-(2-methoxyethyl) (MOE)-modified antisense oligonucleotides.

Step 1.) In vitro screen: Approximately 80 oligonucleotides are typically screened *in vitro* in cultured cells. This process typically identifies 8-10 oligos that show good efficacy and could be used for *in vivo* knockdown.

Step 2.) Brain and spinal cord screen: Prior experience has demonstrated that these antisense oligos will not reach the brain and the spinal cord following delivery in the periphery (intraperitoneal, subcutaneous, or venous), presumably because the oligos do not cross the blood brain barrier. Because the oligos do not cross the blood brain barrier,the antisense oligos need to be delivered directly to the brain. Two methods are used to screen oligos in the brain. The first is a direct brain parenchymal injection. This is an excellent method for screening oligos because the technique is straightforward, does not require insertion of a pump, and leads to reproducible oligo effects after 1 week. This technique addresses the question of whether the oligo is active in the brain.

The second method for screening is intraventricular delivery through an osmotic pump for 1 month. This leads to more widespread delivery as would be required for treatment of an animal model. Cerebral spinal fluid bathes the brain and spinal cord and thus serves as a drug delivery system to the entire brain and spinal cord. To deliver drugs to the cerebral spinal fluid, a catheter is placed in the lateral ventricle. To access the lateral ventricle, a small hole is drilled in the skull (using a stereotaxic apparatus) and a catheter which is connected to an osmotic pump (Alzet) is inserted . The continuous infusion into the right lateral ventricle delivers drug to the cerebral spinal fluid, which is then widely distributed throughout the brain and spinal cord. The typical dose is 100 μg/day for 28 days, and may be optimized for individual oligos. The osmotic pump lasts for 30 days, but can be replaced with a new pump by making a small incision in the skin, disconnecting the plastic tubing, reconnecting to a new pump and then resuturing the skin. These catheters have been maintained for more than 9 months. Mice tolerate this procedure well.

Tolerability of Antisense Oligonucleotides:

Part of the screen in brain involves an assessment of the tolerability of the oligo. One concern with this technology that is often raised is the toxicity associated with many first generation antisense oligonucleotides. Use of the new "second generation" oligos has demonstrated decreased toxicities for the following reasons. First, oligo chemistry has greatly improved over the past decade. The current "second generation" oligos include modifications to increase potency and decrease immune stimulation. Second, there is now better understanding of the biology causing some immune reactions to oligos. Phosphorothioate oligodeoxynucleotides, such as those used here are well recognized to activate cells of the immune system predominantly through interaction with Toll-like receptor 9 (TLR-9), although there are TLR-9 independent pathways as well. Avoiding certain particularly immunogenic sequence motifs and the current chemistries helps to minimize this immune stimulation. Third, careful attention paid to choosing the most potent oligos, minimizes toxicity by using smaller doses. 25-50 fold less oligo is now used to produce the same effects achieved with earlier chemistries. Fourth, the current set of oligos is produced with minimal impurities and no measurable endotoxin, which were a likely source of earlier oligo related toxicities.

Despite these reassurances, the best measure of toxicity of a particular oligo for these animal studies is observation of the animal. Animals are observed behaviorally for any signs of abnormalities and weighed weekly. Loss of weight would be considered a sign of toxicity. Signs of weakness, decreased mobility, infection, and ruffed coat are monitored. This toxicity screen also involves a brain survey for inflammation including H&E, and astroglial/microglial stains. Thus far both the tau knockdown and tau splicing oligos used in these studies have been well tolerated. In addition, the exact same oligo chemistry has been well tolerated in the periphery (subcutaneous injection) by greater than 500 patients in clinical trials.

Mice

Mice used in these studies and planned studies are detailed in Table 1.

Table 1

Mouse Line	Transgene	Promoter	Behavorial Changes	Pathology	Experimental
N279K	Human tau minigene containing Exon 10 and flanking intronic sequence	Human Tau	Deficits in radial arm water maze and rotarod at 6 months. 25% develops ever motor weakness by 6 months.	Accumulation of tau, phosphotau in neurons, astrocytes. Present at 6 months, worse at 12 months.	N279K mutation leads to increased 4R compared to 3R tau. Does decreasing 4R:3R tau ratio in adult mice improve behavior/pathology?

J20 APP	hAPP minigene with Swedish (K670M/N671L) and Indiana (V717F) familial AD mutations	PDGF	Deficits on Morris water maze, y maze, exploration of new environment at 4-7 months. 15% premature death for unclear reasons by 6-8 months.	Amyloid beta deposition. No obvious tau pathology	Does decreasing mouse tau in adult mice improve behavior/pathology?

EXAMPLE SET 2

Example 6: Evaluation of wide-spread tau knockdown in vivo with antisense oligonucleotides

To evaluate tau knockdown in different brain regions using antisense oligos, tau#5 oligo was used in C57/Bl6 mice (Figure 14). A map of the brain regions is provided in Figure 27.

C57/Bl6 mice were administered 25 μg/day tau#5 or PBS by intraventricular infusion with the Alzet pump for 28 days. Pumps were then removed and the mice were allowed to rest for an additional 14days. Brains were then collected. Sections of brain were collected for RNA analysis using qRT-PCR.

Tau mRNA levels significantly decreased in all sections of the brain examined (Figure 14).

Example 7: Effect of antisense inhibition of Tau in P301S mice

The effect of treatment with ASOs# 6, 9, 12, and 13 was evaluated in P301S mice. P301S mice develop filamentous tau lesions at 6 months of age that progressively result in hippocampal and entorhinal cortical atrophy by 9-12 months of age (Yoshiyama, Y. et al., Neuron 53: 337-351, 2007).

Groups of P301S mice were infused with PBS or 100 μg of antisense oligonucleotide into the right lateral ventricle by the Alzet pump for 14 days. The pumps were then removed and mice were allowed to rest for 14 days. The mice were euthanized and tissues were collected and used to prepare mRNA.

Human tau levels and mouse tau mRNA levels were measured and were found to be decreased (Figure 15 and 16). Relative GFAP expression was also measured as a measure of toxicity (Figure 17).

Example 10: Effect antisense inhibition of tau on treating seizures induced by pentelenetetrazoll (PTZ) was evaluated.

Groups of 3 month old C57/BL6 males were infused for 28 days with the Alzet pump at 25 μg/day of ASO. The pumps were removed, and the animals were rested for 3 weeks post-pump removal. Seizures were induced using 55 mg/kg of PTZ by intraperitoneal injection. The mice are videotaped for 15 minutes and scored later in a blinded fashion.

The results show that the knockdown and the splicing oligos (i.e., ISIS 415883) were capable of protection mice against PTZ induced seizures (Figure 12).

EXAMPLE SET 3

Example 1: In vitro dose-dependent inhibition of Tau in human SH-SY5Y cells with gapmer antisense oligonucleotides

Antisense oligonucleotides (ASO A and ASO B) were designed targeting a Tau nucleic acid (SEQ ID NO: 1) and were tested for their effects on Tau mRNA *in vitro*. The chimeric antisense oligonucleotides were designed as 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. Each gapmer is targeted to the human Tau genomic sequence, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NT_010783.14 truncated from nucleotides 2624000 to 2761000), as presented in Table 2.

Table 2

Antisense oligonucleotides targeting SEQ ID NO: 1

ISIS No	Target Region
ASO A	Exon 2
ASO B	Exon 7

SH-SY5Y cells were plated at a density of 20,000 cells per well and transfected using electroporation with 1,250 nM, 2,500 nM, 5,000 nM, 10,000 nM, or 20,000 nM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and Tau mRNA levels were measured by quantitative real-time PCR. Tau mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Tau was reduced in a dose-dependent manner in ASO A and ASO B treated cells, relative to untreated control cells.

Example 2: In vitro dose-dependent reduction of 4R isoform in human A172 cells with uniformly modified antisense oligonucleotides targeting intron 10 of human Tau

Uniformly modified antisense oligonucleotides were tested in vitro in a dose dependent study. The oligonucleotides, ASO C (also ISIS 549620), ISIS 549595, ISIS 549617, and ISIS 549619, are 18 nucleobase uniformly modified antisense oligonucleotides comprising a 2'-MOE modification on each nucleoside was designed targeting intron 10 of human Tau (i.e., SEQ ID NO: 1). Each internucleoside linkage throughout the oligonucleotide are phosphorothioate (P=S) linkages. All cytosine residues throughout the oligonucleotide are 5-methylcytosines.

The antisense oligonucleotide was tested *in vitro*. A172 cells were transfected using LipofectAMINE2000® with 0.3 nM, 1.0 nM, 3.0 nM, 10.0 nM, 30.0 nM, or 100.0 nM concentrations of antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and the mRNA levels of the 4R isoform and total Tau mRNA were measured by quantitative real-time PCR using primer probe set hMAPT_LTS00914_MGB (forward sequence CGGGAAGGTGCAGATAATTAATAAG, designated SEQ ID NO: 21; reverse sequence GGACGTGTTTGATATTATCCTTTGAG, designated SEQ ID NO: 22; probe sequence AGCTGGATCTTAGCAACG, designated SEQ ID NO: 23). Tau mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®.

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. The 4R isoform of Tau was reduced in a dose-dependent manner in ASO C (also ISIS 549620), ISIS 549595, ISIS 549617, and ISIS 549619- treated cells, relative to untreated control cells.

Table 3

Percent 4R isoform to total Tau mRNA in A172 cells

	0.3 nM	1 nM	3 nM	10 nM	30 nM	100 nM	IC_{50} (nM)
ISIS 549595	75	57	33	24	16	31	1.3
ISIS 549617	83	61	46	34	29	26	3.4
ISIS 549619	82	78	51	39	21	17	4.6
ASO C (ISIS 549620)	83	70	55	33	20	23	4.0

Example 3: Effect of treatment with gapmer antisense oligonucleotides on Tau mRNA levels, Tau protein levels, and Tau hyperphosphorylation in P301S transgenic mouse model

P301S mice over-express the mutated form of human Tau (Yoshiyama, Y. et al., Neuron. 2007. 53: 337-51). The mice exhibit Tau pathology with accumulation of hyperphosphorylated Tau protein. The effect of treatment on these mice with gapmers targeting human Tau was assessed in this model.

Study 1

Groups of 3-4 P301S mice were administered ASO A and ASO B at 60µg/day for 14 days via an intracerebroventricular pump. A control group of two mice were similarly treated with PBS. Alzet osmotic pumps were used to continuously deliver the antisense oligonucleotide. Pumps were assembled and implanted, as per the manufacturer's instructions (Durect Corporation). Animals were anesthetized with 3% isofluorane and placed in a stereotactic frame. After sterilizing the surgical site, a one cm midline incision was made over the bregma. Through the use of stereotaxic guides, a cannula was implanted into the right lateral ventricle and secured. A catheter attached to an Alzet osmotic pump was secured to the cannula and the pump was placed subcutaneously in the midcapsular area. The incision was closed with sutures. Tissue was collected from around the catheter site 4 weeks after pump implantation.

RNA analysis

RNA was extracted from the cortex region around the catheter site and analyzed by qRT-PCR for expression levels of human and murine Tau. The data is presented in Table 4. The results indicate that oligonucleotides inhibit levels of human Tau mRNA.

Table 4

% inhibition of Tau mRNA compared to the PBS control

ISIS No	human	murine
ASO A	35	7
ASO B	55	24

Study 2

Groups of five P301S mice each (5 months old) were administered ASO B at 50µg/day for 28 days via an intracerebroventricular pump. A control group of five mice were similarly treated with PBS. Alzet osmotic pumps were used to continuously deliver the antisense oligonucleotide. Pumps were assembled and implanted, as per the manufacturer's instructions (Durect Corporation). Animals were anesthetized with 3% isofluorane and placed in a stereotactic frame. After sterilizing the surgical site, a one cm midline incision was made over the bregma. Through the use of stereotaxic guides, a cannula was implanted into the right lateral

ventricle and secured. A catheter attached to an Alzet osmotic pump was secured to the cannula and the pump was placed subcutaneously in the midcapsular area. Tissues were collected after 2 months.

RNA analysis

RNA was extracted from the hippocampal region around the injection site and analyzed by qRT-PCR for expression levels of human and murine Tau. The results indicate that ASO B inhibited levels of human Tau mRNA by 36% and of murine Tau mRNA by 5% one month post-ASO B active infusion.

Protein analysis

Human Tau protein in the brain was analyzed by ELISA (as previously described by Yamada et al., J. Neurosci. 2011. 31: 13110-117), as well as by western blot analysis using the total tau Tau5E2 antibody. The ELISA results indicate that ASO B inhibited levels of human Tau by 40%.The western blot results were quantified and indicate that ASO B inhibited levels of human Tau by 74%. It should be noted that the ELISA recognizes all forms of Tau, including human and mouse, whereas with the Western Blot, the human Tau can be separated from the mouse Tau by size differences. Thus, the Western Blot human Tau quantification is a more accurate representation of the human Tau specific knockdown levels.

Study 3

Groups of 5 P301S mice each (5 months old) were administered ASO B at 50 μg/day for 28 days via an intracerebroventricular pump. Another Group of 5 P301S mice (5 months old) were administered ASO B at 100μg/day for 14 days via an intracerebroventricular pump. A control group of five mice were similarly treated with PBS. Alzet osmotic pumps were used to continuously deliver the antisense oligonucleotide. Pumps were assembled and implanted, as per the manufacturer's instructions (Durect Corporation). Animals were anesthetized with 3% isofluorane and placed in a stereotactic frame. After sterilizing the surgical site, a one cm midline incision was made over the bregma. Through the use of stereotaxic guides, a cannula was implanted into the right lateral ventricle and secured. A catheter attached to an Alzet osmotic pump was secured to the cannula and the pump was placed subcutaneously in the midcapsular area. Tissues were collected after 2 months.

Hyperphosphorylated Tau analysis

The monoclonal Tau antibody AT8 recognizes Tau protein phosphorylated at both serine 202 and threonine 205 (Goedert, M. et al., Neurosci. Lett. 1995. 189: 167-9) and is therefore is used in a method of detection of hyperphosphorylated Tau. This is also the most commonly used antibody to identify Tau accumulations in human Alzheimer's disease patient brains. Extensive hyperphosphorylated Tau (Ser202 and Thr205) was detected in the entorhinal cortex and the basolateral amygdala by immunohistochemistry using

AT8 antibody in P301S brains at 7 months of age. The percentage of cells stained with the antibody is presented in Figure 25 and Table 5. The results indicate that treatment with ASO B resulted in clearance of hyperphosphorylated Tau.

Table 5

% staining of hyperphosphorylated human Tau

Area	Treatment	%
amygdala	PBS	4.6
	ASO B 50μg	1.4
	ASO B 100μg	2.3
entorhinal cortex	PBS	8.8
	ASO B 50μg	5.4
	ASO B 100μg	6.8

Example 4: In vivo reduction of 4R isoform in the N279K transgenic mouse model with uniformly modified antisense oligonucleotides targeting intron 10 of human Tau

N279K mice express the human Tau mini-gene with FTD mutation (Dawson, H.N. et al., J. Neurosci. 2007. 27: 9155-68). The N279K mutation promotes the inclusion of exon 10 (4R Tau). The effect of uniformly modified antisense oligonucleotides targeting human Tau on the shifting of the 4R isoform to 3R isoform was assessed in this mouse model.

Groups of 4 N279K mice (5 months of age) were administered ASO C (also ISIS 549620) at 60 μg/day for 28 days via an intracerebroventricular pump. A control group of five mice was similarly treated with PBS. Animals were anesthetized with 3% isofluorane and placed in a stereotactic frame. Alzet osmotic pumps were used to continuously deliver the antisense oligonucleotide. Pumps were assembled and implanted, as per the manufacturer's instructions (Durect Corporation). Animals were anesthetized with 3% isofluorane and placed in a stereotactic frame. After sterilizing the surgical site, a one cm midline incision was made over the bregma. Through the use of stereotaxic guides, a cannula was implanted into the right lateral ventricle and secured. A catheter attached to an Alzet osmotic pump was secured to the cannula and the pump was placed subcutaneously in the midcapsular area. Tissues around the cannula region were collected on the 29th day.

RNA analysis

RNA was extracted from the cortex around the cannula, and mRNA expression of the 4R and 3R isoforms of human Tau were analyzed by RT-radioactive PCR. Briefly, 1,000 ng of RNA was reverse transcribed with oligo(dT). The cDNA was then amplified in the presence of α-^{32}P-dCTP. PCR products digested with Hinc II and separated by denaturing PAGE. Exon 10 included and excluded species were

detected by autoradiography and quantitated by PhosphorImage analysis. The signal intensity of each cDNA band was normalized according to its G+C content. The results indicate that treatment with ASO C (also ISIS 549620) resulted in a decrease in 4R Tau by 85% of the total Tau mRNA.

Example 5: Effect of antisense oligonucleotides targeting human Tau on behavior and Tau accumulations in the N279K transgenic mouse model

The effect of gapmers and uniformly modified antisense oligonucleotides on behavioral assays was analyzed in the N279K transgenic model. ASO A, a gamer, which causes reduction of total Tau mRNA, and ASO C (also ISIS 549620), a uniform MOE oligonucleotide, which causes the shifting of the 4R Tau isoform to 3R Tau isoform, were both used in this assay.

Two groups of 6-8 N279K mice each (3 months of age) were administered ASO A or ASO C (also ISIS 549620) at 25 μg/day for 28 days via an intracerebroventricular pump. An N279K transgenic control group of eight mice were similarly treated with PBS. Another control group of eight mice was similarly treated with a scrambled oligonucleotide, ISIS 141923 (CCTTCCCTGAAGGTTCCTCC, 5-10-5 MOE gapmer with no known target (SEQ ID NO: 11)). Another transgenic littermate control group of eight mice were similarly treated with PBS. Animals were anesthetized with 3% isofluorane and placed in a stereotactic frame. Alzet osmotic pumps were used to continuously deliver the antisense oligonucleotide solution. Pumps were assembled and implanted, as per the manufacturer's instructions (Durect Corporation). Animals were anesthetized with 3% isofluorane and placed in a stereotactic frame. After sterilizing the surgical site, a one cm midline incision was made over the bregma. Through the use of stereotaxic guides, a cannula was implanted into the right lateral ventricle and secured. A catheter attached to an Alzet osmotic pump was secured to the cannula and the pump was placed subcutaneously in the midcapsular area. Behavioral studies were performed at 6.5 months of age and mice collected at 7.5 months of age.

Novel object recognition analysis

Novel object recognition is used to determine if the mice can recognize an object that is familiar versus one that is novel (Bevins, R.A. and Besheer, J. Nature Protocols. 2006, 1: 1306-1311). Briefly, the animals are first exposed to two identical objects for 10 minutes; 3 hours later, they are then exposed to this same object (familiar), as well as a new object (novel) for 5 minutes. The mice were videotaped and videos were watched and scored blinded. Non-transgenic mice will spend more time with the novel object compared to the time spent with the familiar object. This is a measure of recall memory in the mice. Human patients affected by a tauopathy, such as Alzheimer's disease, also display deficits in memory recall.

The data are presented in Table 6. The results indicate that mice treated with the uniformly modified antisense oligonucleotide (ASO C also ISIS 549620) spent less time with familiar objects and more time with novel objects compared to the transgenic control.

Table 6

Total Percent Time spent with object over a 5 minute period

	Familiar	Novel
PBS	45	54
ISIS 141923	38	62
ASO A	36	64
ASO C (also ISIS 549620)	25	75
Non-Tg mice	38	62

Nestlet building activity analysis

As a general measure of mouse performance, nestlet building activity was accessed. Mice instinctually build nests when provided with nestlets. Impaired resting performance indicates either an overall cognitive and/or motor deficit. Human tauopathy patients present with general cognition dysfunction and may also present with motor problems. Nestlet building activity (Deacon, R.M. Nat. Protocol. 2006. 1: 1117-9) was initiated by providing the mice with 3.0 grams of pressed cotton material and leaving the mice overnight to assemble a nest. Male nest building activity was assessed. The mice first shred the tightly packed material, then arrange it into a nest. The nesting activity was scored on a five-point scale with '0' being 'no nest' and '5' being a perfect nest surrounding the mouse. Any untorn material left after a bout of nesting was also weighed and provided a further analysis of nesting behavior. A higher untorn nestlet weight signifies a lower quality nest. The nesting scores and untorn nestlet weights are presented in Table 7. Treatment with both the gapmer antisense oligonucleotide (ASO A) and the uniformly modified antisense oligonucleotide (ASO C also ISIS 549620) led to increase in nesting scores and decrease in untorn material as compared to control, indicating improvement of nesting behavior in the mice.

Table 7

Nestlet building activity

	score	Untorn nestlet weight (g)
PBS	1.8	2.2
ISIS 141923	2.3	1.6
ASO A	2.4	1.2
ASO C (also 549620)	4.4	0.8
Non-Tg mice	4.4	0.5

Walking initiation analysis

The N279K mice display age progressive deficits in walking initiation. Walking initiation in mice may be, in part, equated to the parkinsonism component of FTDP-17. Bradykinesia, or slowed initiation of movement, is a common feature in parkinsonism disorders. To measure walking initiation in mice, the mice were placed in the center of a 21cm x 21cm square and time taken for all four paws of the mouse to completely leave the square was measured using a stopwatch. The data are presented in Table 8. The results indicate that mice treated with both the gapmer antisense oligonucleotide (ASO A) and the uniformly modified antisense oligonucleotide (ASO C also ISIS 549620) initiated walking at time intervals faster than the N279K PBS and ISIS 141923 controls.

Table 8

Time to leave square (sec)

	(Sec)
PBS	10.8
ISIS 141923	10.1
ASO A	9.7
ASO C (also ISIS 549620)	7.0
Non-Tg mice	3.4

Hyperphosphorylated Tau analysis

Mice treated with the uniformly modified antisense oligonucleotide (ASO C also ISIS 549620) were euthanized at 7 months of age. The frontal cortex and the dentate nucleus were assessed by immunohistochemistry with the Tau13 antibody, which binds specifically to human Tau protein. The percentage of cells stained with Tau13 somatodendritic accumulations is presented in Table 9 and Figure 26. The results indicate that mice treated with ASO C (also ISIS 549620) had a decrease in the presence of human Tau inclusions compared to the PBS control. The dentate nucleus is, in part, responsible for the initiation of voluntary movements. So a clearance of Tau deposition in the dentate nucleus may be responsible for the improvement in walking initiation in the ASO C (also ISIS 549620) treated mice as compared to the PBS control.

Table 9

Human Tau inclusions (%)

	PBS	ASO C (also ISIS 549620)
Frontal cortex	16	4
Dentate nucleus	29	16

Example 6: Effect of antisense inhibition of Tau on PTZ induced seizures

The effect of antisense inhibition of Tau on treating seizures induced by pentelenetetrazoll (PTZ) was evaluated. The mice were treated with a gapmer antisense oligonucleotide (ASO D) and a uniformly modified antisense oligonucleotide (ISIS 415883). ASO D is a chimeric antisense oligonucleotides 20 nucleosides in length, wherein the central gap segment comprises ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification (i.e., a 5-10-5 MOE gapmer). The internucleoside linkages throughout each gapmer are phosphorothioate linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. Each gapmer is targeted to the human Tau genomic sequence, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NT_010783.14 truncated from nucleotides 2624000 to 2761000), as presented in Table 1. ISIS 141923, an oligonucleotide with no known target (i.e., a "scrambled oligonucleotide") and PBS were used as controls.

Groups of 3 month old C57/BL6 males were administered ASO at 25 μg/day for 28 days via an intracerebroventricular pump. A control group of mice were similarly treated with PBS. The pumps were removed, and the animals were rested for 3 weeks post-pump removal. Seizures were induced using 55 mg/kg of PTZ by intraperitoneal injection. The mice are videotaped for 15 minutes and scored later in a blinded fashion. The final stage reached was recorded.

Seizure severity was rated on a scale of 0-8 with '0' denoting 'no seizures', 1 denoting 'immobility', 2 denoting 'jerk or twitch', 3 denoting 'tail extension', 4 'denoting forelimb clonus', 5 denoting 'generalized seizure', 6 denoting 'running or jumping', 7 denoting 'tonic extension', and '8' denoting 'death'. The results show that both ASO D and ISIS 415883 were capable of protecting mice against PTZ induced seizures as compared to the scrambled oligonucleotide control (Figure 28 and Table 10).

Tau mRNA and protein levels from a 3mm coronal tissue section around the catheter of the mice treated with ASO D were measured and the data is presented in Table 11 and Figure 29. The results show that ASO D significantly reduced both mRNA (Figure 29A) and protein levels (Figure 29B) of Tau. This correlates well with the decrease in seizure severity of the mice.

Tau isoform of mice treated with ISIS 415883 were measured and the data is presented in Table 12. The results show treatment with ISIS 415883 shifted the Tau isoforms from mainly 4R with some 3R Tau to mostly 3R Tau with some 4R Tau. This is demonstrated with a significant decrease in 4R tau levels while maintaining normal total tau levels.

The levels of Tau protein and corresponding seizure severity of the mice treated with ASO D were analyzed in individual mice. As shown in Table 13 and Figure 30A, it was noted that those mice that demonstrated higher levels of Tau were also those to experience the most severe seizures (stage 8 or death), while those mice that demonstrated reduced levels of Tau only had first stage or the least severe seizures of the group. Based on this observation, the total Tau level in each mouse of the study was plotted against the final seizure stage that the mouse reached. There is a significant correlation using Spearman's Correlation ($p<0.0001$) between the total amount of Tau in each mouse and the induced seizure severity, as shown in the linear regression of Figure 30B. This suggests that inhibition of Tau results in protection against seizure activity in a chemically-induced model.

Table 10

Seizure severity (average in each group)

PBS	5.4
ISIS 141923	6.3
ASO D	3.4
ISIS 415883	4.6

Table 11

% inhibition of mRNA and protein levels in mice treated with knockdown oligo (ASO D)

	mRNA	Protein
ISIS 141923	25	8
ASO D	95	70

Table 12

% Tau 4R Tau isoform and total Tau in mice treated with splicing oligo (ISIS 415883)

	4R isoform	Total Tau
ISIS 141923	N/A	25
ISIS 415883	90	26

Table 13

Tau protein levels and seizure severity in mice treated with knockdown oligo (ASO D)

Mouse #	Tau (ng/mg)	Seizure Stage
PBS 1	120	5
PBS 2	142	5
PBS 3	177	6
PBS 4	181	5

PBS 5	276	8
PBS 6	267	8
PBS 7	214	8
PBS 8	148	3
PBS 9	144	5
PBS 10	106	3
PBS 11	135	5
PBS 12	118	5
PBS 13	143	6
PBS 14	159	3
PBS 15	167	5
PBS 16	188	6
PBS 17	120	5
PBS 18	200	5
PBS 19	137	5
PBS 20	261	8
PBS 21	213	5
PBS 22	133	5
PBS 23	109	5
PBS 24	104	5
PBS 25	136	5
PBS 26	126	4
ISIS 141923 1	129	6
ISIS 141923 2	129	6
ISIS 141923 3	120	1
ISIS 141923 4	165	7
ISIS 141923 5	134	6
ISIS 141923 6	166	8
ISIS 141923 7	275	8
ISIS 141923 8	249	8
ISIS 141923 9	123	8
ISIS 141923 10	99	5
ISIS 141923 11	107	8
ISIS 141923 12	193	8
ISIS 141923 13	96	5
ISIS 141923 14	153	8
ISIS 141923 15	144	6
ISIS 141923 16	197	8
ISIS 141923 17	98	3
ISIS 141923 18	88	6
ISIS 141923 19	216	8
ISIS 141923 20	115	7
ISIS 141923 21	121	2

ASO D 1	39	7
ASO D 2	40	6
ASO D 3	38	1
ASO D 4	58	5
ASO D 5	160	8
ASO D 6	87	8
ASO D 7	55	2
ASO D 8	40	4
ASO D 9	38	1
ASO D 10	41	2
ASO D 11	30	2
ASO D 12	33	4
ASO D 13	27	5
ASO D 14	45	1
ASO D 15	38	2
ASO D 16	30	1
ASO D 17	30	1
ASO D 18	37	1
ASO D 19	34	4
ASO D 20	107	8

Example 7: Evaluation of oligonucleotide distribution in P301S mice

The distribution of oligonucleotide in P301S mice after infusion of ASO D was analyzed.

P301S mice at 5 months age were administered ASO D at 50 µg/day for 28 days via an intracerebroventricular pump. A control group of P301S mice were similarly treated with PBS. The pumps were removed, and the animals were rested for 28 days post-pump removal. The mice were euthanized and brain tissue and eyes were collected. Brain sections throughout the whole brain were stained with an antibody against the oligonucleotide (developed in-house) and were counterstained with DAPI.

The results show widespread distribution of ASO D throughout the brain sections of the mice. Sections of 50 µm in thickness were taken throughout the entire left hemisphere and stained with the oligonucleotide antibody. For detection, an Alexa-Fluor-546 anti-rabbit secondary antibody was used and a DAPI counter-stain was applied. The presence of a red or pink fluorescence intensity signified the presence of the oligonucleotide. These results demonstrate that ASO D is widely distributed throughout the entire brain following infusion into the right lateral ventricle.

The eyes of the mice were post-fixed, embedded in paraffin, sliced at 6 µm thickness, and mounted onto slides. The sections were stained with an antibody against the oligonucleotide and sections were counterstained with DAPI. The results show significant presence of ASO D in the retinal layers of the eye as well as in the outer layer of the lens in the eye sections of mice treated with ASO D. The same Alexa-Fluor-546

anti-rabbit secondary antibody was used to detect the oligonucleotide antibody. Due to the high level of autofluorescence in the retina because of the retinal pigment epithelium, the green FITC channel was applied to show exactly where the autofluorescence was coming from. Previous studies have shown the presence of hyperphosphorylated Tau in the eyes in patients with Alzheimer's disease and glaucoma (Frost, S. Digital Teleretinal Screen. 2012, 91-100; Ho, W. L. Et al., Molecular Vision, 2012, 18: 2700-2710; Gupta, N. et al., Can. J. Ophthalmol. 2008, 43: 53-60). Hence, this result suggests that an ASO tau treatment can in fact reach the retinal cell layers and may potentially decrease aberrant tau species that may be impeding vision or used as a clinical marker for measuring reduction of tau expression in the CNS.

Example 8: Inhibitory effect of uniform 2'-MOE modified oligonucleotides on human Tau exon 10

Several modified oligonucleotides were evaluated for their effect on inhibiting human Tau exon 10 expression *in vitro*. ISIS 617782 and 617781 were included in the study for comparison.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is targeted in the human gene sequence. Each modified oligonucleotide listed in the table below is targeted to the human Tau genomic sequence, designated herein as SEQ ID NO: 1 (GENBANK Accession No NT_010783.15 truncated from nucleotides 9240000 to 9381000).

ISIS 617782 is 21 nucleosides in length, wherein each nucleoside has a 2'-OCH_3 modification and is denoted as the subscript "m". Each internucleoside linkage throughout the modified oligonucleotide are phosphorothioate internucleoside linkages (P=S).

ISIS 617781 is 18 nucleosides in length, wherein each nucleoside has a 2'-OCH_3 modification and is denoted as the subscript "m". Each internucleoside linkage throughout the modified oligonucleotide are phosphorothioate internucleoside linkages (P=S).

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.

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 of 617782 and human Tau primer probe set 10_11 was used for ISIS 617781 and 415883.

Human Tau primer probe set 9_10 R5 (forward sequence CACTGAGAACCTGAAGCACC, designated herein as SEQ ID NO: 24; reverse sequence GGACGTTGCTAAGATCCAGCT, designated herein as SEQ ID NO: 25; probe sequence TTAATTATCTGCACCTTCCCGCCTCC, designated herein as

SEQ ID NO: 26). Human Tau exon 10 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®.

Human primer probe set 10_11 (forward sequence GGATAATATCAAACACGTCCCG, designated herein as SEQ ID NO: 27; reverse sequence TGCCTAATGAGCCACACTTG, designated herein as SEQ ID NO: 28; probe sequence GTCTACAAACCAGTTGACCTGAGC, designated herein as SEQ ID NO: 29).

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 14

Inhibitory effect of uniform 2'-MOE modified oligonucleotides on human Tau exon 10 expression

ISIS NO	Sequence	0.1 nM	0.3 nM	1.0 nM	3.0 nM	10 nM	30 nM	IC_{50} (nM)	SEQ ID NO: X Start Site	SEQ ID NO: X Stop Site	SEQ ID NO
617782	$U_mG_mA_mA_mG_mG_mU_mA_mC_mU_m$ $C_mA_mC_mA_mC_mU_mG_mC_mC_mG_mC_m$	100	89	80	55	34	16	4.33	121914	121934	30
617781	$U_mA_mU_mC_mU_mG_mC_mA_mC_mC_m$ $U_mU_mU_mG_mG_mU_mA_mG_m$	100	95	79	82	65	41	20.25	121820	121837	31
415883	TCTTATTAATTATCTGCACC	77	63	41	28	16	11	0.65	121828	121847	12

Example 9: Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10

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*. 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.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is targeted in the human gene sequence. Each modified oligonucleotide listed in the tables below is targeted to the human Tau genomic sequence, designated herein as SEQ ID NO: 32 (GENBANK Accession No NT_010783.15 truncated from nucleotides 9240000 to 9381000).

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 primer probe set 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."

Human primer probe set 10_11 (forward sequence GGATAATATCAAACACGTCCCG, designated herein as SEQ ID NO: 27; reverse sequence TGCCTAATGAGCCACACTTG, designated herein as SEQ ID NO: 28; probe sequence GTCTACAAACCAGTTGACCTGAGC, designated herein as SEQ ID NO: 29) .

Table 15

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.
549595	GGACGTGTGAAGGTACTC	20	121924	121941	0	15
549617	GCCCAAGAAGGATTTATT	31.8	122012	122029	0	16
549619	TCCTGAGAGCCCAAGAAG	41.7	122020	122037	0	17
549620	CAGATCCTGAGAGCCCAA	35.6	122024	122041	0	18

Example 10: Effects of uniform 2'-MOE modified oligonucleotides on human Tau exon 10

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*. The modified oligonucleotides 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.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is targeted in the human gene sequence. Each modified oligonucleotide listed in the tables below is targeted to the human Tau genomic sequence, designated herein as SEQ ID NO: 32 (GENBANK Accession No NT_010783.15 truncated from nucleotides 9240000 to 9381000).

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 9_10 R5 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."

Human Tau primer probe set 9_10 R5 (forward sequence CACTGAGAACCTGAAGCACC, designated herein as SEQ ID NO: 24; reverse sequence GGACGTTGCTAAGATCCAGCT, designated herein as SEQ ID NO:25; probe sequence TTAATTATCTGCACCTTCCCGCCTCC, designated herein as SEQ ID NO: 26).

Table 16

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
549595	GGACGTGTGAAGGTACTC	26	121924	121941	15
549619	TCCTGAGAGCCCAAGAAG	42	122020	122037	17
549620	CAGATCCTGAGAGCCCAA	35	122024	122041	18

CLAIMS

1. An antisense oligonucleotide comprising 20 linked modified nucleosides and having the sequence of SEQ ID NO: 12, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

2. An antisense oligonucleotide comprising 20 linked modified nucleosides and having the sequence of SEQ ID NO: 13, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

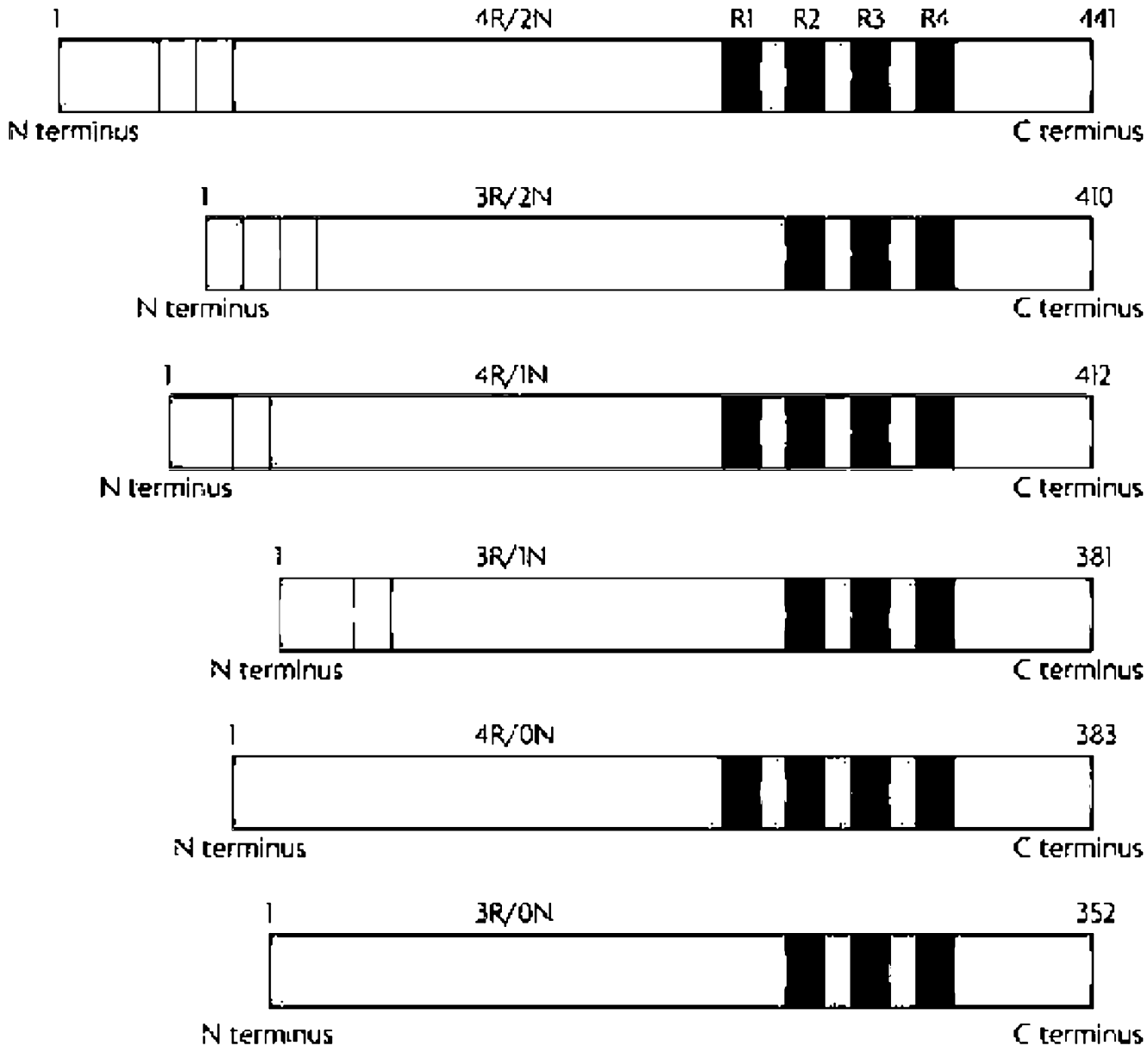
3. An antisense oligonucleotide comprising 20 linked modified nucleosides and having the sequence of SEQ ID NO: 14, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

4. An antisense oligonucleotide comprising 18 linked modified nucleosides and having the sequence of SEQ ID NO: 15, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

5. An antisense oligonucleotide comprising 18 linked modified nucleosides and having the sequence of SEQ ID NO: 16, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

6. An antisense oligonucleotide comprising 18 linked modified nucleosides and having the sequence of SEQ ID NO: 17, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.

7. An antisense oligonucleotide comprising 18 linked modified nucleosides and having the sequence of SEQ ID NO: 18, wherein each internucleoside linkage is a phosphorothioate linkage and each modified nucleoside comprises a 2'-O-methoxyethyl group.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4R/2N
R1
R2
R3
R4
441
N terminus
C terminus
1
3R/2N
410
N terminus
C terminus
1
4R/1N
412
N terminus
C terminus
1
3R/1N
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N terminus
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1
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383
N terminus
C terminus
1
3R/0N
352
N terminus
C terminus

FIG. 1

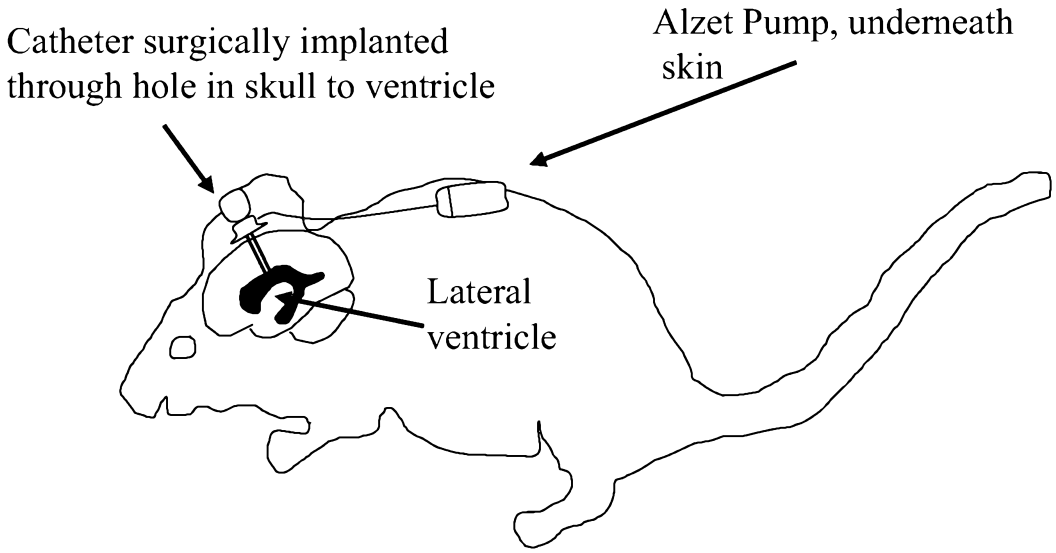

Catheter surgically implanted
through hole in skull to ventricle
Alzet Pump, underneath
skin
Lateral
ventricle

FIG. 2

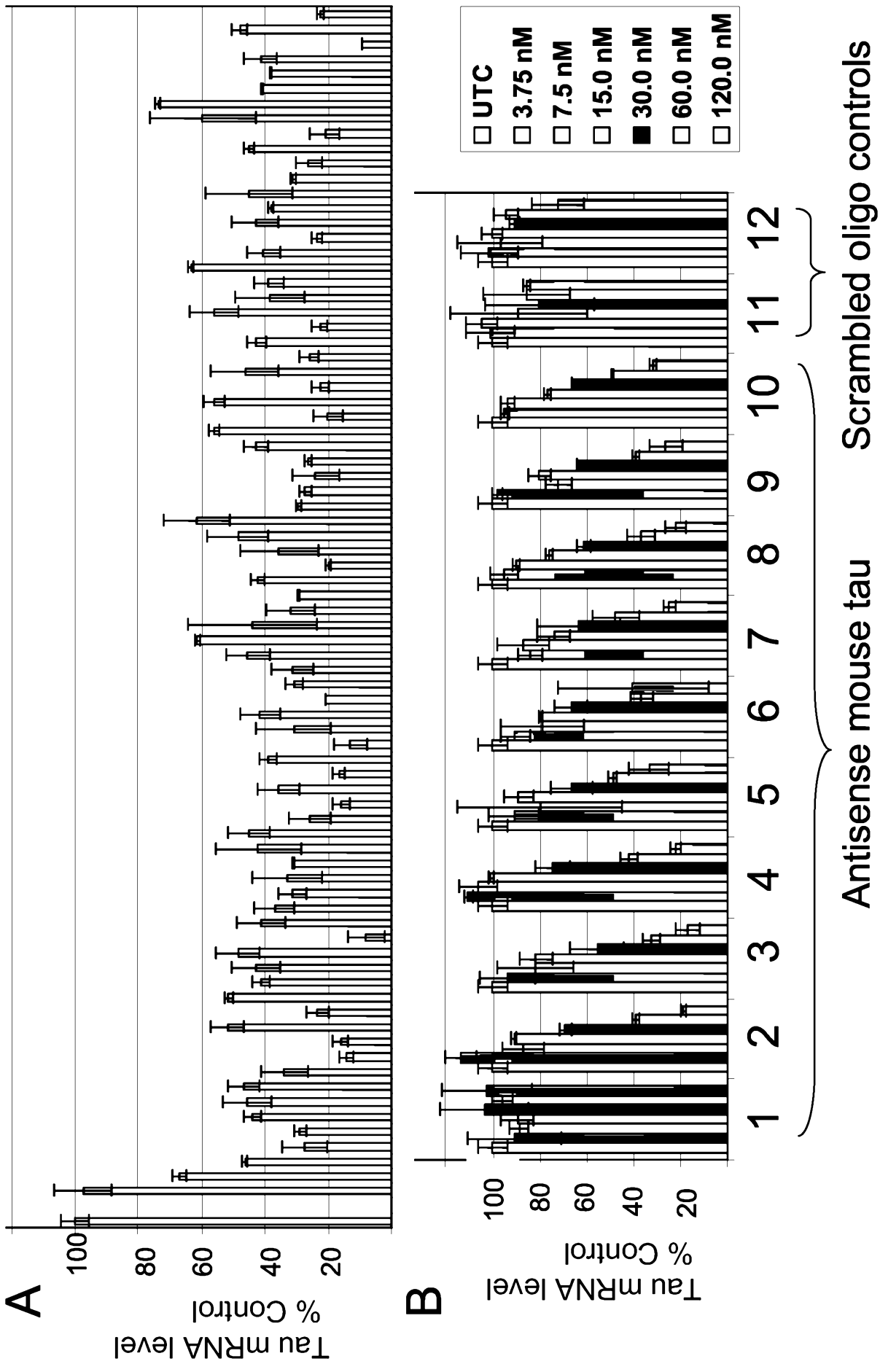

A
Tau mRNA level
% Control
100
80
60
40
20
B
Tau mRNA level
% Control
100
80
60
40
20
UTC
3.75 nM
7.5 nM
15.0 nM
30.0 nM
60.0 nM
120.0 nM
1
2
3
4
5
6
7
8
9
10
11
12
Antisense mouse tau
Scrambled oligo controls

FIG. 3

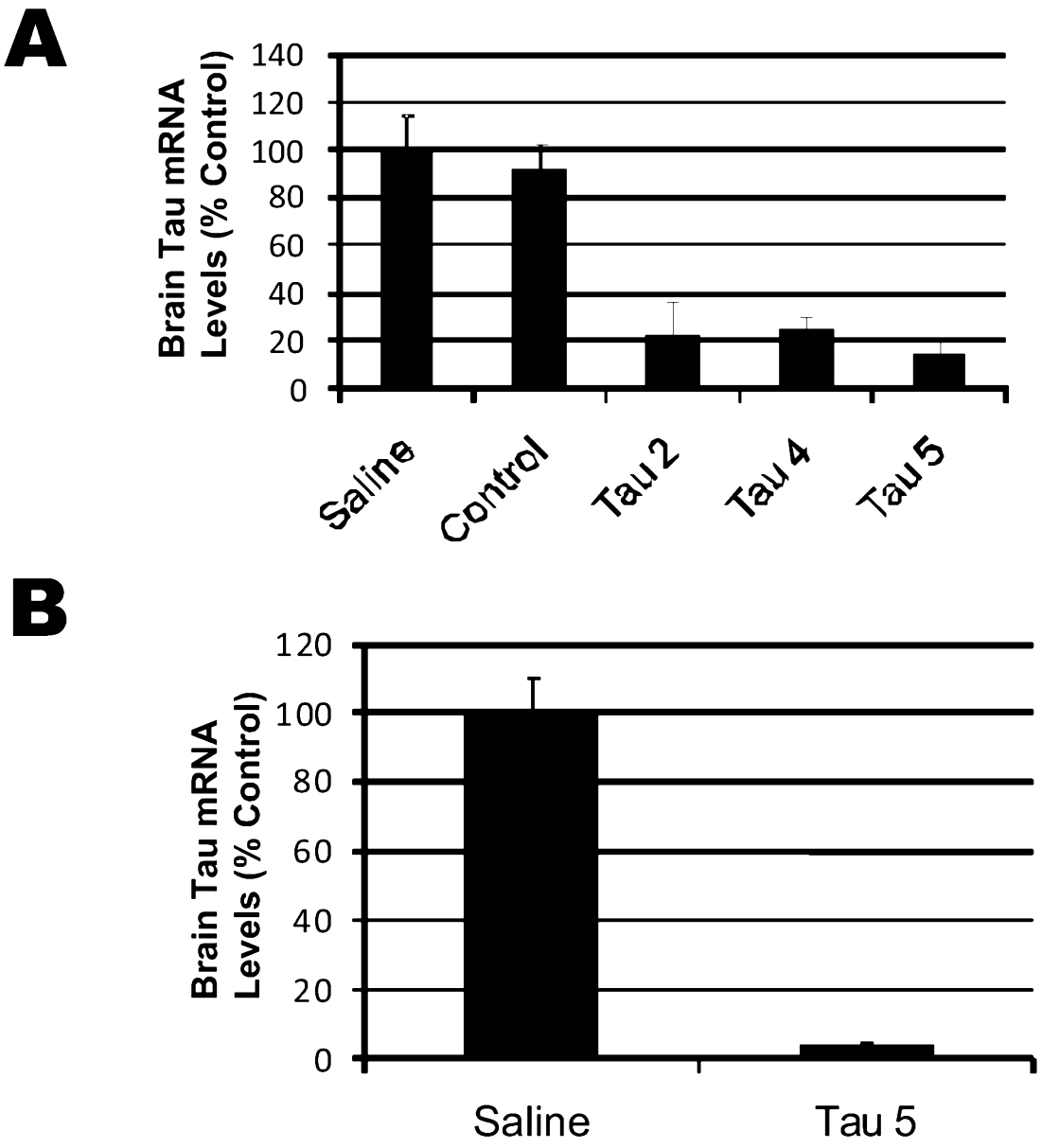

A
Brain Tau mRNA Levels (% Control)
140
120
100
80
60
40
20
0
Saline
Control
Tau 2
Tau 4
Tau 5
B
Brain Tau mRNA Levels (% Control)
120
100
80
60
40
20
0
Saline
Tau 5
C
Saline 1
Saline 2
Saline 3
Tau 5.1
Tau 5.2
Tau 5.3
Tau 5.4
Tau
GAPDH

FIG. 4

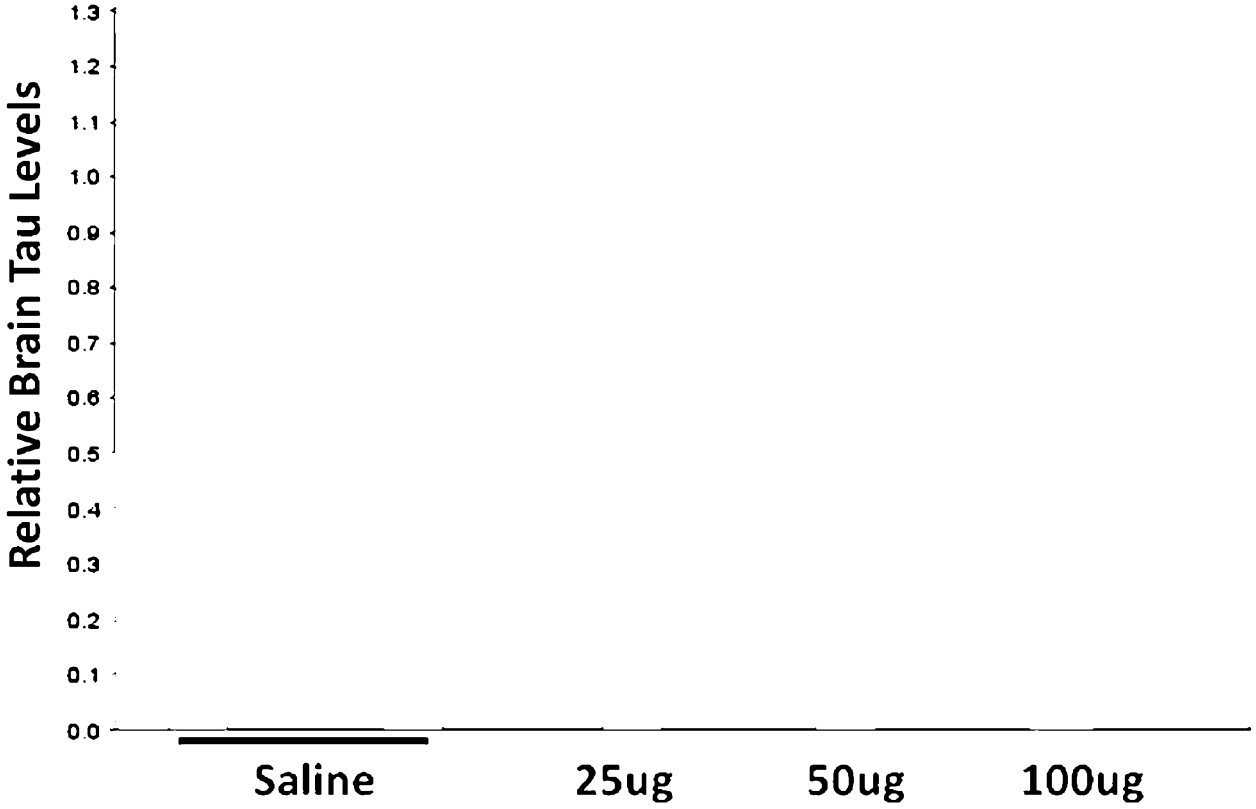

Relative Brain Tau Levels
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Saline
25ug
50ug
100ug

FIG. 5

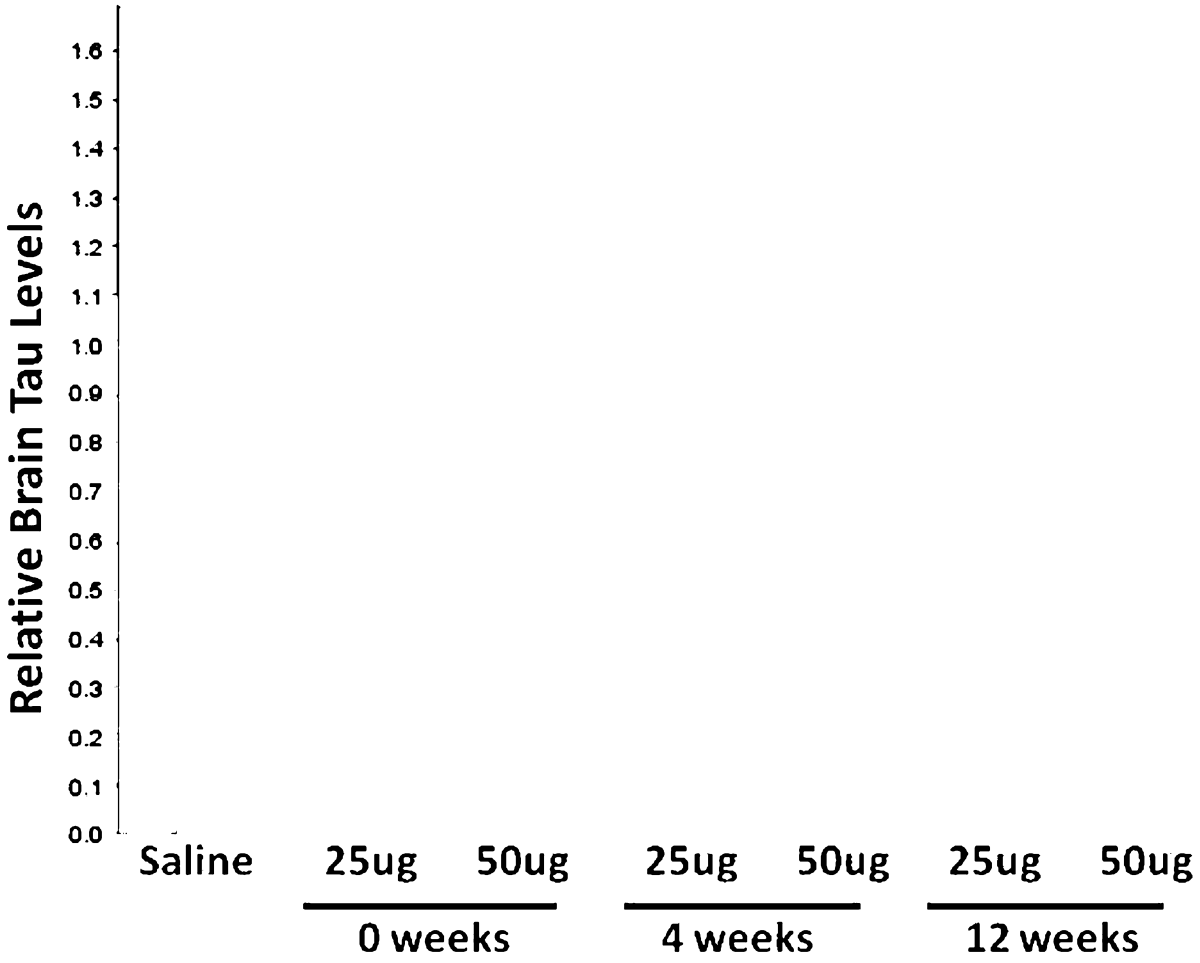

Relative Brain Tau Levels
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Saline
25ug
50ug
25ug
50ug
25ug
50ug
0 weeks
4 weeks
12 weeks

FIG. 6

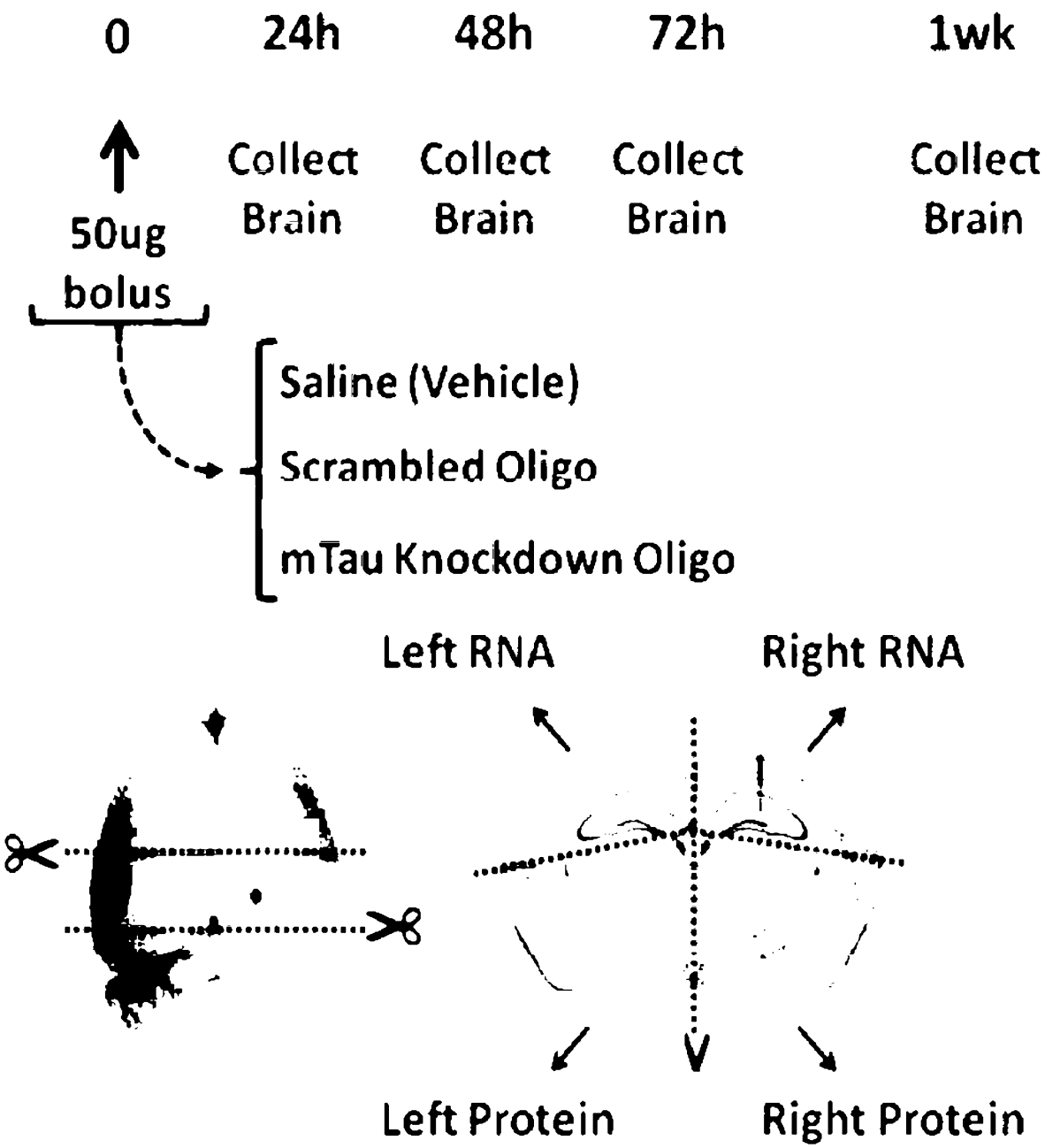

0
24h
48h
72h
1wk
Collect Brain
Collect Brain
Collect Brain
Collect Brain
50ug bolus
Saline (Vehicle)
Scrambled Oligo
mTau Knockdown Oligo
Left RNA
Right RNA
Left Protein
Right Protein

FIG. 7A

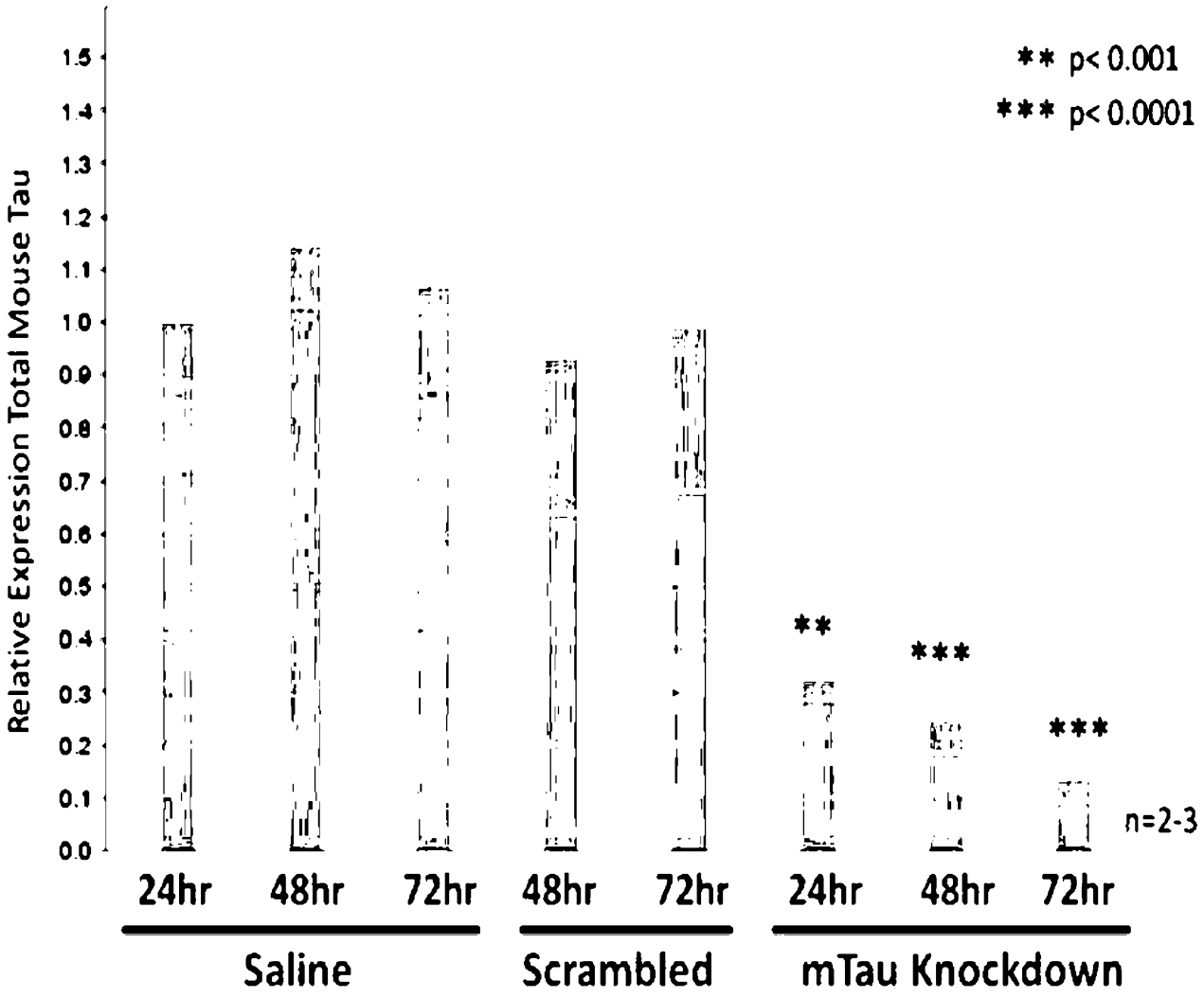

** p< 0.001
*** p< 0.0001
Relative Expression Total Mouse Tau
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
**
***
***
n=2-3
24hr
48hr
72hr
48hr
72hr
24hr
48hr
72hr
Saline
Scrambled
mTau Knockdown

FIG. 7B

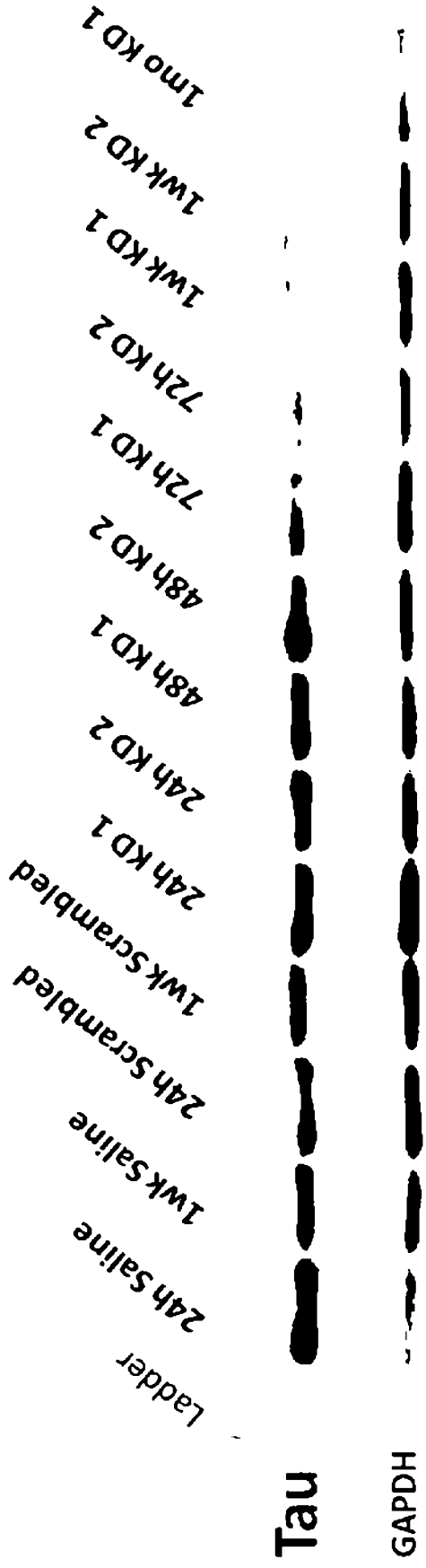

Tau
GAPDH
Ladder
24h Saline
1wk Saline
24h Scrambled
1wk Scrambled
24h KD 1
24h KD 2
48h KD 1
48h KD 2
72h KD 1
72h KD 2
1wk KD 1
1wk KD 2
1mo KD 1

FIG. 7C

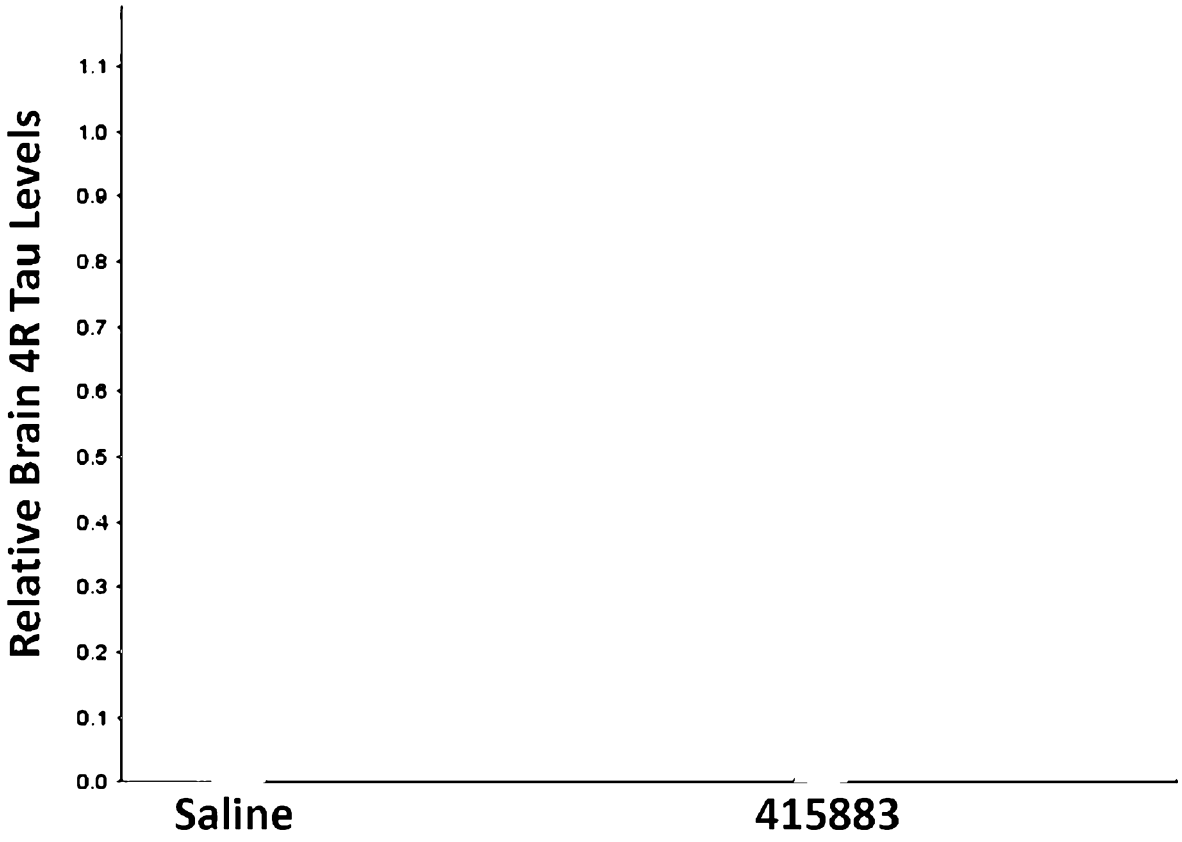

Relative Brain 4R Tau Levels
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Saline
415883

FIG. 8

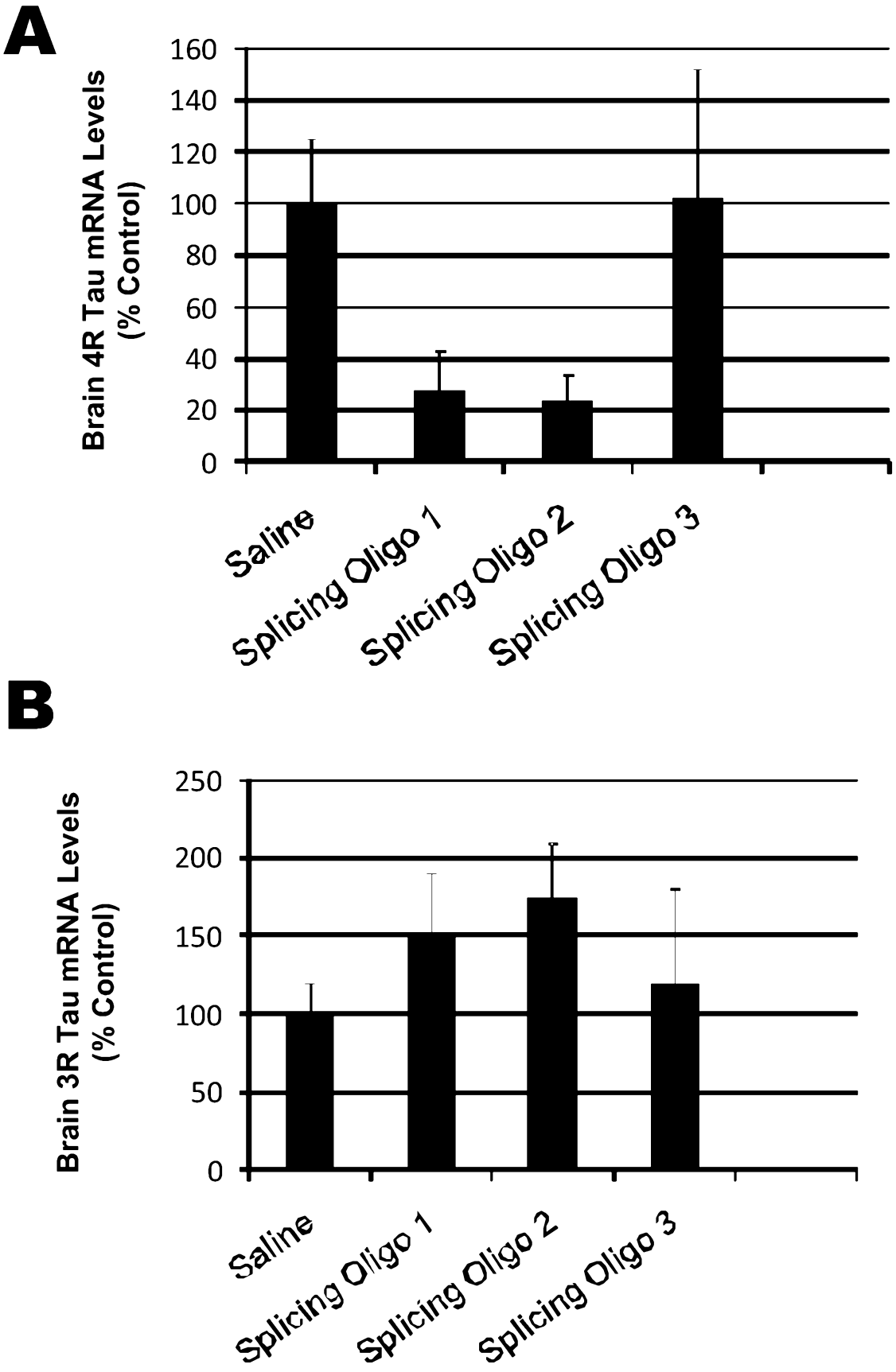

A
Brain 4R Tau mRNA Levels
(% Control)
160
140
120
100
80
60
40
20
0
Saline
Splicing Oligo 1
Splicing Oligo 2
Splicing Oligo 3
B
Brain 3R Tau mRNA Levels
(% Control)
250
200
150
100
50
0
Saline
Splicing Oligo 1
Splicing Oligo 2
Splicing Oligo 3

FIG. 9

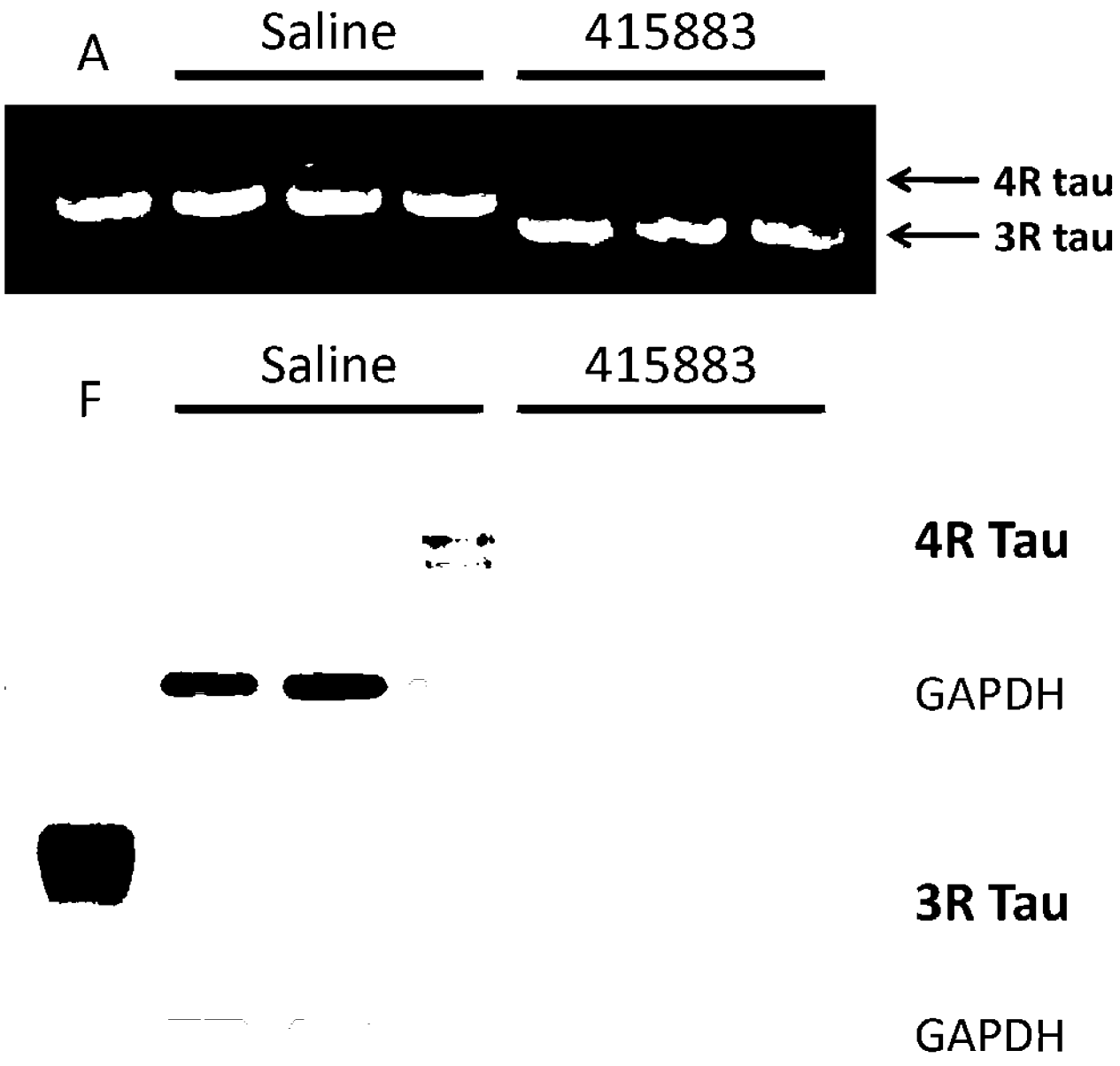

A
Saline
415883
4R tau
3R tau
F
Saline
415883
4R Tau
GAPDH
3R Tau
GAPDH

FIG. 10

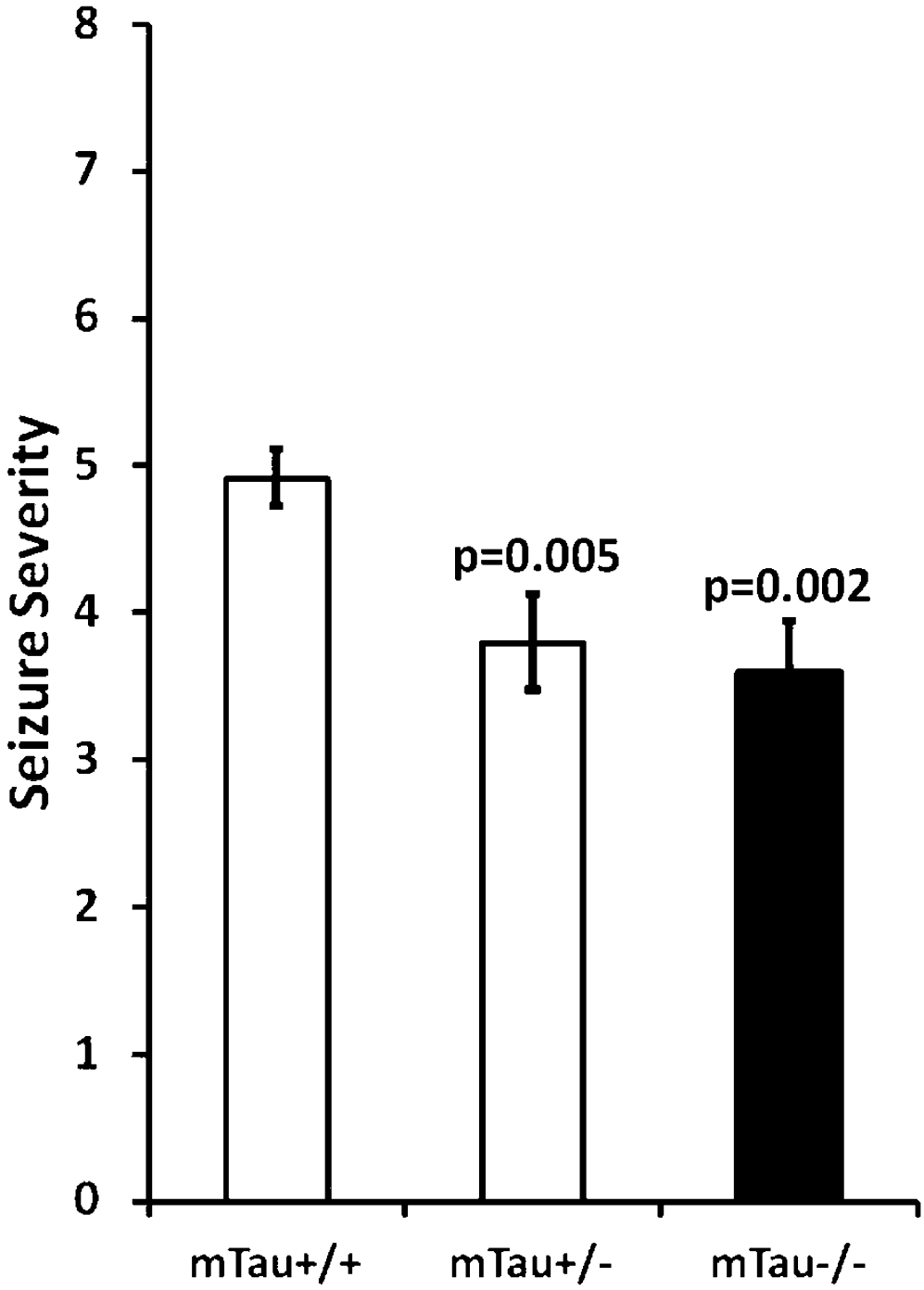


FIG. 11A

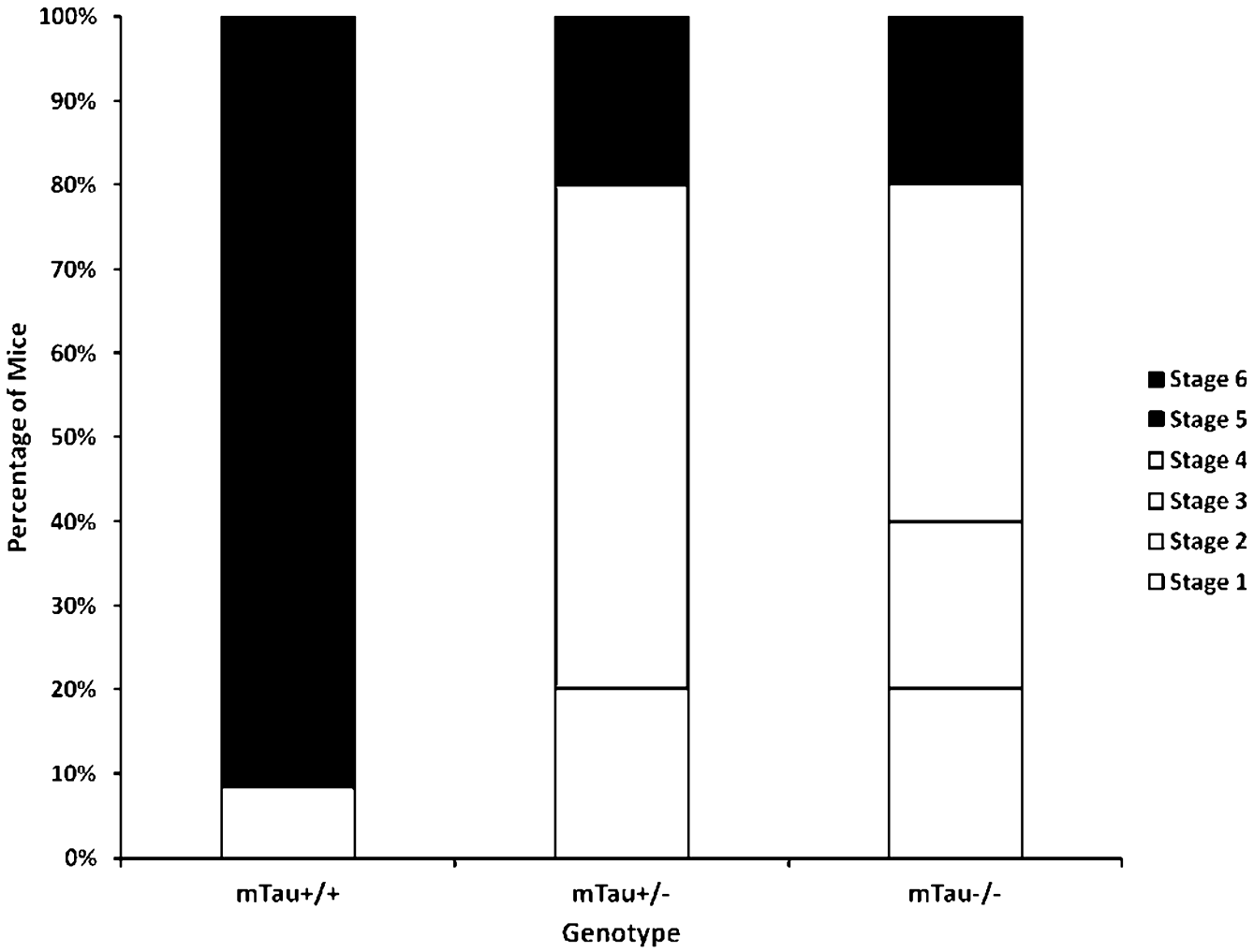

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of Mice
mTau+/+
mTau+/-
mTau-/-
Genotype
Stage 6
Stage 5
Stage 4
Stage 3
Stage 2
Stage 1

FIG. 11B

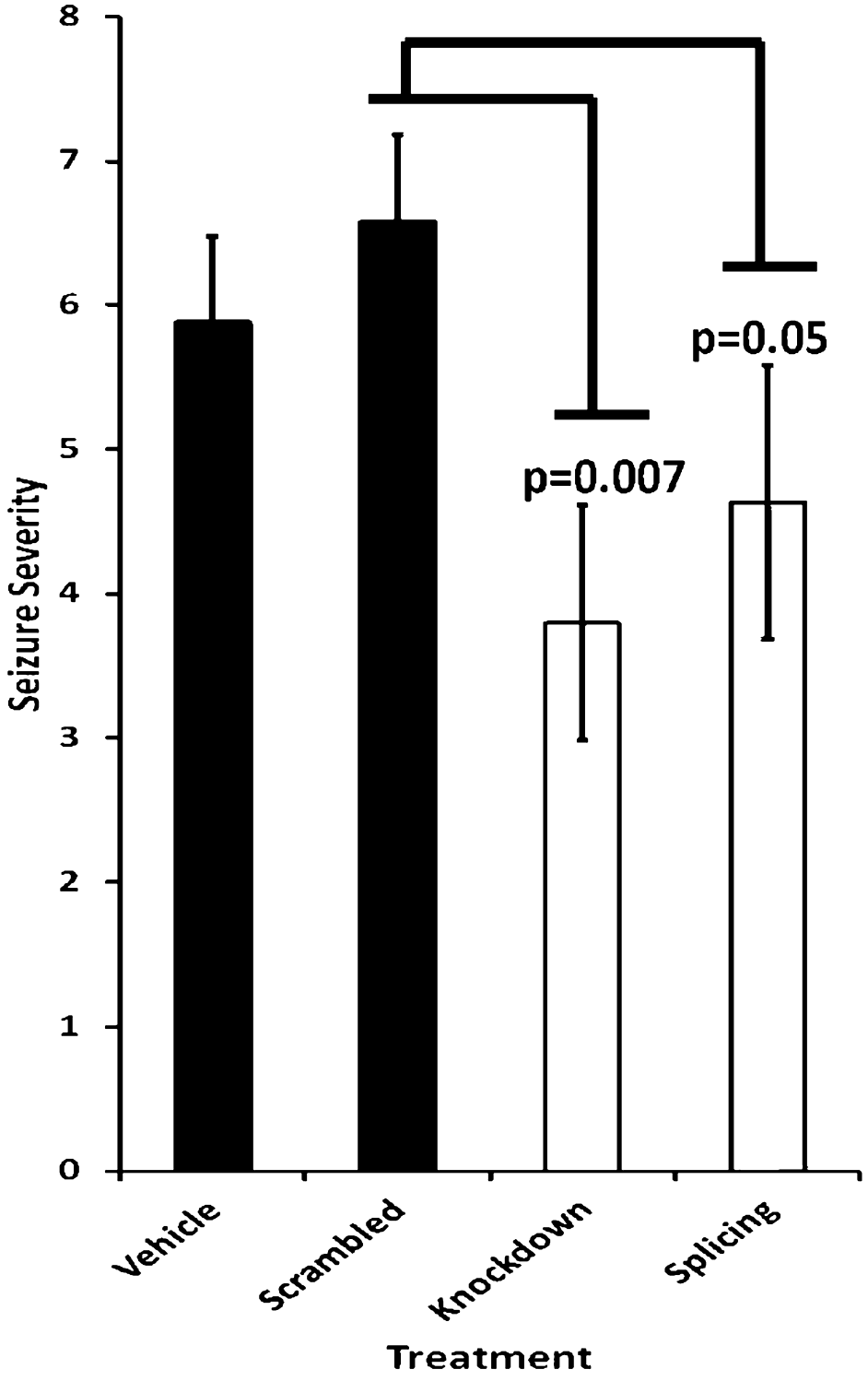

8
7
6
5
4
3
2
1
0
Seizure Severity
p=0.007
p=0.05
Vehicle
Scrambled
Knockdown
Splicing
Treatment

FIG.12A

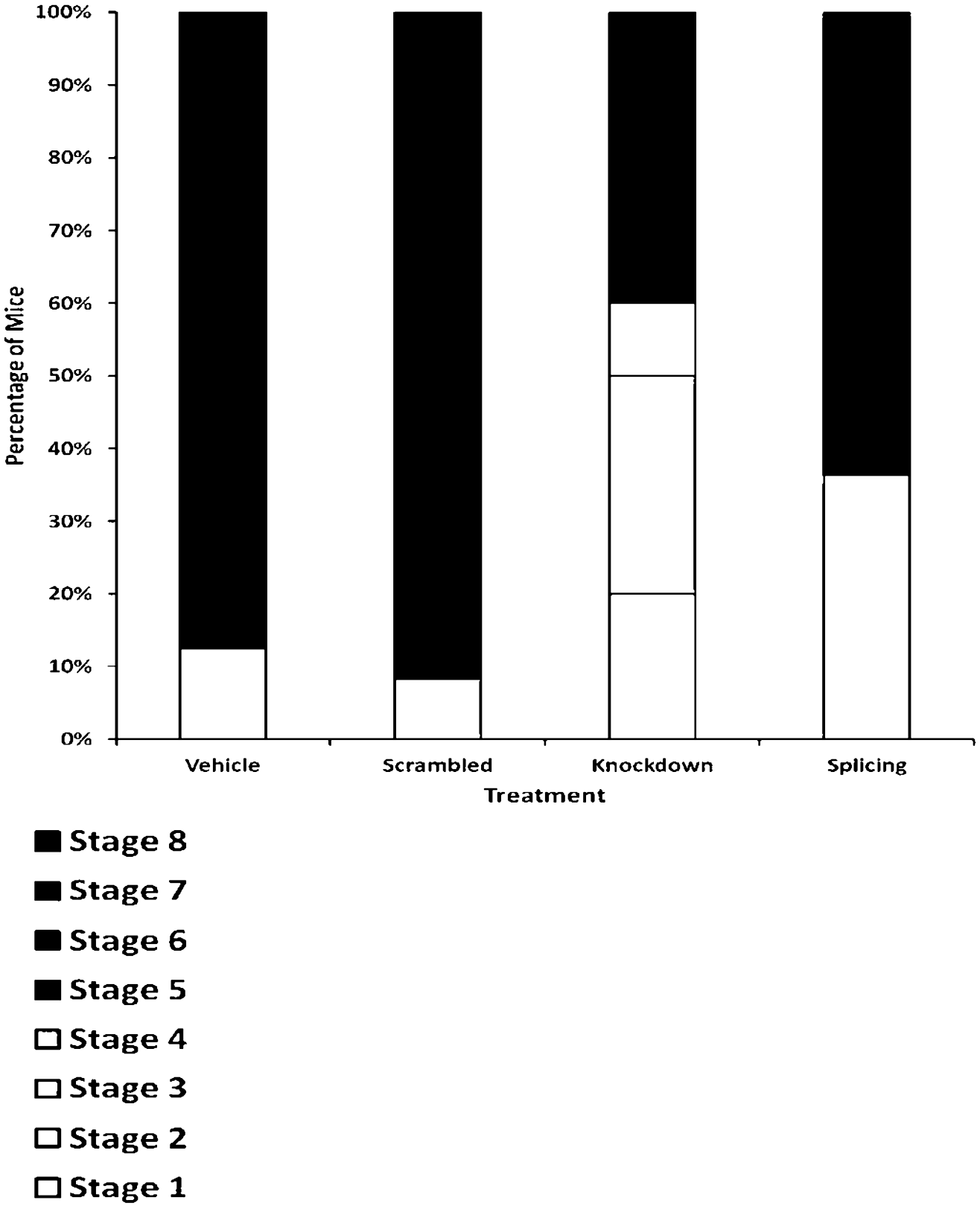

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of Mice
Vehicle
Scrambled
Knockdown
Splicing
Treatment
Stage 8
Stage 7
Stage 6
Stage 5
Stage 4
Stage 3
Stage 2
Stage 1

FIG. 12B

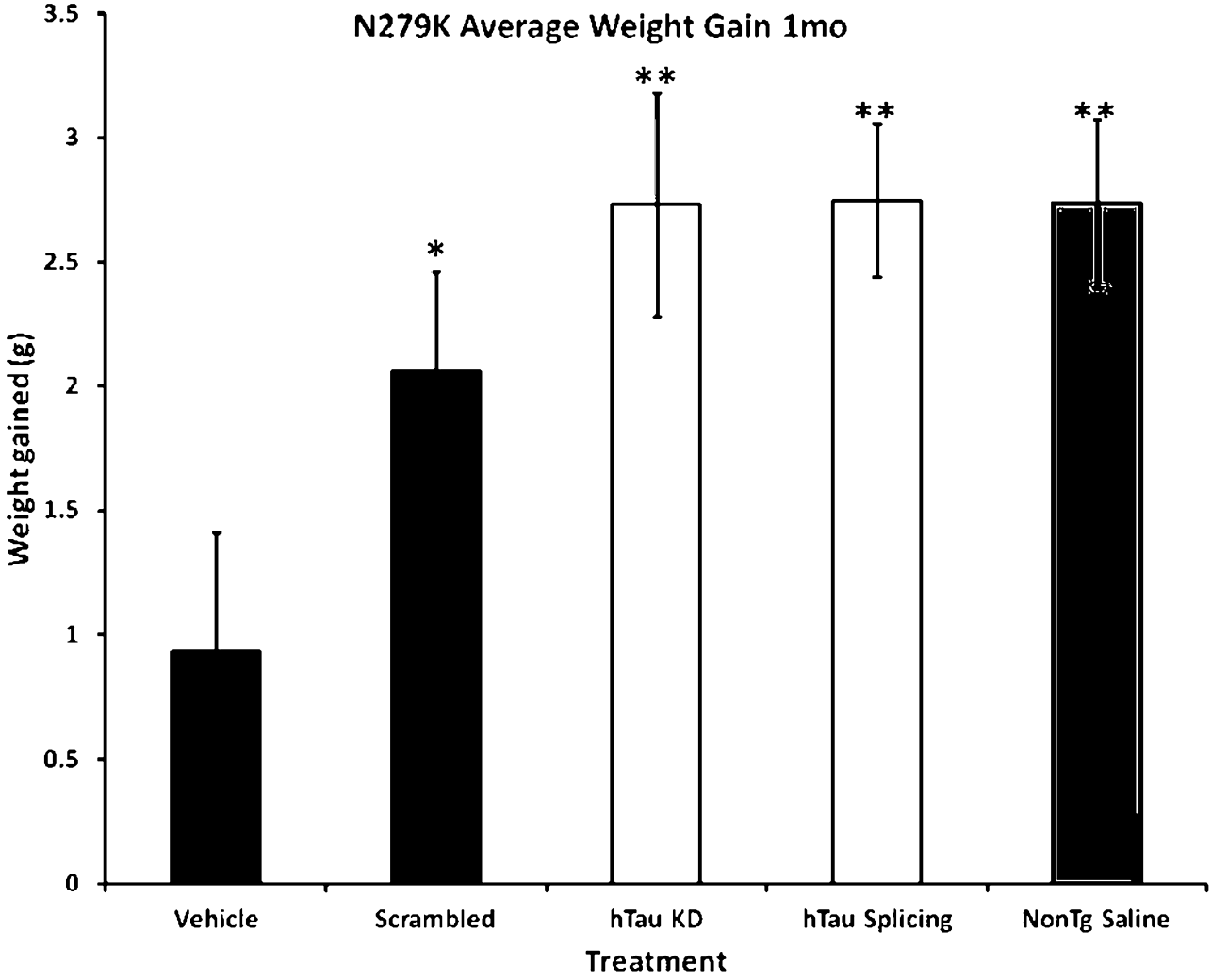

N279K Average Weight Gain 1mo
Weight gained (g)
3.5
3
2.5
2
1.5
1
0.5
0
*
**
**
**
Vehicle
Scrambled
hTau KD
hTau Splicing
NonTg Saline
Treatment

FIG. 13

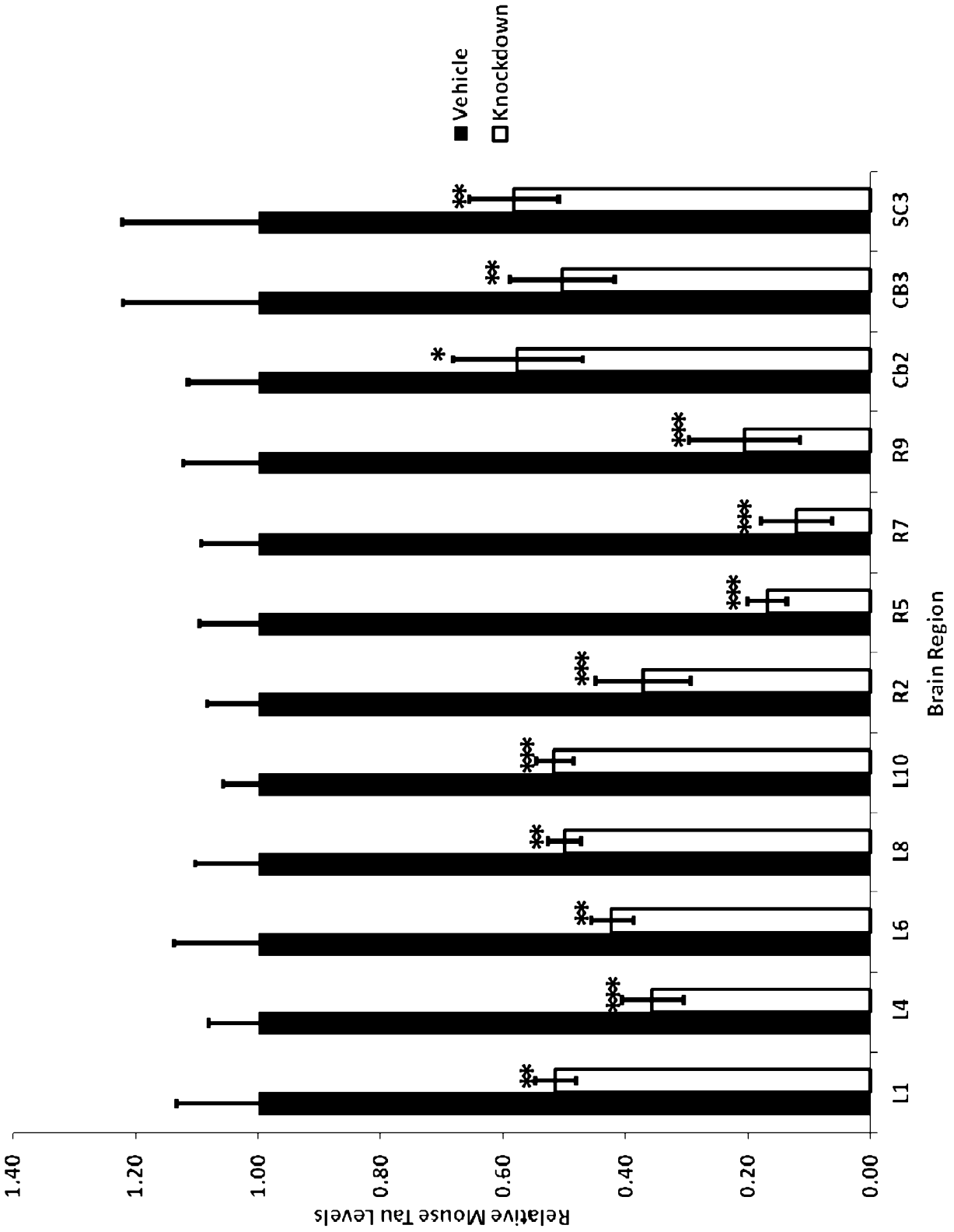

Vehicle
Knockdown
Relative Mouse Tau Levels
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
L1
L4
L6
L8
L10
R2
R5
R7
R9
Cb2
CB3
SC3
Brain Region

FIG. 14

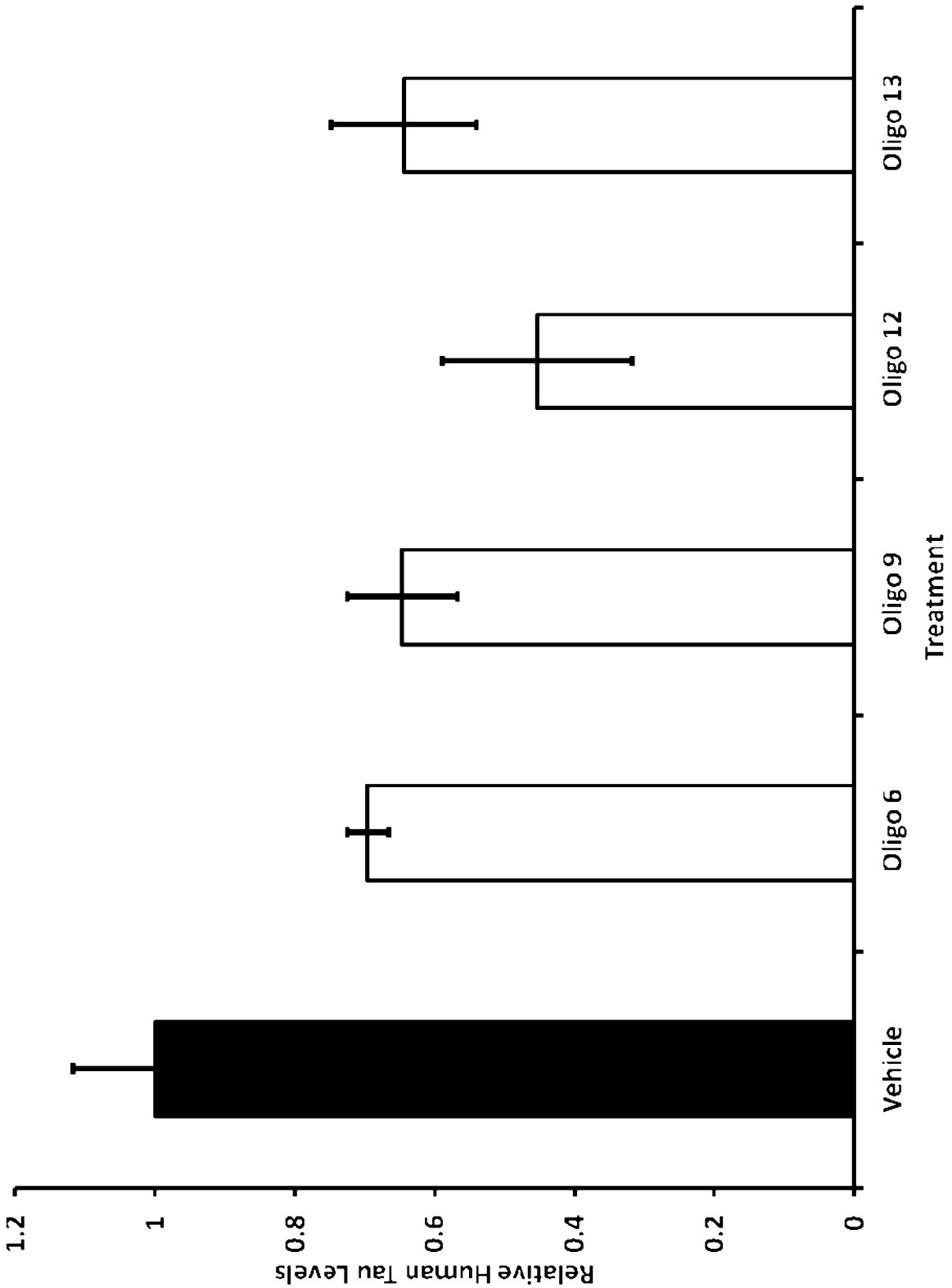

Relative Human Tau Levels
0
0.2
0.4
0.6
0.8
1
1.2
Vehicle
Oligo 6
Oligo 9
Oligo 12
Oligo 13
Treatment

FIG. 15

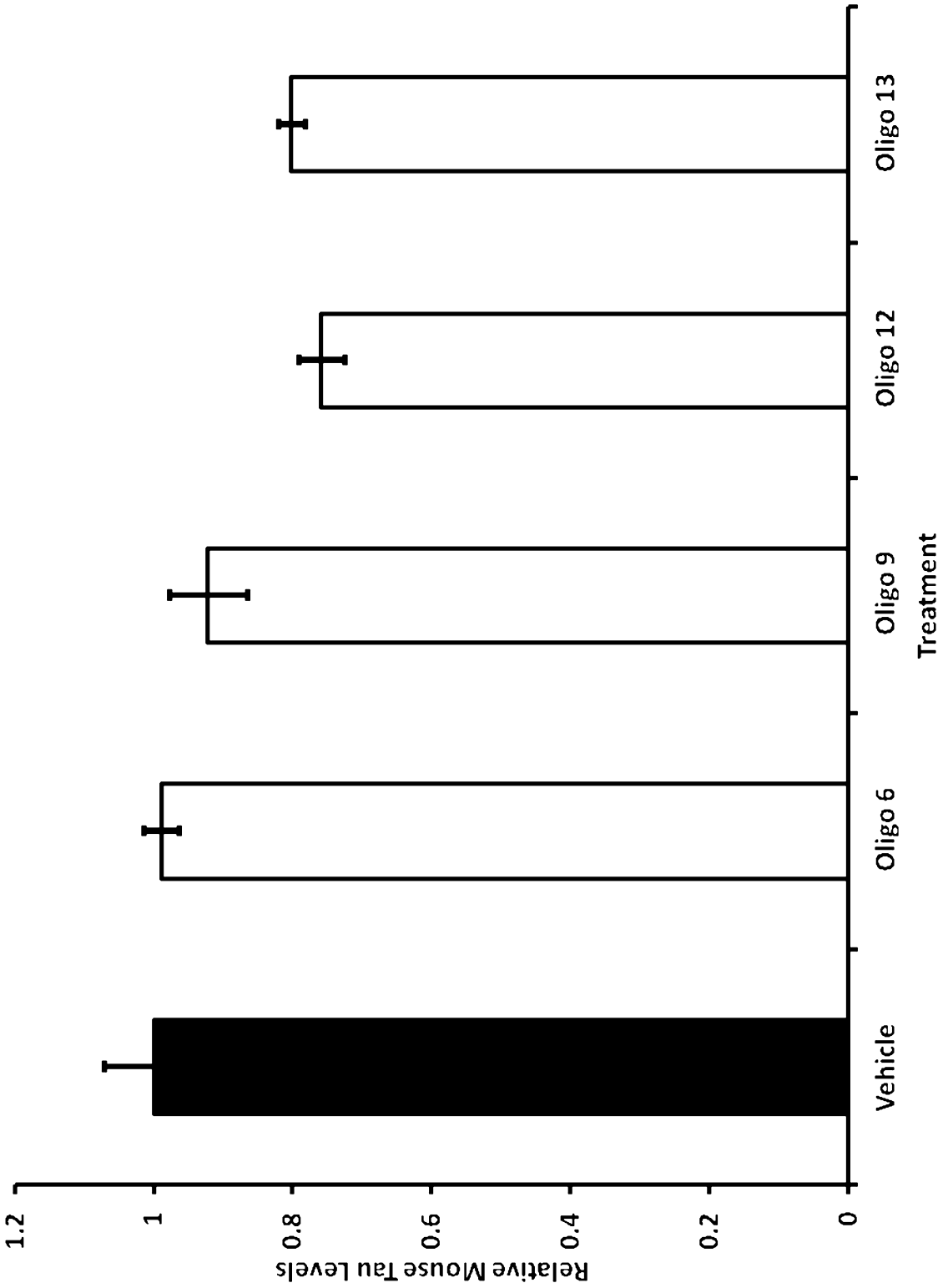

Relative Mouse Tau Levels
0
0.2
0.4
0.6
0.8
1
1.2
Vehicle
Oligo 6
Oligo 9
Oligo 12
Oligo 13
Treatment

FIG. 16

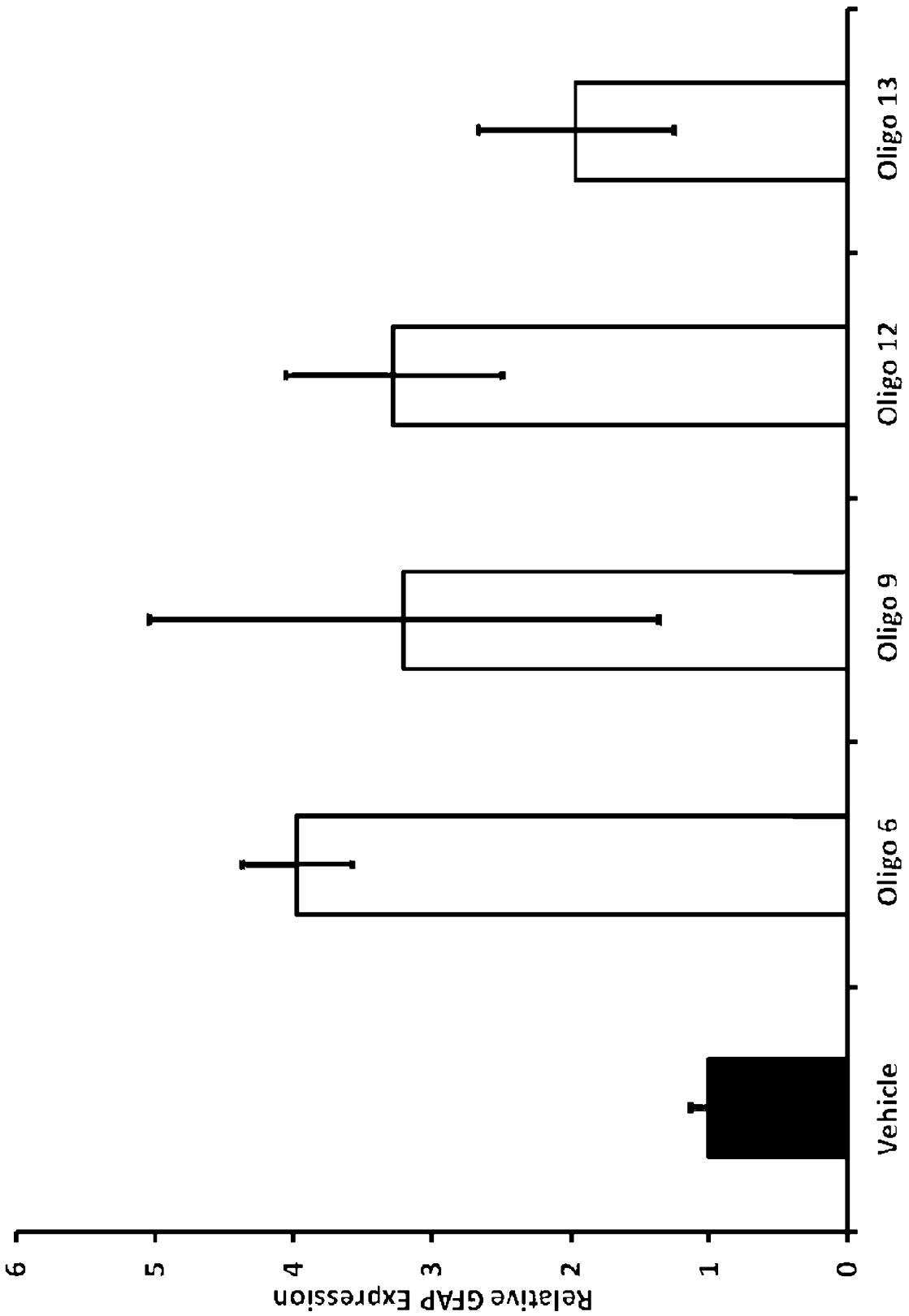

Relative GFAP Expression
0
1
2
3
4
5
6
Vehicle
Oligo 6
Oligo 9
Oligo 12
Oligo 13
Treatment

FIG. 17

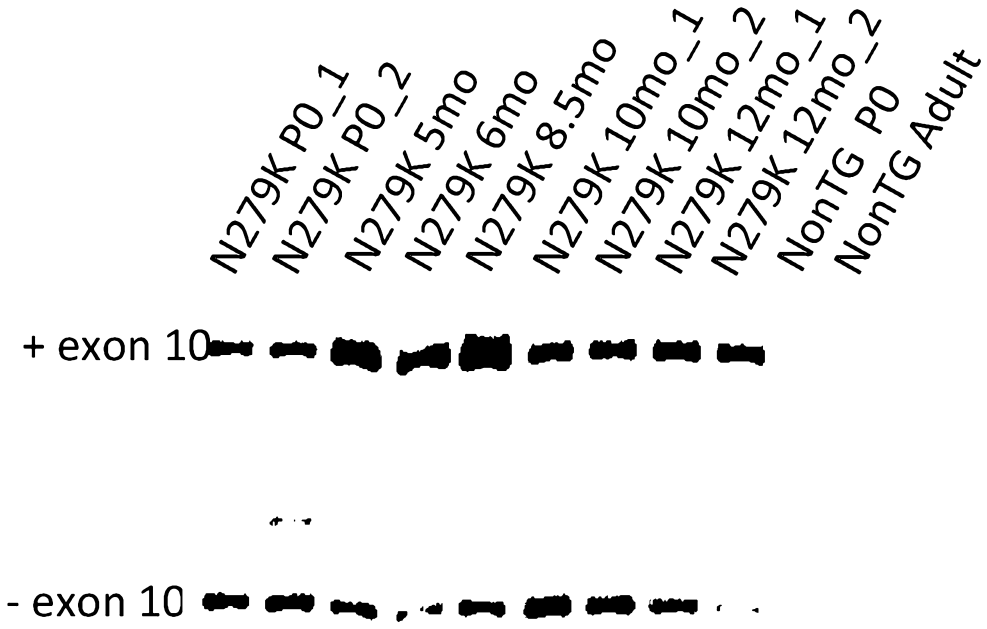

N279K P0_1
N279K P0_2
N279K 5mo
N279K 6mo
N279K 8.5mo
N279K 10mo_1
N279K 10mo_2
N279K 12mo_1
N279K 12mo_2
NonTG P0
NonTG Adult
+ exon 10
- exon 10

FIG. 18A

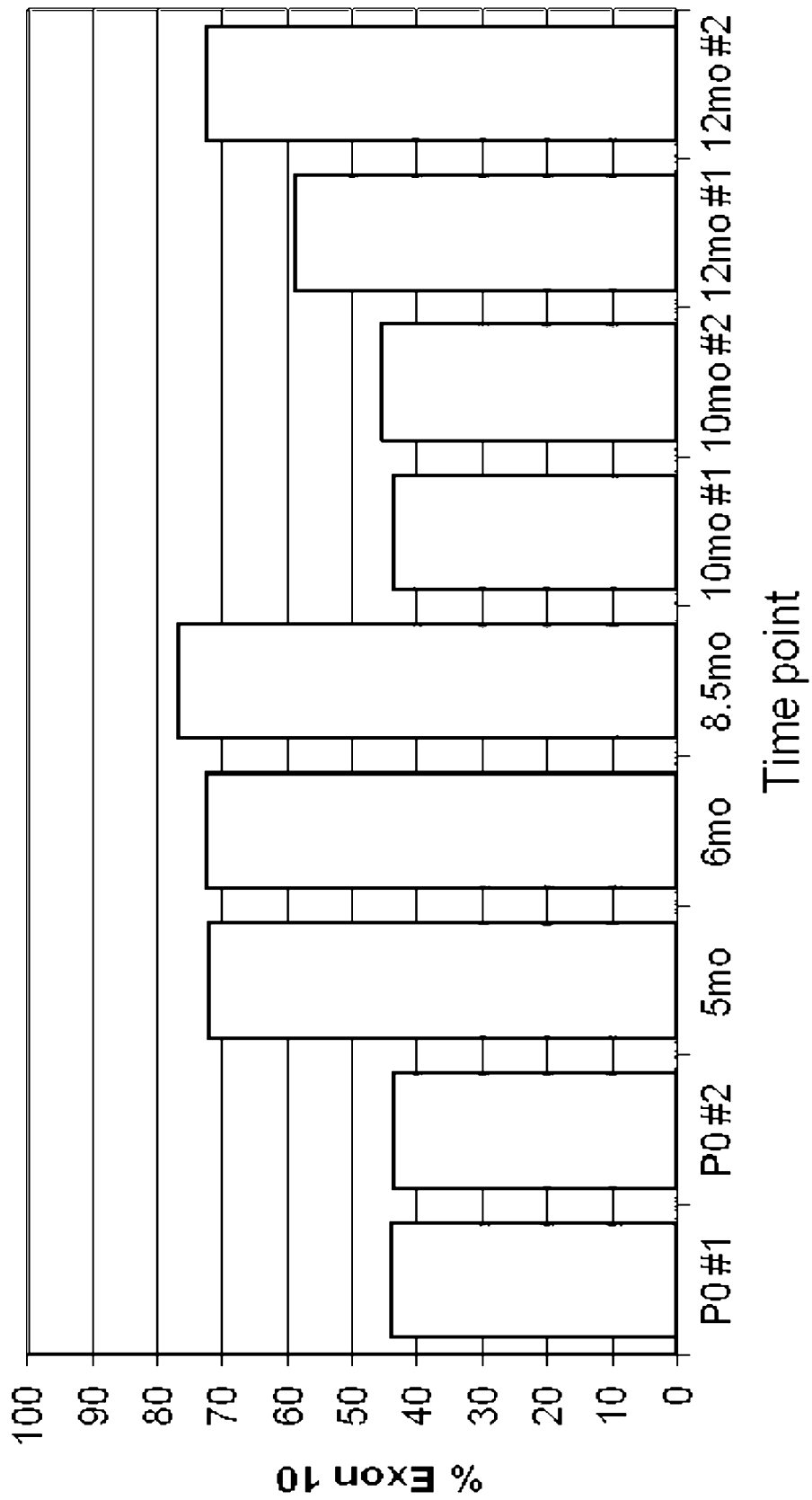

% Exon 10
100
90
80
70
60
50
40
30
20
10
0
P0 #1
P0 #2
5mo
6mo
8.5mo
10mo #1
10mo #2
12mo #1
12mo #2
Time point

FIG. 18B

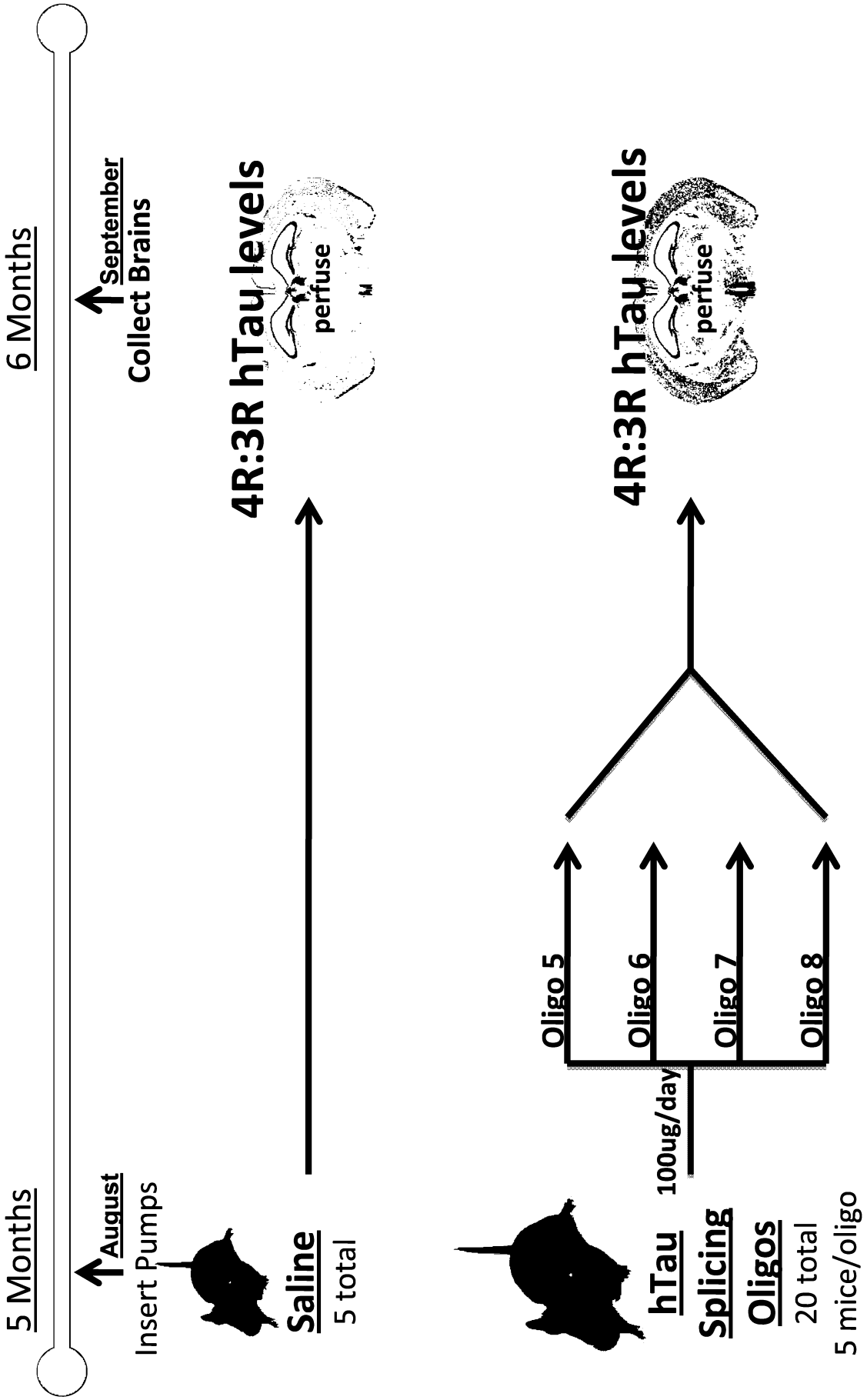

5 Months
6 Months
August
Insert Pumps
September
Collect Brains
Saline
5 total
4R:3R hTau levels
perfuse
hTau
Splicing
Oligos
20 total
5 mice/oligo
100ug/day
Oligo 5
Oligo 6
Oligo 7
Oligo 8
4R:3R hTau levels
perfuse

FIG. 19

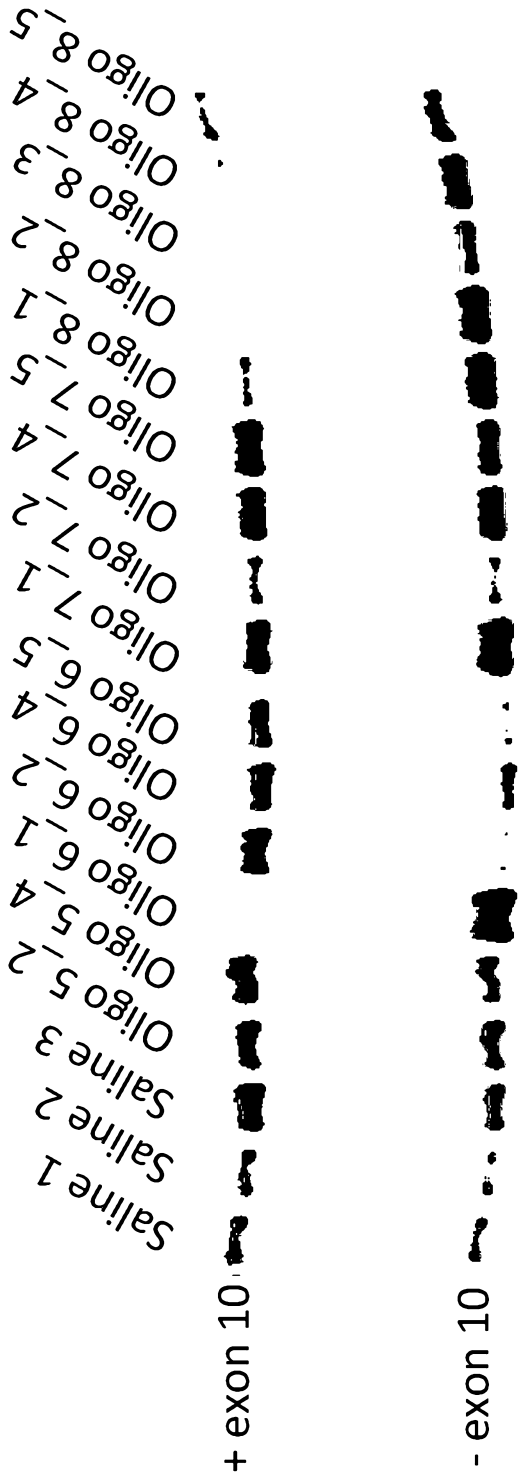

- exon 10
+ exon 10
Saline 1
Saline 2
Saline 3
Oligo 5_2
Oligo 5_4
Oligo 6_1
Oligo 6_2
Oligo 6_4
Oligo 6_5
Oligo 7_1
Oligo 7_2
Oligo 7_4
Oligo 7_5
Oligo 8_1
Oligo 8_2
Oligo 8_3
Oligo 8_4
Oligo 8_5

FIG. 20A

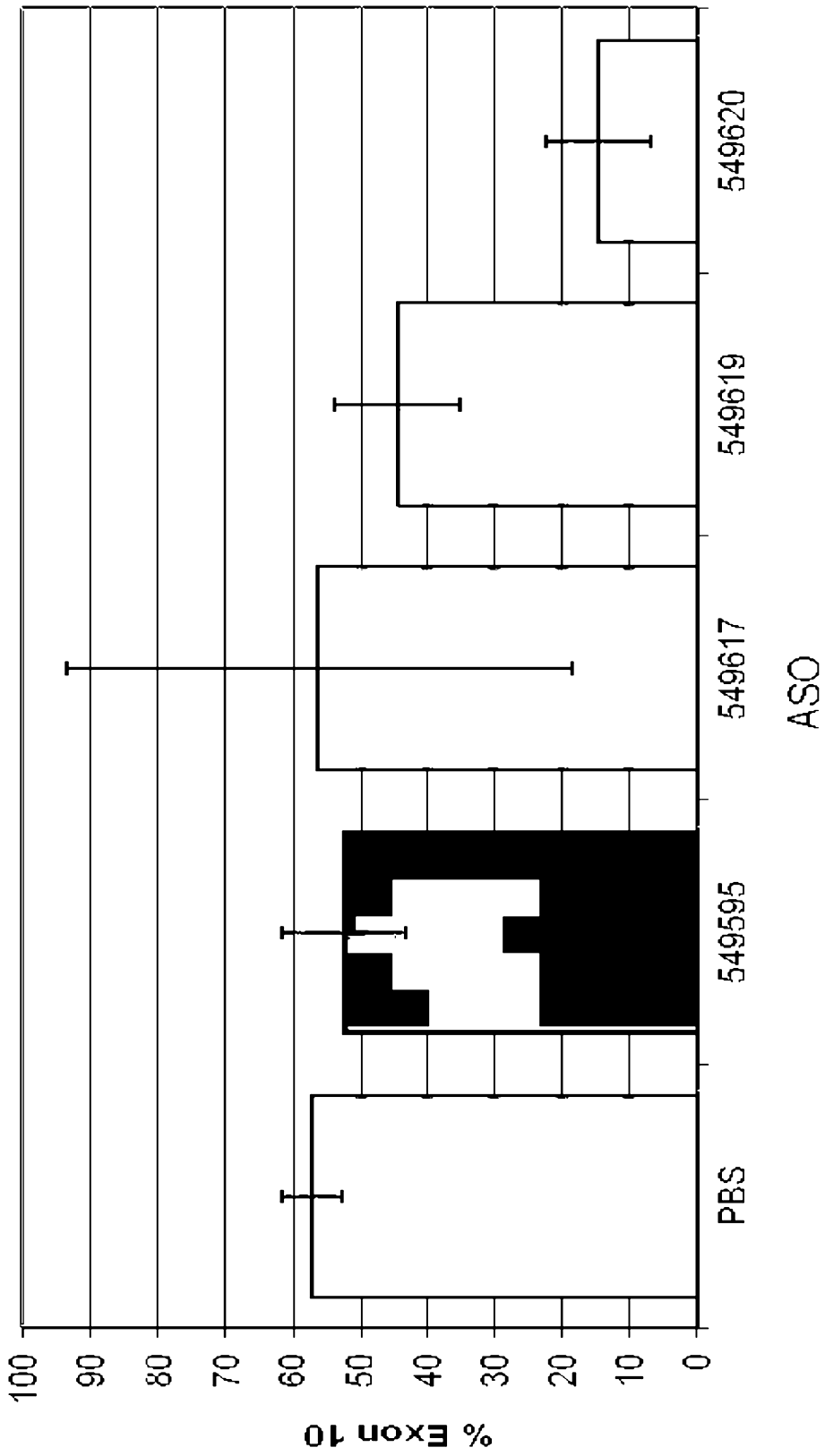

% Exon 10
100
90
80
70
60
50
40
30
20
10
0
PBS
549595
549617
549619
549620
ASO

FIG. 20B

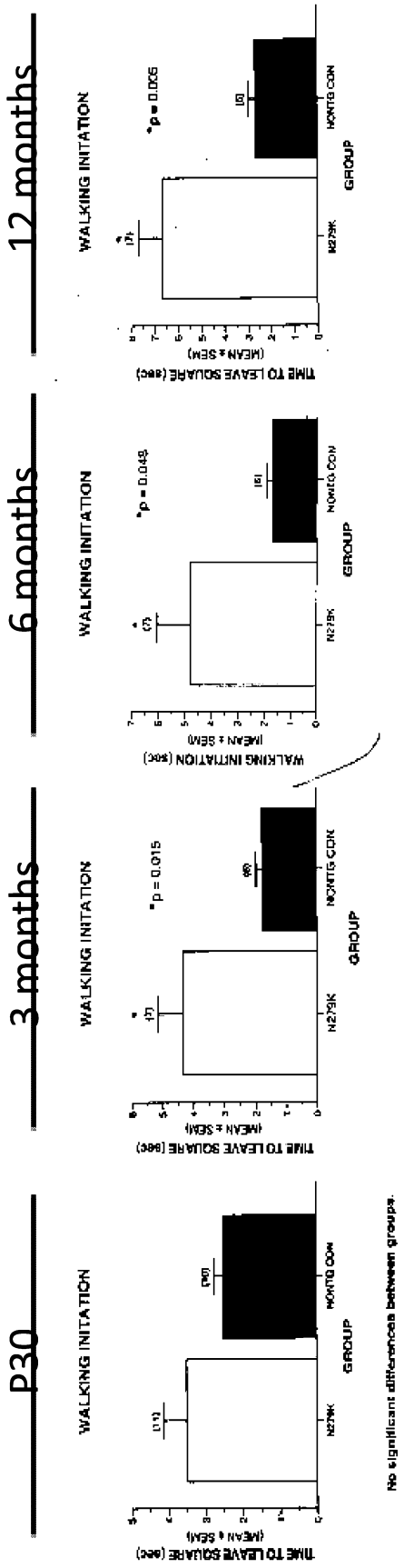

P30
3 months
6 months
12 months
WALKING INITATION
TIME TO LEAVE SQUARE (sec)
(MEAN ± SEM)
GROUP
N279K
NONTG CON
*p = 0.015
*p = 0.049
*p = 0.005
No significant differences between groups.

FIG. 21

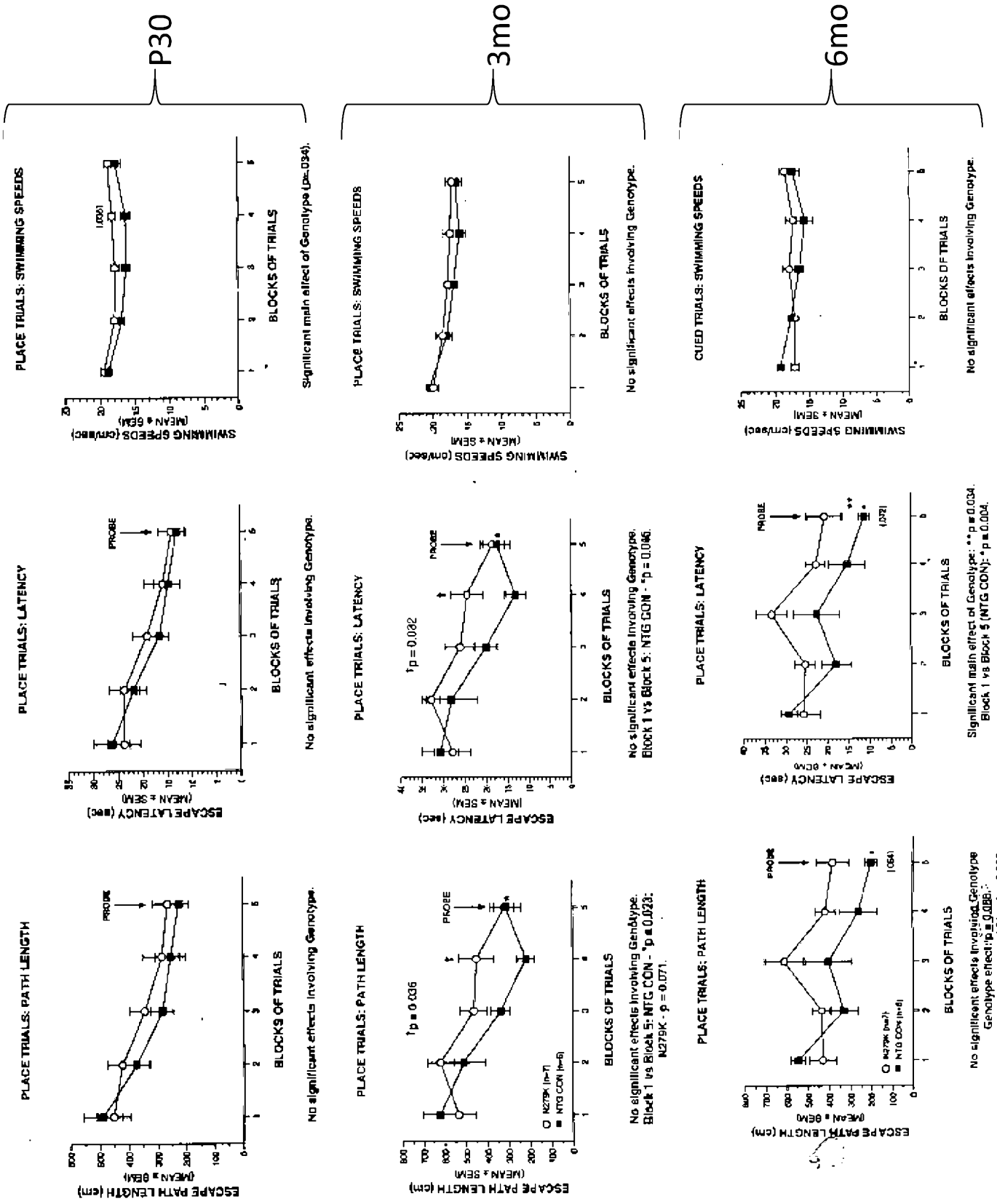

P30
3mo
6mo
PLACE TRIALS: SWIMMING SPEEDS
SWIMMING SPEEDS (cm/sec) (MEAN ± SEM)
BLOCKS OF TRIALS
Significant main effect of Genotype (p<.034).
PLACE TRIALS: LATENCY
ESCAPE LATENCY (sec) (MEAN ± SEM)
PROBE
No significant effects involving Genotype.
PLACE TRIALS: PATH LENGTH
ESCAPE PATH LENGTH (cm) (MEAN ± SEM)
No significant effects involving Genotype.
Block 1 vs Block 5: NTG CON - *p = 0.046.
No significant effects involving Genotype.
Block 1 vs Block 5: NTG CON - *p = 0.023;
N279K - p = 0.071.
CUED TRIALS: SWIMMING SPEEDS
SWIMMING SPEEDS (cm/sec) (MEAN ± SEM)
No significant effects involving Genotype.
ESCAPE LATENCY (sec) (MEAN ± SEM)
Significant main effect of Genotype; ** p = 0.034.
Block 1 vs Block 5 (NTG CON): * p = 0.004.
ESCAPE PATH LENGTH (cm) (MEAN ± SEM)
No significant effects involving Genotype
Genotype effect: p = 0.086.
Block 1 vs Block 5 (NTG CON): * p = 0.002.

FIG. 22

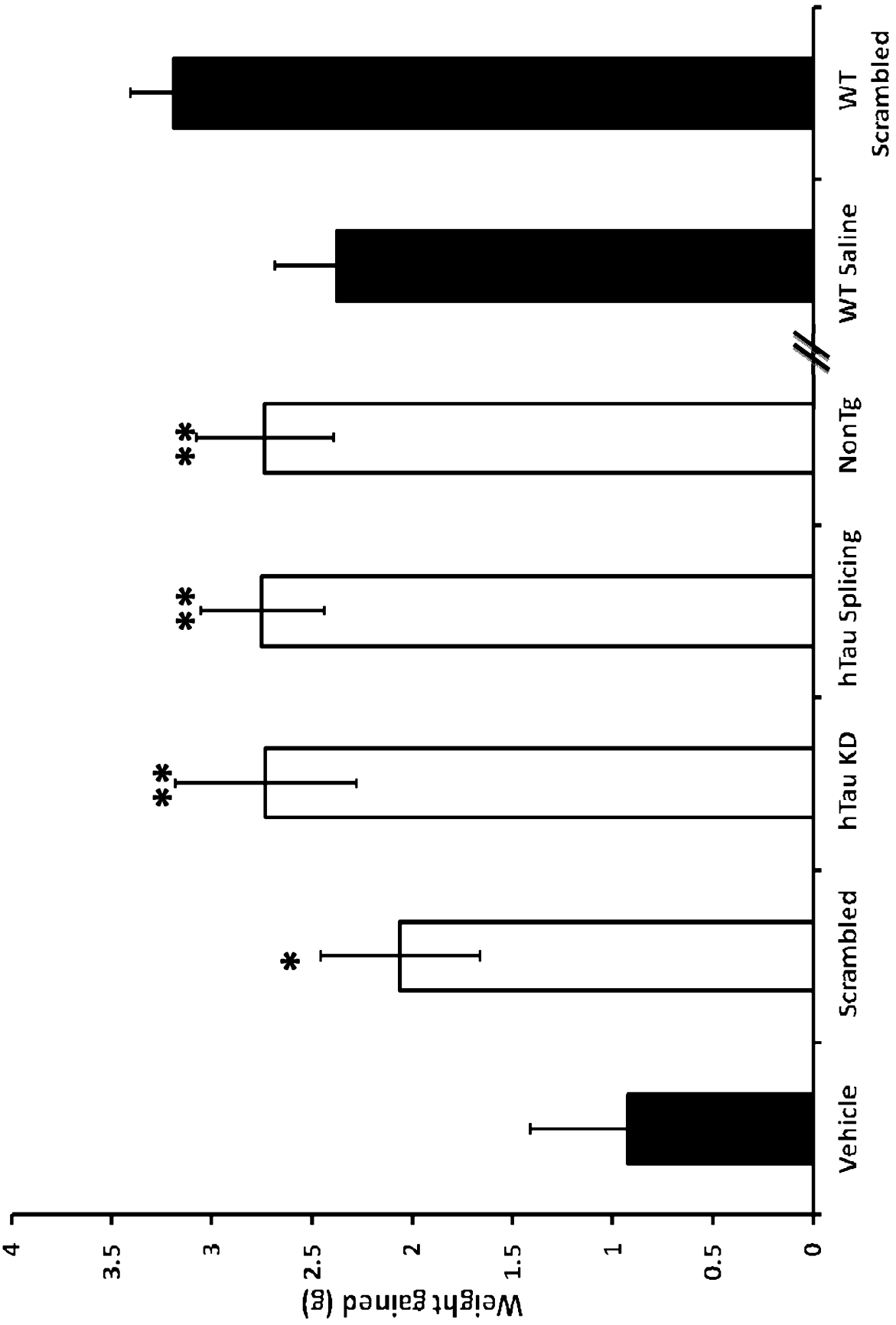

Weight gained (g)
0
0.5
1
1.5
2
2.5
3
3.5
4
*
**
**
**
Vehicle
Scrambled
hTau KD
hTau Splicing
NonTg
WT Saline
WT Scrambled
Treatment

FIG. 23

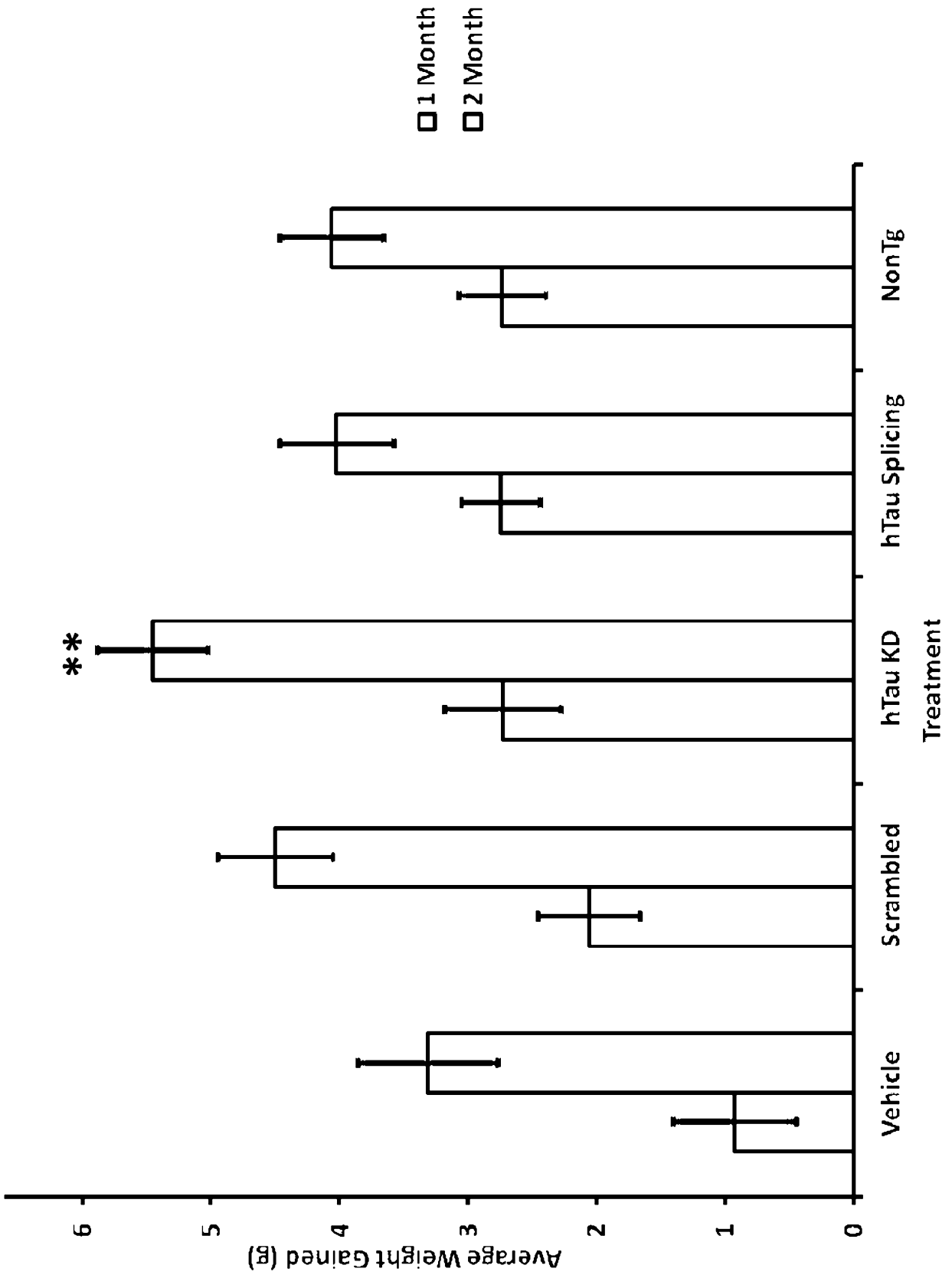

1 Month
2 Month
Average Weight Gained (g)
0
1
2
3
4
5
6
**
Vehicle
Scrambled
hTau KD
hTau Splicing
NonTg
Treatment

FIG. 24

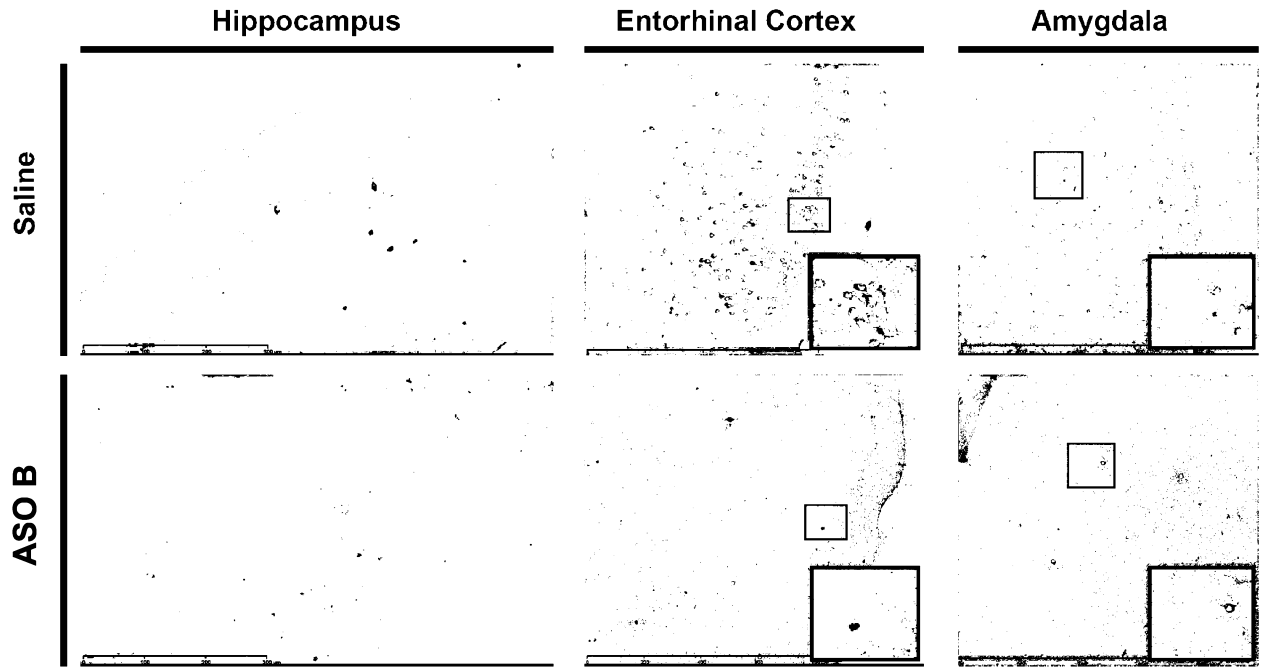


FIG. 25

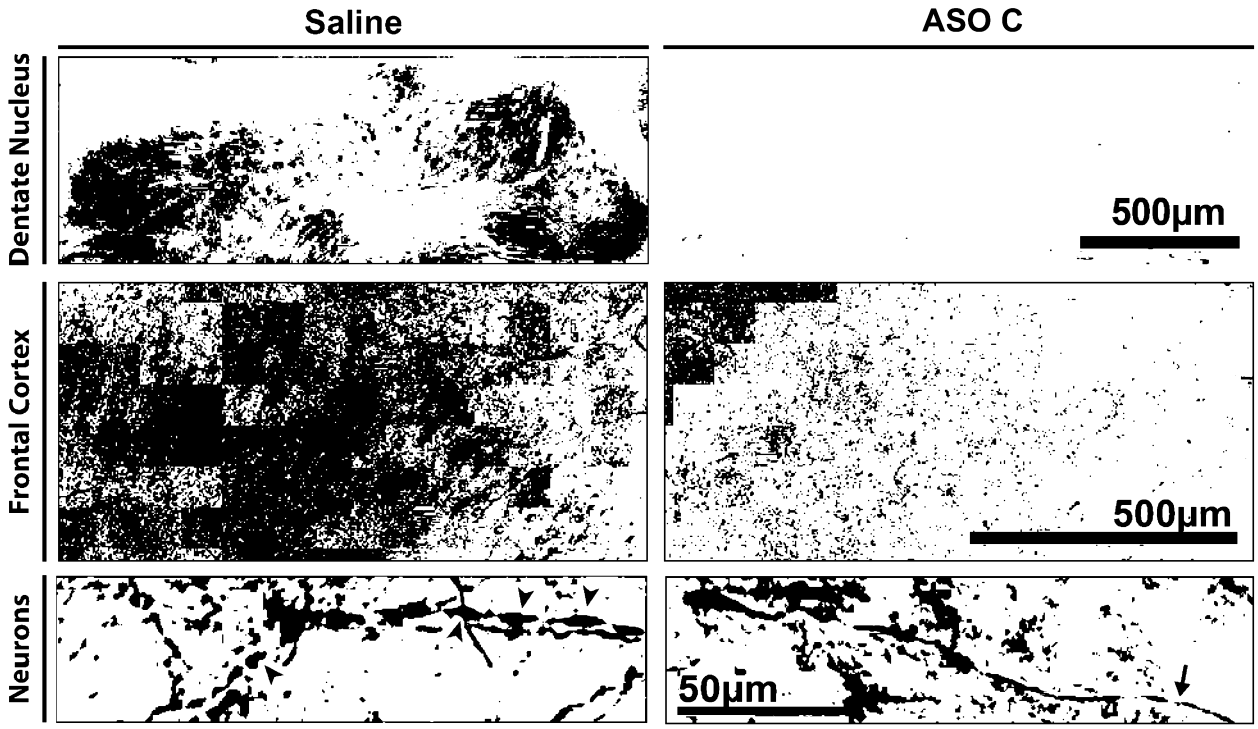

Saline
ASO C
Dentate Nucleus
Frontal Cortex
Neurons
500μm
500μm
50μm

FIG. 26

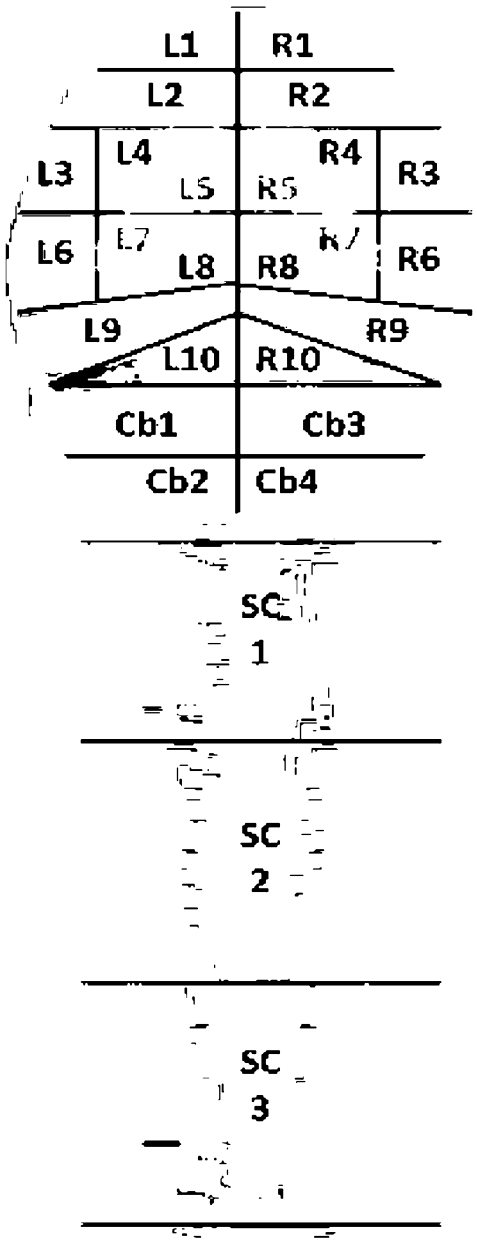

L1
R1
L2
R2
L3
L4
L5
R5
R4
R3
L6
L7
L8
R8
R6
L9
L10
R10
R9
Cb1
Cb3
Cb2
Cb4
SC
1
SC
2
SC
3

FIG. 27

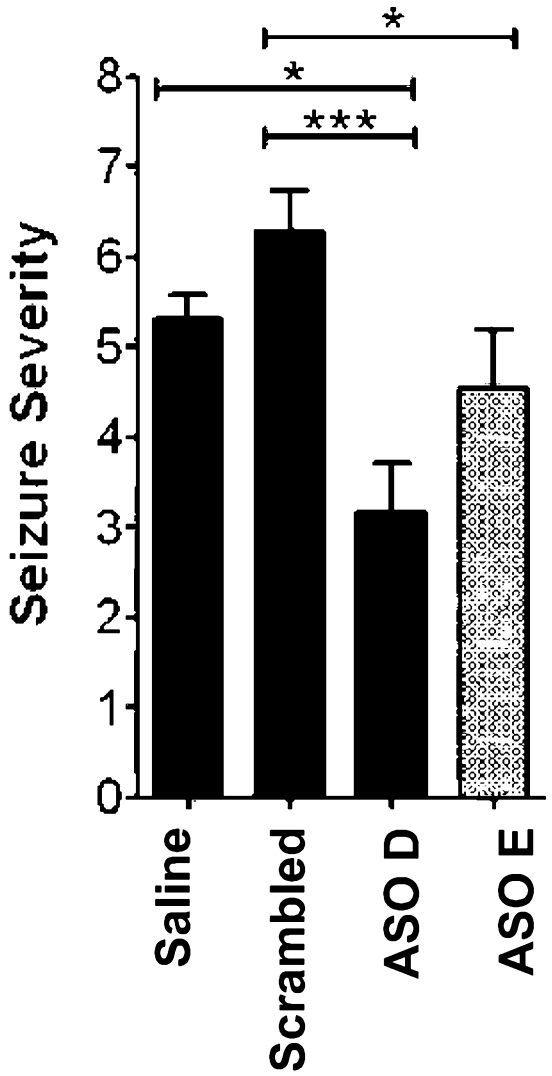


FIG. 28

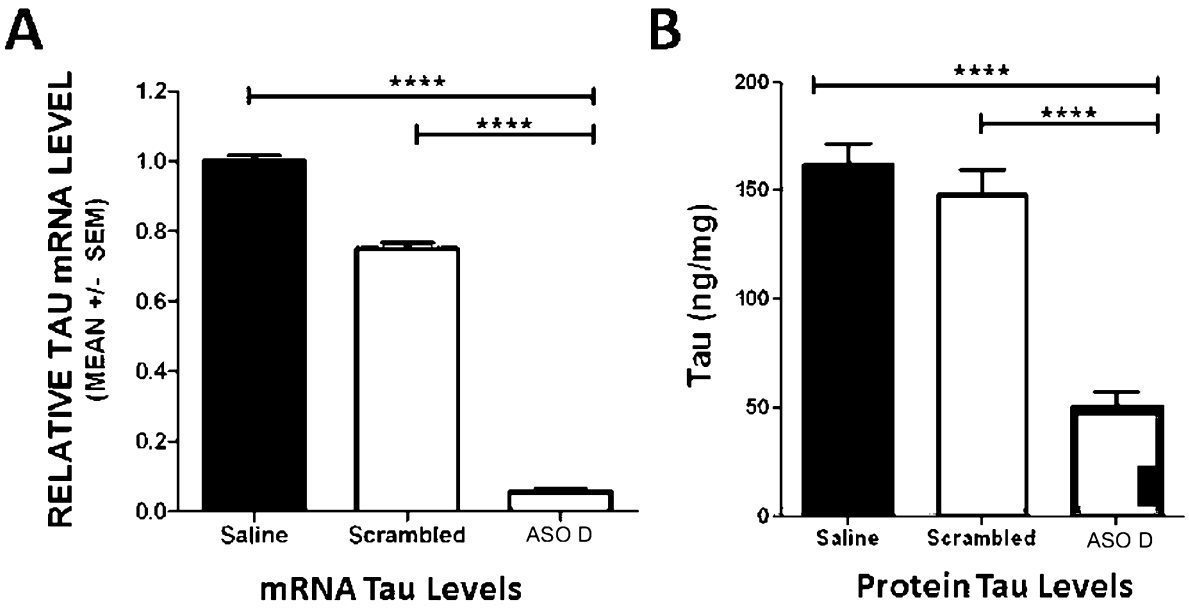
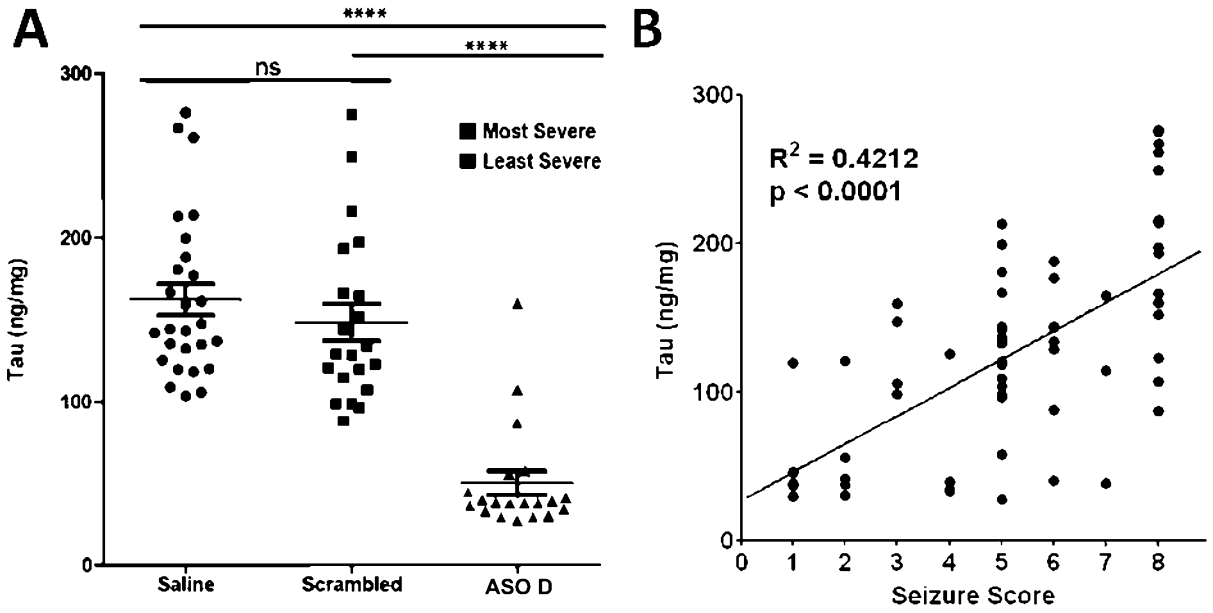

A
RELATIVE TAU mRNA LEVEL
(MEAN +/- SEM)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
****
****
Saline
Scrambled
ASO D
mRNA Tau Levels
B
Tau (ng/mg)
200
150
100
50
0
****
****
Saline
Scrambled
ASO D
Protein Tau Levels

FIG. 29


A
****
****
ns
300
200
100
0
Tau (ng/mg)
Most Severe
Least Severe
Saline
Scrambled
ASO D
B
300
200
100
0
Tau (ng/mg)
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p < 0.0001
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Seizure Score

FIG. 30

SEQUENCE LISTING

<110> Isis Pharmaceuticals, Inc.

C. Frank Bennett

Frank Rigo

Susan M. Freier

<120> COMPOSITIONS AND METHODS FOR MODULATING TAU EXPRESSION FOR REDUCING SEIZURE AND MODIFYING A NEURODEGENERATIVE SYNDROME

<130> BIOL0221WO

<150> 61/719,149

<151> 2012-10-26

<150> 61/660,676

<151> 2012-06-15

<150> 61/618,435

<151> 2012-03-30

<160> 32

<170> FastSEQ for Windows Version 4.0

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<211> 137001

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Leu Lys Glu Ser Pro Leu Gln Thr Pro Thr Glu Asp Gly Ser Glu Glu

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Pro Gly Ser Glu Thr Ser Asp Ala Lys Ser Thr Pro Thr Ala Glu Asp

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Val Thr Ala Pro Leu Val Asp Glu Gly Ala Pro Gly Lys Gln Ala Ala

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Ser Pro Ser Ser Ala Lys Ser Arg Leu Gln Thr Ala Pro Val Pro Met
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Pro Asp Leu Lys Asn Val Lys Ser Lys Ile Gly Ser Thr Glu Asn Leu
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Lys His Gln Pro Gly Gly Gly Lys Val Gln Ile Ile Asn Lys Lys Leu
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His Val Pro Gly Gly Gly Ser Val Gln Ile Val Tyr Lys Pro Val Asp
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Lys Asp Arg Val Gln Ser Lys Ile Gly Ser Leu Asp Asn Ile Thr His
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gtc cct ggc gga gga aat aaa aag att gaa acc cac aag ctg acc ttc   1456
Val Pro Gly Gly Gly Asn Lys Lys Ile Glu Thr His Lys Leu Thr Phe
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cgc gag aac gcc aaa gcc aag aca gac cac ggg gcg gag atc gtg tac   1504
Arg Glu Asn Ala Lys Ala Lys Thr Asp His Gly Ala Glu Ile Val Tyr
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Lys Ser Pro Val Val Ser Gly Asp Thr Ser Pro Arg His Leu Ser Asn
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Leu Lys Ala Glu Glu Ala Gly Ile Gly Asp Thr Pro Ser Leu Glu Asp
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gaa gct gct ggt cac gtg acc caa gct cgc atg gtc agt aaa agc aaa   544
Glu Ala Ala Gly His Val Thr Gln Ala Arg Met Val Ser Lys Ser Lys
    60                  65                  70

gac ggg act gga agc gat gac aaa aaa gcc aag ggg gct gat ggt aaa   592
Asp Gly Thr Gly Ser Asp Asp Lys Lys Ala Lys Gly Ala Asp Gly Lys
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Thr Lys Ile Ala Thr Pro Arg Gly Ala Ala Pro Pro Gly Gln Lys Gly
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cag gcc aac gcc acc agg att cca gca aaa acc ccg ccc gct cca aag   688
Gln Ala Asn Ala Thr Arg Ile Pro Ala Lys Thr Pro Pro Ala Pro Lys
            110                 115                 120

aca cca ccc agc tct ggt gaa cct cca aaa tca ggg gat cgc agc ggc   736
Thr Pro Pro Ser Ser Gly Glu Pro Pro Lys Ser Gly Asp Arg Ser Gly
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Pro Ser Leu Pro Thr Pro Pro Thr Arg Glu Pro Lys Lys Val Ala Val
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Val Arg Thr Pro Pro Lys Ser Pro Ser Ser Ala Lys Ser Arg Leu Gln
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aca gcc ccc gtg ccc atg cca gac ctg aag aat gtc aag tcc aag atc   928
Thr Ala Pro Val Pro Met Pro Asp Leu Lys Asn Val Lys Ser Lys Ile
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Ile Ile Asn Lys Lys Leu Asp Leu Ser Asn Val Gln Ser Lys Cys Gly
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Ser Lys Asp Asn Ile Lys His Val Pro Gly Gly Gly Ser Val Gln Ile
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Ser Glu Lys Leu Asp Phe Lys Asp Arg Val Gln Ser Lys Ile Gly Ser
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Leu Asp Asn Ile Thr His Val Pro Gly Gly Gly Asn Lys Lys Ile Glu
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Thr His Lys Leu Thr Phe Arg Glu Asn Ala Lys Ala Lys Thr Asp His
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Gly Ala Glu Ile Val Tyr Lys Ser Pro Val Val Ser Gly Asp Thr Ser
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