

CLAIMS

1. An RNAi oligonucleotide for reducing *MAPT* gene expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a MAPT mRNA target sequence of any one of SEQ ID NOs: 1095, 912-1094, and 1096-1295, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.
2. The RNAi oligonucleotide of claim 1, wherein the sense strand is 15 to 50 nucleotides in length, optionally wherein the sense strand is 18 to 36 nucleotides in length; and/or wherein the antisense strand is 15 to 30 nucleotides in length, optionally wherein the antisense strand is 22 nucleotides in length, and wherein antisense strand and the sense strand form a duplex region of at least 19 nucleotides in length, optionally at least 20 nucleotides in length, and/or wherein the region of complementarity is at least 19 contiguous nucleotides in length; optionally at least 20 contiguous nucleotides in length.
3. An RNAi oligonucleotide for reducing *MAPT* gene expression, the oligonucleotide comprising:
 - (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a MAPT mRNA target sequence, wherein the region of complementarity is selected from SEQ ID NOs: 1479, 1296-1478, and 1480-1679, and
 - (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands that form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.
4. The RNAi oligonucleotide of any one of claims 1-3, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L

forms a loop between S1 and S2 of 3-5 nucleotides in length, optionally wherein L is a triloop or a tetraloop; optionally wherein the tetraloop comprises the sequence 5'-GAAA-3'.

5. The RNAi oligonucleotide of claim 4, wherein the S1 and S2 are 1-10 nucleotides in length and have the same length; optionally wherein S1 and S2 are 6 nucleotides in length, optionally wherein the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 1680).

6. The RNAi oligonucleotide of any one of claims 1-3, wherein the oligonucleotide comprises a blunt end; optionally wherein the blunt end comprises the 3' end of the sense strand; further optionally wherein the sense strand is 20-22 nucleotides.

7. The RNAi oligonucleotide of any one of claims 1 to 6, wherein the antisense strand comprises a 3' overhang sequence of one or more nucleotides in length; optionally wherein the overhang comprises purine nucleotides; and/or wherein the 3' overhang sequence is 2 nucleotides in length; optionally wherein the 3' overhang is selected from AA, GG, AG, and GA; further optionally wherein the 3' overhang is GG.

8. The RNAi oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified nucleotide; optionally wherein the modified nucleotide comprises a 2'-modification, and/or wherein the 2'-modification is a modification selected from 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid; optionally wherein the modification is a 2'-modification selected from 2'-fluoro and 2'-O-methyl.

9. The RNAi oligonucleotide of claim 8, wherein about 18-23%, 18%, 19%, 20%, 21%, 22%, or 23% of the nucleotides of the sense strand comprise a 2'-fluoro modification, or wherein about 38-43%, 38%, 39%, 40%, 41%, 42%, or 43% of the nucleotides of the sense strand comprise a 2'-fluoro modification, and/or

wherein about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, or 35% of the nucleotides of the antisense strand comprise a 2'-fluoro modification, and/or
wherein about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, or 35% of the nucleotides of the oligonucleotide comprise a 2'-fluoro modification, and/or
wherein about 35-45%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, or 45% of the nucleotides of the oligonucleotide comprise a 2'-fluoro modification.

10. The RNAi oligonucleotide of claim 8 or 9, wherein the sense strand comprises 36 nucleotides with positions 1-36 from 5' to 3', wherein each of positions 3, 5, 8, 10, 12, 13, 15, and 17 comprise a 2'-fluoro modification, and/or
wherein the sense strand comprises 20 nucleotides with positions 1-20 from 5' to 3', wherein each of positions 3, 5, 8, 10, 12, 13, 15, and 17 comprise a 2'-fluoro modification, and/or
wherein the antisense strand comprises 22 nucleotides with positions 1-22 from 5' to 3', and wherein each of positions 2, 3, 4, 5, 7, 10, 14, 16, and 19 comprise a 2'-fluoro modification, and/or
wherein the remaining nucleotides comprise a 2'-O-methyl modification.

11. The RNAi oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified internucleotide linkage; optionally wherein the at least one modified internucleotide linkage is a phosphorothioate linkage, optionally wherein the antisense strand comprises a phosphorothioate linkage (i) between positions 1 and 2, and between positions 2 and 3; or (ii) between positions 1 and 2, between positions 2 and 3, and between positions 3 and 4, wherein positions are numbered 1-4 from 5' to 3', and/or
wherein the antisense strand is 22 nucleotides in length, and wherein the antisense strand comprises a phosphorothioate linkage between positions 20 and 21 and between positions 21 and 22, and wherein positions are numbered 1-22 from 5' to 3', and/or
wherein the sense strand comprises a phosphorothioate linkage between positions 1 and 2, and wherein positions are numbered 1-2 from 5' to 3', and/or
wherein the sense strand is 20 nucleotides in length, wherein the sense strand comprises a phosphorothioate linkage between positions between positions 1 and 2, between positions 18 and 19 and between positions 19 and 20, and wherein positions are numbered 1-20 from 5' to 3'.

12. The RNAi oligonucleotide of any one of the preceding claims, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, optionally wherein the phosphate analog is oxymethyl phosphonate, vinyl phosphonate or malonyl phosphonate, optionally wherein the phosphate analog is a 4'-phosphate analog comprising 4'-oxymethylphosphonate.

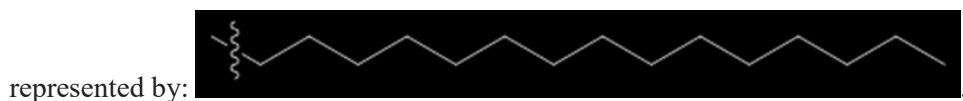
13. The RNAi oligonucleotide of any one of the preceding claims, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands; optionally wherein each targeting ligand comprises a carbohydrate, amino sugar, lipid, cholesterol, or polypeptide.

14. The RNAi oligonucleotide of any one of claims 4, 5 and 7-13, wherein the stem loop comprises one or more targeting ligands conjugated to one or more nucleotides of the stem loop; optionally wherein the one or more targeting ligands is conjugated to one or more nucleotides of the loop; optionally wherein the loop comprises 4 nucleotides numbered 1-4 from 5' to 3', wherein nucleotides at positions 2, 3, and 4 each comprise one or more targeting ligands, and wherein the targeting ligands are the same or different.

15. The RNAi oligonucleotide of claim 14, wherein each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety; optionally wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety; optionally wherein up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

16. The RNAi oligonucleotide of any one of claims 6-13, wherein the one or more targeting ligands is a lipid moiety; optionally wherein the lipid moiety is conjugated to the 5' terminal nucleotide of the sense strand; optionally wherein the lipid moiety is a hydrocarbon chain; optionally wherein the hydrocarbon chain is a C₈-C₃₀ hydrocarbon chain; optionally wherein the

hydrocarbon chain is a C₁₆ hydrocarbon chain; optionally wherein the C₁₆ hydrocarbon chain is



17. The RNAi oligonucleotide of claim 16, wherein the lipid moiety is conjugated to the 2' carbon of the ribose ring of the 5' terminal nucleotide.

18. The RNAi oligonucleotide of any one of claims 1-17, wherein the region of complementarity is fully complementary to the MAPT mRNA target sequence at nucleotide positions 2-8 of the antisense strand, and wherein nucleotide positions are numbered 5' to 3', and/or wherein the region of complementarity is fully complementary to the MAPT mRNA target sequence at nucleotide positions 2-11 of the antisense strand, and wherein nucleotide positions are numbered 5' to 3'.

19. The RNAi oligonucleotide of any one of claims 1 to 18, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 780, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803 and 1681, and/or

wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 815, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, and 838.

20. The RNAi oligonucleotide of any one of claims 1 to 19, wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- a) SEQ ID NOs: 780 and 815, respectively;
- b) SEQ ID NOs: 769 and 804, respectively;
- c) SEQ ID NOs: 770 and 805, respectively;
- d) SEQ ID NOs: 771 and 806, respectively;
- e) SEQ ID NOs: 772 and 807, respectively;
- f) SEQ ID NOs: 773 and 808, respectively;

g) SEQ ID NOs: 774 and 809, respectively;
h) SEQ ID NOs: 775 and 810, respectively;
i) SEQ ID NOs: 776 and 811, respectively;
j) SEQ ID NOs: 777 and 812, respectively;
k) SEQ ID NOs: 778 and 813, respectively;
l) SEQ ID NOs: 779 and 814, respectively;
m) SEQ ID NOs: 781 and 816, respectively;
n) SEQ ID NOs: 782 and 817, respectively;
o) SEQ ID NOs: 783 and 818, respectively;
p) SEQ ID NOs: 784 and 819, respectively;
q) SEQ ID NOs: 785 and 820, respectively;
r) SEQ ID NOs: 786 and 821, respectively;
s) SEQ ID NOs: 787 and 822, respectively;
t) SEQ ID NOs: 788 and 823, respectively;
u) SEQ ID NOs: 789 and 824, respectively;
v) SEQ ID NOs: 790 and 825, respectively;
w) SEQ ID NOs: 791 and 826, respectively;
x) SEQ ID NOs: 792 and 827, respectively;
y) SEQ ID NOs: 793 and 828, respectively;
z) SEQ ID NOs: 794 and 829, respectively;
aa) SEQ ID NOs: 795 and 830, respectively;
bb) SEQ ID NOs: 796 and 831, respectively;
cc) SEQ ID NOs: 797 and 832, respectively;
dd) SEQ ID NOs: 798 and 833, respectively;
ee) SEQ ID NOs: 799 and 834, respectively;
ff) SEQ ID NOs: 800 and 835, respectively;
gg) SEQ ID NOs: 801 and 836, respectively;
hh) SEQ ID NOs: 802 and 837, respectively;
ii) SEQ ID NOs: 803 and 838, respectively; and
jj) SEQ ID NOs: 1681 and 815, respectively.

21. The RNAi oligonucleotide of any one of claims 1-18, wherein the sense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 850, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873 and 1682, and/or wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 885, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907 and 908.

22. The RNAi oligonucleotide of any one of claims 1-18, wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

- a) SEQ ID NOs: 850 and 885, respectively;
- b) SEQ ID NOs: 839 and 874, respectively;
- c) SEQ ID NOs: 840 and 875, respectively;
- d) SEQ ID NOs: 841 and 876, respectively;
- e) SEQ ID NOs: 842 and 877, respectively;
- f) SEQ ID NOs: 843 and 878, respectively;
- g) SEQ ID NOs: 844 and 879, respectively;
- h) SEQ ID NOs: 845 and 880, respectively;
- i) SEQ ID NOs: 846 and 881, respectively;
- j) SEQ ID NOs: 847 and 882, respectively;
- k) SEQ ID NOs: 848 and 883, respectively;
- l) SEQ ID NOs: 849 and 884, respectively;
- m) SEQ ID NOs: 851 and 886, respectively;
- n) SEQ ID NOs: 852 and 887, respectively;
- o) SEQ ID NOs: 853 and 888, respectively;
- p) SEQ ID NOs: 854 and 889, respectively;
- q) SEQ ID NOs: 855 and 890, respectively;
- r) SEQ ID NOs: 856 and 891, respectively;
- s) SEQ ID NOs: 857 and 892, respectively;

- t) SEQ ID NOs: 858 and 893, respectively;
- u) SEQ ID NOs: 859 and 894, respectively;
- v) SEQ ID NOs: 860 and 895, respectively;
- w) SEQ ID NOs: 861 and 896, respectively;
- x) SEQ ID NOs: 862 and 897, respectively;
- y) SEQ ID NOs: 863 and 898, respectively;
- z) SEQ ID NOs: 864 and 899, respectively;
- aa) SEQ ID NOs: 865 and 900, respectively;
- bb) SEQ ID NOs: 866 and 901, respectively;
- cc) SEQ ID NOs: 867 and 902, respectively;
- dd) SEQ ID NOs: 868 and 903, respectively;
- ee) SEQ ID NOs: 869 and 904, respectively;
- ff) SEQ ID NOs: 870 and 905, respectively;
- gg) SEQ ID NOs: 871 and 906, respectively;
- hh) SEQ ID NOs: 872 and 907, respectively;
- ii) SEQ ID NOs: 873 and 908, respectively; and
- jj) SEQ ID NOs: 1682 and 885, respectively.

23. A pharmaceutical composition comprising the RNAi oligonucleotide of any one of claims 1 to 22, and a pharmaceutically acceptable carrier, delivery agent or excipient.

24. Use of RNAi oligonucleotide of any one of claims 1 to 22, or the pharmaceutical composition of claim 23, in the manufacture of a medicament for treating a subject having a disease, disorder, or condition associated with *MAPT* gene expression, optionally wherein the disease, disorder or condition associated with *MAPT* gene expression is Alzheimer's disease (AD), frontotemporal dementia, progressive supranuclear palsy (PSP), Tau protein associated diseases, primary age-related tauopathy, chronic traumatic encephalopathy, corticobasal degeneration, lytico-bodig disease, ganglioglioma, meningioangiomas, Parkinson's Disease (PD), postencephalitic parkinsonism, or subacute sclerosing panencephalitis.

25. An *in vitro* method for reducing *MAPT* gene expression in a cell, or a population of cells, the method comprising the step of:

contacting the cell or the population of cells with the RNAi oligonucleotide of any one of claims 1 to 22, or the pharmaceutical composition of claim 23; optionally wherein reducing *MAPT* gene expression comprises reducing an amount or level of MAPT mRNA, an amount or level of Tau protein, or both.

26. Use of an RNAi oligonucleotide of any one of claims 1 to 22, or the pharmaceutical composition of claim 23, in the manufacture of a medicament for reducing *MAPT* gene expression in a subject; optionally wherein reducing *MAPT* gene expression comprises reducing an amount or level of MAPT mRNA, an amount or level of Tau protein, or both.

27. The use of claim 26, wherein the subject has a disease, disorder, or condition associated with *MAPT* gene expression; optionally wherein the disease, disorder or condition associated with *MAPT* gene expression is Alzheimer's disease (AD), frontotemporal dementia, progressive supranuclear palsy (PSP), Tau protein associated diseases, primary age-related tauopathy, chronic traumatic encephalopathy, corticobasal degeneration, lytico-bodig disease, ganglioglioma, meningioangiomas, Parkinson's Disease (PD), postencephalitic parkinsonism, or subacute sclerosing panencephalitis.

28. The use of any one of claims 24, 26, and 27, wherein *MAPT* is reduced in tissue of one or more regions of the central nervous system (CNS), wherein the tissue is associated with AD; optionally wherein tissue associated with AD is selected from prefrontal cortex, motor cortex, temporal cortex, parietal cortex, and hippocampus; and/or wherein *MAPT* is reduced in tissue of one or more regions of the central nervous system (CNS), wherein the tissue is associated with PSP; optionally wherein tissue associated with PSP is selected from caudate nucleus, globus pallidus, thalamus, midbrain tegmentum, substantia nigra, pons, cerebellar white matter, cerebellar dentate nucleus, medulla, cervical spinal cord, thoracic spinal cord, and lumbar spinal cord; and/or

wherein *MAPT* is reduced in one or more regions of the CNS selected from cervical spinal cord, thoracic spinal cord, lumbar spinal cord, frontal cortex, temporal cortex, cerebellum, midbrain, occipital cortex, parietal cortex, hippocampus, caudate nucleus, thalamus, brainstem, motor cortex, globus pallidus, midbrain tegmentum, substantia nigra, pons, cerebellar white matter, and cerebellar dentate nucleus.

29. The use of any one of Claims 24 and 26 to 28, wherein said medicament is to be administered in combination with a second composition or therapeutic agent.

30. The RNAi oligonucleotide of any one of Claims 1 to 22, or the pharmaceutical composition of Claim 23, for use as a medicament.

31. A kit comprising the RNAi oligonucleotide of any one of claims 1 to 22, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with *MAPT* gene expression; optionally wherein the disease, disorder or condition associated with *MAPT* gene expression is Alzheimer's disease (AD), frontotemporal dementia, progressive supranuclear palsy (PSP), Tau protein-associated diseases, primary age-related tauopathy, chronic traumatic encephalopathy, corticobasal degeneration, lytico-bodig disease, ganglioglioma, meningioangiomas, Parkinson's Disease (PD), postencephalitic parkinsonism, or subacute sclerosing panencephalitis.