Claims

1. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other.

2. The dsRNA agent of claim 1, wherein the dsRNA agent includes a sense strand and an antisense strand, wherein the sense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 165-195, 166-196, 167-197, 165-197, 257-287, 1495-1525, 1525-1555, 1528-1558, 1529-1559, 1525-1559, 1532-1562, 2234-2264, 2235-2265, 2236-2266, 2237-2267, 2238-2268, 2235-2268, 2326-2356, 2327-2357, 2328-2358, 2329-2359, 2330-2360, 2331-2361, 2333-2363, 2334-2364, 2336-2366, 2342-2372, 2326-2372, 2359-2389, 2364-2394, 2359-2394, 2412-2442, 2414-2444, 2412-2444, 2426-2456, 2688-2718, 2775-2805, 2805-2835, 2811-2841, 2835-2865, 2836-2866, 2837-2867, 2838-2868, 2839-2869, 2840-2870, 2841-2871, 2842-2872, 2843-2873, 2845-2875, 2835-2875, 2868-2898 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other;

preferably, the sense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 170-190, 171-191, 172-192, 170-192, 262-282, 1497-1517, 1500-1520, 1530-1550, 1533-1553, 1534-1554, 1530-1554, 1537-1557, 2239-2259, 2240-2260, 2241-2261, 2242-2262, 2243-2263, 2239-2263, 2331-2351, 2332-2352, 2333-2353, 2334-2354, 2335-2355, 2336-2356, 2338-2358, 2339-2359, 2341-2361,

2347-2367, 2331-2367, 2364-2384, 2369-2389, 2364-2389, 2417-2437, 2419-2439, 2417-2439, 2431-2451, 2693-2713, 2780-2800, 2810-2830, 2816-2836, 2840-2860, 2841-2861, 2842-2862, 2843-2863, 2844-2864, 2845-2865, 2846-2866, 2847-2867, 2848-2868, 2850-2870, 2840-2870, 2873-2893 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2; optionally, said antisense strand comprises a region of complementarity to a MAPT RNA transcript which comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from any one of the antisense sequences listed in any one of Tables 1-3; or

said antisense strand comprises a region of complementarity to a MAPT RNA transcript which comprises at least 15 contiguous nucleotides from any one of the antisense sequences listed in any one of Tables 1-3.

3. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT, wherein the dsRNA agent comprises a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand comprising a region of complementarity to a MAPT RNA transcript, wherein the region of complementarity comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3, and optionally comprising a targeting ligand;

preferably, the region of complementarity to a MAPT RNA transcript comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides that differ by no more than 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3.

4. The dsRNA agent of any one of claims 1-3, wherein the antisense strand of dsRNA is substantially or fully complementary to any one of a target region of SEQ ID NO: 1, and preferably the dsRNA agent comprises an antisense strand sequence set forth in any one of Tables 1-3;

preferably, the sense strand sequence is at least substantially complementary to or fully complementary to the antisense strand sequence in the dsRNA agent, preferably, wherein the dsRNA agent comprises a sense strand sequence set forth in any one of Tables 1-3;

preferably, the dsRNA agent comprises the sequences set forth as a duplex sequence in any of Tables 1-3.

5. The dsRNA of any one of claims 1-4, wherein the dsRNA agent comprises at least one modified nucleotide;
preferably, all or substantially all of the nucleotides of the sense strand and/or the antisense strand are modified nucleotides.

6. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to part of a MAPT RNA transcript, wherein each strand is about 15 to about 30 nucleotides in length, wherein the sense strand comprises sequence may be represented by formula (I):

$$5'\text{-}(N'_L)_{n'}N'_L\ N'_L\ N'_L\ N'_L\ N'_F\ N'_L\ N'_F\ N'_L\ N'_{N1}\ N'_{N2}\ N'_L\ N'_L\ N'_L\ N'_L\ N'_L\ (N'_L)_{m'}\text{-}3' \quad (I)$$

wherein:

each N'_F represents a 2'-fluoro-modified nucleotide; each N'_{N1} and N'_{N2} independently represents a modified or unmodified nucleotide; each N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and m′ and n′ are each independently an integer of 0 to 7; or

wherein each strand is about 18 to about 30 nucleotides in length, wherein the antisense strand comprises sequence may be represented by formula (II):

$$3'\text{-}(N_L)_n\ N_{M1}\ N_L\ N_{M2}\ N_L\ N_F\ N_L\ N_{M3}\ N_{M4}\ N_L\ N_L\ N_L\ N_{M5}\ N_L\ N_{M6}\ N_L\ N_L\ N_F\ N_L\text{-}5' \quad (II)$$

wherein:

each N_F represents a 2'-fluoro-modified nucleotide; each N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, and N_{M6} independently represents a modified or unmodified nucleotide; each N_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and n is an integer of 0 to 7; or

wherein the sense strand and the antisense strand form a dsRNA duplex, wherein said sense strand is complementary to the antisense strand, wherein said antisense

strand comprises a region of complementarity to a MAPT RNA transcript, wherein the region of complementarity comprises at least 15 contiguous nucleotides, wherein the dsRNA comprises duplex represented by formula (III):

sense: 5′-$(N'_L)_{n'}N'_L$ N'_L N'_L N'_L N'_F N'_L N'_F N'_L N'_{N1} N'_{N2} N'_L N'_L N'_L N'_L N'_L $(N'_L)_{m'}$-3′

antisense: 3′-$(N_L)_n$ N_{M1} N_L N_{M2} N_L N_F N_L N_{M3} $N_{M4}N_L$ N_L N_L N_{M5} N_L N_{M6} N_L N_L N_F N_L-5′

(III)

wherein:

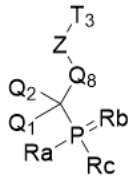
each strand is about 18 to about 30 nucleotides in length;

each N_F and N'_F independently represents a 2'-fluoro-modified nucleotide; N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, N'_{N1}, and N'_{N2} each independently represents a modified or unmodified nucleotide; N'_{N1} and N'_{N2} include only one 2'-Fluorine modified nucleotides; N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, and N_{M6} have only three 2'-fluoro-modified nucleotides; each N_L and N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and m′, n′ and n are each independently an integer of 0 to 7.

7. The dsRNA agent of any one of claims 5-6, wherein the one or more modified nucleotides are independently selected from the group consisting of: a 2’-O-methyl nucleotide, a 2’-Fluoro nucleotide, a 2’-deoxy nucleotide, a 2’3’-seco nucleotide mimic, a locked nucleotide, an unlocked nucleic acid nucleotide (UNA), a glycol nucleic acid nucleotide (GNA), a 2’-F-Arabino nucleotide, a 2’-methoyxyethyl nucleotide, an abasic nucleotide, an ribitol, inverted nucleotide, an inverted abasic nucleotide, an isomannide nucleotide, an inverted 2’-Ome nucleotide, an inverted 2’-deoxy nucleotide, a 2’-amino-modified nucleotide, a 2’-alkyl-modified nucleotide, a mopholino nucleotide, a 3’-OMe nucleotide, a nucleotide comprising a 5’-phosphorothioate group, a 5'- phosphonate modified nucleotide a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2’-amino-modified nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.

8. The dsRNA agent of any one of claims 1-7, comprises an E-vinylphosphonate nucleotide at the 5′ end of the antisense strand, or comprises a 5'-phosphate mimic

nucleotide represented by formula (VIII) or or their stereoisomers or racemates at the 5′- end of the antisense strand



Formula (VIII)

wherein: Q_8 is O, S, SO, SO_2, $PR^{16}R^{17}$ or NR^{11}; R^{16} and R^{17} are independently (=O), (=S), OH, SH, C_1-C_6 alkyl, $NR^{18}R^{19}$; Ra and Rc are each independently selected from hydroxyl or protected hydroxyl, sulfhydryl or protected sulfhydryl, optionally substituted C_1-C_6 alkyl , optionally substituted C_1-C_6 alkoxy , protected or optionally substituted amino, natural or modified nucleosides; and R_b is O or S or NR^{12}, R^{12} is hydrogen, C_1-C_6 alkyl, amino protecting group;

Q_1 and Q_2 are each independently H, halogen, -CN, optionally substituted C_1-C_6 alkyl;

the substituents in the substituted amino group are selected from: optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, sulfinyl, sulfonyl, acetyl;

R^{11}, R^{18} and R^{19} are independently H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, methanesulfonyl, and sulfonic acid group;

Z is a nucleoside containing a sugar or sugar surrogate moiety;

T_3 is an internucleotide linking group that connects the 5'-terminal nucleotide of formula (VIII) or its stereoisomer to the remainder of the 5′-end of the guide strand;

each substituted group comprises one or more substituent groups optionally independently selected from: halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfhydryl, CN;

optionally, the dsRNA agent comprises at least one phosphorothioate internucleoside linkage; or

the sense strand comprises at least one phosphorothioate internucleoside linkage; or

the antisense strand comprises at least one phosphorothioate internucleoside linkage; or

the sense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages; or

the antisense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages;

optionally, the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-3; or

the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-3;

optionally, the sense strand is complementary or substantially complementary to the antisense strand, and the region of complementarity is between 16 and 23 nucleotides in length;

preferably, the region of complementarity is 19-21 nucleotides in length;

preferably, each strand is no more than 30 nucleotides in length; or

each strand is no more than 25 nucleotides in length; or

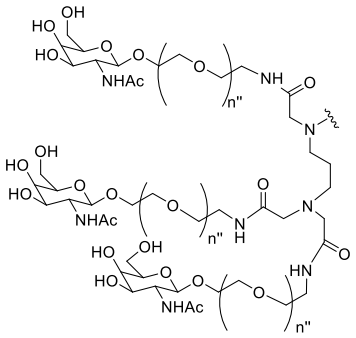
each strand is no more than 23 nucleotides in length.

9. The dsRNA agent of any one of claims 1-8, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups;

preferably, the one or more targeting groups or linking groups are conjugated to the sense strand;

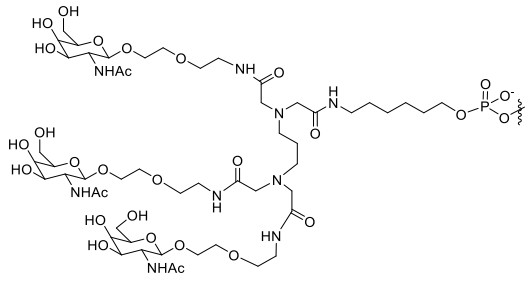
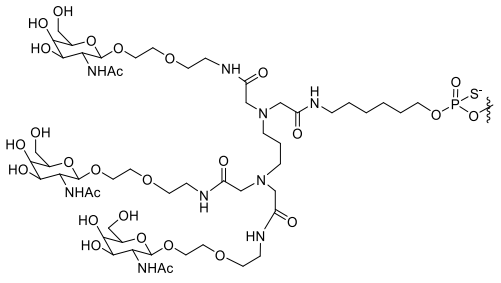
preferably, the targeting group or linking group comprises N-acetyl-galactosamine (GalNAc);

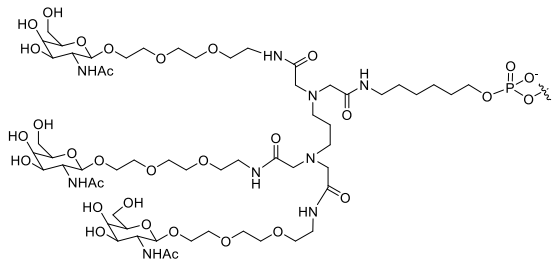
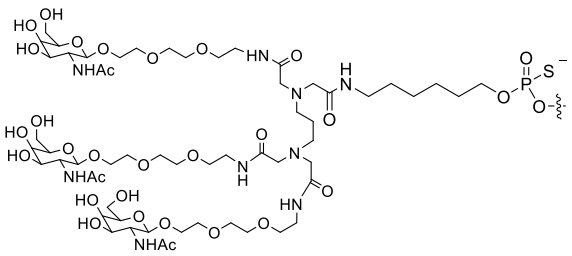
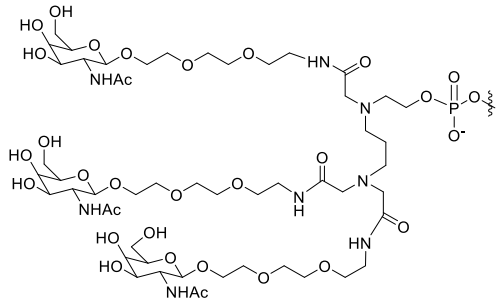
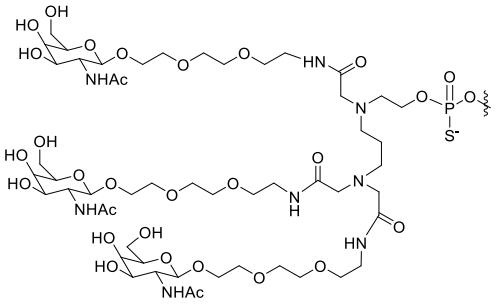
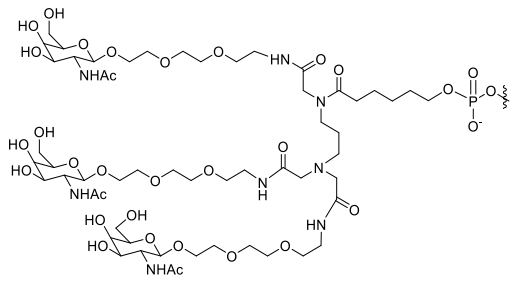
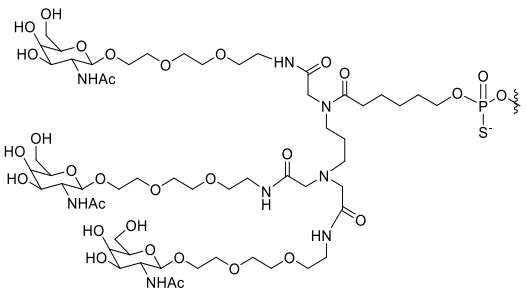
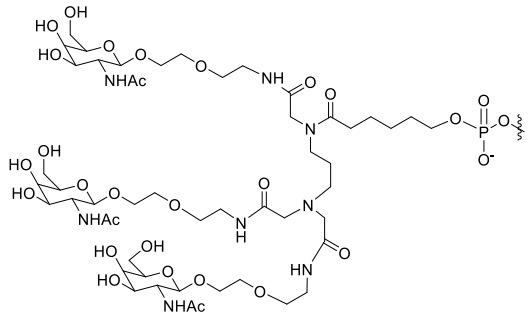
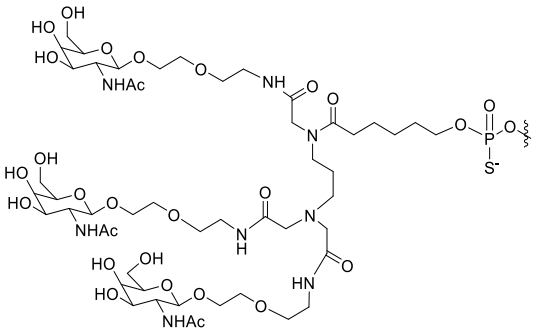
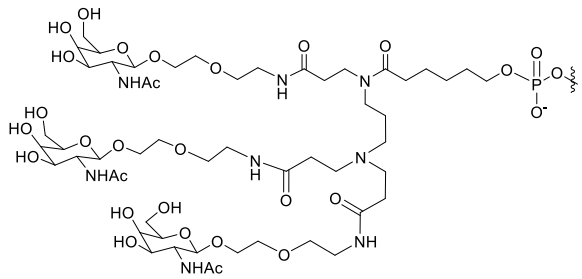
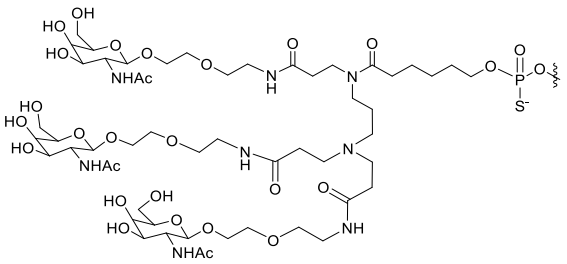
preferably, the targeting group has a structure:

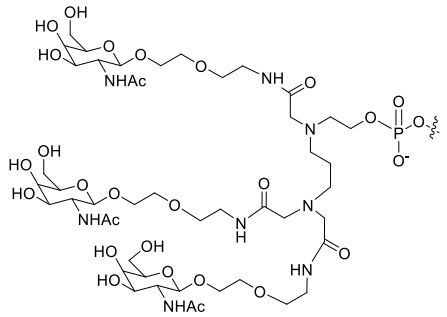
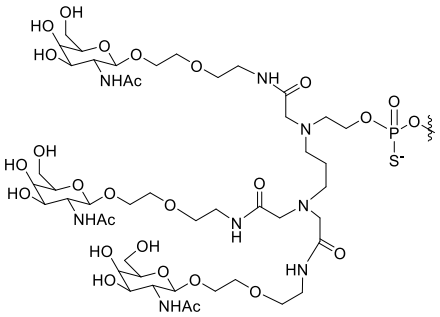
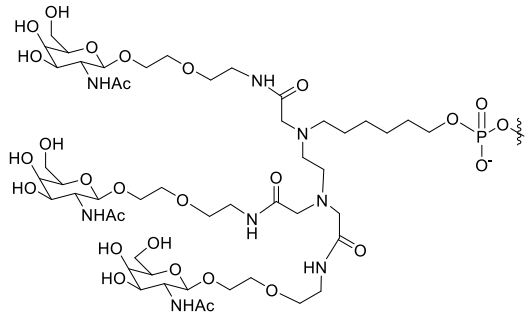
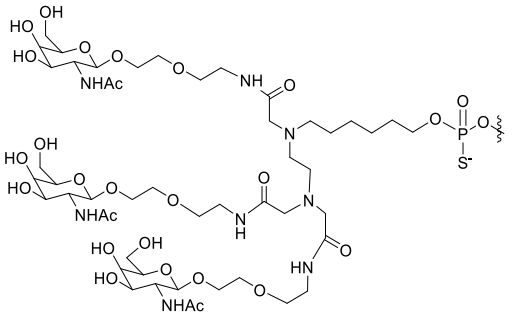
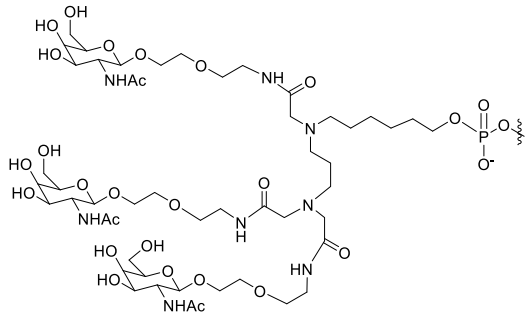
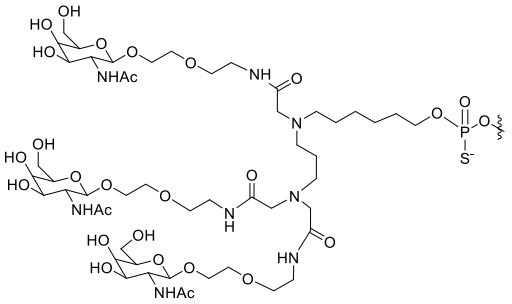
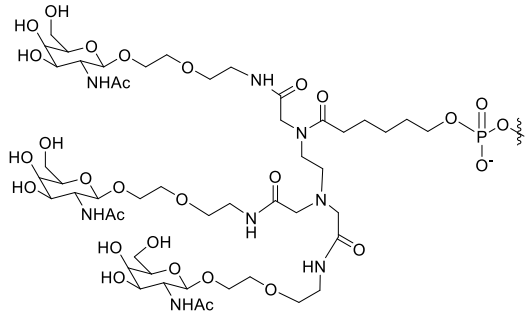
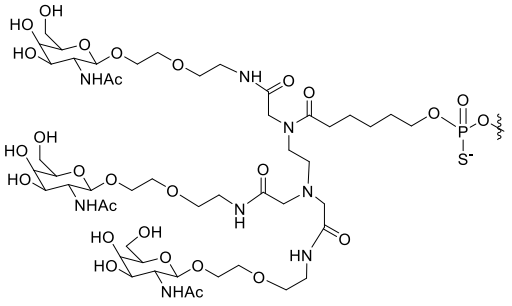
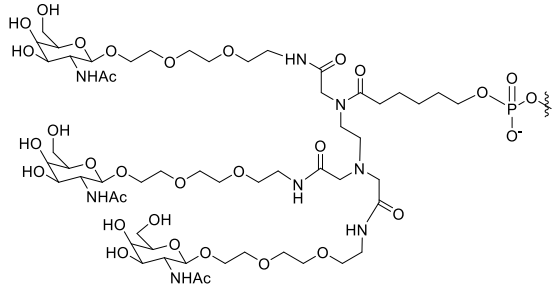
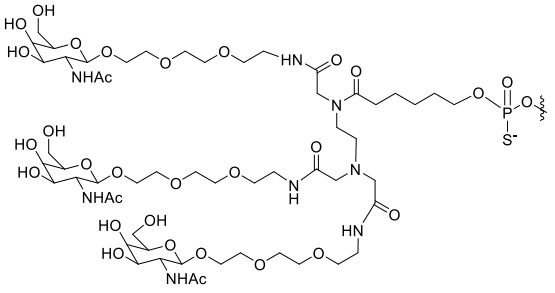


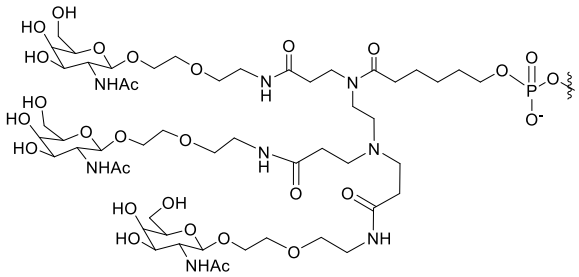
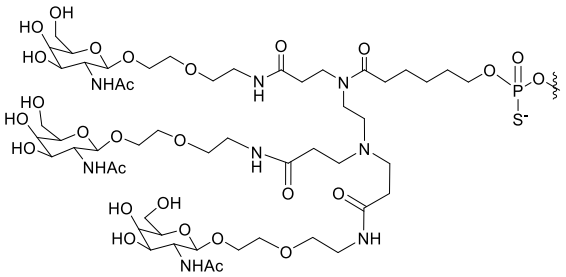
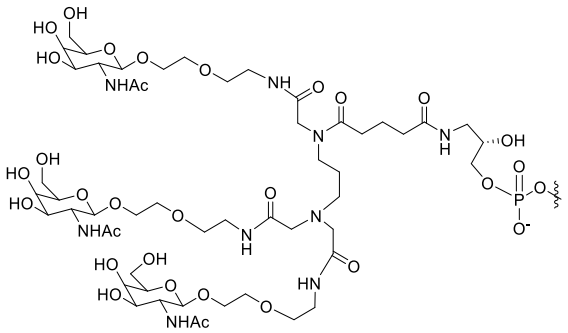
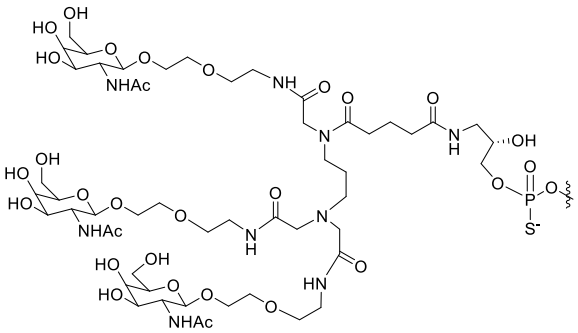
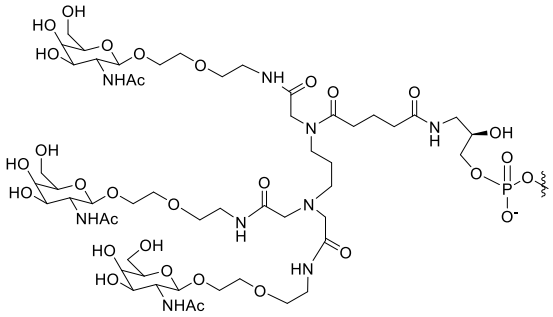
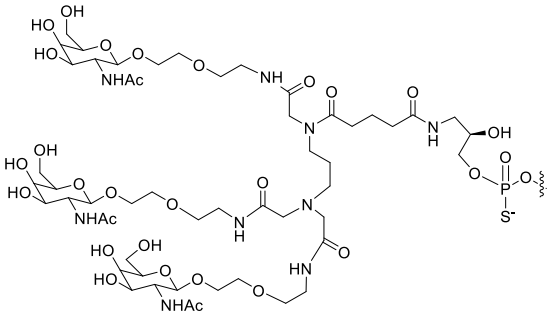
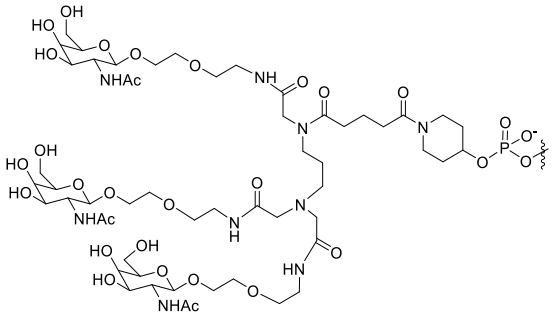
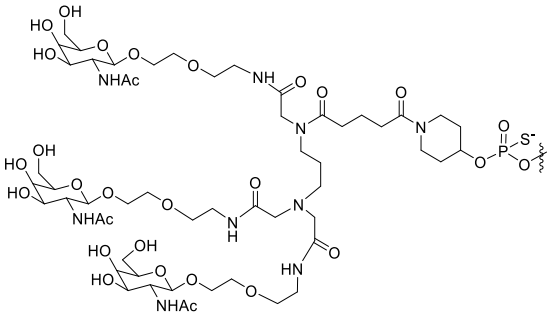
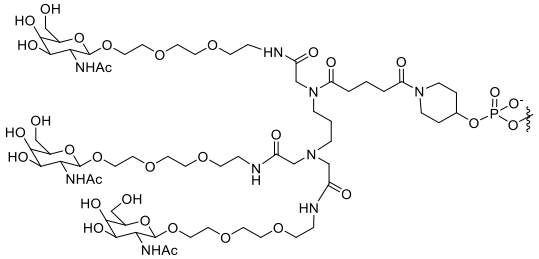
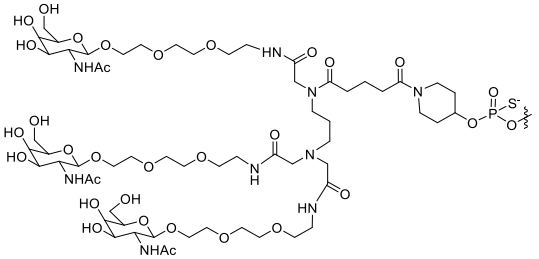
n" are independently selected from 1 or 2;

preferably, the targeting group has a structure:

 GLO-1	 GLS-1*

 GLO-2	 GLS-2*
 GLO-3	 GLS-3*
 GLO-4	 GLS-4*
 GLO-5	 GLS-5*
 GLO-6	 GLS-6*

 GLO-7	 GLS-7*
 GLO-8	 GLS-8*
 GLO-9	 GLS-9*
 GLO-10	 GLS-10*
 GLO-11	 GLS-11*

 GLO-12	 GLS-12*
 GLO-13	 GLS-13*
 GLO-14	 GLS-14*
 GLO-15	 GLS-15*
 GLO-16	 GLS-16*

;

optionally, the dsRNA agent comprises a targeting group that is conjugated to the 5’-terminal end of the sense strand; or
the dsRNA agent comprises a targeting group that is conjugated to the 3'-terminal end of the sense strand; or
the antisense strand comprises one inverted abasic residue at 3’-terminal end; or
the sense strand comprises one or two inverted abasic residues or imann residues at 3’ or/and 5’ terminal end;
preferably, the dsRNA agent has two blunt ends; or
at least one strand comprises a 3’ overhang of at least 1 nucleotide; or
at least one strand comprises a 3’ overhang of at least 2 nucleotides.

10. The dsRNA agent of any one of claims 1-9 wherein the MAPT RNA transcript is SEQ ID NO: 1.

11. A composition comprising a dsRNA agent of any one of claims 1-10;
preferably, the composition further comprises a pharmaceutically acceptable carrier;
preferably, the composition further comprises one or more additional therapeutic agents;
preferably, the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial;
preferably, the composition is formulated for subcutaneous administration, is formulated for intrathecally administration, or is formulated for intravenous (IV) administration.

12. A cell comprising a dsRNA agent of any one of claims 1-10, optionally, the cell is a mammalian cell, optionally a human cell.

13. The double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-10 or the composition of claim 11 for use in inhibiting the expression of a MAPT gene in a cell.

14. The double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-10 or the composition of claim 11 for use in inhibiting expression of a MAPT gene in a subject;

preferably, the dsRNA agent is formulated to be administered to the subject subcutaneously; or
the dsRNA agent is formulated to be administered to the subject by IV administration or by intrathecally administration.

15. The double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-10 or the composition of claim 11 for use in treating a disease or condition associated with the presence of MAPT protein;
preferably, the disease or condition is one or more of: tauopathy, Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), FTLD with MAPT mutations, FTD with motor neuron disease, nonfluent variant primary progressive aphasia (nfvPPA), primary progressive aphasia-semantic (PPA-S), primary progressive aphasia-logopenic (PPA-L), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Pick's disease (PiD), argyrophilic grain disease (AGD), corticobasal degeneration (CBD), multiple system tauopathy with presenile dementia (MSTD), white matter tauopathy with globular glial inclusions (FTLD with GGIs),neurofibrillary tangle (NFT) dementia, amyotrophic lateral sclerosis (ALS), corticobasal syndrome (CBS), progressive supranuclear palsy (PSP), Parkinson's disease, postencephalitic Parkinsonism, Down syndrome (DS), Huntington disease, type 1 myotonic dystrophy, and Niemann-Pick disease;
preferably, the use further comprises an additional therapeutic regimen;
preferably, the additional therapeutic regimen comprises: one or more MAPT antisense polynucleotides of the invention, a non-MAPT dsRNA therapeutic agent, and a behavioral modification in the subject;
preferably, the non-MAPT dsRNA therapeutic agent is one of more of: a monoamine inhibitor, e.g., tetrabenazine (Xenazine), deutetrabenazine (Austedo), and reserpine, an anticonvulsant, e.g., valproic acid (Depakote, Depakene, Depacon), and clonazepam (Klonopin), an antipsychotic agent, e.g., risperidone (Risperdal), and haloperidol (Haldol), and an antidepressant, e.g., paroxetine (Paxil);
optionally, the dsRNA agent is formulated to be administered to the subject subcutaneously; or
the dsRNA agent is formulated to be administered to the subject by IV administration or by intrathecally administration.

16. The double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-10 or the composition of claim 11 for use in decreasing a level of MAPT protein in a subject compared to a baseline pre-treatment level of MAPT protein in the subject
preferably, the dsRNA agent is formulated to be administered to the subject by subcutaneously, to be administered to the subject by intrathecally or to be administered to the subject by IV administration.

17. The double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-10 or the composition of claim 11 for use in altering a physiological characteristic of a MAPT-associated disease or condition in a subject compared to a baseline pre-treatment physiological characteristic of the MAPT-associated disease or condition in the subject;
preferably, the dsRNA agent is formulated to be administered to the subject subcutaneously, to be administered to the subject by intrathecally or to be administered to the subject by IV administration;
preferably, the physiological characteristic is one or more of: the MAPT mRNA level, the MAPT protein level in the subject, variable progression of motor, cognitive, and behavioral impairment, or symptoms and hallmarks include loss of memory, loss of motor function, and/or increase in the number and/or volume of neurofibrillary inclusions.