

COMPOSITIONS AND METHODS FOR INHIBITING EXPRESSION OF MICROTUBULE
ASSOCIATED PROTEIN TAU (MAPT)

Field of the Invention

- 5 The invention relates, in part, to compositions and methods that can be used to inhibit a microtubule associated protein tau (mapt) gene expression.

Background

- 10 The microtubule associated protein tau (MAPT) is encoded by the MAPT gene located on chromosome 17q21. The MAPT gene consists of 16 exons. Alternative mRNA splicing gives rise to six MAPT isoforms with a total of 352-441 amino acids. In three of the six MAPT isoforms, the microtubule-binding domain of MAPT contains three repeated segments, whereas the corresponding domain contains four repeated segments in the other three MAPT isoforms.

- 15 MAPT transcripts are differentially expressed throughout the body, predominantly in the central (i.e., the brain and the spinal cord) and peripheral nervous system. Wild type Tau is involved in stabilizing microtubules in neuronal axons, maintaining dendritic spines, and regulating axonal transport, microtubule dynamics, and cell division. Pathogenic variants of MAPT are found in approximately 10% of patients with primary tauopathy. Variants are primarily missense mutations and localized in exons 9-13 (microtubule binding domains), with
20 many affecting the alternative splicing of exon 10. 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. Microtubules are essential for the maintenance of cellular integrity, for facilitating transport within and between cells, and cell division. As such, microtubules are important for axonal transport and for maintaining the structural integrity of
25 the cell. Tau protein is located within neurons, predominantly within axons. Tau protein is also found in other neuronal cells, such as astrocytes and oligodendrocytes in which it performs similar functions.

- 30 Tauopathies are a heterogeneous class of progressive neurodegenerative disorders pathologically characterized by the presence of Tau aggregates in the brain. Phenotypically, tauopathies show variable progression of motor, cognitive, and behavioral impairment. Tauopathies include, but are not limited to, Alzheimer's disease, frontotemporal dementia (FTD), and progressive supranuclear palsy (PSP). Tau is a major component of neurofibrillary tangles in the neuronal cytoplasm, a hallmark in Alzheimer's disease. The aggregation and deposition of Tau were also observed in approximately 50% of the brains of patients with Parkinson's disease.

- 35 Accordingly, MAPT gene RNAi agents disclosed herein for treating diseases, disorders, and conditions associated with tauopathies, and treatments are only aimed at alleviating the symptoms and improving the patient's quality of life, for example, that subjects having a MAPT-associated disorder, e.g., Alzheimer's disease, FTD, PSP, or another tauopathy, can be effectively treated.

Summary of the Invention

In general, the present disclosure features novel MAPT gene-specific RNAi agents, compositions that include MAPT RNAi agents, and methods for inhibiting expression of a MAPT gene in vitro and/or in vivo using the MAPT RNAi agents and compositions that include
5 MAPT RNAi agents described herein. The MAPT RNAi agents described herein can selectively and efficiently decrease, inhibit, or silence expression of a MAPT gene in a subject, e.g., a human or animal subject.

According to an aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT is provided, wherein the dsRNA agent including a
10 sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2 or 3 nucleotides from the nucleotide sequence of SEQ ID NO: 1, or 3 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2 or 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, or 4, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary
15 to each other.

In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein 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
20 in any one of Tables 1-3. In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein 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.

In some embodiments, the dsRNA agent including a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand including a region of complementarity to a
25 MAPT RNA transcript, wherein the region of complementarity includes 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 including a targeting ligand.

In some embodiments, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting
30 expression of MAPT is provided, 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,
35 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, 1577-1607, 2263-2293, 2332-2362, 2338-2368, 2339-2369, 2338-2369, 2706-2736, 2753-2783, 2754-2784, 2757-2787, 2352-2387, 2761-2791, 2778-2808, 2817-2847, 2818-2848, 2819-2849, 2717-2849, 2826-2856, 2833-2863 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.

In some embodiments, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT is provided, 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 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, 2331-2361, 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, 1582-1602, 2268-2288, 2337-2357, 2343-2363, 2344-2364, 2343-2364, 2711-2731, 2758-2778, 2759-2779, 2762-2782, 2758-2782, 2766-2786, 2783-2803, 2822-2842, 2823-2843, 2824-2844, 2822-2844, 2831-2851, 2838-2858 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.

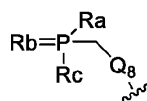
In some embodiments, the MAPT RNA transcript is SEQ ID NO: 1.

In some embodiments, the antisense strand of the dsRNA agent is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments, the antisense strand of the dsRNA agent is fully complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments, the dsRNA agent includes a sense strand sequence set forth in any one of Tables 1-3, wherein the sense strand sequence is at least substantially complementary to the antisense strand sequence in the dsRNA agent. In certain embodiments, the dsRNA agent includes a sense strand sequence set forth in any one of Tables 1-3, wherein the sense strand sequence is fully complementary to the antisense strand sequence in the dsRNA agent. In some embodiments, the dsRNA agent includes an antisense strand sequence set forth in any one of Tables 1-3. In some embodiments, the dsRNA agent includes the sequences set forth as a duplex sequence in any of Tables 1-3.

In some embodiments, the dsRNA agent includes at least one modified nucleotide. In certain embodiments, all or substantially all of the nucleotides of the antisense strand are modified nucleotides. In some embodiments, at least one of the modified nucleotides comprises: 2'-O-methyl nucleotide, 2'-fluoro nucleotide, 2'-deoxy nucleotide, 2'3'-seco nucleotide mimic, locked nucleotide, unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), 2'-F-Arabino nucleotide, 2'-methoxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2'-OMe nucleotide, inverted 2'-deoxy nucleotide, isomannide nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, and 3'-OMe nucleotide, a nucleotide including a 5'-phosphorothioate group, a 5'-phosphonate modified nucleotide or a terminal nucleotide linked to a cholesterol derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidite, or a non-natural base including nucleotide.

In some embodiments, the dsRNA agent further comprises a phosphate or phosphate mimic. In some embodiments, a 5'-phosphate or 5'-phosphate mimic is introduced at the 5'-terminal nucleotide of the antisense strand. In some embodiments, the phosphate mimic is a 5'-vinyl phosphonate (VP).

In certain embodiments, the phosphate mimic of the 5'-terminal nucleotide has a fragment represented by the following formula:



Wherein: Q₈ is O, S, SO, SO₂, PR¹⁶R¹⁷ or NR¹¹; R¹⁶ and R¹⁷ are independently (=O), (=S), OH, SH, C₁-C₆ alkyl, NR¹⁸R¹⁹; R¹⁶ and R¹⁷ are independently (=O), (=S), OH, SH, C₁-C₆ alkyl, NR¹⁸;

Ra and Rc are each independently selected from hydroxyl or protected hydroxyl, sulfhydryl or protected sulfhydryl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, protected or optional substituted amino, natural or modified nucleosides; and R_b is O or S or NR¹², R¹² is hydrogen, C₁-C₆ alkyl, amino protecting group;

the substituents in the substituted amino group are selected from: optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, sulfinyl, sulfonyl, acetyl;

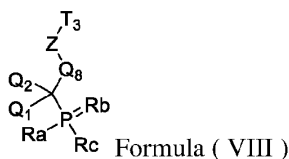
R¹¹, R¹⁸ and R¹⁹ are independently H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, methanesulfonyl, sulfonic acid group;

each substituted group comprises one or more optional substituent groups independently selected from: halogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfhydryl, CN;

" " indicates the linkage to the remainder of the 5'-terminal nucleotide. In certain embodiments, wherein Q₈ is bonded to the 4'-carbon or 5'-carbon of the sugar or sugar surrogate moiety of the 5'-terminal nucleotide.

In some embodiments, the dsRNA agent includes an E-vinylphosphonate nucleotide at the 5'-end of the guide strand.

In some embodiments, the dsRNA agent includes a 5'-phosphate mimic nucleotide represented by formula (VIII) or their stereoisomers or racemates at the 5'-end of the guide strand:



wherein: Q₈ is O, S, SO, SO₂, PR¹⁶R¹⁷ or NR¹¹; R¹⁶ and R¹⁷ are independently (=O), (=S), OH, SH, C₁-C₆ alkyl, NR¹⁸R¹⁹; Ra and Rc are each independently selected from hydroxyl or protected hydroxyl, sulfhydryl or protected sulfhydryl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, protected or optionally substituted amino, natural or modified nucleosides; and R_b is O or S or NR¹², R¹² is hydrogen, C₁-C₆ alkyl, amino protecting group;

Q₁ and Q₂ are each independently H, halogen, -CN, optionally substituted C₁-C₆ alkyl; the substituents in the substituted amino group are selected from: optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, sulfinyl, sulfonyl, acetyl;

R¹¹, R¹⁸ and R¹⁹ are independently H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, methanesulfonyl, and sulfonic acid group;

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

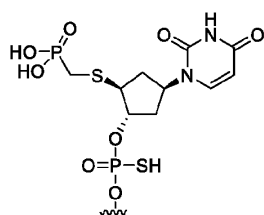
T₃ is an internucleotide linking group that connects the 5'-terminal nucleotide of formula (VIII) or its stereoisomer to the remainder of the 5'-end of the guide strand;

each substituted group comprises one or more substituent groups optionally independently selected from: halogen, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfhydryl, CN.

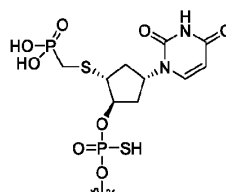
In a particular embodiments, in the provided nucleotide, Q₈ in formula (VIII) is S, SO or SO₂. In a particular embodiments, in the provided nucleotide, Q₁ and Q₂ in formula (VIII) are each independently H. In a particular embodiments, in the nucleotide provided in formula (VIII), in the nucleoside of the sugar or sugar surrogate moiety, the sugar or sugar surrogate moiety includes a 5 membered furanose ring, a non-furanose ring or 5-6 membered carbocyclic

system or open system. In a particular embodiments, in the nucleotide provided in Formula (VIII), in the nucleoside of the sugar or sugar-substituted moiety, the sugar-substituted moiety is selected from morpholinyl, cyclohexenyl, cyclohexyl, cyclopentyl, pyranyl, cyclohexanol. In a particular embodiments, in the nucleoside of the sugar or sugar surrogate moiety, the sugar moiety is a furanose. In a particular embodiments, the nucleoside of the sugar or sugar surrogate moiety includes an unlocked nucleobase analog (UNA) or a glycerol nucleobase analog (GNA). In a particular embodiment, the nucleosides of the sugar or sugar surrogate moiety include locked nucleic acid (LNA) or bridged nucleic acid (BNA). In a particular embodiment, nucleotide of formula (VIII) are provided, wherein Q_8 is bonded to the 4'-carbon or 5'-carbon of the sugar or sugar surrogate moiety. In particular embodiments, nucleotide of formula (VIII) is provided, wherein R_b is oxygen. In a particular embodiment, nucleotide of formula (VIII) is provided, wherein, R_a and R_c are each independently selected from OH, SH, NH_2 , $NHSO_2CH_3$.

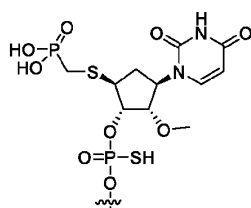
In some embodiments, the dsRNA agent includes a 5'-phosphate mimic nucleotide at the 5'-end of the guide strand select from the following structures or their stereoisomers or racemates:



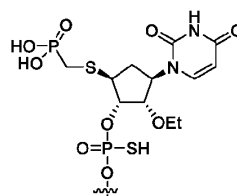
Phos-15-1*,



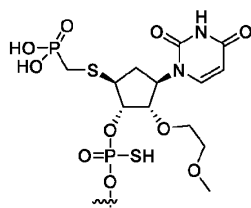
Phos-15-2*,



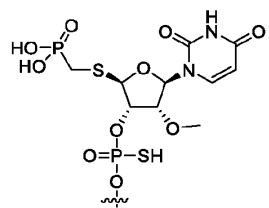
Phos-43*,



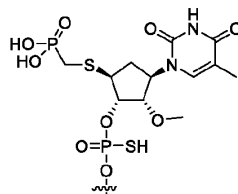
Phos-44*,



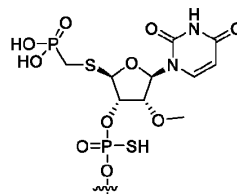
Phos-45*,



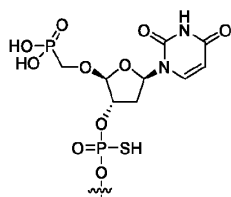
Phos-46*,



Phos-47*,



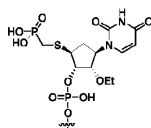
Phos-53*,



phos-16*, or their stereoisomers or racemates,

" " represents the linking moiety to the remainder of the 5'-end of the guide strand.

In certain embodiments, internucleotide linking group is independently select from: a phosphodiester linking group, a phosphotriester linking group, or a phosphorothioate linking group, phosphorodithioate linking group, alkylphosphonate linking group, aminophosphonate linking group, phosphonate linking group, phosphinate linking group, phosphorothioamidate linking group and phosphoramidate linking groups. For illustrate 5'-phosphate mimic nucleotide Phos-15-1* use phosphodiester linking group replacement phosphorothioate linking



10 has following structures Phos-15-1.

In certain embodiments, the dsRNA agent includes at least one phosphorothioate internucleoside linkage. In certain embodiments, the sense strand includes at least one phosphorothioate internucleoside linkage. In some embodiments, the antisense strand includes at least one phosphorothioate internucleoside linkage. In some embodiments, the sense strand includes 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages. In certain embodiments, the antisense strand includes 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages. In some embodiments, the 5' end of antisense strand includes 2 phosphorothioate internucleoside linkages. In some embodiments, the 3' end of antisense strand includes 2 phosphorothioate internucleoside linkages. In some embodiments, the 5' end of antisense strand and 3' end of antisense strand includes independently 2 phosphorothioate internucleoside linkages.

In certain embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first internucleotide linkage at the 3' end of the antisense strand, having the phosphorothioate internucleoside linkage phosphorus atom in Sp configuration. In certain embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first phosphorothioate internucleoside linkage at the 5' end of the antisense strand, having the phosphorothioate internucleoside linkage phosphorus atom in Rp configuration. In certain embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the phosphorothioate internucleoside linkage phosphorus atom in either Rp configuration or Sp configuration. In another embodiment, the dsRNA agent further comprises a terminal, chiral modification occurring at the first and second internucleotide linkages at the 3' end of the

antisense strand, having the phosphorothioate internucleoside linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the phosphorothioate internucleoside linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first
 5 internucleotide linkage at the 5' end of the sense strand, having the phosphorothioate internucleoside linkage phosphorus atom in either Rp or Sp configuration.

In one embodiment, one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand, such as via a linker or carrier. In one embodiment, the internal positions include all positions except the terminal two positions from each end of the at
 10 least one strand. In another embodiment, the internal positions include all positions except the terminal three positions from each end of the at least one strand. In one embodiment, the internal positions exclude a cleavage site region of the sense strand. In one embodiment, the internal positions exclude a cleavage site region of the antisense strand. In one embodiment, the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from
 15 the group consisting of positions 4-8 and 13-18 on the sense strand counting from the 3' end of sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5' end of antisense strand. In another embodiment, the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 5, 6, 15, 16, and 17 on the sense strand counting from the 3' end of sense strand, and positions 15 and 17 on
 20 the antisense strand counting from the 5' end of antisense strand. In one embodiment, the internal positions in the double stranded region exclude a cleavage site region of the sense strand. In one embodiment, the sense strand is 21 nucleotides in length, the antisense strand is 21 nucleotides in length, and the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the
 25 antisense strand counting from the 5' end of antisense strand. In one embodiment, the lipophilic moiety is conjugated to position 1, position 2, position 7, position 21, or position 15 of the sense strand counting from the 3' end of sense strand. In another embodiment, the lipophilic moiety is conjugated to position 1, position 2, or position 7 of the sense strand counting from the 3' end of sense strand. In yet another embodiment, the lipophilic moiety is conjugated to position 2 or
 30 position 7 of the sense strand counting from the 3' end of sense strand. In one embodiment, the lipophilic moiety is conjugated to position 16 of the antisense strands counting from the 5' end of antisense strand.

In one embodiment, the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound. In one embodiment, the lipophilic moiety is selected from the group consisting of
 35 lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl) lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine. In one embodiment, the lipophilic moiety contains a saturated or unsaturated C₄-C₃₀ hydrocarbon chain, and an

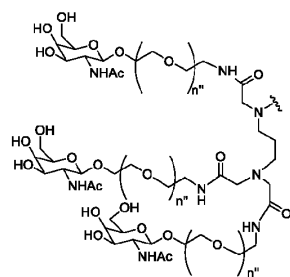
optional substituted functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne. In one embodiment, the lipophilic moiety contains a saturated or unsaturated C₆-C₁₈ hydrocarbon chain. In one embodiment, the lipophilic moiety contains a saturated or unsaturated C₁₆ hydrocarbon chain. In one embodiment, the saturated or unsaturated C₁₆ hydrocarbon chain is conjugated to position 15 or 16, counting from the 5'-end of the strand. In one embodiment, the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region. In one embodiment, the carrier is a cyclic group selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3] dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalanyl, pyridazinonyl, tetrahydrofuranyl, and decalanyl; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone. In one embodiment, the lipophilic moiety is conjugated to the double-stranded iRNA agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate. In one embodiment, the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage. In one embodiment, the lipophilic moiety is conjugated via a bio-linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

In some embodiments, all or substantially all of the nucleotides of the sense strand and the antisense strand are modified nucleotides. In some embodiments, the antisense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide, a 2'-fluoro nucleotide and an UNA modified nucleotide, wherein less than 6 modified nucleotides are 2'-fluoro nucleotides. In some embodiments, the antisense strand comprises 3 or 5 2'-fluoro nucleotides, preferably, the antisense strand comprises 5 2'-fluoro nucleotides. In some embodiments, the sense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein less than 4 modified nucleotides are 2'-fluoro nucleotides. In certain embodiments, the sense strand comprises 3 2'-fluoro nucleotides. In some embodiments, the antisense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least 14 modified nucleotides are 2'-O-methyl nucleotides and the nucleotides at positions 2, 5, 7, 11, 12, 14, 16 and/or 18 counting from the first matching position of the 5' end of the antisense strand are independently a 2'-fluoro nucleotide. In some embodiments, the antisense strand comprises at least one UNA modified nucleotide and 5 2'-fluoro nucleotides. In some embodiments, the antisense strand comprises one UNA modified nucleotide at position 7 and 5 2'-fluoro nucleotides at positions 2, 5, 12, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises one UNA modified nucleotide at position 7 and 5 2'-fluoro nucleotides at positions 2, 5, 12, 14 and 18 counting from the first matching position of the 5' end, and the rest

2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises one UNA modified nucleotide at position 7 and 5 2'-fluoro nucleotides at positions 2, 5, 11, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises 5 2'-fluoro nucleotides at positions 2, 7, 12, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises 5 2'-fluoro nucleotides at positions 2, 7, 11, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises 5 2'-fluoro nucleotides at positions 2, 5, 12, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises 5 2'-fluoro nucleotides at positions 2, 5, 11, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the sense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, preferably, wherein at least 18 modified nucleotides are 2'-O-methyl nucleotides and the nucleotides at positions 9, 11 and/or 13 counting from the first matching position of the 3' end of the sense strand are 2'-fluoro nucleotides. In some embodiments, the sense strand comprises at least 18 modified nucleotides are 2'-O-methyl nucleotides and the nucleotides at positions 8, 11 and/or 13 counting from the first matching position of the 3' end of the sense strand are 2'-fluoro nucleotides. In some embodiments, the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-3. In some embodiments, the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-3.

In some embodiments, the dsRNA agent includes at least one modified nucleotide and further includes one or more targeting groups or linking groups. In some embodiments, the one or more targeting groups or linking groups are conjugated to the sense strand. In some embodiments, the targeting group or linking group includes N-acetyl-galactosamine (GalNAc).

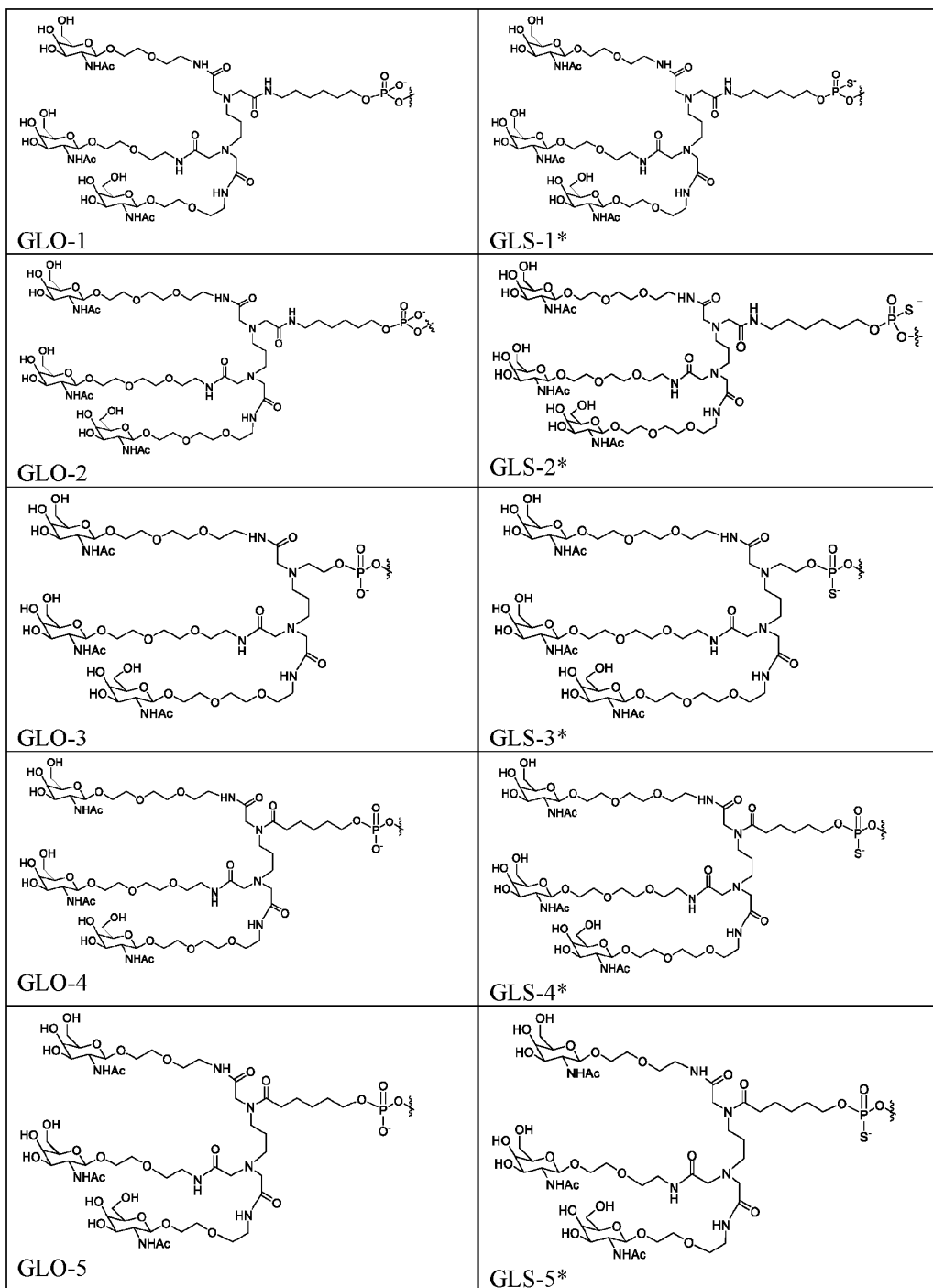
In some embodiments, the targeting group include the following structure:

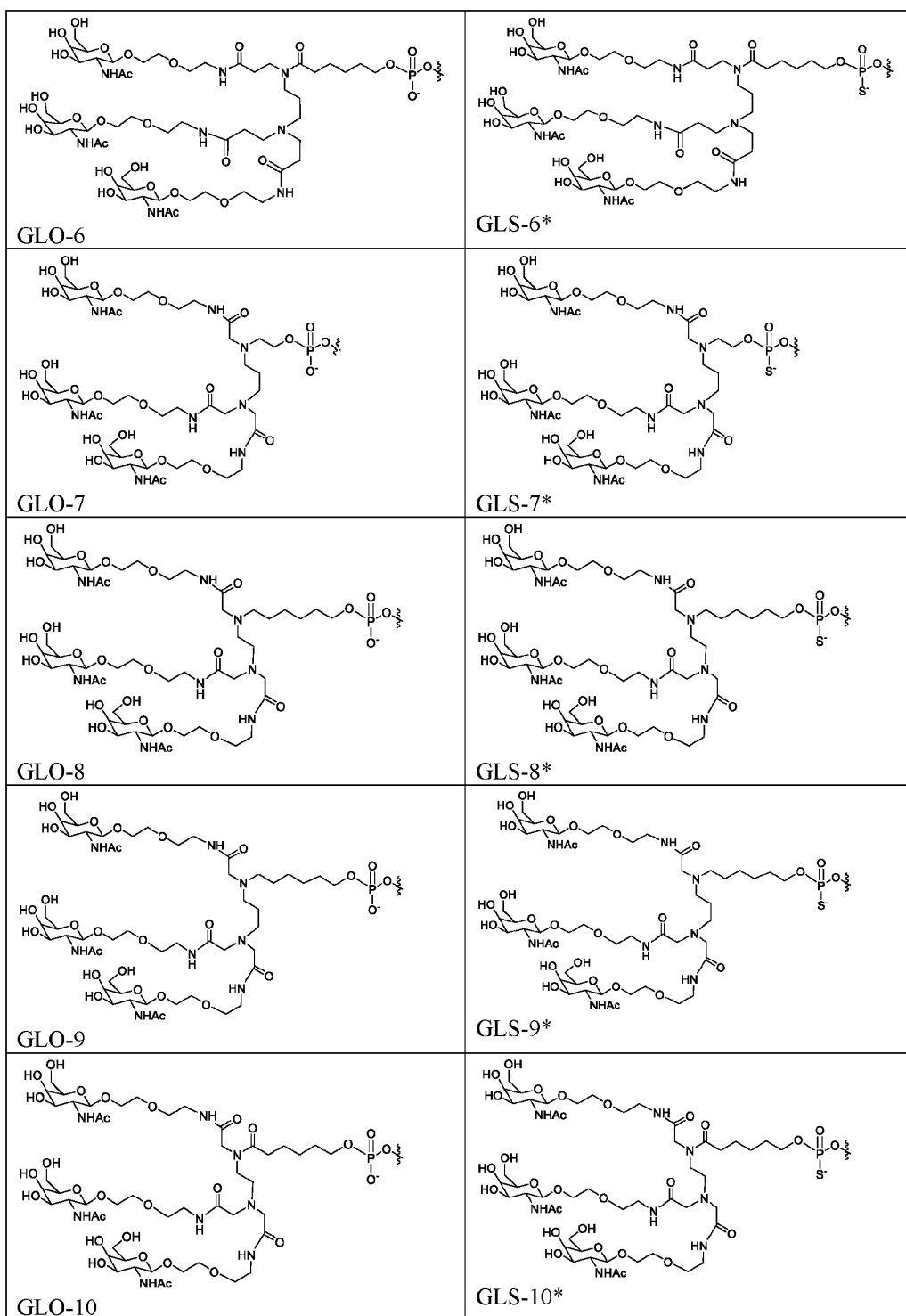


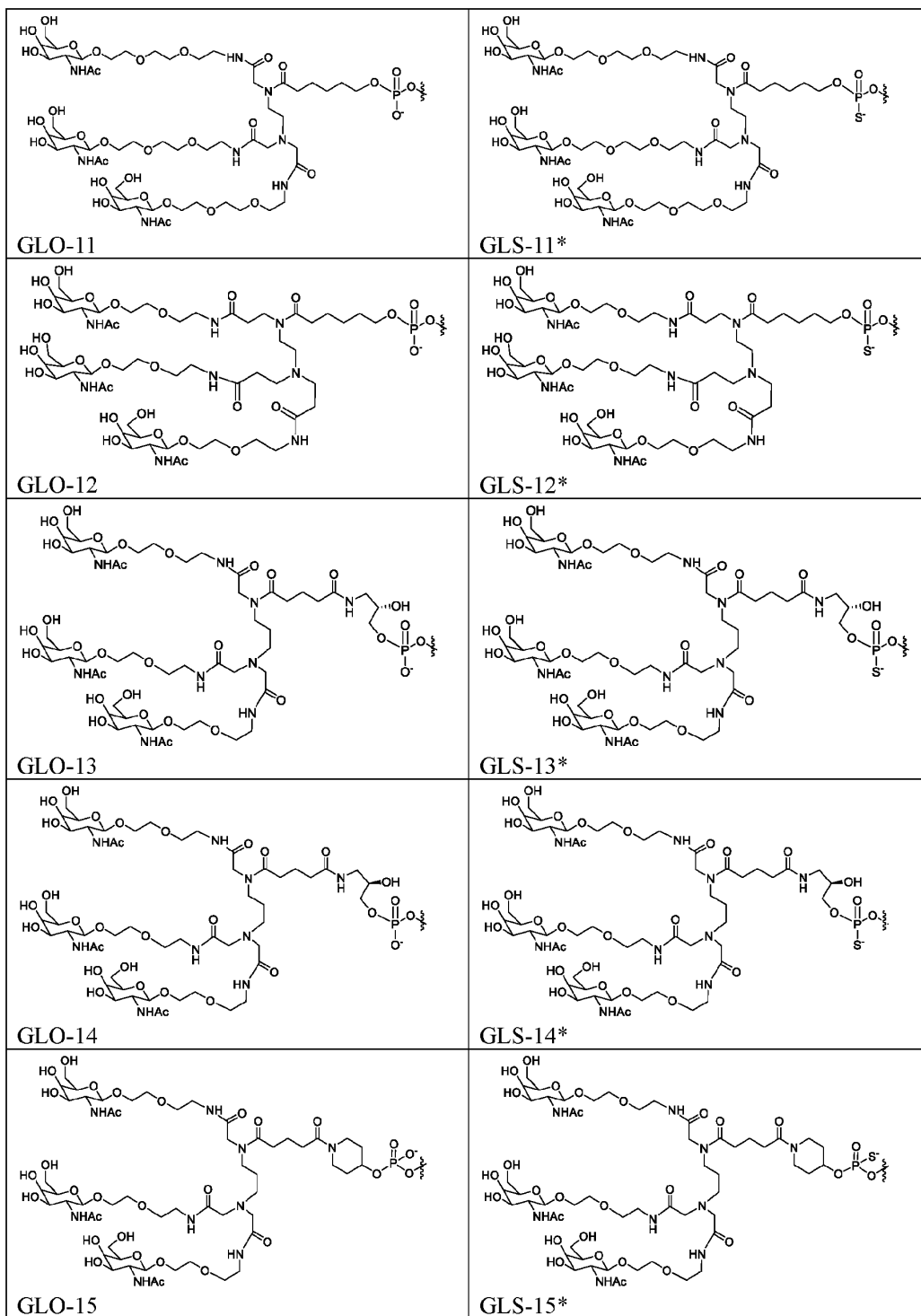
Formula 1

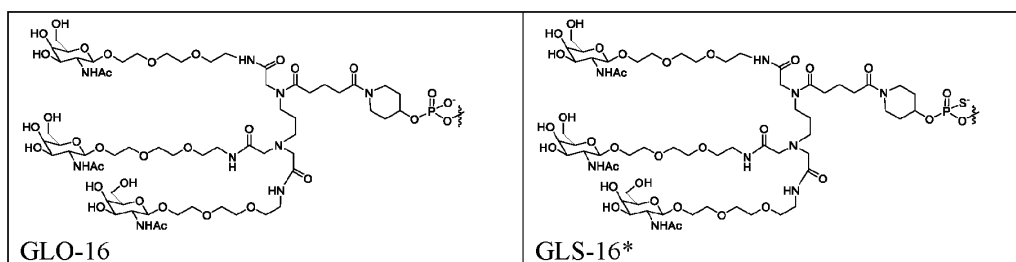
Each n'' is independently selected from 1 or 2.

In some embodiments, the targeting group has a structure:









In certain embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand. In some embodiments, the dsRNA agent includes a targeting group that is conjugated to the 3'-terminal end of the sense strand.

- 5 In some embodiments, the antisense strand includes one inverted abasic residue at 3'-terminal end.

- In certain embodiments, the sense strand includes one or two inverted abasic residues and/or one or two imann residues at 3' or/and 5' terminal end. In certain embodiments, each end of the sense strand includes one inverted abasic residue respectively. In certain embodiments, each end of the sense strand includes one imann residue respectively. In some embodiments, one or more inverted abasic residues or one or more imann residues conjugate to either end or both ends of the sense strand via phosphorothioate linkages. In some embodiments, the targeting group further conjugates to either end of the sense strand via a phosphorothioate linkage. In some embodiments, the targeting group further conjugates to 5'-end of the sense strand via a phosphorothioate linkage. In certain embodiments, one inverted abasic residue or imann residues at the 5' terminal end of the sense strand, wherein inverted abasic residue or imann residues is linked to an adjacent nucleotide via a phosphorothioate linkage to the 5' terminal end of the nucleotide sequence of the sense strand. In certain embodiments, one inverted abasic residue or imann residues at the 3' terminal end of the sense strand, wherein inverted abasic residue or imann residues is linked to an adjacent nucleotide via a phosphorothioate linkage to the 3' terminal end of the nucleotide sequence of the sense strand. In certain embodiments, the sense strand further includes targeting group linked to an inverted abasic residue or an imann residue at the 5' terminal end of the sense strand, wherein targeting group is linked to an adjacent inverted abasic residue or imann via a phosphorothioate linkage, and optionally targeting group is N-acetyl-galactosamine (GalNAc).

In some embodiments, the dsRNA agent has two blunt ends. In some embodiments, at least one strand includes a 3' overhang of at least 1 nucleotide. In some embodiments, at least one strand includes a 3' overhang of at least 2 nucleotides.

- In certain embodiments, the dsRNA comprises a duplex selected from AV03732, AV03733, AV03734, AV03736, AV03739, AV03741, AV03750, AV03751, AV03752, AV03754, AV03768, AV03770, AV03771, AV03791, AV03792, AV03793, AV03794, AV03795, AV03796, AV03797, AV03798, AV03799, AV03800, AV03804, AV03805, AV03806, AV03807, AV03809, AV03817, AV03826, AV03827, AV03829, AV03831, AV03832,

AV03833, AV03834, AV03835, AV03836, AV03837, AV03838, AV03839, AV03840, AV03842, and wherein duplex optionally including a targeting ligand.

According to another aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT is provided, 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):



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.

In some embodiments, N'_{N1} and N'_{N2} include only one 2'-Fluorine modified nucleotides.

In some embodiments, N'_{N1} independently represents a 2'-fluoro-modified nucleotide, optionally, N'_{N2} independently represents a 2'-O-methyl -modified nucleotide.

In some embodiments, N'_{N2} independently represents a 2'-fluoro-modified nucleotide, optionally, N'_{N1} independently represents a 2'-O-methyl -modified nucleotide.

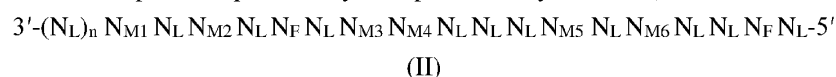
In some embodiments, m' is 2 and n' is 4, or m' is 2 and n' is 2. In some embodiments, m' is 1 and n' is 4, or m' is 1 and n' is 2. In some embodiments, m' is 0 and n' is 4, or m' is 0 and n' is 2.

In some embodiments, each N'_L independently represents a 2'-O-methyl nucleotide.

In some embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand, preferably, the targeting group is any one selected from aforesaid GLO-1 through GLO-16 and GLS-1* through GLS-16*, more preferably, the targeting group is aforesaid GLS-15*. In certain embodiments, the dsRNA agent includes a targeting group that is conjugated to the 3'-terminal end of the sense strand. In certain embodiments, the antisense strand includes one inverted abasic residue at 3'-terminal end. In certain embodiments, the sense strand includes one or two inverted abasic residues and/or one or two imann residues at 3' or/and 5' terminal end. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an inverted abasic residue. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an imann residue. In certain embodiments, the sense strand includes two inverted abasic residues at 3' and 5' terminal end and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, the sense strand includes two imann residues at 3' and 5' terminal end and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, 5' end of

the sense strand includes one inverted abasic residue or imann residues at the 5' terminal end of the sense strand, wherein inverted abasic residue or imann residues is linked to an adjacent nucleotide via a phosphorothioate linkage to the 5' terminal end of the nucleotide sequence of the sense strand. In certain embodiments, 3' end of the sense strand includes one inverted abasic residue or imann residues at the 3' terminal end of the sense strand, wherein inverted abasic residue or imann residues is linked to an adjacent nucleotide via a phosphorothioate linkage to the 3' terminal end of the nucleotide sequence of the sense strand. In certain embodiments, the sense strand further includes targeting group linked to an inverted abasic residue or an imann residue at the 5' terminal end of the sense strand, wherein targeting group is linked to an adjacent inverted abasic residue or imann via a phosphorothioate linkage, and optionally targeting group is N-acetyl-galactosamine (GalNAc). In certain embodiments, at the 5' terminal end of the sense strand includes one inverted abasic residue, wherein inverted abasic residue is linked to an adjacent nucleotide via a phosphorothioate linkage to the 5' terminal end of the nucleotide sequence of the sense strand. In certain embodiments, the sense strand further includes targeting group linked to an inverted abasic residue at the 5' terminal end of the sense strand, wherein targeting group is linked to an adjacent inverted abasic residue via a phosphorothioate linkage, and optionally targeting group is N-acetyl-galactosamine (GalNAc), the each strand is independently 21 nucleotides in length. In some embodiments, the antisense strand of the dsRNA agent is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3.

According to another aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT is provided, 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 a MAPT RNA transcript, wherein each strand is about 18 to about 30 nucleotides in length, wherein the antisense strand comprises sequence may be represented by formula (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.

In some embodiments, N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , and N_{M6} have only three 2'-fluoro-modified nucleotides. In some embodiments, N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , and N_{M6} independently represents a 2'-fluoro-modified nucleotide, a 2'-O-methyl nucleotide, an UNA modified nucleotide or a nucleotide comprising phosphate mimic. In some embodiments, the modified

nucleotide is a modified nucleotide defined above. In some embodiments, each N_L independently represents a 2'-O-methyl nucleotide.

In some embodiments, N_{M2} , N_{M3} and N_{M5} each independently represents a 2'-fluoro-modified nucleotide, optionally, N_{M1} , N_{M4} and N_{M6} independently represents a 2'-O-methyl -
5 modified nucleotide.

In some embodiments, N_{M2} , N_{M4} and N_{M5} each independently represents a 2'-fluoro-modified nucleotide, optionally, N_{M1} , N_{M3} and N_{M6} independently represents a 2'-O-methyl -
modified nucleotide.

In some embodiments, N_{M1} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-
10 modified nucleotide, optionally, N_{M2} , N_{M4} and N_{M5} independently represents a 2'-O-methyl -
modified nucleotide.

In some embodiments, N_{M2} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide, optionally, N_{M1} , N_{M4} and N_{M5} independently represents a 2'-O-methyl -
modified nucleotide.

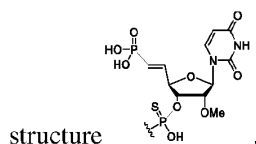
15 In some embodiments, N_{M2} , N_{M4} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide, optionally, N_{M1} , N_{M3} and N_{M5} independently represents a 2'-O-methyl -
modified nucleotide.

In some embodiments, N_{M1} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide and N_{M5} represents an UNA modified nucleotide, optionally, N_{M2} and N_{M4}
20 independently represents a 2'-O-methyl -modified nucleotide.

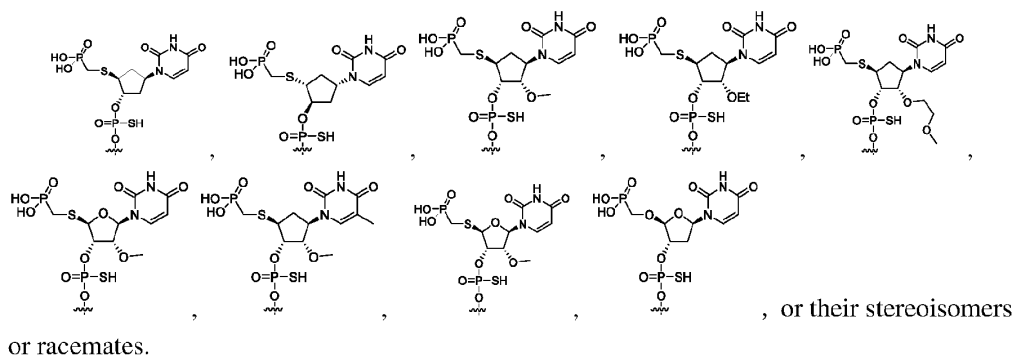
In some embodiments, N_{M2} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide and N_{M5} represents an UNA modified nucleotide, optionally, N_{M1} and N_{M4}
independently represents a 2'-O-methyl -modified nucleotide.

In some embodiments, N_{M2} , N_{M4} and N_{M6} each independently represents a 2'-fluoro-
25 modified nucleotide and N_{M5} represents an UNA modified nucleotide, optionally, N_{M1} and N_{M6}
independently represents a 2'-O-methyl -modified nucleotide.

In some embodiments, the first N_L nucleotide (counting from 5' end) is VPu*, which has the



In some embodiments, the first N_L nucleotide (counting from 5' end) is selected from the
30 group consisting of



In some embodiments, n is 1, or n is 2, or n is 3, or n is 5.

- 5 In some embodiments, the antisense strand of the dsRNA agent is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3.

According to another aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT is provided, wherein the dsRNA agent including a sense strand and an antisense strand, 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 duplex comprises represented by formula (III):

- 15 sense: 5'-(N'_L)_nN'_LN'_LN'_LN'_LN'_LN'_FN'_LN'_FN'_LN'_{N1}N'_{N2}N'_LN'_LN'_LN'_LN'_L(N'_L)_m-3'
 antisense: 3'-(N_L)_nN_{M1}N_LN_{M2}N_LN_FN_LN_{M3}N_{M4}N_LN_LN_LN_{M5}N_LN_{M6}N_LN_LN_FN_L-5'
 (III)

wherein:

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

- 20 each N_F and N'_F independently represents a 2'-fluoro-modified nucleotide; N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, N_{M6}, N'_{N1}, and N'_{N2} each independently represents a modified or unmodified nucleotide; 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.

- In some embodiments, N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, and N_{M6} have only three 2'-fluoro-modified nucleotides, N'_{N1} and N'_{N2} include only one 2'-Fluorine modified nucleotides. In some embodiments, each N'_L and N_L independently represents a 2'-O-methyl nucleotide. In some embodiments, N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, and N_{M6} independently represents a 2'-fluoro-modified nucleotide, a 2'-O-methyl nucleotide, an UNA modified nucleotide or a nucleotide comprising phosphate mimic. In some embodiments, N'_{N1} and N'_{N2} independently represents a 2'-fluoro-modified nucleotide, a 2'-O-methyl nucleotide. In some embodiments, the modified nucleotide is a modified nucleotide defined above.

In some embodiments, m' is 2 and n' is 4, m' is 2 and n' is 6, or m' is 2 and n' is 2. In some embodiments, m' is 1 and n' is 4, or m' is 1 and n' is 2. In some embodiments, m' is 0 and n' is 4, or m' is 0 and n' is 2. In some embodiments, n is 1, or n is 2, or n is 3, or n is 5.

In some embodiments, N'_{N1} independently represents a 2'-fluoro-modified nucleotide.

5 In some embodiments, N'_{N2} independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M2} , N_{M3} and N_{M5} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M2} , N_{M4} and N_{M5} each independently represents a 2'-fluoro-modified nucleotide.

10 In some embodiments, N_{M1} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M2} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide.

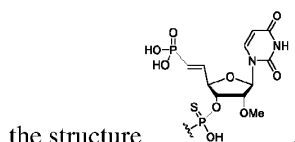
15 In some embodiments, N_{M2} , N_{M4} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M1} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide and N_{M5} represents an UNA modified nucleotide.

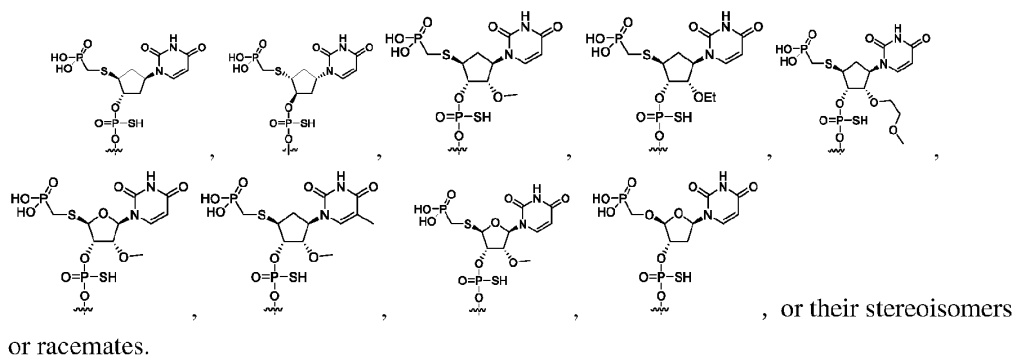
In some embodiments, N_{M2} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide and N_{M5} represents an UNA modified nucleotide.

20 In some embodiments, N_{M2} , N_{M4} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide and N_{M5} represents an UNA modified nucleotide.

In some embodiments, the first N_L nucleotide (counting from 5' end) is VPu^* , which has



25 In some embodiments, the first N_L nucleotide (counting from 5' end) is selected from the group consisting of



In some embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand, preferably, the targeting group is any one selected from aforesaid GLO-1 through GLO-16 and GLS-1* through GLS-16*, more preferably, the targeting group is aforesaid GLS-15*. In certain embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand. In certain embodiments, the antisense strand includes one inverted abasic residue at 3'-terminal end. In certain embodiments, the sense strand includes one or two inverted abasic residues and/or one or two imann residues at 3' or/and 5' terminal end. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an inverted abasic residue. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an imann residue. In certain embodiments, the sense strand includes two inverted abasic residues at 3' and 5' terminal end and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, the sense strand includes two imann residues at 3' and 5' terminal end and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, the dsRNA agent has two blunt ends. In certain embodiments, at least one strand includes a 3' overhang of at least 1 nucleotide. In certain embodiments, at least one strand includes a 3' overhang of at least 2 nucleotides.

In certain embodiments, the antisense strand of the dsRNA agent is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3.

According to an aspect of the invention, a composition is provided that includes any embodiment of the aforementioned dsRNA agent aspect of the invention. In certain embodiments, the composition also includes a pharmaceutically acceptable carrier. In some embodiments, the composition also includes one or more additional therapeutic agents. In certain embodiments, the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial. In some embodiments, the composition is formulated for subcutaneous administration, formulated for intrathecally administration, or is formulated for intravenous (IV) administration.

According to another aspect of the invention a cell is provided that includes any embodiment of an aforementioned dsRNA agent aspect of the invention. In some embodiments, the cell is a mammalian cell, optionally a human cell.

According to another aspect of the invention, a method of inhibiting the expression of a MAPT gene in a cell, is provided, the method including: (i) preparing a cell including an effective amount of any embodiment of the aforementioned dsRNA agent aspect of the invention or any embodiment of an aforementioned composition of the invention. In certain embodiments, the method also includes: (ii) maintaining the prepared cell for a time sufficient to obtain degradation of the mRNA transcript of a MAPT gene, thereby inhibiting expression of the MAPT gene in the cell. In some embodiments, the cell is in a subject and the dsRNA agent is administered to the subject subcutaneously. In some embodiments, the cell is in a subject and the dsRNA agent is administered to the subject by IV administration. In some embodiments, the cell is in a subject and the dsRNA agent is administered to the subject by intrathecally administration. In certain embodiments, the method also includes assessing inhibition of the MAPT gene, following the administration of the dsRNA agent to the subject, wherein a means for the assessing comprises: (i) determining one or more physiological characteristics of a MAPT-associated disease or condition in the subject and (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the MAPT-associated disease or condition and/or to a control physiological characteristic of the MAPT-associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the MAPT gene in the subject. In some embodiments, the physiological characteristic is one or more of: the MAPT mRNA level and the MAPT protein level in a blood, serum, or cerebrospinal fluid sample(s). A reduction in the expression of MAPT may also be assessed indirectly by measuring a decrease in biological activity of MAPT, e.g., or additional pathologies associated with elevated levels of MAPT, preferably in the blood, serum, or cerebrospinal fluid sample(s). a decrease in one or more of: MAPT mRNA level, MAPT protein level.

According to another aspect of the invention, a method of inhibiting expression of a MAPT gene in a subject, is provided, the method including administering to the subject an effective amount of an embodiment of the aforementioned dsRNA agent aspect of the invention or an embodiment of an aforementioned composition of the invention. In some embodiments, the dsRNA agent is administered to the subject subcutaneously. In certain embodiments, the dsRNA agent is administered to the subject by IV administration. In some embodiments, the dsRNA agent is administered to the subject by intrathecally administration. In some embodiments, the method also includes: assessing inhibition of the MAPT gene, following the administration of the dsRNA agent, wherein a means for the assessing comprises: (i) determining one or more physiological characteristics of a MAPT-associated disease or condition in the subject and (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the MAPT-associated disease or condition and/or to a

control physiological characteristic of the MAPT-associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the MAPT gene in the subject. In some embodiments, expression of the MAPT gene can be assessed based on the level or change in level of any variable associated with MAPT gene expression, such as MAPT mRNA level, MAPT protein (tau) level. A reduction in the expression of MAPT may also be assessed indirectly by measuring a decrease in biological activity of MAPT, e.g., or additional pathologies associated with elevated levels of MAPT, preferably in the blood, serum, or cerebrospinal fluid sample(s). Phenotypically, tauopathies show variable progression of motor, cognitive, and behavioral impairment. Tauopathies are a heterogeneous class of progressive neurodegenerative disorders pathologically characterized by the presence of Tau aggregates in the brain. Phenotypically, tauopathies show variable progression of motor, cognitive, and behavioral impairment. Tauopathies are a heterogeneous class of progressive neurodegenerative disorders pathologically characterized by the presence of tau aggregates in the brain.

According to another aspect of the invention, a method of treating a disease or condition associated with the presence of MAPT protein (tau) is provided, the method including: administering to a subject an effective amount of an embodiment of any aforementioned dsRNA agent aspect of the invention or an embodiment of any aforementioned composition of the invention, to inhibit MAPT gene expression. In one embodiment, the disorder is a MAPT associated disorder. In one embodiment, the disorder is associated with an abnormality of MAPT gene encoded protein Tau. In one embodiment, the abnormality of MAPT gene encoded protein Tau results in aggregation of Tau in subject's brain. In certain embodiments, MAPT-associated disorder a neurodegenerative disease. In one embodiment, the neurodegenerative disorder is a familial disorder. In one embodiment, the neurodegenerative disorder is a sporadic disorder. In some embodiments, the disease, disorder or condition associated with MAPT is selected from the group consisting 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.

In some embodiments, the method also includes: administering an additional therapeutic regimen to the subject. In some embodiments, the additional therapeutic regimen includes a treatment for the MAPT-associated disease or condition. In certain embodiments, the additional therapeutic regimen comprises: administering to the subject one or more MAPT antisense

polynucleotides of the invention, administering to the subject a non-MAPT dsRNA therapeutic agent, and a behavioral modification in the subject. In some embodiments, the additional therapeutic agent is selected from the group consisting of an oligonucleotide, a small molecule, a monoclonal antibody, a polyclonal antibody and a peptide. Exemplary additional therapeutics include, for example, 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).

In some embodiments, the dsRNA agent is administered to the subject subcutaneously. In certain embodiments, the dsRNA agent is administered to the subject by IV administration. In some embodiments, the dsRNA agent is administered to the subject by intrathecally. In yet another embodiment, the dsRNA agent is administered to the subject intracisternally. A non-limiting exemplary intracisternal administration comprises an injection into the cisterna magna (cerebellomedullary cistern) by suboccipital puncture. In some embodiments, the method also includes determining an efficacy of the administered double-stranded ribonucleic acid (dsRNA) agent in the subject.

In some embodiments, a means of determining an efficacy of the treatment in the subject comprises: (i) determining one or more physiological characteristics of the MAPT-associated disease or condition in the subject and (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the MAPT-associated disease or condition wherein the comparison indicates one or more of a presence, absence, and level of efficacy of the administration of the double-stranded ribonucleic acid (dsRNA) agent to the subject.

In some embodiments, expression of the MAPT gene can be assessed based on the level or change in level of any variable associated with MAPT gene expression, such as MAPT mRNA level, MAPT(tau) protein level in the subject, or symptoms and hallmarks include loss of memory, loss of motor function, and/or increase in the number and/or volume of neurofibrillary inclusions.

According to another aspect of the invention, a method of decreasing a level of MAPT protein in a subject compared to a baseline pre-treatment level of MAPT protein in the subject, is provided, the method including administering to the subject an effective amount of an embodiment of any aforementioned dsRNA agent of the invention or an embodiment of any aforementioned composition of the invention, to decrease the level of MAPT gene expression. In some embodiments, the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration. In some embodiments, the dsRNA agent is administered to the subject by intrathecally. In yet another embodiment, the dsRNA agent is administered to the subject intracisternally. A non-limiting exemplary intracisternal administration comprises an injection into the cisterna magna (cerebellomedullary cistern) by suboccipital puncture.

According to another aspect of the invention, a method of 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 is provided, the method including administering to the subject an effective amount of an embodiment of any aforementioned dsRNA agent of the invention or an embodiment of any
5 aforementioned composition of the invention, to alter the physiological characteristic of the MAPT-associated disease or condition in the subject. In some embodiments, the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration. In some embodiments, the dsRNA agent is administered to the subject by
10 intrathecally. In yet another embodiment, the dsRNA agent is administered to the subject intracisternally. A non-limiting exemplary intracisternal administration comprises an injection into the cisterna magna (cerebellomedullary cistern) by suboccipital puncture. In certain embodiments, the physiological characteristic and symptoms are one or more of: MAPT mRNA level, MAPT protein level in the subject, or variable progression of motor, cognitive, and
15 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. In certain embodiments, administering the dsRNA causes a decrease in MAPT gene mRNA in one or more of the hippocampus, striatum, cortex, cerebellum, thalamus, hypothalamus, and spinal cord.

According to another aspect of the invention, the aforementioned dsRNA agent for use
20 in a method of treating a disease or condition associated with the presence of MAPT protein is provided. In some embodiments, the disease or condition is one or more of: tauopathy, Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), FTLN with MAPT mutations, FTD with motor neuron disease, nonfluent variant primary progressive aphasia (nfvPPA), primary progressive aphasia-semantic (PPA-S), primary
25 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
30 supranuclear palsy (PSP), Parkinson's disease, postencephalitic Parkinsonism, Down syndrome (DS), Huntington disease, type 1 myotonic dystrophy, and Niemann-Pick disease.

According to another aspect of the invention, an antisense polynucleotide agent for inhibiting expression of MAPT protein is provided, the agent including from 10 to 30 contiguous nucleotides, wherein at least one of the contiguous nucleotides is a modified nucleotide, and
35 wherein the nucleotide sequence of the agent is about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NO: 1. In some embodiments, the equivalent region is any one of the target regions of SEQ ID NO: 1 and the complementary sequence is one provided in one of Tables 1-3. In certain embodiments, the antisense polynucleotide agent includes one of the antisense sequences provided in one of Tables 1-3.

According to another aspect of the invention, a composition including an embodiment of any aforementioned antisense polynucleotide agents is provided. In some embodiments, the composition also includes a pharmaceutically acceptable carrier. In some embodiments, the composition also includes one or more additional therapeutic agents for treatment of a MAPT-associated disease or condition. In certain embodiments, the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial. In certain embodiments, the composition is formulated for subcutaneous, intrathecally or IV administration.

According to another aspect of the invention a cell that includes an embodiment of any of the aforementioned antisense polynucleotide agents is provided. In some embodiments, the cell is a mammalian cell, optionally a human cell.

According to another aspect of the invention, a method of inhibiting the expression of a MAPT gene in a cell is provided, the method including: (i) preparing a cell including an effective amount of an embodiment of any aforementioned antisense polynucleotide agents. In some embodiments, the method also includes (ii) maintaining the cell prepared in (i) for a time sufficient to obtain degradation of the mRNA transcript of a MAPT gene, thereby inhibiting expression of the MAPT gene in the cell.

According to another aspect of the invention, a method of inhibiting expression of a MAPT gene in a subject is provided, the method including administering to the subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agent.

According to another aspect of the invention, a method of treating a disease or condition associated with the presence of MAPT protein, the method including administering to a subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agents or an embodiment of any aforementioned composition of the invention, to inhibit MAPT gene expression. In certain embodiments, the disease or condition is one or more of: tauopathy, Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), FTLN 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.

According to another aspect of the invention, a method of decreasing a level of MAPT protein in a subject compared to a baseline pre-treatment level of MAPT protein in the subject is provided, the method including administering to the subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agents or an embodiment of any aforementioned composition of the invention, to decrease the level of MAPT gene

expression. In certain embodiments, the antisense polynucleotide agent is administered to the subject subcutaneously or by IV administration. In some embodiments, the antisense polynucleotide agent is administered to the subject by intrathecally. In yet another embodiment, the antisense polynucleotide agent is administered to the subject intracisternally. A non-limiting exemplary intracisternal administration comprises an injection into the cisterna magna (cerebellomedullary cistern) by suboccipital puncture.

According to another aspect of the invention, an antisense polynucleotide agent for inhibiting expression of MAPT gene, is provided, the agent including from 10 to 30 contiguous nucleotides, wherein at least one of the contiguous nucleotides is a modified nucleotide, and wherein the nucleotide sequence of the agent is about 80% or about 85% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NO: 1.

According to another aspect of the invention, a method of 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 is provided, the method including administering to the subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agents or an embodiment of any aforementioned composition of the invention, to alter the physiological characteristic of the MAPT disease or condition in the subject. In some embodiments, the antisense polynucleotide agent is administered to the subject subcutaneously or by IV administration. In some embodiments, the antisense polynucleotide agent is administered to the subject by intrathecally. In yet another embodiment, the antisense polynucleotide agent is administered to the subject intracisternally. A non-limiting exemplary intracisternal administration comprises an injection into the cisterna magna (cerebellomedullary cistern) by suboccipital puncture. In certain embodiments, the physiological characteristic and symptoms are one or more of: MAPT mRNA level, MAPT protein level in the subject, or 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.

Brief Description of the Sequences

SEQ ID NO: 1 and SEQ ID NO: 2 (reverse complement) are Homo sapiens MAPT mRNA [NCBI Reference Sequence: NM_001377265.1].

SEQ ID NO: 3 and SEQ ID NO: 4 (reverse complement) are Homo sapiens MAPT mRNA [NCBI Reference Sequence: NM_016841.5].

SEQ ID NO: 5 and SEQ ID NO: 6 (reverse complement) are Mus musculus MAPT mRNA [NCBI Reference Sequence: NM_001038609.3].

SEQ ID NO: 7 and SEQ ID NO: 8 (reverse complement) are *Macaca mulatta* (Rhesus monkey) MAPT mRNA [NCBI Reference Sequence: XM_015119954.2].

5 SEQ ID NOs: 9-500, 1839-1842, 2137-2281, 2427-2571 are shown in Table 1 and are sense strand sequences.

SEQ ID NOs: 501-992, 1843-1846, 2427-2426, 2572-2716 are shown in Table 1 and are antisense strand sequences.

10 SEQ ID NOs: 993-1484 are shown in Table 2 with chemical modifications.

SEQ ID NOs: 1485-1596, 1597-1838, 1847-2136 are shown in Table 3. A delivery molecule is indicated as "GLX-__" at the 3' end or 5' end of each sense strand.

15 Detailed Description

The invention in part, includes RNAi agents, for example, though not limited to double stranded (ds) RNAi agents, which are capable of inhibiting MAPT gene expression. The invention, in part also includes compositions comprising MAPT RNAi agents and methods of use of the compositions. MAPT RNAi agents disclosed herein may be attached to delivery compounds for delivery to cells, including to hepatocytes. Pharmaceutical compositions of the invention may include at least one dsRNA MAPT agent and a delivery compound. In some embodiments of compositions and methods of the invention, the delivery compound is a GalNAc-containing delivery compound. MAPT RNAi agents delivered to cells are capable of inhibiting MAPT gene expression, thereby reducing activity in the cell of the MAPT protein product of the gene. dsRNAi agents of the invention can be used to treat MAPT-associated diseases and conditions.

In some embodiments of the invention reducing MAPT expression in a cell or subject treats a disease or condition associated with MAPT expression in the cell or subject, respectively. Non-limiting examples of diseases and conditions that may be treated by reducing MAPT activity are: alleviation or amelioration of one or more symptoms associated with unwanted or excessive MAPT expression, or variable progression of motor, cognitive, and behavioral impairment. complex. "Treatment" can also mean prolonging survival as compared to expected survival in the absence of treatment.

35 As used herein, "G," "C," "A" and "U" each generally stand for a nucleotide that contains guanine, cytosine, adenine, and uracil as a base, respectively. However, it will be understood that the term "ribonucleotide" or "nucleotide" can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety. The skilled person understands that guanine, cytosine, adenine, and uracil may be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such

replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base may base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine may be replaced in the nucleotide sequences of the invention by a nucleotide containing, for example, inosine. Sequences comprising such replacement moieties are embodiments of the invention.

As used herein, "MAPT" gene, also known as "DDPAC," "FTDP-17," "MAPTL," "MSTD," "MTBT1," "MTBT2," "PPND," "PPP1R1O3," "TAU," "Tau-PHF6," "tau-40," and "microtubule-associated protein tau," refers to the gene encoding for a protein called microtubule-associated protein tau (MAPT) from any vertebrate or mammalian source, including, but not limited to, human, bovine, chicken, rodent, mouse, rat, porcine, ovine, primate, monkey, and guinea pig, unless specified otherwise. As used herein, the term "MAPT" protein and "tau" protein can be used interchangeably. The term also refers to fragments and variants of native MAPT that maintain at least one in vivo or in vitro activity of a native MAPT. The amino acid and complete coding sequences of the reference sequence of the human MAPT gene may be found in, for example, GenBank Ref Seq Accession No. NM_001377265.1 (Homo sapiens MAPT isoform 9, SEQ ID NO: 1, reverse complement, SEQ ID NO: 2); GenBank Accession No. NM_016841.5 (Homo sapiens MAPT isoform 4, SEQ ID NO: 3, reverse complement, SEQ ID NO: 4); GenBank Accession No. NM_001038609.3 (Mus musculus MAPT, SEQ ID NO: 5; reverse complement, SEQ ID NO: 6); GenBank Accession No.: XM_015119954.2 (Macaca mulatta (Rhesus monkey) isoform 1, SEQ ID NO: 7, reverse complement, SEQ ID NO: 8). Additional examples of MAPT mRNA sequences are readily available using publicly available databases, e.g., GenBank, UniProt, Ensembl and OMIM.

As described herein, MAPT refers to the gene encoding for microtubule associated tau protein. The MAPT gene for encoding tau protein is located on chromosome 17q21, containing 16 exons. The major tau protein in the human brain is encoded by 11 exons. Exons 2, 3 and 10 are alternatively spliced, leading to the formation of six tau isoforms, ranging in size from a range of 352-441 amino acids. Tau protein can be divided into four domains: the N-terminal domain, a proline-rich domain, a microtubule-binding domain, and the C-terminal domain. The N-terminal domain plays a role in providing spacing between microtubules. The proline-rich domain plays a role in cell signaling and in interactions with protein kinases. The microtubule-binding domain is important for binding to the microtubule. The C-terminal domain is critical in regulating microtubule polymerization. Normally, tau is unfolded and phosphorylated. In its abnormal form, as found in the brains of patients with primary tauopathies, tau protein is hyperphosphorylated and aggregated comprising β -pleated sheet conformation. The binding of tau to microtubules is regulated by the phosphorylation/dephosphorylation equilibrium of tau. Hyperphosphorylation of tau results in a loss of the interaction of tau with microtubules, leading to microtubule dysfunction and impaired axonal transport, and tau fibrillization.

The following describes how to make and use compositions comprising MAPT single-stranded (ssRNA) and dsRNA agents to inhibit MAPT gene expression, as well as compositions and methods for treating diseases and conditions caused by or modulated by MAPT gene expression. The term “RNAi” is also known in the art and may be referred to as “siRNA”.

5 As used herein, the term “RNAi” refers to an agent that comprises RNA and mediates targeted cleavage of an RNA transcript via an RNA-induced silencing complex (RISC) pathway. As is known in the art, an RNAi target region refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a gene, including messenger RNA (mRNA) that is a product of RNA processing of a primary transcription product. The
10 target portion of the sequence will be at least long enough to serve as a substrate for RNAi-directed cleavage at or near that portion. A target sequence may be from 8-30 nucleotides long (inclusive), from 10 - 30 nucleotides long (inclusive), from 12 - 25 nucleotides long (inclusive), from 15 - 23 nucleotides long (inclusive), from 16 -23 nucleotides long (inclusive), or from 18 – 23 nucleotides long (inclusive), including all shorter lengths within each stated range. In some
15 embodiments of the invention, a target sequence is 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26 nucleotides long. In certain embodiment a target sequence is between 9 and 26 nucleotides long (inclusive), including all sub-ranges and integers there between. For example, though not intended to be limiting, in certain embodiments of the invention a target
20 sequence is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides long, with the sequence fully or at least substantially complementary to at least part of an RNA transcript of a MAPT gene. Some aspects of the invention include pharmaceutical compositions comprising one or more MAPT dsRNA agents and a pharmaceutically acceptable carrier. In certain embodiments of the invention, a MAPT RNAi as described herein inhibits expression of MAPT protein.

25 As used herein, a “dsRNA agent” means a composition that contains an RNA or RNA-like (e.g., chemically modified RNA) oligonucleotide molecule that is capable of degrading or inhibiting translation of messenger RNA (mRNA) transcripts of a target mRNA in a sequence specific manner. Although not wishing to be limited to a particular theory, dsRNA agents of the invention may operate through the RNA interference mechanism (i.e., inducing RNA
30 interference through interaction with the RNA interference pathway machinery (RNA-induced silencing complex or RISC) of mammalian cells), or by any alternative mechanism(s) or pathway(s). Methods for silencing genes in plant, invertebrate, and vertebrate cells are well known in the art [see, for example, (Sharp et al., Genes Dev. 2001, 15:485; Bernstein, et al., (2001) Nature 409:363; Nykanen, et al., (2001) Cell 107:309; and Elbashir, et al., (2001) Genes
35 Dev. 15:188)], the disclosure of each of which is incorporated herein by reference in its entirety.]. Art-known gene silencing procedures can be used in conjunction with the disclosure provided herein to inhibit expression of MAPT.

DsRNA agents disclosed herein are comprised of a sense strand and an antisense strand, and include, but are not limited to: short interfering RNAs (siRNAs), RNAi agents, micro RNAs

(miRNAs), short hairpin RNAs (shRNA), and dicer substrates. The antisense strand of the dsRNA agents described herein is at least partially complementary to the mRNA being targeted. It is understood in the art that different lengths of dsRNA duplex structure can be used to inhibit target gene expression. For example, dsRNAs having a duplex structure of 19, 20, 21, 22, and 23 base pairs are known to be effective to induce RNA interference (Elbashir et al., EMBO 2001, 20:6877-6888). It is also known in the art that shorter or longer RNA duplex structures are also effective to induce RNA interference. In some embodiments, the sense strand and the antisense strand may be the same length or different lengths. In some embodiments, each strand is no more than 40 nucleotides in length. In some embodiments, each strand is no more than 30 nucleotides in length. In some embodiments, each strand is no more than 25 nucleotides in length. In some embodiments, each strand is no more than 23 nucleotides in length. In some embodiments, each strand is no more than 21 nucleotides in length. In some embodiments, the sense and antisense strands of the RNAi agents can each be 15 to 49 nucleotides in length. In some embodiments, the antisense strand is independently 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, the length of the sense strand is independently 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, or 49 nucleotides. In some embodiments, the sense strand and the antisense strand are both 21 nucleotides in length. In some embodiments, the sense strand is complementary or substantially complementary to the antisense strand, and the region of complementarity is between 15 and 23 nucleotides in length. In some embodiments, the region of complementarity is 19-21 nucleotides in length. In some embodiments, the region of complementarity is 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. MAPT dsRNAs in certain embodiments of the invention can include at least one strand of a length of minimally 21 nt or may have shorter duplexes based on one of the sequences set forth in any one of Tables 1-3, but minus 1, 2, 3, or 4 nucleotides on one or both ends may also be effective as compared to the dsRNAs set forth in Tables 1-3, respectively. In some embodiments of the invention, MAPT dsRNA agents may have a partial sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides from one or more sequences of Tables 1-3, and differ in their ability to inhibit the expression of a MAPT gene by not more than 5%, 10%, 15%, 20%, 25%, or 30% from the level of inhibition resulting from a dsRNA comprising the full sequence. A sense sequence, an antisense sequence and a duplex disclosed in Tables 1-3 may be referred to herein as a "parent" sequence, meaning that the sequences disclosed in Tables 1-3 may be modified, shorten, lengthened, include substitutions, etc. as set forth herein, with the resulting sequences retaining all or at least a portion of the efficacy of their parent sequences in methods and compositions of the invention. Sense and antisense strands included in a dsRNA of the invention are independently selected. As used herein the term "independently selected" means each of two or more like elements can be selected independent of the selection of the other elements. For example, though not intended to be limiting, in preparing a dsRNA of the invention, one may select the "elements" of the two strands to include in the duplex. One

selected element, the sense sequence may be SEQ ID NO: 1001 (shown in Table 2) and the other selected element, the antisense sequence, may be SEQ ID NO: 1247, or may be SEQ ID NO: 1247 that is modified, shortened, lengthened, and/or includes 1, 2, or 3 substitutions as compared to its parent sequence SEQ ID NO: 1247. It will be understood that a duplex of the invention need not include both sense and antisense sequences shown as paired in duplexes in Tables 1-3. Each sense and antisense strand sequence in the tables is immediately followed by its SEQ ID NO.

Certain embodiments of compositions and methods of the invention comprise a single-strand RNA in a composition and/or administered to a subject. For example, an antisense strand such as one listed in any one of Tables 1-3 may be a composition or in a composition administered to a subject to reduce MAPT polypeptide activity and/or expression of MAPT gene in the subject. Tables 1 shows certain MAPT dsRNA agent antisense strand and sense strand core stretch base sequences. A single-strand antisense molecule that may be included in certain compositions and/or administered in certain methods of the invention are referred to herein as a “single-strand antisense agent” or an “antisense polynucleotide agent”. A single-strand sense molecule that may be included in certain compositions and/or administered in certain methods of the invention are referred to herein as a “single-strand sense agent” or a “sense polynucleotide agent”. The term “base sequence” is used herein in reference to a polynucleotide sequence without chemical modifications or delivery compounds. For example, the sense strand CACACGGACGCUGGCCUGAAA (SEQ ID NO: 17) shown in Table 1 is the base sequence for SEQ ID NO: 1001 in Table 2 and for SEQ ID NO: 1486 in Table 3, with SEQ ID NO: 1001 and SEQ ID NO: 1486 shown with their chemical modifications and a delivery compound. Sequences disclosed herein may be assigned identifiers. For example, a single-stranded sense sequence may be identified with a “Sense strand SS#”; a single stranded antisense sequence may be identified with an “Antisense strand AS#” and a duplex that includes a sense strand and an antisense strand may be identified with a “Duplex AD#/AV#”.

Table 1 includes sense and antisense strands and provides the identification number of duplexes formed from the sense and antisense strand on the same line in Table 1. In certain embodiments of the invention an antisense sequence includes nucleobase u or nucleobase a in position 1 of the antisense sequence. In certain embodiments of the invention an antisense sequence includes nucleobase u in position 1 of the antisense sequence. As used herein, the term “matching position” in a sense and an antisense strand are the positions in each strand that “pair” when the two strands are duplexed strands. For example, in a 21 nucleobases sense strand and a 21 nucleobases antisense strand, nucleobase in position 1 of the sense strand and position 21 in the antisense strand are in “matching positions”. In yet another non-limiting example in a 23 nucleobases sense strand and a 23 nucleobases antisense strand, nucleobase 2 of the sense strand and position 22 of the antisense strand are in matching positions. In another non-limiting example, in an 18 nucleobases sense strand and an 18 nucleobases antisense strand, nucleobase in position 1 of the sense strand and nucleobase 18 in the antisense strand are in matching

positions, and nucleobase 4 in the sense strand and nucleobase 15 in the antisense strand are in matching positions. A skilled artisan will understand how to identify matching positions in sense and antisense strands that are or will be duplexed strands and paired strands.

5 The final column in Table 1 indicates a Duplex AV# for a duplex that includes the sense and antisense sequences in the same table row. For example, Table 1 discloses the duplex assigned Duplex AV03736.um, which includes sense strand SEQ ID NO: 17 and antisense strand SEQ ID NO: 509. Thus, each row in Table 1 identifies a duplex of the invention, each comprising the sense and antisense sequences shown in the same row, with the assigned identifier for each duplex shown in the first column in the row.

10 In some embodiments of methods of the invention, an RNAi agent comprising a polynucleotide sequence shown in any one of Tables 1-3 is administered to a subject. In some embodiments of the invention an RNAi agent administered to a subject comprises is a duplex comprising at least one of the base sequences set forth in Table 1, including 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 sequence modifications. In some
15 embodiments of methods of the invention an RNAi agent comprising a polynucleotide sequence shown in any one of Tables 1-3 is attached to a delivery molecule, a non-limiting example of which is a delivery compound comprising a GalNAc compound, or a GLS-15* compound.

Table 1: Unmodified MAPT RNAi agent antisense strand and sense strand sequences. All sequences shown 5' to 3' direction. Duplex AV# are the number assigned to the duplex of the two strands in the same row in the table.

Duplex AV#	Sense Strand	SEQ ID NO	Antisense Strand	SEQ ID NO	Position in NM_001377265.1
AV03728.µm	GCCUCCUCCGCGUCCUCUCA	9	UGAGAGGACAGCGGAGGAGGC	501	88-108
AV03729.µm	GGGAGUUUCGAAGUGAGAAA	10	UUUCCAUCACUUUCGAACUCCC	502	167-187
AV03730.µm	CGAGUUUCGAAGUGAGGAGA	11	UUCUCCAUCACUUUCGAACUCG	503	168-188
AV03731.µm	CAGUUUCGAAGUGAGGAGAA	12	UUCUCCAUCACUUUCGAACUG	504	169-189
AV03732.µm	GGUUCGAAGUGAGGAGAU/A	13	U/UUCUCCAUCACUUUCGAACC	505	170-190
AV03733.µm	CUUCGAAGUGAGGAGAUCA	14	UGAUCUUCCAUCACUUUCGAAG	506	171-191
AV03734.µm	GUCGAAGUGAUGGAAAGUCAA	15	UUGAUCUUCCAUCACUUUCGAC	507	172-192
AV03735.µm	CGGCUACACCAU/GCACCAGA	16	UCUUGGUGCAU/GGUGUAGCCG	508	231-251
AV03736.µm	CACACGGACGCU/GGCCUGAAA	17	UUUCAGGCGACGCU/CCTGUG	509	262-282
AV03737.µm	GACCCCCAGCCUGGAAGACGA	18	UCGUCUUCCAAGCGUGGGGUC	510	393-413
AV03738.µm	CAAGCUGCUGGUCACGUGACA	19	UGUCACGUGACCA/GCAGCUG	511	412-432
AV03739.µm	GAAAGCUCGCAUGGUCAGUAAA	20	UUACUGACCAU/GCGAGCUUC	512	1497-1517
AV03740.µm	GAAAGCUCGCAUGGUCAGUAAA	21	UUUACUGACCAU/GCGAGCUUC	513	1498-1518
AV03741.µm	GGCUCGCAUGGUCAGUAAAAA	22	UUUUUACUGACCAU/GCGAGCC	514	1500-1520
AV03742.µm	GUCGCAUGGUCAGUAAAAAGCA	23	UGCUUUUACUGACCAU/GCGAC	515	1502-1522
AV03743.µm	GCGCAUGGUCAGUAAAAAGCAA	24	UUGCUUUUACUGACCAU/GCGC	516	1503-1523
AV03744.µm	GGCAUUGGUCAGUAAAAAGCAAA	25	UUUGCUUUUACUGACCAU/GCC	517	1504-1524
AV03745.µm	CCAUUGGUCAGUAAAAAGCAAAA	26	UUUUUGCUUUUACUGACCAU/GG	518	1505-1525
AV03746.µm	GAUUGGUCAGUAAAAAGCAAAAG	27	UUCUUUGCUUUUACUGACCAU/C	519	1506-1526
AV03747.µm	GGGUCAGUAAAAAGCAAAAGAA	28	UUUCUUUGGCUUUUACUGACCA/C	520	1507-1527
AV03748.µm	GGGUCAGUAAAAAGCAAAAGACA	29	UGUCUUUGGCUUUUACUGACCC	521	1508-1528
AV03749.µm	CGACUUGGAAGCGAU/GACAAAAA	30	UUUUUGUCAU/GCGCUUCGAGUCG	522	1529-1549
AV03750.µm	CACUUGGAAGCGAU/GACAAAAA	31	UUUUUGUCAU/GCGCUUCGAGUG	523	1530-1550
AV03751.µm	GGGAAGCGAU/GACAAAAAAGAGA	32	UUCUUUUUGUCAU/GCGCUUCCC	524	1533-1553
AV03752.µm	CGAAGCGAU/GACAAAAAAGACA	33	UUCUUUUUUUGUCAU/GCGCUUCG	525	1534-1554
AV03753.µm	GAGCGAU/GACAAAAAAGGCCAA	34	UUUGGCUUUUUUGUCAU/GCGUC	526	1536-1556
AV03754.µm	GGCGAU/GACAAAAAAGGCCAAA	35	UUUGGCUUUUUUGUCAU/GGCC	527	1537-1557

AV03755. um	GUCAAAGGGGGCUGAUGGUAAA	36	UUUACCAUACAGCCCCUUGAC	528	1750-1770
AV03756. um	CGGGCUGAUGGUAAAACGAAA	37	UUUCGUUUUACCAUACAGCCG	529	1756-1776
AV03757. um	CGGCUGAUGGUAAAACGAGA	38	UCUUCGUUUUACCAUACAGCCG	530	1757-1777
AV03758. um	CCUGAUGGUAAAACGAGAUA	39	UAUCUUCGUUUUACCAUACAGG	531	1759-1779
AV03759. um	GUGAUGGUAAAACGAGAUGCA	40	UGAUCUUCGUUUUACCAUAC	532	1760-1780
AV03760. um	GGAUUGGUAAAACGAGAUGCA	41	UCGAUCUUCGUUUUACCAUCC	533	1761-1781
AV03761. um	GGCCACCAAGAUUCCAGCAAA	42	UUUGCUGGAUUCUUGUGGCC	534	1827-1847
AV03762. um	GCAAGAUUCCAGCAAAAACCA	43	UGGUUUUUUGUGGAUUCUUGC	535	1832-1852
AV03763. um	GACCACCCAGCUCUGGUGAAA	44	UUUCACCCAGAGCUGGGUGGUC	536	1868-1888
AV03764. um	GCUGGUGAACCUCUCCAAAUA	45	UGAUUUUUUGAGGUCUACCAGC	537	1879-1899
AV03765. um	GUGGUGAACCUCUCCAAAUA	46	UUGAUUUUUGAGGUCUACCAC	538	1880-1900
AV03766. um	GACCUCCAAAUAUCAGGGGAUA	47	UAUCCCCUGAUUUUUUGAGGUC	539	1886-1906
AV03767. um	GUCGGCUCACUCUGAGAACCUA	48	UAGGUUCUACGUGGAGCCGAC	540	2104-2124
AV03768. um	GGUGGCAAAUAGUCUACAAA	49	UUUGUAGACUAAUUUGCACACC	541	2239-2259
AV03769. um	CUGUGCAAAUAGUCUACAAA	50	UUUUUGUAGACUAAUUUGCACAG	542	2240-2260
AV03770. um	GGUGCAAAUAGUCUACAAA	51	UGUUUGUAGACUAAUUUGCAC	543	2241-2261
AV03771. um	CUGCAAAUAGUCUACAAACCA	52	UGGUUUUGUAGACUAAUUUGCAG	544	2242-2262
AV03772. um	GGCAAAUAGUCUACAAACCAA	53	UUGGUUUGUAGACUAAUUUGCC	545	2243-2263
AV03773. um	GAUAGUCUACAAACCAAGUUA	54	UACUUGGUUUUGUAGACUAAUUC	546	2246-2266
AV03774. um	GAUAGUCUACAAACCAAGUUA	55	UCAACUGGUUUUGUAGACUAAU	547	2247-2267
AV03775. um	GUAGUCUACAAACCAAGUUGAA	56	UUCACUGGUUUUGUAGACUAAU	548	2248-2268
AV03776. um	GUACAAACCAAGUUGAACCUGAA	57	UUCAGGUCAACUUGGUUUUGUAC	549	2253-2273
AV03777. um	CCAAAGUGAGCCUCCAAAGUGUA	58	UACACUUUGAGGUGCACCUUGG	550	2273-2293
AV03778. um	GGACCUCCAAAGUGUGGCUCAA	59	UUAGGCCACACUUUGGAGGUCC	551	2279-2299
AV03779. um	GCUCCAAGUGUGGCUCAUUA	60	UAAUGAGCCACACUUUGGAGGC	552	2281-2301
AV03780. um	GUCCAAGUGUGGCUCAUUAAGA	61	UCUAAUGAGCCACACUUUGGAC	553	2283-2303
AV03781. um	CUGUGGCUCAUUAAGGCAACAA	62	UUUGUGCCUAAUAGAGCCACAG	554	2289-2309
AV03782. um	CUGGCUCAUUAAGGCAACAUCA	63	UGAUGUGUGCCUAAUAGAGCCAG	555	2291-2311
AV03783. um	CGCUCAUUAAGGCAACAUCCAA	64	UUGGAUUGUGCCUAAUAGAGCG	556	2293-2313
AV03784. um	CCUCAUUAAGGCAACAUCCAUUA	65	UAUGGAUGUGUGCCUAAUAGAGG	557	2294-2314
AV03785. um	GCAUUAAGGCAACAUCCAUCAA	66	UUGAUUGAUGUUGGCCUAAUUGC	558	2296-2316

AV03786.µm	GUUAGGCAACAUCUCCAUCAUAA	67	UUUAGUUGGAUGUUGCCUAAAC	559	2298-2318
AV03787.µm	GUAGGCAACAUCUCCAUCAUAAA	68	UUUAGUUGGAUGUUGCCUAC	560	2299-2319
AV03788.µm	GGGCAACAUCUCCAUCAUAAACA	69	UGUUUAGUUGGAUGUUGCCC	561	2301-2321
AV03789.µm	CCAACAUCUCCAUCAUAAACCAA	70	UUGGUUUAGUUGGAUGUUGG	562	2303-2323
AV03790.µm	GACAUCCAUCAUAAACCAAGGA	71	UCCUGUUUAGUUGGAUGUUGC	563	2305-2325
AV03791.µm	GCAGGUGGAAGUAAAUAUCUGA	72	UCAGAUUUUACUUCACCUGC	564	2331-2351
AV03792.µm	GAGGUGGAAGUAAAUAUCUGAA	73	UUCAGAUUUUACUUCACCUCC	565	2332-2352
AV03793.µm	GGGUGGAAGUAAAUAUCUGAGA	74	UCUCAGAUUUUACUUCACCC	566	2333-2353
AV03794.µm	CGUGGAAGUAAAUAUCUGAGAA	75	UUCUCAGAUUUUACUUCACAG	567	2334-2354
AV03795.µm	CUUGGAAGUAAAUAUCUGAGAAA	76	UUUCUCAGAUUUUACUUCACAG	568	2335-2355
AV03796.µm	GGGAAGUAAAUAUCUGAGAGAA	77	UCUUCUCAGAUUUUACUUCACC	569	2336-2356
AV03797.µm	CAAGUAAAUAUCUGAGAGAAAGUA	78	UAGCUUCUCAGAUUUUACUUG	570	2338-2358
AV03798.µm	GAGUAAAUAUCUGAGAGAAAGCUA	79	UAAAGCUUCUCAGAUUUUACUC	571	2339-2359
AV03799.µm	CUAAAAUUCUGAGAGAAAGCUAAA	80	UUCAAAGCUUCUCAGAUUUUAG	572	2341-2361
AV03800.µm	GCUGAGAGAGCUUGACUUCAGAAA	81	UUUGAAGUCAAAGCUUCUCAGC	573	2347-2367
AV03801.µm	GUUGAGAGAGCUUGACUUCAGAA	82	UCUUGAAGUCAAAGCUUCUCAC	574	2348-2368
AV03802.µm	GGAAGCUUGACUUCAGAGGACA	83	UGUCCUUGAAGUCAAAGCUUCC	575	2351-2371
AV03803.µm	CAAGCUUGACUUCAGAGGACAA	84	UUUGCCUUGAAGUCAAAGCUUG	576	2352-2372
AV03804.µm	GAAAGACAGAGUCCAGUCCGAAA	85	UUCGACUUGGACUUCUUGCCUUC	577	2364-2384
AV03805.µm	GCAGAGUCCAGUCCGAAGAUUA	86	UAAUCUUCGACUUGGACUUCGC	578	2369-2389
AV03806.µm	GUGGCGGAGGAAAUAUAAAAAGA	87	UCUUUUUAAUUUCCUCCGCCAC	579	2417-2437
AV03807.µm	CGCGGAGGAAAUAUAAAAAGAUUA	88	UAUCUUUUUAAUUUCCUCCGGCG	580	2419-2439
AV03808.µm	GAAUAAAAAGAUUUGAAAAACCCA	89	UUGGUUUCAAUCUUUUUUAAUUC	581	2427-2447
AV03809.µm	GAAAAAGAUUUGAAAAACCCACAAA	90	UUUGUGGGUUUUCAAUCUUUUUC	582	2431-2451
AV03810.µm	GGGAGAUUCGUGUACAAGUGGA	91	UCGACUUUGUACACGAUUCUCCC	583	2495-2515
AV03811.µm	CCAUUCUACGCAAUUGUUCUUA	92	UAGGAGACAUUUGCUGAGAUUGG	584	2544-2564
AV03812.µm	GACCGGACGCAUCGACAUUGGA	93	UCCAUGUUGAUUGCUUGCCGUGC	585	2565-2585
AV03813.µm	GAGCAUCGACAUUGGUAGACUA	94	UAGUCUACCAUUGUAGUUGCUC	586	2571-2591
AV03814.µm	CCCACGCUAGCUGACGAGAGUA	95	UACCUUGUACAGCUAGCGUUGGG	587	2602-2622
AV03815.µm	CCCAAGCAGGGUUUUGUGAUCA	96	UGAUCACAACAAACCUUGCUUGGG	588	2635-2655
AV03816.µm	GCAAGCAGGGUUUUGUGAUCAA	97	UUUGAUCACAACAAACCUUGCUUGC	589	2636-2656

AV03817.µm	GUAGAGAGAGUGUGGAAAAAAAA	98	UUUUUUUCCACACUCUCUCAC	590	2693-2713
AV03818.µm	GAAGAAAAAGAAUAAUGACCCA	99	UGGUGCAUUAUUCUUUUUUUC	591	2708-2728
AV03819.µm	GUCCUCGCAGUCGUGUUAUA	100	UAUUAACCGAACUGCGAGGAC	592	2753-2773
AV03820.µm	GAUUUGGUUAUUCACUUAACA	101	UGUUUAAGUGAUUAACCAAUUC	593	2769-2789
AV03821.µm	GAUUUGGUUAUUCACUUAACCA	102	UGGUUAAGUGAUUAACCAUUC	594	2770-2790
AV03822.µm	GUUGUUUAUUCACUUAACCUGA	103	UCAGGUUAAGUGAUUAACCCAC	595	2772-2792
AV03823.µm	GAUUCACUUAACCUUGCUUUUA	104	UAAAAGCAGGUUAAGUGAUC	596	2777-2797
AV03824.µm	GAUUCACUUAACCUUGCUUUUGA	105	UCAAAAAGCAGGUUAAGUGAUC	597	2778-2798
AV03825.µm	GUACACUUAACCUUGCUUUUGUA	106	UACAAAAGCAGGUUAAGUGAC	598	2779-2799
AV03826.µm	GCACUUAACCUUGCUUUUGUCA	107	UGACAAAAGCAGGUUAAGUGC	599	2780-2800
AV03827.µm	CGUCGCGGACUUCAAAAUCACA	108	UUGAUUUUUGAAGUCCCGAGCG	600	2810-2830
AV03828.µm	GUCCGGGACUUCAAAAUCAGUA	109	UACUGAUUUUGAAGUCCCGAC	601	2812-2832
AV03829.µm	CGACUUCAAAAUCAGUGAUGA	110	UCAUCACUGAUUUUGAAGUCG	602	2816-2836
AV03830.µm	CACUUCAAAAUCAGUGAUGGA	111	UCCAUCACUGAUUUUGAAGUG	603	2817-2837
AV03831.µm	GAAGAGCAAAUUCAGUGAUGUA	112	UAAAGAUGAAAUUUUGCUCUC	604	2840-2860
AV03832.µm	GAGAGCAAAUUCAGUCUUUCA	113	UGAAAGAUGAAAUUUUGCUCUC	605	2841-2861
AV03833.µm	GGAAGCAAAUUCAGUCUUUCCA	114	UGGAAAGAUGAAAUUUUGCUC	606	2842-2862
AV03834.µm	CAGCAAAUUCAGUCUUUCCAA	115	UUGGAAAGAUGAAAUUUUGCUG	607	2843-2863
AV03835.µm	GGCAAAUUCAGUCUUUCCAAAA	116	UUUGGAAAGAUGAAAUUUUGCC	608	2844-2864
AV03836.µm	CCAAAUUUCAGUCUUUCCAAAA	117	UUUUUGGAAAGAUGAAAUUUUGG	609	2845-2865
AV03837.µm	GAAAUUUCAGUCUUUCCAAAUUA	118	UAUUUGGAAAGAUGAAAUUUC	610	2846-2866
AV03838.µm	GAAUUUCAGUCUUUCCAAAUUA	119	UAAUUUGGAAAGAUGAAAUUUC	611	2847-2867
AV03839.µm	GAUUUCAGUCUUUCCAAAUUGA	120	UCAAUUUUGGAAAGAUGAAAUUC	612	2848-2868
AV03840.µm	GUUCAUCUUUCCAAAUUGAUUA	121	UAUCAUUUUUGGAAAGAUUGAAC	613	2850-2870
AV03841.µm	CGUGGGGCUAGUUAUAAAAUA	122	UAUUUUUAUUAUACUAGCCACCG	614	2870-2890
AV03842.µm	GGGCUAGUUAUUAUAAAAUUA	123	UAAUUAUUUAUUAUACUAGCCCC	615	2873-2893
AV03843.µm	GCAGGCAAUUCCUUUGAUUAUA	124	UAAUCAAAAAGGAAAUUGCCUUC	616	2935-2955
AV03844.µm	GGGCAAUUCCUUUGAUUUCUA	125	UAGAUAUCAAAAAGGAAAUUGCCCC	617	2937-2957
AV03845.µm	CGCAGCAACCAAAAGAUUUUGAA	126	UUCAAAUCCUUUGUUUGCUGCG	618	3082-3102
AV03846.µm	GAGCAACCAAAAGAUUUUGAAAAA	127	UUUUCAAAUCCUUUGUUUGCUC	619	3084-3104
AV03847.µm	GGCAACCAAAAGAUUUUGAAAAACA	128	UGUUUCAAAUUCUUUGUUUGCC	620	3085-3105

AV03848. um	CCAACAAAGGAAUUGAAACUA	129	UAGUUUCAAAUCCUUUGUGG	621	3086-3106
AV03849. um	GAACAAAAGAUUUUGAAACUUA	130	UAAGUUUCAAAUCCUUUGUUC	622	3087-3107
AV03850. um	GACAAAAGGAUUUGAAACUUGA	131	UCAAGUUUCAAAUCCUUUGUC	623	3088-3108
AV03851. um	GCAAAAGGAUUUGAAACUUGGA	132	UCCAAGUUUCAAAUCCUUUGC	624	3089-3109
AV03852. um	GAAAGGAUUUGAAACUUGGUA	133	UACCAAGUUUCAAAUCCUUUC	625	3090-3110
AV03853. um	GAGGAUUUGAAACUUGGUGUA	134	UACACCAAGUUUCAAAUCCUC	626	3092-3112
AV03854. um	GGAUUUUUGAAACUUGGUGUA	135	UCACACCAAGUUUCAAAUCCC	627	3093-3113
AV03855. um	CAUUUUGAAACUUGGUGUGUA	136	UACACACCAAGUUUCAAAUUG	628	3095-3115
AV03856. um	GUUUUGAAACUUGGUGUGUCA	137	UGAACACACCAAGUUUCAAAAC	629	3096-3116
AV03857. um	GGCCAUUGAUUUUGGCCACUUA	138	UAAGUGGCCAAAUUCAUUGGC	630	3609-3629
AV03858. um	GUUUGGCCACUUUGCAGACCUA	139	UAGUUCUGCAAAGUGGCCAAC	631	3618-3638
AV03859. um	GUUUGCAGACCUGGGACUUUA	140	UAAAGUCCCAAGGUCUGCAAAC	632	3626-3646
AV03860. um	CACCUGGGACUUUAGGGCUAA	141	UUAGCCCUAAAGUCCCAAGUG	633	3633-3653
AV03861. um	CACUUUAGGGCUAAACGAGUUA	142	UAAUGGUUAGCCCUAAAAGUG	634	3640-3660
AV03862. um	CGGCUAACCAGUUCUUCUUUGA	143	UCAAGAGAAACUUGGUUAGCCG	635	3647-3667
AV03863. um	CGCUAACCAGUUCUUCUUUGUA	144	UACAAAGAGAAACUUGGUUAGCG	636	3648-3668
AV03864. um	GUAAACCAGUUCUUCUUUGUAAA	145	UUUACAAAGAGAAACUUGUAC	637	3650-3670
AV03865. um	GAACCAGUUCUUCUUUGUAAGA	146	UCUUACAAAGAGAAACUUGUUC	638	3651-3671
AV03866. um	GACCAGUUCUUCUUUGUAAGGA	147	UCCUUACAAAGAGAAACUUGUC	639	3652-3672
AV03867. um	GCCAGUUCUUCUUUGUAAGGAA	148	UUCUUUACAAAGAGAAACUUGC	640	3653-3673
AV03868. um	GCAGUUCUUCUUUGUAAGGACA	149	UGUCCUUACAAAGAGAAACUUGC	641	3654-3674
AV03869. um	GGUUCUUCUUUGUAAGGACUUA	150	UAGUCCUUUACAAAGAGAAACC	642	3656-3676
AV03870. um	GUUCUUUUUGUAAGGACUUGUA	151	UACAAGUCCUUUACAAAGAGAGAC	643	3658-3678
AV03871. um	GAAUCACUCGCCUUAUACCCCUA	152	UAGGGGUUAUAGGCAGUGAUUUC	644	3834-3854
AV03872. um	GUACUCCAUACUGAGGGUGAAA	153	UUCACCCUCAGUAUUGGAGUAC	645	3933-3953
AV03873. um	GCAUACUGAGGGUGAAAUUAAA	154	UUAAUUUUCACCCUUCAGUAUUGC	646	3938-3958
AV03874. um	GAUACUGAGGGUGAAAUUAAA	155	UUUAAUUUUCACCCUUCAGUAUUC	647	3939-3959
AV03875. um	GUACUGAGGGUGAAAUUAAAGA	156	UCCUUAAUUUUCACCCUUCAGUAC	648	3940-3960
AV03876. um	GACUGAGGGUGAAAUUAAAGGA	157	UCCUUAAUUUUCACCCUUCAGUUC	649	3941-3961
AV03877. um	CAGGGUGAAAUUAAAGGAAGA	158	UCUUCCCUUAAUUUUCACCCUG	650	3945-3965
AV03878. um	CGACCCCAAGCCUCUCACUCUA	159	UAGAGUGAGAGGCUUGGGUCG	651	3987-4007

AV03879.µm	GA GCCUCUCACUCUCAGUUC A	160	UGAACUGAGAGUGAGAGGCUC	652	3993-4013
AV03880.µm	CCCUCUCACUCUCAGUCCAA	161	UUGGACUGAGAGUGAGAGGG	653	3995-4015
AV03881.µm	GCACUCUCAGUUCACUCUA	162	U AUGAGUGGAACUGAGAGUGC	654	4000-4020
AV03882.µm	GACUCUCAGUUCACUCUA	163	UGAUGAGUGGAACUGAGAGUC	655	4001-4021
AV03883.µm	GUCAGUUCACUCACUACA	164	UGUUGG AUGAGUGGAACUGAC	656	4005-4025
AV03884.µm	GUAGGUGUUCUGCCUUGUA	165	UAACAAGGCAGAAACACCUC	657	4118-4138
AV03885.µm	CUGUUUCUGCCUUGUGACAA	166	UUGUCAACAAGGCAGAAACAG	658	4122-4142
AV03886.µm	GGUUUCUGCCUUGUGACAA	167	UAUGUCAACAAGGCAGAAACC	659	4123-4143
AV03887.µm	CCUGGAAGCCAUUGCUCUGA	168	UCAGACAGCAUGGCUCUCAGG	660	4424-4444
AV03888.µm	CGAAGCCAUUGCUCUGUUA	169	UGAACAGACAGCAUGGCUCG	661	4427-4447
AV03889.µm	GAGCCAUUGCUCUGUUA	170	UCAGAACAGACAGCAUGGCUC	662	4429-4449
AV03890.µm	CCC AUGCUCUGUUCUGCUA	171	UAGCAGAACAGACAGCAUGGG	663	4431-4451
AV03891.µm	CCUGGAGCAGCUGAACAUUA	172	UAUAUGUUCAGCUGCUCAGG	664	4448-4468
AV03892.µm	GUGGAGCAGCUGAACAUUA	173	UUAUAUGUUCAGCUGCUCAC	665	4449-4469
AV03893.µm	CAGCAGCUGAACAUUAGUA	174	UAUGUAUAUGUUCAGCUGCUG	666	4452-4472
AV03894.µm	CCAGCUGAACAUUAGUA	175	UCUAUGUAUAUGUUCAGCUGG	667	4454-4474
AV03895.µm	GAGCUGAACAUUAGUAGAA	176	UUCUAUGUAUAUGUUCAGCUC	668	4455-4475
AV03896.µm	GGCUGAACAUUAGAUAGUA	177	UAUCUAUGUAUAUGUUCAGCC	669	4456-4476
AV03897.µm	CCUGAACAUUAGAUAGUA	178	UCAUCUAUGUAUAUGUUCAGG	670	4457-4477
AV03898.µm	GUGAACAUUAGAUAGUUA	179	UACAUUCUAUGUAUAUGUUCAC	671	4458-4478
AV03899.µm	GGAACAUUAGAUAGUUA	180	UAACAUUCUAUGUAUAUGUUC	672	4459-4479
AV03900.µm	CAACAUUAGAUAGUUGA	181	UCAACAUUCUAUGUAUAUGUUG	673	4460-4480
AV03901.µm	GACAUUAGAUAGAUUGUCA	182	UGCAACAUUCUAUGUAUAUGUC	674	4461-4481
AV03902.µm	GGAGUUGAUUGAUUGUUA	183	UACAAUUCCAACUACAACUCC	675	4506-4526
AV03903.µm	CAGUUGAUUGAUUGUCA	184	UGACAAUUCCAACUACAACUG	676	4507-4527
AV03904.µm	GGUUGAUUGAUUGUUA	185	UAGACAAUUCCAACUACAACC	677	4508-4528
AV03905.µm	CUUGAUUGAUUGUUGUCA	186	UCAGACAAUUCCAACUACAAG	678	4509-4529
AV03906.µm	GUUGAUUGAUUGUUGUUA	187	UACAGACAAUUCCAACUACAC	679	4510-4530
AV03907.µm	GGUAGUUGAUUGUUGUUA	188	U AACAGACAAUUCCAACUACC	680	4511-4531
AV03908.µm	CUAGUUGAUUGUUGUUA	189	UAAACAGACAAUUCCAACUAG	681	4512-4532
AV03909.µm	GAGUUGAUUGUUGUUA	190	UUAACAGACAAUUCCAACUUC	682	4513-4533

AV03910.µm	GGUUGGAUUUGUCUUGUUUA	191	UAUAAACAGACAAAUCCAAACC	683	4514-4534
AV03911.µm	CUUGGAUUUGUCUUGUUUAUGA	192	UCAUAAACAGACAAAUCCAAG	684	4515-4535
AV03912.µm	GUUGAUUUUGUCUUGUUUAUGCA	193	UGCAUAAACAGACAAAUCCAC	685	4516-4536
AV03913.µm	GGGAUUUGUCUUGUUUAUGCUA	194	UAGCAUAAACAGACAAAUCCC	686	4517-4537
AV03914.µm	CGAUUUUGUCUUGUUUAUGCUUA	195	UAAGCAUAAACAGACAAAUCCG	687	4518-4538
AV03915.µm	CAUUUGUCUUGUUUAUGCUUGA	196	UCAAGCAUAAACAGACAAAUUG	688	4519-4539
AV03916.µm	GUUUUGUCUUGUUUAUGCUUGGA	197	UCCAAGCAUAAACAGACAAAC	689	4520-4540
AV03917.µm	GUUGUCUUGUUUAUGCUUGGAA	198	UUCCAAGCAUAAACAGACAAAC	690	4521-4541
AV03918.µm	GUUCUCUUGUUUAUGCUUGGAUA	199	UAUCCAAGCAUAAACAGACAC	691	4522-4542
AV03919.µm	GGUCUUGUUUAUGCUUGGAUUA	200	UAUCCAAGCAUAAACAGACACC	692	4523-4543
AV03920.µm	CUUCUUGUUUAUGCUUGGAUUA	201	UGAAUCCAAGCAUAAACAGAG	693	4524-4544
AV03921.µm	GCUGUUUAUGCUUGGAUUCAA	202	UUGAAUCCAAGCAUAAACAGC	694	4525-4545
AV03922.µm	GUGUUUAUGCUUGGAUUCACA	203	UGUGAAUCCAAGCAUAAACAC	695	4526-4546
AV03923.µm	GUUUGCUUUGGAUUCACCAAGAA	204	UUCUGGUGAUUCCAAGCAUAC	696	4530-4550
AV03924.µm	GGGAUUCACCAAGAGUGACUAA	205	UUAGUCACUCUGGUGAAUCCC	697	4537-4557
AV03925.µm	CGAUUUCACCAAGAGUGACUUA	206	UAUAGUCACUCUGGUGAAUCCG	698	4538-4558
AV03926.µm	CAUUCACCAAGAGUGACUUAUGA	207	UCAUAGUCACUCUGGUGAAUUG	699	4539-4559
AV03927.µm	GAAAAAAAAAAGGACGCACUUGUA	208	UACAUGCGUCCUUUUUUUUUC	700	4578-4598
AV03928.µm	GAAAAAAAAAAGGACGCACUUGUAA	209	UUACAUGCGUCCUUUUUUUUUC	701	4579-4599
AV03929.µm	GAAAAAAAAAAGGACGCACUUGUA	210	UAUACAUGCGUCCUUUUUUUUUC	702	4580-4600
AV03930.µm	GAAAAAAAAAAGGACGCACUUGUA	211	UGAUACAUGCGUCCUUUUUUUC	703	4581-4601
AV03931.µm	GAAAAAGGACGCACUUGUACUUA	212	UAAGAUACAUUGCGUCCUUUC	704	4583-4603
AV03932.µm	GAAAAAGGACGCACUUGUACUUGA	213	UCAAGAUACAUUGCGUCCUUUC	705	4584-4604
AV03933.µm	GAAAGGACGCACUUGUACUUGAA	214	UUCAAAGAUACAUUGCGUCCUUC	706	4585-4605
AV03934.µm	GAGGACGCACUUGUACUUGAAAA	215	UUUCAAGAUACAUUGCGUCCUC	707	4586-4606
AV03935.µm	CGACGCACUUGUACUUGAAAUUA	216	UAUUUCAAGAUACAUUGCGUCG	708	4588-4608
AV03936.µm	GCAACUCUUGCAUUCACAAGAA	217	UUUCUUGUAGAUAAAAGUGAGUG	709	4961-4981
AV03937.µm	CACUCACUUUAUCAUUAUGUUA	218	UAACUAUUGAUAAAAGUGAGGC	710	5941-5961
AV03938.µm	GCUCACUUUAUCAUUAUGUUA	219	UGAACUUAUUGAUAAAAGUGAGC	711	5942-5962
AV03939.µm	GUACACUUUAUCAUUAUGUUA	220	UGGAACUUAUUGAUAAAAGUGAC	712	5943-5963
AV03940.µm	GCACUUUAUCAUUAUGUUA	221	UUUGAACUUAUUGAUAAAAGUGC	713	5944-5964

AV03941. um	GCSUUVAUCAUAGUCCAUVA	222	UAAUGAACUAVUAGUAAAAGC	714	5946-5966
AV03942. um	GUUAVCAUVAUUGUCCAUUVA	223	UUAAUUGAACUAVUAGUAAAC	715	5948-5968
AV03943. um	GUUAVCAUVAUUGUCCAUUVA	224	UUUAAUUGAACUAVUAGUAVAC	716	5949-5969
AV03944. um	GAUVAUUGUCCAUUVAUAAUUGA	225	UCAUUVUAAUUGAACUAVUUC	717	5953-5973
AV03945. um	GAUAGUUGCAUUVUAAAUUGAA	226	UUCAUUVUAAUUGAACUAVUC	718	5954-5974
AV03946. um	GUAGUUGCAUUVUAAAUUGACA	227	UGUCAUUVUAAUUGAACUAVC	719	5955-5975
AV03947. um	CUUCCAUUVUAAAUUGACUUA	228	UGAACUCAUUVUAAUUGAAAG	720	5958-5978
AV03948. um	GACUUGCAAGUCCCAUGAUUUA	229	UAAUCAUGGACUUGCAAGUC	721	6635-6655
AV03949. um	GUUGCAAGUCCCAUGAUUUA	230	UGAAAUUCAUGGACUUGCAAC	722	6637-6657
AV03950. um	GUUGCAAGUCCCAUGAUUUA	231	UAGAAAUUCAUGGACUUGCAC	723	6638-6658
AV03951. um	GGCAAGUCCCAUGAUUUA	232	UAGAAAUUCAUGGACUUGCC	724	6639-6659
AV03952. um	GGAAAUUCAUUCUUAAGCUAAGCA	233	UGCUAAGCUAAGAUUUAUUC	725	6688-6708
AV03953. um	GAUUCAUUCUUAAGCUUAGCUVA	234	UAAAGCUAAGCUAAGAUUUC	726	6690-6710
AV03954. um	GGUCUAVUUAAGUGUAVUUGUA	235	UCACAAUACACUAVUAVAGACC	727	6722-6742
AV03955. um	GAUUGAUUUAACACUGACUGUA	236	UACAGUCAGUGUAAAUCAUUC	728	6751-6771
AV03956. um	GUUACACUGACUGUUGCUUUA	237	UACAGUCAGUGUAAAUCAUUC	729	6753-6773
AV03957. um	GUUACACUGACUGUUGCUUUA	238	UACAGCAACAGUCAGUGUAAAC	730	6757-6777
AV03958. um	GUACACUGACUGUUGCUUUA	239	UUACAGCAACAGUCAGUGUAC	731	6758-6778
AV03959. um	GACACUGACUGUUGCUUUA	240	UUUACAGCAACAGUCAGUGUC	732	6759-6779
AV03960. um	GCACUGACUGUUGCUUUA	241	UUUUACAGCAACAGUCAGUGC	733	6760-6780
AV03961. um	GCUGACUGUUGCUUUA	242	UCUUUUACAGCAACAGUCAGC	734	6762-6782
AV03962. um	GUAGACUGUUGCUUUA	243	UACUUUUACAGCAACAGUCAC	735	6763-6783
AV03963. um	GGACUGUUGCUUUA	244	UCACUUUUACAGCAACAGUCC	736	6764-6784
AV03964. um	CACUUGUUGCUUUA	245	UUCACUUUUACAGCAACAGUG	737	6765-6785
AV03965. um	GCUGUUGCUUUA	246	UUUACUUUUACAGCAACAGC	738	6766-6786
AV03966. um	GUUGUUGCUUUA	247	UUUACUUUUACAGCAACAGC	739	6767-6787
AV03967. um	CCUUGUAAAAAGUAAUUGGAA	248	UUCCAAAUUACUUUUACAGG	740	6772-6792
AV03968. um	GUUGUAAAAAGUAAUUGGAAA	249	UUUCCAAAUUACUUUUACAC	741	6773-6793
AV03969. um	GGUGAAUUVUUGGAAUAAAGUA	250	UACUUUUUUUCCAAAUUUCACC	742	6780-6800
AV03970. um	GGGAAAUUAAAGUUVUUVACUCA	251	UGAGUAAUVAACUUUUUUUUCCC	743	6788-6808
AV03971. um	CGAAAUUAAAGUUVUUVACUCUA	252	UAGAGUAAUVAACUUUUUUUCCG	744	6789-6809

AV03972-19-1.µm	GAUAAAAGUUUAVUACUCUGAUA	253	UAUCAGAGUAUAUAACTUUUAUC	745	6792-6812
AV03973-19-1.µm	GAAAGUUAVUACUCUGAUAUAAA	254	UUUAUUCAGAGUAUAUAACTUUC	746	6795-6815
AV03728-19-1.µm	CUCCUCCGCGUCUCCUCUCA	255	UGAGAGGACAGCGGAGAG	747	90-108
AV03729-19-1.µm	GAGUUUCGAAAGUGAUGGAAA	256	UUUCCAUACUUUCGAACUC	748	169-187
AV03730-19-1.µm	AGUUUCGAAAGUGAUGGAAAG	257	UUUUCCAUACUUUCGAACU	749	170-188
AV03731-19-1.µm	GUUCCGAAAGUGAUGGAAAGAA	258	UUUUCCAUACUUUCGAAC	750	171-189
AV03732-19-1.µm	UUCGAAAGUGAUGGAAAGAU	259	UAUUCCAUACUUUCGAA	751	172-190
AV03733-19-1.µm	UCCGAAAGUGAUGGAAAGAUCA	260	UGAUUUCCAUACUUUCGA	752	173-191
AV03734-19-1.µm	CGAAGUGAUGGAAAGAUCAA	261	UUGAUUUUCCAUACUUUCG	753	174-192
AV03735-19-1.µm	GCUACACCAUUGCACCAAGA	262	UUUUUGUGCAUUGGUUAGC	754	233-251
AV03736-19-1.µm	CACGGACGCUGGCCUGAAA	263	UUUCAGGCCAGCGUCCGUG	755	264-282
AV03737-19-1.µm	CCCCAGCCUUGGAAAGACGA	264	UUGUUUUCCAGGCGUUGGGG	756	395-413
AV03738-19-1.µm	AGCUGCGUGGUCACGUAGACA	265	UUUCACGUUGACCAAGCAGCU	757	414-432
AV03739-19-1.µm	AAGCUCGCAUUGGUCAGUAAA	266	UUACUGACCAUUGCGAGCUU	758	1499-1517
AV03740-19-1.µm	AGCUCGCAUUGGUCAGUAAA	267	UUUACUGACCAUUGCGAGCU	759	1500-1518
AV03741-19-1.µm	CUCCGCAUUGGUCAGUAAAA	268	UUUUUACUGACCAUUGCGAG	760	1502-1520
AV03742-19-1.µm	CGCAUUGGUCAGUAAAAAGCA	269	UUGCUUUUACUGACCAUUGCG	761	1504-1522
AV03743-19-1.µm	GCAUUGGUCAGUAAAAAGCAA	270	UUGCUUUUACUGACCAUUGC	762	1505-1523
AV03744-19-1.µm	CAUUGGUCAGUAAAAAGCAAAA	271	UUUGCUUUUACUGACCAUUG	763	1506-1524
AV03745-19-1.µm	AUUGGUCAGUAAAAAGCAAAA	272	UUUUUGCUUUUACUGACCAU	764	1507-1525
AV03746-19-1.µm	UUGGUCAGUAAAAAGCAAGA	273	UUUUUGCUUUUACUGACCA	765	1508-1526
AV03747-19-1.µm	GGUCAGUAAAAAGCAAGAAGAA	274	UUUUUUUGCUUUUACUGACC	766	1509-1527
AV03748-19-1.µm	GUCAGUAAAAAGCAAGAAGACA	275	UUUUUUUGCUUUUACUGAC	767	1510-1528
AV03749-19-1.µm	ACUUGAAAGCGAUGACAAAAA	276	UUUUUUUGCAUUGCUUCCAGU	768	1531-1549
AV03750-19-1.µm	CUUGAAAGCGAUGACAAAAA	277	UUUUUUUGCAUUGCUUCCAG	769	1532-1550
AV03751-19-1.µm	GAAAGCGAUGACAAAAAAGAA	278	UUUUUUUUUGCAUUGCUUCC	770	1535-1553
AV03752-19-1.µm	AAGCGAUGACAAAAAAGCAA	279	UUUUUUUUUUUGCAUUGCGUU	771	1536-1554
AV03753-19-1.µm	GCGAUGACAAAAAAGCCAA	280	UUUUUUUUUUUUUGCAUUGCG	772	1538-1556
AV03754-19-1.µm	CGAUGACAAAAAAGCCAA	281	UUUUUUUUUUUUUUUGCAUUG	773	1539-1557
AV03755-19-1.µm	CAAGGGGGCUGAUUGUAAA	282	UUUACCAUACAGCCCCCUUG	774	1752-1770
AV03756-19-1.µm	GGCUGAUUGGUAAAAAGAAA	283	UUUUUUUUUUUACCAUACAGCC	775	1758-1776

AV03757-19-1.µm	GCGUAGUGGUAAAACGAGA	284	UCUUCGUSUUUACCAUCAGC	776	1759-1777
AV03758-19-1.µm	UGAUGGUAAAACGAGAUA	285	UAUCUUCGUSUUUACCAUCA	777	1761-1779
AV03759-19-1.µm	GAUGGUAAAACGAGAUA	286	UGAUCUUCGUSUUUACCAUC	778	1762-1780
AV03760-19-1.µm	AUGGUAAAACGAGAUA	287	UCGAUCUUCGUSUUUACCAU	779	1763-1781
AV03761-19-1.µm	CCACCAGGAUUCACAGCAA	288	UUUGCUGGAUUCUUGGUGG	780	1829-1847
AV03762-19-1.µm	AGGAUUCACGCAAAAACCA	289	UGGUSUUUGGUAUCCUGGCU	781	1834-1852
AV03763-19-1.µm	CCACCAGCUCUGUGAAA	290	UUUCACCAAGAGCUGGGUGG	782	1870-1888
AV03764-19-1.µm	UGGUGAACCUCCAAAAUCA	291	UGAUSUUUGAGGUAUCACCA	783	1881-1899
AV03765-19-1.µm	GGUGAACCUCCAAAAUCA	292	UUGAUSUUUGAGGUAUCACC	784	1882-1900
AV03766-19-1.µm	CCUCCAAAAUCAGGGGAUA	293	UAUCCCCUGAUSUUUGGAGG	785	1888-1906
AV03767-19-1.µm	CGGCUCCACUAGAACCUA	294	UAGGUSUCUAGUGGAGCCG	786	2106-2124
AV03768-19-1.µm	UGUGCAAAUAGUCUACAAA	295	UUUGUAAGCUAUUUUGCACA	787	2241-2259
AV03769-19-1.µm	GUGCAAAUAGUCUACAAA	296	UUUUUGUAGCUAUUUUGCAC	788	2242-2260
AV03770-19-1.µm	UGCAAAUAGUCUACAAA	297	UGUUUGUAGACUAUUUGCA	789	2243-2261
AV03771-19-1.µm	GCAAAUAGUCUACAAACCA	298	UGGUUUUGUAGACUAUUUGC	790	2244-2262
AV03772-19-1.µm	CAAAUAGUCUACAAACCA	299	UUGGUUUUGUAGACUAUUUG	791	2245-2263
AV03773-19-1.µm	AUAGUCUACAAACCAGUUA	300	UAACUGGUSUUUGUAGACUAU	792	2248-2266
AV03774-19-1.µm	UAGUCUACAAACCAGUUGA	301	UCAACUGGUSUUUGUAGACUA	793	2249-2267
AV03775-19-1.µm	AGUCUACAAACCAAGUUGAA	302	UUCACUGGUSUUUGUAGACU	794	2250-2268
AV03776-19-1.µm	ACAAACCAAGUUGACCUGAA	303	UUCAGGUCACUUGGUSUUGU	795	2255-2273
AV03777-19-1.µm	AAGGUGACCUCCAAGUGUA	304	UACACUUGGAGGUCACCUCU	796	2275-2293
AV03778-19-1.µm	ACCUCCAAGUGUGGCUCAA	305	UUGAGCCACACUUGGAGGU	797	2281-2299
AV03779-19-1.µm	CUCCAAGUGUGGCUCAUUA	306	UAAUGAGCCACACUUGGAG	798	2283-2301
AV03780-19-1.µm	CCAAGUGUGGCUCAUUA	307	UCUAAUGAGCCACACUUGG	799	2285-2303
AV03781-19-1.µm	GUGGCUCAUUAAGGCAACAA	308	UUUGUGCCUAUUAAGGCCAC	800	2291-2309
AV03782-19-1.µm	GGCUCAUUAAGGCAACAUCA	309	UGAUGUGGCCUAUUAAGGCC	801	2293-2311
AV03783-19-1.µm	CUCAUUAAGGCAACAUCCAA	310	UUUGAUGGUGGCCUAUUA	802	2295-2313
AV03784-19-1.µm	UCAUUAAGGCAACAUCCAUUA	311	UAUGGAUGUUGGCCUAUUA	803	2296-2314
AV03785-19-1.µm	AUUAAGGCAACAUCCAUCAA	312	UUGAUGGAUGUUGGCCUAU	804	2298-2316
AV03786-19-1.µm	UAGGCAACAUCCAUCAUUA	313	UUUAUGAUGAUGUUGGCCUA	805	2300-2318
AV03787-19-1.µm	AGGCAACAUCCAUCAUUA	314	UUUAUGAUGAUGUUGGCCU	806	2301-2319

AV03788-19-1.µm	GCAACAUCCAUCAUAAAA	315	UGUUUAVUGAUGAUGUGC	807	2303-2321
AV03789-19-1.µm	AACAUCCAUCAUAAAA	316	UUGUUUAVUGAUGAUGUU	808	2305-2323
AV03790-19-1.µm	CAUCCAUCAUAAAA	317	UCCUGUUUAVUGAUGAUG	809	2307-2325
AV03791-19-1.µm	AGUGGAAGUAAAAUCUGA	318	UCAGAUUUUACUCCACCU	810	2333-2351
AV03792-19-1.µm	GGUGGAAGUAAAAUCUGAA	319	UUCAGAUUUUACUCCACC	811	2334-2352
AV03793-19-1.µm	GUUGGAAGUAAAAUCUGAGA	320	UCUCAGAUUUUACUCCAC	812	2335-2353
AV03794-19-1.µm	UGGAAGUAAAAUCUGAGAA	321	UUCUCAGAUUUUACUCCA	813	2336-2354
AV03795-19-1.µm	GGAAGUAAAAUCUGAGAAA	322	UUUCUCAGAUUUUACUCC	814	2337-2355
AV03796-19-1.µm	GAAGUAAAAUCUGAGAGAA	323	UCUUCUCAGAUUUUACUUC	815	2338-2356
AV03797-19-1.µm	AGUAAAAUUCUGAGAGAA	324	UAGCUUUCUCAGAUUUUACU	816	2340-2358
AV03798-19-1.µm	GUAAAAUUCUGAGAGAGCUA	325	UAAGCUUUCUCAGAUUUUAC	817	2341-2359
AV03799-19-1.µm	AAAAUUCUGAGAGAGCUUAA	326	UUCAGCUUUCUCAGAUUUU	818	2343-2361
AV03800-19-1.µm	UGAGAGAGCUUAGACUUCAAA	327	UUUGAAGUCAAAGCUUCUCA	819	2349-2367
AV03801-19-1.µm	GAGAGAGCUUAGACUUCAGAA	328	UCUUGAAGUCAAAGCUUCUC	820	2350-2368
AV03802-19-1.µm	AAGCUUAGACUUCAGAGACA	329	UGUCCUUGAAGUCAAAGCUU	821	2353-2371
AV03803-19-1.µm	AGCUUAGACUUCAGAGCAA	330	UUGUCCUUGAAGUCAAAGCU	822	2354-2372
AV03804-19-1.µm	AGGACAGAGUCCAGUCCGAA	331	UUCGACUUGAGACUCUGUCCU	823	2366-2384
AV03805-19-1.µm	AGAGUCCAGUCCGAGAAUUA	332	UAUVCUUCGACUUGGACUCU	824	2371-2389
AV03806-19-1.µm	GGCGGAGGAAAUAAAAAGA	333	UCUUUUUAUUUCCUCCGCC	825	2419-2437
AV03807-19-1.µm	CGGAGGAAAUAAAAAGAUUA	334	UAUVCUUUUUAUUUCCUCCG	826	2421-2439
AV03808-19-1.µm	AUAAAAAGAUUUGAAACC	335	UUGGUUUCAAUCUUUUUAU	827	2429-2447
AV03809-19-1.µm	AAAGAUUUGAAACCACCAAA	336	UUUGUGGUUUCAAUCUUUU	828	2433-2451
AV03810-19-1.µm	GAGAUCCGUGUACAAGUCGA	337	UCGACUUUGUACAAGAUUC	829	2497-2515
AV03811-19-1.µm	AUUCUACAGCAAUUGUCUUA	338	UAGGAGACAUUGCUGAGAU	830	2546-2564
AV03812-19-1.µm	CCGGCAGCAUCGACAUUGGA	339	UCCAUGUCGAUUGCUGCCG	831	2567-2585
AV03813-19-1.µm	GCAUCGACAUUGUAGACUA	340	UAGUCUACCAUUGCAGUAGC	832	2573-2591
AV03814-19-1.µm	CACGCUAAGCUGACGAGGUA	341	UACCUAGCAGCUAGCGUG	833	2604-2622
AV03815-19-1.µm	CAAGCAGGCUUUUGAUAUCA	342	UGAUCACAACCCUCCUG	834	2637-2655
AV03816-19-1.µm	AAGCAGGCUUUUGAUAUCA	343	UUGAUACACAACCCUCCUU	835	2638-2656
AV03817-19-1.µm	GAGAGAGUUGGAAAAAAA	344	UUUUUUUCCACACUUCUC	836	2695-2713
AV03818-19-1.µm	AAAAAAGAAUAUUGACCCA	345	UGGUCUAUUAUUCCUUUUU	837	2710-2728

AV03819-19-1.µm	CCUCCGACGUAUCGGUAAUA	346	UAUUAACCGAACUCGCGAGG	838	2755-2773
AV03820-19-1.µm	AUUGGUUAUUCACUUAACA	347	UGUUAGAUGAUUAACCAAU	839	2771-2789
AV03821-19-1.µm	UUGGUUAUUCACUUAACCA	348	UGGUUAAGUGAUUAACCAA	840	2772-2790
AV03822-19-1.µm	GGUUAAUUCACUUAACCUGA	349	UCAGGUUAAGUGAUUAACC	841	2774-2792
AV03823-19-1.µm	AUCCACUUAACCUGCUUUUA	350	UAAAAGCAGGUUAAGUGAU	842	2779-2797
AV03824-19-1.µm	UCACUUAACCUGCUUUUGA	351	UCAAAGCAGGUUAAGUGA	843	2780-2798
AV03825-19-1.µm	CACUUAACCUGCUUUUGUA	352	UACAAAAGCAGGUUAAGUG	844	2781-2799
AV03826-19-1.µm	ACUUAACCUGCUUUUGUCA	353	UGACAAAAGCAGGUUAAGU	845	2782-2800
AV03827-19-1.µm	CUCGGGACUUCAAAAUCAGUA	354	UUGAUUUUGAAGUCCCGAG	846	2812-2830
AV03828-19-1.µm	CGGGACUUCAAAAUCAGUA	355	UACUGAUUUUGAAGUCCCG	847	2814-2832
AV03829-19-1.µm	ACUUCAAAAUCAGUGAUGA	356	UCAUCACUGAUUUUUGAAGU	848	2818-2836
AV03830-19-1.µm	CUUCAAAAUCAGUGAUGGA	357	UCCAUCACUGAUUUUUGAAG	849	2819-2837
AV03831-19-1.µm	AGAAGCAAAUUCAUUCUUUA	358	UAAAAGAUGAAAUUUGCUCU	850	2842-2860
AV03832-19-1.µm	GAGCAAAUUCAUUCUUUCA	359	UGAAAGAUGAAAUUUGCUC	851	2843-2861
AV03833-19-1.µm	AGCAAAUUCAUUCUUCCA	360	UGGAAAGAUGAAAUUUGCU	852	2844-2862
AV03834-19-1.µm	GCAAAUUCAUUCUUCCA	361	UUGGAAAGAUGAAAUUUGC	853	2845-2863
AV03835-19-1.µm	CAAAUUCAUUCUUCCA	362	UUUGGAAAGAUGAAAUUUG	854	2846-2864
AV03836-19-1.µm	AAAUUCAUUCUUCCA	363	UUUUGGAAAGAUGAAAUUU	855	2847-2865
AV03837-19-1.µm	AAUUCAUUCUUCCA	364	UAUUUGGAAAGAUGAAAUU	856	2848-2866
AV03838-19-1.µm	AUUUCAUUCUUCCA	365	UAUUUGGAAAGAUGAAAU	857	2849-2867
AV03839-19-1.µm	UUUCAUCUUUCCA	366	UCAUUUGGAAAGAUGAAA	858	2850-2868
AV03840-19-1.µm	UCAUCUUUCCA	367	UAUCAUUUGGAAAGAUGA	859	2852-2870
AV03841-19-1.µm	GUUGGCUAGUAUAAAAUA	368	UAUUUAUUACUAGCCAC	860	2872-2890
AV03842-19-1.µm	GGCUAGUAUAAAAUUA	369	UAUUUAUUUAUACUAGCC	861	2875-2893
AV03843-19-1.µm	AGGCAAUUCUUUUGAUUA	370	UAUCAAAAAGGAUUUGCU	862	2937-2955
AV03844-19-1.µm	GCAAUUCUUUUGAUUCUA	371	UAGAUAUCAAAGGAUUUGC	863	2939-2957
AV03845-19-1.µm	CAGCAACAAAGAUUUUGAAA	372	UUCAAUUCUUUUGUUGCUG	864	3084-3102
AV03846-19-1.µm	GCAACAAAGAUUUUGAAAA	373	UUUUCAAUUCUUUUGUUGC	865	3086-3104
AV03847-19-1.µm	CAACAAAGAUUUUGAAACA	374	UGUUUCAAAUUCUUUGUUG	866	3087-3105
AV03848-19-1.µm	AACAAAGAUUUUGAAACUA	375	UAGUUUCAAAUUCUUUGUU	867	3088-3106
AV03849-19-1.µm	ACAAAAGAUUUUGAAACUA	376	UAAGUUUCAAAUUCUUUGU	868	3089-3107

AV03850-19-1.µm	CAAAAGGAVUUGAAACUUGA	377	UCAAGUUUCAAAUCCUUUG	869	3090-3108
AV03851-19-1.µm	AAAAGAVUUUGAAACUUGGA	378	UCCAAGUUUCAAAUCCUUU	870	3091-3109
AV03852-19-1.µm	AAGGAVUUUGAAACUUGGUA	379	UACCAAGUUUCAAAUCCUU	871	3092-3110
AV03853-19-1.µm	GGAUUUUUGAAACUUGGUGUA	380	UACACCAAGUUUCAAAUCC	872	3094-3112
AV03854-19-1.µm	GAUUUUUGAAACUUGGUGUGA	381	UCACACCAAGUUUCAAAUUC	873	3095-3113
AV03855-19-1.µm	UUUUGAAACUUGGUGUGUUA	382	UAAACACCAAGUUUCAAAA	874	3097-3115
AV03856-19-1.µm	UUUGAAACUUGGUGUGUUCA	383	UGAACACACCAAGUUUCAAA	875	3098-3116
AV03857-19-1.µm	CCAUGAUUUUUGGCCACUUA	384	UAGUGGCCAAAUAUCAUUG	876	3611-3629
AV03858-19-1.µm	UGGCCACUUUGGCAGACCUA	385	UAGUUCUGCAAAAGUGGCCA	877	3620-3638
AV03859-19-1.µm	UUGCAGACUUUGGCAGACCUA	386	UAAAGUCCCAAGGUCUGCAA	878	3628-3646
AV03860-19-1.µm	CCUUGGACUUUAGGGCUAA	387	UUAGCCCUAAAGUCCCAAG	879	3635-3653
AV03861-19-1.µm	CUUUAGGGCUAACCAGUUA	388	UAAUUGGUUAGCCCUAAAG	880	3642-3660
AV03862-19-1.µm	GCUAACCAGUUCUCUUUGA	389	UCAAAGAGAACUUGGUUAGC	881	3649-3667
AV03863-19-1.µm	CUAACCAGUUCUCUUUGUA	390	UACAAGAGAACUUGGUUAG	882	3650-3668
AV03864-19-1.µm	AACCAGUUCUCUUUGUAAA	391	UUUACAAGAGAACUUGGUU	883	3652-3670
AV03865-19-1.µm	ACCAGUUCUCUUUGUAAGA	392	UCUUACAAGAGAACUUGGU	884	3653-3671
AV03866-19-1.µm	CCAGUUCUCUUUGUAAGGA	393	UCCUUACAAGAGAACUUGG	885	3654-3672
AV03867-19-1.µm	CAGUUCUCUUUGUAAGGAA	394	UUCCUUACAAGAGAACUUG	886	3655-3673
AV03868-19-1.µm	AGUUCUCUUUGUAAGGACA	395	UGUCCUUACAAGAGAACU	887	3656-3674
AV03869-19-1.µm	UUCUCUUUGUAAGGACUUA	396	UAAGUCCUUAACAAGAGAA	888	3658-3676
AV03870-19-1.µm	CUCUUUGUAAGGACUUGUA	397	UACAAGUCCUUAACAAGAG	889	3660-3678
AV03871-19-1.µm	AUCCACUGCCUAUACCCCUA	398	UAGGGGUUAAGGCAGUGAU	890	3836-3854
AV03872-19-1.µm	ACUCCAUACUGAGGGUGAAA	399	UUCACCCUACAGUUAUGAGU	891	3935-3953
AV03873-19-1.µm	AUACUGAGGGUGAAAUUAAA	400	UUAAUUUACACCCUACAGUA	892	3940-3958
AV03874-19-1.µm	UACUGAGGGUGAAAUUAAA	401	UUUAAUUUACACCCUACAGU	893	3941-3959
AV03875-19-1.µm	ACUGAGGGUGAAAUUAAAGA	402	UCUUAAUUUACACCCUACAGU	894	3942-3960
AV03876-19-1.µm	CUGAGGGUGAAAUUAAAGA	403	UCCUUAUUUACACCCUACAG	895	3943-3961
AV03877-19-1.µm	GGGUGAAAUUAAAGGGAAGA	404	UCUUCCCUUAUUUACACCC	896	3947-3965
AV03878-19-1.µm	ACCCACAGCCUCUCACUCUA	405	UAGAGUGAGAGGCUGGGGU	897	3989-4007
AV03879-19-1.µm	GCUCUCACUCUCUAGUUCA	406	UGAACUGAGAGUGAGAGGC	898	3995-4013
AV03880-19-1.µm	CUUCUCACUCUCUAGUCCAA	407	UUUGAACUUGAGAGUGAGAG	899	3997-4015

AV03881-19-1.µm	ACUCUCAGUUCACUCACUA	408	UAVGAGUGGAACUAGAAGU	900	4002-4020
AV03882-19-1.µm	CUUCUCAGUUCACUCACUCA	409	UGAUGAGUGGAACUGAGAG	901	4003-4021
AV03883-19-1.µm	CAGUUCACUCACUCACACA	410	UGUUGGAGUGAGUGGAACUG	902	4007-4025
AV03884-19-1.µm	AGGUGUUCUCGCCUUGUUA	411	UACAGGCGAGAAACACCU	903	4120-4138
AV03885-19-1.µm	GUUCUCGCCUUGUUGACAA	412	UUGUCAACAGGCGAGAAAC	904	4124-4142
AV03886-19-1.µm	UUUCUGCCUUGUUGACAU	413	UAUUCACAGGCGAGAAA	905	4125-4143
AV03887-19-1.µm	UGGAAGCCAUGCCUGUCUA	414	UCAGACAGCAUGGCCUCCA	906	4426-4444
AV03888-19-1.µm	AAGCCAUGCCUGUCUGUCA	415	UGAACAGACAGCAUGGCCU	907	4429-4447
AV03889-19-1.µm	GCCAUGCCUGUCUGUCUA	416	UCAGACAGACAGCAUGGC	908	4431-4449
AV03890-19-1.µm	CAUGCUGUCUGUUCUCUA	417	UAGCAGACAGACAGCAUG	909	4433-4451
AV03891-19-1.µm	UGGAGCAGCUGAACAUUA	418	UAUAUGUUCAGCUGCUCCA	910	4450-4468
AV03892-19-1.µm	GGAAGCAGCUGAACAUUAA	419	UUAUAUGUUCAGCUGCUCC	911	4451-4469
AV03893-19-1.µm	GCAGCUGAACAUUACAU	420	UAUGUAUAUGUUCAGCUGC	912	4454-4472
AV03894-19-1.µm	AGCUGAACAUUACAUAGA	421	UCUAUGUAUAUGUUCAGCU	913	4456-4474
AV03895-19-1.µm	GCUGAACAUUACAUAGAA	422	UUCUAUGUAUAUGUUCAGC	914	4457-4475
AV03896-19-1.µm	CUGAACAUUACAUAGAU	423	UAUCUAUGUAUAUGUUCAG	915	4458-4476
AV03897-19-1.µm	UGAACAUUACAUAGAU	424	UCAUCUAUGUAUAUGUUCA	916	4459-4477
AV03898-19-1.µm	GAACAUUACAUAGAU	425	UACAUUCUAUGUAUAUGUUC	917	4460-4478
AV03899-19-1.µm	AACAUUACAUAGAU	426	UAACAUUCUAUGUAUAUGUU	918	4461-4479
AV03900-19-1.µm	ACAUUACAUAGAU	427	UCAACAUUCUAUGUAUGU	919	4462-4480
AV03901-19-1.µm	CAUUAUACAUAGAU	428	UGCAACAUUCUAUGUAUG	920	4463-4481
AV03902-19-1.µm	AGUUGUAGUUGAU	429	UACAABUCCAACUACAACU	921	4508-4526
AV03903-19-1.µm	GUUGUAGUUGAU	430	UGACAAUCCAACUACAAC	922	4509-4527
AV03904-19-1.µm	UUGUAGUUGAU	431	UAGACAAUCCAACUACAA	923	4510-4528
AV03905-19-1.µm	UGUAGUUGAU	432	UCAGACAAUCCAACUACA	924	4511-4529
AV03906-19-1.µm	GUAGUUGAU	433	UACAGACAAUCCAACUAC	925	4512-4530
AV03907-19-1.µm	UAGUUGAU	434	UAAACAGACAAUCCAACUA	926	4513-4531
AV03908-19-1.µm	AGUUGAU	435	UAAACAGACAAUCCAACU	927	4514-4532
AV03909-19-1.µm	GUUGAU	436	UUAAACAGACAAAUCCAAC	928	4515-4533
AV03910-19-1.µm	UUGAU	437	UAUAACAGACAAAUCCA	929	4516-4534
AV03911-19-1.µm	UGGAUUUGUCUGUUUAUGA	438	UCAUAACAGACAAAUCCA	930	4517-4535

AV03912-19-1.µm	GGAUUTUGUCUGUUAUUGCA	439	UGCAUUAACAGACAAAUCC	931	4518-4536
AV03913-19-1.µm	GAUUTUGUCUGUUAUUGCUA	440	UAGCAUUAACAGACAAAUUC	932	4519-4537
AV03914-19-1.µm	AUUTUGUCUGUUAUUGCUUA	441	UAAGCAUUAACAGACAAAU	933	4520-4538
AV03915-19-1.µm	UUTUGUCUGUUAUUGCUUGA	442	UCAAGCAUUAACAGACAAA	934	4521-4539
AV03916-19-1.µm	UUGUCUGUUAUUGCUUGGA	443	UCCAAGCAUUAACAGACAA	935	4522-4540
AV03917-19-1.µm	UGUCUGUUAUUGCUUGGAA	444	UUCCAAGCAUUAACAGACA	936	4523-4541
AV03918-19-1.µm	GUCUGUUAUUGCUUGGAUA	445	UAUCCAAGCAUUAACAGAC	937	4524-4542
AV03919-19-1.µm	UCUGUUAUUGCUUGGAUUA	446	UAAUCCAAGCAUUAACAGAG	938	4525-4543
AV03920-19-1.µm	CUUGUUAUUGCUUGGAUUCA	447	UGAAUCCAAGCAUUAACAG	939	4526-4544
AV03921-19-1.µm	UGUUAUUGCUUGGAUUCAA	448	UUGAAUCCAAGCAUUAACAA	940	4527-4545
AV03922-19-1.µm	GUUUAUUGCUUGGAUUCACA	449	UGUGAAUCCAAGCAUUAAC	941	4528-4546
AV03923-19-1.µm	AUGCUUGGAUUCACACAGAA	450	UUCUGGUGAAUCCAAGCAU	942	4532-4550
AV03924-19-1.µm	GAUUCACCCAGAGUGACUAA	451	UUAGUCACUCUGGUGAAUC	943	4539-4557
AV03925-19-1.µm	AUUCACCCAGAGUGACUUA	452	UAUAGUCACUCUGGUGAAU	944	4540-4558
AV03926-19-1.µm	UUCACCCAGAGUGACUUAUGA	453	UCAUAGUCACUCUGGUGAA	945	4541-4559
AV03927-19-1.µm	AAAAAAAAGGACGCAUGUA	454	UACAUUGGUGCCUUUUUUUU	946	4580-4598
AV03928-19-1.µm	AAAAAAAAGGACGCAUGUAA	455	UUACAUUGGUGCCUUUUUUUU	947	4581-4599
AV03929-19-1.µm	AAAAAAGGACGCAUGUUAUA	456	UAUACAUUGGUGCCUUUUUUUU	948	4582-4600
AV03930-19-1.µm	AAAAAAGGACGCAUGUAUCA	457	UGAUACAUUGGUGCCUUUUUU	949	4583-4601
AV03931-19-1.µm	AAAGGACGCAUGUAUCUUA	458	UAAGAUACAUUGGUGCCUUU	950	4585-4603
AV03932-19-1.µm	AAAGGACGCAUGUAUCUUGA	459	UCAAGAUACAUUGGUGCCUU	951	4586-4604
AV03933-19-1.µm	AGGACGCAUGUAUCUUGAAA	460	UUCAAGAUACAUUGGUGCCU	952	4587-4605
AV03934-19-1.µm	GGACGCAUGUAUCUUGAAAA	461	UUUCAAAGAUACAUUGCGUCC	953	4588-4606
AV03935-19-1.µm	ACGCAUGUAUCUUGAAAAUA	462	UAUUUCAAGAUACAUUGCGU	954	4590-4608
AV03936-19-1.µm	AACUCCUUGCAUUCACAAGAA	463	UUUUUGGAGUCAAAGUGAG	955	4963-4981
AV03937-19-1.µm	CUACAUUUUAUCAUUAUGUUA	464	UAACTAUUUUGAUAAAAGUGAG	956	5943-5961
AV03938-19-1.µm	UCACAUUUUAUCAUUAUGUUA	465	UGAACTAUUUUGAUAAAAGUGA	957	5944-5962
AV03939-19-1.µm	CACAUUUUAUCAUUAUGUCCA	466	UGGAACUUAUUUGAUAAAAGUG	958	5945-5963
AV03940-19-1.µm	ACUUAUUAUCAUUAUGUCCAA	467	UUUGAACUUAUUUGAUAAAAGU	959	5946-5964
AV03941-19-1.µm	UUUAUCAUUAUGUCCAUUA	468	UAAUUGAACUUAUUUGAUAAA	960	5948-5966
AV03942-19-1.µm	UAUCAAUUAUGUCCAUUUAA	469	UUAAAUUGAACUUAUUUGAUA	961	5950-5968

AV03943-19-1.µm	AUCCAAGUAGUCCCAUUA	470	UUUAAUUGAACUUAUUGAU	962	5951-5969
AV03944-19-1.µm	AUAGUUCCAUUAUAUUGA	471	UCAUUAUAUUGGAACUUAU	963	5955-5973
AV03945-19-1.µm	UAGUUCCAUUAUAUUGAA	472	UUCAUUAUAUUGGAACUA	964	5956-5974
AV03946-19-1.µm	AGUUCCAUUAUAUUGACA	473	UGUCAUUAUAUUGGAACU	965	5957-5975
AV03947-19-1.µm	UCCAUAUUAUAUUGACUUA	474	UGAAGUCAUUAUAUUGGA	966	5960-5978
AV03948-19-1.µm	CUUGCAAGUCCCAUUGAUA	475	UAUCAUGGACUUGCAAG	967	6637-6655
AV03949-19-1.µm	UGCAAGUCCCAUUGAUUA	476	UGAAAUCAUGGACUUGCA	968	6639-6657
AV03950-19-1.µm	GCAAGUCCCAUUGAUUA	477	UAGAAUCAUGGACUUGC	969	6640-6658
AV03951-19-1.µm	CAAGUCCCAUUGAUUA	478	UAAGAAUCAUGGACUUG	970	6641-6659
AV03952-19-1.µm	AAAUCAUUAUAGCUUA	479	UGCUAAGCUAAGAUUAU	971	6690-6708
AV03953-19-1.µm	AUCAUUAUAGCUUA	480	UAAGCUAAGCUAAGAUUA	972	6692-6710
AV03954-19-1.µm	UCUAUUAUAGCUUAUUGA	481	UCACAUAUACACUUAUAGA	973	6724-6742
AV03955-19-1.µm	AUGAUUAUACACUUGUA	482	UACAGUCAGUUAUAUUAU	974	6753-6771
AV03956-19-1.µm	GAUUAUACACUUGUUA	483	UCAACAGUCAGUUAUAU	975	6755-6773
AV03957-19-1.µm	UACACUAGCUUGCUUA	484	UACAGCAACAGUCAGUUA	976	6759-6777
AV03958-19-1.µm	ACACUAGCUUGCUUA	485	UUACAGCAACAGUCAGU	977	6760-6778
AV03959-19-1.µm	CACUAGCUUGCUUA	486	UUUACAGCAACAGUCAGU	978	6761-6779
AV03960-19-1.µm	ACUGACUUGCUUAAAA	487	UUUUACAGCAACAGUCAGU	979	6762-6780
AV03961-19-1.µm	UGACUUGCUUGCUUAAAA	488	UCUUUUACAGCAACAGUCA	980	6764-6782
AV03962-19-1.µm	GACUUGCUUGCUUAAAA	489	UACUUUUACAGCAACAGUC	981	6765-6783
AV03963-19-1.µm	ACUUGCUUGCUUAAAA	490	UCACUUUUACAGCAACAGU	982	6766-6784
AV03964-19-1.µm	CUUGUUGCUUAAAA	491	UUCACUUUUACAGCAACAG	983	6767-6785
AV03965-19-1.µm	UGUUGCUUGCUUAAAA	492	UUUCACUUUUACAGCAACA	984	6768-6786
AV03966-19-1.µm	GUGUUGCUUGCUUAAAA	493	UAUUCACUUUUACAGCAAC	985	6769-6787
AV03967-19-1.µm	UGUAAAAAGUAAUUGGAA	494	UUCCAUAUUCACUUUACA	986	6774-6792
AV03968-19-1.µm	GUAAAAAGUAAUUGGAAA	495	UUUCCAUAUUCACUUUAC	987	6775-6793
AV03969-19-1.µm	UGAAUUAUUGAAAUAAAA	496	UACUUUAUUAUUCAAAAUUA	988	6782-6800
AV03970-19-1.µm	GAAAUUAUUGAAAUAAAA	497	UGAGUUAUUAACUUUAUUUC	989	6790-6808
AV03971-19-1.µm	AAAUAAAAAGUAAUUAUUA	498	UAGAGUUAUUAACUUUAUUU	990	6791-6809
AV03972-19-1.µm	UAAAGUUAUUAUUAUUA	499	UAUCAGAGUUAUUAACUUUA	991	6794-6812
AV03973-19-1.µm	AGUUAUUAUUAUUAUUA	500	UUUAUAUUAUUAUUAUUA	992	6797-6815

AD03098-1.µm	CAGGUGGAAGUAAAAUUCUA	1839	UCAGAUUUUACUUCACCCUGGG	1843	2331-2351
AD03099.µm	GUUGAAGUAAAAUUCUGAGAAA	1840	UUUUCAGAUUUUACUUCACCCU	1844	2335-2355
AD03100.µm	CGCAUGGUCAGUAAAAAGCAAA	1841	UUUUGCUUUUACUGACCAUGCGAG	1845	1504-1524
AD02153-1.µm	UAAGUAAAAUUCUGAGAAGCUA	1842	UAGCUUCUCAGAUUUUACUUA	1846	2338-2358
AV07298.µm	GCGCUGGGGACGUAACGGGUUA	2137	UCAACCCGUAACGUCCCAAGCCG	2427	191-211
AV07299.µm	CGACGUAACGGGUUUGGGGACAA	2138	UGUCCCCCAACCCGUAACGUUG	2428	197-217
AV07300.µm	CACGUAACGGGUUUGGGGACAA	2139	UGCUUCGGAAGGUCAAGCCUCC	2284	198-218
AV07301.µm	GGAGGCUGACCUUCCAGAGCCA	2140	UGGCUUCUGGAAGGUCAAGCCUCC	2285	1416-1436
AV07302.µm	CAGGCUGACCUUCCAGAGCCA	2141	UGGCUUCUGGAAGGUCAAGCCUCC	2286	1417-1437
AV07303.µm	GAGCCUAGCUUGCUUGCCCGCA	2142	UCGCGAGCAGCAGCAGGCUCC	2287	1447-1467
AV07304.µm	CGUCAGUAAAAAGCAAAAGACGA	2143	UCGUUCUUUGCUUUUACUGACG	2288	1509-1529
AV07305.µm	CUCAGUAAAAAGCAAAAGACGGA	2144	UCCGUUCUUUGCUUUUACUGAG	2289	1510-1530
AV07306.µm	GAGUAAAAAGCAAAAGACGGGA	2145	UUCCCGUCUUUGCUUUUACUC	2290	1512-1532
AV07307.µm	GCUGGAAGCGAUGACAAAAAA	2146	UUUUUUUGUCAUCGCUUCCAGC	2291	1531-1551
AV07308.µm	GUUGGAAGCGAUGACAAAAAA	2147	UUUUUUUGUCAUCGCUUCCAGC	2292	1532-1552
AV07309.µm	CAAGCGAUGACAAAAAAAGCCA	2148	UGGCUUUUUUGUCAUCGCUUCC	2293	1535-1555
AV07310.µm	CCGAUGACAAAAAAAGCCAAGA	2149	UCUUGGCUUUUUUGUCAUCGG	2294	1538-1558
AV07311.µm	GCCUUGAAAAAAUAGGCCUUGA	2150	UCAAGGCCUAAUUUUUCAAGGC	2295	1582-1602
AV07312.µm	GCUUGAAAAAAUAGGCCUUGCA	2151	UGCAAGGCCUAAUUUUUCAAGC	2296	1583-1603
AV07313.µm	GUUGAAAAAAUAGGCCUUGCCA	2152	UGGCAAGGCCUAAUUUUUCAAG	2297	1584-1604
AV07314.µm	GAGGCCUUGCCUUAAGCCCCAA	2153	UUGGGGCUAAGGCAAGGCCUC	2298	1593-1613
AV07315.µm	CCAAAUAGUCUACAAACCCAGA	2154	UCUGGUUUUGUAGACUAAUUUGG	2299	2244-2264
AV07316.µm	GAAAUAGUCUACAAACCCAGUA	2155	UACUGGUUUUGUAGACUAAUUUC	2300	2245-2265
AV07317.µm	GAGUCUACAAACCCAGUUGACA	2156	UGUCAACUGGUUUUGUAGACUC	2301	2249-2269
AV07318.µm	CUCUACAAACCCAGUUGACCUA	2157	UAGGUCAACUGGUUUUGUAGAG	2302	2251-2271
AV07319.µm	GACAAACCCAGUUGACCUAGAGA	2158	UCUCAGGUCAACUGGUUUUGUC	2303	2254-2274
AV07320.µm	GAACCCAGUUGACCUAGAGCAAA	2159	UUUGCUCAGGUCAACUGGUUC	2304	2257-2277
AV07321.µm	GCCAGUUGACCUAGAGCAAGGA	2160	UCCUUGCUCAGGUCAACUGGGC	2305	2259-2279
AV07322.µm	GCUGAGCAAGGUAGACCUCCAA	2161	UUUGAGGUCAACCUUGCUCAGC	2306	2268-2288
AV07323.µm	GAAAGUGAACCUCCAAAGUGUGA	2162	UCACACUUUGAGAGGUCAACCUUC	2307	2274-2294
AV07324.µm	CACCUCCAAAGUGUGGCUCAUA	2163	UAUGAGCCACACACUUGGAGGUG	2308	2280-2300

AV07325.µm	GCAAGUGUGGCUCAUUAAGGCA	2164	UGCCUAAUGAGCCACACUUGC	2309	2285-2305
AV07326.µm	GAGUGUGGCUCAUUAAGCAAA	2165	UUUGCCUAAUGAGCCACACUC	2310	2287-2307
AV07327.µm	GGUGUGGCUCAUUAAGCAACA	2166	UGUUGCCUAAUGAGCCACACC	2311	2288-2308
AV07328.µm	GUCAUUAAGCAACAUCCAUCA	2167	UGAUGGAUGUUGCCUAAUGAC	2312	2295-2315
AV07329.µm	GAUUAAGCAACAUCCAUCAUA	2168	UAUGAUGGAUGUUGCCUAAUC	2313	2297-2317
AV07330.µm	GAGCAACAUCCAUCAUAAAAA	2169	UUUUAUGAUGGAUGUUGCCUC	2314	2300-2320
AV07331.µm	CGCAACAUCCAUCAUAAAAACA	2170	UGGUUUAUGAUGGAUGUUGCG	2315	2302-2322
AV07332.µm	GAACAUCCAUCAUAAAAACAGA	2171	UCUGGUUUAUGAUGGAUGUUC	2316	2304-2324
AV07333.µm	GCAUCCAUCAUAAACCAGGAA	2172	UACCUGGUUUAUGAUGGAUGC	2317	2306-2326
AV07334.µm	GCCAUCAUAAACCAGAGGUA	2173	UACCUCCUGGUUUAUGAUGGC	2318	2309-2329
AV07335.µm	GAACCAAGAGUGGCCAGGUA	2174	UACCUGGCCACCUCCUGGUC	2319	2317-2337
AV07336.µm	CCCAGUGGAAAGUAAAAUCUA	2175	UAGAUUUUACUUCACCACCUGGG	2320	2330-2350
AV07337.µm	CGAAGUAAAAUCUGAGAAGCA	2176	UGCUUCUAGAUAUUUUAUCUCG	2321	2337-2357
AV07338.µm	GGUAAAAUUCUGAGAAGCUUGA	2177	UCAAGCUUCUCAGAUUUUUAAC	2322	2340-2360
AV07339.µm	GAAAAUUCUGAGAAGCUUGACA	2178	UGUCAAGCUUCUCAGAUUUUUC	2323	2342-2362
AV07340.µm	GAAAUUCUGAGAAGCUUGACUA	2179	UAGUCAAGCUUCUCAGAUUUUC	2324	2343-2363
AV07341.µm	GAAUCUGAGAAGCUUGACUUA	2180	UAGUCAAGCUUCUCAGAUUUC	2325	2344-2364
AV07342.µm	GAUCUGAGAAGCUUGACUUCA	2181	UGAAGUCAAGCUUCUCAGAUUC	2326	2345-2365
AV07343.µm	GUUCUGAGAAGCUUGACUUCAA	2182	UUGAAGUCAAGCUUCUCAGAGC	2327	2346-2366
AV07344.µm	GGAGAAGCUUGACUUCAAAGGA	2183	UCCUUGAAGUCAAGCUUCUCC	2328	2349-2369
AV07345.µm	CAGAAGCUUGACUUCAAAGGAA	2184	UUCCUUGAAGUCAAGCUUCUG	2329	2350-2370
AV07346.µm	GAGCUUGACUUCAAAGGACAGA	2185	UCUGUCCUUGAAGUCAAGCUC	2330	2353-2373
AV07347.µm	GGCUUGACUUCAAAGGACAGAA	2186	UUCUGUCCUUGAAGUCAAGCC	2331	2354-2374
AV07348.µm	CCUUGACUUCAAAGGACAGAGA	2187	UCUCUGUCCUUGAAGUCAAGG	2332	2355-2375
AV07349.µm	GUUGACUUCAAAGGACAGAGUA	2188	UACUCUGUCCUUGAAGUCAAC	2333	2356-2376
AV07350.µm	GUGACUUCAAAGGACAGAGUCA	2189	UGACUCUGUCCUUGAAGUCAC	2334	2357-2377
AV07351.µm	CACAGAGUCCAGUCGAAGAUUA	2190	UAUCUUGGACUUGGACUCUGG	2335	2368-2388
AV07352.µm	GAGAGUCCAGUCGAAGAUUGA	2191	UCAUUCUUGGACUUGGACUCUC	2336	2370-2390
AV07353.µm	GCAGUCGAAGAUUGGUCCCA	2192	UGGGAACCAAUUCUUCGACUGC	2337	2376-2396
AV07354.µm	GAGUCGAAGAUUGGUCCCUA	2193	UAAGGACCCAUAUCUUCGACUC	2338	2377-2397
AV07355.µm	GGAAGAUUGGUCCCUUGGACA	2194	UGUCCAGGAGACCAAUUCUUC	2339	2381-2401

AV07356.µm	CAUUGGGGUCCUGGACAUAUA	2195	UUUUGUCCAGGGACCCAAUG	2340	2385-2405
AV07357.µm	CGGUCCCUGGACAAUAUCACA	2196	UGUGAUUUGUCCAGGGACCG	2341	2389-2409
AV07358.µm	GCCCUUGGACAUAUACACCCAA	2197	UUGGUGAUUUGUCCAGGGC	2342	2392-2412
AV07359.µm	GCUGGACAUAUACACCCACGA	2198	UCGUGGUGAUUUGUCCAGC	2343	2394-2414
AV07360.µm	GUUGACAUAUACACCCACGUA	2199	UACGUGGUGAUUUGUCCAC	2344	2395-2415
AV07361.µm	GAAGAAAAGAAUAUAGACCCGA	2200	UCGGGUCAUUUAUUCUUUUUC	2345	2709-2729
AV07362.µm	GAAGAAAAGAAUAUAGACCCGA	2201	UCCGGGUCAUUUAUUCUUUUUC	2346	2710-2730
AV07363.µm	GAAGAAAAGAAUAUAGACCCGCA	2202	UGCCGGGUCAUUUAUUCUUUUUC	2347	2711-2731
AV07364.µm	CGCCCCCGCCUUCUCCCCCA	2203	UGGGGGCAGAGGGCCGGGGCG	2348	2728-2748
AV07365.µm	GCCCCCGCCUUCUCCCCCAGA	2204	UCUGGGGGCAGAGGGCCGGGGC	2349	2730-2750
AV07366.µm	GUGCCCCCGCAGCUCUCCUGA	2205	UCGAGGAGCAGCUGGGGGCAC	2350	2740-2760
AV07367.µm	GCCCCAGCUCUCUCCUGCAGA	2206	UCUCGAGGAGCAGCUGGGGC	2351	2743-2763
AV07368.µm	CCUCCUCGCAGUUCGGUUAAA	2207	UUUAACCGAACUCCGAGGAGG	2352	2752-2772
AV07369.µm	GUCCGAGUUCGGUUAAUUGGA	2208	UCCAUAUUAACCGAACUCGGAC	2353	2756-2776
AV07370.µm	GCGCAGUUCGGUUAAUUGGUA	2209	UACCAUAUUAACCGAACUGGC	2354	2757-2777
AV07371.µm	GCGAGUUCGGUUAAUUGGUA	2210	UAACCAUAUUAACCGAACUGCC	2355	2758-2778
AV07372.µm	CCAGUUCGGUUAAUUGGUAAA	2211	UUAAACCAUUAACCGAACUGG	2356	2759-2779
AV07373.µm	GAGUUCGGUUAAUUGGUAAA	2212	UUUAACCAUUAACCGAACUC	2357	2760-2780
AV07374.µm	GGUUCGGUUAAUUGGUAAUA	2213	UAUUAACCAUUAACCGAACCC	2358	2761-2781
AV07375.µm	CUUCGGUUAAUUGGUUAUCA	2214	UGAUUAACCAUUAACCGAAG	2359	2762-2782
AV07376.µm	GUCCGGUUAAUUGGUUAUCAA	2215	UUGAUUAACCAUUAACCGAG	2360	2763-2783
AV07377.µm	GCGGUUAUUGGUUAUUCACA	2216	UGUGAUUAACCAUUAACCGC	2361	2764-2784
AV07378.µm	GGGUUAUUGGUUAUUCACUA	2217	UAGUGAUUAACCAUUAACCC	2362	2765-2785
AV07379.µm	CGUUAUUGGUUAUUCACUUA	2218	UAAGUGAUUAACCAUUAACG	2363	2766-2786
AV07380.µm	CUUAUUGGUUAUUCACUAAA	2219	UUAAUGAUUAACCAUUAAG	2364	2767-2787
AV07381.µm	GUAAUUGGUUAUUCACUAAAA	2220	UUUAAGUGAUUAACCAAUUAC	2365	2768-2788
AV07382.µm	GUUGGUUAUUCACUUAACCUA	2221	UAGGUUAAGUGAUUAACCAAC	2366	2771-2791
AV07383.µm	GGGUUAUUCACUUAACCUGCA	2222	UGCAGGUUAAGUGAUUAACCC	2367	2773-2793
AV07384.µm	CGUUAUUCACUUAACCUGCUA	2223	UAAGCAGGUUAAGUGAUUAACG	2368	2774-2794
AV07385.µm	CUUAUUCACUUAACCUUGCUUA	2224	UAAAGCAGGUUAAGUGAUUAAG	2369	2775-2795
AV07386.µm	GUAAUUCACUUAACCUUGCUUA	2225	UAAAGCAGGUUAAGUGAUUAC	2370	2776-2796

AV07387.µm	GACUUAACCGUCUUUUGUCA	2226	UUGACAAAAAGCAGGUUAAAGUC	2371	2781-2801
AV07388.µm	GCUUAACCGUCUUUUGUCACA	2227	UGUGACAAAAAGCAGGUUAAAGC	2372	2782-2802
AV07389.µm	GUUAACCGUCUUUUGUCACUA	2228	UAGUGACAAAAAGCAGGUUAAAC	2373	2783-2803
AV07390.µm	GUAAACCGUCUUUUGUCACUCA	2229	UGAGUGACAAAAAGCAGGUUAC	2374	2784-2804
AV07391.µm	GAACCGUCUUUUGUCACUCGA	2230	UCGAGUGACAAAAAGCAGGUUC	2375	2785-2805
AV07392.µm	GCCUGUCUUUUGUCACUCGGCA	2231	UGCCGAGUGACAAAAAGCAGGC	2376	2787-2807
AV07393.µm	GUUCUUUUGUCACUCGGCUUA	2232	UAAAGCCGAGUGACAAAAAGCAC	2377	2789-2809
AV07394.µm	GGCUUUUUGUCACUCGGCUUA	2233	UAAAGCCGAGUGACAAAAAGCC	2378	2790-2810
AV07395.µm	CCUUUUUGUCACUCGGCUUUA	2234	UCAAGCCGAGUGACAAAAAGG	2379	2791-2811
AV07396.µm	GGUCACUCGGCUUUUGGCUCA	2235	UCGAGCCCAAAGCCGAGUGACC	2380	2796-2816
AV07397.µm	CUCACUCGGCUUUUGGCUCGGA	2236	UCCGAGCCCAAAGCCGAGUGAG	2381	2797-2817
AV07398.µm	GUUUUGGCUCCGGACUUCAAAA	2237	UUUUUGAAAGUCCCGAGCCAAAC	2382	2806-2826
AV07399.µm	GGGCUCCGGACUUCAAAAUCA	2238	UGAUUUUUUGAAAGUCCCGAGCC	2383	2809-2829
AV07400.µm	CCUCGGGACUUCAAAAUCAGA	2239	UCUGAUUUUUUGAAAGUCCGAGG	2384	2811-2831
AV07401.µm	GGGGACUUCAAAAUCAGUGAA	2240	UUCACUGAUUUUUUGAAGUCCCG	2385	2814-2834
AV07402.µm	CGGACUUCAAAAUCAGUGAUA	2241	UAUCCACUGAUUUUUUGAAGUCCG	2386	2815-2835
AV07403.µm	GCUUCAAAAUUCAGUGAUGGGA	2242	UCCCAUCCACUGAUUUUUUGAAGC	2387	2818-2838
AV07404.µm	GUUCAAAAUUCAGUGAUGGGAA	2243	UUCCCAUCCACUGAUUUUUUGAAC	2388	2819-2839
AV07405.µm	GUCAAAAUUCAGUGAUGGGAGA	2244	UCUCCCAUCCACUGAUUUUUUGAC	2389	2820-2840
AV07406.µm	GAAAAUUCAGUGAUGGGAGUAA	2245	UUACUCCCAUCCACUGAUUUUUC	2390	2822-2842
AV07407.µm	GAAAUUCAGUGAUGGGAGUAAA	2246	UUUACUCCCAUCCACUGAUUUUC	2391	2823-2843
AV07408.µm	GAAUCAGUGAUGGGAGUUAAGA	2247	UCUUACUCCCAUCCACUGAUUUC	2392	2824-2844
AV07409.µm	GAUCAGUGAUGGGAGUUAAGAA	2248	UUCUUACUCCCAUCCACUGAUUC	2393	2825-2845
AV07410.µm	GUUCAGUGAUGGGAGUUAAGAGA	2249	UUCUUUACUCCCAUCCACUGAG	2394	2826-2846
AV07411.µm	GAGUGAUGGGAGUUAAGAGCAA	2250	UUUCUUUACUCCCAUCCACUUC	2395	2828-2848
AV07412.µm	GGUGAUGGGAGUUAAGAGCAAAA	2251	UUUGCUUUUACUCCCAUCCACCC	2396	2829-2849
AV07413.µm	CUGAUGGGAGUUAAGAGCAAAAA	2252	UUUUUGCUUUUACUCCCAUCCAG	2397	2830-2850
AV07414.µm	GGAUUGGGAGUUAAGAGCAAAUA	2253	UAAUUUGCUUUUACUCCCAUCC	2398	2831-2851
AV07415.µm	CAUUGGGAGUUAAGAGCAAAUUA	2254	UAAUUUUUGCUUUUACUCCCAUG	2399	2832-2852
AV07416.µm	GUUGGAGUUAAGAGCAAAUUAUA	2255	UAAAUUUUGCUUUUACUCCCAAC	2400	2833-2853
AV07417.µm	GGGGAGUUAAGAGCAAAUUAUCA	2256	UGAAAUUUUGCUUUUACUCCCC	2401	2834-2854

AV07418.µm	CGGAGUAAAGAGCAAAUUCAAA	2257	UUGAAAUUUGCUCUUAUCUCCG	2402	2835-2855
AV07419.µm	CGAGUAAAGAGCAAAUUCAUAA	2258	UAUGAAAAUUGCUCUUAUCUG	2403	2836-2856
AV07420.µm	CAGUAAAGAGCAAAUUCAUCA	2259	UGAUGAAAAUUGCUCUUAUCUG	2404	2837-2857
AV07421.µm	GGUAAAGAGCAAAUUCAUUCA	2260	UAGAUGAAAAUUGCUCUUAACC	2405	2838-2858
AV07422.µm	CUAAGAGCAAAUUCAUUCUAA	2261	UAAGAUGAAAAUUGCUCUUAAG	2406	2839-2859
AV07423.µm	GUUUCAUUCUUCCAAUUGAA	2262	UUCAAUUUGGAAAGAUUGAAAC	2407	2849-2869
AV07424.µm	GUUCUUCCAAUUGAUUGGGUA	2263	UACCCAUCAAUUGGAAAGAC	2408	2854-2874
AV07425.µm	GCUUUCCCAAUUGAUUGGUGA	2264	UACCCCAUCAAUUGGAAAGC	2409	2855-2875
AV07426.µm	GUUUUCCCAAUUGAUUGGUGGA	2265	UCCACCCAUCAAUUGGAAAC	2410	2856-2876
AV07427.µm	GUCCCAAUUGAUUGGUGGGCA	2266	UGCCCAUCCCAUCAAUUGGAC	2411	2858-2878
AV07428.µm	GAAUUGAUUGGUGGGGCUAGUA	2267	UACUAGCCCAUCCCAUUAUUC	2412	2862-2882
AV07429.µm	GAUUGAUUGGUGGGGCUAGUAA	2268	UUACUAGCCCAUCCCAUUAUC	2413	2863-2883
AV07430.µm	GUUGAUUGGUGGGGCUAGUAAA	2269	UUUACUAGCCCAUCCCAUUAAC	2414	2864-2884
AV07431.µm	GUUGAUUGGUGGGGCUAGUAAUA	2270	UAUUAUUAUAGCCCAUCCCAUUCAC	2415	2865-2885
AV07432.µm	CAUGGGUGGGGCUAGUAAUAAA	2271	UUUAUUAUUAUAGCCCAUCCCAUUG	2416	2867-2887
AV07433.µm	GUUGGGUGGGGCUAGUAAUAAAA	2272	UUUUUAUUAUUAUAGCCCAUCCCAU	2417	2868-2888
AV07434.µm	GUAGUAAUAAAAUUAUUUAAAAA	2273	UUUUAAAUUAUUUUUAUUAUUAUAC	2418	2877-2897
AV07435.µm	GAGUAAUAAAAUUAUUUAAAAAA	2274	UUUUUAAAUUAUUUUUAUUAUUAUC	2419	2878-2898
AV07436.µm	GGUAAUAAAAUUAUUUAAAAAA	2275	UUUUUUAAAUUAUUUUUAUUAUUAAC	2420	2879-2899
AV07437.µm	CUAAUAAAAUUAUUUAAAAAA	2276	UUUUUUUAAAUUAUUUUUAUUAUAG	2421	2880-2900
AV07438.µm	GAAUAAAAUUAUUUAAAAAA	2277	UUUUUUUUAAAUUAUUUUUAUUAUC	2422	2881-2901
AV07439.µm	GAUAAAAUUAUUUAAAAAA	2278	UUUUUUUUUAAAUUAUUUUUAUUC	2423	2882-2902
AV07440.µm	GUAAAAUUAUUUAAAAAA	2279	UUUUUUUUUUAAAUUAUUUUUAUAC	2424	2883-2903
AV07441.µm	GUAAAAAAUAAACAUAUCAA	2280	UUUUUUGAAUGUUUUUUUUUAUAC	2425	2892-2912
AV07442.µm	GAAAAAAUAAACAUAUCAA	2281	UUUUUUUGAAUGUUUUUUUUUAUC	2426	2893-2913
AV07298-19-1.µm	GCUGGGAGCGUACGGGUGUA	2427	UCAACCGUACGUCCAGC	2572	193-211
AV07299-19-1.µm	ACGUACGGGUGUGGGGAGACA	2428	UGUCCCCCAACCCGUACGU	2573	199-217
AV07300-19-1.µm	CGUACGGGUGUGGGGAGACA	2429	UUUGCCCCCAACCCGUACG	2574	200-218
AV07301-19-1.µm	AGGCUGACCUUCCAGAGACA	2430	UGCUCUGGAAAGGUCAGCCU	2575	1418-1436
AV07302-19-1.µm	GGCUGACCUUCCAGAGACA	2431	UGGCUUCUGGAAAGGUCAGCC	2576	1419-1437
AV07303-19-1.µm	GCCUGCUGCUGCUCGCGA	2432	UCGCGAGAGCAGCAGCAGGC	2577	1449-1467

AV07304-19-1.µm	UCAGUAAAAGCAAAAGACGA	2433	UCGUCUUUGCUUUUACUGA	2578	1511-1529
AV07305-19-1.µm	CAGUAAAAGCAAAAGACGGA	2434	UCCGUCUUUGCUUUUACUG	2579	1512-1530
AV07306-19-1.µm	GUAAAAGCAAAAGACGGGAA	2435	UUCCCGUCUUUGCUUUUAC	2580	1514-1532
AV07307-19-1.µm	UGGAAGCGAUUGACAAAATAA	2436	UUUUUUUGUACUCCGCUCCA	2581	1533-1551
AV07308-19-1.µm	GGAAGCGAUUGACAAAATAA	2437	UUUUUUUGUACUCCGCUCC	2582	1534-1552
AV07309-19-1.µm	AGCGAUUGACAAAATAAGCCA	2438	UGGCUUUUUUGUCAUCGCU	2583	1537-1555
AV07310-19-1.µm	GAUGACAAAATAAGCCACAGA	2439	UCUUUGGCUUUUUUGUCAUC	2584	1540-1558
AV07311-19-1.µm	CUUGAAAAAUUAGGCCUUUGA	2440	UCAAGGCCUAAUUUUUCAAG	2585	1584-1602
AV07312-19-1.µm	UUGAAAAAUUAGGCCUUUGCA	2441	UGCAAGGCCUAAUUUUUCA	2586	1585-1603
AV07313-19-1.µm	UGAAAAAUUAGGCCUUUGCCA	2442	UGGCAAGGCCUAAUUUUUCA	2587	1586-1604
AV07314-19-1.µm	GGCCUUUGCCUUUAGCCCCAA	2443	UUUGGGCUAAAGGCCAAGGCC	2588	1595-1613
AV07315-19-1.µm	AAAUAGUUCUACAAACCAAGA	2444	UCUUGUUUUUAGACUAAUU	2589	2246-2264
AV07316-19-1.µm	AAUAGUUCUACAAACCAAGUA	2445	UACUUGUUUUUAGACUAAUU	2590	2247-2265
AV07317-19-1.µm	GUUCUACAAACCAAGUUGACA	2446	UGUCAACUGUUUUUGUAGAC	2591	2251-2269
AV07318-19-1.µm	CUACAAACCAAGUUGACCUA	2447	UAGGUCAACUGUUUUUGUAG	2592	2253-2271
AV07319-19-1.µm	CAAAACCAAGUUGACCUAGAGA	2448	UCUCAGGUCAACUGGUUUUG	2593	2256-2274
AV07320-19-1.µm	ACCAGUUGACCUUGAGCAAAA	2449	UUUGUCUAGGUCAACUGGU	2594	2259-2277
AV07321-19-1.µm	CAGUUGACCUUGAGCAAGGA	2450	UCCUUUGUCAGGUCAACUG	2595	2261-2279
AV07322-19-1.µm	UGAGCAAGGUUGACCUCCAA	2451	UUUGAGGUUCACCUUGGCUCA	2596	2270-2288
AV07323-19-1.µm	AGGUGACCUCCAAAGUGUGA	2452	UCACACUUUGAGGUCAACCU	2597	2276-2294
AV07324-19-1.µm	CCUCCAAGUGUGGCUCAUA	2453	UAUGAGCCACACUUGGAGG	2598	2282-2300
AV07325-19-1.µm	AAGUGUGGCUCAUUAAGGCA	2454	UGCCUAAUUGAGCCACACUU	2599	2287-2305
AV07326-19-1.µm	GUUGGGCUCAUUAAGGCAAA	2455	UUUGCCUAAUUGAGCCACAC	2600	2289-2307
AV07327-19-1.µm	UGUGGGCUCAUUAAGGCAACA	2456	UGUUGCCUAAUUGAGCCACA	2601	2290-2308
AV07328-19-1.µm	CAUUAAGGCAACAUCCAUA	2457	UGAUUGGAUUGUUGCCUAAUG	2602	2297-2315
AV07329-19-1.µm	UUAGGCAACAUCCAUAUA	2458	UAUGAUUGAUUGUUGCCUAA	2603	2299-2317
AV07330-19-1.µm	GGCAACAUCCAUCAUAAAAA	2459	UUUUUAUGAUUGAUUGUCC	2604	2302-2320
AV07331-19-1.µm	CAACAUCCAUCAUAAAAACA	2460	UGGUUUUAUGAUUGGAUGUG	2605	2304-2322
AV07332-19-1.µm	ACAUCCAUCAUAAAAACAGA	2461	UCUGGUUUUAUGAUUGGAUGU	2606	2306-2324
AV07333-19-1.µm	AUCCAUCAUAAAAACAGGAA	2462	UUCCUGGUUUUAUGAUUGGAU	2607	2308-2326
AV07334-19-1.µm	CAUCAUAAAAACAGAGGUA	2463	UACCUCUUGGUUUUAUGAUG	2608	2311-2329

AV07335-19-1.µm	ACCAGGAGGUGGCCAGGUA	2464	UACCGGGCCACCUCUGGU	2609	2319-2337
AV07336-19-1.µm	CAGGUGGAAGUAAAAUCUA	2465	UAGAUUUUACUUCACCUG	2610	2332-2350
AV07337-19-1.µm	AAGUAAAUCUGAGAAGCA	2466	UGCUCUCAGAUUUUACUU	2611	2339-2357
AV07338-19-1.µm	UAAAAUCUGAGAAGCUUGA	2467	UCAAGCUCUCAGAUUUUA	2612	2342-2360
AV07339-19-1.µm	AAAUUCUGAGAAGCUUGACA	2468	UGUCAAGCUCUCAGAUUU	2613	2344-2362
AV07340-19-1.µm	AAUCUGAGAAGCUUGACUA	2469	UAGUCAAGCUCUCAGAUU	2614	2345-2363
AV07341-19-1.µm	AUCUGAGAAGCUUGACUUA	2470	UAAGUCAAAGCUCUCAGAU	2615	2346-2364
AV07342-19-1.µm	UCUGAGAAGCUUGACUUCU	2471	UGAAGUCAAAGCUCUCAGAG	2616	2347-2365
AV07343-19-1.µm	CUGAGAAGCUUGACUUCAA	2472	UUGAAGUCAAAGCUCUCAG	2617	2348-2366
AV07344-19-1.µm	AGAAAGCUUGACUUCCAAGGA	2473	UCCUUGAAAGUCAAAGCUCU	2618	2351-2369
AV07345-19-1.µm	GAAGCUUGACUUCCAAGGAA	2474	UUCCUUGAAAGUCAAAGCUC	2619	2352-2370
AV07346-19-1.µm	GCUUGACUUCCAAGGACAGA	2475	UCUGUCCUUGAAGUCAGC	2620	2355-2373
AV07347-19-1.µm	CUUGACUUCCAAGGACAGAA	2476	UUCUGUCCUUGAAGUCAG	2621	2356-2374
AV07348-19-1.µm	UUGACUUCCAAGGACAGAGA	2477	UCUCUGUCCUUGAAGUCAA	2622	2357-2375
AV07349-19-1.µm	UGACUUCCAAGGACAGAGUA	2478	UACUCUGUCCUUGAAGUCA	2623	2358-2376
AV07350-19-1.µm	GACUUCCAAGGACAGAGUCA	2479	UGACUCUGUCCUUGAAGUC	2624	2359-2377
AV07351-19-1.µm	CAGAGUCCAGUCGAAGAUUA	2480	UAUCUUCGACUGGACUCUG	2625	2370-2388
AV07352-19-1.µm	GAGUCCAGUCGAAGAUUGA	2481	UCAUCUUCGACUCUGGACUC	2626	2372-2390
AV07353-19-1.µm	AGUCGAAGAUUGGGUCCCA	2482	UGGGACCCAAUCUUCGACU	2627	2378-2396
AV07354-19-1.µm	GUCCGAAGAUUGGGUCCCUA	2483	UAGGGACCCAAUCUUCGAC	2628	2379-2397
AV07355-19-1.µm	AAGAUUGGGUCCCUUGGACA	2484	UGUCCAGGGACCCAAUCUU	2629	2383-2401
AV07356-19-1.µm	UUGGGUCCCUUGGACAUAUA	2485	UUAUUGUCCAGGGACCCAA	2630	2387-2405
AV07357-19-1.µm	GUCCCUUGGACAUAUACACA	2486	UGUGAUUAUUGUCCAGGGAC	2631	2391-2409
AV07358-19-1.µm	CCUGGACAUAUACACCCAA	2487	UUGGUGAUUAUUGUCCAGG	2632	2394-2412
AV07359-19-1.µm	UGGACAUAUACACCCACGA	2488	UCGUUGGUGAUUAUUGUCCA	2633	2396-2414
AV07360-19-1.µm	GGACAUAUACACCCACGUUA	2489	UACGUUGGUGAUUAUUGUCC	2634	2397-2415
AV07361-19-1.µm	AAAAAGAAUAUAGACCCGGA	2490	UCGGGUCAUUAUUCUUUUU	2635	2711-2729
AV07362-19-1.µm	AAAAAGAAUAUAGACCCGGA	2491	UCCGGGUCAUUAUUCUUUU	2636	2712-2730
AV07363-19-1.µm	AAAAGAAUAUAGACCCGGCA	2492	UGCCGGGUCAUUAUUCUUU	2637	2713-2731
AV07364-19-1.µm	CCCCCGCCUCUCGCCCCA	2493	UGGGGGCAGAGGGCGGGGG	2638	2730-2748
AV07365-19-1.µm	CCCCGCCUCUCGCCCCAGA	2494	UCUCGGGGCAGAGGGCGGG	2639	2732-2750

AV07366-19-1.µm	GCCCCCAGCUGCUCUCCA	2495	UCGAGGAGCAGCUGGGGC	2640	2742-2760
AV07367-19-1.µm	CCCAGCUGCUCUCCGAGAG	2496	UCUCGAGAGAGCAGCUGGG	2641	2745-2763
AV07368-19-1.µm	UCCUCGCGAGUUCGGUAAA	2497	UUUAACCGAAGCUGGAGGA	2642	2754-2772
AV07369-19-1.µm	CGCAGUUCGGUUAUUUGGA	2498	UCCAAUUAAACCGAACUCGG	2643	2758-2776
AV07370-19-1.µm	GCAGUUCGGUUAUUUGGUA	2499	UACCAUUAAACCGGAACUCG	2644	2759-2777
AV07371-19-1.µm	CAGUUCGGUUAUUUGGUUA	2500	UAACCAUUAAACCGGAACUG	2645	2760-2778
AV07372-19-1.µm	AGUUCGGUUAUUUGGUUAA	2501	UUAAACCAAUUAACCGAACU	2646	2761-2779
AV07373-19-1.µm	GUUCGGUUAUUUGGUUAAA	2502	UUUAACCAAUUAACCGAAC	2647	2762-2780
AV07374-19-1.µm	UUCGGUUAUUUGGUUAUUA	2503	UAUUAAACCAAUUAACCGAA	2648	2763-2781
AV07375-19-1.µm	UCGGUUAUUUGGUUAUUA	2504	UGAUUAAACCAAUUAACCGA	2649	2764-2782
AV07376-19-1.µm	CGGUUAUUUGGUUAUUCAA	2505	UUGAUUAAACCAAUUAACCG	2650	2765-2783
AV07377-19-1.µm	GGUUAUUUGGUUAUUCACA	2506	UGUGAUUAAACCAAUUAACC	2651	2766-2784
AV07378-19-1.µm	GUUUAUUUGGUUAUUCACUA	2507	UAGUGAUUAAACCAAUUAAC	2652	2767-2785
AV07379-19-1.µm	UUAAUUUGGUUAUUCACUUA	2508	UAAGUGAUUAAACCAAUUAA	2653	2768-2786
AV07380-19-1.µm	UAAUUUGGUUAUUCACUUAA	2509	UUAAUGUUAUUAACCAAUUA	2654	2769-2787
AV07381-19-1.µm	AAUUUGGUUAUUCACUUAAA	2510	UUUAAGUGAUUUAACCAAUU	2655	2770-2788
AV07382-19-1.µm	UGGUUAUUCACUUAACCUA	2511	UAGGUUAAGUGAUUUAACCA	2656	2773-2791
AV07383-19-1.µm	GUUUAUUCACUUAACCUGCA	2512	UGCAGGUUAAGUGAUUUAAC	2657	2775-2793
AV07384-19-1.µm	UUAAUUCACUUAACCUGCUA	2513	UAGCAGGUUAAGUGAUUUA	2658	2776-2794
AV07385-19-1.µm	UAAUUCACUUAACCUGCUUA	2514	UAAGCAGGUUAAGUGAUUA	2659	2777-2795
AV07386-19-1.µm	AAUCACUUAACCUGCUUUA	2515	UAAAGCAGGUUAAGUGAUU	2660	2778-2796
AV07387-19-1.µm	CUUAACCUGCUUUUGUCAAA	2516	UUGACAAAAGCAGGUUAAG	2661	2783-2801
AV07388-19-1.µm	UUAAACCUGCUUUUGUCACA	2517	UGUGACAAAAGCAGGUUAA	2662	2784-2802
AV07389-19-1.µm	UAAACCUGCUUUUGUCACUA	2518	UAGUGACAAAAGCAGGUUA	2663	2785-2803
AV07390-19-1.µm	AACCUGCUUUUGUCACUCA	2519	UGAGUGACAAAAGCAGGUU	2664	2786-2804
AV07391-19-1.µm	ACCUGCUUUUGUCACUCGA	2520	UCGAGUGACAAAAGCAGGU	2665	2787-2805
AV07392-19-1.µm	CUGCUUUUGUCACUCGGCA	2521	UGCCGAGUGACAAAAGCAG	2666	2789-2807
AV07393-19-1.µm	GCUUUUGUCACUCGGCUUA	2522	UAAAGCCGAGUGACAAAAGC	2667	2791-2809
AV07394-19-1.µm	CUUUUGUCACUCGGCUUUA	2523	UAAAAGCCGAGUGACAAAAG	2668	2792-2810
AV07395-19-1.µm	UUUUUGUCACUCGGCUUUGA	2524	UCAAAAGCCGAGUGACAAA	2669	2793-2811
AV07396-19-1.µm	UCACUCGGCUUUUGGUCGA	2525	UCGAGCCAAAAGCCGAGUGA	2670	2798-2816

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AV07397-19-1.µm	CACUCGGGCUUUGGUCGGA	2526	UCCGAGCCAAAAGCCGAGUG	2671	2799-2817
AV07398-19-1.µm	UUUGGUCGGGACUUCAAAAA	2527	UUUUUGAAGUCCCGAGCCAA	2672	2808-2826
AV07399-19-1.µm	GCUCCGGGACUUCAAAAUUA	2528	UGAUUUUUUGAAGUCCCGAGC	2673	2811-2829
AV07400-19-1.µm	UCCGGACUUCAAAAUUCAGA	2529	UCUGAUUUUUUGAAGUCCGA	2674	2813-2831
AV07401-19-1.µm	GGACUUCAAAAUUCAGUGAA	2530	UUCACUGAUUUUUUGAAGUCC	2675	2816-2834
AV07402-19-1.µm	GACUUCAAAAUUCAGUGAUA	2531	UAUCACUGAUUUUUUGAAGUC	2676	2817-2835
AV07403-19-1.µm	UUCAAAAUUCAGUGAUGGGA	2532	UCCCAUCACUGAUUUUUUGAA	2677	2820-2838
AV07404-19-1.µm	UCAAAAUUCAGUGAUGGGA	2533	UUCCCAUCACUGAUUUUUUGA	2678	2821-2839
AV07405-19-1.µm	CAAAAUUCAGUGAUGGGA	2534	UCUCCCAUCACUGAUUUUG	2679	2822-2840
AV07406-19-1.µm	AAAUUCAGUGAUGGGAUUA	2535	UUACUCCCAUCACUGAUUU	2680	2824-2842
AV07407-19-1.µm	AAUUCAGUGAUGGGAUAAA	2536	UUUACUCCCAUCACUGAUU	2681	2825-2843
AV07408-19-1.µm	AUCAGUGAUGGGAUUAAGA	2537	UCUUACUCCCAUCACUGAU	2682	2826-2844
AV07409-19-1.µm	UCAGUGAUGGGAUUAAGAA	2538	UUCUACUCCCAUCACUGA	2683	2827-2845
AV07410-19-1.µm	CAGUGAUGGGAUUAAGAGA	2539	UCUCUACUCCCAUCACUG	2684	2828-2846
AV07411-19-1.µm	GUGAUGGGAUUAAGAGCAA	2540	UUUGCUCUACUCCCAUCAC	2685	2830-2848
AV07412-19-1.µm	UGAUGGGAUUAAGAGCAAA	2541	UUUGCUCUACUCCCAUCA	2686	2831-2849
AV07413-19-1.µm	GAUGGGAUUAAGAGCAAAA	2542	UUUUGCUCUACUCCCAUC	2687	2832-2850
AV07414-19-1.µm	AUGGGAUUAAGAGCAAAUA	2543	UAUUUGCUCUACUCCCAU	2688	2833-2851
AV07415-19-1.µm	UGGGAUUAAGAGCAAAUUA	2544	UAAUUUGCUCUACUCCCA	2689	2834-2852
AV07416-19-1.µm	GGGAGUUAAGAGCAAAUUA	2545	UAAAUUUUGCUCUACUCCC	2690	2835-2853
AV07417-19-1.µm	GGAGUUAAGAGCAAAUUA	2546	UGAAAUUUUGCUCUACUCC	2691	2836-2854
AV07418-19-1.µm	GAGUUAAGAGCAAAUUA	2547	UUGAAAUUUUGCUCUACUC	2692	2837-2855
AV07419-19-1.µm	AGUUAAGAGCAAAUUA	2548	UAUGAAAUUUUGCUCUACU	2693	2838-2856
AV07420-19-1.µm	GUAAAGAGCAAAUUA	2549	UGAUGAUAUUUGCUCUAC	2694	2839-2857
AV07421-19-1.µm	UAAAGAGCAAAUUA	2550	UAGAUGAUAUUUGCUCUA	2695	2840-2858
AV07422-19-1.µm	AAGAGCAAAUUA	2551	UAAGAUGAUAUUUGCUCU	2696	2841-2859
AV07423-19-1.µm	UUCAUUUUUUCCAAAAUUGAA	2552	UUCAUUUUUGAAAGAUUGAA	2697	2851-2869
AV07424-19-1.µm	CUUUCCAAAAUUGAUGGGUA	2553	UACCCAUCAAUUUUGGAAAG	2698	2856-2874
AV07425-19-1.µm	UUUUCCAAAAUUGAUGGGUGA	2554	UACCCCAUCAAUUUUGGAAA	2699	2857-2875
AV07426-19-1.µm	UUCCAAAAUUGAUGGGUGGA	2555	UCCACCCAUCAAUUUUGGAA	2700	2858-2876
AV07427-19-1.µm	CCAAAAUUGAUGGGUGGGCA	2556	UGCCCAUCCAUCAAUUUUG	2701	2860-2878

AV07428-19-1.µm	AUUGAUGGGUGGGCUAGUA	2557	UACUAGCCCAACCCAUCAAU	2702	2864-2882
AV07429-19-1.µm	UUGAUUGGGUGGGCUAGUAA	2558	UUACUAGCCCAACCCAUCAA	2703	2865-2883
AV07430-19-1.µm	UGAUGGGUGGGCUAGUAAA	2559	UUUACUAGCCCAACCCAUCA	2704	2866-2884
AV07431-19-1.µm	GAUGGGUGGGCUAGUAAUA	2560	UAUUACUAGCCCAACCCAUUC	2705	2867-2885
AV07432-19-1.µm	UGGGUGGGCUAGUAAUAAAA	2561	UUUAUUACUAGCCCAACCCA	2706	2869-2887
AV07433-19-1.µm	GGGUGGGCUAGUAAUAAAA	2562	UUUUUUUUUUUUUUUUUUUUUU	2707	2870-2888
AV07434-19-1.µm	AGUAAUAAAAAUUUUUAAAA	2563	UUUUUUUUUUUUUUUUUUUUUU	2708	2879-2897
AV07435-19-1.µm	GUAAUAAAAAUUUUUAAAA	2564	UUUUUUUUUUUUUUUUUUUUUU	2709	2880-2898
AV07436-19-1.µm	UAAUAAAAAUUUUUAAAA	2565	UUUUUUUUUUUUUUUUUUUUUU	2710	2881-2899
AV07437-19-1.µm	AAUAAAAAUUUUUAAAA	2566	UUUUUUUUUUUUUUUUUUUUUU	2711	2882-2900
AV07438-19-1.µm	AUUAAAAAUUUUUAAAA	2567	UUUUUUUUUUUUUUUUUUUUUU	2712	2883-2901
AV07439-19-1.µm	UUAAAAAUUUUUAAAA	2568	UUUUUUUUUUUUUUUUUUUUUU	2713	2884-2902
AV07440-19-1.µm	AAAAUUUUUUUUAAAA	2569	UUUUUUUUUUUUUUUUUUUUUU	2714	2885-2903
AV07441-19-1.µm	AAAAAAAAAACAUUUCAAAA	2570	UUUUUUUUUUUUUUUUUUUUUU	2715	2894-2912
AV07442-19-1.µm	AAAAAAAAAACAUUUCAAAA	2571	UUUUUUUUUUUUUUUUUUUUUU	2716	2895-2913

Table 2 shows certain chemically modified MAPT RNAi agent antisense strand and sense strand sequences of the invention. In some embodiments of methods of the invention, an RNAi agent with a polynucleotide sequence shown in Table 2 is administered to a cell and/or subject. In some embodiments of methods of the invention, a RNAi agent with a polynucleotide sequence shown in Table 2 is administered to a subject. In some embodiments of the invention an RNAi agent administered to a subject comprises is a duplex identified in a row in Table 2, column one and includes the sequence modifications show in the sense and antisense strand sequences in the same row in Table 2, columns three and six, respectively. In some embodiments of methods of the invention, a sequence shown in Table 2 may be attached to (also referred to herein as “conjugated to”) a compound capable of delivering the RNAi agent to a cell and/or tissue in a subject. A non-limiting example of a delivery compound that may be used in certain embodiments of the invention is a GalNAc-containing compound or a GLS-15*-containing compound. In Table 2, the first column indicates the Duplex AV# of the base sequences as shown in Table 1. Table 2 discloses Duplex AV# and also shows chemical modifications included in sense and antisense sequence of the duplexes. For example, Table 1 shows base single-strand sequences SEQ ID NO: 17 (sense) and SEQ ID NO: 509 (antisense), which together are the double-stranded duplex identified as: Duplex AV# AV03736.um and Table 2 lists Duplex AV# AV03736, which indicates that the duplex of SEQ ID NO: 1001 and SEQ ID NO: 1247 includes base sequences of SEQ ID NO: 17 and SEQ ID NO: 509, respectively, but with the chemical modifications shown in the sense and antisense sequences shown in columns three and six, respectively. The “Sense strand SS#” in Table 2 column two is the assigned identifier for the Sense Sequence (including modifications) shown column 3 in the same row. The “Antisense strand AS#” in Table 2 column five is the assigned identifier for the Antisense sequence (including modifications) shown in column six.

Table 2: provides chemically modified MAPT RNAi agent antisense strand and sense strand sequences. All sequences shown 5' to 3'. These sequences were used in certain *in vitro* testing studies described herein.

Duplex AV#	Sense strand SS#	Sense Sequence	SEQ ID NO.	Antisense strand AS#	Antisense Sequence	SEQ ID NO.
AV03728	AV03728-SS	g*c*c*ucucucCfGChGfucucU*c*a	993	AV03728-AS	u*Gf*agAfG(gUNA)acAGfcGfAGfGg*c*c	1239
AV03729	AV03729-SS	g*g*gaunucGfaAfGfUfgauGgga*a*a	994	AV03729-AS	u*Uf*uecaUfcaUfucGfaAfcue*c*c	1240
AV03730	AV03730-SS	c*c*gaunucGfAGfChGfauGga*a*a	995	AV03730-AS	u*CF*unucAfucAGfauUfcGfAcu*c*c	1241
AV03731	AV03731-SS	c*a*gaunucGfAGfUfGfAfugga*a*a	996	AV03731-AS	u*Uf*cuucCfaucAfauUfcGfAcu*c*c	1242
AV03732	AV03732-SS	g*g*unucgaGfAGfUfGgaaga*a*a	997	AV03732-AS	u*Af*ucuuCfauCfauUfcGfAcu*c*c	1243
AV03733	AV03733-SS	c*U*ucgaagUfGfAGfGfagaau*c*a	998	AV03733-AS	u*Gf*aucuUfccaUfcaChUfGga*a*a	1244
AV03734	AV03734-SS	g*U*cgaagUGfAGfGfagauc*c*a	999	AV03734-AS	u*Uf*gaucUfuccAfucAfUfucg*a*a	1245
AV03735	AV03735-SS	c*c*gaucacGfAGfAGfaccac*a*a	1000	AV03735-AS	u*CF*uuGfG(gUNA)gcaUfGgUfGfAGc*c*c	1246
AV03736	AV03736-SS	c*a*caucggaCfGChGfGccuGa*a	1001	AV03736-AS	u*Uf*ucAfG(gUNA)ccAGfcgUfcCfGgU*a*a	1247
AV03737	AV03737-SS	g*a*cccccaGfAGfChGfagaag*a*a	1002	AV03737-AS	u*CF*guCfG(gUNA)ccAGfcgUfGfGgU*a*a	1248
AV03738	AV03738-SS	c*a*agucugUfGChCfAcguGa*c*a	1003	AV03738-AS	u*Gf*ucAfG(gUNA)ugaCfcaGfcafGcu*a*a	1249
AV03739	AV03739-SS	g*a*gaugucGfAGfAGfGfucgu*a*a	1004	AV03739-AS	u*Uf*acugAfccaUfGcGfAGfauu*a*c	1250
AV03740	AV03740-SS	g*a*gaugucGfAGfAGfGfucgaGa*a	1005	AV03740-AS	u*Uf*uaucGfaccAfugCfGfAGfauu*a*c	1251
AV03741	AV03741-SS	g*g*cuugcaUfGChCfagaGa*a	1006	AV03741-AS	u*Uf*uuuaCfugaCfcaUfGfGgaG*c*c	1252
AV03742	AV03742-SS	g*U*cgaugGfAGfAGfGfuaaag*c*a	1007	AV03742-AS	u*Gf*cuuuUfauCfGfAGfAGfUfGg*a*a	1253
AV03743	AV03743-SS	g*c*gaugUGfAGfUfGfGfuaag*c*a	1008	AV03743-AS	u*Uf*gcuUfuaCfGfAGfAGfAGfUfGg*c*c	1254
AV03744	AV03744-SS	g*g*caugUGfAGfUfGfGfuaag*c*a	1009	AV03744-AS	u*Uf*ugcuUfuaCfGfAGfAGfAGfUfGg*c*c	1255
AV03745	AV03745-SS	c*c*gaugUGfAGfUfGfGfuaag*c*a	1010	AV03745-AS	u*Uf*ugcuUfuaCfGfAGfAGfAGfUfGg*c*c	1256
AV03746	AV03746-SS	g*a*ugucGfAGfAGfAGfGfuaag*c*a	1011	AV03746-AS	u*CF*uuugCfuuUfAGfAGfAGfAGfUfGg*c*c	1257
AV03747	AV03747-SS	g*U*gaugUGfAGfAGfAGfGfuaag*c*a	1012	AV03747-AS	u*Uf*cuuGfauUfAGfAGfAGfAGfUfGg*c*c	1258
AV03748	AV03748-SS	g*g*gaugUGfAGfAGfAGfGfuaag*c*a	1013	AV03748-AS	u*Gf*ucuuUfGcuUfAGfAGfAGfAGfUfGg*c*c	1259
AV03749	AV03749-SS	c*c*gaugUGfAGfAGfAGfGfuaag*c*a	1014	AV03749-AS	u*Uf*uuugCfauCfAGfAGfAGfAGfUfGg*c*c	1260
AV03750	AV03750-SS	c*a*cuugaGfAGfAGfAGfGfuaag*c*a	1015	AV03750-AS	u*Uf*uuugUfauCfAGfAGfAGfAGfUfGg*c*c	1261
AV03751	AV03751-SS	g*g*gaugUGfAGfAGfAGfGfuaag*c*a	1016	AV03751-AS	u*CF*uuuuUfGcuCfAGfAGfAGfAGfUfGg*c*c	1262
AV03752	AV03752-SS	c*c*gaugUGfAGfAGfAGfGfuaag*c*a	1017	AV03752-AS	u*Gf*cuuuUfauGfAGfAGfAGfAGfUfGg*c*c	1263

AV03753	AV03753-SS	g*a*ggauugAfcAfaAfaagcc*a*a	1018	AV03753-AS	u*Uf*ggcuUfuuUfugCfaUfegc*u*c	1264
AV03754	AV03754-SS	g*g*cguguCfaAfaAfaagcc*a*a	1019	AV03754-AS	u*Uf*ugcuUfuuUfugUfcAfuagc*c*c	1265
AV03755	AV03755-SS	g*u*caagggGfgCfuCfuaggu*a*a	1020	AV03755-AS	u*Uf*uaacAfuaCfcecCfcChug*a*c	1266
AV03756	AV03756-SS	c*g*ggcuugUfgCfuAfaagca*a*a	1021	AV03756-AS	u*Uf*ugcuUfuuAfcacCfcAfegc*c*g	1267
AV03757	AV03757-SS	c*g*ggcuugUfgUfaAfaagca*a*a	1022	AV03757-AS	u*CF*ungcUfuuAfcacCfcAfegc*c*g	1268
AV03758	AV03758-SS	c*c*ugugugUfaAfaAfcagga*u*a	1023	AV03758-AS	u*AF*uecuCfguUfuaCfcAfuaa*g*g	1269
AV03759	AV03759-SS	g*u*gaugugUfaAfaCfagga*u*a	1024	AV03759-AS	u*CF*aucuUfegUfuuAfcCfauc*a*c	1270
AV03760	AV03760-SS	g*g*auuguaAfaAfcCfaagau*c*a	1025	AV03760-AS	u*CF*gaucUfueUfuuUfaCfcau*c*c	1271
AV03761	AV03761-SS	g*g*ccaccaGfgAfuUfccagca*a*a	1026	AV03761-AS	u*Uf*ugCfu(gUNA)gaUfcecUfgGfuagc*c*c	1272
AV03762	AV03762-SS	g*c*aggaucCfcAfgCfaaac*c*a	1027	AV03762-AS	u*GF*guuuUfugUfegUfgAfaUfecu*g*c	1273
AV03763	AV03763-SS	g*a*ccaccAfgCfuCfuaggu*a*a	1028	AV03763-AS	u*Uf*uaacCfaagCfcuGfgGfuagc*u*c	1274
AV03764	AV03764-SS	g*c*uguguaAfcCfuCfaaau*c*a	1029	AV03764-AS	u*GF*auuuUfegagGfgUfcAfeca*g*c	1275
AV03765	AV03765-SS	g*u*ggugaaCfcUfcCfaaau*c*a	1030	AV03765-AS	u*Uf*gauuUfugAfgUfuCfaac*a*c	1276
AV03766	AV03766-SS	g*a*ccuuccAfaAfuCfagga*u*a	1031	AV03766-AS	u*AF*ueCfc(gUNA)uagUfuuUfgGfaagc*u*c	1277
AV03767	AV03767-SS	g*u*cgugucCfaCfuGfagaa*c*u*a	1032	AV03767-AS	u*AF*gguuCfucaGfuagGfaGfegc*a*c	1278
AV03768	AV03768-SS	g*g*ugugaaAfaUfaCfuaa*c*a	1033	AV03768-AS	u*Uf*uguaGfaucAfuUfgCfaac*c*c	1279
AV03769	AV03769-SS	c*u*ggucuaAfuAfgUfcuaa*a*a	1034	AV03769-AS	u*Uf*uuuuAfgacUfaUfuGfcau*c*a	1280
AV03770	AV03770-SS	g*g*ugcauUfaGfuCfuacaa*c*a	1035	AV03770-AS	u*GF*uuugUfagacCfuUfuUfgca*c*c	1281
AV03771	AV03771-SS	c*u*gcauuAfgUfcUfcaaac*c*a	1036	AV03771-AS	u*GF*guuuGfuagAfcuAfuUfugc*a*a	1282
AV03772	AV03772-SS	g*g*caauaGfuCfuAfcana*c*a	1037	AV03772-AS	u*Uf*gguuUfuaGfaUfaUfug*c*c	1283
AV03773	AV03773-SS	g*a*auagucUfaCfaAfcagau*u*a	1038	AV03773-AS	u*AF*acugGfuuuGfuagGfaCfuau*u*c	1284
AV03774	AV03774-SS	g*a*ugucuaAfcAfaAfcagau*g*a	1039	AV03774-AS	u*CF*aaCfu(gUNA)guuUfguaAfgAfcua*u*c	1285
AV03775	AV03775-SS	g*u*agucuaCfaAfcCfaguu*g*a	1040	AV03775-AS	u*Uf*caacUfegUfuuUfaGfauc*a*c	1286
AV03776	AV03776-SS	g*u*acaaacCfaGfuUfagcu*g*a	1041	AV03776-AS	u*Uf*caGfg(uUNA)caacCfuagGfuUfugc*a*c	1287
AV03777	AV03777-SS	c*c*agugugAfcCfuCfagau*u*a	1042	AV03777-AS	u*AF*caacuUfegagGfguacCfcuu*g*g	1288
AV03778	AV03778-SS	g*g*agucucAfaGfuGfuaguc*a*a	1043	AV03778-AS	u*Uf*gaGfc(gUNA)aacCfuagGfaAfguc*c*c	1289
AV03779	AV03779-SS	g*c*cuuccaGfuGfuGfugau*u*a	1044	AV03779-AS	u*AF*augagCfcaacCfaUfuGfagc*g*c	1290
AV03780	AV03780-SS	g*u*caagugGfuGfgCfuaa*a*a	1045	AV03780-AS	u*CF*naauGfagcCfaAfcUfugc*a*c	1291
AV03781	AV03781-SS	c*u*ggugucUfaUfaAfgcaac*a*a	1046	AV03781-AS	u*Uf*guUfg(cUNA)cuuaAfuagAfgCfaac*a*a	1292
AV03782	AV03782-SS	c*u*ggucuaUfaAfgCfaaau*c*a	1047	AV03782-AS	u*GF*auguUfegcUfaaUfgAfgcc*a*a	1293
AV03783	AV03783-SS	c*g*cucauuAfgGfaAfaauc*a*a	1048	AV03783-AS	u*Uf*ggauCfuugCfcauAfaUfagc*c*g	1294

AV03784	AV03784-SS	c*c*ucanuuaGfgCfaAfcuacac* ^u *a	1049	AV03784-AS	u*Af*ugauUfguuGfecUfaAfhuga* ^g *g	1295
AV03785	AV03785-SS	g*c*auuaggaCfaAfcAfhucanuc* ^a *a	1050	AV03785-AS	u*Uf*gaugCfauugUfhugCfcUfaau* ^g *c	1296
AV03786	AV03786-SS	g* ^u *uaggaCfaAfcAfhCfcuacau* ^a *a	1051	AV03786-AS	u*Uf*augauUfgauUfguUfhugCfcUfaa* ^a *c	1297
AV03787	AV03787-SS	g* ^u *uaggaCfaUfcCfaucanua* ^a *a	1052	AV03787-AS	u*Uf*uaugAfhugAfhugUfhGfecu* ^a *c	1298
AV03788	AV03788-SS	g* ^g *ggaacUfcCfaUfcuauaa* ^c *a	1053	AV03788-AS	u*Gf*uuuaUfgauGfgaUfhugC* ^c *c	1299
AV03789	AV03789-SS	c*c*faucanucCfaUfcAfhuaac* ^a *a	1054	AV03789-AS	u*Uf*ggauUfgauAfhugGfaUfhug* ^g *g	1300
AV03790	AV03790-SS	g* ^a *cauacUfcAfhAfaaccag* ^g *a	1055	AV03790-AS	u*CF*cuGfg(uUNA)uuauUfgaUfhGfauug* ^u *c	1301
AV03791	AV03791-SS	g*c*agguaggaCfaCfuAfaauac* ^g *a	1056	AV03791-AS	u*CF*agauUfhuaCfuuCfcAfcu* ^g *c	1302
AV03792	AV03792-SS	g* ^a *guggaAfgUfaAfaucug* ^a *a	1057	AV03792-AS	u*Uf*cauUfhuaAfcuUfhCfacc* ^u *c	1303
AV03793	AV03793-SS	g* ^g *guggaCfuAfaAfaucug* ^g *a	1058	AV03793-AS	u*CF*ucagAfhuaUfhacUfhCfacc* ^c *c	1304
AV03794	AV03794-SS	c* ^g *uuggaUfaAfaAfhucug* ^a *a	1059	AV03794-AS	u*Uf*ucuaCfhuaUfhuaCfuUfhcca* ^c *g	1305
AV03795	AV03795-SS	c* ^u *guggaUfaAfaUfhucug* ^a *a	1060	AV03795-AS	u*Uf*ucuaCfhuaUfhuaAfcUfhucc* ^a *g	1306
AV03796	AV03796-SS	g* ^g *gaaugAfaAfaCfuCfhugag* ^g *a	1061	AV03796-AS	u*CF*uuuUfhuaUfhuaCfhuc* ^c *c	1307
AV03797	AV03797-SS	c* ^a *aguuaaAfhCfuCfhugagc* ^u *a	1062	AV03797-AS	u*Af*geuuCfhuaCfhuaUfhuaCfu* ^u *g	1308
AV03798	AV03798-SS	g* ^a *guuaaUfcUfhAfgaagcu* ^u *a	1063	AV03798-AS	u*Af*agcuUfhuaCfhuaUfhuaCfu* ^u *c	1309
AV03799	AV03799-SS	c* ^u *aaauUfhAfgAfhagcu* ^g *a	1064	AV03799-AS	u*Uf*caagCfhuaUfhuaCfhuaCfu* ^u *g	1310
AV03800	AV03800-SS	g* ^c *uuggaCfuUfhGfauuca* ^a *a	1065	AV03800-AS	u*Uf*ugaaCfhuaAfgcUfhCfhua* ^g *c	1311
AV03801	AV03801-SS	g* ^u *uaggaCfuUfhAfcuucac* ^g *a	1066	AV03801-AS	u*CF*uuugaAfhuaAfhuaCfuUfhua* ^c *c	1312
AV03802	AV03802-SS	g* ^g *gaugcuGfaCfuUfhcaagga* ^c *a	1067	AV03802-AS	u*Gf*ucCfu(uUNA)gaagfhuaAfhagcuu* ^c *c	1313
AV03803	AV03803-SS	c* ^a *agcuugAfcUfhCfhagga* ^c *a	1068	AV03803-AS	u*Uf*guccUfhuaAfhuaCfhuaAfhua* ^u *g	1314
AV03804	AV03804-SS	g* ^a *aggaCfaGfhCfhaguc* ^g *a	1069	AV03804-AS	u*Uf*cgAfc(uUNA)ggagfhuaUfhuaCfu* ^u *c	1315
AV03805	AV03805-SS	g* ^c *aggaCfaGfhCfhagau* ^u *a	1070	AV03805-AS	u*Af*aucuUfhuaCfhuaCfhuaCfu* ^g *c	1316
AV03806	AV03806-SS	g* ^u *uuggaCfaGfhCfhagau* ^g *a	1071	AV03806-AS	u*CF*uuuuUfhuaUfhuaCfhuaCfu* ^c *c	1317
AV03807	AV03807-SS	c* ^g *cggaUfhAfaAfaaagga* ^u *a	1072	AV03807-AS	u*Af*ucuuUfhuaUfhuaCfhuaCfu* ^g *c	1318
AV03808	AV03808-SS	g* ^a *aauaaAfhAfhUfhagac* ^c *a	1073	AV03808-AS	u*Gf*ggUfh(uUNA)cuuUfhuaCfhuaCfu* ^u *c	1319
AV03809	AV03809-SS	g* ^a *aauaaUfhAfaAfaaagga* ^u *a	1074	AV03809-AS	u*Uf*guUfh(uUNA)cuuUfhuaCfhuaCfu* ^u *c	1320
AV03810	AV03810-SS	g* ^g *gaugcuGfhCfhAfaaagcu* ^g *a	1075	AV03810-AS	u*CF*gaCfu(uUNA)gaagfhuaCfhuaCfu* ^c *c	1321
AV03811	AV03811-SS	c* ^c *aauuaCfaGfaAfhUfhaguc* ^u *a	1076	AV03811-AS	u*Af*ggAfg(uUNA)cuuUfhuaCfhuaCfu* ^g *g	1322
AV03812	AV03812-SS	g* ^a *ccgggaGfaAfhCfhagcu* ^g *a	1077	AV03812-AS	u*CF*caUfh(uUNA)gaagfhuaCfhuaCfu* ^u *c	1323
AV03813	AV03813-SS	g* ^a *gaugcuAfhAfhCfhagcu* ^u *a	1078	AV03813-AS	u*Af*gucaAfhuaCfhuaCfhuaCfu* ^u *c	1324
AV03814	AV03814-SS	c* ^c *cagcuAfhCfhCfhagcu* ^u *a	1079	AV03814-AS	u*Af*ccUfh(uUNA)cucaCfhuaCfhuaCfu* ^g *g	1325

AV03815	AV03815-SS	c*c*caagcaGfgCfuUfhuuguu*c*a	1080	AV03815-AS	u*Gf*aucaCfaacCfocUfgCfuug*c*g	1326
AV03816	AV03816-SS	g*c*agcagGfgUfuUfhuugau*c*a	1081	AV03816-AS	u*Uf*gaucAfcaafAfccChuOfcuu*c*c	1327
AV03817	AV03817-SS	g*u*gaagagGfuCfuGfgaanaa*c*a	1082	AV03817-AS	u*Uf*nuuuUfccacCfaeUfclFcuu*c*c	1328
AV03818	AV03818-SS	g*a*aaanaaGfaAfuAfauagac*c*a	1083	AV03818-AS	u*Gf*ggUfcl(aUN)uuuUfuclUfuuu*c*c	1329
AV03819	AV03819-SS	g*u*ccuagCfUfuCfuguua*c*a	1084	AV03819-AS	u*Af*uuacCfagAfccUfocCfag*c*c	1330
AV03820	AV03820-SS	g*a*auuugUfUfaAfuCfaauaa*c*a	1085	AV03820-AS	u*Gf*uuacCfugaUfuaAfccCfaa*c*c	1331
AV03821	AV03821-SS	g*a*uuuguuAfuUfaAfcuuaa*c*a	1086	AV03821-AS	u*Gf*uuuaAfugAfuuAfcaCfaa*c*c	1332
AV03822	AV03822-SS	g*u*guuaaUfcaUfUfaacu*c*a	1087	AV03822-AS	u*CF*agguUfaaUfUfaUfuAfacc*c*c	1333
AV03823	AV03823-SS	g*a*aucaauUfaAfcCfuguuu*c*a	1088	AV03823-AS	u*Af*aaagCfaaUfuaAfgUfgau*c*c	1334
AV03824	AV03824-SS	g*a*ucauuAfaCfcUfuguuu*c*a	1089	AV03824-AS	u*CF*aaaaCfaagCfuuaAfaCfuga*c*c	1335
AV03825	AV03825-SS	g*u*ucauuAfcCfuCfuuuu*c*a	1090	AV03825-AS	u*Af*caaaAfcaagCfuUfaAfgu*c*c	1336
AV03826	AV03826-SS	g*c*c*acuuaCfcUfCfuuuu*c*a	1091	AV03826-AS	u*Gf*accaAfagcAfgUfuAfagu*c*c	1337
AV03827	AV03827-SS	c*g*cuugagAfcUfuCfaaau*c*a	1092	AV03827-AS	u*Uf*gaauUfugaAfguCfcCfag*c*c	1338
AV03828	AV03828-SS	g*u*c*ggagacUfuCfaAfaaua*c*a	1093	AV03828-AS	u*Af*cuagUfuuuGfaaGfuCfcg*c*c	1339
AV03829	AV03829-SS	c*g*aucauAfaAfuCfaguug*c*a	1094	AV03829-AS	u*CF*aucaCfugaUfuUfgAfagu*c*c	1340
AV03830	AV03830-SS	c*a*cuucaAfaUfUfaguug*c*a	1095	AV03830-AS	u*CF*caUfcl(aUN)cuuAfuuUfuGfag*c*c	1341
AV03831	AV03831-SS	g*a*agaagcaAfaUfuUfcauu*c*a	1096	AV03831-AS	u*Af*aaagUfgaaAfuuUfgCfuuc*c*c	1342
AV03832	AV03832-SS	g*a*gaagcaAfuUfuCfauuu*c*a	1097	AV03832-AS	u*Gf*aaagAfugaAfauUfuCfuuc*c*c	1343
AV03833	AV03833-SS	g*g*agcaaaUfuUfUfaAfuuuu*c*a	1098	AV03833-AS	u*Gf*gaagGfaugAfauUfuUfgu*c*c	1344
AV03834	AV03834-SS	c*a*gaauuUfuCfaUfuuuu*c*a	1099	AV03834-AS	u*Uf*ggaaAfgaugGfaaAfuUfug*c*c	1345
AV03835	AV03835-SS	g*g*caauuUfUfaAfuCfuuuu*c*a	1100	AV03835-AS	u*Uf*uggaAfagUfUfaAfaUfug*c*c	1346
AV03836	AV03836-SS	c*c*aaauuUfaUfUfuuu*c*a	1101	AV03836-AS	u*Uf*uuugAfagAfugAfauAfuu*c*c	1347
AV03837	AV03837-SS	g*a*aaauuAfuCfuUfuuu*c*a	1102	AV03837-AS	u*Af*uuugGfaagAfauGfaAfau*c*c	1348
AV03838	AV03838-SS	g*a*auuuaUfUfuUfcaauu*c*a	1103	AV03838-AS	u*Af*auuUfgaaAfgaUfgAfauu*c*c	1349
AV03839	AV03839-SS	g*a*uuuuaCfuUfuCfcaauu*c*a	1104	AV03839-AS	u*CF*auuUfgaaAfagAfuaAfuGfaa*c*c	1350
AV03840	AV03840-SS	g*u*uuuuaUfuCfUfaauu*c*a	1105	AV03840-AS	u*Af*uuuaUfuugGfaaAfgAfua*c*c	1351
AV03841	AV03841-SS	c*g*guugguUfuCfuAfaanaa*c*a	1106	AV03841-AS	u*Af*uuuaAfuaCfuacCfcaac*c*c	1352
AV03842	AV03842-SS	g*g*ggcagUfUfaAfuAfaauu*c*a	1107	AV03842-AS	u*Af*auuUfuuaUfuCfuAfcc*c*c	1353
AV03843	AV03843-SS	g*c*agagcaUfuCfUfuuuu*c*a	1108	AV03843-AS	u*Af*auaAfagGfaaUfuCfuu*c*c	1354
AV03844	AV03844-SS	g*g*gaauuUfuUfuUfuuuu*c*a	1109	AV03844-AS	u*Af*gaauCfaaAfgaAfuaUfuug*c*c	1355
AV03845	AV03845-SS	c*g*cgagcaCfaAfaGfgauuu*c*a	1110	AV03845-AS	u*Uf*caauUfculUfuUfuCfug*c*c	1356

AV03846	AV03846-SS	g*a*gcacaaAfaGfgAfhuuagaa*a*a	1111	AV03846-AS	u*Uf*nucaAfaucFhuUfGfhugc*u*c	1357
AV03847	AV03847-SS	g*g*caacaaAfgGfaUfhugaaac*c*a	1112	AV03847-AS	u*Gf*nuccAfaucFceUfhGfhugc*c*c	1358
AV03848	AV03848-SS	c*c*aacaaAGfgAfuUfhugaac*u*a	1113	AV03848-AS	u*Af*guuCFhaaUfcecUfhUfguu*g*g	1359
AV03849	AV03849-SS	g*a*acaaagGfaUfhUfgaacuu*a	1114	AV03849-AS	u*Af*aguUfhcaAfhucFhuUfguu*u*c	1360
AV03850	AV03850-SS	g*a*caaggaAfuUfhGhaacuu*g*a	1115	AV03850-AS	u*CF*aaгуUfhcaAfhucFhuUfguu*g*c	1361
AV03851	AV03851-SS	g*c*aaaggaUfhUfGfaaacuu*g*a	1116	AV03851-AS	u*CF*caagUfhucAfhUfCchuu*g*c	1362
AV03852	AV03852-SS	g*a*aaaggaUfhGfaAfaucuu*g*a	1117	AV03852-AS	u*Af*ccaaGfhuuCFhaAfhCfeu*u*c	1363
AV03853	AV03853-SS	g*a*aaaggaUfhGfaAfaucuu*g*a	1118	AV03853-AS	u*Af*caaccAfaгуUfhcaAfhucc*u*c	1364
AV03854	AV03854-SS	g*g*gaauuGfaAfcUfhuguuu*g*a	1119	AV03854-AS	u*CF*acAfc(cUNA)aaгуUfhUfCfaAfauc*c*c	1365
AV03855	AV03855-SS	c*a*uuuugaAfcUfhGfhuguuu*u*a	1120	AV03855-AS	u*Af*gaacAfhcaAfgUfhCfaa*u*c	1366
AV03856	AV03856-SS	g*u*uuugaaChUfhGfhuguuu*c*a	1121	AV03856-AS	u*Gf*aaacAfhccAfgUfhUfhcau*a*c	1367
AV03857	AV03857-SS	g*g*ccauгуUfhUfhGfhuccau*u*a	1122	AV03857-AS	u*Af*agUfh(cUNA)ccaAfaUfhcAfhugc*c*c	1368
AV03858	AV03858-SS	g*u*uuugccaChUfhGfhuccau*u*a	1123	AV03858-AS	u*Af*ggUfh(cUNA)gcaAfaUfhGfhcca*a*c	1369
AV03859	AV03859-SS	g*u*uuugcaAfcChUfhGfhugaaу*a	1124	AV03859-AS	u*Af*aaгуUfhccAfhucChUfhcau*a*c	1370
AV03860	AV03860-SS	c*a*ccuugGfgAfcUfhUfhagggcu*a	1125	AV03860-AS	u*Uf*agCfc(cUNA)uaaAfhucCfcCfhagc*u*g	1371
AV03861	AV03861-SS	c*a*cuuugGfgAfcUfhUfhagggcu*a	1126	AV03861-AS	u*Af*acugGfhuaGfhccChUfhagc*u*g	1372
AV03862	AV03862-SS	c*p*guuaacCfaGhuUfhucuuu*g*a	1127	AV03862-AS	u*CF*aaagAfhgaCfhGfhUfhagc*c*g	1373
AV03863	AV03863-SS	c*p*cuuaacAfhGhuUfhCfhucuuu*g*a	1128	AV03863-AS	u*Af*caagAfhgaAfcuGfhUfhagc*c*g	1374
AV03864	AV03864-SS	g*u*aaacagUfhCfhCfhuguaa*a	1129	AV03864-AS	u*Uf*uaaAfhgaAfhacChUfhguu*a*c	1375
AV03865	AV03865-SS	g*a*accagUfhUfhUfhuguaa*g*a	1130	AV03865-AS	u*CF*uuacAfhagAfhgaAfcUfhguu*u*c	1376
AV03866	AV03866-SS	g*a*ccaguuCfhCfhUfhuguaaу*a	1131	AV03866-AS	u*CF*cuuaCFhaaGfhagAfhcFhugc*u*c	1377
AV03867	AV03867-SS	g*c*caugucUfhUfhUfhuaagc*a	1132	AV03867-AS	u*Uf*cuuaAfhcaAfhgaAfhcugc*g*c	1378
AV03868	AV03868-SS	g*c*aguuuChUfhCfhuaagc*a	1133	AV03868-AS	u*Gf*nuccUfhcaAfhgaAfhacu*g*c	1379
AV03869	AV03869-SS	g*g*uuuUfhCfhAfhagaaу*a	1134	AV03869-AS	u*Af*agucCFhaaCFhaAfhgAfhga*c*c	1380
AV03870	AV03870-SS	g*u*uuuGhuAfaGfhaguuu*g*a	1135	AV03870-AS	u*Af*caagUfhcuUfhcaAfhagc*a*c	1381
AV03871	AV03871-SS	g*a*aucaacGfcChUfhacccu*a	1136	AV03871-AS	u*Af*ggGfh(cUNA)aaagGfhcAfhUfhguu*u*c	1382
AV03872	AV03872-SS	g*u*auucaUfhCfhGfhaguuu*g*a	1137	AV03872-AS	u*Uf*caCfc(cUNA)ucaGfhUfhGfhguu*a*c	1383
AV03873	AV03873-SS	g*c*anaagUfhGfhUfhgaauu*a	1138	AV03873-AS	u*Uf*aaunUfhacCFcuCFaGfhau*g*c	1384
AV03874	AV03874-SS	g*a*uaagGfhGfhCfhaaaua*a	1139	AV03874-AS	u*Uf*aaunUfhcaCFcuUfhcafhuaa*u*c	1385
AV03875	AV03875-SS	g*u*auugGfhUfhGfhaaaua*g*a	1140	AV03875-AS	u*CF*uaaUfhucAfhccChUfhagu*a*c	1386
AV03876	AV03876-SS	g*a*cuaggaGhuCfhAfaauuaaу*a	1141	AV03876-AS	u*CF*cuuaAfhucFhaCfhUfhcagc*u*c	1387

AV03877	AV03877-SS	c* ^a g ^g guguaAfAfuAfAgg ^g aa ^a g* ^g a	1142	AV03877-AS	u* ^C F* ^u Cu(Cfc(cUNA))nuA ^A fuA ^u fA ^f Ac ^c * ^u g	1388
AV03878	AV03878-SS	c* ^g g ^g accaccaCfCfuCfuC ^u acuc ^u * ^u a	1143	AV03878-AS	u* ^A F* ^g gugucFgAgGfCufUfUfGfUg ^u * ^C g	1389
AV03879	AV03879-SS	g* ^a g ^g ucucucCfAChuCfuC ^u acug ^u * ^C a	1144	AV03879-AS	u* ^G F* ^a aucuCfAgagCfGfuGfUfUfAlfUg ^C * ^u C	1390
AV03880	AV03880-SS	c* ^C c ^u cucucAChuCfuCfAg ^u uc ^C * ^a a	1145	AV03880-AS	u* ^U F* ^g gaaCfUgagCfAgUfUfAlfUg ^g * ^g g	1391
AV03881	AV03881-SS	g* ^C c ^u acucAcAfUfuCfU ^u C ^u acua ^C * ^u a	1146	AV03881-AS	u* ^A I* ^u agugUfUgagAfcUcGfA ^u gag ^u * ^g C	1392
AV03882	AV03882-SS	g* ^a g ^g ucucucAfuUfCfA ^u ccua ^C * ^u a	1147	AV03882-AS	u* ^G F* ^u ugagCfUgagAfcUfUfAlfUg ^g * ^u C	1393
AV03883	AV03883-SS	g* ^u * ^u ccagucCfAChuCfuCfA ^u ccua ^C * ^C a	1148	AV03883-AS	u* ^G F* ^u ugagCfUgagCfGfuGfA ^u fcUc ^u * ^C	1394
AV03884	AV03884-SS	g* ^u * ^u agugugUfuCfGfuCfG ^u ccu ^u * ^u a	1149	AV03884-AS	u* ^A I* ^u acaaCfUgagCfGfuGfA ^u fcUc ^u * ^C	1395
AV03885	AV03885-SS	c* ^u * ^u g ^u ucucCfCfuCfuUfUg ^u agac ^C * ^a a	1150	AV03885-AS	u* ^U F* ^g uicaAfcaA ^u GfUcAfUfA ^u ac ^C * ^a g	1396
AV03886	AV03886-SS	g* ^g g ^g uucucCfCfuCfuGfuG ^u ccua ^C * ^u a	1151	AV03886-AS	u* ^A I* ^u gucAfcaA ^u AlfUcCfA ^u gaa ^C * ^C C	1397
AV03887	AV03887-SS	c* ^C c* ^u ugugaaCfCfuCfuGfUcug ^u * ^g a	1152	AV03887-AS	u* ^C F* ^u agAfC(aUNA)gcaUfUgCfuUfca ^C * ^g g	1398
AV03888	AV03888-SS	c* ^g g ^g aa ^g cccaUfUcCfuCfuC ^u ccu ^u * ^C a	1153	AV03888-AS	u* ^G F* ^u aaacAfcaA ^u CfcaUfUfGfC ^u * ^C g	1399
AV03889	AV03889-SS	g* ^a g ^g ccaaugCfuCfuCfuC ^u ccu ^u * ^g a	1154	AV03889-AS	u* ^C F* ^u agaaCfUgagCfAgCfuUfUg ^C * ^u C	1400
AV03890	AV03890-SS	c* ^C c* ^u aaugucCfuCfuCfuC ^u ccu ^u * ^u a	1155	AV03890-AS	u* ^A I* ^u gagAfcaA ^u GfA ^u CfUgCfUg ^C * ^g g	1401
AV03891	AV03891-SS	c* ^C c* ^u gugugucAfUcCfuGfA ^u caua ^C * ^u a	1156	AV03891-AS	u* ^A I* ^u aaugUfUcagCfGfuGfUfUfca ^C * ^g g	1402
AV03892	AV03892-SS	g* ^u * ^u gugagCfUfUfUfA ^u caua ^C * ^a a	1157	AV03892-AS	u* ^U F* ^u aaugCfUcAfUgCfUfUfC ^u * ^a C	1403
AV03893	AV03893-SS	c* ^a g ^g agucCfA ^u AfC ^u Afu ^u acaa ^C * ^u a	1158	AV03893-AS	u* ^A I* ^u guguaUfagUfUfCAlfUfC ^u * ^u g	1404
AV03894	AV03894-SS	c* ^C C* ^u gugugAfcAfuAfu ^u acaa ^C * ^g a	1159	AV03894-AS	u* ^C F* ^u aaugUfuaaUfUgUfUfCAlfUc ^u * ^g g	1405
AV03895	AV03895-SS	g* ^a g ^g agucagCfuAfuAfu ^u acaa ^C * ^a a	1160	AV03895-AS	u* ^U F* ^u cuauGfuauAfuGfuUfuC ^u * ^u C	1406
AV03896	AV03896-SS	g* ^g g ^g cugaaCfuAfuAfuAfu ^u acaa ^C * ^u a	1161	AV03896-AS	u* ^A I* ^u cuauUfuaaUfagGfuUfuCag ^u * ^C C	1407
AV03897	AV03897-SS	c* ^C C* ^u gagacUfAfuCfA ^u ccu ^u ag ^u * ^g a	1162	AV03897-AS	u* ^C F* ^u cuauAfUgucAfuAfuUfUfUfca ^C * ^g g	1408
AV03898	AV03898-SS	g* ^u * ^u gagaaUfuAfuAfuCfuAfu ^u ag ^u * ^u a	1163	AV03898-AS	u* ^A I* ^u caucUfagugUfauAfuCfuC ^u * ^a C	1409
AV03899	AV03899-SS	g* ^g g ^g aaacaaUfAfcCfuUfAfu ^u ag ^u * ^u a	1164	AV03899-AS	u* ^A I* ^u aaacCfuagGfuAfuUfUg ^u * ^C C	1410
AV03900	AV03900-SS	c* ^a g ^g aaacaaAfCfuAfuAfu ^u ag ^u * ^g a	1165	AV03900-AS	u* ^C F* ^u aaacUfcaUfUgUfUfAfuAfu ^u g ^u * ^u C	1411
AV03901	AV03901-SS	g* ^g g ^g aaacaaCfuAfuCfAfu ^u ag ^u * ^C a	1166	AV03901-AS	u* ^G F* ^a caacAfuucAfuGfuUfuUfag ^u * ^u C	1412
AV03902	AV03902-SS	g* ^g g ^g aaugugAfUcUfuGfG ^u aaug ^u * ^u a	1167	AV03902-AS	u* ^A I* ^u caaaUfcaAfcUcAfcAfcu ^C * ^C C	1413
AV03903	AV03903-SS	c* ^a g ^g aaugugAfUcUfuGfG ^u aaug ^u * ^C a	1168	AV03903-AS	u* ^G F* ^a caaaAfuucAfcaUfUfCfAfc ^u * ^u g	1414
AV03904	AV03904-SS	g* ^g g ^g aaugugUfuCfGfCfAfu ^u ag ^u * ^u a	1169	AV03904-AS	u* ^A I* ^u gucacAfuaucCfAChU ^u Afcac ^C * ^C C	1415
AV03905	AV03905-SS	c* ^u * ^u gugagUfUgGfuAfuGfu ^u ag ^u * ^g a	1170	AV03905-AS	u* ^C F* ^u agacAfuaucCfcaAfcUfca ^C * ^a g	1416
AV03906	AV03906-SS	g* ^u * ^u gaaugugGfCfuAfuUfUgucuc ^u * ^u a	1171	AV03906-AS	u* ^A I* ^u ccagacCfcaAUfCcaAfcAfcua ^C * ^C C	1417
AV03907	AV03907-SS	g* ^g g ^g aaugugGfuAfuUfUgucuc ^u * ^u a	1172	AV03907-AS	u* ^A I* ^u acagAfcaAfuucCfcaAfcua ^C * ^C C	1418

AV03939	AV03939-SS	g* ^u *caccuuuAfuCfaAfuauguc*c*a	1204	AV03939-AS	u*Gf*gaucUfaunGfaunAfaAfugc*a*c	1450
AV03940	AV03940-SS	g*c*acuuuaUfcAfaUfiguuc*c*a	1205	AV03940-AS	u*Uf*ggaaCfaunUfgaUfaAfagu*c*c	1451
AV03941	AV03941-SS	g*c*uuuaucAfaUfcGfuuccu*u*a	1206	AV03941-AS	u*Af*augcAfcuAfhuGfaUfaa*g*c	1452
AV03942	AV03942-SS	g* ^u *uaucuaUfaGfuUfccaun*u*a	1207	AV03942-AS	u*Uf*aaunGfgaaCfuUfuGfaa*a*c	1453
AV03943	AV03943-SS	g* ^u *aucauuAfgUfuCfcauuu*a*a	1208	AV03943-AS	u*Uf*uaauUfgaaAfcuAfuUfgau*a*c	1454
AV03944	AV03944-SS	g*a*uaaaguuCfcAfuUfaaauu*g*a	1209	AV03944-AS	u*CF*aaunUfaaUfgaAfcAfcuau*u*c	1455
AV03945	AV03945-SS	g*a*uaaguuCfaUfuUfaaauu*g*a	1210	AV03945-AS	u*Uf*caauUfaaUfgaAfcAfcua*a*c	1456
AV03946	AV03946-SS	g* ^u *aguuucAfuUfuAfaunug*c*a	1211	AV03946-AS	u*Gf*uaaaUfuaaAfaucfGfAfcu*a*c	1457
AV03947	AV03947-SS	c* ^u *uccaunUfaAfaUfhgacuu*c*a	1212	AV03947-AS	u*Gf*aaagCfaunUfuaAfaUfgga*a*g	1458
AV03948	AV03948-SS	g*a*cuuugcaAfgUfcCfcaunug*u*a	1213	AV03948-AS	u*Af*aucaUfgggAfcuUfgCfaag*u*c	1459
AV03949	AV03949-SS	g* ^u *u*ggcagUfcCfcAfuagauu*c*a	1214	AV03949-AS	u*Gf*aaauCfaugGfgaCfuUfgca*a*c	1460
AV03950	AV03950-SS	g* ^u *u*gcaagUfcCfaUfgauuu*c*a	1215	AV03950-AS	u*Af*gaauUfcauGfgaAfcUfhgc*a*c	1461
AV03951	AV03951-SS	g*c*caagucCfcAfuGfaunuu*u*a	1216	AV03951-AS	u*Af*agaaAfuaUfgGfcaCuug*c*c	1462
AV03952	AV03952-SS	g* ^g *aaucalUfcUfuAfgcuag*c*a	1217	AV03952-AS	u*Gf*cuAfa(gUNA)cuaAfgaUfgAfuuu*c*c	1463
AV03953	AV03953-SS	g*a*aucaucUfuAfgCfuuauc*u*a	1218	AV03953-AS	u*Af*agcuAfaagUfaaGfaUfgau*u*c	1464
AV03954	AV03954-SS	g* ^g *ucauaUfaGfuGfuauug*c*a	1219	AV03954-AS	u*CF*acaaUfacaCfaUfaUfga*c*c	1465
AV03955	AV03955-SS	g*a*auagauUfaCfaCfhgacuu*g*a	1220	AV03955-AS	u*Af*caugCfaguGfuafuaAfaUfcau*u*c	1466
AV03956	AV03956-SS	g* ^u *u*gaauuCfaCfuGfiacuuu*g*a	1221	AV03956-AS	u*CF*aaacGfuacGfugUfaAfauc*a*c	1467
AV03957	AV03957-SS	g* ^u *u*uaacuGfaCfuGhuugcu*g*a	1222	AV03957-AS	u*Af*caagAfaacGfucAfgUfgua*a*c	1468
AV03958	AV03958-SS	g* ^u *u*acacugAfcUfgUfhgucugu*a*a	1223	AV03958-AS	u*Uf*acagCfaacAfguCfaGfugu*a*c	1469
AV03959	AV03959-SS	g*a*caucugCfuGfuUfgucugua*a*a	1224	AV03959-AS	u*Uf*uaaaGfcauCfaUfcAfgug*u*c	1470
AV03960	AV03960-SS	g*c*acugracUfgUfuGfucuguaa*a*a	1225	AV03960-AS	u*Uf*uaacAfgcaAfcuGfuCfagu*g*c	1471
AV03961	AV03961-SS	g*c*ugacugUfhGfcUfguaaa*g*a	1226	AV03961-AS	u*CF*uuuuAfcagCfaaCfaGfuca*g*c	1472
AV03962	AV03962-SS	g* ^u *u*gaucuuUfgCfuGfuuaag*u*a	1227	AV03962-AS	u*Af*cuuuUfacaGfcaAfcAfguc*a*c	1473
AV03963	AV03963-SS	g*c*gaucuuCfuGfuAfaaagug*a*a	1228	AV03963-AS	u*CF*acuuUfhacaAfgcAfaCfagu*a*c	1474
AV03964	AV03964-SS	c*a*cuugugCfuGfuAfaaagug*a*a	1229	AV03964-AS	u*Uf*cauuUfhuaCfaaCfaAfcag*u*g	1475
AV03965	AV03965-SS	g*c*uguuugUfgUfaAfaagug*a*a	1230	AV03965-AS	u*Uf*uaaaUfhuaAfcuGfcaAfcua*a*c	1476
AV03966	AV03966-SS	g* ^u *u*guugcuGfuAfaAfaagug*a*a	1231	AV03966-AS	u*Af*uaaaCfuuuUfacaAfgCfaac*a*c	1477
AV03967	AV03967-SS	c*c*uguaaaAfgUfgAfaauugg*a*a	1232	AV03967-AS	u*Uf*ccaaAfuuaAfcuUfuUfaca*g*g	1478
AV03968	AV03968-SS	g* ^u *u*guaaaaGfuGfaAfuugga*a*a	1233	AV03968-AS	u*Uf*uaaaAfaunCfaaCfuUfuUfaa*a*c	1479
AV03969	AV03969-SS	g* ^g *u*gaauuUfgGfaAfaaaag*u*a	1234	AV03969-AS	u*Af*cuuuAfuuuCfaaAfaUfca*c*c	1480

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AV03970	AV03970-SS	g* ^g *gaaanaAfaGhuUfauuacu*c*a	1235	AV03970-AS	u*Gf* ^g aguaAfaacChuuUfaUfmu*c*c	1481
AV03971	AV03971-SS	c* ^g *aaanaaAfgUfuAfuuaac*u*a	1236	AV03971-AS	u*Af* ^g aguaAfaaAfcuuUfuAfuuu*c*c ^g	1482
AV03972	AV03972-SS	g* ^a *uaaaguUfaUfuAfcuug*a*u*a	1237	AV03972-AS	u*Af* ^g ucagAfguaAfuAfcUfuua*u*c	1483
AV03973	AV03973-SS	g* ^a *aguuaaUfaChuCfhuanaa*a*a	1238	AV03973-AS	u*Uf* ^g uaaCfagaGfuaAfuAfcu*u*c	1484
AV07298	AV07298-SS	g*c* ^g ccgggAfcGfuAfcggguu*c*a	1847	AV07298-AS	u*CF* ^g aaCfc(cUNA)guacGfuCfcCfagc*c*c	1992
AV07299	AV07299-SS	c* ^g *acguacGfgUfuGfggggac*c*a	1848	AV07299-AS	u*Gf* ^g ucCfc(cUNA)caacCfcGfuAfcgu*c*c ^g	1993
AV07300	AV07300-SS	c* ^g *acguacGfgUfuGfggggac*c*a	1849	AV07300-AS	u*Uf* ^g guCfc(cUNA)ccaaCfcCfGUfacg*u* ^g	1994
AV07301	AV07301-SS	g* ^g *agggcuAfcChUfccaag*c*a	1850	AV07301-AS	u*Gf* ^g cuChU(gUNA)gaaGfuCfagccu*c*c	1995
AV07302	AV07302-SS	c* ^a *ggcuGfcUfuCfcaagc*c*a	1851	AV07302-AS	u*Gf* ^g ccUfc(cUNA)ggaaCfGUfcAfcg*c*c ^g	1996
AV07303	AV07303-SS	g* ^a *ggcuGfcUfuCfcaagc*c*a	1852	AV07303-AS	u*CF* ^g ccGfc(aUNA)gccagCfagCfcAfgcc*u* ^g	1997
AV07304	AV07304-SS	c* ^g *uacguAfaAfgCfagaagc*c*a	1853	AV07304-AS	u*CF* ^g guCfu(cUNA)uccuUfuUfaChuga*c*c ^g	1998
AV07305	AV07305-SS	c* ^u *acguaaAfaGfcAfaagcc*c*a	1854	AV07305-AS	u*CF* ^g ccUfc(cUNA)uccuUfuUfaAfcu*c*c ^g	1999
AV07306	AV07306-SS	g* ^a *guaaagGfcAfaAfaagcc*c*a	1855	AV07306-AS	u*Uf* ^g ccCfG(cUNA)ccuuGfcUfuUfuac*u*c	2000
AV07307	AV07307-SS	g* ^c *uaggagCfGAfuGfacaaga*a*a	1856	AV07307-AS	u*Uf* ^g uuUfu(gUNA)uccuUfcGfuUfeca*a*c	2001
AV07308	AV07308-SS	g* ^u *uaggagCfGAfuGfacaaga*a*a	1857	AV07308-AS	u*Uf* ^g uuUfu(cUNA)gucaUfcGfcUfuca*a*c	2002
AV07309	AV07309-SS	c* ^a *agccguGfAfaAfaaagc*c*a	1858	AV07309-AS	u*Gf* ^g ccUfu(cUNA)uuugUfcAfuCfgeu*u* ^g	2003
AV07310	AV07310-SS	c* ^c *gaugacAfaAfaAfaagcc*c*a	1859	AV07310-AS	u*CF* ^g uuGfG(cUNA)uuuuUfuGfuCfanc*c*c ^g	2004
AV07311	AV07311-SS	g* ^c *cuugaaAfaAfaAfaagccu*u* ^g a	1860	AV07311-AS	u*CF* ^g aaGfG(cUNA)ccuuUfuUfuCfagc*c*c	2005
AV07312	AV07312-SS	g* ^c *uuagaaAfaUfaGfgecuu*c*a	1861	AV07312-AS	u*Gf* ^g caAfg(gUNA)ccuaUfuUfuUfca*a*c	2006
AV07313	AV07313-SS	g* ^u *uagaaAfaAfgGfgecuu*c*a	1862	AV07313-AS	u*Gf* ^g ccAfa(gUNA)gccuAfuUfuUfuca*a*c	2007
AV07314	AV07314-SS	g* ^a *ggcuuGfcChUfagcc*c*a	1863	AV07314-AS	u*Uf* ^g ggGfG(cUNA)uagGfcAfaGfgec*u*c	2008
AV07315	AV07315-SS	c* ^c *aaauugUfcUfaCfhaacca*c*a	1864	AV07315-AS	u*CF* ^g uGGfu(cUNA)uugaaGfAfaAfuuu*c*c ^g	2009
AV07316	AV07316-SS	g* ^a *aaauugCfuAfaAfaaccag*c*a	1865	AV07316-AS	u*Af* ^g cuGfG(cUNA)uuuuAfgAfcUfauu*u*c	2010
AV07317	AV07317-SS	g* ^a *gucaacAfaCfaGfhuuagc*c*a	1866	AV07317-AS	u*Gf* ^g ucAfa(cUNA)uccuUfuGfuAfgac*u*c	2011
AV07318	AV07318-SS	c* ^u *uaaacaAfaCfaGfhuuagc*c*a	1867	AV07318-AS	u*Af* ^g ggUfc(aUNA)accuGfuUfuGfhuagc*c*a	2012
AV07319	AV07319-SS	g* ^a *caaacAfgUfuGfhaagc*c*a	1868	AV07319-AS	u*CF* ^g ucAfg(gUNA)uccaCfuCfgeUfuuu*c*c	2013
AV07320	AV07320-SS	g* ^a *aacaguUfaAfcChugaagc*c*a	1869	AV07320-AS	u*Uf* ^g uGGfu(cUNA)agguCfhaAfcUfgeu*u*c	2014
AV07321	AV07321-SS	g* ^c *caguuAfcChGfagcag*c*a	1870	AV07321-AS	u*CF* ^g cuUfG(cUNA)uccagGfuCfhaAfcu*c*c	2015
AV07322	AV07322-SS	g* ^c *cugagcAfgGhuCfaccuc*c*a	1871	AV07322-AS	u*Uf* ^g ggAfg(gUNA)uccaCfuUfGfhuca*c*c	2016
AV07323	AV07323-SS	g* ^a *agguGfcUfcCfaguug*c*a	1872	AV07323-AS	u*CF* ^g ucAfc(cUNA)uccaGfGUfcAfcu*u*c	2017
AV07324	AV07324-SS	c* ^a *ccucaaAfgUfuGfgeuca*u*a	1873	AV07324-AS	u*Af* ^g uGfAfg(cUNA)caacCfuUfGfagc*c*a	2018

AV07325	AV07325-SS	g* ^a c* ^a auguugCf <u>g</u> C <u>h</u> iC <u>h</u> iC <u>h</u> auuug* ^a c* ^a	1874	AV07325-AS	u* ^a Gf* ^a ccUf <u>h</u> a(uUN <u>A</u>)u <u>g</u> u <u>g</u> Cf <u>e</u> Cf <u>e</u> Af <u>e</u> Uf <u>u</u> * ^a g* ^c	2019
AV07326	AV07326-SS	g* ^a a* ^a gugugC <u>h</u> iC <u>h</u> iC <u>h</u> iC <u>h</u> uagga* ^a a	1875	AV07326-AS	u* ^a Uf* ^a u <u>g</u> Cf <u>e</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>g</u> Cf <u>e</u> Af <u>e</u> cc* ^a u* ^c	2020
AV07327	AV07327-SS	g* ^a g* ^a uugugC <u>h</u> iC <u>h</u> iC <u>h</u> iC <u>h</u> uagga* ^a c* ^a	1876	AV07327-AS	u* ^a Gf* ^a u <u>g</u> Gf <u>e</u> (cUN <u>A</u>)u <u>g</u> u <u>g</u> Cf <u>e</u> Cf <u>e</u> Af <u>e</u> cc* ^a c	2021
AV07328	AV07328-SS	g* ^a u* ^a cauugCf <u>e</u> Af <u>i</u> Cf <u>i</u> Cf <u>i</u> uacaa* ^a c* ^a	1877	AV07328-AS	u* ^a Gf* ^a u <u>g</u> Gf <u>e</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Cf <u>e</u> Cf <u>i</u> Af <u>u</u> agga* ^a c	2022
AV07329	AV07329-SS	g* ^a a* ^a uaggaCf <u>i</u> Cf <u>i</u> Cf <u>i</u> Uf <u>u</u> ccaa* ^a u* ^a	1878	AV07329-AS	u* ^a Af* ^a u <u>g</u> Af <u>i</u> (cUN <u>A</u>)u <u>g</u> u <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uua* ^a u* ^c	2023
AV07330	AV07330-SS	g* ^a a* ^a ggaacAf <u>h</u> iCf <u>i</u> Cf <u>i</u> uacaa* ^a a	1879	AV07330-AS	u* ^a Uf* ^a u <u>g</u> Af <u>i</u> (cUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>i</u> Cf <u>i</u> Uf <u>u</u> cc* ^a u* ^c	2024
AV07331	AV07331-SS	c* ^a g* ^a caacaaCf <u>i</u> Cf <u>i</u> Cf <u>i</u> uuaac* ^a c* ^a	1880	AV07331-AS	u* ^a Gf* ^a u <u>g</u> Uf <u>h</u> a(uUN <u>A</u>)u <u>g</u> u <u>g</u> Cf <u>g</u> Af <u>i</u> Cf <u>i</u> uugc* ^a g	2025
AV07332	AV07332-SS	g* ^a a* ^a cauucAf <u>h</u> iCf <u>i</u> Cf <u>i</u> uuaac* ^a g* ^a	1881	AV07332-AS	u* ^a CF* ^a u <u>g</u> Gf <u>h</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>i</u> Cf <u>i</u> Af <u>u</u> gu* ^a u* ^c	2026
AV07333	AV07333-SS	g* ^a c* ^a cauucAf <u>h</u> iCf <u>i</u> Cf <u>i</u> uuaac* ^a g* ^a	1882	AV07333-AS	u* ^a Uf* ^a ccUf <u>g</u> (cUN <u>A</u>)u <u>g</u> u <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2027
AV07334	AV07334-SS	g* ^a c* ^a cauucAf <u>h</u> iCf <u>i</u> Cf <u>i</u> uuaac* ^a g* ^a	1883	AV07334-AS	u* ^a Af* ^a ccUf <u>g</u> (cUN <u>A</u>)u <u>g</u> u <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2028
AV07335	AV07335-SS	g* ^a a* ^a accagCf <u>i</u> Cf <u>i</u> Cf <u>i</u> uuaac* ^a u* ^a	1884	AV07335-AS	u* ^a Af* ^a ccUf <u>g</u> (cUN <u>A</u>)u <u>g</u> u <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2029
AV07336	AV07336-SS	c* ^a c* ^a cugugCf <u>i</u> Cf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a u* ^a	1885	AV07336-AS	u* ^a Af* ^a g <u>u</u> Uf <u>h</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2030
AV07337	AV07337-SS	c* ^a g* ^a aggaacAf <u>h</u> iCf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a c* ^a	1886	AV07337-AS	u* ^a Gf* ^a ccUf <u>h</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2031
AV07338	AV07338-SS	g* ^a g* ^a uuaauCf <u>h</u> iCf <u>i</u> Cf <u>i</u> uuaac* ^a g* ^a	1887	AV07338-AS	u* ^a CF* ^a aaGf <u>e</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>i</u> Cf <u>i</u> Uf <u>h</u> uaa* ^a c* ^c	2032
AV07339	AV07339-SS	g* ^a a* ^a aaauCf <u>h</u> iCf <u>i</u> Cf <u>i</u> uuaac* ^a c* ^a	1888	AV07339-AS	u* ^a Gf* ^a u <u>g</u> Cf <u>i</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Cf <u>i</u> Cf <u>i</u> Af <u>u</u> u* ^a u* ^c	2033
AV07340	AV07340-SS	g* ^a a* ^a aaucCf <u>h</u> iCf <u>i</u> Cf <u>i</u> uuaac* ^a u* ^a	1889	AV07340-AS	u* ^a Af* ^a g <u>u</u> Cf <u>i</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Cf <u>i</u> Cf <u>i</u> Af <u>u</u> u* ^a u* ^c	2034
AV07341	AV07341-SS	g* ^a a* ^a aaucCf <u>h</u> iCf <u>i</u> Cf <u>i</u> uuaac* ^a u* ^a	1890	AV07341-AS	u* ^a Af* ^a g <u>u</u> Uf <u>h</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2035
AV07342	AV07342-SS	g* ^a a* ^a aaucCf <u>h</u> iCf <u>i</u> Cf <u>i</u> uuaac* ^a u* ^a	1891	AV07342-AS	u* ^a Gf* ^a aaGf <u>h</u> (cUN <u>A</u>)u <u>g</u> u <u>g</u> Cf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2036
AV07343	AV07343-SS	g* ^a u* ^a cuaggaCf <u>h</u> iCf <u>i</u> Cf <u>i</u> uuaac* ^a g* ^a	1892	AV07343-AS	u* ^a Uf* ^a gaAf <u>g</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Cf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2037
AV07344	AV07344-SS	g* ^a g* ^a aggaacCf <u>h</u> iCf <u>i</u> Cf <u>i</u> uuaac* ^a g* ^a	1893	AV07344-AS	u* ^a CF* ^a cuUf <u>g</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Cf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2038
AV07345	AV07345-SS	c* ^a a* ^a gaagCf <u>h</u> iCf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a g* ^a	1894	AV07345-AS	u* ^a Uf* ^a ccUf <u>h</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Cf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2039
AV07346	AV07346-SS	g* ^a a* ^a gcuugCf <u>h</u> iCf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a g* ^a	1895	AV07346-AS	u* ^a CF* ^a u <u>g</u> Uf <u>h</u> (cUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2040
AV07347	AV07347-SS	g* ^a g* ^a cuugCf <u>h</u> iCf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a g* ^a	1896	AV07347-AS	u* ^a Uf* ^a cuGf <u>h</u> (cUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2041
AV07348	AV07348-SS	c* ^a c* ^a uugCf <u>h</u> iCf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a g* ^a	1897	AV07348-AS	u* ^a CF* ^a u <u>g</u> Uf <u>g</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2042
AV07349	AV07349-SS	g* ^a u* ^a uugCf <u>h</u> iCf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a g* ^a	1898	AV07349-AS	u* ^a Af* ^a cuCf <u>h</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2043
AV07350	AV07350-SS	g* ^a u* ^a gaucCf <u>h</u> iCf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a g* ^a	1899	AV07350-AS	u* ^a Gf* ^a u <u>g</u> Uf <u>h</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2044
AV07351	AV07351-SS	c* ^a a* ^a cuagCf <u>h</u> iCf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a g* ^a	1900	AV07351-AS	u* ^a Af* ^a u <u>g</u> Uf <u>h</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2045
AV07352	AV07352-SS	g* ^a a* ^a gaucCf <u>h</u> iCf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a g* ^a	1901	AV07352-AS	u* ^a CF* ^a aaUf <u>h</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2046
AV07353	AV07353-SS	g* ^a c* ^a agucCf <u>h</u> iCf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a g* ^a	1902	AV07353-AS	u* ^a Gf* ^a g <u>u</u> Af <u>h</u> (cUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2047
AV07354	AV07354-SS	g* ^a a* ^a gucCf <u>h</u> iCf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a g* ^a	1903	AV07354-AS	u* ^a Af* ^a g <u>u</u> Gf <u>h</u> (cUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2048
AV07355	AV07355-SS	g* ^a g* ^a aggaauCf <u>h</u> iCf <u>i</u> Cf <u>i</u> Uf <u>h</u> iaaau* ^a g* ^a	1904	AV07355-AS	u* ^a Gf* ^a u <u>g</u> Cf <u>h</u> (uUN <u>A</u>)u <u>g</u> u <u>g</u> Af <u>g</u> Uf <u>h</u> iCf <u>i</u> Cf <u>i</u> uugc* ^a g	2049

AV07356	AV07356-SS	c* _g a* _u gggucCfcCfuGfagcau* _g a	1905	AV07356-AS	u* _U f* _{au} Ufg(uUNA)ccagGfgeAfcCfcau* _u g	2050
AV07357	AV07357-SS	c* _g g* _u ccuccGfgAfaFauuac* _c a	1906	AV07357-AS	u* _G f* _u gAfu(aUNA)uugucCfcAfgGfgac* _c g	2051
AV07358	AV07358-SS	g* _c c* _u ccggGcfaAfuAfuaccc* _a a	1907	AV07358-AS	u* _U f* _g gGfu(cUNA)auauUfgUfcCfag* _g c	2052
AV07359	AV07359-SS	g* _c c* _u ggacAfuAfuCfaccac* _g a	1908	AV07359-AS	u* _C f* _g uGfg(cUNA)uugauAfuUfgUfcac* _g c	2053
AV07360	AV07360-SS	g* _u u* _g gcaUfaUfaAfccac* _u a	1909	AV07360-AS	u* _A f* _c gUfg(cUNA)gugauAfuGfuacc* _a c	2054
AV07361	AV07361-SS	g* _a a* _a aaagAfaUfaAfuagacc* _g a	1910	AV07361-AS	u* _C f* _g gGfu(cUNA)auuaUfuCfuUuuu* _u c	2055
AV07362	AV07362-SS	g* _a a* _a aaagAfaUfaUfgaccg* _g a	1911	AV07362-AS	u* _C f* _g gGfu(cUNA)cauuAfuUfuUuuu* _u c	2056
AV07363	AV07363-SS	g* _a a* _a aaagAfaAfuGfaccg* _c a	1912	AV07363-AS	u* _G f* _c ccGfg(cUNA)ucauUfaUfuCfuuu* _u c	2057
AV07364	AV07364-SS	c* _g g* _c cccccCfcCfuGfcccc* _c a	1913	AV07364-AS	u* _G f* _g gGfg(cUNA)agagCfcCfcGfagg* _c g	2058
AV07365	AV07365-SS	g* _c c* _u cccccCfuCfuGfcccc* _g a	1914	AV07365-AS	u* _C f* _u gGfg(cUNA)gcaAfcGfcCfagg* _g c	2059
AV07366	AV07366-SS	g* _u u* _g cccccAfcCfuGfuccuc* _g a	1915	AV07366-AS	u* _C f* _g aGfg(aUNA)gcaAfcCfcGfagg* _a c	2060
AV07367	AV07367-SS	g* _c c* _u ccagcUfgCfuCfuccga* _g a	1916	AV07367-AS	u* _C f* _u gCfg(aUNA)ggagCfaGfuUfggg* _g c	2061
AV07368	AV07368-SS	c* _c c* _u uccucGcfaGfuUfgguaa* _a a	1917	AV07368-AS	u* _U f* _u aAfc(cUNA)gaacUfgCfcAfgga* _g g	2062
AV07369	AV07369-SS	g* _u u* _c gcauUfcGfgUfuauu* _g a	1918	AV07369-AS	u* _C f* _c aAfu(aUNA)aacGfaAfcUfgc* _g a	2063
AV07370	AV07370-SS	g* _c c* _g cauUfcGfgUfuauu* _g a	1919	AV07370-AS	u* _A f* _c ccAfa(aUNA)uacCfgeAfcCfucc* _g c	2064
AV07371	AV07371-SS	g* _g g* _c agucCfgeUfuAfauggu* _u a	1920	AV07371-AS	u* _A f* _g accaFuuaCfcGfaAfcucc* _c c	2065
AV07372	AV07372-SS	c* _c c* _a guucGfuUfaAfuuggu* _a a	1921	AV07372-AS	u* _U f* _g aaccAfauaAfcCfgeAfcu* _g g	2066
AV07373	AV07373-SS	g* _a a* _g uucggUfuAfaUfugguu* _a a	1922	AV07373-AS	u* _U f* _g uacCfaauAfaCfcGfaac* _u c	2067
AV07374	AV07374-SS	g* _g g* _u ucggUfaAfuUfuguaa* _u a	1923	AV07374-AS	u* _A f* _u uaaCfcauUfaAfcCfgea* _c c	2068
AV07375	AV07375-SS	c* _u u* _u cgguaAfaUfuGfuguau* _a a	1924	AV07375-AS	u* _G f* _g auuaAfcacUfuAfaCfgea* _a g	2069
AV07376	AV07376-SS	g* _u u* _c gguaAfuUfgeGfuuauc* _a a	1925	AV07376-AS	u* _U f* _g auUfu(aUNA)accaAfuUfaAfcg* _a c	2070
AV07377	AV07377-SS	g* _g c* _g guuaUfuGfgeUfuuauc* _a a	1926	AV07377-AS	u* _G f* _g gaUfaaccAfaUfuAfaacc* _g c	2071
AV07378	AV07378-SS	g* _g g* _g guuaUfgeGfuUfaaacc* _a a	1927	AV07378-AS	u* _A f* _g guGfa(cUNA)uacCfaAfuUfaac* _c c	2072
AV07379	AV07379-SS	c* _g g* _u uaauGfgUfuAfaucac* _u a	1928	AV07379-AS	u* _A f* _g agugAfuuaCfcAfaUfuua* _c g	2073
AV07380	AV07380-SS	c* _u u* _u aaugGfuUfaAfuacau* _a a	1929	AV07380-AS	u* _U f* _g aagGfu(cUNA)auuaAfcCfaAfuua* _a g	2074
AV07381	AV07381-SS	g* _u u* _a auugUfuAfaUfcaua* _a a	1930	AV07381-AS	u* _U f* _u aAfg(cUNA)gaauAfaCfcAfauu* _a c	2075
AV07382	AV07382-SS	g* _u u* _u gguaAfuCfaCfuuaac* _a a	1931	AV07382-AS	u* _A f* _g gUfu(aUNA)gugAfuUfaAfcac* _a c	2076
AV07383	AV07383-SS	g* _g g* _g guuaCfaCfuUfaaccug* _c a	1932	AV07383-AS	u* _G f* _g caGfg(cUNA)uaagUfgAfuUfaac* _c c	2077
AV07384	AV07384-SS	c* _g g* _u uaucAfcUfuAfaacugc* _u a	1933	AV07384-AS	u* _A f* _g cAfg(cUNA)uaaCfuGfaUfuua* _c g	2078
AV07385	AV07385-SS	c* _u u* _u uaucAfuUfaAfcugcu* _u a	1934	AV07385-AS	u* _A f* _g agCfa(gUNA)guuaAfgUfgAfuua* _a g	2079
AV07386	AV07386-SS	g* _u u* _a aacacUfuAfaCfcugcu* _u a	1935	AV07386-AS	u* _A f* _g aaGfc(aUNA)gguuAfaCfuGfauu* _a c	2080

AV07387	AV07387-SS	g*a*cuuaacCfuGfcUfhuuguc*a*a	1936	AV07387-AS	u*Uf*gaCfa(aUNA)aagcAfgCfuUfhaag*a*η*c	2081
AV07388	AV07388-SS	g*c*uaaacUfgCfuUfhuugua*c*a	1937	AV07388-AS	u*Gf*ugAfc(aUNA)aagCfaGfgUfuaa*g*c	2082
AV07389	AV07389-SS	g*u*uaaccGfcUfuUfhuugac*η*a	1938	AV07389-AS	u*Af*ugacCfaaaGfcAfgCfuua*a*c	2083
AV07390	AV07390-SS	g*u*uaaccGfuUfuUfhuucau*c*a	1939	AV07390-AS	u*Gf*agUfg(aUNA)caaaAfgCfaGfgu*a*c	2084
AV07391	AV07391-SS	g*a*accugUfuUfuGfuacac*c*a	1940	AV07391-AS	u*CF*gaGfu(gUNA)acaaAfaGfcAfgu*η*c	2085
AV07392	AV07392-SS	g*c*cuugcuUfuGfuCfaucg*c*a	1941	AV07392-AS	u*Gf*ccGfa(gUNA)ugacAfaaGfcag*c*c	2086
AV07393	AV07393-SS	g*u*gcuumuGfuCfaCfuagc*c*a	1942	AV07393-AS	u*Af*agCfc(gUNA)agugAfaaGfcag*c*c	2087
AV07394	AV07394-SS	g*g*cuuuuUfcAfcUfcgcuu*η*a	1943	AV07394-AS	u*Af*aaGfc(gUNA)gaugCfaCfaaag*c*c	2088
AV07395	AV07395-SS	c*c*uuuuuGfuCfaCfuagc*c*a	1944	AV07395-AS	u*CF*aaAfg(cUNA)cgaugUfgAfaaag*c*c	2089
AV07396	AV07396-SS	g*g*uaacucGfcCfuUfhuagc*c*a	1945	AV07396-AS	u*CF*gaGfc(gUNA)aaagCfcGfaGfuag*c*c	2090
AV07397	AV07397-SS	c*η*caucugGfcUfuUfhuagc*c*a	1946	AV07397-AS	u*CF*gaGfc(gUNA)caaaGfcCfaAfgu*a*g	2091
AV07398	AV07398-SS	g*η*huugcuCfuGfcAfaucua*η*a	1947	AV07398-AS	u*Uf*huGfa(aUNA)guccCfaAfgCfaa*a*c	2092
AV07399	AV07399-SS	g*g*gcucugGfaCfuUfcaaaη*c*a	1948	AV07399-AS	u*Gf*auUfu(aUNA)gaugUfcCfaGfag*c*c	2093
AV07400	AV07400-SS	c*c*ucgugGfuUfcAfaaaua*c*a	1949	AV07400-AS	u*CF*ugAfu(aUNA)uuuAfgUfcCfaag*c*c	2094
AV07401	AV07401-SS	g*g*gcucucCfaAfaaafuag*c*a	1950	AV07401-AS	u*Uf*caCfu(gUNA)auuuUfgAfaGfucc*c*c	2095
AV07402	AV07402-SS	c*g*gaucucAfaAfaUfcaugc*η*a	1951	AV07402-AS	u*Af*ucAfc(aUNA)gaauUfuGfaAfguc*c*g	2096
AV07403	AV07403-SS	g*c*uaacaaAfuCfaGfuagug*c*a	1952	AV07403-AS	u*CF*ccAfu(cUNA)acugAfuUfuUfgaa*g*c	2097
AV07404	AV07404-SS	g*η*uaacaaUfcAfgUfhuagug*c*a	1953	AV07404-AS	u*Uf*ccCfa(aUNA)caucGfaUfuUfuga*a*c	2098
AV07405	AV07405-SS	g*η*caaaauCfaGfuGfaugugc*a	1954	AV07405-AS	u*CF*ucCfa(aUNA)ucauUfgAfuUfhuag*a*c	2099
AV07406	AV07406-SS	g*a*aaaucaGfuGfaUfhuagugc*a	1955	AV07406-AS	u*Uf*acUfc(cUNA)caucAfcUfgAfuuu*η*c	2100
AV07407	AV07407-SS	g*a*aaucagUfgAfuGfhuagugc*a	1956	AV07407-AS	u*Uf*uaucCfcauCfaCfuGfauu*η*c	2101
AV07408	AV07408-SS	g*a*aucaugGfaUfhuGfhuagugc*a	1957	AV07408-AS	u*CF*uuAfc(aUNA)cccaUfcAfcUfhuu*η*c	2102
AV07409	AV07409-SS	g*a*uaucugAfuGfhuGfaugugc*a	1958	AV07409-AS	u*Uf*cuuaCfuuccAfuCfaCfuag*a*η*c	2103
AV07410	AV07410-SS	g*η*ucagugUfgCfhuGfaaagugc*a	1959	AV07410-AS	u*CF*ucUfu(aUNA)cuccCfaUfcAfcug*a*c	2104
AV07411	AV07411-SS	g*a*uaucugGfhuGfaUfhuagugc*a	1960	AV07411-AS	u*Uf*gcUfc(aUNA)uaucCfaUfcauc*η*c	2105
AV07412	AV07412-SS	g*g*uaucugGfhuGfaaagugc*a	1961	AV07412-AS	u*Uf*ugCfu(cUNA)uaucUfcCfaa*η*c	2106
AV07413	AV07413-SS	c*η*gaugugGfuAfaAfgugc*a	1962	AV07413-AS	u*Uf*uuGfc(aUNA)cuuaCfuCfauc*a*g	2107
AV07414	AV07414-SS	g*g*uaucugGfuAfaGfaagugc*a	1963	AV07414-AS	u*Af*uuUfg(cUNA)ucuuAfcUfcCfauc*a*c	2108
AV07415	AV07415-SS	c*a*ugugugUfaAfaAfgugc*a	1964	AV07415-AS	u*Af*auUfu(gUNA)ucuuUfcCfuCfauc*a*η*g	2109
AV07416	AV07416-SS	g*η*ugugugAfaCfaGfaaauu*η*a	1965	AV07416-AS	u*Af*aaUfu(aUNA)guccUfuAfcUfcc*a*c	2110
AV07417	AV07417-SS	g*g*ugugugAfgAfgCfaaauu*c*a	1966	AV07417-AS	u*Gf*aaauUfhuugCfuUfcaCfucc*c*c	2111

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AV07418	AV07418-SS	c* ^g *gaguaaGfaGfcAfaauuc* ^a *a	1967	AV07418-AS	u*Uf* ^g aAfa(uUNA)uugcUfcUfuAfcuc* ^c *g	2112
AV07419	AV07419-SS	c* ^g *gaguagAfgCfaAfaauuca* ^u *a	1968	AV07419-AS	u*Af* ^u gaaAfuugCfuChUfacu* ^c *g	2113
AV07420	AV07420-SS	c* ^a * ^g uaagaGfcAfaAfuuccu* ^c *a	1969	AV07420-AS	u*Gf* ^u auGfa(uUNA)auuGfcUfcUfuac* ^u *g	2114
AV07421	AV07421-SS	g* ^g * ^g uaagaCfaAfaUfuuccu* ^u *a	1970	AV07421-AS	u*Af* ^g auUfg(aUNA)aaauUfgCfuChua* ^c *c	2115
AV07422	AV07422-SS	c* ^u * ^g aaagaCfaAfaUfuuccu* ^u *a	1971	AV07422-AS	u*Af* ^g agAfu(gUNA)aaauUfuGfcUfcu* ^a *g	2116
AV07423	AV07423-SS	g* ^u * ^u uuccuAfuUfuCfaauug* ^a *a	1972	AV07423-AS	u*Uf* ^g caAfu(uUNA)uugaaAfaGfaUfgaa* ^a *c	2117
AV07424	AV07424-SS	g* ^u * ^u uuccAfaAfuUfgauug* ^u *a	1973	AV07424-AS	u*Af* ^g ccCfa(uUNA)caauUfuGfgAfaag* ^a *c	2118
AV07425	AV07425-SS	g* ^c * ^u uuccaAfaUfuGfaug* ^g *a	1974	AV07425-AS	u*CF* ^u acCfa(uUNA)ucauUfuUfgGfaa* ^g *c	2119
AV07426	AV07426-SS	g* ^u * ^u uuccaAfuUfgAfuug* ^g *a	1975	AV07426-AS	u*CF* ^g caCfc(uUNA)ucaAfuUfuGfgaa* ^a *c	2120
AV07427	AV07427-SS	g* ^u * ^u *ccaauUfgAfuGfgug* ^g *a	1976	AV07427-AS	u*Gf* ^g ccCfa(uUNA)ccauCfaAfuUfuug* ^a *c	2121
AV07428	AV07428-SS	g* ^a * ^u auugaGfgGfuGfgug* ^u *a	1977	AV07428-AS	u*Af* ^g cuAfg(uUNA)ccacCfcAfuCfaa* ^u *c	2122
AV07429	AV07429-SS	g* ^a * ^u ugaugGfuUfgGfcua* ^u *a	1978	AV07429-AS	u*Uf* ^g acUfa(gUNA)cccaCfcCfaUfcaa* ^u *c	2123
AV07430	AV07430-SS	g* ^u * ^u *ugaugGfuGfgGfcua* ^a *a	1979	AV07430-AS	u*Uf* ^g uaCfu(aUNA)gccAfcCfcAfuca* ^a *c	2124
AV07431	AV07431-SS	g* ^u * ^u *gaugGfuGfgCfuag* ^u *a	1980	AV07431-AS	u*Af* ^u uuAfc(uUNA)gccCfaCfcCfauc* ^a *c	2125
AV07432	AV07432-SS	c* ^a * ^u ggugGfuCfuAfuuaa* ^a *a	1981	AV07432-AS	u*Uf* ^u uuuAfcuagCfcCfaCfcca* ^u *g	2126
AV07433	AV07433-SS	g* ^u * ^u *ggugGfuCfuAfuuaa* ^a *a	1982	AV07433-AS	u*Uf* ^u uuAfu(uUNA)acuagCfcCfaAfcc* ^a *c	2127
AV07434	AV07434-SS	g* ^u * ^u *guauAfaAfuAfuuaa* ^a *a	1983	AV07434-AS	u*Uf* ^u uuuAfa(aUNA)aaauUfuAfuUfauc* ^u *c	2128
AV07435	AV07435-SS	g* ^a * ^u uaauAfaAfuAfuuaa* ^a *a	1984	AV07435-AS	u*Uf* ^u uuuAfaaUfuUfaUfuac* ^u *c	2129
AV07436	AV07436-SS	g* ^g * ^g *uaauaAfaUfaUfuuaa* ^a *a	1985	AV07436-AS	u*Uf* ^u uuUfu(aUNA)aaauUfuUfuAfuua* ^c *c	2130
AV07437	AV07437-SS	c* ^u * ^u *aaauaAfuAfuUfuuaa* ^a *a	1986	AV07437-AS	u*Uf* ^u uuuuUfaaauAfuUfuUfaa* ^a *g	2131
AV07438	AV07438-SS	g* ^a * ^u aaauaUfaUfuUfaa* ^a *a	1987	AV07438-AS	u*Uf* ^u uuuuUfaaauAfuUfuUfaa* ^u *c	2132
AV07439	AV07439-SS	g* ^a * ^u *aaauAfuUfaAfaa* ^a *a	1988	AV07439-AS	u*Uf* ^u uuuuUfuuaaAfuAfuUfuua* ^u *c	2133
AV07440	AV07440-SS	g* ^u * ^u *aaauUfuUfaAfaa* ^a *a	1989	AV07440-AS	u*Uf* ^u uuUfu(uUNA)uuuaAfaUfaUfuua* ^a *c	2134
AV07441	AV07441-SS	g* ^u * ^u *aaauaAfaAfcAfuca* ^a *a	1990	AV07441-AS	u*Uf* ^u uuUfg(aUNA)auuuUfuUfuUfuua* ^a *c	2135
AV07442	AV07442-SS	g* ^a * ^u *aaauaAfaCfaUfuca* ^a *a	1991	AV07442-AS	u*Uf* ^u uuUfu(gUNA)auuuUfuUfuUfuua* ^u *c	2136

Table 3 shows certain chemically modified MAPT RNAi agent antisense strand and sense strand sequences of the invention. In some embodiments of methods of the invention, RNAi agents shown in Table 3 are administered to a cell and/or subject. In some embodiments of methods of the invention, a RNAi agent with a polynucleotide sequence shown in Table 3 is administered to a subject. In some embodiments of the invention an RNAi agent administered to a subject comprises is a duplex identified in a row in Table 3, column one and includes the sequence modifications

and/or delivery compound show in the sense and antisense strand sequences in the same row in Table 3, columns three and six, respectively. The sequences were used in certain *in vivo* testing studies described elsewhere herein. In some embodiments of methods of the invention, a sequence shown in Table 3 may be attached to (also referred to herein as “conjugated to”) a compound for delivery, a non-limiting example of which is a GalNAc-containing compound, with a delivery compound identified in Table 3 as “GLX-n” on sense strands in column three. As used herein, “GLX-n” is used to represent either a “GLS-n*” or a GLO-n” delivery compound (“X” can be either “S” or “O”) and GLX-0 can be any of the “GLS-n*” and “GLO-n” delivery compounds that can be attached to 3'-end of oligonucleotide during synthesis. As used herein and shown in Table 3, “GLX-n” is used to indicate the attached GalNAc-containing compound is any one of compounds GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16, the structure of each of which is provided elsewhere herein. One skilled in the art will be able to prepare and use a dsRNA compound of the invention in which the attached delivery compound is one of GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16. Column one of Table 3 provides a Duplex AD# assigned to the duplex of the sense and antisense sequences in that row of the table. For example, Duplex AD# AD01093 is the duplex of sense strand SEQ ID NO: 1393 and antisense strand SEQ ID NO: 1441. Each line in Table 3 provides a sense strand and an antisense strand, and discloses the duplex of the sense and antisense strands shown. The “Sense strand SS#” in Table 3 column two is the assigned identifier for the Sense Sequence (including modifications) shown column 3 in the same row. The “Antisense strand AS#” in Table 3 column five is the assigned identifier for the Antisense sequence (including modifications) shown in column six. An identifier for certain attached GalNAc-containing “GLO-n” or “GLS-n*” compounds is shown as GLS-5*, GLS-15* or GLX-0, and it will be understood that another of the “GLO-n” or “GLS-n*” compounds may be substituted for the compound shown as GLO-0, with the resulting compound included in an embodiment of a method and/or a composition of the invention.

Table 3 provides chemically modified MAPT RNAi agent antisense strand and sense strand sequences. All sequences shown 5' to 3'. The sequences were used in certain in vivo testing studies described elsewhere herein. A delivery molecule used in the in vivo studies is indicated as “GL-O-n” or “GL-S-n” at the 3'-end or 5'-end of each sense strand.

Duplex AD#	Sense strand SS#	Sense Sequence	SEQ ID NO	Antisense strand AS#	Antisense Sequence	SEQ ID NO
AD01564	AD01564-SS	(GL-S-15*)(imann*)cunucgaugUfgAfuGfagauc*a*(imann)	1485	AD01564-AS	u*Gf*aucuUfecaUfcaCfuUfega*a*g	1541
AD01565	AD01565-SS	(GL-S-15*)(imann*)cacacggaCfgyCfuGfgcucgaa*a*(imann)	1486	AD01565-AS	u*Uf*ucAfgy(gUNA)ccaGfegUfCfgyg*u*g	1542
AD01566	AD01566-SS	(GL-S-15*)(imann*)ggcgaucaCfaAfaAfaagcaa*a*(imann)	1487	AD01566-AS	u*Uf*uggcUfuuuUfugUfcaAfueg*c*c	1543
AD01567	AD01567-SS	(GL-S-15*)(imann*)cgcgcucaUfgyGfuAfaacgaa*a*(imann)	1488	AD01567-AS	u*Uf*ucguUfuucCfaUfcaAfec*c*g	1544
AD01568	AD01568-SS	(GL-S-15*)(imann*)gcugcguaAfcCfuCfcaanauc*a*(imann)	1489	AD01568-AS	u*Gf*auuuUfegacFgyUfcaAfeca*a*g	1545
AD01569	AD01569-SS	(GL-S-15*)(imann*)gugcguaaCfcaUfcafaanauc*a*(imann)	1490	AD01569-AS	u*Uf*gaauUfugeAfgyUfuCfacc*a*c	1546
AD01570	AD01570-SS	(GL-S-15*)(imann*)gacucuccaAfaAfuCfagcggauc*a*(imann)	1491	AD01570-AS	u*Af*ucCfca(cUNA)ugcaUfuUfGfGfagug*u*c	1547
AD01571	AD01571-SS	(GL-S-15*)(imann*)guuagcaAfcAfuCfcaucaaa*a*(imann)	1492	AD01571-AS	u*Uf*aucaUfegauUfguUfgyCfcaaa*a*c	1548
AD01572	AD01572-SS	(GL-S-15*)(imann*)gcagcgugAfaGfuAfaauncg*a*(imann)	1493	AD01572-AS	u*Cf*agauUfuuaCfuCfuCfcaAfcu*a*g	1549
AD01573	AD01573-SS	(GL-S-15*)(imann*)caaguuaaAfuCfuGfagaaucg*a*(imann)	1494	AD01573-AS	u*Af*gcuuCfucaCfauUfuUfacu*u*g	1550
AD01574	AD01574-SS	(GL-S-15*)(imann*)gcugagaaGfcaUfuGfacuucaa*a*(imann)	1495	AD01574-AS	u*Uf*ugaaGfucaAfycUfuCfuca*a*g	1551
AD01575	AD01575-SS	(GL-S-15*)(imann*)gcagagucCfaGfuCfagaauu*a*(imann)	1496	AD01575-AS	u*Af*aucuUfegacCfugGfcaCfucuu*a*g	1552
AD01576	AD01576-SS	(GL-S-15*)(imann*)cgcgagagAfaAfuAfaaagaauc*a*(imann)	1497	AD01576-AS	u*Af*aucuUfegacCfugGfcaCfucuu*a*g	1553
AD01577	AD01577-SS	(GL-S-15*)(imann*)gucacuaaAfcCfuGfcauuuug*a*(imann)	1498	AD01577-AS	u*Af*caaaAfycagCfgyUfaAfgyg*a*c	1554
AD01578	AD01578-SS	(GL-S-15*)(imann*)cgacuuaaAfaAfuCfagugaaucg*a*(imann)	1499	AD01578-AS	u*Cf*aucaCfugauUfuUfgyAfagu*a*c	1555
AD01579	AD01579-SS	(GL-S-15*)(imann*)gagagcaaaAfuUfuCfauucucg*a*(imann)	1500	AD01579-AS	u*Gf*aaagAfugaaAfaUfuGfcauc*u*c	1556
AD01580	AD01580-SS	(GL-S-15*)(imann*)cgcuacacAfgyUfuCfcauuuug*a*(imann)	1501	AD01580-AS	u*Af*caaaGfagaaAfcuGfgyUfuag*c*g	1557
AD01581	AD01581-SS	(GL-S-15*)(imann*)ggcgauuugAfgyUfuCfcauuuug*a*(imann)	1502	AD01581-AS	u*Af*caaaUfecaAfcuAfcAfacu*c*c	1558
AD01582	AD01582-SS	(GL-S-15*)(imann*)gcugcuuaaUfgyCfuUfegauuca*a*(imann)	1503	AD01582-AS	u*Uf*gaauCfcaagCfcaUfaAfaca*a*g	1559
AD01583	AD01583-SS	(GL-S-15*)(imann*)gacucgcaCfuGfuUfegcuuaa*a*(imann)	1504	AD01583-AS	u*Uf*uaaaGfcaagCfagUfcaAfgyg*u*c	1560
AD02147	AD02147-SS	(GL-S-15*)(imann*)gagcguaaGfuAfaAfugcaaaucg*a*(imann)	1505	AD02147-AS	u*Cf*uuugCfuuuuAfcUfgyAfcca*u*c	1561
AD02148	AD02148-SS	(GL-S-15*)(imann*)cacuguaaGfcaUfcaacaaucg*a*(imann)	1506	AD02148-AS	u*Uf*uuugUfcaucGfcaUfuCfcaag*u*g	1562
AD02149	AD02149-SS	(GL-S-15*)(imann*)gaaaggaUfgyAfcAfcaaaagc*a*(imann)	1507	AD02149-AS	u*Gf*cuuuUfuuguCfaUfcaGfcau*c*g	1563
AD02150	AD02150-SS	(GL-S-15*)(imann*)ggugcucaaUfaGfuCfuacaacg*a*(imann)	1508	AD02150-AS	u*Gf*uuugUfagacUfaUfuUfgyca*c*c	1564

AD02151	AD02151-SS	(GL-S-15*)(imann*) ² g ² uug ² gcaAfcAfuCfcaucaaa* ² *(imann)	1509	AD02151-AS	u*Uf* ² aug ² Uf ² ggauf ² fuUf ² gCfcau ² * ² a ² c	1565
AD02152	AD02152-SS	(GL-S-15*)(imann*) ² cug ² gcauAfaAfaUf ² fcug ² gaa* ² *(imann)	1510	AD02152-AS	u*Uf* ² uc ² Afcgauf ² fuAfcUf ² uc ² * ² a ² g	1566
AD02153	AD02153-SS	(GL-S-15*)(imann*) ² gag ² uaaAfuCfuGfag ² gaa ² * ² *(imann)	1511	AD02153-AS	u*Af* ² gcuuf ² ucAfuUfuUf ² acu* ² u* ² g	1567
AD02154	AD02154-SS	(GL-S-15*)(imann*) ² gag ² uaaAfuUf ² gAfcag ² cuu* ² *(imann)	1512	AD02154-AS	u*Af* ² agcuUf ² ucaAfaUfuUf ² acu* ² u* ² c	1568
AD02155	AD02155-SS	(GL-S-15*)(imann*) ² cuaaauUf ² gAfcAfcag ² cuu* ² *(imann)	1513	AD02155-AS	u*Uf* ² caagCfuucCfaGfuUfuuu* ² a ² g	1569
AD02156	AD02156-SS	(GL-S-15*)(imann*) ² ggaug ² cuGfaCfuUf ² caug ² ac* ² *(imann)	1514	AD02156-AS	u*Gf* ² ucCfu(uUNA)g ² aagUf ² cAfaGfcau* ² c ² c	1570
AD02157	AD02157-SS	(GL-S-15*)(imann*) ² ggaug ² caGfaGfuCfcaug ² ac* ² *(imann)	1515	AD02157-AS	u*Uf* ² c ² gAfc(uUNA)g ² gaUf ² cUf ² gUf ² cu* ² u* ² c	1571
AD02158	AD02158-SS	(GL-S-15*)(imann*) ² gug ² gag ² caGfuGfuGfcaaa ² * ² *(imann)	1516	AD02158-AS	u*Uf* ² uuuuUf ² ccacAfcUf ² cUf ² cu* ² a ² c	1572
AD02159	AD02159-SS	(GL-S-15*)(imann*) ² gaaaaAfaAfuAfaug ² ac ² * ² *(imann)	1517	AD02159-AS	u*Gf* ² g ² gUf ² c(aUNA)uuauUf ² cUfuUfuuu* ² u* ² c	1573
AD02160	AD02160-SS	(GL-S-15*)(imann*) ² gug ² guuaUf ² cAfcUf ² haacug ² * ² *(imann)	1518	AD02160-AS	u*Cf* ² a ² gguUf ² aguf ² GfaUfuAfaac ² * ² a* ² c	1574
AD02161	AD02161-SS	(GL-S-15*)(imann*) ² gaucacuAfaCfcUf ² cuuuu ² g* ² *(imann)	1519	AD02161-AS	u*Cf* ² aaacGfcaug ² UfuAfaGfu ² ga* ² u* ² c	1575
AD02162	AD02162-SS	(GL-S-15*)(imann*) ² gcaucuuaCfcUf ² gCfuuuu ² guc* ² *(imann)	1520	AD02162-AS	u*Gf* ² acaaAfagaGfuUfuAfa ² gu* ² g ² c	1576
AD02163	AD02163-SS	(GL-S-15*)(imann*) ² gcu ² cg ² g ² AfcUfuCfaaauca* ² * ² (imann)	1521	AD02163-AS	u*Uf* ² g ² auUf ² ugaGfuCfcCfag ² * ² c ² g	1577
AD02164	AD02164-SS	(GL-S-15*)(imann*) ² gaag ² gcaAfaUfuUf ² caucuu* ² *(imann)	1522	AD02164-AS	u*Af* ² aagUf ² gaauUfuUf ² gCfu ² cu* ² u* ² c	1578
AD02165	AD02165-SS	(GL-S-15*)(imann*) ² gag ² gcaAfuUfuCfaucuu ² c* ² *(imann)	1523	AD02165-AS	u*Gf* ² aaagAfu ² gaAfuUfuGf ² cu ² * ² u* ² c	1579
AD02166	AD02166-SS	(GL-S-15*)(imann*) ² ggag ² caauUfuUf ² cAfcuuc ² * ² *(imann)	1524	AD02166-AS	u*Gf* ² gaagAfu ² gaAfaUfuUf ² gcu* ² c ² c	1580
AD02167	AD02167-SS	(GL-S-15*)(imann*) ² cag ² caauUfuCfaUfcauuca* ² *(imann)	1525	AD02167-AS	u*Uf* ² g ² gaAfagaAfaAfuUf ² guc* ² u* ² g	1581
AD02168	AD02168-SS	(GL-S-15*)(imann*) ² ggcaauUf ² cAfuCfuucca* ² *(imann)	1526	AD02168-AS	u*Uf* ² u ² ggaAfagaGfaAfaUfu ² guc* ² c ² c	1582
AD02169	AD02169-SS	(GL-S-15*)(imann*) ² ccaauuUf ² cAfcUf ² fuuccaa* ² *(imann)	1527	AD02169-AS	u*Uf* ² u ² ggAfagaUf ² gAfa ² fuuu* ² g ² c	1583
AD02170	AD02170-SS	(GL-S-15*)(imann*) ² gaaauucAfuCfuUf ² ccaa ² * ² *(imann)	1528	AD02170-AS	u*Af* ² uuugGfaagAfuGfa ² fauu* ² u* ² c	1584
AD02171	AD02171-SS	(GL-S-15*)(imann*) ² gaaauucaUf ² cUfuUf ² ccaa ² * ² *(imann)	1529	AD02171-AS	u*Af* ² auuuUf ² gaagAfaUf ² gAfa ² u* ² u* ² c	1585
AD02172	AD02172-SS	(GL-S-15*)(imann*) ² gaaauucAfuUfuCfcaauug* ² *(imann)	1530	AD02172-AS	u*Cf* ² aauUf ² ggaAf ² gAfuGfaa ² * ² u* ² c	1586
AD02173	AD02173-SS	(GL-S-15*)(imann*) ² guucauUfuCfcAfaauug ² * ² *(imann)	1531	AD02173-AS	u*Af* ² ucauUfuug ² AfaAfa ² gAfu ² ga* ² a* ² c	1587
AD02174	AD02174-SS	(GL-S-15*)(imann*) ² ggu ² g ² g ² Uf ² gAfa ² faaau* ² *(imann)	1532	AD02174-AS	u*Af* ² uuuuAfuacUf ² gGfcCfca ² * ² c ² g	1588
AD02175	AD02175-SS	(GL-S-15*)(imann*) ² ggg ² g ² g ² Uf ² gAfa ² faaau* ² *(imann)	1533	AD02175-AS	u*Af* ² auauUfuauUf ² gCfuAfa ² g ² c* ² c ² c	1589
AD02176	AD02176-SS	(GL-S-15*)(imann*) ² gag ² caAfaGf ² gAfuug ² aa* ² *(imann)	1534	AD02176-AS	u*Uf* ² u ² ucaAfaucUfuUf ² gUf ² guc* ² u* ² c	1590
AD02177	AD02177-SS	(GL-S-15*)(imann*) ² cauuug ² aaAfcUfuGf ² gug ² u ² * ² *(imann)	1535	AD02177-AS	u*Af* ² acacAfcaAfuUfuCfaa ² * ² u* ² g	1591
AD02178	AD02178-SS	(GL-S-15*)(imann*) ² ggcuacCfaGfuUf ² cuuug* ² *(imann)	1536	AD02178-AS	u*Cf* ² aaagAfgaUf ² gGfuUf ² gac ² * ² c* ² g	1592
AD01562	AD01562-SS	u* ² g* ² caa(Ahd)Uf ² gCfuUf ² caacca(L96)	1537	AD01562-AS	(Vpu*)Uf* ² g ² (dU)u(Tgn)g ² agacUf ² afuug ² ca* ² c* ² a	1593
AD01563	AD01563-SS	u* ² g* ² gaauUf ² afGfuuuuucac(L96)	1538	AD01563-AS	(Vpu*)Gf* ² aguAfaUf ² afacuuUf ² afuucca* ² a* ² a	1594

AD01562-1	AD01562-1-SS	(GL.S-15*) (imann*) ugc aaaua Gfu Cfu Afcaaacca* a* (imann)	1539	AD01562-1-AS	u* Uf* ugcuuUfguagAfcUfaUfhuug* c* a	1595
AD01563-1	AD01563-1-SS	(GL.S-15*) (imann*) ugc aaaua AfiaGfuUfauuacuc* a* (imann)	1540	AD01563-1-AS	u* Gf* aguaAfuacUfuUfaUfuuc* c* a	1596
AD02754	AD02754-SS	(GL.S-15*) g* ugc ugcucCfaGfuAfiaagucca* a* (invab)	1597	AD02754-AS	u* Uf* ugcUfuuaacUfgAfccfiauug* c* c	1718
AD02755	AD02755-SS	(GL.S-15*) g* ugc ugcuaAfiaAfiaGfcaagucca* a* (invab)	1598	AD02755-AS	u* Gf* ucUfu(uUNA) guuuUfuAfcUfguac* c* c	1719
AD02756	AD02756-SS	(GL.S-15*) c* ugc ugcuaAficCfGfuAfuugcaaa* a* (invab)	1599	AD02756-AS	u* Uf* ugcUfcaugCfuUfcCfagu* c* g	1720
AD02757	AD02757-SS	(GL.S-15*) g* ggc ugc ugcAfuGfuCfcaaaag* a* (invab)	1600	AD02757-AS	u* Cf* uuuuUfhuugCfuCfGcfhuuc* c* c	1721
AD02758	AD02758-SS	(GL.S-15*) g* agc ugc ugcAfcaAfiaaguccca* a* (invab)	1601	AD02758-AS	u* Uf* ggcUfuuuuGfuCfuUfgec* u* c	1722
AD02759	AD02759-SS	(GL.S-15*) g* ggc ugc ugcAfiaAfiaaguccca* a* (invab)	1602	AD02759-AS	u* Uf* ugcUfuuuuUfgUfcAfucg* c* c	1723
AD02760	AD02760-SS	(GL.S-15*) g* ugc ugc ugcCfuGfuGfagaaacu* a* (invab)	1603	AD02760-AS	u* Af* gguuCfucagUfgGfagfcccg* a* c	1724
AD02761	AD02761-SS	(GL.S-15*) g* ugc ugc ugcAfiaGfuGfuuaaca* a* (invab)	1604	AD02761-AS	u* Uf* ugUfa(gUNA) acuaUfuUfgCfaca* c* c	1725
AD02762	AD02762-SS	(GL.S-15*) c* ugc ugc aaAfiaUfgUfcuacaad* a* (invab)	1605	AD02762-AS	u* Uf* ugc ugcAfcauAfuUfuCfcaac* a* g	1726
AD02763	AD02763-SS	(GL.S-15*) c* ugc aaauAfguUfcUfcaaac* a* a* (invab)	1606	AD02763-AS	u* Gf* guUfu(gUNA) uagacCfuAfuUfugc* a* g	1727
AD02764	AD02764-SS	(GL.S-15*) g* gca aaauCfuCfuAfcaaacca* a* a* (invab)	1607	AD02764-AS	u* Uf* ggcUfu(uUNA) guagAfcUfaUfhuug* c* c	1728
AD02765	AD02765-SS	(GL.S-15*) g* aa ugc ugc ugcCfuAfcaaacguu* a* (invab)	1608	AD02765-AS	u* Af* acUfg(gUNA) juuugUfagGfagCfuau* u* c	1729
AD02766	AD02766-SS	(GL.S-15*) g* aa ugc ugc ugcAfcaAfcaaacguu* a* (invab)	1609	AD02766-AS	u* Cf* aaCfu(gUNA) guuuGfuAfgaAfcau* u* c	1730
AD02767	AD02767-SS	(GL.S-15*) g* aa ugc ugc ugcAfcaAfcaaacguu* a* (invab)	1610	AD02767-AS	u* Uf* caacUfgguuUfgUfaGfiau* a* c	1731
AD02768	AD02768-SS	(GL.S-15*) g* aa ugc ugc ugcAfcaAfcaaacguu* a* (invab)	1611	AD02768-AS	u* Uf* caGfg(uUNA) caacUfgGfuUfugu* a* c	1732
AD02769	AD02769-SS	(GL.S-15*) c* ugc ugc ugcAfiaAfiaauncu* a* (invab)	1612	AD02769-AS	u* Uf* guUfg(cUNA) ceuaUfgAfgcCfcaac* a* g	1733
AD02770	AD02770-SS	(GL.S-15*) c* ugc ugc ugcAfiaAfiaauncu* a* (invab)	1613	AD02770-AS	u* Gf* auguUfgcuAfiaUfgAfgec* a* g	1734
AD02771	AD02771-SS	(GL.S-15*) c* cucauuaficCfAfcauucca* a* a* (invab)	1614	AD02771-AS	u* Af* ugcGfa(uUNA) guugCfcUfaAfuga* g* g	1735
AD02772	AD02772-SS	(GL.S-15*) g* ugc ugc ugcAfiaAfiaauna* a* a* (invab)	1615	AD02772-AS	u* Uf* uauGfuAfuGfuUfuGficc* a* c	1736
AD02773	AD02773-SS	(GL.S-15*) g* aa ugc ugc ugcAfiaAfiaauncu* a* (invab)	1616	AD02773-AS	u* Cf* cuGfg(uUNA) juuaGfuUfgGfauug* u* c	1737
AD02774	AD02774-SS	(GL.S-15*) g* aa ugc ugc ugcAfiaAfiaauncu* a* (invab)	1617	AD02774-AS	u* Cf* agAfu(uUNA) juuaUfuCfAfccu* g* c	1738
AD02775	AD02775-SS	(GL.S-15*) g* aa ugc ugc ugcAfiaAfiaauncu* a* (invab)	1618	AD02775-AS	u* Uf* caGfa(uUNA) juuaCfuUfcCfacc* u* c	1739
AD02776	AD02776-SS	(GL.S-15*) g* aa ugc ugc ugcAfiaAfiaauncu* a* (invab)	1619	AD02776-AS	u* Cf* ucAf(gUNA) juuuAfcUfuCfcaac* c* c	1740
AD02777	AD02777-SS	(GL.S-15*) g* aa ugc ugc ugcAfiaAfiaauncu* a* (invab)	1620	AD02777-AS	u* Uf* cucaGfauuUfaCfuUfeca* c* g	1741
AD02778	AD02778-SS	(GL.S-15*) g* aa ugc ugc ugcAfiaAfiaauncu* a* (invab)	1621	AD02778-AS	u* Cf* uuCfu(cUNA) aguuUfuUfaCfhuuc* c* c	1742
AD02779	AD02779-SS	(GL.S-15*) g* cuca ugc ugc ugcAfiaAfiaauncu* a* (invab)	1622	AD02779-AS	u* Uf* ugc aaGfucaGfcUfuCfhuca* g* c	1743
AD02780	AD02780-SS	(GL.S-15*) c* aa ugc ugc ugcAfiaAfiaauncu* a* (invab)	1623	AD02780-AS	u* Uf* guCfc(uUNA) ugc aaGfuCfuAfiaGfcu* u* g	1744

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AD02781	AD02781-SS	(GL-S-15*)g*cagugucFtaCftuCFtaagaua*a*(invab)	1624	AD02781-AS	u*A*faucnuUfcagucUfGfGfaCftucU*g*c	1745
AD02782	AD02782-SS	(GL-S-15*)g*ggcaumCfcUfuUfugauucU*a*(invab)	1625	AD02782-AS	u*A*fgauuCFaaatGfGfAfaUfugc*c*c	1746
AD02783	AD02783-SS	(GL-S-15*)g*cacaagaGfgAfuUfugaacu*a*(invab)	1626	AD02783-AS	u*A*fguuuCFaaauCfcUfuUfguu*g*g	1747
AD02784	AD02784-SS	(GL-S-15*)g*aaacaaGfuUfuUfgaaacu*a*(invab)	1627	AD02784-AS	u*A*aguuUfcaauUfcCfuUfuguu*a*c	1748
AD02785	AD02785-SS	(GL-S-15*)g*uaacagUfuCfuCftuuuaa*a*(invab)	1628	AD02785-AS	u*U*uaaAfagagAfACfuGfguu*a*c	1749
AD02786	AD02786-SS	(GL-S-15*)g*accguuChuCfuUfugaagU*a*(invab)	1629	AD02786-AS	u*CF*cuuaCFaaGfGfAfaCftugU*c	1750
AD02787	AD02787-SS	(GL-S-15*)g*ccaguuUfcUfuUfugaagU*a*(invab)	1630	AD02787-AS	u*U*fcuuAfcaaaGfGfAfaCfcugU*c	1751
AD02788	AD02788-SS	(GL-S-15*)g*guuucUfuGfuAfagacuU*a*(invab)	1631	AD02788-AS	u*A*fgucCfuacAfAafGfAfgaU*c*c	1752
AD02789	AD02789-SS	(GL-S-15*)g*auacugaCfGfuGfAaauaa*a*(invab)	1632	AD02789-AS	u*U*uaauUfcaacCfcUfcAfguaa*U*c	1753
AD02790	AD02790-SS	(GL-S-15*)c*agguugaAfaUfuAfagggaaU*a*(invab)	1633	AD02790-AS	u*CF*unCfc(cUNA)uuaUfuUfcAfccu*U*g	1754
AD02791	AD02791-SS	(GL-S-15*)g*caucucAfGUfuCfcaucuu*a*(invab)	1634	AD02791-AS	u*A*fgugUfGfgaaCfuGfGfaguU*g*c	1755
AD02792	AD02792-SS	(GL-S-15*)g*uaugguUfuCfuGfcuuuuU*a*(invab)	1635	AD02792-AS	u*A*acaaGfGcagAfAafAfccu*a*c	1756
AD02793	AD02793-SS	(GL-S-15*)g*guuucCfcUfuGfuugacuU*a*(invab)	1636	AD02793-AS	u*A*fgucAfcaaaGfGfGfAfaa*c*c	1757
AD02794	AD02794-SS	(GL-S-15*)c*cagucugaAfcAfuAfuaacaaU*a*(invab)	1637	AD02794-AS	u*CF*uaugUfauuGfuUfcAfGcuU*g*g	1758
AD02795	AD02795-SS	(GL-S-15*)g*uguaugUfGUfuUfugucguU*a*(invab)	1638	AD02795-AS	u*A*fgagCfaauCfcAfACfuacU*a*c	1759
AD02796	AD02796-SS	(GL-S-15*)g*gauguuGfAUfuUfugucuuU*a*(invab)	1639	AD02796-AS	u*A*fgagAfcaauUfcCfaAfcua*c*c	1760
AD02797	AD02797-SS	(GL-S-15*)c*uauguuGfAUfuGfucguuuU*a*(invab)	1640	AD02797-AS	u*A*aaaaGfcaaaAfACfuAfcuU*a*g	1761
AD02798	AD02798-SS	(GL-S-15*)g*uggaauuGfuCfuGfuuaugU*a*(invab)	1641	AD02798-AS	u*G*caaaAfcaagAfACfuAfuccU*a*c	1762
AD02799	AD02799-SS	(GL-S-15*)c*gaauuGfuCfuUfuaucuU*a*(invab)	1642	AD02799-AS	u*A*agcaUfaaacAfGfAfCAfaau*c*g	1763
AD02800	AD02800-SS	(GL-S-15*)g*uuugucUfuUfuAfugcuugU*a*(invab)	1643	AD02800-AS	u*CF*caAfG(cUNA)uaaaAfCfGfAfcaaa*a*c	1764
AD02801	AD02801-SS	(GL-S-15*)g*ugucguUfuAfuGfuuugaaU*a*(invab)	1644	AD02801-AS	u*A*fguuccaAfGcuuAfAafAfGacU*a*c	1765
AD03099	AD03099-SS	g*U*ggaaGfuAfAfAfAfuUhdxcugaaU*a*a	1645	AD03099-AS	(Vpu*)Uf*ucUfaguuuuAfCufuuccac*c*U	1766
AD03099-1-1	AD03099-1-SS	(GL-S-15*)(invab)g*U*ggaaGfuAfAfAfauucugaaU*a*(invab)	1646	AD03099-1-AS	(Vpu*)Uf*ucUfaguuuuAfCufuuccac*c*U	1767
AD03100	AD03100-SS	c*g*caugGfuCfAfGfuuaagcaaaU(96)	1647	AD03100-AS	(Vpu*)Uf*ugcUfuUfuUfucugAfCfGfagcU*a*g	1768
AD03148	AD03148-SS	(GL-S-15*)g*aaugucUfuUfGfGfucagaaU*a*(invab)	1648	AD03148-AS	u*U*fg*uaauGfcaaaUfGfGfAfGcuU*a*c	1769
AD03149	AD03149-SS	(GL-S-15*)g*ugucgaUfGfuCfuuaaaU*a*(invab)	1649	AD03149-AS	u*U*fuUfAf(cUNA)ugacCfaUfGfGfagU*c*c	1770
AD03150	AD03150-SS	(GL-S-15*)g*ucgcuugGfuCfuGfuuaagU*a*(invab)	1650	AD03150-AS	u*G*fcUfu(cUNA)acugAfCfAfuGfgU*a*c	1771
AD03151	AD03151-SS	(GL-S-15*)g*cgaugUfCAfGUfaaaagcaU*a*(invab)	1651	AD03151-AS	u*U*fguuUfcauGfACfCAfugcU*g*c	1772
AD03152	AD03152-SS	(GL-S-15*)c*caugucAfGUfaAfagcaaaU*a*(invab)	1652	AD03152-AS	u*U*fu*nuGfc(cUNA)uuaCfuGfGfCfcauU*g*g	1773
AD03153	AD03153-SS	(GL-S-15*)g*ugucagUfaAfAfagcaagU*a*(invab)	1653	AD03153-AS	u*U*fcUfu(cUNA)cuuuUfACfuGfaccU*a*c	1774

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AD03154-	AD03154-SS	(GL.S-1.5*)g*caagugAfCChuCfcaagugu*a*(invab)	1654	AD03154-AS	u*A*f*caCfu(uUNA)gugugFhuCfaCfcwu*g*g	1775
AD03155	AD03155-SS	(GL.S-1.5*)g*gcuccaAfCChuCfhuugucca*a*(invab)	1655	AD03155-AS	u*U*f*gaCfc(cUNA)acacUfuGfGAFfgu*a*c*c	1776
AD03156	AD03156-SS	(GL.S-1.5*)g*ccuccaGfuCChuCfhuugucca*u*(invab)	1656	AD03156-AS	u*A*f*auGfa(gUNA)ccacAfCfUfuGfGag*g*c	1777
AD03157	AD03157-SS	(GL.S-1.5*)g*uccaaguCfuGfGfCfucuuag*a*(invab)	1657	AD03157-AS	u*C*f*uaauGfagccAfCfAfCfhuug*a*c	1778
AD03158	AD03158-SS	(GL.S-1.5*)g*gcuccuuAfGfGfCfAcucca*a*(invab)	1658	AD03158-AS	u*U*f*gGAfu(gUNA)uuugCfuAfAfUfgag*c*g	1779
AD03159	AD03159-SS	(GL.S-1.5*)g*cauuagCfAfCfCfucca*a*(invab)	1659	AD03159-AS	u*U*f*gaUfg(gUNA)auguUfgCfcUfau*g*c	1780
AD03160	AD03160-SS	(GL.S-1.5*)g*ggcaacUfCChUfcauaac*a*(invab)	1660	AD03160-AS	u*G*f*uuUfa(uUNA)gaugGfaUfgUfugc*c*c	1781
AD03161	AD03161-SS	(GL.S-1.5*)c*caacauCfaUfCfAfuaacca*a*(invab)	1661	AD03161-AS	u*U*f*gUfu(uUNA)auguUfgGfaUfguu*g*g	1782
AD03162	AD03162-SS	(GL.S-1.5*)g*ugagaCfuUfGfAfucuaag*a*(invab)	1662	AD03162-AS	u*C*f*uuGfa(aUNA)gucaAfGfCfuUfCuc*a*c	1783
AD03163	AD03163-SS	(GL.S-1.5*)g*uccucgcAfGfUfuCfuguuau*a*(invab)	1663	AD03163-AS	u*A*f*uuuaCfCgaCfuGfCfGfagge*a*c	1784
AD03164	AD03164-SS	(GL.S-1.5*)g*aaugguUfaAfCfAcuuac*a*(invab)	1664	AD03164-AS	u*G*f*uuuaGfugauUfaAfCfCfau*u*c	1785
AD03165	AD03165-SS	(GL.S-1.5*)g*aaucacuUfaUfCfCuuac*c*a*(invab)	1665	AD03165-AS	u*G*f*guuaAfugauUfaAfCfCfcau*a*u*c	1786
AD03166	AD03166-SS	(GL.S-1.5*)g*aaucacuUfaAfCfCfuguuu*a*(invab)	1666	AD03166-AS	u*A*f*aaAfG(cUNA)agguUfaAfGfUfgau*u*c	1787
AD03167	AD03167-SS	(GL.S-1.5*)g*ucggacUfuCfaAfacaugu*a*(invab)	1667	AD03167-AS	u*A*f*cugaUfuuuuAfGfGfCfCccg*a*c	1788
AD03168	AD03168-SS	(GL.S-1.5*)c*acuucaAfafUfCfAfgugaug*a*(invab)	1668	AD03168-AS	u*C*f*caUf(cUNA)cugaUfuUfuGfagge*a*u*g	1789
AD02148-	AD02148-1-SS			AD02148-1-		
1	SS	(GL.S-1.5*)c*acuggaCfCfUfUfgacaana*a*(invab)	1669	AS	(Vpu*)Uf*uuugUfcaucGfCfUfuCfCag*u*u*g	1790
AD02757-	AD02757-1-SS	(GL.S-1.5*)g*ggagagCfuGfGfCfacaaga*a*(invab)	1670	AD02757-1-AS	(Vpu*)Cf*uuuuUfugucAfCfCfCfuc*c*c	1791
AD02149-	AD02149-1-SS	(GL.S-1.5*)g*gaagcguUfgAfCfAfacaagc*a*(invab)	1671	AD02149-1-AS	(Vpu*)Gf*cuuuUfuuuGfhuCfaUfCfCcuu*c*c*g	1792
AD02758-	AD02758-1-SS			AD02758-1-		
1	SS	(GL.S-1.5*)g*agcgauGfCfAfAfacaagcca*a*(invab)	1672	AS	(Vpu*)Uf*ggcUfuuuGfhuCfaUfCfCg*c*u*c	1793
AD02759-	AD02759-1-SS	(GL.S-1.5*)g*gcgaugCfAfAfAfagcca*a*(invab)	1673	AD02759-1-AS	(Vpu*)Uf*uggcUfuuuUfgUfCfAfucg*c*c	1794
AD01567-	AD01567-1-SS	(GL.S-1.5*)c*ggcgugUfgGfuAfacaagaa*a*(invab)	1674	AD01567-1-AS	(Vpu*)Uf*ucguUfuuaCfAfUfCfAfgcc*c*c*g	1795
AD02150-	AD02150-1-SS	(GL.S-1.5*)g*guucauUfaGfuCfuacaac*a*(invab)	1675	AD02150-1-AS	(Vpu*)Gf*uuuUfagacUfaUfuUfgca*c*c	1796
AD02764-	AD02764-1-SS	(GL.S-1.5*)g*gaauaCfuCfuAfacaacca*a*(invab)	1676	AD02764-1-AS	(Vpu*)Uf*ggUfu(uUNA)guagAfCfUfaUfuug*c*c	1797

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AD02767-1	AD02767-1-1	(GL.S-1.5*)g*uaugucuaCfaAfaCfcaguu ^a *a*(invab)	1677	AD02767-1-AS	(Vpu*)Uf*caacUf ^g gguUf ^g UfaGfa ^{cu} *a*c	1798
AD02151-1	AD02151-1-SS	(GL.S-1.5*)g*uaugcaAfcAfuCfcacua ^a *a*(invab)	1678	AD02151-1-AS	(Vpu*)Uf*augaf ^g gguGfuUf ^g Cfc ^{ua} *a*c	1799
AD01572-1	AD01572-1-SS	(GL.S-1.5*)g*cagug ^a gAfaGfuAfaa ^u cu ^a *a*(invab)	1679	AD01572-1-AS	(Vpu*)Cf*agauUf ^{ua} acUfuCfcAfc ^u *g*c	1800
AD02153-1	AD02153-1-SS	(GL.S-1.5*)u*aaguaaAfuCfuGfagag ^{cu} *a*(invab)	1680	AD02153-1-AS	(Vpu*)Af*g ^{cu} cuCf ^u acagAfuUfuUfa ^{cu} *u*a	1801
AD02173-1	AD02173-1-SS	(GL.S-1.5*)g*uauc ^u UfuCfcAfaa ^u gu ^a *a*(invab)	1681	AD02173-1-AS	(Vpu*)Af*ua ^a Uf ^u g ^g AfaAf ^g Afu ^g *a*c	1802
AD02782-1	AD02782-1-SS	(GL.S-1.5*)g*ggcaauCfcUfuUf ^u g ^u u ^{cu} *a*(invab)	1682	AD02782-1-AS	(Vpu*)Af*g ^{ua} u ^u Cfaa ^a Cf ^g AfaUfu ^g *c*c	1803
AD02783-1	AD02783-1-SS	(GL.S-1.5*)c*caacaaGf ^g AfuUf ^u g ^{ua} cu ^a *a*(invab)	1683	AD02783-1-AS	(Vpu*)Af*guu ^u Cfaa ^u CfcUfuUf ^g u ^a *g* ^g	1804
AD02784-1	AD02784-1-SS	(GL.S-1.5*)g*aacaa ^g GfuUfuUf ^u g ^{ua} cu ^a *a*(invab)	1684	AD02784-1-AS	(Vpu*)Af*ag ^u uUf ^{ca} aUf ^c CfuUfu ^g *u*c	1805
AD02148-2	AD02148-2-SS	(GL.S-1.5*)c*acug ^g uGfcCfuUf ^g caaa ^a *a*(invab)	1685	AD02148-2-AS	(Phos-4.3*)Uf*uu ^g Uf ^{ca} u ^c GfcUfuCf ^{ag} *u* ^g	1806
AD02757-2	AD02757-2-SS	(GL.S-1.5*)g*ggag ^g cgAfuGfaCfaa ^a ag ^a *a*(invab)	1686	AD02757-2-AS	(Phos-4.3*)Cf*uuuuUf ^u g ^u cAfuCf ^g Cfu ^u *c*c	1807
AD02149-2	AD02149-2-SS	(GL.S-1.5*)c*gaa ^g cgUf ^g AfcAfaa ^a g ^c *a*(invab)	1687	AD02149-2-AS	(Phos-4.3*)Gf*cuuUf ^u g ^u cuCfaUf ^c Gf ^{cu} *c* ^g	1808
AD02758-2	AD02758-2-SS	(GL.S-1.5*)g*ag ^g cu ^g uGfcAfaAfaa ^g cc ^a *a*(invab)	1688	AD02758-2-AS	(Phos-4.3*)Uf*gg ^{cu} UfuuuGfuCfaUf ^c g ^c *u*c	1809
AD02759-2	AD02759-2-SS	(GL.S-1.5*)g*gg ^g au ^g uGfaAfaAfaa ^g cc ^a *a*(invab)	1689	AD02759-2-AS	(Phos-4.3*)Uf*ug ^g cuUfuuuUf ^g Uf ^c Afu ^c *c*c	1810
AD01567-2	AD01567-2-SS	(GL.S-1.5*)c*gg ^g cu ^g uUf ^g GfuAfaa ^g cu ^a *a*(invab)	1690	AD01567-2-AS	(Phos-4.3*)Uf*uc ^g uUfuacCfaUf ^c Af ^g cc*c* ^g	1811
AD02150-2	AD02150-2-SS	(GL.S-1.5*)g*gu ^g caauUfaGfuCfuac ^a ac ^a *a*(invab)	1691	AD02150-2-AS	(Phos-4.3*)Gf*uu ^g Uf ^{ag} acUfaUfuUf ^g ca*c*c	1812
AD02764-2	AD02764-2-SS	(GL.S-1.5*)g*gcaauGfuCfuAfaa ^a cc ^a *a*(invab)	1692	AD02764-2-AS	(Phos-4.3*)Uf*ggUfu(uUNA)guagAfcUfaUf ^u g*c*c	1813
AD02767-2	AD02767-2-SS	(GL.S-1.5*)g*uaug ^u cuAfaAfaCfcaguu ^g *a*(invab)	1693	AD02767-2-AS	(Phos-4.3*)Uf*caacUf ^g gguUf ^g UfaGfa ^{cu} *a*c	1814

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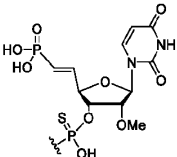
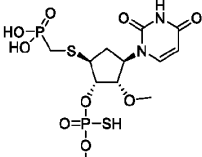
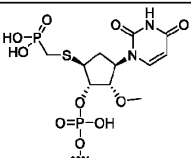
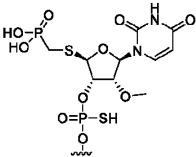
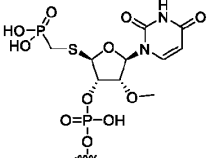
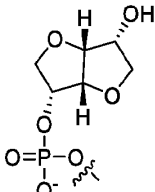
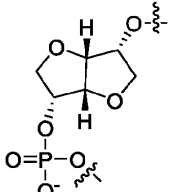
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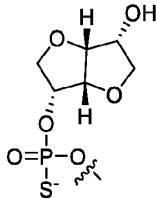
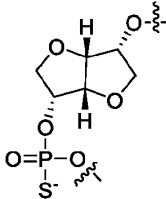
AD02151-2-SS	AD02151-2-SS	(GL-S-15*)g*uuaggcaAfcAfuCfcuacua*a*(invab)	1694	AD02151-2-AS	(Phos-43*)Uf*augauUfggauGfuUfgCfcua*a*c	1815
AD01572-2-SS	AD01572-2-SS	(GL-S-15*)g*cagugugAfaGfuAfaaauug*a*(invab)	1695	AD01572-2-AS	(Phos-43*)Cf*agauUfmuacUfuCfcAfccu*g*c	1816
AD02153-2-SS	AD02153-2-SS	(GL-S-15*)u*aaguanaaAfuCfuGfaagaagcu*a*(invab)	1696	AD02153-2-AS	(Phos-43*)Af*gcuuCfucagAfuUfuUfacu*u*a	1817
AD02173-2-SS	AD02173-2-SS	(GL-S-15*)g*uucauclUfuCfcAfaauugau*a*(invab)	1697	AD02173-2-AS	(Phos-43*)Af*ucauUfuuugAfaAfgAfuiga*a*c	1818
AD02782-2-SS	AD02782-2-SS	(GL-S-15*)g*ggcauuCfcUfuUfuuaucu*a*(invab)	1698	AD02782-2-AS	(Phos-43*)Af*gnauCfaanaGfgAfaUfugc*c*c	1819
AD02783-2-SS	AD02783-2-SS	(GL-S-15*)c*caacaaaGfgAfuUfugaacu*a*(invab)	1699	AD02783-2-AS	(Phos-43*)Af*gunuCfaaanCfcUfuUfguu*g*g	1820
AD02784-2-SS	AD02784-2-SS	(GL-S-15*)g*aacaaagGfaUfuUfgaaacu*a*(invab)	1700	AD02784-2-AS	(Phos-43*)Af*aguuUfcaaaUfcaUfuUfugu*u*c	1821
AD02148-3-SS	AD02148-3-SS	(GL-S-15*)c*acuugaaCfcCfaUfgaacaan*a*(invab)	1701	AD02148-3-AS	(Phos-53*)Uf*uuuuUfcaucGfcUfuCfcag*u*g	1822
AD02757-3-SS	AD02757-3-SS	(GL-S-15*)g*ggagagAfuGfaCfaanaag*a*(invab)	1702	AD02757-3-AS	(Phos-53*)Cf*uuuuUfugucAfuCfGCfuuc*c*c	1823
AD02149-3-SS	AD02149-3-SS	(GL-S-15*)c*gaagcgUfgAfcAfaaagcca*a*(invab)	1703	AD02149-3-AS	(Phos-53*)Gf*cuuuUfuuugCfaUfCfGfcuu*c*g	1824
AD02758-3-SS	AD02758-3-SS	(GL-S-15*)g*agcgauGfcAfaAfaagcca*a*(invab)	1704	AD02758-3-AS	(Phos-53*)Uf*ggcuUfuuuuGfuCfaUfCfcu*u*c	1825
AD02759-3-SS	AD02759-3-SS	(GL-S-15*)g*gcgaugAfaAfaagcca*a*(invab)	1705	AD02759-3-AS	(Phos-53*)Uf*uggcUfuuuuUfgUfCfAfuag*c*c	1826
AD01567-3-SS	AD01567-3-SS	(GL-S-15*)c*ggcgugUfgGfuAfaaagcu*a*(invab)	1706	AD01567-3-AS	(Phos-53*)Uf*ueguUfuaacCfaUfCfAfgcc*c*g	1827
AD02150-3-SS	AD02150-3-SS	(GL-S-15*)g*guugcaalUfaGfuCfuacaaac*a*(invab)	1707	AD02150-3-AS	(Phos-53*)Gf*uuuUfagaacUfaUfuUfgea*c*c	1828
AD02764-3-SS	AD02764-3-SS	(GL-S-15*)g*gcaauuGfuCfuAfaaaca*a*(invab)	1708	AD02764-3-AS	(Phos-53*)Uf*egUfu(uUNa)guagAfcUfaUfuug*c*c	1829
AD02767-3-SS	AD02767-3-SS	(GL-S-15*)g*uaugucuaCfaAfaCfcaguuu*a*(invab)	1709	AD02767-3-AS	(Phos-53*)Uf*caacUfgguuUfgUfaGfacu*a*c	1830
AD02151-3-SS	AD02151-3-SS	(GL-S-15*)g*uuaggcaAfcAfuCfcuacua*a*(invab)	1710	AD02151-3-AS	(Phos-53*)Uf*augauUfggauGfuUfgCfcua*a*c	1831

AD01572-3	AD01572-3-SS	(GLS-15*)g*cagguugGAtaGfuAfaaaucu ^a *(invab)	1711	AD01572-3-AS	(Phos-53*)Cf*agauUfhuacUfuCfcAfcu ^a *g*c	1832
AD02153-3	AD02153-3-SS	(GLS-15*)u ^a *aaguanaaAfuChuGfagaagcu ^a *(invab)	1712	AD02153-3-AS	(Phos-53*)Af*geuuCfueagAfuUfuUfacu ^a *u ^a	1833
AD02173-3	AD02173-3-SS	(GLS-15*)g ^a *uucauUfuCfcAfaaungau ^a *(invab)	1713	AD02173-3-AS	(Phos-53*)Af ^a *ucaUfhuugAfaAf ^a gAfu ^a *a*c	1834
AD02782-3	AD02782-3-SS	(GLS-15*)g ^a *ggcaauCfcUfuUfugauncu ^a *(invab)	1714	AD02782-3-AS	(Phos-53*)Af ^a *gaucCfaaaGf ^a gAfaUfugc ^a *c*c	1835
AD02783-3	AD02783-3-SS	(GLS-15*)c ^a *caacaaGf ^a gAfuUfugaacu ^a *(invab)	1715	AD02783-3-AS	(Phos-53*)Af ^a *guuCfaaauCfcUfuUf ^a uu ^a *g ^a *g	1836
AD02784-3	AD02784-3-SS	(GLS-15*)g ^a *aacaagGfaUfuUfgaacuu ^a *(invab)	1716	AD02784-3-AS	(Phos-53*)Af ^a *aguUfcaaaUfcCfuUfugu ^a *u ^a *c	1837
AD03098-1	AD03098-1-SS	(GLS-15*)(invab*)caGf ^a gUf ^a gAfaGfuAfaAfuCfu ^a *a*(invab)	1717	AD03098-1-AS	(Vpu ^a *)Cf*AfGfAfuUfuUf ^a fcuuCfcAfcUf ^a g ^a *g	1838

L96 is refers to the compound GalNAc3 in Jayaprakash, et al., (2014) J. Am. Chem. Soc., 136, 16958–16961.

Table 4: Abbreviations of nucleotide monomers used in nucleic acid sequence representation. It will be understood that these monomers, when present in an oligonucleotide, are mutually linked by 5'-3'-phosphodiester bonds, and it is understood that when the nucleotide contains a 2'-fluoro modification, then the fluoro replaces the hydroxy at that position of the parent nucleotide (i.e., it is a 2'-deoxy-2'- fluoronucleotide). It will also be understood that the abbreviations correspond to nucleotides which omit the 3'-phosphate when found at the 3'-terminal position (i.e., they are 3'-OH). A skilled artisan will understand that these abbreviations are just identification symbols and are able to determine the linking modes of the nucleotide sequences containing these abbreviations.	
Abbreviations	Nucleotide(s)
A	adenosine-3'-phosphate
C	cytidine-3'-phosphate
G	guanosine-3'-phosphate
T	5-methyluridine-3'-phosphate
U	uridine-3'-phosphate
a	2'-O-methyladenosine-3'-phosphate
c	2'-O-methylcytidine-3'-phosphate
g	2'-O-methylguanosine-3'-phosphate
t	2'-O-methyl-5-methyluridine-3'-phosphate
u	2'-O-methyluridine-3'-phosphate
Af	2'-fluoroadenosine-3'-phosphate
Cf	2'-fluorocytidine-3'-phosphate
Gf	2'-fluoroguanosine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Af*	2'-fluoroadenosine-3'-phosphorothioate
Cf*	2'-fluorocytidine-3'-phosphorothioate
Gf*	2'-fluoroguanosine-3'-phosphorothioate
Tf*	2'-fluoro-5-methyluridine-3'-phosphorothioate
Uf*	2'-fluorouridine-3'-phosphorothioate
a*	2'-O-methyladenosine-3'-phosphorothioate
c*	2'-O-methylcytidine-3'-phosphorothioate
g*	2'-O-methylguanosine-3'-phosphorothioate
t*	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u*	2'-O-methyluridine-3'-phosphorothioate
aUNA	2', 3'-seco-adenosine-3'-phosphate
cUNA	2', 3'-seco-cytidine-3'-phosphate
gUNA	2', 3'-seco-guanosine-3'-phosphate
tUNA	2', 3'-seco-5-methyluridine-3'-phosphate
uUNA	2', 3'-seco- uridine-3'-phosphate
Ahd	2'-O-hexadecyl-adenosine-3'-phosphate
Tgn	Thymidine-glycol nucleic acid(GNA) S-Isomer

dT	2'-deoxythymidine-3'-phosphate	
Vp	Vinyl-phosphate	
Vpu*		
Phos-43*		
Phos-43		
Phos-53*		
Phos-53		
invab	inverted abasic-5'-phosphate. linked to adjacent nucleotide via a substituent at its 3' position (a 3'-3' linkage) when on the 3' end of a strand; linked to adjacent nucleotide via a substituent at its 5' position (a 5'-5' internucleotide linkage) when on the 5' end of a strand, It will also be understood that the abbreviations correspond to invab which omit the 5'-phosphate when found at the 3'-terminal position (i.e., they are 5'-OH)	
invab*	inverted abasic-5'-phosphorothioate. linked to adjacent nucleotide via a substituent at its 3' position (a 3'-3' linkage) when on the 3' end of a strandlinked to adjacent nucleotide via a substituent at its 5' position (a 5'-5' internucleotide linkage) when on the 5' end of a strand, It will also be understood that the abbreviations correspond to invab* which omit the 5'-phosphorothioate when found at the 3'-terminal position (i.e., they are 5'-OH);	
imann	imann when at the end of each strand 	imann when in the middle of each strand 

imann*	isomannide residue- phosphorothioate	
	imann* when at the end of each strand 	imann* when in the middle of each strand 

In certain embodiments of the invention a dsRNA (also referred to herein as a “duplex”) is one disclosed in one of Tables 1-3. Each row in Tables 1-3 discloses a duplex comprising the sequence of the sense strand and the sequence of the antisense strand in that table row. In addition to the duplexes disclosed in Tables 1-3, it will be understood that in some embodiments, a duplex of the invention may include sense and antisense sequences shown in Tables 1-3, that differ by zero, one, two, or three nucleotides shown in a sequence shown in Tables 1-3. Thus, as non-limiting examples, in some embodiments, an antisense strand in a duplex of the invention may be SEQ ID NO: 1542, 1543, 1544, 1545,1546, 1547, or 1548, with zero, one, two, or three different nucleotides than those in SEQ ID:1542, 1543, 1544, 1545,1546, 1547, or 1548 respectively.

It will be understood that the sequence of the sense strand and the sequence of the antisense strand in a duplex of the invention may be independently selected. Thus, a dsRNA of the invention may comprise a sense strand and an antisense strand of a duplex disclosed in a row in Tables 1-3. Alternatively, in a dsRNA of the invention, one or both of the selected sense and antisense strand in the dsRNA may include sequences shown in Tables 1-3 but with one or both of the sense and antisense sequences including 1, 2, 3, or more nucleobase substitutions from the parent sequence. The selected sequences may in some embodiments be longer or shorter than their parent sequence. Thus, dsRNA agents included in the invention can but need not include exact sequences of the sense and antisense pairs disclosed as duplexes in Tables 1-3.

In some embodiments, a 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 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. In some instances, the region of complementarity to the 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. In some embodiments of a dsRNA agent of the invention, the antisense strand of the dsRNA is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments, an antisense strand of a dsRNA agent of the invention is fully complementary to any one of a target region of SEQ

ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments a dsRNA agent includes a sense strand sequence set forth in any one of Tables 1-3, and the sense strand sequence is at least substantially complementary to the antisense strand sequence in the dsRNA agent. In other embodiments, a dsRNA agent of the invention comprises a sense strand sequence set forth in any one of Tables 1-3, and the sense strand sequence is fully complementary to the antisense strand sequence in the dsRNA agent. In some instances, a dsRNA agent of the invention comprises an antisense strand sequence set forth in any one of Tables 1-3. Some embodiments of a dsRNA agent of the invention comprises the sense and antisense sequences disclosed as duplex in any of Tables 1-3. As described herein, it will be understood that the sense and antisense strands in a duplex of the invention may be independently selected.

Mismatches

It is known to skilled in art, mismatches are tolerated for efficacy in dsRNA, especially the mismatches are within terminal region of dsRNA. Certain mismatches tolerate better, for example mismatches with wobble base pairs G:U and A:C are tolerated better for efficacy (Du et al., A systematic analysis of the silencing effects of an active siRNA at all single-nucleotide mismatched target sites. *Nucleic Acids Res.* 2005 Mar 21;33(5):1671-7. Doi: 10.1093/nar/gki312. *Nucleic Acids Res.* 2005;33(11):3698). Some embodiments of methods and compounds of the invention a MAPT dsRNA agent may contain one or more mismatches to the MAPT target sequence. In some embodiments, MAPT dsRNA agent of the invention includes no mismatches. In certain embodiments, MAPT dsRNA agent of the invention includes no more than 1 mismatch. In some embodiments, MAPT dsRNA agent of the invention includes no more than 2 mismatches. In certain embodiments, MAPT dsRNA agent of the invention includes no more than 3 mismatches. In some embodiments of the invention, an antisense strand of a MAPT dsRNA agent contains mismatches to a MAPT target sequence that are not located in the center of the region of complementarity. In some embodiments, the antisense strand of the MAPT dsRNA agent includes 1, 2, 3, 4, or more mismatches that are within the last 5, 4, 3, 2, or 1 nucleotide from one or both of the 5' or 3' end of the region of complementarity. Methods described herein and/or methods known in the art can be used to determine whether a MAPT dsRNA agent containing a mismatch to a MAPT target sequence is effective in inhibiting the expression of the MAPT gene.

Complementarity

As used herein, unless otherwise indicated, the term "complementary," when used to describe a first nucleotide sequence (e.g., MAPT dsRNA agent sense strand or targeted MAPT mRNA) in relation to a second nucleotide sequence (e.g., MAPT dsRNA agent antisense strand or a single-stranded antisense polynucleotide), means the ability of an oligonucleotide or polynucleotide including the first nucleotide sequence to hybridize [form base pair hydrogen bonds under mammalian physiological conditions (or similar conditions *in vitro*)] and form a

duplex or double helical structure under certain conditions with an oligonucleotide or polynucleotide including the second nucleotide sequence. Other conditions, such as physiologically relevant conditions as can be encountered inside an organism, can apply. A skilled artisan will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides. Complementary sequences include Watson-Crick base pairs or non-Watson-Crick base pairs and include natural or modified nucleotides or nucleotide mimics, at least to the extent that the above hybridization requirements are fulfilled. Sequence identity or complementarity is independent of modification.

Complementary sequences, for example, within a MAPT dsRNA as described herein, include base-pairing of the oligonucleotide or polynucleotide comprising a first nucleotide sequence to an oligonucleotide or polynucleotide comprising a second nucleotide sequence over the entire length of one or both nucleotide sequences. Such sequences can be referred to as “fully complementary” with respect to each other herein. It will be understood that in embodiments when two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs are not regarded herein as mismatches with regard to the determination of complementarity. For example, a MAPT dsRNA agent comprising one oligonucleotide 19 nucleotides in length and another oligonucleotide 20 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 19 nucleotides that is fully complementary to the shorter oligonucleotide, can yet be referred to as “fully complementary” for the purposes described herein. Thus, as used herein, “fully complementary” means that all (100%) of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

The term “substantially complementary” as used herein means that in a hybridized pair of nucleobase sequences, at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, but not all, of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. The term “substantially complementary” can be used in reference to a first sequence with respect to a second sequence if the two sequences include one or more, for example at least 1, 2, 3, 4, or 5 mismatched base pairs upon hybridization for a duplex up to 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 base pairs (bp), while retaining the ability to hybridize under the conditions most relevant to their ultimate application, e.g., inhibition of MAPT gene expression via a RISC pathway.

The term, “partially complementary” may be used herein in reference to a hybridized pair of nucleobase sequences, in which at least 75%, but not all, of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. In some embodiments, “partially complementary” means at least 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%,

91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide.

The terms “complementary,” “fully complementary,” “substantially complementary,”
5 and “partially complimentary” are used herein in reference to the base matching between the sense strand and the antisense strand of a MAPT dsRNA agent, between the antisense strand of a MAPT dsRNA agent and a sequence of a target MAPT mRNA, or between a single-stranded antisense oligonucleotide and a sequence of a target MAPT mRNA. It will be understood that the term “antisense strand of a MAPT dsRNA agent” may refer to the same sequence of an
10 “MAPT antisense polynucleotide agent”.

As used herein, the term “substantially identical” or “substantial identity” used in reference to a nucleic acid sequence means a nucleic acid sequence comprising a sequence with at least about 85% sequence identity or more, preferably at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%,
15 compared to a reference sequence. Percentage of sequence identity is determined by comparing two optimally aligned sequences over a comparison window. The percentage is calculated by determining the number of positions at which the identical nucleic acid base occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100
20 to yield the percentage of sequence identity. The inventions disclosed herein encompasses nucleotide sequences substantially identical to those disclosed herein. e.g., in Tables 1-3. In some embodiments, the sequences disclosed herein are exactly identical, or at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% percent identical to those disclosed herein, e.g., in Tables 1-3.

As used herein, the term “strand comprising a sequence” means an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature. The term “double-stranded RNA” or “dsRNA,” as used herein, refers to an RNAi that includes an RNA molecule or complex of molecules having a hybridized duplex region comprising two anti-parallel and substantially or fully complementary nucleic acid
30 strands, which are referred to as having “sense” and “antisense” orientations with respect to a target MAPT RNA. The duplex region can be of any length that permits specific degradation of a desired target MAPT RNA through a RISC pathway but will typically range from 9 to 30 base pairs in length, e.g., 15-30 base pairs in length. Considering a duplex between 9 and 30 base pairs, the duplex can be any length in this range, for example, 9, 10, 11, 12, 13, 14, 15, 16, 17,
35 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, and any sub-range therein between, including, but not limited to 15-30 base pairs, 15-26 base pairs, 15-23 base pairs, 15-22 base pairs, 15-21 base pairs, 15-20 base pairs, 15-19 base pairs, 15-18 base pairs, 15-17 base pairs, 18-30 base pairs, 18-26 base pairs, 18-23 base pairs, 18-22 base pairs, 18-21 base pairs, 18-20 base pairs, 19-30 base pairs, 19-26 base pairs, 19-23 base pairs, 19-22 base pairs, 19-21 base pairs, 19-20

base pairs, 20-30 base pairs, 20-26 base pairs, 20-25 base pairs, 20-24 base pairs, 20-23 base pairs, 20-22 base pairs, 20-21 base pairs, 21-30 base pairs, 21-26 base pairs, 21-25 base pairs, 21-24 base pairs, 21-23 base pairs, or 21-22 base pairs. MAPT dsRNA agents generated in the cell by processing with Dicer and similar enzymes are generally in the range of 19-22 base pairs in length. One strand of the duplex region of a MAPT dsDNA agent comprises a sequence that is substantially complementary to a region of a target MAPT RNA. The two strands forming the duplex structure can be from a single RNA molecule having at least one self-complementary region, or can be formed from two or more separate RNA molecules. Where the duplex region is formed from two strands of a single molecule, the molecule can have a duplex region separated by a single stranded chain of nucleotides (herein referred to as a “hairpin loop”) between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure. In some embodiments of the invention, a hairpin look comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more unpaired nucleotides. Where the two substantially complementary strands of a MAPT dsRNA agent are comprised by separate RNA molecules, those molecules need not, but can be covalently connected. Where the two strands are connected covalently by means other than a hairpin loop, the connecting structure is referred to as a “linker.” The term “siRNA” is also used herein to refer to a dsRNA agent as described herein.

In some embodiments of the invention a MAPT dsRNA agent may include a sense and antisense sequence that have no-unpaired nucleotides or nucleotide analogs at one or both terminal ends of the dsRNA agent. An end with no unpaired nucleotides is referred to as a “blunt end” and as having no nucleotide overhang. If both ends of a dsRNA agent are blunt, the dsRNA is referred to as “blunt ended.” In some embodiments of the invention, a first end of a dsRNA agent is blunt, in some embodiments a second end of a dsRNA agent is blunt, and in certain embodiments of the invention, both ends of a MAPT dsRNA agent are blunt.

In some embodiments of dsRNA agents of the invention, the dsRNA does not have one or two blunt ends. In such instances there is at least one unpaired nucleotide at the end of a strand of a dsRNA agent. For example, when a 3'-end of one strand of a dsRNA extends beyond the 5'-end of the other strand, or vice versa, there is a nucleotide overhang. A dsRNA can comprise an overhang of at least 1, 2, 3, 4, 5, 6, or more nucleotides. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. It will be understood that in some embodiments a nucleotide overhang is on a sense strand of a dsRNA agent, on an antisense strand of a dsRNA agent, or on both ends of a dsRNA agent and nucleotide(s) of an overhang can be present on the 5' end, 3' end or both ends of either an antisense or sense strand of a dsRNA. In certain embodiments of the invention, one or more of the nucleotides in an overhang is replaced with a nucleoside thiophosphate.

As used herein, the term “antisense strand” or “guide strand” refers to the strand of a MAPT dsRNA agent that includes a region that is substantially complementary to a MAPT target sequence. As used herein the term “sense strand,” or “passenger strand” refers to the strand of

a MAPT dsRNA agent that includes a region that is substantially complementary to a region of the antisense strand of the MAPT dsRNA agent.

Modifications

5 In some embodiments of the invention the RNA of a MAPT RNAi agent is chemically modified to enhance stability and/or one or more other beneficial characteristics. Nucleic acids in certain embodiments of the invention may be synthesized and/or modified by methods well established in the art, for example, those described in "Current protocols in Nucleic Acid Chemistry," Beaucage, S. L. et al. (Eds.), John Wiley & Sons, Inc., New York, N.Y., USA, 10 which is incorporated herein by reference. Modifications that can be present in certain embodiments of MAPT dsRNA agents of the invention include, for example, (a) end modifications, e.g., 5' end modifications (phosphorylation, conjugation, inverted linkages, etc.) 3' end modifications (conjugation, DNA nucleotides, inverted linkages, etc.), (b) base modifications, e.g., replacement with stabilizing bases, destabilizing bases, or bases that base 15 pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases, (c) sugar modifications (e.g., at the 2' position or 4' position) or replacement of the sugar, as well as (d) backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of RNA compounds useful in certain embodiments of MAPT dsRNA agents, MAPT antisense polynucleotides, and MAPT sense polynucleotides 20 of the invention include, but are not limited to RNAs comprising modified backbones or no natural internucleoside linkages. As a non-limiting example, an RNA having a modified backbone may not have a phosphorus atom in the backbone. RNAs that do not have a phosphorus atom in their internucleoside backbone may be referred to as oligonucleosides. In certain embodiments of the invention, a modified RNA has a phosphorus atom in its 25 internucleoside backbone.

It will be understood that the term "RNA molecule" or "RNA" or "ribonucleic acid molecule" encompasses not only RNA molecules as expressed or found in nature, but also analogs and derivatives of RNA comprising one or more ribonucleotide/ribonucleoside analogs or derivatives as described herein or as known in the art. The terms "ribonucleoside" and 30 "ribonucleotide" may be used interchangeably herein. An RNA molecule can be modified in the nucleobase structure or in the ribose-phosphate backbone structure, e.g., as described herein below, and molecules comprising ribonucleoside analogs or derivatives must retain the ability to form a duplex. As non-limiting examples, an RNA molecule can also include at least one modified ribonucleoside including but not limited to a 2'-O-methyl modified nucleoside, a 35 nucleoside comprising a 5' phosphorothioate group, a terminal nucleoside linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a locked nucleoside, an abasic nucleoside, a 2'-deoxy-2'-fluoro modified nucleoside, a 2'-amino-modified nucleoside, 2'-alkyl-modified nucleoside, morpholino nucleoside, a phosphoramidate or a non-natural base comprising nucleoside, or any combination thereof. In some embodiments of the invention, an RNA

molecule comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or up to the full length of the MAPT dsRNA agent molecule's ribonucleosides that are modified ribonucleosides. The modifications need not be the same for each of such a plurality of modified ribonucleosides in an RNA molecule.

5 DsRNA agents, MAPT antisense polynucleotides, and/or MAPT sense polynucleotides of the invention may, in some embodiments comprise one or more independently selected modified nucleotide and/or one or more independently selected non-phosphodiester linkage. As used herein the term "independently selected" used in reference to a selected element, such as a modified nucleotide, non-phosphodiester linkage, etc., means that two or more selected
10 elements can but need not be the same as each other.

As used herein, a "nucleotide base," "nucleotide," or "nucleobase" is a heterocyclic pyrimidine or purine compound, which is a standard constituent of all nucleic acids, and includes the bases that form the nucleotides adenine, guanine, cytosine, thymine, and uracil. A nucleobase may further be modified to include, though not intended to be limiting: universal bases,
15 hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. The term "ribonucleotide" or "nucleotide" may be used herein to refer to an unmodified nucleotide, a modified nucleotide, or a surrogate replacement moiety. Those in the art will recognize that guanine, cytosine, adenine, and uracil can be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such
20 replacement moiety.

As used herein, "optionally" or "optionally" means that the event or environment described later may, but need not, occur, including where the event or environment occurred or did not occur. As used herein, "  " or "  " used in the chemical formulas of the present disclosure may be attached to any one or more groups according to the scope of the
25 invention described herein. As used herein, in the chemical structures of the compounds of the present disclosure, the bond  represents an unspecified configuration, i.e., if a chiral isomer is present in the chemical structure, the bond  can be  or  or both  and  two configurations.

In one embodiment, modified RNAs contemplated for use in methods and compositions described herein are peptide nucleic acids (PNAs) that have the ability to form the required
30 duplex structure and that permit or mediate the specific degradation of a target RNA via a RISC pathway. In certain embodiments of the invention, a MAPT RNA interference agent includes a single stranded RNA that interacts with a target MAPT RNA sequence to direct the cleavage of the target MAPT RNA.

35 Modified RNA backbones can include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and

aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those) having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included. Means of preparing phosphorus-containing linkages are routinely practiced in the art and such methods can be used to prepare certain modified MAPT dsRNA agents, certain modified MAPT antisense polynucleotides, and/or certain modified MAPT sense polynucleotides of the invention.

Modified RNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts. Means of preparing modified RNA backbones that do not include a phosphorus atom are routinely practiced in the art and such methods can be used to prepare certain modified MAPT dsRNA agents, certain modified MAPT antisense polynucleotides, and/or certain modified MAPT sense polynucleotides of the invention.

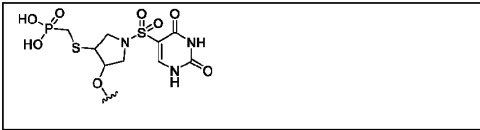
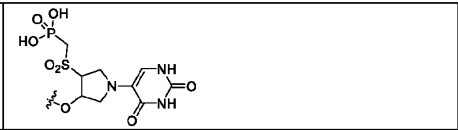
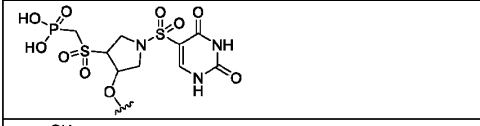
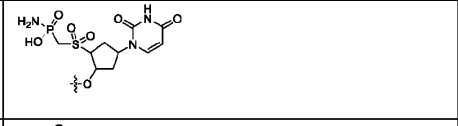
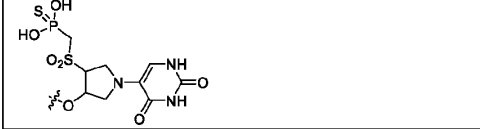
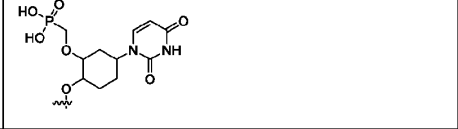
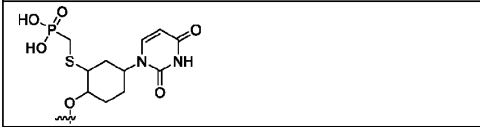
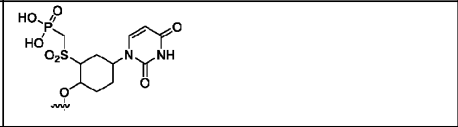
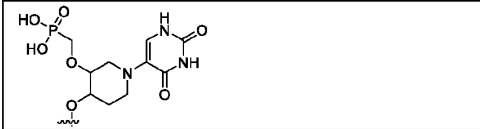
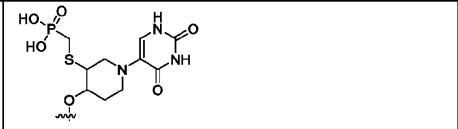
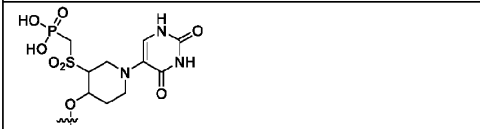
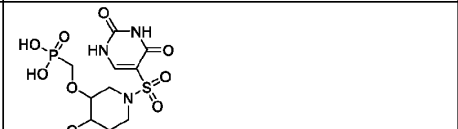
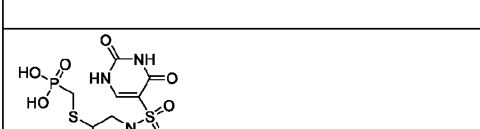
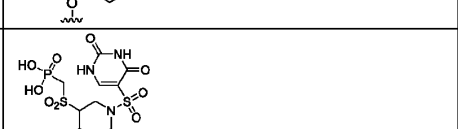
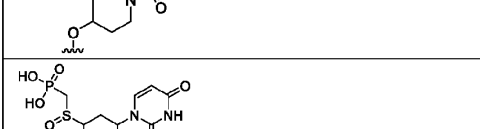
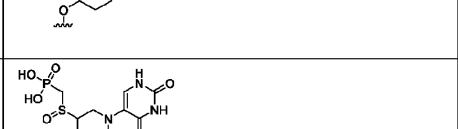
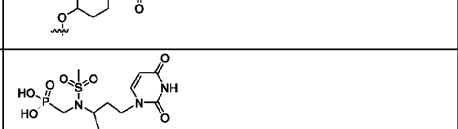
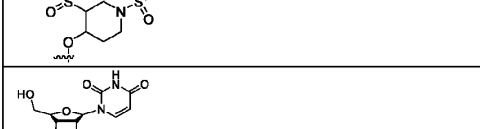
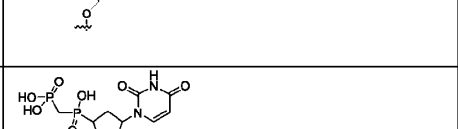
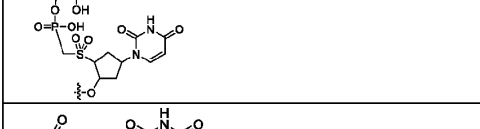
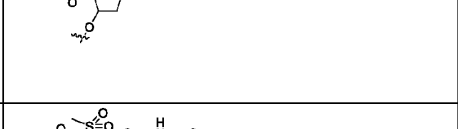
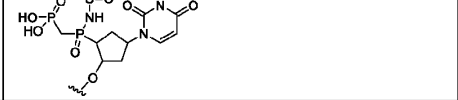
In certain embodiments of the invention, RNA mimetics are included in MAPT dsRNAs, MAPT antisense polynucleotides, and/or MAPT sense polynucleotides, such as, but not limited to: replacement of the sugar and the internucleoside linkage, i.e., the backbone, of the nucleotide units with novel groups. In such embodiments, base units are maintained for hybridization with an appropriate MAPT nucleic acid target compound. One such oligomeric compound, an RNA mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an RNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Means of preparing RNA mimetics are routinely practiced in the art and such methods can be used to prepare certain modified MAPT dsRNA agents of the invention.

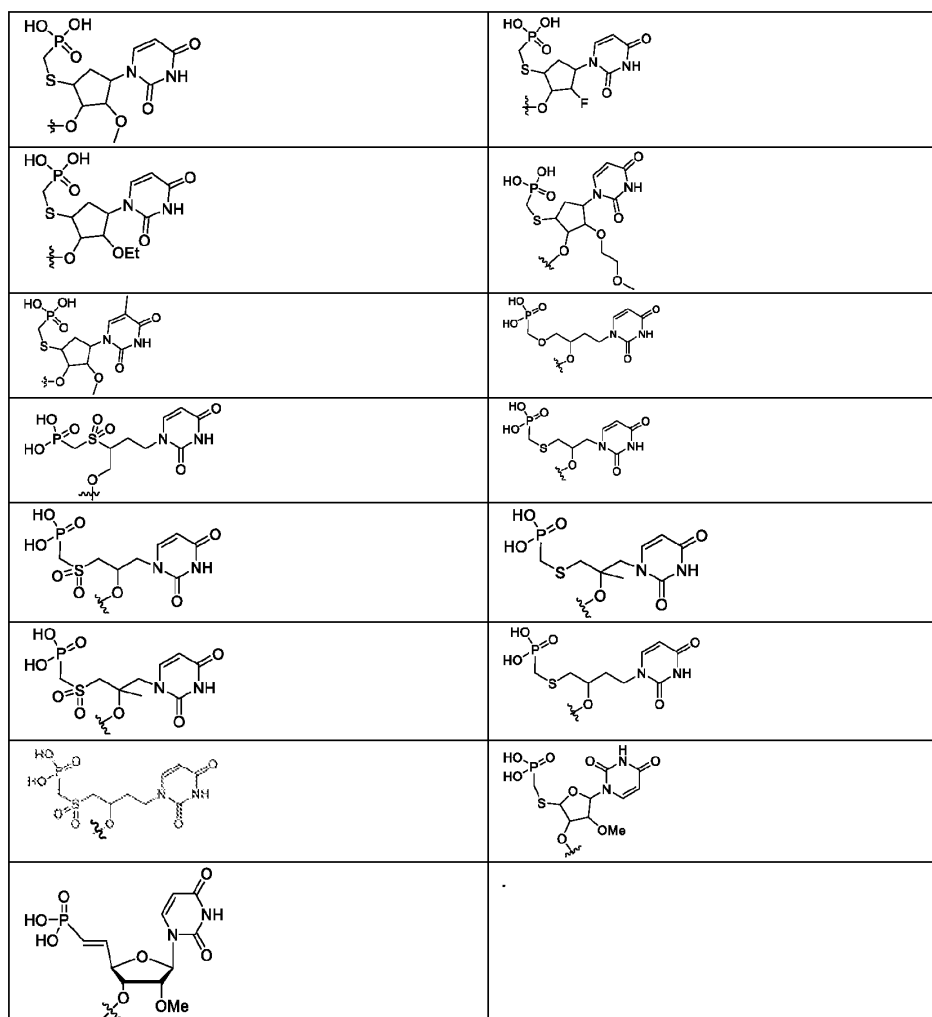
Some embodiments of the invention include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular -CH₂-NH-CH₂-, -CH₂-N(CH₃)-O-CH₂-[known as a methylene (methylimino) or MMI backbone], -CH₂-O-N(CH₃)-CH₂-, -CH₂-N(CH₃)-N(CH₃)-CH₂- and -N(CH₃)-CH₂-[wherein the native phosphodiester backbone is represented as -O-P-O-CH₂-]. Means of preparing RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones are routinely practiced in the art and such methods can be used to prepare certain modified MAPT dsRNA agents, certain MAPT antisense polynucleotides, and/or certain MAPT sense polynucleotides of the invention.

Modified RNAs can also contain one or more substituted sugar moieties. MAPT dsRNAs, MAPT antisense polynucleotides, and/or MAPT sense polynucleotides of the invention may comprise one of the following at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Exemplary suitable modifications include O[(CH₂)_nO]_mCH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of a MAPT dsRNA agent, or a group for improving the pharmacodynamic properties of a MAPT dsRNA agent, MAPT antisense polynucleotide, and/or MAPT sense polynucleotide, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O-CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., *Helv. Chim. Acta*, 1995, 78:486-504) i.e., an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminoethoxy, i.e., a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O-CH₂-O-CH₂-N(CH₂)₂. Means of preparing modified RNAs such as those described are routinely practiced in the art and such methods can be used to prepare certain modified MAPT dsRNA agents of the invention.

Other modifications include 2'-methoxy (2'-OCH₃), 2'-aminopropoxy (2'-OCH₂CH₂CH₂NH₂) and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of a MAPT dsRNA agent, MAPT antisense polynucleotide, and/or MAPT sense polynucleotide of the invention, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked MAPT dsRNAs, MAPT antisense polynucleotides, or MAPT sense polynucleotides, and the 5' position of 5' terminal nucleotide. MAPT dsRNA agents, MAPT antisense polynucleotides, and/or MAPT sense polynucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Means of preparing modified RNAs such as those described are routinely practiced in the art and such methods can be used to prepare certain modified MAPT dsRNA agents, MAPT antisense polynucleotides, and/or MAPT sense polynucleotides of the invention.

As used herein, the term "5'-phosphate" or "5'-phosphate mimic" refers to a 5'-carbon of nucleotide modify or replace by phosphate group or phosphate analogs. In some embodiments of the invention, the dsRNA comprises a phosphate or phosphate mimic at the 5'-terminal nucleotide at the of the guide strand, wherein the 5'-terminal nucleoside represented by one of the following specific structures or stereoisomers thereof:



An MAPT dsRNA agent, MAPT antisense polynucleotide, and/or MAPT sense polynucleotide may, in some embodiments, include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine and guanine, and the pyrimidine bases thymine, cytosine and uracil. Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-Me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine. Additional nucleobases that may be included in certain embodiments of MAPT dsRNA agents

of the invention are known in the art, see for example: *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*, Herdewijn, P. Ed. Wiley-VCH, 2008; *The Concise Encyclopedia Of Polymer Science And Engineering*, pages 858-859, Kroschwitz, J. L., Ed. John Wiley & Sons, 1990, English et al., *Angewandte Chemie, International Edition*, 1991, 30, 613, Sanghvi, Y S., Chapter 15, *dsRNA Research and Applications*, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Means of preparing dsRNAs, MAPT antisense strand polynucleotides and/or MAPT sense strand polynucleotides that comprise nucleobase modifications and/or substitutions such as those described herein are routinely practiced in the art and such methods can be used to prepare certain modified MAPT dsRNA agents, MAPT sense polynucleotides, and/or MAPT antisense polynucleotides of the invention.

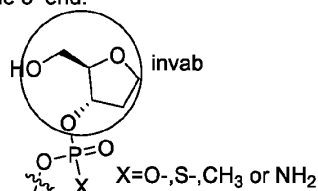
Certain embodiments of MAPT dsRNA agents, MAPT antisense polynucleotides, and/or MAPT sense polynucleotides of the invention include RNA modified to include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide with a modified ribose moiety comprising an extra bridge connecting the 2' and 4' carbons. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids in a MAPT dsRNA agent, MAPT antisense polynucleotides, and/or MAPT sense polynucleotides of the invention may increase stability in serum, and to reduce off-target effects (Elmen, J. et al., (2005) *Nucleic Acids Research* 33(1):439-447; Mook, O R. et al., (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. et al., (2003) *Nucleic Acids Research* 31(12):3185-3193). Means of preparing dsRNA agents, MAPT antisense polynucleotides, and/or MAPT sense polynucleotides that comprise locked nucleic acid(s) are routinely practiced in the art and such methods can be used to prepare certain modified MAPT dsRNA agents of the invention.

Certain embodiments of MAPT dsRNA compounds, sense polynucleotides, and/or antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises: a 2'-O-methyl nucleotide, 2'-Fluoro nucleotide, 2'-deoxy nucleotide, 2'3'-seco nucleotide mimic, locked nucleotide, 2'-F-Arabino nucleotide, 2'-methoxyethyl nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, and 3'-OMe nucleotide, a nucleotide comprising a 5'-phosphorothioate group, or 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. In some embodiments, a MAPT dsRNA compound includes an E-vinylphosphonate nucleotide at the 5' -end of the antisense strand, also referred to herein as the guide strand.

Certain embodiments of MAPT dsRNA compounds, 3' and 5' end of sense polynucleotides, and/or 3' end of antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises: abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2'-OMe nucleotide, inverted 2'-deoxy nucleotide. It is known to skilled in art, including an abasic or inverted abasic nucleotide at the end of oligonucleotide enhances stability (Czaderna et al. Structural variations and

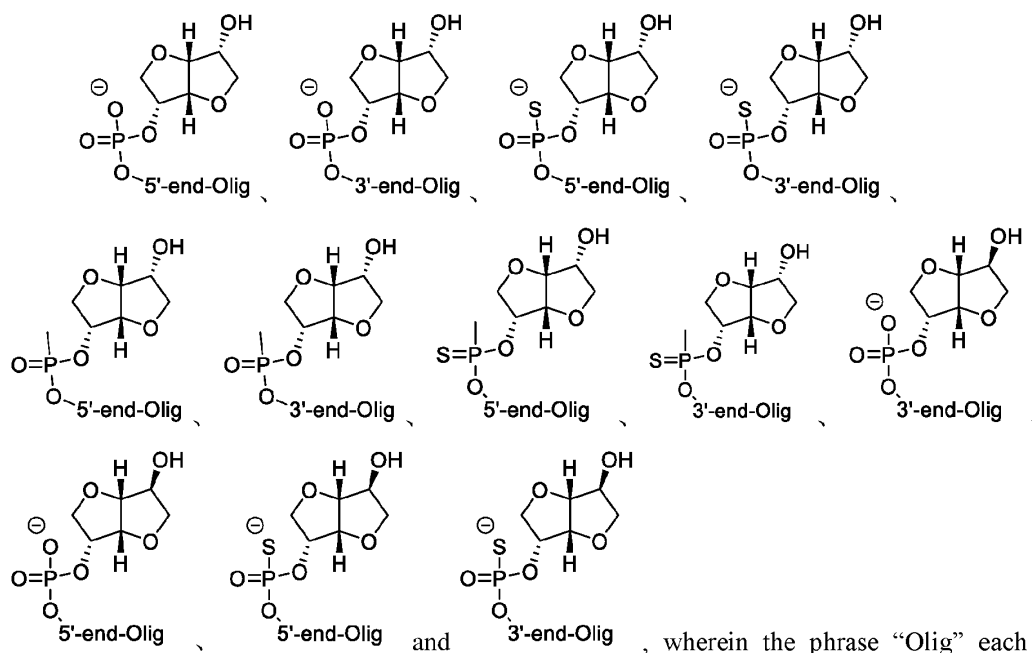
stabilizing modifications of synthetic siRNAs in mammalian cells. Nucleic Acids Res. 2003;31(11):2705-2716. doi:10.1093/nar/gkg393). In some embodiments, a MAPT dsRNA compound includes one or more inverted abasic residues (invab) at either 3'-end or 5'-end, or both 3'-end and 5'-end. Exemplified inverted abasic residues (invab) include, but are not limited to the following:

when at the 3'-end:

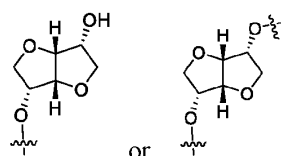


attached to 3'-end of oligonucleotide

Certain embodiments of MAPT dsRNA compounds, 3' and 5' end of sense polynucleotides, and/or 3' end of antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises: isomannide nucleotide or stereoisomer of said isomannide nucleotide. Specific examples of isomannide nucleotides or stereoisomers of said isomannide nucleotides include, but are not limited to:



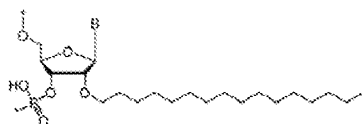
independently represents a polynucleotide moiety. Exemplified isomannide residues (imann) include, but are not limited to, the following:



In certain embodiments, the isomannide nucleotides may further conjugate to one or more targeting groups or delivery molecules, such as GalNAc moieties.

Certain embodiments of MAPT dsRNA compounds, antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises unlocked nucleic acid nucleotide (UNA) or/and glycol nucleic acid nucleotide (GNA). It is known to skilled in art, UNA and GNA are thermally destabilizing chemical modifications, can significantly improves the off-target profile of a siRNA compound (Janas, et al., Selection of GalNAc-conjugated siRNAs with limited off-target-driven rat hepatotoxicity. *Nat Commun.* 2018;9(1):723. doi:10.1038/s41467-018-02989-4; Laursen et al., Utilization of unlocked nucleic acid (UNA) to enhance siRNA performance in vitro and in vivo. *Mol BioSyst.* 2010;6:862–70).

Certain embodiments of MAPT dsRNA compounds, include at least one the lipophilic moiety, wherein contains a saturated or unsaturated C₁₆ hydrocarbon chain (e.g., a linear C16 alkyl or alkenyl). A lipophilic moiety included in any of the positions provided in the instant application. In some embodiments, the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage of the double-stranded iRNA agent. For example, a C₁₆ moiety may be conjugated via the 2'-oxygen of a ribonucleotide as shown in the following structure:



As used herein, “lipophile” or “lipophilic moiety” broadly refers to any compound or chemical moiety having an affinity for lipids. One way to characterize the lipophilicity of the lipophilic moiety is by the octanol-water partition coefficient, logKow, where Kow is the ratio of a chemical’s concentration in the octanol-phase to its concentration in the aqueous phase of a two-phase system at equilibrium. The octanol-water partition coefficient is a laboratory-measured property of a substance. However, it may also be predicted by using coefficients attributed to the structural components of a chemical which are calculated using first-principle or empirical methods (see, for example, Tetko et al., *J. Chem. Inf. Comput. Sci.* 41:1407-21 (2001), which is incorporated herein by reference in its entirety). It provides a thermodynamic measure of the tendency of the substance to prefer a non-aqueous or oily milieu rather than water (i.e. its hydrophilic/lipophilic balance). In principle, a chemical substance is lipophilic in character when its logKow exceeds 0.

Another modification that may be included in the RNA of certain embodiments of MAPT dsRNA agents, MAPT antisense polynucleotides, and/or MAPT sense polynucleotides of the invention, comprises chemically linking to the RNA one or more ligands, moieties or conjugates that enhance one or more characteristics of the MAPT dsRNA agent, MAPT antisense polynucleotide, and/or MAPT sense polynucleotide, respectively. Non-limiting examples of characteristics that may be enhanced are: MAPT dsRNA agent, MAPT antisense polynucleotide,

and/or MAPT sense polynucleotide activity, cellular distribution, delivery of a MAPT dsRNA agent, pharmacokinetic properties of a MAPT dsRNA agent, and cellular uptake of the MAPT dsRNA agent. In some embodiments of the invention, a MAPT dsRNA agent comprises one or more targeting groups or linking groups, which in certain embodiments of MAPT dsRNA agents of the invention are conjugated to the sense strand. A non-limiting example of a targeting group is a compound comprising N-acetyl-galactosamine (GalNAc). A non-limiting example of a targeting group is a compound comprising lipophilic moiety. The terms “targeting group”, “targeting agent”, “linking agent”, “targeting compound”, “delivery molecule”, “delivery compound” and “targeting ligand” may be used interchangeably herein. In certain embodiments of the invention a MAPT dsRNA agent comprises a targeting compound that is conjugated to the 5'-terminal end of the sense strand. In certain embodiments of the invention a MAPT dsRNA agent comprises a targeting compound that is conjugated to the 3'-terminal end of the sense strand. In some embodiments of the invention, a MAPT dsRNA agent comprises a targeting group that comprises GalNAc. In certain embodiments of the invention a MAPT dsRNA agent does not include a targeting compound conjugated to one or both of the 3'-terminal end and the 5'-terminal end of the sense strand. In certain embodiments of the invention a MAPT dsRNA agent does not include a GalNAc containing targeting compound conjugated to one or both of the 5'-terminal end and the 3'-terminal end of the sense strand.

Additional targeting and linking agents are well known in the art, for example, targeting and linking agents that may be used in certain embodiments of the invention include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86: 6553-6556), cholic acid (Manoharan et al., Biorg. Med. Chem. Lett., 1994, 4:1053-1060), a thioether, e.g., beryl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660:306-309; Manoharan et al., Biorg. Med. Chem. Lett., 1993, 3:2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20:533-538), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J, 1991, 10:1111-1118; Kabanov et al., FEBS Lett., 1990, 259:327-330; Svinarchuk et al., Biochimie, 1993, 75:49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654; Shea et al., Nucl. Acids Res., 1990, 18:3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14:969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264:229-237), or an octadecylamine or hexylamino-carboxycholesterol moiety (Cooke et al., J. Pharmacol. Exp. Ther., 1996, 277:923-937).

Certain embodiments of a composition comprising a MAPT dsRNA agent, MAPT antisense polynucleotide, and/or MAPT sense polynucleotide may comprise a ligand that alters distribution, targeting, or etc. of the MAPT dsRNA agent. In some embodiments of a composition comprising a MAPT dsRNA agent of the invention, the ligand increases affinity for a selected target, e.g., molecule, cell or cell type, compartment, e.g., a cellular or organ

compartment, tissue, organ or region of the body, as, e.g., compared to a species absent such a ligand. A ligand useful in a composition and/or method of the invention may be a naturally occurring substance, such as a protein (e.g., human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); a carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. A ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, e.g., a synthetic polyamino acid or polyamine. Examples of polyamino acids are a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolide) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymers, or polyphosphazene. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

A ligand included in a composition and/or method of the invention may comprise a targeting group, non-limiting examples of which are a cell or tissue targeting agent, e.g., a lectin, glycoprotein, lipid or protein, e.g., an antibody that binds to a specified cell type such as a kidney cell or a liver cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, vitamin A, biotin, or an RGD peptide or RGD peptide mimetic.

Other examples of ligands include dyes, intercalating agents (e.g. acridines), cross-linkers (e.g. psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine), artificial endonucleases (e.g. EDTA), lipophilic molecules, e.g., cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine and peptide conjugates (e.g., antennapedia peptide, Tat peptide), alkylating agents, phosphate, amino, mercapto, PEG (e.g., PEG-40K), MPEG, [MPEG]₂, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (e.g., biotin), transport/absorption facilitators (e.g., aspirin, vitamin E, folic acid), synthetic ribonucleases (e.g., imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu³⁺ complexes of tetraazamacrocycles), dinitrophenyl, HRP, or AP.

A ligand included in a composition and/or method of the invention may be a protein, e.g., glycoprotein, or peptide, for example a molecule with a specific affinity for a co-ligand, or an antibody, for example an antibody, that binds to a specified cell type such as a cancer cell,

endothelial cell, cardiac cell, or bone cell. A ligand useful in an embodiment of a composition and/or method of the invention can be a hormone or hormone receptor. A ligand useful in an embodiment of a composition and/or method of the invention can be a lipid, lectin, carbohydrates, vitamin, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, or multivalent fucose. A ligand useful in an embodiment of a composition and/or method of the invention can be a substance that can increase uptake of the MAPT dsRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, e.g., by disrupting the cell's microtubules, microfilaments, and/or intermediate filaments. Non-limiting examples of this type of agent are: taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, and myoservin.

In some embodiments, a ligand attached to a MAPT dsRNA agent of the invention functions as a pharmacokinetic (PK) modulator. An example of a PK modulator that may be used in compositions and methods of the invention includes but is not limited to: a lipophiles, a bile acid, a steroid, a phospholipid analogue, a peptide, a protein binding agent, PEG, a vitamin, cholesterol, a fatty acid, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, a phospholipid, a sphingolipid, naproxen, ibuprofen, vitamin E, biotin, an aptamer that binds a serum protein, etc. Oligonucleotides comprising a number of phosphorothioate linkages are also known to bind to serum protein, thus short oligonucleotides, e.g., oligonucleotides of about 5 bases, 10 bases, 15 bases or 20 bases, comprising multiple of phosphorothioate linkages in the backbone may also be used in compositions and/or methods of the invention as ligands.

MAPT dsRNA agent compositions

In some embodiments of the invention, a MAPT dsRNA agent is in a composition. A composition of the invention may include one or more MAPT dsRNA agent and optionally one or more of a pharmaceutically acceptable carrier, a delivery agent, a targeting agent, detectable label, etc. A non-limiting example of a targeting agent that may be useful according to some embodiments of methods of the invention is an agent that directs a MAPT dsRNA agent of the invention to and/or into a cell to be treated. A targeting agent of choice will depend upon such elements as: the nature of the MAPT-associated disease or condition, and on the cell type being targeted. In a non-limiting example, in some embodiments of the invention it may be desirable to target a MAPT dsRNA agent to and/or into a liver cell. It will be understood that in some embodiments of methods of the invention, a therapeutic agent comprises a MAPT dsRNA agent with only a delivery agent, such as a delivery agent comprising N-Acetylgalactosamine (GalNAc), without any additional attached elements. For example, in some aspects of the invention a MAPT dsRNA agent may be attached to a delivery compound comprising GalNAc and included in a composition comprising a pharmaceutically acceptable carrier and administered to a cell or subject without any detectable labels, or targeting agents, etc. attached to the MAPT dsRNA agent.

In cases where a MAPT dsRNA agent of the invention is administered with and/or attached to one or more delivery agents, targeting agents, labeling agents, etc. a skilled artisan will be aware of and able to select and use suitable agents for use in methods of the invention. Labeling agents may be used in certain methods of the invention to determine the location of a
5 MAPT dsRNA agent in cells and tissues and may be used to determine a cell, tissue, or organ location of a treatment composition comprising a MAPT dsRNA agent that has been administered in methods of the invention. Procedures for attaching and utilizing labeling agents such as enzymatic labels, dyes, radiolabels, etc. are well known in the art. It will be understood that in some embodiments of compositions and methods of the invention, a labeling agent is
10 attached to one or both of a sense polynucleotide and an antisense polynucleotide included in a MAPT dsRNA agent.

Delivery of MAPT dsRNA agents and MAPT antisense polynucleotide agents

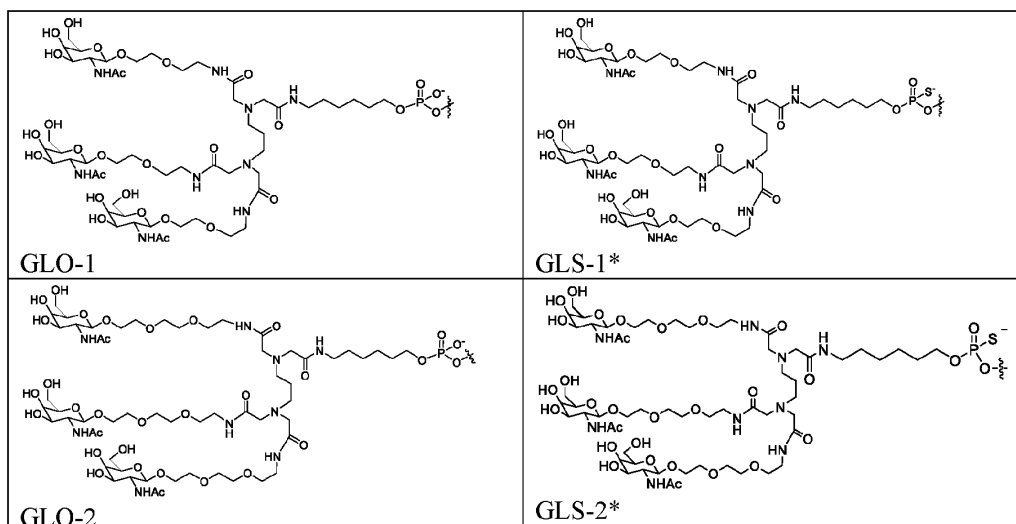
Certain embodiments of methods of the invention, includes delivery of a MAPT dsRNA
15 agent into a cell. As used herein the term, "delivery" means facilitating or effecting uptake or absorption into the cell. Absorption or uptake of a MAPT dsRNA agent can occur through unaided diffusive or active cellular processes, or by use of delivery agents, targeting agents, etc. that may be associated with a MAPT dsRNA agent of the invention. Delivery means that are suitable for use in methods of the invention include, but are not limited to: *in vivo* delivery, in
20 which a MAPT dsRNA agent is injected into a tissue site or administered systemically. In some embodiments of the invention, a MAPT dsRNA agent is attached to a delivery agent.

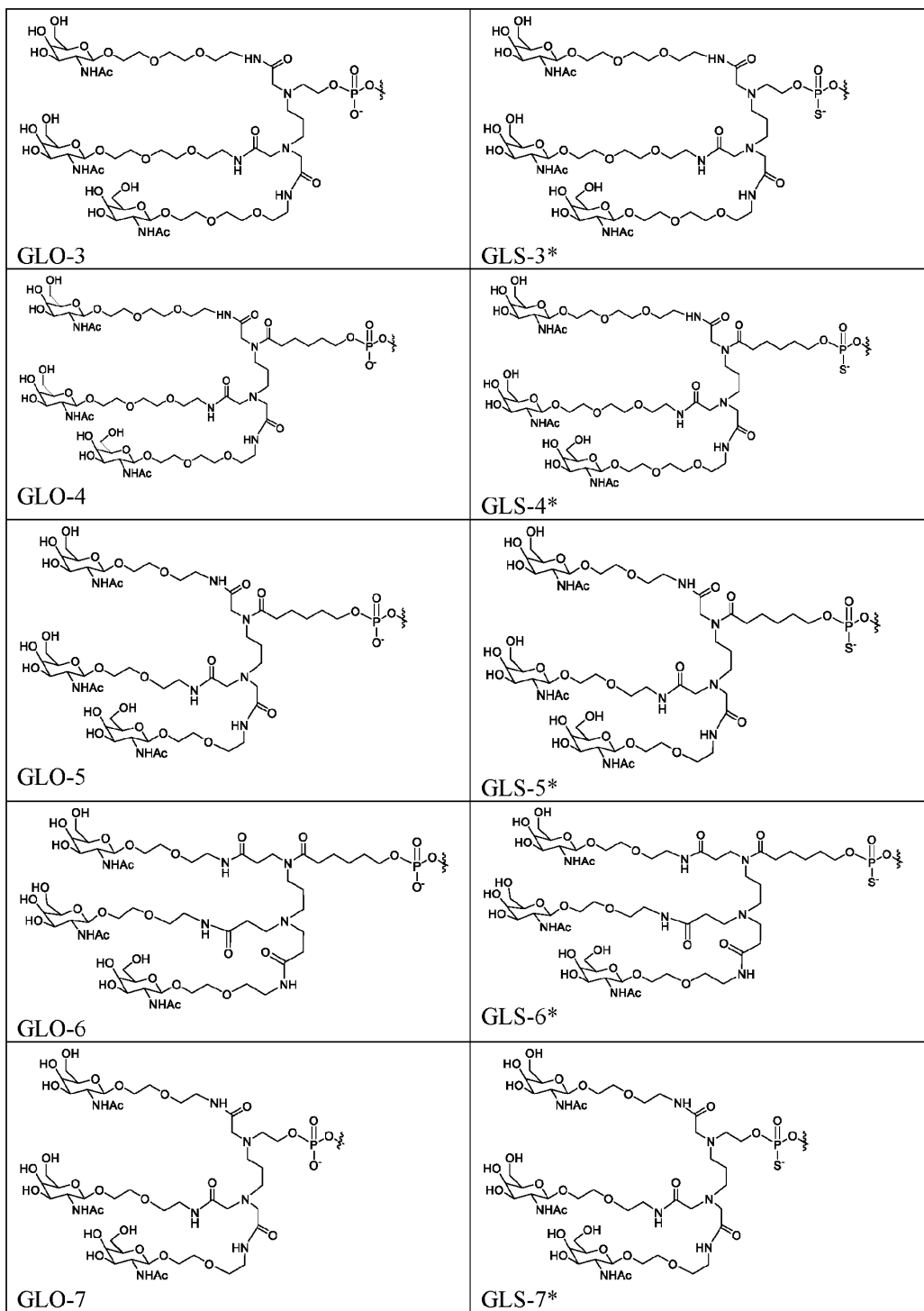
Non-limiting examples of methods that can be used to deliver MAPT dsRNA agents to cells, tissues and/or subjects include: MAPT dsRNA-GalNAc conjugates, SAMiRNA technology, LNP-based delivery methods, and naked RNA delivery. These and other delivery
25 methods have been used successfully in the art to deliver therapeutic RNAi agents for treatment of various diseases and conditions, such as but not limited to: liver diseases, acute intermittent porphyria (AIP), hemophilia, pulmonary fibrosis, etc. Details of various delivery means are found in publications such as: Nikam, R.R. & K. R. Gore (2018) Nucleic Acid Ther, 28 (4), 209-224 Aug 2018; Springer A.D. & S.F. Dowdy (2018) Nucleic Acid Ther. Jun 1; 28(3): 109-118;
30 Lee, K. et al., (2018) Arch Pharm Res, 41(9), 867-874; and Nair, J.K. et al., (2014) J. Am. Chem. Soc. 136:16958-16961, the content each of which is incorporated by reference herein.

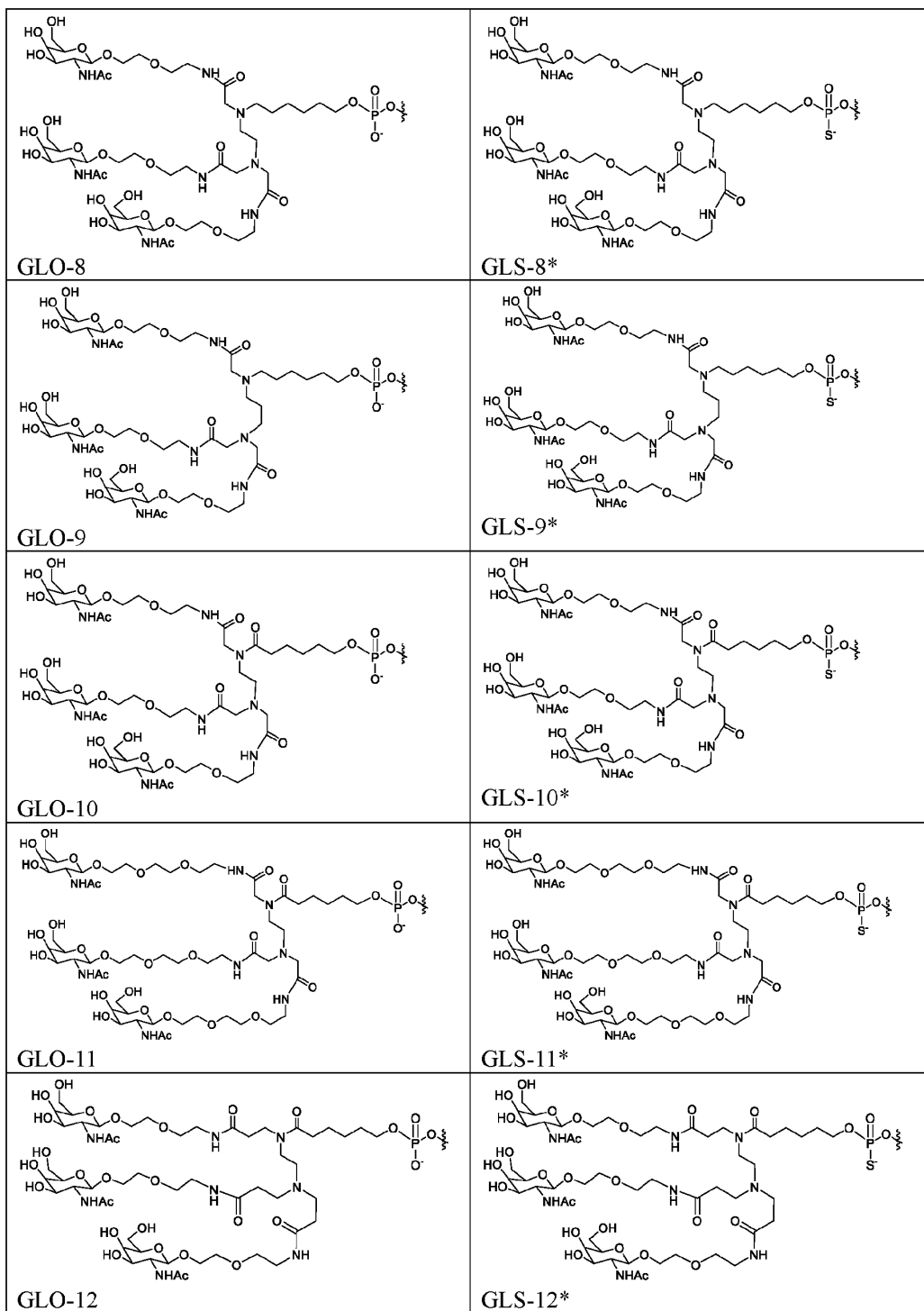
Some embodiments of the invention comprise use of lipid nanoparticles (LNPs) to deliver a MAPT dsRNA agent of the invention to a cell, tissue, and/or subject. LNPs are routinely used for *in vivo* delivery of MAPT dsRNA agents, including therapeutic MAPT dsRNA
35 agents. One benefit of using an LNP or other delivery agent is an increased stability of the MAPT RNA agent when it is delivered to a subject using the LNP or other delivery agent. In some embodiments of the invention an LNP comprises a cationic LNP that is loaded with one or more MAPT RNAi molecules of the invention. The LNP comprising the MAPT RNAi molecule(s) is administered to a subject, the LNPs and their attached MAPT RNAi molecules

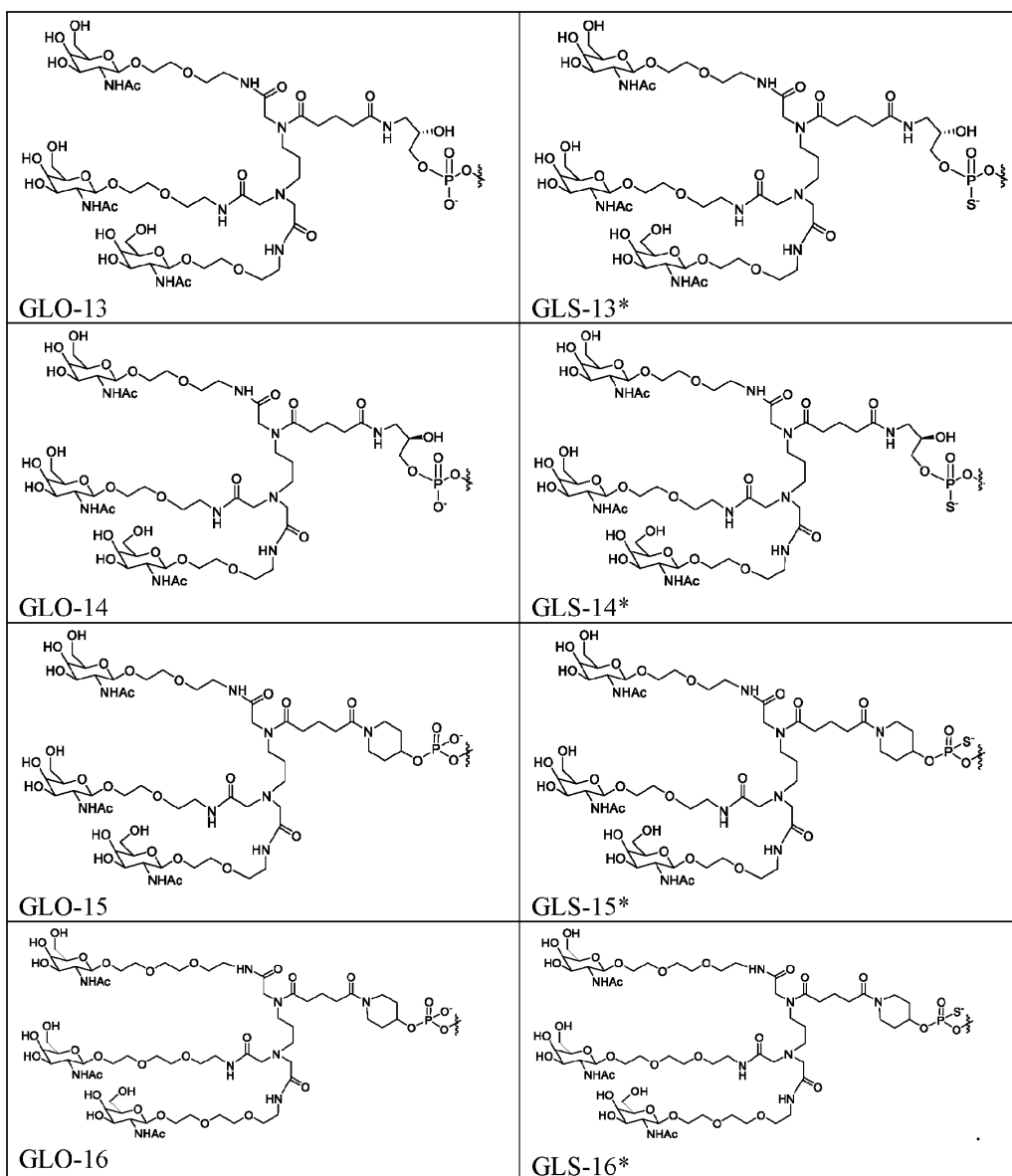
are taken up by cells via endocytosis, their presence results in release of RNAi trigger molecules, which mediate RNAi.

Another non-limiting example of a delivery agent that may be used in embodiments of the invention to delivery a MAPT dsRNA agent of the invention to a cell, tissue and/or subject is an agent comprising GalNAc that is attached to a MAPT dsRNA agent of the invention and delivers the MAPT dsRNA agent to a cell, tissue, and/or subject. Examples of certain additional delivery agents comprising GalNAc that can be used in certain embodiments of methods and composition of the invention are disclosed in PCT Application: WO2020191183A1 (incorporated herein in its entirety). A non-limiting example of a GalNAc targeting ligand that can be used in compositions and methods of the invention to deliver a MAPT dsRNA agent to a cell is a targeting ligand cluster. Examples of targeting ligand clusters that are presented herein are referred to as: GalNAc Ligand with phosphodiester link (GLO) and GalNAc Ligand with phosphorothioate link (GLS). The term "GLX-n" may be used herein to indicate the attached GalNAc-containing compound is any one of compounds GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16, the structure of each of which is shown below, with the below with location of attachment of the GalNAc-targeting ligand to an RNAi agent of the invention at far right of each (shown with "}"). It will be understood that any RNAi and dsRNA molecule of the invention can be attached to the GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16, GLO-1 through GLO-16 and GLS-1* through GLS-16* structures are shown below.

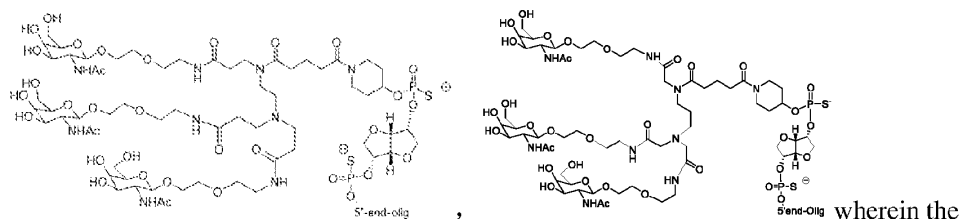








In certain embodiments, the aforesaid isomannide nucleotides may further conjugate to one or more GalNAc targeting ligands. Specific examples of isomannide nucleotides conjugated to a GalNAc targeting ligand include, but are not limited to:



phrase "olig" each independently represents a polynucleotide moiety.

In some embodiments of the invention, *in vivo* delivery can also be by a beta-glucan delivery system, such as those described in U.S. Pat. Nos. 5,032,401 and 5,607,677, and U.S. Publication No. 2005/0281781, which are hereby incorporated by reference in their entirety. *In vitro* introduction of a MAPT RNAi agent into a cell may also be done using art-known methods such as electroporation and lipofection. In certain embodiments of methods of the invention, a MAPT dsRNA is delivered without a targeting agent. These RNAs may be delivered as "naked" RNA molecules. As a non-limiting example, a MAPT dsRNA of the invention may be administered to a subject to treat a MAPT-associated disease or condition in the subject, such as a cardiovascular disease, in a pharmaceutical composition comprising the RNAi agent, but not including a targeting agent such as a GalNAc targeting compound.

In addition to certain delivery means described herein, it will be understood that RNAi delivery means, such as but not limited to those described herein and those used in the art, can be used in conjunction with embodiments of MAPT RNAi agents and treatment methods described herein.

MAPT dsRNA agents of the invention may be administered to a subject in an amount and manner effective to reduce a level and activity of MAPT polypeptide in a cell and/or subject. In some embodiments of methods of the invention one or more MAPT dsRNA agents are administered to a cell and/or subject to treat a disease or condition associated with MAPT expression and activity. Methods of the invention, in some embodiments, include administering one or more MAPT dsRNA agents to a subject in need of such treatment to reduce a disease or condition associated with MAPT expression in the subject. MAPT dsRNA agents or MAPT antisense polynucleotide agents of the invention can be administered to reduce MAPT expression and/or activity in one more of *in vitro*, *ex vivo*, and *in vivo* cells.

In some embodiments of the invention, a level, and thus an activity, of MAPT polypeptide in a cell is reduced by delivering (e.g. introducing) an MAPT dsRNA agent or MAPT antisense polynucleotide agent into a cell. Targeting agents and methods may be used to aid in delivery of a MAPT dsRNA agent or MAPT antisense polynucleotide agent to a specific cell type, cell subtype, organ, spatial region within a subject, and/or to a sub-cellular region within a cell. An MAPT dsRNA agent can be administered in certain methods of the invention singly or in combination with one or more additional MAPT dsRNA agents. In some embodiments, 2, 3, 4, or more independently selected MAPT dsRNA agents are administered to a subject.

In certain embodiments of the invention, an MAPT dsRNA agent is administered to a subject to treat a MAPT-associated disease or condition in conjunction with one or more additional therapeutic regimens for treating the MAPT-associated disease or condition. Non-limiting examples of additional therapeutic regimens are: administering one or more MAPT antisense polynucleotides of the invention, administering a non-MAPT dsRNA therapeutic agent, and a behavioral modification. An additional therapeutic regimen may be administered at a time that is one or more of: prior to, simultaneous with, and following administration of a MAPT dsRNA agent of the invention. It will be understood that simultaneous with as used herein, within five minutes of time zero, within 10 minutes of time zero, within 30 minutes of time zero, within 45 minutes of time zero, and within 60 minutes of time zero, with "time zero" the time of administration of the MAPT dsRNA agent of the invention to the subject. Non-limiting examples of non-MAPT dsRNA therapeutic agents are: a monoamine inhibitor, e.g., tetrabenazine (Xenazine), deutetabenazine (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). These and other therapeutic agents and behavior modifications are known in the art and used to treat a MAPT-associated disease or condition in a subject and may be administered to a subject in combination with the administration of one or more MAPT dsRNA agents of the invention to treat the MAPT-associated disease or condition. A MAPT dsRNA agent of the invention administered to a cell or subject to treat a MAPT-associated disease or condition may act in a synergistic manner with one or more other therapeutic agents or activities and increase the effectiveness of the one or more therapeutic agents or activities and/or to increase the effectiveness of the MAPT dsRNA agent at treating the MAPT-associated disease or condition.

Treatment methods of the invention that include administration of a MAPT dsRNA agent can be used prior to the onset of a MAPT-associated disease or condition and/or when a MAPT-associated disease or condition is present, including at an early stage, mid-stage, and late stage of the disease or condition and all times before and after any of these stages. Methods of the invention may also be to treat subjects who have previously been treated for a MAPT-associated disease or condition with one or more other therapeutic agents and/or therapeutic activities that were not successful, were minimally successful, and/or are no longer successful at treating the MAPT-associated disease or condition in the subject.

Vector Encoded dsRNAs

In certain embodiments of the invention, a MAPT dsRNA agent can be delivered into a cell using a vector. MAPT dsRNA agent transcription units can be included in a DNA or RNA vector. Prepare and use of such vectors encoding transgenes for delivering sequences into a cell and or subject are well known in the art. Vectors can be used in methods of the invention that result in transient expression of MAPT dsRNA, for example for at least 1, 2, 3, 4, 5, 6, 7, 8, 9,

10 or more hours, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more weeks. The length of the transient expression can be determined using routine methods based on elements such as, but not limited to the specific vector construct selected and the target cell and/or tissue. Such transgenes can be introduced as a linear construct, a circular plasmid, or a viral vector, which can be an
5 integrating or non-integrating vector. The transgene can also be constructed to permit it to be inherited as an extrachromosomal plasmid (Gassmann, et al., Proc. Natl. Acad. Sci. USA (1995) 92:1292).

An individual strand or strands of a MAPT dsRNA agent can be transcribed from a promoter on an expression vector. Where two separate strands are to be expressed to generate,
10 for example, a dsRNA, two separate expression vectors can be co-introduced to a cell using means such as transfection or infection. In certain embodiments each individual strand of a MAPT dsRNA agent of the invention can be transcribed by promoters that are both included on the same expression vector. In certain embodiments of the invention a MAPT dsRNA agent is expressed as inverted repeat polynucleotides joined by a linker polynucleotide sequence such
15 that the MAPT dsRNA agent has a stem and loop structure.

Non-limiting examples of RNA expression vectors are DNA plasmids or viral vectors. Expression vectors useful in embodiments of the invention can be compatible with eukaryotic cells. Eukaryotic cell expression vectors are routinely used in the art and are available from a number of commercial sources. Delivery of MAPT dsRNA expressing vectors can be systemic,
20 such as by intravenous or intramuscular administration, by administration to target cells explanted from a subject followed by reintroduction into the subject, or by any other means that allows for introduction into a desired target cell.

Viral vector systems that may be included in an embodiment of a method of the include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but not limited to
25 lentiviral vectors, moloney murine leukemia virus, etc.; (c) adeno-associated virus vectors; (d) herpes simplex virus vectors; (e) SV 40 vectors; (f) polyoma virus vectors; (g) papilloma virus vectors; (h) picornavirus vectors; (i) pox virus vectors such as an orthopox, e.g., vaccinia virus vectors or avipox, e.g. canary pox or fowl pox; and (j) a helper-dependent or gutless adenovirus. Constructs for the recombinant expression of a MAPT dsRNA agent may include regulatory
30 elements, such as promoters, enhancers, etc., which may be selected to provide constitutive or regulated/inducible expression. Viral vector systems, and the use of promoters and enhancers, etc. are routine in the art and can be used in conjunction with methods and compositions described herein.

Certain embodiments of the invention include use of viral vectors for delivery of MAPT
35 dsRNA agents into cells. Numerous adenovirus-based delivery systems are routinely used in the art for deliver to, for example, lung, liver, the central nervous system, endothelial cells, and muscle. Non-limiting examples of viral vectors that may be used in methods of the invention are: AAV vectors, a pox virus such as a vaccinia virus, a Modified Virus Ankara (MVA), NYVAC, an avipox such as fowl pox or canary pox.

Certain embodiments of the invention include methods of delivering MAPT dsRNA agents into cells using a vector and such vectors may be in a pharmaceutically acceptable carrier that may, but need not, include a slow release matrix in which the gene delivery vehicle is imbedded. In some embodiments, a vector for delivering a MAPT dsRNA can be produced
5 from a recombinant cell, and a pharmaceutical composition of the invention may include one or more cells that produced the MAPT dsRNA delivery system.

Pharmaceutical Compositions Containing MAPT dsRNA or ssRNA agents

Certain embodiments of the invention include use of pharmaceutical compositions
10 containing a MAPT dsRNA agent or MAPT antisense polynucleotide agent and a pharmaceutically acceptable carrier. The pharmaceutical composition containing the MAPT dsRNA agent or MAPT antisense polynucleotide agent can be used in methods of the invention to reduce MAPT gene expression and MAPT activity in a cell and is useful to treat a MAPT-associated disease or condition. Such pharmaceutical compositions can be formulated based on
15 the mode of delivery. Non-limiting examples of formulations for modes of delivery are: a composition formulated for subcutaneous delivery, a composition formulated for systemic administration via parenteral delivery, a composition formulated for intravenous (IV) delivery, a composition formulated for intrathecal delivery, a composition formulated for direct delivery into brain, etc. Administration of a pharmaceutic composition of the invention to deliver a
20 MAPT dsRNA agent or MAPT antisense polynucleotide agent into a cell may be done using one or more means such as: topical (e.g., by a transdermal patch), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal, e.g., via an
25 implanted device; or intracranial, e.g., by intraparenchymal, intrathecal or intraventricular, administration. A MAPT dsRNA agent or MAPT antisense polynucleotide agent can also be delivered directly to a target tissue, for example directly into the liver, directly into a kidney, etc. It will be understood that “delivering a MAPT dsRNA agent” or “delivering a MAPT antisense polynucleotide agent” into a cell encompasses delivering a MAPT dsRNA agent or MAPT
30 antisense polynucleotide agent, respectively, directly as well as expressing a MAPT dsRNA agent in a cell from an encoding vector that is delivered into a cell, or by any suitable means with which the MAPT dsRNA or MAPT antisense polynucleotide agent becomes present in a cell. Preparation and use of formulations and means for delivering inhibitory RNAs are well known and routinely used in the art.

35 As used herein, a “pharmaceutical composition” comprises a pharmacologically effective amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention and a pharmaceutically acceptable carrier. The term “pharmaceutically acceptable carrier” refers to a carrier for administration of a therapeutic agent. Such carriers include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The term

specifically excludes cell culture medium. For drugs administered orally, pharmaceutically acceptable carriers include, but are not limited to pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract. Agents included in drug formulations are described further herein below.

As used herein terms such as: “pharmacologically effective amount,” “therapeutically effective amount” and “effective amount” refers to that amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention to produce the intended pharmacological, therapeutic or preventive result. For example, if a given clinical treatment is considered effective when there is at least a 10% reduction in a measurable parameter associated with a disease or disorder, a therapeutically effective amount of a drug for the treatment of that disease or disorder is the amount necessary to effect at least a 10% reduction in that parameter. For example, a therapeutically effective amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent can reduce MAPT polypeptide levels by at least 10%.

Effective amounts

Methods of the invention, in some respects comprise contacting a cell with a MAPT dsRNA agent or MAPT antisense polynucleotide agent in an effective amount to reduce MAPT gene expression in the contacted cell. Certain embodiments of methods of the invention comprise administering a MAPT dsRNA agent or a MAPT antisense polynucleotide agent to a subject in an amount effective to reduce MAPT gene expression and treat a MAPT-associated disease or condition in the subject. An “effective amount” used in terms of reducing expression of MAPT and/or for treating a MAPT-associated disease or condition, is an amount necessary or sufficient to realize a desired biologic effect. For example, an effective amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent to treat a MAPT-associated disease or condition could be that amount necessary to (i) slow or halt progression of the disease or condition; or (ii) reverse, reduce, or eliminate one or more symptoms of the disease or condition. In some aspects of the invention, an effective amount is that amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent that when administered to a subject in need of a treatment of a MAPT-associated disease or condition, results in a therapeutic response that prevents and/or treats the disease or condition. According to some aspects of the invention, an effective amount is that amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention that when combined or co-administered with another therapeutic treatment for a MAPT-associated disease or condition, results in a therapeutic response that prevents

and/or treats the disease or condition. In some embodiments of the invention, a biologic effect of treating a subject with a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention may be the amelioration and or absolute elimination of symptoms resulting from the MAPT-associated disease or condition. In some embodiments of the invention, a biologic effect is the complete abrogation of the MAPT-associated disease or condition, as evidenced for example, by a diagnostic test that indicates the subject is free of the MAPT-associated disease or condition. A non-limiting example of a physiological symptom that may be detected includes a reduction in MAPT level in liver of a subject following administration of an agent of the invention. Additional art-known means of assessing the status of a MAPT-associated disease or condition can be used to determine an effect of an agent and/or methods of the invention on a MAPT-associated disease or condition.

Typically, an effective amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent to decrease MAPT polypeptide activity to a level to treat a MAPT-associated disease or condition will be determined in clinical trials, establishing an effective dose for a test population versus a control population in a blind study. In some embodiments, an effective amount will be that results in a desired response, e.g., an amount that diminishes a MAPT-associated disease or condition in cells, tissues, and/or subjects with the disease or condition. Thus, an effective amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent to treat a MAPT-associated disease or condition that can be treated by reducing MAPT polypeptide activity may be the amount that when administered decreases the amount of MAPT polypeptide activity in the subject to an amount that is less than the amount that would be present in the cell, tissue, and/or subject without the administration of the MAPT dsRNA agent or MAPT antisense polynucleotide agent. In certain aspects of the invention the level of MAPT polypeptide activity, and/or MAPT gene expression present in a cell, tissue, and/or subject that has not been contacted with or administered a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention is referred to as a “control” amount. In some embodiments of methods of the invention a control amount for a subject is a pre-treatment amount for the subject, in other words, a level in a subject before administration of a MAPT agent can be a control level for that subject and compared to a level of MAPT polypeptide activity and/or MAPT gene expression in the subject following siRNA administered to the subject. In the case of treating a MAPT-associated disease or condition the desired response may be reducing or eliminating one or more symptoms of the disease or condition in the cell, tissue, and/or subject. The reduction or elimination may be temporary or may be permanent. It will be understood that the status of a MAPT-associated disease or condition can be monitored using methods of determining MAPT polypeptide activity, MAPT gene expression, symptom evaluation, clinical testing, etc. In some aspects of the invention, a desired response to treatment of a MAPT-associated disease or condition is delaying the onset or even preventing the onset of the disease or condition.

An effective amount of a compound that decreases MAPT polypeptide activity may also be determined by assessing physiological effects of administration of a MAPT dsRNA agent or MAPT antisense polynucleotide agent on a cell or subject, such as a decrease of a MAPT-associated disease or condition following administration. Assays and/or symptomatic monitoring of a subject can be used to determine efficacy of a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention, which may be administered in a pharmaceutical compound of the invention, and to determine the presence or absence of a response to the treatment. A non-limiting example, is that one or more art-known tests of a decrease in biological activity of MAPT, e.g., or additional pathologies associated with elevated levels of MAPT, preferably in the blood, serum, or cerebrospinal fluid sample(s). Phenotypically, tauopathies show variable progression of motor, cognitive, and behavioral impairment.

Some embodiments of the invention include methods of determining an efficacy of an dsRNA agent or MAPT antisense polynucleotide agent of the invention administered to a subject, to treat a MAPT-associated disease or condition by assessing and/or monitoring one or more “physiological characteristics” of the MAPT-associated disease or condition in the subject. Non-limiting examples of physiological characteristics of a MAPT-associated disease or condition are the MAPT mRNA level, the MAPT protein level, or variable progression of motor, cognitive, and behavioral impairment.

It will be understood that the amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent administered to a subject can be modified based, at least in part, on such determinations of disease and/or condition status and/or physiological characteristics determined for a subject. The amount of a treatment may be varied for example by increasing or decreasing the amount of a MAPT-dsRNA agent or MAPT antisense polynucleotide agent, by changing the composition in which the MAPT dsRNA agent or MAPT antisense polynucleotide agent, respectively, is administered, by changing the route of administration, by changing the dosage timing and so on. The effective amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent will vary with the particular condition being treated, the age and physical condition of the subject being treated; the severity of the condition, the duration of the treatment, the nature of the concurrent therapy (if any), the specific route of administration, and additional factors within the knowledge and expertise of the health practitioner. For example, an effective amount may depend upon the desired level of MAPT polypeptide activity and or MAPT gene expression that is effective to treat the MAPT-associated disease or condition. A skilled artisan can empirically determine an effective amount of a particular MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention for use in methods of the invention without necessitating undue experimentation. Combined with the teachings provided herein, by selecting from among various MAPT dsRNA agents or MAPT antisense polynucleotide agents of the invention, and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned that is effective to treat the

particular subject. As used in embodiments of the invention, an effective amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention can be that amount that when contacted with a cell results in a desired biological effect in the cell.

It will be recognized that MAPT gene silencing may be determined in any cell expressing MAPT, either constitutively or by genomic engineering, and by any appropriate assay. In some embodiments of the invention, MAPT gene expression is reduced by at least 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% by administration of a MAPT dsRNA agent of the invention. In some embodiments of the invention, MAPT gene expression is reduced by at between 5% and 10%, 5% and 25%, 10% and 50%, 10% and 75%, 25% and 75%, 25% and 100%, or 50% and 100% by administration of a MAPT dsRNA agent of the invention.

Dosing

MAPT dsRNA agents and MAPT antisense polynucleotide agents are delivered in pharmaceutical compositions in dosages sufficient to inhibit expression of MAPT genes. In certain embodiments of the invention, a dose of MAPT dsRNA agent or MAPT antisense polynucleotide agent is in a range of 0.01 to 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of 1 to 50 mg per kilogram body weight, 5 to 40 mg/kg body weight, 10 to 30 mg/kg body weight, 1 to 20 mg/kg body weight, 1 to 10 mg/kg body weight, 4 to 15 mg/kg body weight per day, inclusive. For example, the MAPT dsRNA agent or MAPT antisense polynucleotide agent can be administered in an amount that is from about 0.01 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 1 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3.0 mg/kg, 3.1 mg/kg, 3.2 mg/kg, 3.3 mg/kg, 3.4 mg/kg, 3.5 mg/kg, 3.6 mg/kg, 3.7 mg/kg, 3.8 mg/kg, 3.9 mg/kg, 4 mg/kg, 4.1 mg/kg, 4.2 mg/kg, 4.3 mg/kg, 4.4 mg/kg, 4.5 mg/kg, 4.6 mg/kg, 4.7 mg/kg, 4.8 mg/kg, 4.9 mg/kg, 5 mg/kg, 5.1 mg/kg, 5.2 mg/kg, 5.3 mg/kg, 5.4 mg/kg, 5.5 mg/kg, 5.6 mg/kg, 5.7 mg/kg, 5.8 mg/kg, 5.9 mg/kg, 6 mg/kg, 6.1 mg/kg, 6.2 mg/kg, 6.3 mg/kg, 6.4 mg/kg, 6.5 mg/kg, 6.6 mg/kg, 6.7 mg/kg, 6.8 mg/kg, 6.9 mg/kg, 7 mg/kg, 7.1 mg/kg, 7.2 mg/kg, 7.3 mg/kg, 7.4 mg/kg, 7.5 mg/kg, 7.6 mg/kg, 7.7 mg/kg, 7.8 mg/kg, 7.9 mg/kg, 8 mg/kg, 8.1 mg/kg, 8.2 mg/kg, 8.3 mg/kg, 8.4 mg/kg, 8.5 mg/kg, 8.6 mg/kg, 8.7 mg/kg, 8.8 mg/kg, 8.9 mg/kg, 9 mg/kg, 9.1 mg/kg, 9.2 mg/kg, 9.3 mg/kg, 9.4 mg/kg, 9.5 mg/kg, 9.6 mg/kg, 9.7 mg/kg, 9.8 mg/kg, 9.9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, 32 mg/kg, 33mg/kg, 34 mg/kg, 35 mg/kg, 36 mg/kg, 37 mg/kg, 38 mg/kg, 39 mg/kg, 40 mg/kg, 41 mg/kg, 42 mg/kg, 43mg/kg, 44 mg/kg, 45 mg/kg, 46 mg/kg, 47 mg/kg, 48 mg/kg, 49 mg/kg, through 50 mg/kg body per single dose.

Various factors may be considered in the determination of dosage and timing of delivery of a MAPT dsRNA agent of the invention. The absolute amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent delivered will depend upon a variety of factors including a concurrent treatment, the number of doses and the individual subject parameters including age, physical condition, size and weight. These are factors well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. In some embodiments, a maximum dose can be used, that is, the highest safe dose according to sound medical judgment.

Methods of the invention may in some embodiments include administering to a subject 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more doses of a MAPT dsRNA agent or MAPT antisense polynucleotide agent. In some instances, a pharmaceutical compound, (e.g., comprising a MAPT dsRNA agent or comprising a MAPT antisense polynucleotide agent) can be administered to a subject at least daily, every other day, weekly, every other week, monthly, etc. Doses may be administered once per day or more than once per day, for example, 2, 3, 4, 5, or more times in one 24-hour period. A pharmaceutical composition of the invention may be administered once daily, or the MAPT dsRNA agent or MAPT antisense polynucleotide agent may be administered as two, three, or more sub-doses at appropriate intervals throughout the day or even using continuous infusion or delivery through a controlled release formulation. In some embodiments of methods of the invention, a pharmaceutical composition of the invention is administered to a subject one or more times per day, one or more times per week, one or more times per month, or one or more times per year.

Methods of the invention, in some aspects, include administration of a pharmaceutical compound alone, in combination with one or more other MAPT dsRNA agents or MAPT antisense polynucleotide agents, and/or in combination with other drug therapies or treatment activities or regimens that are administered to subjects with a MAPT-associated disease or condition. Pharmaceutical compounds may be administered in pharmaceutical compositions. Pharmaceutical compositions used in methods of the invention may be sterile and contain an amount of a MAPT dsRNA agent or MAPT antisense polynucleotide agent that will reduce activity of a MAPT polypeptide to a level sufficient to produce the desired response in a unit of weight or volume suitable for administration to a subject. A dose administered to a subject of a pharmaceutical composition that includes a MAPT dsRNA agent or MAPT antisense polynucleotide agent to reduce MAPT protein activity can be chosen in accordance with different parameters, in particular in accordance with the mode of administration used and the state of the subject. Other factors include the desired period of treatment. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits.

Treatment

As used herein, “MAPT-associated disease”, “MAPT-associated diseases and conditions” and “diseases and conditions caused and/or modulated by MAPT” is intended to include any disease associated with the MAPT gene or protein. Such diseases may be caused, for example, by overproduction of MAPT protein, by mutation of the MAPT gene, by abnormal cleavage of the MAPT protein, by abnormal interaction between MAPT and other proteins or other endogenous or exogenous substances. Exemplary MAPT -associated diseases include, but are not limited to: tauopathy, Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), FTLT 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.

Mutations in MAPT cause frontotemporal dementia with parkinsonism and progressive supranuclear palsy. Mutations in MAPT and hyperphosphorylated tau protein are further associated with Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, and traumatic brain injury, affecting millions of people world-wide. Under pathological conditions, tau protein undergoes a variety of intra-molecular modifications and forms toxic oligomeric tau protein and paired helical filaments, which further assemble into neurofibrillary tangles and form deposits in the brain (tauopathy). Since regulation of tau is critical for memory, tauopathies have been linked to cognitive impairment. Therapies effective at halting or reversing the progression of the highly prevalent Alzheimer's and Parkinson's diseases, both implicating tau protein, are still lacking. Accordingly, there exists a need to efficiently and potently silence MAPT mRNA expression, which the present application addresses.

Tauopathies are a heterogeneous class of progressive neurodegenerative disorders pathologically characterized by the presence of Tau aggregates in the brain. Phenotypically, tauopathies show variable progression of motor, cognitive, and behavioral impairment. Tauopathies include, but are not limited to, Alzheimer's disease, frontotemporal dementia (FTD), and progressive supranuclear palsy (PSP). Tau is a major component of neurofibrillary tangles in the neuronal cytoplasm, a hallmark in Alzheimer's disease. The aggregation and deposition of Tau were also observed in approximately 50% of the brains of patients with Parkinson's disease. FTD includes, but is not limited to, behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), and corticobasal syndrome (CBS).

Also provided are methods useful for ameliorating at least one symptom or hallmark of a neurodegenerative disease. In certain embodiments, the neurodegenerative disease is a tauopathy,

Alzheimer's disease, frontotemporal dementia (FTD), FTDP-17, progressive supranuclear palsy (PSP), chronic traumatic encephalopathy (CTE), corticobasal ganglionic degeneration (CBD), epilepsy, or Dravet's Syndrome. In certain embodiments, the neurodegenerative disease is AD or FTD. In certain embodiments, the symptom or hallmark includes loss of memory, loss of motor function, and increase in the number and/or volume of neurofibrillary inclusions.

As used herein, "symptom" or "hallmark" means any physical feature or test result that indicates the existence or extent of a disease or disorder. In certain embodiments, a symptom is apparent to a subject or to a medical professional examining or testing the subject. In certain embodiments, a hallmark is apparent upon invasive diagnostic testing, including, but not limited to, post-mortem tests. In certain embodiments, a hallmark is apparent on a brain MRI scan. In certain embodiments, symptoms and hallmarks include loss of memory, loss of motor function, and/or increase in the number and/or volume of neurofibrillary inclusions.

Available treatments are only aimed at alleviating the symptoms and improving the patient's quality of life as the disease progresses. Drugs in preclinical or clinical development include active and passive immunotherapies; inhibitors of O-deglycosylation, aggregation, kinases, acetylation, caspases or tau expression; phosphatase activators; microtubule stabilizers; and modulators of autophagy or proteosomal degradation. Biomarkers and testing used in clinical trials to assess tauopathy include tau protein phosphorylated at threonine 181 (pTau), total tau protein (tTau), neurofilament light chain (NfL), and volumetric MRI (vMRI).

In certain aspects of the invention, a subject may be administered a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention at a time that is one or more of before or after diagnosis of a MAPT-associated disease or condition. In some aspects of the invention, a subject is at risk of having or developing a MAPT-associated disease or condition. A subject at risk of developing a MAPT-associated disease or condition is one who has an increased probability of developing the MAPT-associated disease or condition, compared to a control risk of developing the MAPT-associated disease or condition. In some embodiments of the invention, a level of risk may be statistically significant compared to a control level of risk. A subject at risk may include, for instance, a subject who is, or will be, a subject who has a preexisting disease and/or a genetic abnormality that makes the subject more susceptible to a MAPT-associated disease or condition than a control subject without the preexisting disease or genetic abnormality; a subject having a family and/or personal medical history of the MAPT-associated disease or condition; and a subject who has previously been treated for a MAPT-associated disease or condition. It will be understood that a preexisting disease and/or a genetic abnormality that makes the subject more susceptible to a MAPT-associated disease or condition, may be a disease or genetic abnormality that when present has been previously identified as having a correlative relation to a higher likelihood of developing a MAPT-associated disease or condition.

It will be understood that a MAPT dsRNA agent or MAPT antisense polynucleotide agent may be administered to a subject based on a medical status of the individual subject. For

example, a health-care provided for a subject may assess a MAPT level measured in a sample obtained from a subject and determine it is desirable to reduce the subject's MAPT level, by administration of a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention. In this example, the MAPT level may be considered to be a physiological characteristic of a MAPT-associated condition, even if the subject is not diagnosed as having a MAPT-associated disease such as one disclosed herein. A healthcare provider may monitor changes in the subject's MAPT level, as a measure of efficacy of the administered MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention. In a non-limiting example, a biological sample, such as a blood or serum sample may be obtained from a subject and a MAPT level for the subject determined in the sample. A MAPT dsRNA agent or MAPT antisense polynucleotide agent is administered to the subject and a blood sample is obtained from the subject following the administration and the MAPT level determined using the sample and the results compared to the results determined in the subject's pre-administration (prior) sample. A reduction in the subject's MAPT level in the later sample compared to the pre-administration level indicates the administered MAPT dsRNA agent or MAPT antisense polynucleotide agent efficacy in reducing the lipid level in the subject. Certain embodiments of methods of the invention include adjusting a treatment that includes administering a dsRNA agent or a MAPT antisense polynucleotide agent of the invention to a subject based at least in part on assessment of a change in one or more of the subject's physiological characteristics of a MAPT-associated disease or condition resulting from the treatment. For example, in some embodiments of the invention, an effect of an administered dsRNA agent or MAPT antisense polynucleotide agent of the invention may be determined for a subject and used to assist in adjusting an amount of a dsRNA agent or MAPT antisense polynucleotide agent of the invention subsequently administered to the subject. In a non-limiting example, a subject is administered a dsRNA agent or MAPT antisense polynucleotide agent of the invention, the subject's MAPT level is determined after the administration, and based at least in part on the determined level, a greater amount of the dsRNA agent or MAPT antisense polynucleotide agent is determined to be desirable in order to increase the physiological effect of the administered agent, for example to reduce or further reduce the subject's MAPT level. In another non-limiting example, a subject is administered a dsRNA agent or MAPT antisense polynucleotide agent of the invention, the subject's MAPT level is determined after the administration and based at least in part on the determined level, a lower amount of the dsRNA agent or MAPT antisense polynucleotide agent is desirable to administer to the subject.

Thus, some embodiments of the invention include assessing a change in one or more physiological characteristics of resulting from a subject's previous treatment to adjust an amount of a dsRNA agent or MAPT antisense polynucleotide agent of the invention subsequently administered to the subject. Some embodiments of methods of the invention include 1, 2, 3, 4, 5, 6, or more determinations of a physiological characteristic of a MAPT-associated disease or condition to assess and/or monitor the efficacy of an administered MAPT dsRNA agent or

MAPT antisense polynucleotide agent of the invention, and optionally using the determinations to adjust one or more of: a dose, administration regimen, and or administration frequency of a dsRNA agent or MAPT antisense polynucleotide agent of the invention to treat a MAPT-associated disease or condition in a subject. In some embodiments of methods of the invention, a desired result of administering an effective amount of a dsRNA agent or MAPT antisense polynucleotide agent of the invention to a subject is a reduction of the subject's the MAPT mRNA level, the MAPT protein level in the subject, or variable progression of motor, cognitive, and behavioral impairment. Tauopathies are a heterogeneous class of progressive neurodegenerative disorders pathologically characterized by the presence of Tau aggregates in the brain. Phenotypically, tauopathies show variable progression of motor, cognitive, and behavioral impairment. Tauopathies are a heterogeneous class of progressive neurodegenerative disorders pathologically characterized by the presence of Tau aggregates in the brain. In the embodiments, the methods include a clinically relevant inhibition of expression of MAPT, e.g. as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of MAPT, such as, for example, stabilization or inhibition of caudate atrophy (e.g. as assessed by volumetric MRI (VMRI)), a stabilization or reduction in neurofilament light chain (NfL) levels in a CSF sample from a subject, a reduction in mutant MAPT mRNA or a cleaved mutant Tau, e.g. full-length mutant MAPT mRNA or protein and a cleaved mutant MAPT mRNA or protein.

As used herein, the terms "treat", "treated", or "treating" when used with respect to a MAPT-associated disease or condition may refer to a prophylactic treatment that decreases the likelihood of a subject developing the MAPT-associated disease or condition, and also may refer to a treatment after the subject has developed a MAPT-associated disease or condition in order to eliminate or reduce the level of the MAPT-associated disease or condition, prevent the MAPT-associated disease or condition from becoming more advanced (e.g., more severe), and/or slow the progression of the MAPT-associated disease or condition in a subject compared to the subject in the absence of the therapy to reduce activity in the subject of MAPT polypeptide.

Certain embodiments of agents, compositions, and methods of the invention can be used to inhibit MAPT gene expression. As used herein in reference to expression of a MAPT gene, the terms "inhibit," "silence," "reduce," "down-regulate," and "knockdown" mean the expression of the MAPT gene, as measured by one or more of: a level of RNA transcribed from the gene, a level of activity of MAPT expressed, and a level of MAPT polypeptide, protein or protein subunit translated from the mRNA in a cell, group of cells, tissue, organ, or subject in which the MAPT gene is transcribed, is reduced when the cell, group of cells, tissue, organ, or subject is contacted with (e.g., treated with) a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention, compared to a control level of RNA transcribed from the MAPT gene, a level of activity of expressed MAPT, or a level of MAPT translated from the mRNA, respectively. In some embodiments, a control level is a level in a cell, tissue, organ or

subject that has not been contacted with (e.g., treated with) the MAPT dsRNA agent or MAPT antisense polynucleotide agent.

Administration methods

5 A variety of administration routes for a MAPT dsRNA agent or MAPT antisense polynucleotide agent are available for use in methods of the invention. The particular delivery mode selected will depend at least in part, upon the particular condition being treated and the dosage required for therapeutic efficacy. Methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode
10 that produces effective levels of treatment of a MAPT-associated disease or condition without causing clinically unacceptable adverse effects. In some embodiments of the invention, a MAPT dsRNA agent or MAPT antisense polynucleotide agent may be administered via an oral, enteral, mucosal, subcutaneous, and/or parenteral route. The term “parenteral” includes subcutaneous, intravenous, intrathecal, intramuscular, intraperitoneal, and intrasternal injection,
15 or infusion techniques. Other routes include but are not limited to nasal (e.g., via a gastro-nasal tube), dermal, vaginal, rectal, sublingual, and inhalation. Delivery routes of the invention may include intrathecal, intraventricular, or intracranial. In some embodiments of the invention, a MAPT dsRNA agent or MAPT antisense polynucleotide agent may be placed within a slow-release matrix and administered by placement of the matrix in the subject. In some aspects of
20 the invention, a MAPT dsRNA agent or MAPT antisense polynucleotide agent may be delivered to a subject cell using nanoparticles coated with a delivery agent that targets a specific cell or organelle. Various delivery means, methods, agents are known in the art. Non-limiting examples of delivery methods and delivery agents are additionally provided elsewhere herein. In some aspects of the invention, the term “delivering” in reference to a MAPT dsRNA agent or
25 MAPT antisense polynucleotide agent may mean administration to a cell or subject of one or more “naked” MAPT dsRNA agent or MAPT antisense polynucleotide agent sequences and in certain aspects of the invention “delivering” means administration to a cell or subject via transfection means, delivering a cell comprising a MAPT dsRNA agent or MAPT antisense polynucleotide agent to a subject, delivering a vector encoding a MAPT dsRNA agent or MAPT
30 antisense polynucleotide agent into a cell and/or subject, etc. Delivery of a MAPT dsRNA agent or MAPT antisense polynucleotide agent using a transfection means may include administration of a vector to a cell and/or subject.

In some methods of the invention one or more MAPT dsRNA agents or MAPT antisense polynucleotide agents may be administered in formulations, which may be administered in
35 pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients. In some embodiments of the invention a MAPT dsRNA agent or MAPT antisense polynucleotide agent may be formulated with another therapeutic agent for simultaneous administration. According to methods of the invention, a

MAPT dsRNA agent or MAPT antisense polynucleotide agent may be administered in a pharmaceutical composition. In general, a pharmaceutical composition comprises a MAPT dsRNA agent or MAPT antisense polynucleotide agent and optionally, a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well-known to those of ordinary skill in the art. As used herein, a pharmaceutically acceptable carrier means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients, e.g., the ability of the MAPT dsRNA agent or MAPT antisense polynucleotide agent to inhibit MAPT gene expression in a cell or subject. Numerous methods to administer and deliver dsRNA agents or MAPT antisense polynucleotide agents for therapeutic use are known in the art and may be utilized in methods of the invention.

Pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers and other materials that are well-known in the art. Exemplary pharmaceutically acceptable carriers are described in U.S. Pat. No. 5,211,657 and others are known by those skilled in the art. Such preparations may routinely contain salt, buffering agents, preservatives, compatible carriers, and optionally other therapeutic agents. When used in medicine, the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic, malonic, succinic, and the like. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Some embodiments of methods of the invention include administering one or more MAPT dsRNA agents or MAPT antisense polynucleotide agents directly to a tissue. In some embodiments, the tissue to which the compound is administered is a tissue in which the MAPT-associated disease or condition is present or is likely to arise, non-limiting examples of which are the heart. Direct tissue administration may be achieved by direct injection or other means. Many orally delivered compounds naturally travel to and through the liver and kidneys and some embodiments of treatment methods of the invention include oral administration of one or more MAPT dsRNA agents to a subject. MAPT dsRNA agents or MAPT antisense polynucleotide agents, either alone or in conjunction with other therapeutic agents, may be administered once, or alternatively they may be administered in a plurality of administrations. If administered multiple times, the MAPT dsRNA agent or MAPT antisense polynucleotide agent may be administered via different routes. For example, though not intended to be limiting, a first (or first several) administrations may be made via subcutaneous means and one or more additional administrations may be oral and/or systemic administrations. In some embodiments, the dsRNA agent is administered to the subject subcutaneously. In certain embodiments, the dsRNA agent is administered to the subject by IV administration. In some embodiments, the dsRNA agent is administered to the subject by intrathecally. In yet another embodiment, the dsRNA agent is

administered to the subject intracisternally. A non-limiting exemplary intracisternal administration comprises an injection into the cisterna magna (cerebellomedullary cistern) by suboccipital puncture. In certain embodiments, the dsRNA is administered by intracerebroventricular (ICV) injection, intrastriatal (IS) injection, intravenous (IV) injection, 5 subcutaneous (SQ) injection, or a combination thereof.

For embodiments of the invention in which it is desirable to administer a MAPT dsRNA agent or MAPT antisense polynucleotide agent systemically, the MAPT dsRNA agent or MAPT antisense polynucleotide agent may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit 10 dosage form, e.g., in ampoules or in multi-dose containers, with or without an added preservative. MAPT dsRNA agent formulations (also referred to as pharmaceutical compositions) may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Preparations for parenteral administration include sterile aqueous or non-aqueous 15 solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous 20 vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. Lower doses will result from other forms of administration, such as intravenous administration. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or 25 effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Multiple doses per day may be used as needed to achieve appropriate systemic or local levels of one or more MAPT dsRNA agents or MAPT antisense polynucleotide agents and to achieve appropriate reduction in MAPT protein activity.

In yet other embodiments, methods of the invention include use of a delivery vehicle 30 such as biocompatible microparticle, nanoparticle, or implant suitable for implantation into a recipient, e.g., a subject. Exemplary bioerodible implants that may be useful in accordance with this method are described in PCT Publication No. WO 95/24929 (incorporated by reference herein), which describes a biocompatible, biodegradable polymeric matrix for containing a biological macromolecule.

35 Both non-biodegradable and biodegradable polymeric matrices can be used in methods of the invention to deliver one or more MAPT dsRNA agents or MAPT antisense polynucleotide agents to a subject. In some embodiments, a matrix may be biodegradable. Matrix polymers may be natural or synthetic polymers. A polymer can be selected based on the period of time over which release is desired, generally in the order of a few hours to a year or longer. Typically,

release over a period ranging from between a few hours and three to twelve months can be used. The polymer optionally is in the form of a hydrogel that can absorb up to about 90% of its weight in water and further, optionally is cross-linked with multivalent ions or other polymers.

In general, MAPT dsRNA agents or MAPT antisense polynucleotide agents may be delivered in some embodiments of the invention using the bioerodible implant by way of diffusion, or by degradation of the polymeric matrix. Exemplary synthetic polymers for such use are well known in the art. Biodegradable polymers and non-biodegradable polymers can be used for delivery of MAPT dsRNA agents or MAPT antisense polynucleotide agents using art-known methods. Bioadhesive polymers such as bioerodible hydrogels (see H. S. Sawhney, C. P. Pathak and J. A. Hubell in *Macromolecules*, 1993, 26, 581-587, the teachings of which are incorporated by reference herein) may also be used to deliver MAPT dsRNA agents or MAPT antisense polynucleotide agents for treatment of a MAPT-associated disease or condition. Additional suitable delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of a MAPT dsRNA agent or MAPT antisense polynucleotide agent, increasing convenience to the subject and the medical care professional. Many types of release delivery systems are available and known to those of ordinary skill in the art. (See for example: U.S. Pat. Nos. 5,075,109; 4,452,775; 4,675,189; 5,736,152; 3,854,480; 5,133,974; and 5,407,686 (the teaching of each of which is incorporated herein by reference). In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

Use of a long-term sustained release implant may be suitable for prophylactic treatment of subjects and for subjects at risk of developing a recurrent MAPT-associated disease or condition. Long-term release, as used herein, means that the implant is constructed and arranged to deliver a therapeutic level of a MAPT dsRNA agent or MAPT antisense polynucleotide agent for at least up to 10 days, 20 days, 30 days, 60 days, 90 days, six months, a year, or longer. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

Therapeutic formulations of MAPT dsRNA agents or MAPT antisense polynucleotide agents may be prepared for storage by mixing the molecule or compound having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers [Remington's *Pharmaceutical Sciences* 21st edition, (2006)], in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone;

amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or
5 non-ionic surfactants such as TWEEN®, PLURONICS® or polyethylene glycol (PEG).

Cells, Subjects, and Controls

Methods of the invention may be used in conjunction with cells, tissues, organs and/or subjects. In some aspects of the invention a subject is a human or vertebrate mammal including
10 but not limited to a dog, cat, horse, cow, goat, mouse, rat, and primate, e.g., monkey. Thus, the invention can be used to treat MAPT-associated diseases or conditions in human and non-human subjects. In some aspects of the invention a subject may be a farm animal, a zoo animal, a domesticated animal or non-domesticated animal and methods of the invention can be used in veterinary prevention and treatment regimens. In some embodiments of the invention, the subject
15 is a human and methods of the invention can be used in human prevention and treatment regimens.

Non-limiting examples of subjects to which the present invention can be applied are subjects who are diagnosed with, suspected of having, or at risk of having a disease or condition associated with a higher than desirable MAPT expression and/or activity, also referred to as
20 “elevated levels of MAPT expression”. Non-limiting examples of diseases and conditions associated with a higher than desirable levels of MAPT expression and/or activity are described elsewhere herein. Methods of the invention may be applied to a subject who, at the time of treatment, has been diagnosed as having the disease or condition associated with a higher than desirable MAPT expression and/or activity, or a subject who is considered to be at risk for having
25 or developing a disease or condition associated with a higher than desirable MAPT expression and/or activity. In some aspects of the invention a disease or condition associated with a higher than desirable MAPT level of expression and/or activity is an acute disease or condition, and in certain aspects of the invention a disease or condition associated with a higher than desirable MAPT level of expression and/or activity is a chronic disease or condition.

In a non-limiting example, a MAPT dsRNA agent of the invention is administered to a subject diagnosed with, suspected of having, or at risk of having loss of memory, loss of motor function, and/or increase in the number and/or volume of neurofibrillary inclusions, which is a disease in which it is desirable to reduce MAPT expression. Methods of the invention may be applied to the subject who, at the time of treatment, has been diagnosed as having the disease or
30 condition, or a subject who is considered to be at risk for having or developing the disease or condition.

In another non-limiting example, a MAPT dsRNA agent of the invention is administered to a subject diagnosed with, suspected of having, or at risk of having, loss of memory, loss of motor function, and/or increase in the number and/or volume of neurofibrillary inclusions, which

is a disease in which it is desirable to reduce MAPT expression. Methods of the invention may be applied to the subject who, at the time of treatment, has been diagnosed as having the disease or condition, or a subject who is considered to be at risk for having or developing the disease or condition.

5 A cell to which methods of the invention may be applied include cells that are *in vitro*, *in vivo*, *ex vivo* cells. Cells may be in a subject, in culture, and/or in suspension, or in any other suitable state or condition. A cell to which a method of the invention may be applied can be a liver cell, a hepatocyte, a cardiac cell, a pancreatic cell, a cardiovascular cell, kidney cell or other type of vertebrate cell, including human and non-human mammalian cells. In certain aspects of
10 the invention, a cell to which methods of the invention may be applied is a healthy, normal cell that is not known to be a disease cell. In certain embodiments of the invention a cell to which methods and compositions of the invention are applied to a liver cell, a hepatocyte, a cardiac cell, a pancreatic cell, a cardiovascular cell, and/or a kidney cell. In certain aspects of the invention, a control cell is a normal cell, but it will be understood that a cell having a disease or condition
15 may also serve as a control cell in particular circumstances for example to compare results in a treated cell having a disease or condition versus an untreated cell having the disease or condition, etc.

A level of MAPT polypeptide activity can be determined and compared to control level of MAPT polypeptide activity, according to methods of the invention. A control may be a
20 predetermined value, which can take a variety of forms. It can be a single cut-off value, such as a median or mean. It can be established based upon comparative groups, such as in groups having normal levels of MAPT polypeptide and/or MAPT polypeptide activity and groups having increased levels of MAPT polypeptide and/or MAPT polypeptide activity. Another non-limiting example of comparative groups may be groups having one or more symptoms of or a
25 diagnosis of a MAPT-associated disease or condition; groups without having one or more symptoms of or a diagnosis of the disease or condition; groups of subjects to whom an siRNA treatment of the invention has been administered; groups of subjects to whom an siRNA treatment of the invention has not been administered. Typically, a control may be based on apparently healthy normal individuals in an appropriate age bracket or apparently healthy cells.
30 It will be understood that controls according to the invention may be, in addition to predetermined values, samples of materials tested in parallel with the experimental materials. Examples include samples from control populations or control samples generated through manufacture to be tested in parallel with the experimental samples. In some embodiments of the invention, a control may include a cell or subject not contacted or treated with a MAPT
35 dsRNA agent of the invention and in such instances, a control level of MAPT polypeptide and/or MAPT polypeptide activity can be compared to a level of MAPT polypeptide and/or MAPT polypeptide activity in a cell or subject contacted with a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention.

In some embodiments of the invention a level of MAPT polypeptide determined for a

subject can be a control level against which a level of MAPT polypeptide determined for the same subject at a different time is compared. In a non-limiting example, a level of MAPT is determined in a biological sample obtained from a subject who has not been administered a MAPT treatment of the invention. In some embodiments, the biological sample is a serum sample. The level of MAPT polypeptide determined in the sample obtained from the subject can serve as a baseline or control value for the subject. After one or more administrations of a MAPT dsRNA agent to the subject in a treatment method of the invention, one or more additional serum samples can be obtained from the subject and the level of MAPT polypeptide in the subsequent sample or samples can be compared to the control/baseline level for the subject. Such comparisons can be used to assess onset, progression, or recession of a MAPT associated disease or condition in the subject. For example, a level of MAPT polypeptide in the baseline sample obtained from the subject that is higher than a level obtained from the same subject after the subject has been administered a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention indicates regression of the MAPT-associated disease or condition and indicates efficacy of the administered MAPT dsRNA agent of the invention for treatment of the MAPT-associated disease or condition.

In some aspects of the invention, values of one or more of a level of MAPT polypeptide and/or MAPT polypeptide activity determined for a subject may serve as control values for later comparison of levels of MAPT polypeptide and/or MAPT activity, in that same subject, thus permitting assessment of changes from a “baseline” MAPT polypeptide activity in a subject. Thus, an initial MAPT polypeptide level and/or initial MAPT polypeptide activity level may be present and/or determined in a subject and methods and compounds of the invention may be used to decrease the level of MAPT polypeptide and/or MAPT polypeptide activity in the subject, with the initial level serving as a control level for that subject.

Using methods of the invention, MAPT dsRNA agents and/or MAPT antisense polynucleotide agents of the invention may be administered to a subject. Efficacy of the administration and treatment of the invention can be assessed when a level of MAPT polypeptide in a serum sample obtained from a subject is decreased by at least 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared to a pre-administration level of MAPT polypeptide in a serum sample obtained from the subject at a prior time point, or compared to a non-contacted control level, for example a level of MAPT polypeptide in a control serum sample. It will be understood that a level of MAPT polypeptide and a level of MAPT polypeptide activity both correlate with a level of MAPT gene expression. Certain embodiments of methods of the invention comprise administering a MAPT dsRNA and/or MAPT antisense agent of the invention to a subject in an amount effective to inhibit MAPT gene expression and thereby reduce a level of MAPT polypeptide and reduce a level of MAPT polypeptide activity in the subject.

Some embodiments of the invention, include determining presence, absence, and/or an amount (also referred to herein as a level) of MAPT polypeptide in one or more biological

samples obtained from one or more subjects. The determination can be used to assess efficacy of a treatment method of the invention. For example, methods and compositions of the invention can be used to determine a level of MAPT polypeptide in a biological sample obtained from a subject previously treated with administration of a MAPT dsRNA agent and/or a MAPT antisense agent of the invention. A level of MAPT polypeptide determined in a serum sample obtained from the treated subject that is lower by at least 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared to a pretreatment level of MAPT polypeptide determined for the subject, or compared to a non-contacted control biological sample level, indicates a level of efficacy of the treatment administered to the subject.

In some embodiments of the invention a physiological characteristic of a MAPT-associated disease or condition determined for a subject can be a control determination against which a determination of the physiological characteristic in the same subject at a different time is compared. In a non-limiting example, a physiological characteristic such as the reduction in the expression of MAPT may also be assessed indirectly by measuring a decrease in biological activity of MAPT, e.g., or additional pathologies associated with elevated levels of MAPT, preferably in the blood, serum, or cerebrospinal fluid sample(s). Phenotypically, tauopathies show variable progression of motor, cognitive, and behavioral impairment. Tauopathies are a heterogeneous class of progressive neurodegenerative disorders pathologically characterized by the presence of Tau aggregates in the brain. Phenotypically, tauopathies show variable progression of motor, cognitive, and behavioral impairment. Tauopathies are a heterogeneous class of progressive neurodegenerative disorders pathologically characterized by the presence of Tau aggregates in the brain.

The MAPT mRNA level (and/or other physiological characteristic of a MAPT disease or condition) determined in the sample obtained from the subject can serve as a baseline or control value for the subject. After one or more administrations of a MAPT dsRNA agent to the subject in a treatment method of the invention, one or more additional serum samples can be obtained from the subject and MAPT mRNA level and/or MAPT protein level in the subsequent sample or samples are compared to the control/baseline level and/or ratio, respectively, for the subject. Such comparisons can be used to assess onset, progression, or recession of a MAPT associated disease or condition in the subject. For example, MAPT mRNA level in the baseline sample obtained from the subject that is higher than MAPT mRNA level determined in a sample obtained from the same subject after the subject has been administered a MAPT dsRNA agent or MAPT antisense polynucleotide agent of the invention indicates regression of the MAPT-associated disease or condition and indicates efficacy of the administered MAPT dsRNA agent of the invention for treatment of the MAPT-associated disease or condition.

In some aspects of the invention, values of one or more of a physiological characteristic of a MAPT-associated disease or condition determined for a subject may serve as control values for later comparison of the physiological characteristics in that same subject, thus permitting assessment of changes from a "baseline" physiological characteristic in a subject. Thus, an

initial physiological characteristic may be present and/or determined in a subject and methods and compounds of the invention may be used to decrease the level of MAPT polypeptide and/or MAPT polypeptide activity in the subject, with the initial physiological characteristic determination serving as a control for that subject.

- 5 Using methods of the invention, MAPT dsRNA agents and/or MAPT antisense polynucleotide agents of the invention may be administered to a subject in an effective amount to treat a MAPT disease or condition. Efficacy of the administration and treatment of the invention can be assessed by determining a change in one or more physiological characteristics of the MAPT disease or condition. In a non-limiting example, a MAPT mRNA level in a serum
- 10 sample obtained from a subject is decreased by at least 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared to a pre-administration lipid in a serum sample obtained from the subject at a prior time point, or compared to a non-contacted control level, for example MAPT mRNA level in a control serum sample. It will be understood that the MAPT mRNA level, the MAPT protein level in the subject, or the lipid level. Certain
- 15 embodiments of methods of the invention comprise administering a MAPT dsRNA and/or MAPT antisense agent of the invention to a subject in an amount effective to inhibit MAPT gene expression and thereby reduce the MAPT mRNA level, the MAPT protein level in the subject, or otherwise positively impact a physiological characteristic of a MAPT-associated disease or condition in the subject.
- 20 Some embodiments of the invention, include determining presence, absence, and/or a change in a physiological characteristic of a MAPT-associated disease or condition using methods such as but not limited to: (1) assessing one or more biological samples obtained from one or more subjects for the physiological characteristic; (2) imaging a subject (for example but not limited to obtaining a liver image); and (3) or physical examination of the subject. The
- 25 determination can be used to assess efficacy of a treatment method of the invention.

Kits

- Also within the scope of the invention are kits that comprise one or more MAPT dsRNA agents and/or MAPT antisense polynucleotide agents and instructions for its use in methods of
- 30 the invention. Kits of the invention may include one or more of a MAPT dsRNA agent, MAPT sense polynucleotide, and MAPT antisense polynucleotide agent that may be used to treat a MAPT-associated disease or condition. Kits containing one or more MAPT dsRNA agents, MAPT sense polynucleotides, and MAPT antisense polynucleotide agents can be prepared for use in treatment methods of the invention. Components of kits of the invention may be
- 35 packaged either in aqueous medium or in lyophilized form. A kit of the invention may comprise a carrier being compartmentalized to receive in close confinement therein one or more container means or series of container means such as test tubes, vials, flasks, bottles, syringes, or the like. A first container means or series of container means may contain one or more compounds such as a MAPT dsRNA agent and/or MAPT sense or antisense polynucleotide agent. A second

container means or series of container means may contain a targeting agent, a labelling agent, a delivery agent, etc. that may be included as a portion of a MAPT dsRNA agent and/or MAPT antisense polynucleotide to be administered in an embodiment of a treatment method of the invention.

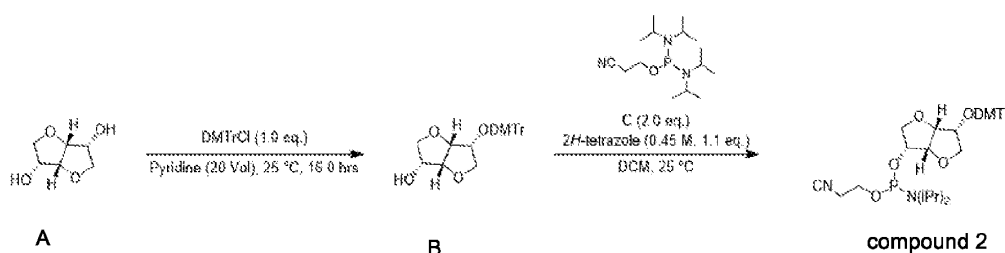
- 5 A kit of the invention may also include instructions. Instructions typically will be in written form and will provide guidance for carrying-out a treatment embodied by the kit and for making a determination based upon that treatment.

The following examples are provided to illustrate specific instances of the practice of the present invention and are not intended to limit the scope of the invention. As will be apparent
10 to one of ordinary skill in the art, the present invention will find application in a variety of compositions and methods.

Examples

Example 1.

15 Phosphoramidite Compound 2



DMTrCl (232 g, 684 mmol, 1.0 *eq*) in pyridine (400 mL) was added to the solution of isomannide compound **A** (100 g, 684 mmol, 1.0 *eq*) in pyridine (600 mL), and the mixture was stirred at 25 °C for 12 hrs. LC-MS showed compound **A** was consumed completely and one
20 main peak with desired mass was detected. The resulting reaction mixture was diluted with water (500 mL), extracted with DCM (500 mL *2), and the combined organic phases were washed with brine (500 mL), dried over Na₂SO₄ and concentrated in vacuum to get the residue. The residue was purified by column chromatography (DCM/MeOH=100/1 to 50/1, 0.1% Et₃N) to give compound **B** (150 g, 48.9% yield) a yellow solid.

25 ¹H NMR: EC4783-404-P1B1_C (400 MHz, DMSO-*d*₆) δ ppm 7.46 (br d, *J*=7.63 Hz, 2 H) 7.28 - 7.37 (m, 6 H) 7.19 - 7.25 (m, 1 H) 6.90 (br d, *J*=7.88 Hz, 4 H) 4.70 (d, *J*=6.50 Hz, 1 H) 3.99 - 4.09 (m, 6 H) 3.88 - 3.96 (m, 2 H) 3.83 (br dd, *J*=7.82, 6.94 Hz, 1 H) 3.74 (s, 6 H) 3.41 (br t, *J*=8.13 Hz, 1 H) 3.05 (t, *J*=8.44 Hz, 1 H) 2.85 (br t, *J*=7.50 Hz, 1 H).

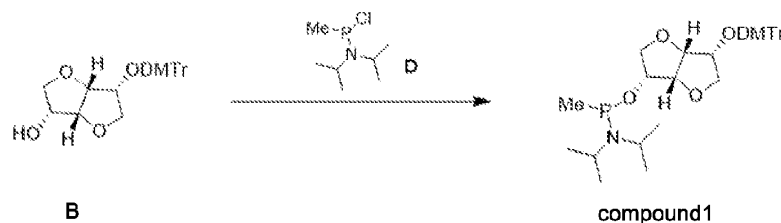
To a solution of compound **B** (80.0 g, 178 mmol, 1.0 *eq*) in DCM (800 mL) at 25 °C under
30 N₂ atmosphere was added dropwise 2H-tetrazole (0.45 M, 436 mL, 1.1 *eq*), then compound **C** (80.6 g, 267 mmol, 85.0 mL, 1.5 *eq*) in DCM (200 mL) was added dropwise to the mixture. The reaction mixture was stirred at 25°C under for 1.0 hr. LC-MS showed compound **B** was consumed completely and one main peak with desired mass was detected. The resulting

reaction mixture was cooled to -20 °C and poured into ice cold sat.NaHCO₃ (500 mL), extracted with DCM (500 mL *3), the combined organic layers were washed with sat.NaHCO₃/brine=1:1 (3 00 mL/300 mL), dried over Na₂SO₄ and concentrated in vacuum (35 °C) to get the residue (100 mL). The residue was purified by column chromatography (Al₂O₃, DCM/MeOH=100/1 to 50/1, 0.1% Et₃N) to give compound2 (77 g, 119 mmol, 66.5% yield) as a white solid.

¹H NMR: EC4783-423-P1B1_C (400 MHz, DMSO-*d*₆) δ ppm 7.22 (br d, *J*=7.50 Hz, 2 H) 7.05 - 7.14 (m, 6 H) 6.96 - 7.02 (m, 1 H) 6.67 (br dd, *J*=8.82, 1.81 Hz, 4 H) 3.95 - 4.07 (m, 2 H) 3.73 - 3.83 (m, 1 H) 3.62 - 3.72 (m, 2 H) 3.48 - 3.53 (m, 6 H) 3.27 - 3.37 (m, 3 H) 3.11 (s, 6 H) 2.82 (td, *J*=8.54, 2.31 Hz, 1 H) 2.47 - 2.63 (m, 3 H) 2.28 (br d, *J*=1.63 Hz, 3 H) 0.82 - 1.00 (m, 13 H).

10

Phosphoramidite Compound 1

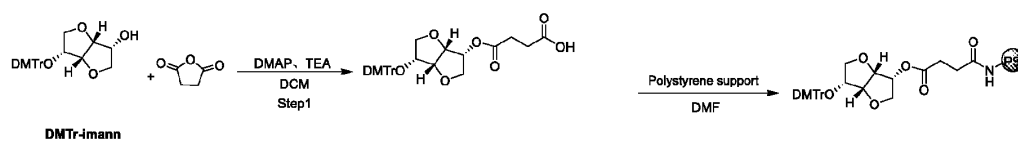


To a solution of compound **B** (500 mg, 1.11 mmol, 1.0 eq) in DCM (5.0 mL) was added compound **D** (607 mg, 3.34 mmol, 3.0 eq) and DIEA (432 mg, 3.34 mmol, 582 μL, 3.0 eq) under N₂ atmosphere at 0-5 °C, the mixture was stirred at 25 °C for 1.0 hrs. LC-MS showed Compound **B** was consumed completely, several new peaks were shown on LC-MS and ~70.9% of desired compound was detected. The resulting reaction mixture was cooled to -20 °C and poured into cold (0-5 °C) sat.NaHCO₃ (5.0 mL) solution, extracted with DCM (5.0 mL *2), the combined organic layers were washed with cold (0-5 °C) sat.NaHCO₃/brine =1:1 (5.0 mL/5.0 mL), dried over Na₂SO₄ and concentrated in vacuum to get the residue (~5 mL). The residue was purified by column chromatography (alkaline Al₂O₃, Petroleum ether/Ethyl acetate=10/1 to 5/1, 0.1% Et₃N) to give compound **1** (280 mg, 471 μmol, 42.3% yield) was obtained as a white solid.

¹H NMR: EC10615-49-P1N (400 MHz, DMSO-*d*₆) δ ppm 7.44 (br d, *J*=7.63 Hz, 2 H), 7.31 (br t, *J*=7.94 Hz, 6 H), 7.18 - 7.26 (m, 1 H), 6.89 (brd, *J*=8.00 Hz, 4 H), 4.08 - 4.13 (m, 1 H), 3.95 - 4.03 (m, 1 H), 3.84 - 3.93 (m, 1 H), 3.77 - 3.83 (m, 1 H), 3.74 (s, 6 H), 3.43 - 3.53 (m, 3 H), 3.38 (br d, *J*=6.75 Hz, 1 H), 2.94 - 3.04 (m, 1 H), 2.70 - 2.85 (m, 1 H), 1.09 - 1.15 (m, 12 H), 1.07 (br s, 3 H).

Other phosphoramidites may be prepared according to procedures described herein and/or prior arts such as, but are not limited to, US426,220 and WO02/36743.

Example 2. Preparation of a solid support comprising phosphoramidites monomers of the present invention



represents amine methyl polyethylene macroporous resin carrier part

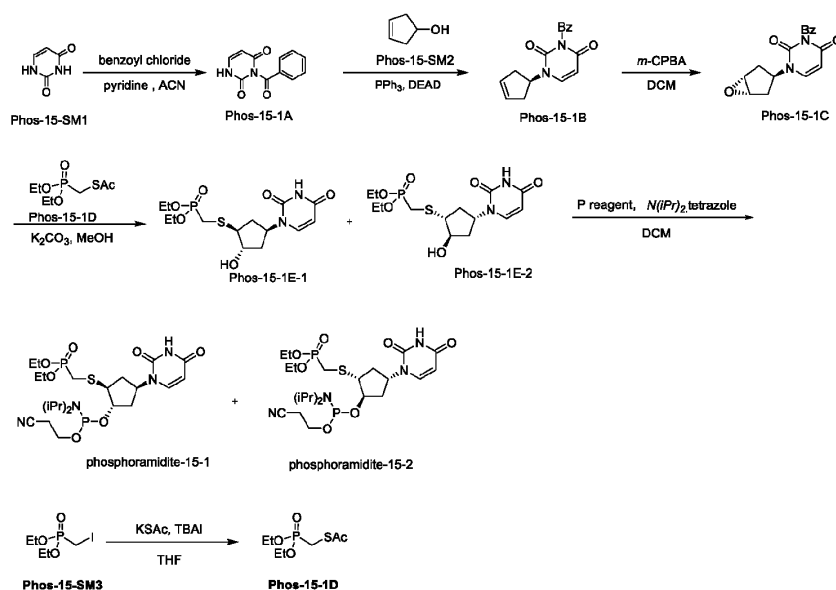
Dichloromethane (19.50kg) was added to the 50 L glass kettle under the protection of nitrogen and started stirring. The temperature was controlled at 20~30 °C, and DMTr imann (1.47 kg), triethylamine (1.50 kg), 4-dimethylaminopyridine (0.164 kg) and succinic anhydride (1.34 kg) was added to the glass kettle. The system was kept at 20~30 °C for 18h, samples were taken and the reaction was ended. Saturated sodium bicarbonate solution (22.50 kg) was added into the reaction system, stirred for 10-20 min, and allowed to separate into layers. The organic phase was separated, and the aqueous phase was extracted twice with dichloromethane, and the organic phase was combined and dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum to get the residue forming a gray to off-white solid of 1.83 kg.

N, N-dimethylformamide (23.50 kg) was added into a 100L glass kettle and stirred. The temperature was controlled at 20~30 °C. Under the protection of nitrogen, the products of the previous step, O-benzotriazole tetramethylurea hexafluorophosphate (0.33 kg) and N, N-diisopropylethylamine (0.13 kg) were added into the aforesaid 100L glass kettle through the solid feeding funnel and stirred for 10~30 minutes and were discharged into a 50 L zinc barrel for use. Macroporous amine methyl resin (3.25 kg) (purchased from Tianjin Nankai Hecheng Science and Technology Co., Ltd., batch number HA2X1209, load capacity 0.48 mmol/g) were added into the aforesaid 100 L solid phase synthesis reactor through the solid feeding funnel, the temperature was controlled at 20~30 °C, N, N-dimethylformamide (21.00 kg+21.00 kg) and the reaction solution in the zinc barrel of the previous step were add into the solid phase synthesis reactor. The system was subject to thermal insulation reaction, and the solid load was tracked to $\geq 250\mu\text{mol/g}$, and the load detection method was UV. The system was filtered under the pressure of nitrogen, the filter cake was washed with N, N-dimethylformamide for three times (26.00kg+26.10kg+26.00kg), and the filter cake was left in the kettle. CAP.A (50% acetonitrile and 50% acetic anhydride, 4.40kg+4.42kg+4.30kg) and CAP.B (20% pyridine and 30% N-methylimidazole and 50% acetonitrile, 4.40kg+4.40kg+4.47kg) were added into the 80L glass kettle, and stirred for 3~8min before use. This operation was repeated for three times to cap, and acetonitrile (18.00 kg+18.00 kg+18.00 kg+17.50 kg+17.50 kg) was added into the solid phase synthesis kettle. Filter-pressed after nitrogen bubbling for 10~30 min. This operation was repeated for four times, the filter cake was purged in the solid phase synthesis kettle with nitrogen for 2-4 h, and then was transferred to a 50 L filter press tank. The temperature was controlled at 15~30 °C, continued drying, and obtained yellow to white solid product after drying, weight: 3.516 kg.

The isomannide residue can be added to the 5' -end or 3' -end of the oligonucleotide chain by a method well known to those skilled in the art, such as the reverse abasic (invab) method, and further added to the target to the group.

5 Example 3 . Preparation of 5'-phosphate mimic phosphoramidite

Preparation of Enantiomeric phosphoramidite-15-1 and enantiomeric phosphoramidite-15-2



10 Benzoyl chloride (126 g, 893 mmol, 104 mL) was added to a solution containing uracil (50.0 g, 446 mmol) in pyridine (735 g, 9.29 mol, 750 mL) and acetonitrile (1.50 L) at 0°C, the reaction solution was stirred at 20-25°C for 12.0 hours, and TLC showed that the compound uracil was completely consumed. The reaction mixture was concentrated in vacuo to obtain a residue. The residue was diluted with cold water (1.0 L) and extracted with ethyl acetate (1.0 L

15 * 3). The combined organic layers were washed with brine (500 mL) and dried over anhydrous sodium sulfate to obtain The residue was purified by column chromatography (SiO₂, ethyl acetate/petroleum ether = 1/10 to 1/1) to obtain white solid Phos-15-1A (63 g, 65.3% yield).

¹H NMR: EC4783-420-P1N (400 MHz, DMSO-*d*₆) δ ppm 7.96 (dd, *J* = 8.4, 1.2 Hz, 2 H), 7.76-7.81 (m, 1 H), 7.67 (dd, *J* = 7.6, 5.6 Hz, 1 H), 7.58-7.64 (m, 2 H), 5.75 (dd, *J* = 7.6, 1.2 Hz,

20 1 H).

To a solution of Phos-15-SM2 (4.0 g, 47.6 mmol) and compound Phos-15-1A (7.91 g, 36.6 mmol) in tetrahydrofuran (80 mL) was added triphenylphosphine (11.5 g, 43.9 mmol) and azo Diethyl dicarboxylate (7.64g, 43.9 mmol, 7.98 mL), the mixture was stirred at 20-25°C for 16

hours. LC-MS showed that compound Phos-15-1A was completely consumed. The reaction mixture was concentrated under reduced pressure to remove tetrahydrofuran. The residue was diluted with water (80 mL), and then extracted with ethyl acetate (80 mL * 3). The combined organic phases were washed with brine (80 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, MeOH/DCM=0/10 to 1/10) to obtain compound Phos-15-1B (14 g, crude product) as a white solid.

Under nitrogen protection, a mixture of compound Phos-15-1B (7.0 g, 9.30 mmol) and *m*-chloroperoxybenzoic acid (2.27 g, 11.1 mmol, 85% purity) in dichloromethane (70 mL) was heated at 0-5°C. After 16 hours of reaction, TLC showed that compound Phos-15-1B was completely consumed, and a major new spot with lower polarity was detected. Slowly adjust the pH of the reaction mixture to 7~8 with saturated NaHSO₃ and NaHCO₃ solutions (1:1), then extract with ethyl acetate (70 mL * 3), and wash the combined organic phases with brine (700mL). Dry over anhydrous sodium sulfate and concentrate under reduced pressure. The residue was purified by silica gel column chromatography (100-200 mesh silica gel), eluting with ethyl acetate:petroleum ether (1:30~1:1) to obtain white solid compound Phos-15-1C (1.2 g, crude product).

To a solution of compound Phos-15-SM3 (4.0 g, 14.4 mmol) in tetrahydrofuran (24.0 mL) was added KSAc (1.81 g, 15.8 mmol) and tetrabutylammonium iodide (TBAI, 531.4 mg, 1.44 mmol), and the mixture was stirred at 70°C for 4.0 hours. LC-MS showed that the raw material Phos-15-SM3 was completely consumed, and a main peak with the desired target molecule molecular weight was detected. The reaction mixture was cooled and concentrated under reduced pressure. The solid residue was removed by filtration with a short silica gel pad and rinsed with ethyl acetate. The filtrate was concentrated in vacuo to obtain compound Phos-15-1D (3.50 g, 98.5% yield) as a brown oil. Compound Phos-15-1D was used in the next step without further purification.

¹H NMR: EC11950-13-P1B (400 MHz, DMSO- *d*₆) δ ppm 3.96-4.07 (m, 4H) 3.27 (d, *J* =14.0 Hz, 2H) 2.40 (s, 3H) 1.22 (t, *J* =7.2 Hz, 6H).

To a solution of compound Phos-15-1C (1.20 g, 4.02 mmol) in ethanol (15.0 mL) were added potassium carbonate (1.11 g, 8.05 mmol) and compound Phos-15-1D (1.91 g, 8.45 mmol), and the mixture was added Stir at 20-25°C for 3.0 hours. TLC showed that compound Phos-15-1C was completely consumed and a major new spot with greater polarity was detected. The resulting reaction mixture was filtered, diluted with water (20 mL), extracted with dichloromethane (20 mL* 3), the combined organic layers were washed with brine, dried over

anhydrous sodium sulfate and concentrated in vacuo to obtain a residue. The residue was purified by column chromatography (SiO_2 , $\text{MeOH}/\text{DCM} = 1/100$ to $10/100$) to obtain compound Phos-15-1E as a brown oil (1.00 g, 65.7% yield, 1:1 mixture of enantiomeric compound-1E-1 and compound-1E-2).

5 ^1H NMR: EC10615-82-P1N1 (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.23 (br s, 1 H), 7.69 (d, $J = 8.0$ Hz, 1 H), 5.58 (dd, $J = 8.0, 1.6$ Hz, 1 H), 4.93 (q, $J = 8.8$ Hz, 1 H), 3.96-4.17 (m, 5 H), 3.08-3.17 (m, 1 H), 3.03 (dd, $J = 14.0, 2.0$ Hz, 2 H), 2.38-2.47 (m, 1 H), 2.04-2.07 (m, 1 H), 1.82-1.90 (m, 1 H), 1.56-1.59 (m, 1 H), 1.25 (t, $J = 6.8$ Hz, 6 H).

Compound Phos-15-1E can obtain enantiomers Phos-15-1E-1 and Phos-15-1E-2 through
10 chiral resolution. Resolution conditions: DAICELCHIRALPAK AD 40mm column, 140 mL/min, ethanol: carbon dioxide = 35:75. It can be understood that when it is necessary to obtain enantiomeric phosphoramidite-15-1 or enantiomeric phosphoramidite-15-2, as long as the corresponding enantiomer Phos-15-1E-1 or Phos-15-1E-2 is used as the starting material and reacted with the phosphorus reagent, it can be obtained

15 Under a nitrogen atmosphere at room temperature, to a solution of compound Phos-15-1E (400 mg, 1.06 mmol) and di-isopropylamine-tetrazolium salt (199 mg, 1.16 mmol) in dichloromethane (4.0 mL) was added a solution of bis(diisopropylamino)(2-cyanoethoxy)phosphine(P reagent, 956 mg, 3.17 mmol, 1.01 mL) in dichloromethane (0.5 mL), and the mixture was stirred at 40°C for 1.0 h. LC-MS showed that compound Phos-15-1E was
20 completely consumed, several new peaks appeared on LC-MS, and approximately 80% of the desired compound was detected. The resulting reaction mixture was cooled to -20°C and poured into cold ($0-5^\circ\text{C}$) saturated aqueous sodium bicarbonate solution (10 mL), extracted with dichloromethane (10 mL* 2), and the combined organic layers were washed with cold($0-5^\circ\text{C}$) saturated aqueous sodium bicarbonate solution/brine (5 mL/5 mL), dry over anhydrous sodium
25 sulfate, and concentrate in vacuo to obtain a residue (~ 2.0 mL). The residue was purified by column chromatography (basic Al_2O_3 , $\text{MeOH}/\text{DCM} = 1/80$ to $1/40$, 0.1% Et_3N) to give phosphoramidite-15 as a colorless oil (350 mg, 0.6 mmol, 57.2% yield, 1:1 mixture of enantiomeric phosphoramidite-15-1 and enantiomeric phosphoramidite-15-2).

Enantiophosphoramidite-15-1 or enantiophosphoramidite-15-2 can be obtained, from the
30 corresponding Phos-15-1E-1 or Phos-15-1E-2 obtained by SFC separation and purification as the starting material, according the same process as above.

δ ppm 11.23 (br s, 1 H), 7.70 (d, $J = 8.0$ Hz, 1 H), 5.55-5.60 (m, 1 H), 4.89 (q, $J = 8.4$ Hz, 1H), 4.29-4.42 (m, 1H), 3.99-4.09 (m, 4H), 3.65-3.84 (m, 2H), 3.53-3.62 (m, 2H), 3.35-3.41 (m,

1H), 3.02 (dd, J =14.0 , 8.0 Hz, 2H), 2.76-2.79 (m, 2H), 2.40-2.49 (m, 1H), 2.15-2.25 (m, 1H), 1.95-2.07 (m, 1H), 1.65-1.75 (m, 1H), 1.23-1.26 (m, 6H) 1.12-1.21 (m, 12H).

The specific preparation method of Phos-15-1E-1 or Phos-15-1E-2 chiral is as follows:

System: Waters SFC 150

5 Column name: DAICELCHIRALCEL®AD

Column model: 250*50 mm 10 m

Mobile phase A: Supercritical CO₂

Mobile phase B: EtOH

Wavelength: 214 nm

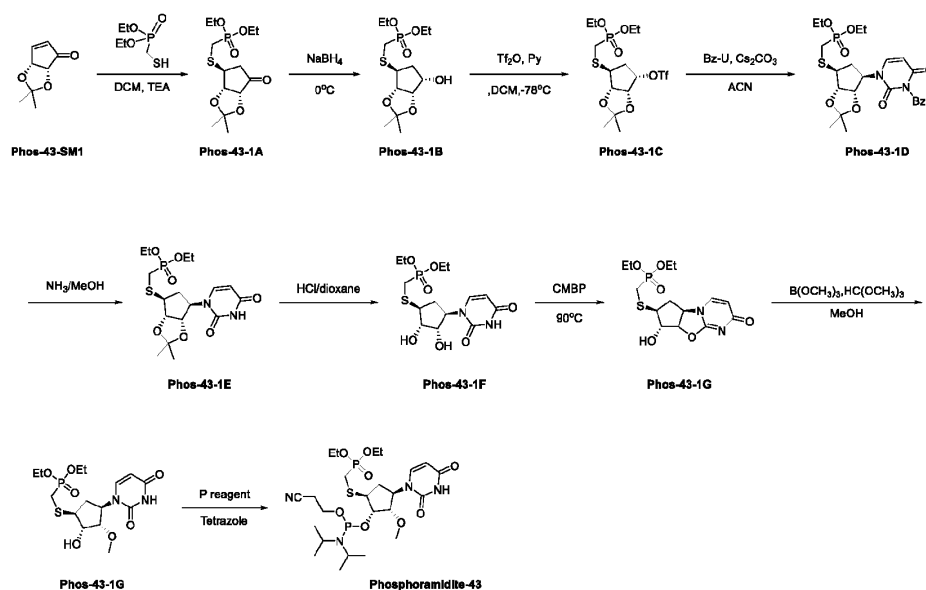
10 Flow rate: 140 mL/min

Column temperature: RT

Injection volume: 7.0 mL Cycle time: 10.0 min

Solvent: supercritical CO₂: food grade EtOH: redistilled grade;

Preparation of Phosphoramidite-43



15

Add (3aR, 6aR)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxole-4(6aH)-one (phos-43-SM1, 16.2 g, 105 mmol, 1.0eq), diethyl (mercaptomethyl)phosphonate (19.3 g, 105 mmol, 1.0eq) and dichloromethane (200mL) to 500mL flask. The flask was stirred and cooled to 0-5°C under nitrogen protection, and then triethylamine (1.06 g, 10.5mmol, 0.1 eq) was added dropwise. After the addition was completed, the temperature was returned to 25°C and stirred overnight under nitrogen protection. LCMS detected that the reaction was complete, and the

20

reaction solution was concentrated in vacuo to obtain crude product. The crude product was purified by flash column, and the eluent was (EA: DCM = 0% -15 %) to wash out the product. The product was concentrated in vacuum to obtain 25g of Phos-43-1A as a light yellow oil , 70.3% yield.

5 LCMS: M+H=339.5

Add Phos-43-1A (25 g , 73.9mmol , 1.0eq) and ethanol (250mL) to the 500mL flask. Stir and cool the flask to 0-5°C under nitrogen protection, then add sodium borohydride (3.1 g, 81.3m mol, 1.1 eq) in batches. After the addition is completed, keep stirring at 0-5°C for 0.5h. LCMS detected that the reaction was complete. Ice water (200 mL) was added dropwise to the
10 reaction solution and stirred for 10 min. Then, the mixture was extracted twice with dichloromethane (500 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated in vacuo to obtain the crude product. The crude product was purified by flash column, and the eluent was (MeOH: DCM = 0 % -5 %) to wash out the product. The product was concentrated in vacuum to obtain 24.5 g of Phos-43-1B as a light yellow oil. The
15 yield was 97.4 % .

LCMS:M+H=341.5

¹H NMR: (400 MHz, CD₃CN), δ ppm 4.67-4.65 (d, J=8.0, 1 H), 4.47-4.42 (m, 2 H), 4.08-4.01 (m, 5 H), 3.27-3.25 (m, 1 H), 2.97-2.93 (d, J=16.0, 2 H), 2.03-1.99 (m, 1 H), 1.73-1.71 (m, 1 H), 1.38 (s, 3 H), 1.26-1.22 (m, 9 H).

20 Add Phos-43-1B (10g, 29.4mmol, 1.0eq), pyridine (7g, 88.1mmol, 3.0eq) and dichloromethane (100mL) to a 250mL flask. The flask was stirred and cooled to -78°C under nitrogen protection, and then trifluoromethanesulfonic anhydride (12.4g, 44.1mmol, 1.5eq) was added dropwise. After the dropwise addition was completed, the flask was kept at -78°C and stirred under nitrogen protection for 3 hours. LCMS detected that the reaction was complete.
25 The reaction solution is poured into 50mL of ice water, and then extracted twice with dichloromethane (100mL). The combined organic phases are dried with anhydrous sodium sulfate and concentrated in vacuo to obtain the crude product Phos-43-1C, which is directly used to the next step.

LCMS:M+H=473.4

30 Add Phos-43-1C(16g, 33.8mmol, 1.0eq), 3-benzoyluracil(8.8g, 40.6mmol, 1.2eq), cesium carbonate (22g, 67.7mmol) and acetonitrile (200mL) to a 500mL flask. The flask was stirred overnight at 25°C under nitrogen protection. LCMS detected that the reaction was complete, the reaction solution was filtered, and the filtrate was concentrated in vacuum to obtain the crude product. The crude product was purified by flash column, and the eluent was (MeOH:DCM=0%-

5%) to wash out the product. The product was concentrated in vacuum to obtain 18g of Phos-43-1D as a brown oil, with a yield of 98.7%.

LCMS:M+H=539.4

To a 500 mL flask were added Phos-43-1D (18 g, 33.4 mmol, 1.0 eq) and methanol (180 mL). Ammonia methanol (180 mL) was added dropwise to the flask under nitrogen protection. After the dropwise addition was completed, the mixture was stirred at 25°C for 5 hours under nitrogen protection. LCMS detected that the reaction was complete, and the reaction solution was concentrated in vacuum to obtain the crude product Phos-43-1E, which was directly used in the next step.

10 LCMS:M+H=435.4

To a 500 mL flask was added Phos-43-1E (14.5 g, 33.4 mmol, 1.0 eq) and dioxane (180 mL). Add dioxane hydrochloride (4M 180mL) dropwise and stir the flask at 25°C overnight under nitrogen protection. LCMS detected that the reaction was complete, and the reaction solution was concentrated in vacuum to obtain crude product. The crude product was purified by flash column, and the eluent was (MeOH:DCM=0%-10%) to wash out the product. The product was concentrated in vacuum to obtain 5.2g of Phos-43-1F as a white solid, with a yield of 39.5%.

LCMS:M+H=395.4

Add Phos-43-1F (5.2g, 13.2mmol, 1.0eq), toluene (100mL) and acetonitrile (20mL) to a 250mL flask, then add cyanomethylenetri-n-butylphosphine (6.4g, 26.5mmol, 2.0eq) and stir the flask at 90°C for 48h under nitrogen protection. LCMS detected that the reaction was complete, and the reaction solution was concentrated in vacuum to obtain crude product. The crude product was purified by flash column using the eluant (MeOH:DCM=0%-10%) to elute the product. The product was concentrated in vacuum to obtain 3.5 g of Phos-43-1G as a white solid, with a yield of 70.5%.

25 LCMS:M+H=377.3

Add Phos-43-1G (2.0g, 5.3mmol, 1.0eq), anhydrous methanol (20mL), trimethyl borate (1.1g, 10.6mmol, 2.0eq), and methyl orthoformate (0.56g, 5.3mmol, 1.0eq) and sodium bicarbonate (44.5mg, 0.52mmol, 0.2eq) into a 250mL stuffy jar. The above mixture was heated to 120°C and stirred for 48 h. The stuffy jar was cooled to room temperature. LCMS detected that the reaction was complete, and the reaction solution was concentrated in vacuum to obtain a crude product. The crude product was purified by flash column using the eluant (MeOH:DCM=0%-10%) to elute the product. The product was concentrated in vacuum to obtain 1.3 g of Phos-43-1H as a white solid, with a yield of 60%.

LCMS:M+H=409.4

Add Phos-43-1G (0.6g, 1.47 mmol, 1.0eq), anhydrous dichloromethane (10mL) to the 50mL flask, and then add tetrazole (0.13g, 1.76 mmol, 1.2eq), bis(diisopropyl)(2-cyanoethoxy)phosphine (0.66 g, 2.2 mmol, 1.5eq) in sequence. The above mixture was stirred at 25°C for 1 h under nitrogen protection. LCMS detected that the reaction was complete. The reaction solution was poured into a sodium bicarbonate aqueous solution and extracted twice with dichloromethane (20 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated in vacuo to obtain the crude product. The crude product was purified through a flash silica gel column, and the product was eluted with the eluent (DCM:MeOH:TEA=0%-5%+0.2%TEA). Concentrate under vacuum at 35°C to obtain phosphoramidite-43 (0.89g, yield 100%) as a colorless oil.

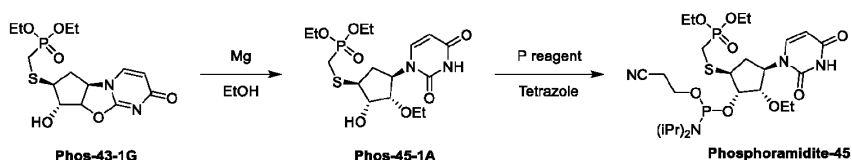
LCMS:M+H=609.6

¹H NMR: (400 MHz, CD₃CN), δ ppm 8.97 (s, 1 H), 7.43-7.41 (d, J=8.0, 1 H), 5.61-5.59 (d, J=8.0, 1 H), 4.76-4.69 (m, 1 H), 4.44-4.34 (m, 1 H), 4.14-4.04 (m, 5 H), 3.90-3.81 (m, 2 H), 3.69-3.62 (m, 2 H), 3.46-3.44 (m, 1 H), 3.36-3.33 (d, J=12.0, 3 H), 2.97-2.87 (m, 2 H), 2.77-2.65 (m, 3 H), 1.67-1.56 (m, 1 H), 1.32-1.27 (m, 6 H), 1.24-1.18 (m, 12 H).

³¹P NMR: (400 MHz, CD₃CN), δ ppm 150.03, 148.62; 23.44, 23.24.

The preparation method of phosphoramidite-47 is the same as that of phosphoramidite-43, except that the starting material 5-methyluracil is used as the nucleobase.

20 Preparation of Phosphoramidite-45



Add magnesium chips (0.26g, 10.6 mmol, 10.0eq) and absolute ethanol (40mL) to a 100mL stuffy jar, and heat the above mixture to 90°C and stir for 18h. Cool the stuffy jar to room temperature, add Phos-43-1G (0.4g, 1.06 mmol, 1.0eq), heat to 90°C and stir for 18h. The stuffy jar was cooled to room temperature. LCMS detected that the reaction was incomplete and about 50% was converted into Phos-45-1A. The reaction solution was concentrated in vacuo to obtain crude product. The crude product was purified by flash column using the eluent (MeOH:DCM=0%-8%) to elute out the product. The product was concentrated in vacuum to obtain 0.13g of Phos-45-1A as a light yellow oil, with a yield of 29%.

LCMS: M+H=423.4

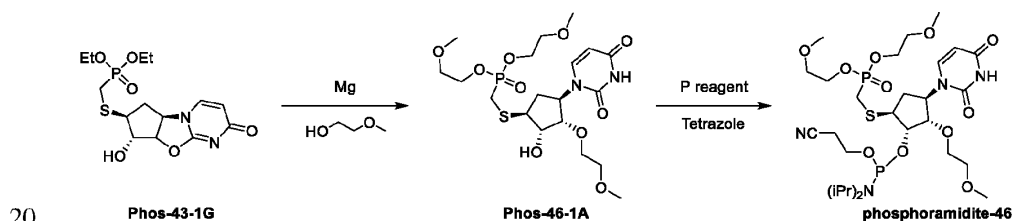
Add Phos-45-1A (0.11g, 0.26 mmol, 1.0eq) and anhydrous dichloromethane (3mL) to the 50mL flask, then add tetrazole (22 mg, 0.31 mmol, 1.2eq), bis(diiso) Propylamino)(2-cyanoethoxy)phosphine (0.12 g, 0.4 mmol, 1.5eq) in sequence. The above mixture was stirred at 25°C for 1 h under nitrogen protection. LCMS detected that the reaction was complete. The reaction solution was poured into aqueous sodium bicarbonate solution and extracted twice with dichloromethane (10 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated in vacuo to obtain the crude product. The crude product was purified through a flash silica gel column, and the product was eluted with the eluent (DCM:MeOH:TEA=0%-3%+0.2%TEA). Concentrate under vacuum at 35°C to obtain phosphonamidite yellow oil Phos-45 (0.1g, yield 61.7%).

LCMS: M+H=623.5,

¹H NMR: (400 MHz, CD₃CN), δ ppm 7.42-7.40 (d, J=8.0, 1 H), 5.61-5.59 (d, J=8.0, 1 H), 4.73-4.68 (m, 1 H), 4.34-4.30 (m, 1 H), 4.12-4.06 (m, 5 H), 3.88-3.83 (m, 2 H), 3.68-3.65 (m, 2 H), 3.58-3.42 (m, 2 H), 2.97-2.86 (m, 3 H), 2.72-2.62 (m, 3 H), 1.65-1.53 (m, 1 H), 1.32-1.17 (m, 18 H), 1.13-1.10 (t, J=6.8, 3 H).

³¹P NMR: (400 MHz, CD₃CN), δ ppm 149.85, 148.50; 23.46, 23.25.

Preparation of phosphoramidite-46



25 Add magnesium chips (0.48g, 20.0 mmol, 15.0eq) and anhydrous ethylene glycol monomethyl ether (50mL) to a 100mL stuffy jar, and heat the above mixture to 90°C and stir for 1 hour. Cool the stuffy jar to room temperature, add Phos-43-1G (0.5g, 1.33 mmol, 1.0eq), heat to 90°C and stir for 18h. The stuffy jar was cooled to room temperature, and LCMS detected that the reaction raw materials disappeared completely. The reaction solution was transferred into a flask, 0.5N dilute hydrochloric acid was added dropwise at 0°C to adjust the pH to 6, and extract 5 times with dichloromethane (50mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated in vacuo to obtain the crude product. The crude product was purified by flash column using the eluant (MeOH:DCM=0%-

10%) to elute the product. The product was concentrated under vacuum to obtain 0.13g of Phos-46-1A as a light yellow oil, with a yield of 20%.

LCMS: M+H=513.4 .

Add Phos-46-1A (0.1g, 0.19 mmol, 1.0eq), anhydrous dichloromethane (3mL) to the 50mL
5 flask, and then add tetrazole (16 mg, 0.23 mmol, 1.2eq) bis(diisopropyl) (2-cyanoethoxy)phosphine (0.09 g, 0.3 mmol, 1.5eq) in sequence. The above mixture was stirred at 25°C for 1 h under nitrogen protection. LCMS detected that the reaction was complete. The reaction solution was poured into a sodium bicarbonate aqueous solution and extracted twice with dichloromethane (10 mL). The combined organic phases were dried over anhydrous sodium
10 sulfate and concentrated in vacuo to obtain the crude product. The crude product was purified through a flash silica gel column, and the product was eluted with the eluent (DCM:MeOH:TEA=0%-5%+0.2%TEA). Concentrate under vacuum at 35°C to obtain phosphoramidite yellow oil Phos-46 (93 mg, yield 66.9%).

LCMS: M+H=713.6 .

15 ¹H NMR: (400 MHz, CD₃CN), δ ppm 8.92 (s, 1 H), 7.47-7.44 (dd, J=8.0, J=2.8, 1 H), 5.64-5.62 (d, J=8.0, 1 H), 4.78-4.68 (m, 1 H), 4.42-4.22 (m, 2H), 4.18-4.15 (m, 4 H), 3.92-3.85 (m, 2 H), 3.78-3.66 (m, 3 H), 3.60-3.52 (m, 5 H), 3.48-3.45 (m, 3 H), 3.36-3.35 (dd, J=2.4, J=0.8, 6 H), 3.28-3.27 (d, J=5.6, 3 H), 3.03-2.94 (m, 2 H), 2.75-2.63(m,3 H), 1.65-1.53 (m, 1 H), 1.22-1.17 (m, 12 H).

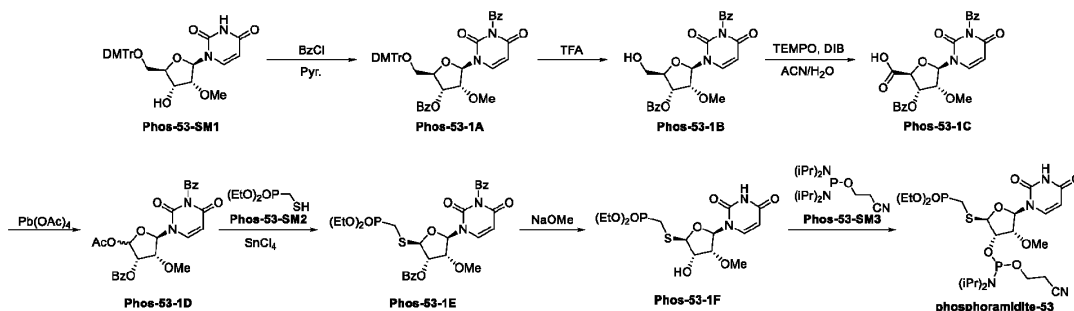
20 ³¹P NMR: (400 MHz, CD₃CN), δ ppm 149.85, 148.42; 24.43, 24.22.

5'-phosphonate modified nucleoside analogs herein can be prepared using similar methods or synthetic routes well known in the art.

The phosphoramidite compound described here is coupled into the 5' end of the oligonucleotide, thereby producing a 5'-terminal nucleotide, as described in CN110072530A and
25 CN103154014A, with each phosphonate group having a hydroxyl protecting group atoms, such as oxygen atoms containing two methyl or ethyl protections, remove one or both of the methyl or ethyl groups according to the deprotection step used. In some embodiments, use carbonitrile:trimethylsilyl iodide:pyridine v=50:2:2 (v/v/v) deethylation solution to remove ethyl protection.

30

Preparation of phosphoramidite-53



To a mixture of Phos-53-SM1 (25.00 g, 1.0 eq.) and DMAP (2.72 g, 0.5 eq.) in pyridine (250 mL) was added BzCl (31.34 g, 5.0 eq.) dropwise at 0°C and stirred at 24°C for 18 hrs. LCMS indicated Phos-53-1A was generated and Phos-53-SM1 was consumed. The mixture was quenched by MeOH and evaporated under reduced pressure to give the crude which was used for next step directly. Analytical data: MS: [M-H]⁻=768.

To a solution of Phos-53-1A (100 g, crude) in DCM (500 mL) was added TFA (15 mL) and stirred at 24°C for 2 hrs. LCMS indicated Phos-53-1A was consumed and Phos-53-1B was generated. The mixture was quenched by MeOH and evaporated under reduced pressure to give the crude which was purified by silica gel chromatography with a gradient of MeOH in DCM (0-50%) to give Phos-53-1B (20 g, 96% over two steps). Analytical data: [M+H]⁺=467.

To a solution of Phos-53-1B (20 g, 1.0 eq.) in ACN (210 mL) and H₂O (140 mL) was added 4-OH TEMPO (2.95 g, 0.4 eq.) and DIB (27.62 g, 2.0 eq.) then stirred at 24°C for 18 hrs. To the mixture was added 4-OH TEMPO (1.5 g, 0.2 eq.) and DIB (13 g, 0.95 eq.) and stirred at 24°C for 4 hrs. The mixture was diluted with ethyl acetate. The organic layer was separated and washed with water, brine, dried over Na₂SO₄, filtered and concentrated to give the crude which was purified by silica gel chromatography (MeOH in DCM=0-10%) to give Phos-53-1C (26 g, quant.). Analytical data: MS: [M+H]⁺=481.

To a solution of Phos-53-1C (26 g, 1.0 eq.) in THF (500 mL) was added Pb(OAc)₄ (71.98 g, 3.0 eq.) and stirred at 24°C for 18 hrs. LCMS indicated Phos-53-1C was consumed and Phos-53-1D was generated. The mixture quenched by water and diluted with EA then filtered through celite pad. The organic layer was washed with brine, dried over Na₂SO₄, filtered, evaporated under reduced pressure to give the crude which was purified by silica gel chromatography with a gradient of EA in PE (0-60%) to give Phos-53-1D (11.2 g, 53% over two steps). Analytical data: MS: [M+H]⁺=495.

To a solution of Phos-53-1D (8.0 g, 1.0 eq.) in DCM (80 mL) was added SnCl_4 (0.1 M, 17 mL, 1.05 eq.) dropwise at 0°C and stirred at 23°C for 20 min. Phos-53-SM2 (3.3 g, 1.1 eq.) was added to above mixture and stirred at rt overnight. LCMS indicated Phos-53-1D was consumed and Phos-53-1E was generated. The mixture quenched by water and diluted with EA. The organic layer was separated and washed with sat. NaHCO_3 aq., brine, dried over Na_2SO_4 , filtered and concentrated to give the crude (14 g). Analytical data: MS: $[\text{M}+\text{H}]^+=619$.

To a solution of Phos-53-1E (14 g, crude) in MeOH (150 mL) was added NaOMe (10.2 g, 2.5 eq., 30% wt. in MeOH) and stirred at 25°C for 1 hr. LCMS indicated Phos-53-1E was consumed and Phos-53-1F was generated. The mixture was neutralized by AcOH and concentrated to give the crude which was purified by silica gel chromatography with a gradient of MeOH in DCM (0-10%) to give Phos-53-1F (970 mg, 15% over two steps). Analytical data: MS: $[\text{M}+\text{H}]^+=411$.

To a mixture of Phos-53-1F (970 mg, 1.0 eq.) and tetrazole (265 mg, 1.6 eq.) in DCM (10 mL) was added Phos-53-SM3 (1.425 g, 2.0 eq.) and stirred at 24°C for 1 hr. LCMS indicated Phos-53-1F was consumed and Phos-53 was generated. The mixture was washed with sat. NaHCO_3 aq. then brine, dried over Na_2SO_4 , filtered, evaporated under reduced pressure to give the crude which was purified by reverse phase to give phosphoramidite -53 (1.1 g, 76%). Analytical data: MS: $[\text{M}+\text{H}]^+=611$,

^1H NMR (400 MHz, CD_3CN) δ 9.10 (s, 1H), 7.62 (t, 1H), 6.01 (dd, 1H), 5.62 (dd, 1H), 5.48 (dd, 1H), 4.32 (dddd, 1H), 4.12-3.92 (m, 5H), 3.83-3.64 (m, 2H), 3.61-3.49 (m, 2H), 3.30 (d, 3H), 3.00-2.71 (m, 2H), 2.60 (m, 2H), 1.21-1.15 (m, 6H), 1.13-1.08 (m, 1H).

Others 5'-phosphonate mimic phosphoramidite herein can be prepared using similar methods or synthetic routes well known in the art. The 5'-phosphonate mimic phosphoramidite compound described in Example is coupled into the 5' end of the oligonucleotide, thereby producing a 5'-terminal nucleotide well known in the art, such as described in CN110072530A and CN103154014A, with each phosphonate group having a hydroxyl protecting group atoms, such as oxygen atoms containing two methyl or ethyl protections, remove one or both of the methyl or ethyl groups according to the deprotection step used. In some embodiments, use carbonitrile:trimethylsilyl iodide:pyridine = 50:2:2 (v/v/v) deethylation solution to remove ethyl protection. In some embodiments, use phosphoramidite-53 is introduced to the 5' end of antisense strand producing a 5'-terminal phos-53 and/or phos-53* nucleotide.

Example 4. Synthesis of MAPT RNAi Agents.

MAPT RNAi agent duplexes shown in Table 2-3, above, were synthesized in accordance with the following general procedures:

Sense and antisense strand sequences of siRNA were synthesized on oligonucleotide synthesizers using a well-established solid phase synthesis method based on phosphoramidite chemistry. Oligonucleotide chain propagation is achieved through 4-step cycles: a deprotection, a condensation, a capping and an oxidation or a sulfurization step for addition of each nucleotide. Syntheses were performed on a solid support made of controlled pore glass (CPG, 1000 Å). Monomer phosphoramidites may be purchased from commercial sources or may be the phosphoramidite compounds in example 1. The phosphoramidite compounds herein may be attached to the 3'-end as a monomeric phosphoramidite, and further be attached to the CPG solid support. In the case of attachment at the 5'-end, the phosphoramidite compounds may be used for the final coupling reaction, and can be further conjugated to target ligands if necessary. Phosphoramidites with GalNAc ligand cluster (GLS-5* or GLS-15* Phosphoramidites as non-limiting examples) were public in WO2023/045995A1 (incorporated herein in its entirety). For siRNAs used for *in vitro* screening (Table 2), syntheses were carried out at 2 µmol scale, and for siRNAs used for *in vivo* testing (Table 3), syntheses were carried out at scale of 5 µmol or larger. In the case where the GalNAc ligand (GLO-n Phosphoramidites as non-limiting examples) were public in WO2023/045995A1 (incorporated herein in its entirety)) is attached at 3'-end of sense strand, GalNAc ligand attached CPG solid support was used. In the case where the GalNAc ligand (GLS-5* or GLS-15* as non-limiting example are attached at 5'-end of sense strand, GLS-5* or GLS-15* Phosphoramidites with GalNAc ligand cluster were public in WO2023/045995A1 (incorporated herein in its entirety)) are attached at 5'-end of sense strand, a GalNAc phosphoramidite was used for the last coupling reaction. Trichloroacetic acid (TCA) 3% in dichloromethane was used for deprotection of 4,4'-dimethoxytrityl protecting group (DMT). 5-Ethylthio-1H-tetrazole was used as an activator. I₂ in THF/Py/H₂O and phenylacetyl disulfide (PADS) in pyridine/MeCN was used for oxidation and sulfurization reactions, respectively. After the final solid phase synthesis step, solid support bound oligomer was cleaved and protecting groups were removed by treating with a 1:1 volume solution of 40 wt. % methylamine in water and 28% ammonium hydroxide solution. For the synthesis of siRNAs used for *in vitro* screening, crude mixture was concentrated. The remaining solid was dissolved in 1.0 M NaOAc, and ice cold EtOH was added to precipitate out the single strand product as the sodium salt, which was used for annealing without further purification. For the synthesis of siRNAs used for *in vivo* testing, crude single strand product was further purified by ion pairing reversed phase HPLC (IP-RP-HPLC). Purified single strand oligonucleotide product from IP-RP-HPLC was converted to sodium salt by dissolving in 1.0 M NaOAc and precipitation by addition of ice cold EtOH. Annealing of equimolar complementary sense stand and antisense strand oligonucleotide in water was performed to form the double strand siRNA product, which was lyophilized to afford a fluffy white solid.

In certain studies, a method used to attach a targeting group comprising GalNAc (also referred to herein as a GalNAc delivery compound) to the 5'-end of a sense strand included use of a GalNAc phosphoramidite (GLS-5* or GLS-15* Phosphoramidites) in the last coupling step in the solid phase synthesis, using a synthetic process such as the process used if oligonucleotide chain propagation of adding a nucleotide to the 5'-end of the sense strand is performed.

In some studies a method of attaching a targeting group comprising GalNAc to the 3'-end of a sense strand comprised use of a solid support (CPG) that included a GLO-n. In some studies, a method of attaching a targeting group comprising GalNAc to the 3'-end of a sense strand comprises attaching a GalNAc targeting group to CPG solid support through an ester bond and using the resulting CPG with the attached GalNAc targeting group when synthesizing the sense strand, which results in the GalNAc targeting group attached at the 3'-end of the sense strand.

The imann residues can be added to the 5' end or 3' end of the oligonucleotide chain by a method well known to those skilled in the art, such as the inverted abasic residues (invab) method, and/or further added to the target to the GalNAc targeting group.

Example 5. *In Vitro* Screening of MAPT siRNA Duplexes

Huh7 cells were trypsinized and adjusted to appropriate density, mixed with the complexes of MAPT-psiCHECK^(TM)-2 and Lipofectamine 2000 (Invitrogen-11668-019) and seeded into 96-well plates. Cells were transfected with test siRNAs or a control siRNA using Lipofectamine RNAiMax (Invitrogen -13778-150) at the same time of seeding following the protocol according to manufacturer's recommendation. The siRNAs were tested at two concentrations (0.5 nM and 5 nM) in triplicate.

Day 1, MAPT-psiCHECK^(TM)-2 transfection (one plate)

(1) Transfer 2.5μg MAPT-psiCHECK^(TM)-2 Vector plasmid into an RNASE free Eppendorf tube (solution mix#1)

(2) Add trypsin to disassociate Huh7 cells in one flask, and count cells using Vi-Cell counting machine, adjust the cell density to 1×10^5 /ml

(3) Transfer 7.5μL Lipofectamine 2000 (Invitrogen-11668-019) into solution mix#1 tube, mix.

(4) Add solution in Step 3 into cell suspension, mix, and dispense suspension into the 96 well plate (100 μl/well)

Day 2, siRNAs transfection

(1) Dilute Lipofectamine®RNAiMAX Reagent with Opti-MEM® Medium.

(2) Dilute the siRNA with RNA-free water to make 12× stock.

(3) Mix equal volume of diluted RNAiMax and siRNA. Incubate the mixture at RT for 15 min to allow complex formation.

(4) Add 45µl /well compound Lipofectamine® RNAiMAX(Opti-MEM) mix into 225µl /well DMEM fresh medium, and discard the supernatants in assay plate, add 120µl /well

5 compound mix into 96 well plates.

(5) No compound control well was defined as cells transfected with MAPT-psiCHECK^(TM)-2 and without siRNA treatment; blank control was cell only wells.

Day 3, Dual-Glo® Luciferase Assay

(1) Add Reagent to assay plate, wait 10 minutes to allow for cell lysis to occur.

10 (2) Transfer 100 µl cell lysates into a plate, then measure the firefly luminescence.

(3) Add 50µl of Dual-Glo® Stop & Glo® Reagent to the assay plates and mix, wait 10 minutes, then measure Renilla luminescence.

(4) Calculate the relative expression

Data analysis

15 Ratio of sample well= (sample Renilla luminescence-background blank)/ (sample Fireflyluminescence-background blank)

Ratio of no compound control well= (control Renilla luminescence-background blank)/ (control sample Fireflyluminescence-background blank)

20 % inhibition= 100-(Ratio of sample well/ the average Ratio of no compound control) ×100%

The duplex sequences used correspond to those shown in Table 5-6.

Table 5 provides experimental results of *in vitro* studies using various MAPT RNAi agents to inhibit MAPT expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Average Inhibition % (Mean ± SD)	
	5nM	0.5nM
AV03728	-3.75±9.00	-6.50±7.47
AV03729	31.25±5.39	3.18±6.40
AV03730	32.44±6.90	8.58±10.77
AV03731	23.92±3.58	-14.47±4.24
AV03732	46.25±5.58	1.64±7.08
AV03733	51.55±5.66	9.83±7.92
AV03734	42.12±6.28	12.81±2.14
AV03735	40.80±2.29	16.82±3.84
AV03736	46.75±6.72	-3.15±5.29
AV03737	35.07±5.43	-21.56±2.81
AV03738	7.69±3.09	-8.54±12.31
AV03739	46.71±0.66	1.21±19.37

AV03741	48.29±1.47	11.33±16.11
AV03743	29.15±3.38	4.45±5.80
AV03744	39.30±3.51	14.28±4.13
AV03745	20.71±5.49	-14.86±7.33
AV03746	54.40±11.71	19.16±4.70
AV03747	44.08±5.54	4.21±5.09
AV03748	26.37±3.71	-15.31±11.45
AV03749	20.65±10.49	-2.90±3.65
AV03750	60.45±5.16	23.42±5.39
AV03751	28.33±4.63	0.44±10.64
AV03752	50.68±5.59	15.57±5.99
AV03753	8.17±8.83	-33.71±3.83
AV03754	54.43±5.29	23.53±4.90
AV03755	5.92±5.64	-9.12±6.80
AV03756	26.43±8.49	3.13±9.69
AV03757	27.05±3.36	2.57±3.03
AV03761	23.78±2.50	-5.82±19.78
AV03764	33.54±5.17	5.90±8.15
AV03765	42.52±4.26	12.67±3.24
AV03768	57.98±7.00	21.13±7.27
AV03771	38.85±5.72	1.07±2.50
AV03779	43.75±5.54	3.43±3.14
AV03791	44.93±6.69	20.23±5.37
AV03793	53.42±5.73	12.84±6.45
AV03794	46.23±1.14	7.70±11.35
AV03795	52.68±4.13	0.66±14.20
AV03798	67.56±3.15	39.55±5.94
AV03799	50.96±3.56	31.72±5.45
AV03800	48.05±9.64	14.14±3.74
AV03801	6.04±18.49	-11.97±6.95
AV03802	47.42±10.27	12.80±3.98
AV03803	42.69±7.55	2.92±1.89
AV03804	61.36±4.84	43.00±5.68
AV03807	56.18±0.58	37.62±3.16
AV03808	25.13±3.05	10.04±9.67
AV03809	54.52±1.17	23.34±10.04
AV03810	1.25±13.07	0.98±9.01
AV03811	10.41±5.63	11.80±2.52
AV03812	40.76±3.18	8.67±7.66
AV03813	28.59±3.26	5.51±8.71
AV03814	13.81±14.00	2.09±4.06
AV03815	34.19±6.56	8.80±7.25
AV03816	31.63±8.28	6.65±0.76
AV03817	61.39±4.31	43.83±5.93
AV03818	53.40±5.74	5.43±12.91
AV03819	6.32±4.22	0.76±1.83

AV03820	35.16±5.82	13.95±15.05
AV03821	-0.37±9.52	-5.90±10.30
AV03822	42.92±4.60	27.23±3.12
AV03823	32.16±10.12	8.29±6.60
AV03825	32.08±3.60	6.36±6.63
AV03826	60.11±5.13	13.62±10.84
AV03827	63.03±10.53	20.89±3.24
AV03828	47.25±5.28	-1.29±3.26
AV03829	62.71±2.04	12.90±8.60
AV03831	79.56±1.94	62.16±10.27
AV03832	75.66±6.64	38.35±6.89
AV03833	65.72±5.25	21.43±14.84
AV03834	62.75±5.36	34.54±6.44
AV03835	77.18±5.27	71.79±2.49
AV03836	70.54±3.45	63.11±3.63
AV03837	76.94±4.67	51.71±4.75
AV03838	75.17±4.47	57.04±2.27
AV03839	64.12±3.33	23.05±7.57
AV03840	63.26±8.76	4.81±7.68
AV03841	51.19±6.87	14.75±10.24
AV03842	70.23±2.67	32.15±8.36
AV03843	8.03±11.11	2.39±12.84
AV03844	12.04±4.29	0.13±8.67
AV03845	15.08±22.24	9.26±7.42
AV03846	16.64±9.90	15.92±12.38
AV03847	9.43±18.06	13.73±16.87
AV03848	3.02±19.90	5.36±22.51
AV03849	-18.55±12.79	-7.46±25.01
AV03850	19.46±2.41	2.61±7.12
AV03851	8.39±8.63	4.58±2.65
AV03852	-3.89±7.53	10.40±22.14
AV03853	10.87±15.36	-2.30±16.24
AV03854	5.74±1.65	3.61±9.55
AV03855	15.83±8.99	16.28±9.98
AV03856	-22.70±12.09	-10.04±17.18
AV03857	1.48±9.36	-15.04±8.34
AV03858	16.10±6.93	12.79±4.81
AV03859	5.31±10.92	1.87±11.62
AV03860	15.29±15.88	-2.10±13.00
AV03861	11.21±5.12	12.03±8.47
AV03862	24.62±8.33	16.73±7.92
AV03863	21.81±10.11	0.82±15.24
AV03864	-11.57±20.31	6.95±21.73
AV03865	-1.44±5.77	-1.17±7.67
AV03866	5.68±10.89	2.26±8.42
AV03867	2.61±7.07	10.00±5.60

AV03868	4.00±8.13	9.62±14.53
AV03869	3.01±6.33	5.42±16.56
AV03870	-2.34±5.96	8.47±9.11
AV03871	7.80±19.47	4.81±13.38
AV03872	-33.16±7.77	-74.66±24.29
AV03873	-26.94±14.87	-31.04±5.02
AV03874	-26.74±9.41	-36.03±11.97
AV03875	-17.97±22.75	-26.68±12.82
AV03876	-31.98±11.52	-16.84±29.85
AV03877	-0.81±26.89	-18.85±17.07
AV03878	-24.92±6.87	-16.60±20.45
AV03879	23.88±11.98	1.72±4.87
AV03880	-29.74±14.68	-3.51±35.47
AV03881	-26.97±17.44	-2.24±6.32
AV03882	-19.59±13.44	-1.33±41.75
AV03883	-3.75±13.95	-1.08±24.10
AV03884	-20.65±14.71	-1.29±20.51
AV03885	-31.09±5.28	-0.67±24.60
AV03886	-31.95±13.67	0.20±27.80
AV03887	-15.47±14.59	-3.20±17.75
AV03888	-31.99±10.74	-12.79±14.63
AV03889	-17.91±14.64	-14.28±27.40
AV03890	-5.94±9.17	-9.76±4.73
AV03891	-0.57±25.07	15.90±13.29
AV03892	11.34±11.05	-6.91±23.88
AV03893	-0.59±7.23	-3.53±4.95
AV03894	15.47±7.73	-2.85±20.42
AV03895	13.13±21.28	7.29±14.66
AV03896	-26.36±26.50	7.53±13.41
AV03897	-6.91±23.00	-9.66±22.23
AV03898	-1.40±3.60	5.09±24.17
AV03899	-1.08±17.49	-4.39±23.55
AV03900	1.87±17.37	5.04±20.63
AV03901	14.14±14.69	-2.21±21.88
AV03902	1.04±6.58	-8.89±7.03
AV03903	27.26±12.04	1.31±17.46
AV03904	-9.18±18.95	-26.31±18.14
AV03905	-5.65±2.70	-10.16±18.59
AV03906	-35.28±16.32	-8.37±15.50
AV03907	7.00±21.94	-15.68±15.05
AV03908	-14.93±13.27	-24.75±26.83
AV03909	7.39±21.17	-2.20±1.85
AV03910	-5.51±10.59	-13.41±16.87
AV03911	22.82±12.20	6.39±11.85
AV03912	-9.97±14.08	-19.91±18.47
AV03913	-8.38±13.93	-8.24±20.59

AV03914	-8.73±2.75	2.47±12.56
AV03915	-16.02±8.05	-12.61±13.45
AV03916	-0.10±6.80	8.08±9.70
AV03917	-5.16±8.95	-5.49±13.56
AV03918	-1.83±20.61	-3.63±5.72
AV03919	16.28±7.42	9.98±3.07
AV03920	-16.66±8.35	-15.16±6.44
AV03921	-13.44±10.57	-13.09±2.51
AV03922	-12.20±9.38	-21.91±1.68
AV03923	-5.13±15.47	-8.23±4.92
AV03924	-1.62±11.43	-14.70±9.35
AV03925	-0.04±11.17	-10.54±6.42
AV03926	-6.27±10.07	-6.53±10.43
AV03927	-28.75±16.80	-0.60±9.92
AV03928	-17.26±19.70	-23.23±5.41
AV03929	-30.56±10.76	-32.94±4.27
AV03930	-9.30±15.75	-23.02±5.35
AV03931	-17.05±9.45	-17.56±13.51
AV03932	-10.65±14.69	-17.33±9.01
AV03933	-12.32±3.68	-15.23±3.86
AV03934	-9.87±12.55	-12.24±6.08
AV03935	-6.52±11.89	-1.83±13.80
AV03936	-10.67±9.39	-4.45±1.84
AV03937	-3.47±8.69	-2.71±8.09
AV03938	9.35±0.69	13.38±6.36
AV03939	10.60±1.57	1.95±9.74
AV03940	8.15±5.69	0.46±4.82
AV03941	13.31±4.04	11.09±14.28
AV03942	14.49±6.14	4.53±4.09
AV03943	2.03±12.09	4.31±7.48
AV03944	5.26±10.82	-11.52±7.33
AV03945	-6.48±7.70	-8.88±18.01
AV03946	12.54±7.99	10.86±5.10
AV03947	4.14±7.07	9.48±2.92
AV03948	11.83±2.98	7.69±6.25
AV03949	14.18±9.47	6.04±5.25
AV03950	2.08±8.96	0.11±8.31
AV03951	2.87±9.23	0.50±4.71
AV03952	-18.99±7.76	-25.61±6.82
AV03953	-18.13±16.39	-21.16±7.60
AV03954	-14.59±9.06	-12.77±10.89
AV03955	-9.79±6.81	-4.39±12.29
AV03956	-0.88±2.73	-13.21±6.56
AV03957	-9.51±10.58	2.36±5.29
AV03958	-2.12±4.58	0.20±12.37
AV03959	4.69±4.41	7.78±4.07

AV03960	-11.83±9.00	-13.65±8.93
AV03961	-12.71±5.41	-16.80±4.42
AV03962	-7.22±0.87	-5.76±2.84
AV03963	-0.38±15.09	-16.96±10.06
AV03964	-7.36±8.95	-10.79±7.00
AV03965	-8.53±10.37	6.99±6.76
AV03966	-0.61±2.83	-1.34±7.06
AV03967	0.72±7.37	-5.51±1.05
AV03968	-28.35±14.71	-33.46±7.26
AV03969	-19.64±10.20	-14.59±10.51
AV03970	-11.62±5.70	-6.55±6.40
AV03971	-12.76±8.06	-5.91±4.86
AV03972	-4.89±2.01	-5.80±8.43
AV03973	-6.54±7.99	-6.31±8.08

Table 6 provides experimental results of *in vitro* studies using various MAPT RNAi agents to inhibit MAPT expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Average Inhibition % (Mean ± SD)	
	5nM	0.5nM
AV03739	40.99±11.21	12.36±3.75
AV03740	17.49±7.73	12.26±7.82
AV03741	44.62±9.53	4.60±14.12
AV03743	19.72±3.35	-24.59±19.24
AV03746	56.78±10.86	10.17±8.60
AV03748	26.74±9.49	-11.95±6.79
AV03749	25.25±13.17	-7.44±13.40
AV03750	58.79±6.89	15.47±1.82
AV03752	56.50±3.58	20.16±13.39
AV03756	30.39±3.13	-10.78±11.66
AV03757	27.19±9.90	9.81±8.59
AV03758	21.49±2.76	-6.96±11.74
AV03759	30.70±4.21	-21.60±13.98
AV03760	21.24±10.91	4.08±20.63
AV03761	29.25±1.39	-1.98±18.24
AV03762	11.16±11.24	19.60±3.63
AV03763	4.11±12.88	2.25±7.53
AV03764	44.38±7.75	-2.37±5.82
AV03765	46.93±9.42	9.06±17.00
AV03766	21.68±2.43	5.46±6.75
AV03767	7.90±14.05	7.70±13.43
AV03768	62.80±9.36	17.52±7.26
AV03769	41.78±13.33	12.95±9.84
AV03770	54.04±2.06	12.97±18.56
AV03772	65.74±1.83	38.59±9.69
AV03773	42.54±5.45	-7.71±20.16

AV03774	50.90±3.85	11.28±13.45
AV03775	50.79±9.15	-6.88±10.65
AV03776	10.54±14.21	-1.55±19.87
AV03777	29.09±12.38	11.65±11.98
AV03778	4.45±5.66	9.35±13.18
AV03779	40.96±10.10	9.71±14.36
AV03780	-0.99±4.66	-6.74±11.45
AV03781	6.65±17.90	-0.56±10.98
AV03782	29.41±12.82	5.10±17.53
AV03783	3.67±11.73	-4.90±12.37
AV03784	43.44±6.25	1.47±16.97
AV03785	42.09±5.71	2.21±14.44
AV03786	59.23±6.10	2.04±4.27
AV03787	29.91±6.78	1.49±1.06
AV03788	12.83±6.63	1.77±16.67
AV03789	9.42±12.52	1.39±13.80
AV03790	26.38±8.73	1.77±8.52
AV03792	60.51±5.97	-4.46±13.00
AV03793	55.14±3.08	1.19±37.31
AV03794	44.91±9.89	-3.48±28.48
AV03795	58.78±5.15	12.99±14.28
AV03796	56.06±2.46	4.98±9.28
AV03797	64.67±9.43	23.43±2.11
AV03798	68.32±2.13	38.74±12.23
AV03799	49.14±3.65	10.50±14.35
AV03804	62.33±1.83	41.89±9.77
AV03805	51.78±6.70	-1.32±0.76
AV03806	47.39±9.04	2.58±10.19
AV03807	53.06±6.52	19.12±4.46
AV03811	10.78±12.30	-3.78±5.64

Example 6 . *In Vivo* Screening of MAPT siRNA Duplexes

At day 1, female C57BL/6J mice (3 in each group) were infected by intravenous administration of a solution of adeno-associated virus 8 (AAV8) vector encoding human MAPT (respectively fused to MAPT target sequence comprising nucleotides 148-3521 Of SEQ ID NO: 1). At day 8, mice were subcutaneously administered a single 5 mg/kg of MAPT siRNA agents or Saline. Liver tissue samples were collected at day 15 for quantification of MAPT mRNA level through QPCR protocol. The results are shown in Tables 7. All the MAPT RNAi agents tested exhibited MAPT inhibition in MAPT transduced mice.

Tables 7 provides experimental results of in vivo studies using various MAPT RNAi agents to inhibit MAPT expression. The duplex sequences used correspond to those shown in Table 3.

Compound_ID	MAPT-A remaining relative to control (Mean ± SEM)	Dosage mg/kg
	D15	

AD01562	0.13±0.02	5.00
AD01562-1	0.09±0.01	5.00
AD01564	0.43±0.03	5.00
AD01565	0.2±0.03	5.00
AD01566	0.09±0.02	5.00
AD01567	0.11±0.01	5.00
AD01568	0.17±0.02	5.00
AD01569	0.3±0.17	5.00
AD01570	0.51±0.12	5.00
AD01571	0.19±0.02	5.00
AD01572	0.13±0.04	5.00
AD01573	0.1±0.05	5.00
AD01574	0.34±0.06	5.00
AD01575	0.27±0.02	5.00
AD01576	0.15±0.03	5.00
AD01577	0.73±0.11	5.00
AD01578	0.56±0.11	5.00
AD01579	0.35±0.08	5.00
AD02147	0.33±0.1	5.00
AD02148	0.08±0.04	5.00
AD02149	0.11±0.04	5.00
AD02150	0.13±0.01	5.00
AD02151	0.12±0.05	5.00
AD02152	0.23±0.07	5.00
AD02153	0.11±0.03	5.00
AD02154	0.22±0.1	5.00
AD02155	0.33±0.01	5.00
AD02156	0.44±0.13	5.00
AD02157	0.32±0.09	5.00
AD02158	0.15±0.02	5.00
AD02159	0.51±0.04	5.00
AD02160	0.56±0.04	5.00
AD02161	0.54±0.12	5.00
AD02162	0.21±0.1	5.00
AD02163	0.25±0.11	5.00
AD02164	0.2±0.06	5.00
AD02165	0.41±0.16	5.00
AD02166	0.5±0.19	5.00
AD02167	0.29±0.13	5.00
AD02168	0.17±0.02	5.00
AD02169	0.25±0.03	5.00
AD02170	0.22±0.08	5.00
AD02171	0.3±0.09	5.00
AD02172	0.27±0.04	5.00
AD02173	0.14±0.11	5.00
AD02174	0.47±0.02	5.00

AD02175	0.39±0.02	5.00
AD02176	0.54±0.09	5.00
AD02177	0.56±0.15	5.00

Example 7 . *In Vivo* Screening of MAPT siRNA Duplexes

At day 1, female C57BL/6J mice (3 in each group) were infected by intravenous administration of a solution of adeno-associated virus 8 (AAV8) vector encoding human MAPT (respectively fused to MAPT target sequence comprising nucleotides 148-3521 Of SEQ ID NO: 1). At day 8, mice were subcutaneously administered a single 2 mg/kg of MAPT siRNA agents or Saline. Liver tissue samples were collected at day 15 for quantification of MAPT mRNA level through QPCR protocol. The results are shown in Tables 8-9. All the MAPT RNAi agents tested exhibited MAPT inhibition in MAPT transduced mice.

Tables 8 provides experimental results of in vivo studies using various MAPT RNAi agents to inhibit MAPT expression. The duplex sequences used correspond to those shown in Table 3.

Compoud_ID	MAPT-A remaining relative to control (Mean ± SEM)	Dosage mg/kg
	D15	
Saline	1±0.03	/
AD01562	0.37±0.04	2.00
AD01562-1	0.15±0.02	2.00
AD01566	0.3±0.12	2.00
AD01567	0.22±0.02	2.00
AD01568	0.36±0.04	2.00
AD01571	0.28±0.04	2.00
AD01572	0.21±0.06	2.00
AD01573	0.28±0.06	2.00
AD01576	0.25±0.01	2.00
AD02148	0.16±0.03	2.00
AD02149	0.2±0.02	2.00
AD02150	0.19±0.01	2.00
AD02151	0.19±0.02	2.00
AD02153	0.2±0.02	2.00
AD02158	0.24±0.03	2.00
AD02168	0.25±0.03	2.00
AD02173	0.74±0.03	2.00

Tables 9 provides experimental results of in vivo studies using various MAPT RNAi agents to inhibit MAPT expression. The duplex sequences used correspond to those shown in Table 3.

Compoud_ID	MAPT-A remaining relative to control (Mean ± SEM)	Dosage mg/kg
	D15	
AD01562-1	0.17±0.04	2.00
AD02754	0.34±0.01	2.00
AD02755	1.25±0.39	2.00

AD02756	0.59±0.07	2.00
AD02757	0.16±0.03	2.00
AD02758	0.2±0.12	2.00
AD02759	0.21±0.07	2.00
AD02760	0.5±0.11	2.00
AD02761	0.38±0.13	2.00
AD02762	0.36±0.1	2.00
AD02763	0.42±0.08	2.00
AD02764	0.17±0.09	2.00
AD02765	0.45±0.08	2.00
AD02766	0.37±0.03	2.00
AD02767	0.43±0.22	2.00
AD02768	0.63±0.02	2.00
AD02769	0.71±0.08	2.00
AD02770	0.46±0.07	2.00
AD02771	1.15±0.23	2.00
AD02772	0.79±0.18	2.00
AD02773	0.66±0.16	2.00
AD02774	0.32±0.05	2.00
AD02775	0.49±0.02	2.00
AD02776	1.19±0.57	2.00
AD02777	0.51±0.16	2.00
AD02778	0.5±0.02	2.00
AD02779	0.95±0.02	2.00
AD02780	0.52±0.06	2.00
AD02781	0.44±0.07	2.00
AD02782	0.24±0.03	2.00
AD02783	0.22±0.07	2.00
AD02784	0.02±0.01	2.00

Example 8. *In Vitro* Screening of MAPT siRNA Duplexes

Huh7 cells were trypsinized and adjusted to appropriate density seeded into 96-well plates. Cells were transfected with the complexes of psiCHECK(TM)-2 Vector plasmid, blank vector PCNDA3.0, siRNAs or a control siRNA using Lipofectamine 2000 (Invitrogen-
5 11668-019) at the next day of seeding following the protocol according to manufacturer's recommendation. The siRNAs were tested at different concentrations (0.5nM and 5nM) in triplicate.

Day 1, Add trypsin to disassociate Huh7 cells in one flask, and count cells using Vi-Cell counting machine, adjust the cell density to 1×10^5 /ml and culture with DMEM medium.

10 Day 2, MAPT-psiCHECK(TM)-2 Vector/blank vector pCDNA3.0/siRNAs/
Lipofectamine 2000 mixture transfection

(1) Mix appropriate Lipofectamine 2000 (Invitrogen-11668-019) with Opti-MEM® Medium (solution mix#1). Final equal 0.3 µl Lipofectamine 2000 and Opti-MEM® Medium 4.7 µl per well.

(2) Mix appropriate MAPT-psiCHECK(TM)-2 Vector, blank pCNDNA 3.0 vector and
5 siRNAs with Opti-MEM® Medium per well (solution mix#2).

(3) Mix equal volume of solution mix#1 and mix#2, final 10 µl per well. Incubate the mixture at RT for 15 min to allow complex formation.

(4) Remove DMEM medium, add 10 µl mixed solution mix#1 and mix#2 and 90 µl fresh DMEM medium.

10 (5) No compound control well was defined as cells transfected with MAPT-psiCHECK(TM)-2 Vector and blank vector pCNDNA 3.0 and without siRNA treatment; blank control was cell only wells.

Day 3, Dual Glo Luciferase Assay

15 (1) Add the Renilla luciferase detection reagent that is equilibrated to room temperature, and the sample volume is the same as that of the initial cell culture medium and mixed thoroughly. (For example, for a 96-well plate, it is recommended to add 80 ul of culture medium and 80 ul of detection reagents accordingly.

(2) Mix at room temperature on a horizontal shaker for at least 10 minutes.

20 (3) Detect the luminescence signal of Renilla luciferase on a chemiluminescence detector or a multifunctional microplate reader with a chemiluminescence module, and complete the detection within 2 hours after adding the detection reagent. The detection sequence of Renilla luciferase on the microtiter plate should be the same as that of firefly luciferase.

25 Data analysis

Experimental design: According to different experimental purposes, a blank control group, experimental group and control group should be set in each culture plate.

a. Blank control groups

Background F: untransfected cells + firefly luciferase detection reagent.

30 Background R: untransfected cells + firefly luciferase detection reagent + Renilla luciferase detection reagent

Note: The amount of sample used in the blank control group must be the same as that of the experimental sample, and contain the same medium/serum combination as the experimental sample.

b. Experimental group: Transfected cells are treated with experimental compounds (ie experimental group F and experimental group R).

c. Control group: The transfected cells are not treated to standardize the results (ie, control group F and control group R).

5 Calculation result:

The ratio of the experimental group=(experimental group F-background F)/(experimental group R-background R), the ratio of the control group=(control group F-background F)/(control group R-background R).

Expression multiple = ratio of experimental group/ratio of control group.

10 The duplex sequences used correspond to those shown in Table 10-11.

Table 10 provides experimental results of *in vitro* studies using various MAPT RNAi agents to inhibit MAPT expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Inhibition%	
	5nM	0.5nM
	MEAN±SD	
AV07298	-11.50±0.82	-11.09±10.62
AV07299	-16.79±5.81	-16.57±6.26
AV07300	3.29±3.31	12.99±1.50
AV07301	-4.42±1.44	-9.18±7.31
AV07302	25.68±0.93	5.72±6.08
AV07303	4.14±7.15	-8.51±1.93
AV07304	33.93±1.60	26.51±3.28
AV07306	40.08±3.34	33.69±1.87
AV07307	47.84±4.38	70.36±0.55
AV07308	25.00±3.65	35.10±2.91
AV07309	39.49±2.29	34.35±3.06
AV07310	38.87±4.18	29.95±3.70
AV07311	71.40±1.00	60.41±2.95
AV07312	49.34±2.57	33.52±4.57
AV07314	55.73±1.09	29.38±5.07
AV07315	37.19±1.77	32.77±0.12
AV07316	17.63±2.41	19.82±9.16
AV07317	11.92±7.11	-6.29±5.63
AV07318	63.03±0.40	56.37±3.61
AV07319	46.64±2.46	4.90±11.20
AV07320	3.57±7.16	3.04±8.75
AV07322	74.50±1.12	68.18±1.85
AV07323	31.90±4.41	21.62±5.49
AV07324	31.08±2.45	37.85±2.10
AV07325	41.45±4.19	19.37±0.18
AV07326	-16.60±8.34	-15.00±9.39

AV07327	-4.74±3.29	-14.56±11.71
AV07328	13.24±6.76	6.87±6.72
AV07330	-8.43±6.15	-9.20±7.81
AV07331	56.20±2.03	44.28±2.97
AV07332	-12.09±2.33	-12.14±2.37
AV07333	-10.46±0.96	-4.54±4.72
AV07334	-8.32±3.73	-3.92±13.67
AV07335	-3.34±4.63	-13.54±6.12
AV07336	5.88±5.01	19.74±1.09
AV07338	66.10±0.45	62.68±1.38
AV07339	66.47±2.75	44.63±2.15
AV07340	73.25±2.02	68.93±4.08
AV07341	77.09±0.97	74.85±2.12
AV07342	16.00±4.99	-6.51±0.81
AV07343	57.53±3.51	29.58±2.78
AV07344	12.57±2.57	11.97±7.04
AV07346	37.00±5.22	26.98±5.70
AV07347	-9.59±3.03	-7.60±5.62
AV07348	53.95±1.22	32.42±3.81
AV07349	25.00±4.51	11.22±2.05
AV07350	3.79±4.89	-4.89±6.16
AV07351	11.35±3.65	19.06±3.97
AV07352	36.47±4.20	30.42±1.21
AV07354	60.71±2.78	50.83±1.96
AV07355	17.44±5.90	-3.31±5.50
AV07356	48.76±3.24	54.35±0.41
AV07357	46.47±3.78	23.27±2.82
AV07358	45.66±1.33	32.97±0.56
AV07359	39.52±2.37	18.32±3.66
AV07360	35.85±6.65	18.02±5.14
AV07362	32.70±1.34	22.27±5.25
AV07363	72.58±1.97	53.43±1.68
AV07364	-4.69±6.96	-1.85±6.51
AV07365	-2.05±3.71	0.11±12.16
AV07366	7.25±3.82	6.79±6.49
AV07367	8.54±6.55	-5.90±3.69
AV07368	11.09±2.12	16.74±12.80
AV07370	45.28±3.98	45.14±3.25
AV07371	72.29±2.08	64.50±2.70
AV07372	69.73±1.79	72.31±0.53
AV07373	55.74±0.50	52.62±1.17
AV07374	55.03±5.48	46.40±2.44
AV07375	80.21±1.10	74.86±1.48
AV07376	47.96±3.54	44.78±2.27
AV07378	39.52±5.48	16.61±5.24
AV07379	72.12±1.42	74.01±1.62

AV07380	-9.33±9.05	-6.11±4.06
AV07381	9.37±5.32	15.64±6.10
AV07382	28.63±2.92	20.10±0.19
AV07383	48.26±4.69	19.91±1.81
AV07384	55.79±1.71	45.27±3.38
AV07386	0.90±8.78	0.43±7.52
AV07387	-12.46±2.80	-9.71±3.73
AV07388	55.74±4.92	51.50±3.13
AV07389	76.79±0.69	76.73±0.94
AV07390	38.37±2.77	35.94±4.39
AV07391	19.87±0.74	16.65±4.56
AV07392	44.86±2.00	19.75±2.97
AV07305	14.38±3.12	14.29±5.66
AV07313	48.89±2.03	27.27±1.02
AV07321	23.77±2.44	4.15±4.21
AV07329	18.23±0.50	10.93±1.69
AV07337	69.33±0.88	53.70±5.15
AV07345	66.25±2.24	59.08±3.66
AV07353	56.01±10.60	51.80±0.57
AV07361	7.01±2.61	-11.90±4.80
AV07369	-1.05±1.09	-10.86±4.47
AV07377	40.89±2.69	26.03±2.12
AV07385	31.03±4.43	26.41±5.49
AV07393	28.67±4.47	19.39±6.39

Table 11 provides experimental results of *in vitro* studies using various MAPT RNAi agents to inhibit MAPT expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Inhibition%	
	5nM	0.5nM
	MEAN±SD	
AV07394	12.02±10.17	1.14±10.04
AV07395	36.55±5.32	14.64±1.56
AV07396	1.11±9.52	4.01±6.54
AV07397	-10.63±7.01	-2.77±8.65
AV07398	-4.94±4.18	7.87±3.18
AV07399	6.28±2.76	17.15±3.61
AV07400	-1.88±9.97	0.52±5.95
AV07402	-6.47±2.65	-14.32±2.01
AV07403	-17.11±5.51	-17.46±5.32
AV07404	30.78±2.87	17.43±7.99
AV07405	60.23±2.63	39.27±3.22
AV07406	71.01±1.94	66.87±2.67
AV07407	76.23±1.05	70.18±1.98
AV07408	69.41±1.37	59.87±1.15
AV07410	60.71±3.29	26.74±3.36

AV07411	55.26±2.36	64.38±1.69
AV07412	29.59±4.31	40.28±0.44
AV07413	52.89±3.72	70.54±2.93
AV07414	70.84±1.52	69.62±1.91
AV07415	50.07±1.59	59.75±0.99
AV07416	21.64±6.77	21.54±6.72
AV07418	64.26±2.84	56.52±4.73
AV07419	62.43±0.94	45.53±2.87
AV07420	63.56±2.08	36.56±3.87
AV07421	75.70±1.06	62.24±2.62
AV07422	37.56±3.82	40.03±4.00
AV07423	12.40±4.32	3.23±3.39
AV07424	-8.08±2.84	-2.43±4.48
AV07426	-13.81±6.40	-9.61±13.34
AV07427	41.25±5.95	10.44±3.14
AV07428	63.03±4.32	50.54±4.26
AV07429	23.54±8.44	29.88±2.45
AV07430	-0.02±6.15	-1.03±2.75
AV07431	-0.06±3.39	12.23±0.79
AV07432	33.36±3.06	52.89±2.16
AV07434	-24.10±9.67	-18.82±5.35
AV07435	-15.57±9.09	-8.59±9.91
AV07436	-15.51±2.38	-6.55±6.71
AV07437	14.95±6.24	2.42±6.77
AV07438	3.29±2.28	-2.43±5.47
AV07439	12.50±4.18	9.56±3.34
AV07440	-7.37±1.49	-11.36±8.28
AV07401	3.47±4.65	-8.42±0.99
AV07409	-0.83±3.61	-7.91±8.11
AV07417	55.95±6.46	47.04±2.51
AV07425	45.74±4.05	28.82±4.66
AV07433	-1.98±8.75	14.47±3.20
AV07441	-10.50±0.94	-11.49±7.00
AV07442	-5.76±1.63	-6.18±7.10

Example 9 . *In Vivo* Screening of MAPT siRNA Duplexes

At day 1, female C57BL/6J mice (3 in each group) were infected by intravenous administration of a solution of adeno-associated virus 8 (AAV8) vector encoding human MAPT (respectively fused to MAPT target sequence comprising nucleotides 148-3521 Of SEQ ID NO: 1). At day 12, mice were subcutaneously administered a single 2 mg/kg of MAPT siRNA agents or Saline. Liver tissue samples were collected at day 19 for quantification of MAPT mRNA level through QPCR protocol. The results are shown in Tables 12. All the MAPT RNAi agents tested exhibited MAPT inhibition in MAPT transduced mice.

Tables 12 provides experimental results of in vivo studies using various MAPT RNAi agents to inhibit MAPT expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	MAPT remaining relative to control (Mean $\pm$ SEM)	Dosage mg/kg
	D19	
Saline	1.07 $\pm$ 0.26	/
AD01562-1	0.18 $\pm$ 0.05	2
AD03098-1	0.16 $\pm$ 0.05	2
AD03099-1	0.12 $\pm$ 0.05	2
AD03100	0.15 $\pm$ 0.09	2
AD02148-1	0.18 $\pm$ 0.08	2
AD02757-1	0.31 $\pm$ 0.13	2
AD02149-1	0.06 $\pm$ 0.02	2
AD02758-1	0.39 $\pm$ 0.13	2
AD02759-1	0.09 $\pm$ 0.04	2
AD01567-1	0.09 $\pm$ 0.02	2
AD02150-1	0.13 $\pm$ 0.07	2
AD02764-1	0.3 $\pm$ 0.05	2
AD02767-1	0.1 $\pm$ 0.01	2
AD02151-1	0.15 $\pm$ 0.01	2
AD01572-1	0.24 $\pm$ 0.07	2
AD02153-1	0.1 $\pm$ 0.06	2
AD02173-1	0.39 $\pm$ 0.08	2
AD02782-1	0.22 $\pm$ 0.06	2
AD02783-1	0.18 $\pm$ 0.03	2
AD02148-2	0.08 $\pm$ 0.04	2
AD02757-2	0.35 $\pm$ 0.07	2
AD02149-2	0.21 $\pm$ 0.12	2
AD02758-2	0.3 $\pm$ 0.14	2
AD02759-2	0.15 $\pm$ 0.05	2
AD01567-2	0.32 $\pm$ 0.11	2
AD02150-2	0.17 $\pm$ 0.03	2
AD02764-2	0.35 $\pm$ 0.13	2
AD02767-2	0.11 $\pm$ 0.02	2
AD02151-2	0.19 $\pm$ 0.08	2
AD01572-2	0.21 $\pm$ 0.02	2
AD02153-2	0.14 $\pm$ 0.02	2
AD02173-2	0.38 $\pm$ 0.11	2
AD02782-2	0.47 $\pm$ 0.17	2
AD02148-3	0.14 $\pm$ 0.02	2
AD02757-3	0.18 $\pm$ 0.01	2
AD02149-3	0.1 $\pm$ 0.02	2
AD02758-3	0.32 $\pm$ 0.04	2
AD02759-3	0.12 $\pm$ 0.03	2

AD01567-3	0.11±0.04	2
AD02150-3	0.12±0.03	2
AD02764-3	0.17±0.05	2
AD02767-3	0.05±0.01	2
AD02151-3	0.18±0.04	2
AD01572-3	0.09±0.02	2
AD02153-3	0.09±0.02	2
AD02782-3	0.25±0.01	2

Equivalents

Although several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto; the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, and/or methods, if such features, systems, articles, materials, and/or methods are not mutually inconsistent, is included within the scope of the present invention.

All definitions, as defined and used herein, should be understood to control over dictionary definitions, definitions in documents incorporated by reference, and/or ordinary meanings of the defined terms.

The indefinite articles “a” and “an,” as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean “at least one.”

The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified, unless clearly indicated to the contrary.

All references, patents and patent applications and publications that are cited or referred to in this application are incorporated herein in their entirety herein by reference.

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.
3. The dsRNA agent of claim 2, 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 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.

4. The dsRNA agent of claim 1, wherein 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.
5. The dsRNA agent of claim 1, wherein 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.
6. 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.
7. The dsRNA agent of claim 6, wherein 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.
8. The dsRNA agent of any one of claims 1-7, 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.
9. The dsRNA agent of any one of claims 1-8, wherein 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.
10. The dsRNA agent of any one of claims 1-9, wherein the dsRNA agent comprises the sequences set forth as a duplex sequence in any of Tables 1-3.
11. The dsRNA of any one of claims 1-10, wherein the dsRNA agent comprises at least one modified nucleotide.
12. The dsRNA agent of any one of claims 1-11, wherein all or substantially all of the nucleotides of the sense strand and/or the antisense strand are modified nucleotides.

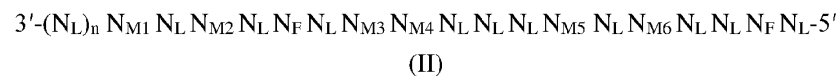
13. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to part of 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):



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.

14. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT is provided, 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 18 to about 30 nucleotides in length, wherein the antisense strand comprises sequence may be represented by formula (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.

15. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of MAPT is provided, wherein the dsRNA agent including a sense strand and an antisense strand, 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):



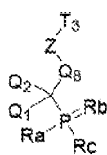
(III)

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.

16. The dsRNA agent of any one of claims 11-15, 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'-methoxyethyl 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 morpholino 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.
17. The dsRNA agent of any one of claims 1-16, 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, $NR^{18}R^{19}$; R_a and R_c 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;

T₃ 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, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfhydryl, CN.

5

18. The dsRNA agent of any one of claims 1-17, wherein the dsRNA agent comprises at least one phosphorothioate internucleoside linkage.

10

19. The dsRNA agent of any one of claims 1-17 wherein the sense strand comprises at least one phosphorothioate internucleoside linkage.

20. The dsRNA agent of any one of claims 1-17, wherein the antisense strand comprises at least one phosphorothioate internucleoside linkage.

15

21. The dsRNA agent of any one of claims 1-17, wherein the sense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages.

22. The dsRNA agent of any one of claims 1-17, wherein the antisense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages.

20

23. The dsRNA agent of any one of claims 1-22, wherein the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-3.

25

24. The dsRNA agent of any one of claims 1-22, wherein the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-3.

25. The dsRNA agent of any one of claims 1-24, wherein 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.

30

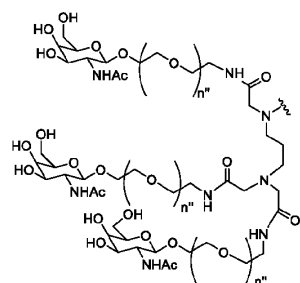
26. The dsRNA agent of any one of claims 1-25, wherein the region of complementarity is 19-21 nucleotides in length.

35

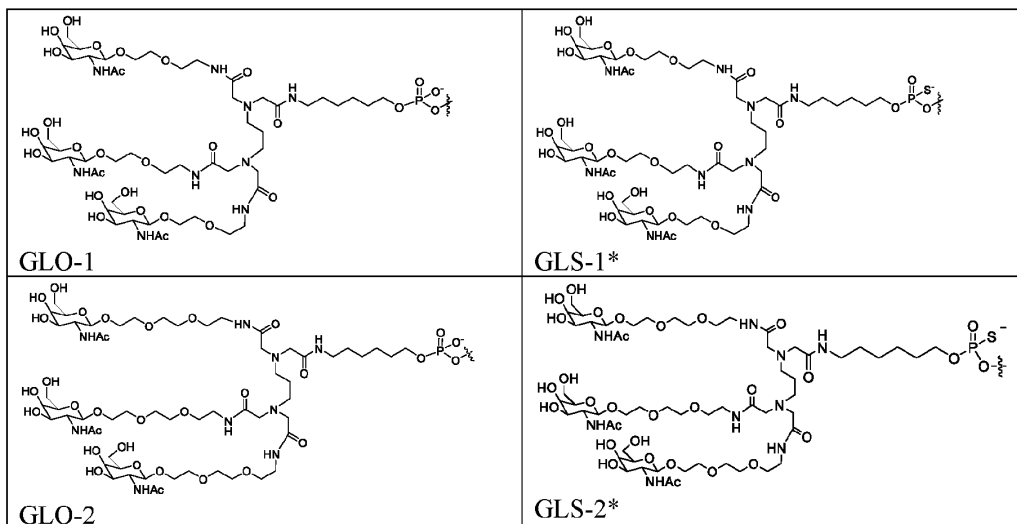
27. The dsRNA agent of any one of claims 1-26, wherein each strand is no more than 30 nucleotides in length.

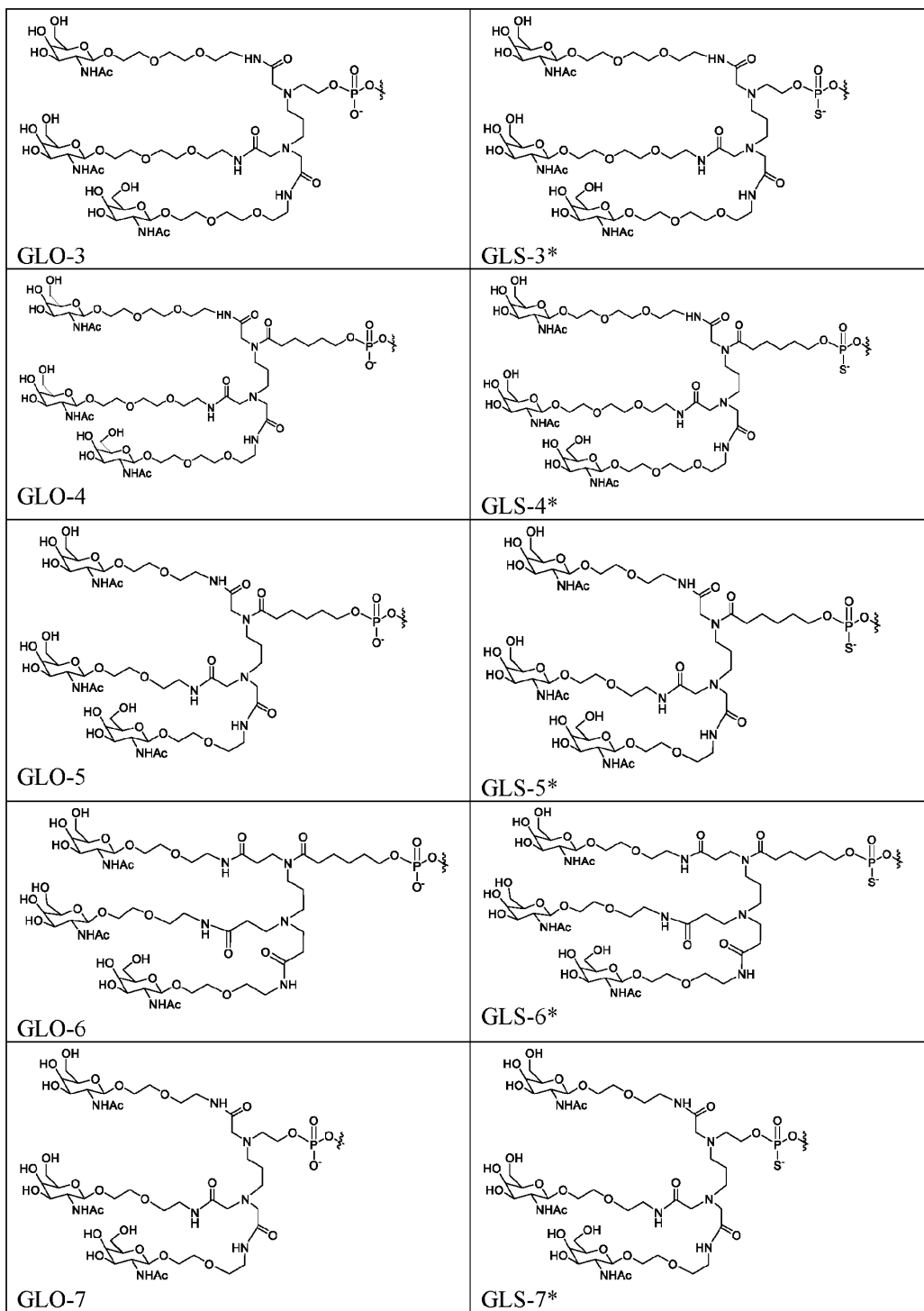
28. The dsRNA agent of any one of claims 1-26, wherein each strand is no more than 25 nucleotides in length.

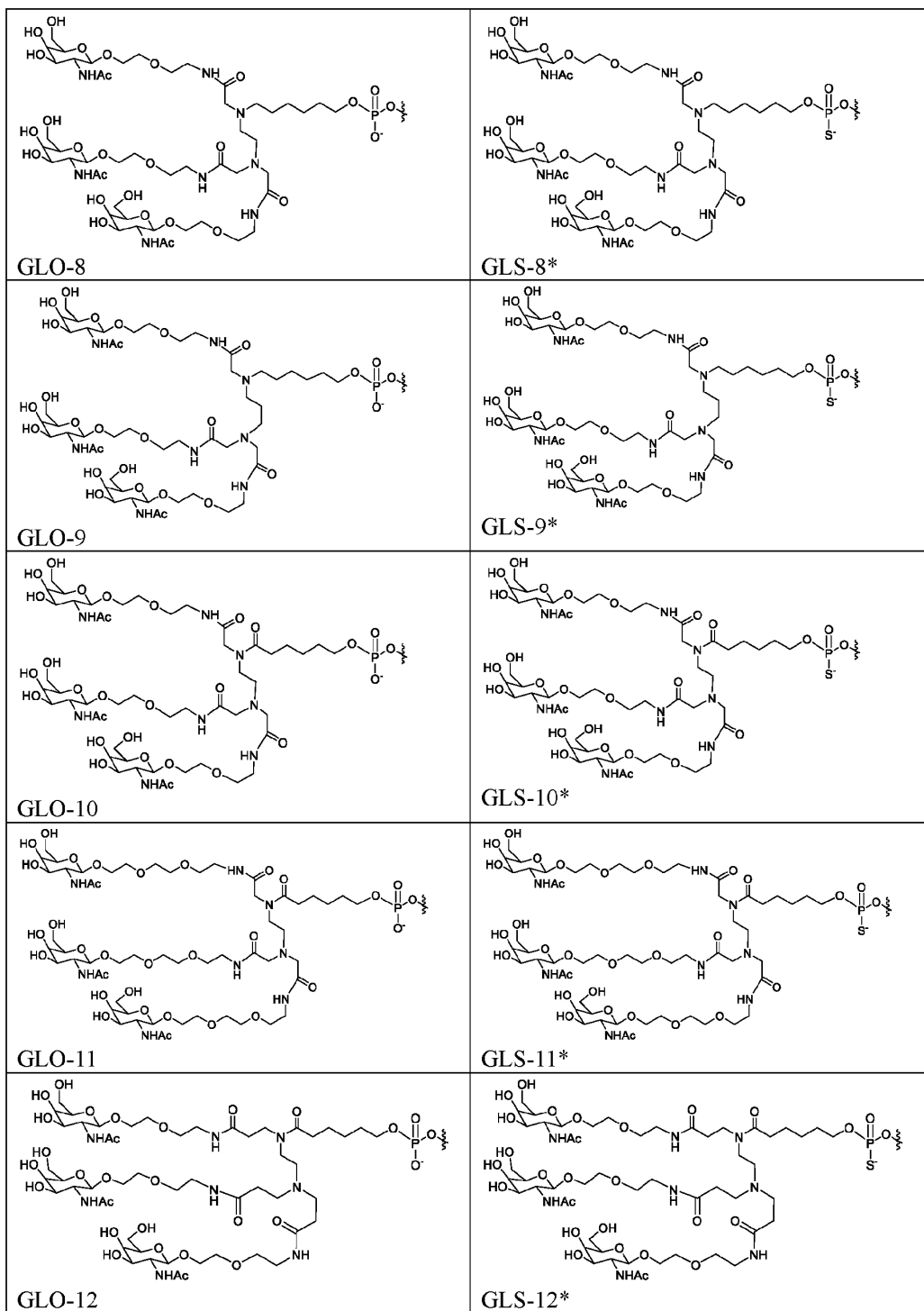
29. The dsRNA agent of any one of claims 1-26, wherein each strand is no more than 23 nucleotides in length.
30. The dsRNA agent of any one of claims 1-29, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups.
31. The dsRNA agent of claim 30, wherein the one or more targeting groups or linking groups are conjugated to the sense strand.
32. The dsRNA agent of claim 30 or 31, wherein the targeting group or linking group comprises N-acetyl-galactosamine (GalNAc).
33. The dsRNA agent of claim 30-32, wherein the targeting group has a structure:

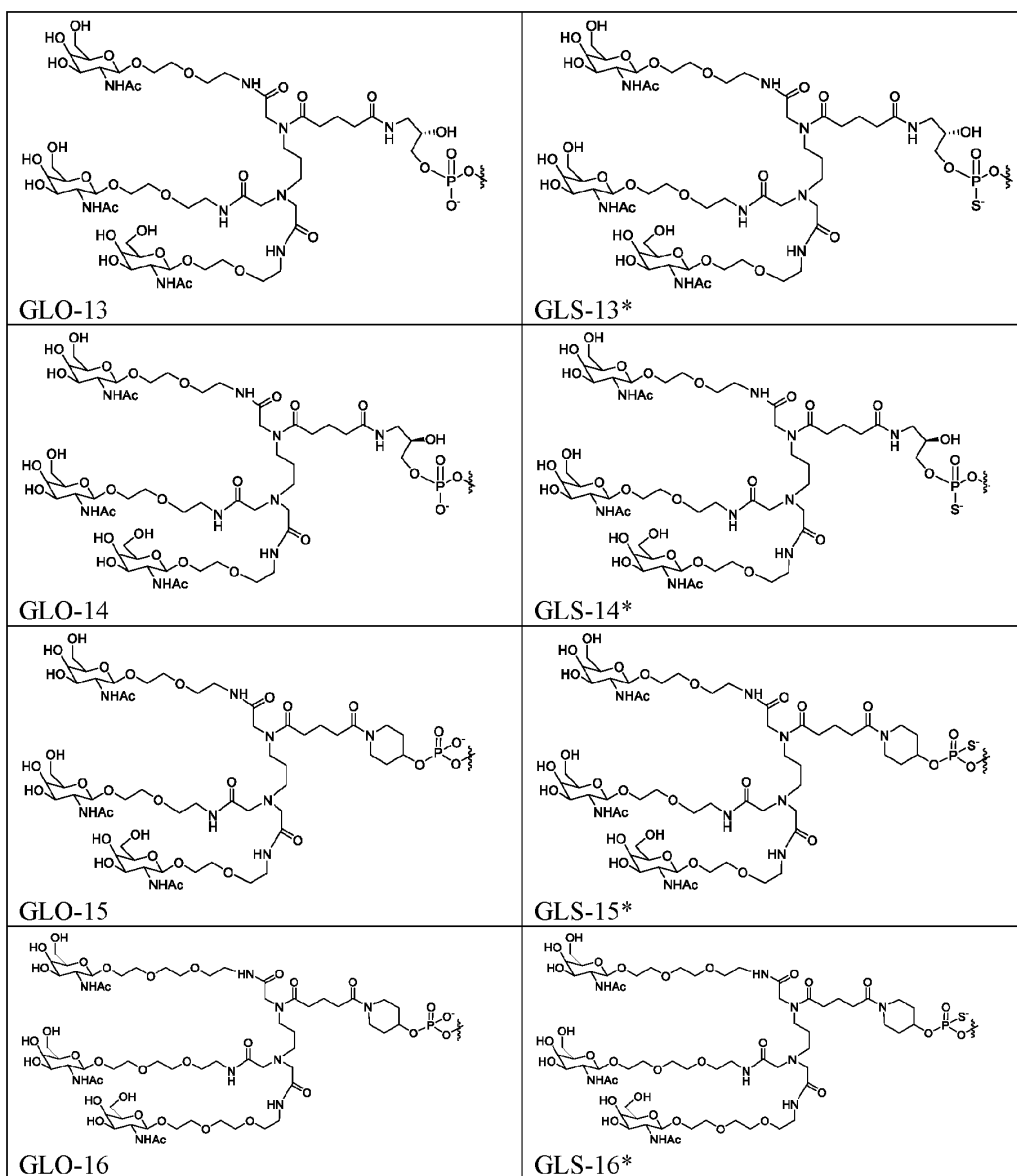


34. The dsRNA agent of claim 30-33, wherein the targeting group has a structure:









35. The dsRNA agent of any one of claims 1-34, wherein the dsRNA agent comprises a targeting group that is conjugated to the 5'-terminal end of the sense strand.

5 36. The dsRNA agent of any one of claims 1-34, wherein the dsRNA agent comprises a targeting group that is conjugated to the 3'-terminal end of the sense strand.

37. The dsRNA agent of any one of claims 1-34, wherein the antisense strand comprises one inverted abasic residue at 3'-terminal end.

38. The dsRNA agent of any one of claims 1-34, wherein the sense strand comprises one or two inverted abasic residues or imann residues at 3' or/and 5' terminal end.
39. The dsRNA agent of any one of claims 1-38, wherein the dsRNA agent has two blunt ends.
- 5 40. The dsRNA agent of any one of claims 1-38, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.
41. The dsRNA agent of any one of claims 1-38, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.
- 10 42. The dsRNA agent of any one of claims 1-41 wherein the MAPT RNA transcript is SEQ ID NO: 1.
- 15 43. A composition comprising a dsRNA agent of any one of claims 1-42.
44. The composition of claim 43, further comprising a pharmaceutically acceptable carrier.
45. The composition of claim 44, further comprising one or more additional therapeutic agents.
- 20 46. The composition of claim 45, wherein the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial.
47. The composition of any one of claims 43-46, wherein the composition is formulated for subcutaneous administration, is formulated for intrathecally administration, or is formulated for intravenous (IV) administration.
- 25 48. A cell comprising a dsRNA agent of any one of claims 1-42, optionally, the cell is a mammalian cell, optionally a human cell.
- 30 49. A method of inhibiting the expression of a MAPT gene in a cell, the method comprising:
(i) preparing a cell comprising an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-42 or a composition of any one of claims 43-47.
- 35 50. The method of claim 49, further comprising:
(ii) maintaining the cell prepared in claim 49 (i) for a time sufficient to obtain degradation of the mRNA transcript of a MAPT gene, thereby inhibiting expression of the MAPT gene in the cell.

51. The method of any one of claims 49-50, wherein the cell is in a subject and the dsRNA agent is administered to the subject subcutaneously.
52. The method of any one of claims 49-50, wherein the cell is in a subject and the dsRNA agent
5 is administered to the subject by IV administration or by intrathecally administration.
53. The method of claim 51 or 52, further comprising assessing inhibition of the MAPT gene, following the administration of the dsRNA agent to the subject, wherein a means for the assessing comprises:
- 10 (i) determining one or more physiological characteristics of a MAPT-associated disease or condition in the subject and
- (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the MAPT-associated disease or condition and/or to a control physiological characteristic of the MAPT-associated disease or condition,
- 15 wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the MAPT gene in the subject.
54. The method of claim 53, wherein the determined physiological characteristic is one or more of: the MAPT mRNA level, the MAPT protein level in the subject, variable progression of motor,
20 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.
55. The method of claim 54, wherein a reduction in one or more of the subject's MAPT mRNA level, the MAPT protein level in the subject, and/or a decrease in MAPT gene mRNA in one or
25 more of the hippocampus, striatum, cortex, cerebellum, thalamus, hypothalamus, and spinal cord.
56. A method of inhibiting expression of a MAPT gene in a subject, the method comprising administering to the subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-42 or a composition of any one of claims 43-47.
- 30 57. The method of claim 56, wherein the dsRNA agent is administered to the subject subcutaneously.
58. The method of claim 56, wherein the dsRNA agent is administered to the subject by IV
35 administration or by intrathecally administration.
59. The method of any one of claims 56-58, further comprising assessing inhibition of the MAPT gene, following the administration of the dsRNA agent, wherein a means for the assessing comprises:

- (i) determining one or more physiological characteristics of a MAPT-associated disease or condition in the subject and
- (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the MAPT-associated disease or condition and/or to a control physiological characteristic of the MAPT-associated disease or condition,
- 5 wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the MAPT gene in the subject.
60. The method of claim 59, wherein the determined 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.
- 10 61. The method of claim 60, wherein a reduction in one or more of the subject's MAPT mRNA level, the MAPT protein level in the subject, and/or a decrease in MAPT gene mRNA in one or more of the hippocampus, striatum, cortex, cerebellum, thalamus, hypothalamus, and spinal cord.
- 15 62. A method of treating a disease or condition associated with the presence of MAPT protein, the method comprising administering to a subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-42, or a composition of any one of claims 20 43-47, to inhibit MAPT gene expression.
63. The method of claim 62, wherein the disease or condition is one or more of: tauopathy, Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), FTLN 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.
- 25 30 35 64. The method of claim 63, further comprising administering an additional therapeutic regimen to the subject.
65. The method of claim 64, wherein the additional therapeutic regimen comprises: administering to the subject one or more MAPT antisense polynucleotides of the invention,

administering to the subject a non-MAPT dsRNA therapeutic agent, and a behavioral modification in the subject.

5 66. The method of claim 65, wherein 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).

10 67. The method of any one of claims 62-66, wherein the dsRNA agent is administered to the subject subcutaneously.

68. The method of any one of claims 62-66, wherein the dsRNA agent is administered to the subject by IV administration or by intrathecally administration.

15 69. The method of any one of claims 62-68, further comprising determining an efficacy of the administered double-stranded ribonucleic acid (dsRNA) agent in the subject.

20 70. The method of claim 69, wherein a means of determining an efficacy of the treatment in the subject comprises:

(i) determining one or more physiological characteristics of the MAPT-associated disease or condition in the subject and

(ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the MAPT-associated disease or condition

25 wherein the comparison indicates one or more of a presence, absence, and level of efficacy of the administration of the double-stranded ribonucleic acid (dsRNA) agent to the subject.

30 71. The method of claim 70, wherein the determined physiological characteristic is: the MAPT mRNA level, the MAPT protein level in the subject, or 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.

35 72. The method of claim 70, wherein a reduction in one or more of the MAPT mRNA level, the MAPT protein level in the subject, and/or a decrease in MAPT gene mRNA in one or more of the hippocampus, striatum, cortex, cerebellum, thalamus, hypothalamus, and spinal cord.

73. A method of decreasing a level of MAPT protein in a subject compared to a baseline pre-treatment level of MAPT protein in the subject, the method comprising administering to the subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of

claims 1-42, or a composition of any one of claims 43-47, to decrease the level of MAPT gene expression.

74. The method of claim 73, wherein the dsRNA agent is administered to the subject by
5 subcutaneously, is administered to the subject by intrathecally or is administered to the subject by IV administration.

75. A method of altering a physiological characteristic of a MAPT-associated disease or
condition in a subject compared to a baseline pre-treatment physiological characteristic of the
10 MAPT-associated disease or condition in the subject, the method comprising administering to the subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-42, or a composition of any one of claims 43-47, to alter the physiological characteristic of the MAPT-associated disease or condition in the subject.

76. The method of claim 75, wherein the dsRNA agent is administered to the subject
15 subcutaneously, is administered to the subject by intrathecally or is administered to the subject by IV administration.

77. The method of any one of claims 75-76, wherein the physiological characteristic is one or
20 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.