(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 September 2021 (23.09.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/188626 A1

(51) International Patent Classification:
C12N 15/113 (2010.01)

(21) International Application Number:
PCT/US2021/022688

(22) International Filing Date:
17 March 2021 (17.03.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/991,405 18 March 2020 (18.03.2020) US
63/071,106 27 August 2020 (27.08.2020) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) Title: OLIGONUCLEOTIDES FOR MAPT MODULATION

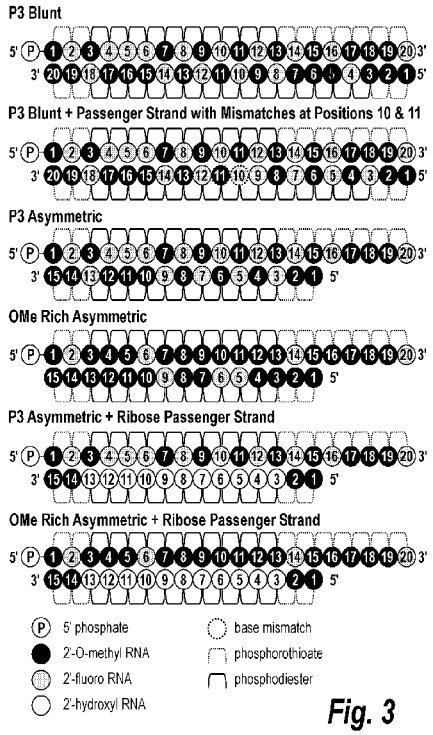

Fig. 3

(57) Abstract: This disclosure relates to novel *MAPT* targeting sequences. Novel *MAPT* targeting oligonucleotides for the treatment of neurodegenerative diseases are also provided.

[Continued on next page]

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TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

OLIGONUCLEOTIDES FOR MAPT MODULATION

Cross-Reference to Related Applications

[001] This application claims the benefit of U.S. Provisional Application Serial No. 62/991,405, filed March 18, 2020, and U.S. Provisional Application Serial No. 63/071,106, filed August 27, 2020, the entire disclosures of which are incorporated herein by reference.

Field of the Invention

[002] This disclosure relates to novel MAPT targeting sequences, novel branched oligonucleotides, and novel methods for treating and preventing MAPT-related neurodegeneration.

Background

[003] Microtubule associated protein tau (tau) is encoded by the *MAPT* gene located on chromosome 17q21 and is expressed throughout the central nervous system. Tau protein functions in the assembly and stabilization of microtubules in brain cells. 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 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.

[004] 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.

Summary

[005] In a first aspect, the disclosure provides an RNA molecule having a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 1. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 2. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 3. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 4. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 5. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 6. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 7. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 8. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 9. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 10. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 11. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 12. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 13. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 292. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 295.

[006] In another aspect, the disclosure provides an RNA molecule having a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 14-33, 299, and 302. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 14. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 15. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 16. In some

embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 17. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 18. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 19. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 20. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 21. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 22. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 23. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 24. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 25. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 26. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 27. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 28. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 29. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 30. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 31. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 32. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 33. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 292. In some embodiments, the nucleic acid sequence is substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NO: 302.

[007] In another aspect, the disclosure provides an RNA molecule having a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46. In some embodiments, the RNA molecule has a nucleic acid sequence that is at

least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 34. In some embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 35. In some embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 36. In some embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 37. In some embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 38. In some embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 39. In some embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 40. In some embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 41. In some embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 42. In some embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 43. In some embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 44. In some embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 45. In some embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% (e.g., 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to the nucleic acid sequence of SEQ ID NO: 46.

[008] In one aspect, the disclosure provides an RNA molecule having a length of from about 8 nucleotides to about 80 nucleotides; and a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295. In certain embodiments, the RNA molecule is from 8 nucleotides to 80 nucleotides in length (e.g., 8 nucleotides, 9 nucleotides, 10 nucleotides, 11 nucleotides, 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, 30 nucleotides, 31 nucleotides, 32 nucleotides, 33 nucleotides, 34 nucleotides, 35 nucleotides, 36 nucleotides, 37 nucleotides, 38 nucleotides, 39 nucleotides, 40 nucleotides, 41 nucleotides, 42 nucleotides, 43 nucleotides, 44 nucleotides, 45 nucleotides, 46 nucleotides, 47 nucleotides, 48 nucleotides, 49 nucleotides, 50 nucleotides, 51 nucleotides, 52 nucleotides, 53 nucleotides, 54 nucleotides, 55 nucleotides, 56 nucleotides, 57 nucleotides, 58 nucleotides, 59 nucleotides, 60 nucleotides, 61 nucleotides, 62 nucleotides, 63 nucleotides, 64 nucleotides, 65 nucleotides, 66 nucleotides, 67 nucleotides, 68 nucleotides, 69 nucleotides, 70 nucleotides, 71 nucleotides, 72 nucleotides, 73 nucleotides, 74 nucleotides, 75 nucleotides, 76 nucleotides, 77 nucleotides, 78 nucleotides, 79 nucleotides, or 80 nucleotides in length).

[009] In certain embodiments, the RNA molecule is from 10 to 50 nucleotides in length (e.g., 10 nucleotides, 11 nucleotides, 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, 30 nucleotides, 31 nucleotides, 32 nucleotides, 33 nucleotides, 34 nucleotides, 35 nucleotides, 36 nucleotides, 37 nucleotides, 38 nucleotides, 39 nucleotides, 40 nucleotides, 41 nucleotides, 42 nucleotides, 43 nucleotides, 44 nucleotides, 45 nucleotides, 46 nucleotides, 47 nucleotides, 48 nucleotides, 49 nucleotides, or 50 nucleotides in length).

[010] In certain embodiments, the RNA molecule comprises about 15 nucleotides to about 25 nucleotides in length. In certain embodiments, the RNA molecule is from 15 to 25 nucleotides in length (e.g., 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, or 25 nucleotides in length).

[011] In certain embodiments, the RNA molecule has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 14-33, 299, and 302.

[012] In certain embodiments, the RNA molecule has a nucleic acid sequence that is at least 85% identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46 (e.g., 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46). In certain embodiments, the RNA molecule has a nucleic acid sequence that is at least 90% identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46 (e.g., 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46). In certain embodiments, the RNA molecule has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46 (e.g., 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46). In certain embodiments, the RNA molecule has the nucleic acid sequence of any one of SEQ ID NOs: 34-46.

[013] In certain embodiments, the RNA molecule comprises single stranded (ss) RNA or double stranded (ds) RNA.

[014] In certain embodiments, the RNA molecule is a dsRNA comprising a sense strand and an antisense strand. The antisesne strand may comprise a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295. For example, in certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 1. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 2. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 3. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 4. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 5. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 6. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 7. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 8. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO:

9. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 10. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 11. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 12. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 13. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 292. In certain embodiments, the antisense sequence is substantially complementary to the nucleic acid sequence of SEQ ID NO: 295.

[015] In certain embodiments, the dsRNA comprises an antisense strand having complementarity to at least 10, 11, 12 or 13 contiguous nucleotides of a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295. For example, in certain embodiments, the dsRNA comprises an antisense strand having complementarity to a segment of from 10 to 25 contiguous nucleotides of the nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295 (e.g., a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 2510, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 1, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 2, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 3, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 4, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 5, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 6, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 7, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 8, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 9, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 10, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 11, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the

nucleic acid sequence of SEQ ID NO: 12, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 13, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 292, or a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 295).

[016] In certain embodiments, the dsRNA comprises an antisense strand having complementarity to a segment of from 15 to 35 contiguous nucleotides of the nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295. For example, the antisense strand may have complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 1. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 2. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 3. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous

nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 4. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 5. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 6. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 7. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous

nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 8. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 9. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 10. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 11. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35

contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 12. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 13. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 292. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, or 35 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 295.

[017] In certain embodiments, the dsRNA comprises an antisense strand having no more than 3 mismatches with a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295. For example, the antisense strand may have from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 1. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 2. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the

nucleic acid sequence of SEQ ID NO: 3. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 4. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 5. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 6. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 7. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 8. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 9. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 10. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 11. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 12. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 13. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 292. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 295.

[018] In certain embodiments, the dsRNA comprises an antisense strand that is fully complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

[019] In certain embodiments, the dsRNA comprises an antisense strand that is at least 85% identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46 (e.g., 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46). In certain

embodiments, the dsRNA comprises an antisense strand that is at least 90% identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46 (e.g., 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46). In certain embodiments, the dsRNA comprises an antisense strand that is at least 95% identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46 (e.g., 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid sequence of any one of SEQ ID NOs: 34-46). In certain embodiments, the dsRNA comprises an antisense strand that has the nucleic acid sequence of any one of SEQ ID NOs: 34-46.

[020] In certain embodiments, the antisense strand and/or sense strand comprises about 13 nucleotides to 35 nucleotides in length. For example, in certain embodiments, the antisense strand and/or sense strand is 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 nucleotides in length.

[021] In some embodiments of any one of the foregoing aspects, the antisense strand is 15 nucleotides in length. In some embodiments, the antisense strand is 16 nucleotides in length. In some embodiments, the antisense strand is 17 nucleotides in length. In some embodiments, the antisense strand is 18 nucleotides in length. In some embodiments, the antisense strand is 19 nucleotides in length. In certain embodiments, the antisense strand is 20 nucleotides in length. In certain embodiments, the antisense strand is 21 nucleotides in length. In certain embodiments, the antisense strand is 22 nucleotides in length. In some embodiments, the antisense strand is 23 nucleotides in length. In some embodiments, the antisense strand is 24 nucleotides in length. In some embodiments, the antisense strand is 25 nucleotides in length. In some embodiments, the antisense strand is 26 nucleotides in length. In some embodiments, the antisense strand is 27 nucleotides in length. In some embodiments, the antisense strand is 28 nucleotides in length. In some embodiments, the antisense strand is 29 nucleotides in length. In some embodiments, the antisense strand is 30 nucleotides in length. In some embodiments, the antisense strand is 31 nucleotides in length. In some embodiments, the antisense strand is 32 nucleotides in length. In some embodiments, the antisense strand is 33 nucleotides in length. In some embodiments, the antisense strand is 34 nucleotides in length. In some embodiments, the antisense strand is 35 nucleotides in length. In some embodiments, the sense strand is 13 nucleotides in length. In some embodiments, the sense strand is 14 nucleotides in length. In certain embodiments, the sense strand is 15 nucleotides in length. In certain embodiments, the sense strand is 16 nucleotides in length. In certain embodiments, the sense strand is 18 nucleotides in length. In certain embodiments, the sense strand is 20 nucleotides in length. In

some embodiments, the sense strand is 21 nucleotides in length. In some embodiments, the sense strand is 22 nucleotides in length. In some embodiments, the sense strand is 23 nucleotides in length. In some embodiments, the sense strand is 24 nucleotides in length. In some embodiments, the sense strand is 25 nucleotides in length. In some embodiments, the sense strand is 26 nucleotides in length. In some embodiments, the sense strand is 27 nucleotides in length. In some embodiments, the sense strand is 29 nucleotides in length. In some embodiments, the sense strand is 30 nucleotides in length. In some embodiments, the sense strand is 31 nucleotides in length. In some embodiments, the sense strand is 32 nucleotides in length. In some embodiments, the sense strand is 33 nucleotides in length. In some embodiments, the sense strand is 34 nucleotides in length. In some embodiments, the sense strand is 35 nucleotides in length.

[022] In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 14 nucleotides in length.

[023] In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 15 nucleotides in length.

[024] In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 16 nucleotides in length.

[025] In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 17 nucleotides in length.

[026] In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 18 nucleotides in length.

[027] In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 14 nucleotides in length.

[028] In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 15 nucleotides in length.

[029] In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 16 nucleotides in length.

[030] In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 17 nucleotides in length.

[031] In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 18 nucleotides in length.

[032] In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 19 nucleotides in length.

[033] In certain embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 15 nucleotides in length or 16 nucleotides in length.

[034] In certain embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 15 nucleotides in length or 16 nucleotides in length.

[035] In certain embodiments, the antisense strand is 20 nucleotides in length or 21 nucleotides in length and the sense strand is 15 nucleotides in length.

[036] In certain embodiments, the antisense strand is 20 nucleotides in length or 21 nucleotides in length and the sense strand is 16 nucleotides in length.

[037] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 14 nucleotides in length.

[038] In certain embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 15 nucleotides in length.

[039] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 16 nucleotides in length.

[040] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 17 nucleotides in length.

[041] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 18 nucleotides in length.

[042] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 19 nucleotides in length.

[043] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 20 nucleotides in length.

[044] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 14 nucleotides in length.

[045] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 15 nucleotides in length.

[046] In certain embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 16 nucleotides in length.

[047] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 17 nucleotides in length.

[048] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 18 nucleotides in length.

[049] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 19 nucleotides in length.

[050] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 20 nucleotides in length.

[051] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 21 nucleotides in length.

[052] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 14 nucleotides in length.

[053] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 15 nucleotides in length.

[054] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 16 nucleotides in length.

[055] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 17 nucleotides in length.

[056] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 18 nucleotides in length.

[057] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 19 nucleotides in length.

[058] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 20 nucleotides in length.

[059] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 21 nucleotides in length.

[060] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 22 nucleotides in length.

[061] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 14 nucleotides in length.

[062] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 15 nucleotides in length.

[063] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 16 nucleotides in length.

[064] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 17 nucleotides in length.

[065] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 18 nucleotides in length.

[066] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 19 nucleotides in length.

[067] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 20 nucleotides in length.

[068] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 21 nucleotides in length.

[069] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 22 nucleotides in length.

[070] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 23 nucleotides in length.

[071] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 14 nucleotides in length.

[072] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 15 nucleotides in length.

[073] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 16 nucleotides in length.

[074] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 17 nucleotides in length.

[075] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 18 nucleotides in length.

[076] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 19 nucleotides in length.

[077] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 20 nucleotides in length.

[078] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 21 nucleotides in length.

[079] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 22 nucleotides in length.

[080] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 23 nucleotides in length.

[081] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 24 nucleotides in length.

[082] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 14 nucleotides in length.

[083] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 15 nucleotides in length.

[084] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 16 nucleotides in length.

[085] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 17 nucleotides in length.

[086] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 18 nucleotides in length.

[087] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 19 nucleotides in length.

[088] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 20 nucleotides in length.

[089] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 21 nucleotides in length.

[090] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 22 nucleotides in length.

[091] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 23 nucleotides in length.

[092] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 24 nucleotides in length.

[093] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 25 nucleotides in length.

[094] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 14 nucleotides in length.

[095] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 15 nucleotides in length.

[096] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 16 nucleotides in length.

[097] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 17 nucleotides in length.

[098] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 18 nucleotides in length.

[099] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 19 nucleotides in length.

[0100] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 20 nucleotides in length.

[0101] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 21 nucleotides in length.

[0102] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 22 nucleotides in length.

[0103] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 23 nucleotides in length.

[0104] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 24 nucleotides in length.

[0105] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 25 nucleotides in length.

[0106] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 26 nucleotides in length.

[0107] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 14 nucleotides in length.

[0108] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 15 nucleotides in length.

[0109] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 16 nucleotides in length.

[0110] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 17 nucleotides in length.

[0111] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 18 nucleotides in length.

[0112] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 19 nucleotides in length.

[0113] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 20 nucleotides in length.

[0114] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 21 nucleotides in length.

[0115] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 22 nucleotides in length.

[0116] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 23 nucleotides in length.

[0117] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 24 nucleotides in length.

[0118] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 25 nucleotides in length.

[0119] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 26 nucleotides in length.

[0120] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 27 nucleotides in length.

[0121] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 14 nucleotides in length.

[0122] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 15 nucleotides in length.

[0123] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 16 nucleotides in length.

[0124] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 17 nucleotides in length.

[0125] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 18 nucleotides in length.

[0126] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 19 nucleotides in length.

[0127] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 20 nucleotides in length.

[0128] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 21 nucleotides in length.

[0129] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 22 nucleotides in length.

[0130] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 23 nucleotides in length.

[0131] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 24 nucleotides in length.

[0132] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 25 nucleotides in length.

[0133] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 26 nucleotides in length.

[0134] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 27 nucleotides in length.

[0135] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 28 nucleotides in length.

[0136] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 14 nucleotides in length.

[0137] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 15 nucleotides in length.

[0138] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 16 nucleotides in length.

[0139] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 17 nucleotides in length.

[0140] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 18 nucleotides in length.

[0141] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 19 nucleotides in length.

[0142] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 20 nucleotides in length.

[0143] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 21 nucleotides in length.

[0144] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 22 nucleotides in length.

[0145] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 23 nucleotides in length.

[0146] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 24 nucleotides in length.

[0147] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 25 nucleotides in length.

[0148] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 26 nucleotides in length.

[0149] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 27 nucleotides in length.

[0150] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 28 nucleotides in length.

[0151] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 29 nucleotides in length.

[0152] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 14 nucleotides in length.

[0153] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 15 nucleotides in length.

[0154] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 16 nucleotides in length.

[0155] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 17 nucleotides in length.

[0156] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 18 nucleotides in length.

[0157] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 19 nucleotides in length.

[0158] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 20 nucleotides in length.

[0159] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 21 nucleotides in length.

[0160] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 22 nucleotides in length.

[0161] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 23 nucleotides in length.

[0162] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 24 nucleotides in length.

[0163] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 25 nucleotides in length.

[0164] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 26 nucleotides in length.

[0165] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 27 nucleotides in length.

[0166] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 28 nucleotides in length.

[0167] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 29 nucleotides in length.

[0168] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 30 nucleotides in length.

[0169] In certain embodiments, the dsRNA comprises a double-stranded region of 14 base pairs to 30 base pairs (e.g., 14 base pairs, 15 base pairs, 16 base pairs, 17 base pairs, 18 base pairs, 19 base pairs, 20 base pairs, 21 base pairs, 22 base pairs, 23 base pairs, 24 base pairs, 25 base pairs, 26 base pairs, 27 base pairs, 28 base pairs, 29 base pairs, or 30 base pairs). In certain embodiments, the dsRNA comprises a double-stranded region of 14 base pairs. In certain embodiments, the dsRNA comprises a double-stranded region of 15 base pairs. In certain embodiments, the dsRNA comprises a double-stranded region of 16 base pairs. In certain embodiments, the dsRNA comprises a double-stranded region of 17 base pairs. In certain

embodiments, the dsRNA comprises a double-stranded region of 18 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 19 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 20 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 21 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 22 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 23 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 24 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 25 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 26 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 27 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 28 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 29 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 30 base pairs.

[0170] In certain embodiments, the dsRNA comprises a blunt-end. In certain embodiments, the dsRNA comprises at least one single stranded nucleotide overhang. In certain embodiments, the dsRNA comprises about a 2-nucleotide to 5-nucleotide single stranded nucleotide overhang.

[0171] In certain embodiments, the dsRNA comprises naturally occurring nucleotides.

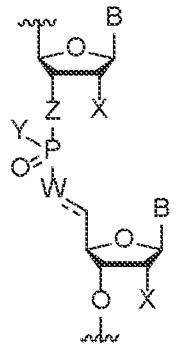
[0172] In certain embodiments, the dsRNA comprises at least one modified nucleotide.

[0173] In certain embodiments, the modified nucleotide comprises a 2'-O-methyl modified nucleotide, a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, or a mixture thereof.

[0174] In certain embodiments, the dsRNA comprises at least one modified internucleotide linkage.

[0175] In certain embodiments, the modified internucleotide linkage comprises a phosphorothioate internucleotide linkage. In certain embodiments, the dsRNA comprises 4-16 phosphorothioate internucleotide linkages (e.g., 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 phosphorothioate linkages). In certain embodiments, the dsRNA comprises 8-13 phosphorothioate internucleotide linkages (e.g., 9, 10, 11, 12, or 13 phosphorothioate linkages).

[0176] In certain embodiments, the dsRNA comprises at least one modified internucleotide linkage of Formula I:



(I);

wherein:

B is a base pairing moiety;

W is selected from the group consisting of O, OCH_2, OCH, CH_2, and CH;

X is selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

Y is selected from the group consisting of O^-, OH, OR, NH^-, NH_2, S^-, and SH;

Z is selected from the group consisting of O and CH_2;

R is a protecting group; and

=== is an optional double bond.

[0177] In certain embodiments, when W is CH, === is a double bond.

[0178] In certain embodiments, when W is selected from the group consisting of O, OCH_2, OCH, CH_2, === is a single bond.

[0179] In certain embodiments, the dsRNA comprises at least 70% chemically modified nucleotides (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% chemically modified nucleotides).

[0180] In certain embodiments, the dsRNA is fully chemically modified. In certain embodiments, the dsRNA comprises at least 60% 2'-O-methyl nucleotide modifications (e.g., 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% 2'-O-methyl modifications).

[0181] In certain embodiments, the dsRNA comprises from about 80% to about 90% 2'-O-methyl nucleotide modifications (e.g., about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%,

88%, 89%, or 90% 2'-O-methyl nucleotide modifications). In certain embodiments, the dsRNA comprises from about 83% to about 86% 2'-O-methyl modifications (e.g., about 83%, 84%, 85%, or 86% 2'-O-methyl modifications).

[0182] In certain embodiments, the dsRNA comprises from about 70% to about 80% 2'-O-methyl nucleotide modifications (e.g., about 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80% 2'-O-methyl nucleotide modifications). In certain embodiments, the dsRNA comprises from about 75% to about 78% 2'-O-methyl modifications (e.g., about 75%, 76%, 77%, or 78% 2'-O-methyl modifications).

[0183] In some embodiments of any one of the foregoing aspects, the dsRNA comprises from about 60% to about 70% 2'-O-methyl nucleotide modifications (e.g., about 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70% 2'-O-methyl nucleotide modifications). In some embodiments, the dsRNA comprises from about 60% to about 65% 2'-O-methyl modifications (e.g., about 60%, 61%, 62%, or 63% 2'-O-methyl modifications).

[0184] In certain embodiments, the antisense strand comprises at least 70% chemically modified nucleotides (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% chemically modified nucleotides).

[0185] In certain embodiments, the antisense strand is fully chemically modified. In certain embodiments, the antisense strand comprises at least 55% 2'-O-methyl nucleotide modifications (e.g., 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% 2'-O-methyl modifications). In some embodiments, the antisense strand comprises about 55% to 90% 2'-O-methyl nucleotide modifications (e.g., 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, or 90% 2'-O-methyl modifications).

[0186] In certain embodiments, the antisense strand comprises about 70% to 90% 2'-O-methyl nucleotide modifications (e.g., about 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, or 90% 2'-O-methyl modifications). In certain embodiments, the antisense strand comprises from about 85% to about 90% 2'-O-

methyl modifications (e.g., about 85%, 86%, 87%, 88%, 89%, or 90% 2'-O-methyl modifications).

[0187] In certain embodiments, the antisense strand comprises about 75% to 85% 2'-O-methyl nucleotide modifications (e.g., about 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, or 85% 2'-O-methyl modifications). In certain embodiments, the antisense strand comprises from about 76% to about 80% 2'-O-methyl modifications (e.g., about 76%, 77%, 78%, 79%, or 80% 2'-O-methyl modifications).

[0188] In certain embodiments, the sense strand comprises at least 70% chemically modified nucleotides (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% chemically modified nucleotides).

[0189] In certain embodiments, the sense strand is fully chemically modified. In certain embodiments, the sense strand comprises at least 55% 2'-O-methyl nucleotide modifications (e.g., 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% 2'-O-methyl modifications). In certain embodiments, the sense strand comprises 100% 2'-O-methyl nucleotide modifications.

[0190] In certain embodiments, the sense strand comprises from about 70% to about 85% 2'-O-methyl nucleotide modifications (e.g., about 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, or 85% 2'-O-methyl nucleotide modifications). In certain embodiments, the sense strand comprises from about 75% to about 80% 2'-O-methyl nucleotide modifications (e.g., about 75%, 76%, 77%, 78%, 79%, or 80% 2'-O-methyl nucleotide modifications).

[0191] In certain embodiments, the sense strand comprises from about 65% to about 75% 2'-O-methyl nucleotide modifications (e.g., about 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, or 75% 2'-O-methyl nucleotide modifications).

[0192] In certain embodiments, the sense strand comprises from about 67% to about 73% 2'-O-methyl nucleotide modifications (e.g., about 67%, 68%, 69%, 70%, 71%, 72%, or 73% 2'-O-methyl nucleotide modifications).

[0193] In some embodiments of any one of the foregoing aspects, the sense strand comprises from about 55% to about 65% 2'-O-methyl nucleotide modifications (e.g., about 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, or 65% 2'-O-methyl nucleotide modifications).

[0194] In certain embodiments, the sense strand comprises one or more nucleotide mismatches between the antisense strand and the sense strand. In certain embodiments, the one or more nucleotide mismatches are present at positions 2, 6, and 12 from the 5' end of sense strand. In certain embodiments, the nucleotide mismatches are present at positions 2, 6, and 12 from the 5' end of the sense strand.

[0195] In certain embodiments, the antisense strand comprises a 5' phosphate, a 5'-alkyl phosphonate, a 5' alkylene phosphonate, or a 5' alkenyl phosphonate.

[0196] In certain embodiments, the antisense strand comprises a 5' vinyl phosphonate.

[0197] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises alternating 2'-methoxy-ribonucleotides and 2'-fluoro-ribonucleotides; (3) the nucleotides at positions 2 and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides; (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises alternating 2'-methoxy-ribonucleotides and 2'-fluoro-ribonucleotides; and (7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0198] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 55% 2'-O-methyl modifications (e.g., 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90% 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% 2'-O-methyl modifications); (3) the nucleotide at position 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides; (4) the nucleotides at positions 1-2 to 1-7 from the

3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises at least 55% 2'-O-methyl modifications (e.g., 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% 2'-O-methyl modifications); and (7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0199] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucelic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 85% 2'-O-methyl modifications; (3) the nucleotides at positions 2 and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides; (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises 100% 2'-O-methyl modifications; and (7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0200] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 75% 2'-O-methyl modifications; (3) the nucleotides at positions 4, 5, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides; (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises 100% 2'-O-methyl modifications; and (7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0201] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of

SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 75% 2'-O-methyl modifications; (3) the nucleotides at positions 2, 4, 5, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides; (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises 100% 2'-O-methyl modifications; and (7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0202] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 85% 2'-O-methyl modifications (e.g., from about 85% to about 90% 2'-O-methyl modifications); (3) the nucleotides at positions 2 and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides (e.g., the nucleotides at positions 2 and 14 from the 5' end of the antisense strand may be 2'-fluoro nucleotides); (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises at least 75% 2'-O-methyl modifications (e.g., from about 75% to about 80% 2'-O-methyl modifications); (7) the nucleotides at positions 7, 10, and 11 from the 3' end of the sense strand are not 2'-methoxy-ribonucleotides (e.g., the nucleotides at positions 7, 10, and 11 from the 3' end of the sense strand are 2'-fluoro nucleotides); and (8) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0203] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 75% 2'-O-methyl modifications (e.g., from about 75% to about 80% 2'-O-methyl modifications); (3) the nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides (e.g., the nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand may be 2'-fluoro nucleotides); (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate

internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises at least 65% 2'-O-methyl modifications (e.g., from about 65% to about 75% 2'-O-methyl modifications); (7) the nucleotides at positions 7, 9, 10, and 11 from the 3' end of the sense strand are not 2'-methoxy-ribonucleotides (e.g., the nucleotides at positions 7, 9, 10, and 11 from the 3' end of the sense strand are 2'-fluoro nucleotides); and (8) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0204] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 75% 2'-O-methyl modifications; (3) the nucleotides at positions 2, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides; (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises at least 80% 2'-O-methyl modifications; (7) the nucleotides at positions 7, 10, and 11 from the 3' end of the sense strand are not 2'-methoxy-ribonucleotides; and (8) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0205] In certain embodiments, a functional moiety is linked to the 5' end and/or 3' end of the antisense strand. In certain embodiments, a functional moiety is linked to the 5' end and/or 3' end of the sense strand. In certain embodiments, a functional moiety is linked to the 3' end of the sense strand.

[0206] In certain embodiments, the functional moiety comprises a hydrophobic moiety.

[0207] In certain embodiments, the hydrophobic moiety is selected from the group consisting of fatty acids, steroids, secosteroids, lipids, gangliosides, nucleoside analogs, endocannabinoids, vitamins, and a mixture thereof.

[0208] In certain embodiments, the steroid is selected from the group consisting of cholesterol and Lithocholic acid (LCA).

[0209] In certain embodiments, the fatty acid is selected from the group consisting of Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA) and Docosanoic acid (DCA).

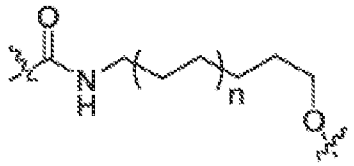
[0210] In certain embodiments, the vitamin is selected from the group consisting of choline, vitamin A, vitamin E, derivatives thereof, and metabolites thereof.

[0211] In certain embodiments, the vitamin is selected from the group consisting of retinoic acid and alpha-tocopheryl succinate.

[0212] In certain embodiments, the functional moiety is linked to the antisense strand and/or sense strand by a linker.

[0213] In certain embodiments, the linker comprises a divalent or trivalent linker.

[0214] In certain embodiments, the divalent or trivalent linker is selected from the group consisting of: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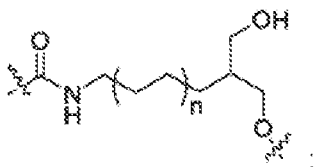
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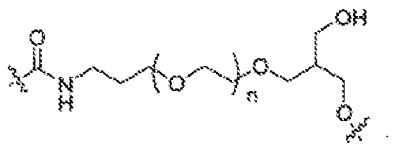
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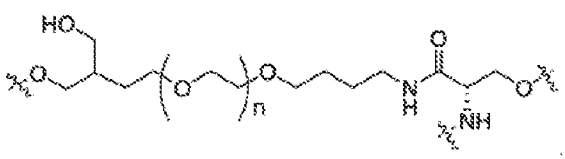
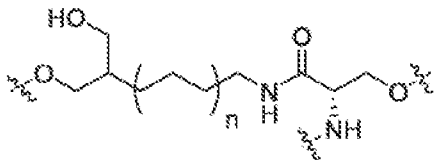
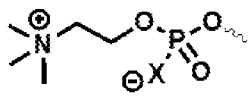


; and ,

wherein n is 1, 2, 3, 4, or 5.

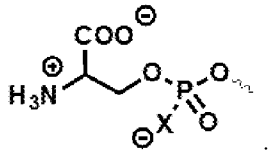
[0215] In certain embodiments, the linker comprises an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphodiester, a phosphorothioate, a phosphoramidate, an amide, a carbamate, or a combination thereof.

[0216] In certain embodiments, when the linker is a trivalent linker, the linker further links a phosphodiester or phosphodiester derivative.

[0217] In certain embodiments, the phosphodiester or phosphodiester derivative is selected from the group consisting of:

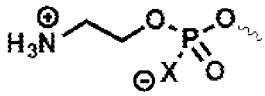

;

(Zc1);



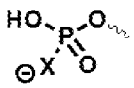
;

(Zc2);



; and

(Zc3)



;

(Zc4)

wherein X is O, S or BH_3.

[0218] In certain embodiments, the nucleotides at positions 1 and 2 from the 3' end of sense strand, and the nucleotides at positions 1 and 2 from the 5' end of antisense strand, are connected to adjacent ribonucleotides via phosphorothioate linkages.

[0219] In one aspect, the disclosure provides a pharmaceutical composition for inhibiting the expression of tau protein (*MAPT*) gene in an organism, comprising the dsRNA recited above and a pharmaceutically acceptable carrier.

[0220] In certain embodiments, the dsRNA inhibits the expression of said *MAPT* gene by at least 50%. In certain embodiments, the dsRNA inhibits the expression of said *MAPT* gene by at least 80%.

[0221] In one aspect, the disclosure provides a method for inhibiting expression of *MAPT* gene in a cell, the method comprising: (a) introducing into the cell a double-stranded ribonucleic acid (dsRNA) recited above; and (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of the *MAPT* gene, thereby inhibiting expression of the *MAPT* gene in the cell.

[0222] In one aspect, the disclosure provides a method of treating or managing a neurodegenerative disease comprising administering to a patient in need of such treatment or management a therapeutically effective amount of said dsRNA recited above.

[0223] In certain embodiments, the dsRNA is administered to the brain of the patient.

[0224] In certain embodiments, the dsRNA is administered by intracerebroventricular (ICV) injection, intrastriatal (IS) injection, intravenous (IV) injection, subcutaneous (SQ) injection or a combination thereof.

[0225] 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.

[0226] In certain embodiments, the dsRNA inhibits the expression of said *MAPT* gene by at least 50%. In certain embodiments, the dsRNA inhibits the expression of said *MAPT* gene by at least 80%.

[0227] In one aspect, the disclosure provides a vector comprising a regulatory sequence operably linked to a nucleotide sequence that encodes an RNA molecule substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

[0228] In certain embodiments, the RNA molecule inhibits the expression of said *MAPT* gene by at least 50%. In certain embodiments, the RNA molecule inhibits the expression of said *MAPT* gene by at least 80%.

[0229] In certain embodiments, the RNA molecule comprises ssRNA or dsRNA.

[0230] In certain embodiments, the dsRNA comprises a sense strand and an antisense strand, wherein the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

[0231] In one aspect, the disclosure provides a cell comprising the vector recited above.

[0232] In one aspect, the disclosure provides a recombinant adeno-associated virus (rAAV) comprising the vector above and an AAV capsid.

[0233] In one aspect, the disclosure provides a branched RNA compound comprising two or more RNA molecules, such as two or more RNA molecules that each comprise from 14 to 40 nucleotides in length (e.g., 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides in length), wherein each RNA molecule comprises a portion having a nucleic acid sequence that is substantially complementary to a segment of a *MAPT* mRNA. In certain embodiments, the two RNA molecules may be connected to one another by one or more moieties independently selected from a linker, a spacer and a branching point.

[0234] In certain embodiments, the branched RNA molecule comprises one or both of ssRNA and dsRNA.

[0235] In certain embodiments, the branched RNA molecule comprises an antisense oligonucleotide.

[0236] In certain embodiments, each RNA molecule comprises a dsRNA comprising a sense strand and an antisense strand, wherein each antisense strand independently comprises a sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

[0237] In certain embodiments, the branched RNA compound comprises two or more copies of the RNA molecule of any of the above aspects or embodiments of the disclosure covalently bound to one another (e.g., by way of a linker, spacer, or branching point).

[0238] In certain embodiments, the branched RNA compound comprises a portion having a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295. For example, the branched RNA compound may comprise two or more dsRNA molecules that are covalently bound to one another (e.g., by way of a linker, spacer, or branching point) and that each comprise an antisense strand having complementarity to at least 10, 11, 12 or 13 contiguous nucleotides of a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295. For example, in certain embodiments, the dsRNA comprises an antisense strand having complementarity to a segment of from 10 to 25 contiguous nucleotides of the nucleic acid sequence of any one of SEQ ID NOs: 1-13 (e.g., a segment of from 10 to 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 1, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 2, a segment of fro10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 3, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 4, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 5, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 6, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 7, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of

SEQ ID NO: 8, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 9, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 10, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 11, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 12, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 13, a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 292, or a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 295).

[0239] In certain embodiments, each dsRNA in the branched RNA compound comprises an antisense strand having complementarity to a segment of from 15 to 25 contiguous nucleotides (e.g., a segment of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides) of the nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295. For example, the antisense strand may have complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 1. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 2. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 3. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous

nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 4. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 5. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 6. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 7. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 8. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 9. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 10. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides,

24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 11. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 12. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 13. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 292. In certain embodiments, the antisense strand has complementarity to a segment of 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, or 25 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO: 295.

[0240] In certain embodiments, each dsRNA in the branched RNA compound comprises an antisense strand having no more than 3 mismatches with a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295. For example, the antisense strand may have from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 1. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 2. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 3. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 4. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3

mismatches) relative to the nucleic acid sequence of SEQ ID NO: 5. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 6. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 7. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 8. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 9. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 10. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 11. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 12. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 13. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 292. In certain embodiments, the antisense strand has from 0-3 mismatches (e.g., 0 mismatches, 1 mismatch, 2 mismatches, or 3 mismatches) relative to the nucleic acid sequence of SEQ ID NO: 295.

[0241] In certain embodiments, each dsRNA in the branched RNA compound comprises an antisense strand that is fully complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

[0242] In certain embodiments, the branched RNA compound comprises a portion having a nucleic acid sequence that is substantially complementary to one or more of a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 14-33, 299, and 302.

[0243] In certain embodiments, the RNA molecule comprises an antisense oligonucleotide.

[0244] In certain embodiments, each RNA molecule comprises 14 to 35 (e.g., 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides in length.

[0245] In certain embodiments, the antisense strand and/or sense strand comprises about 13 nucleotides to 35 nucleotides in length. For example, in certain embodiments, the antisense strand and/or sense strand is 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35nucleotides in length. In some embodiments, the antisense strand is 14 nucleotides in length. In some embodiments, the antisense strand is 15 nucleotides in length. In some embodiments, the antisense strand is 16 nucleotides in length. In some embodiments, the antisense strand is 17 nucleotides in length. In some embodiments, the antisense strand is 18 nucleotides in length. In some embodiments, the antisense strand is 19 nucleotides in length. In certain embodiments, the antisense strand is 20 nucleotides in length. In certain embodiments, the antisense strand is 21 nucleotides in length. In certain embodiments, the antisense strand is 22 nucleotides in length. In some embodiments, the antisense strand is 23 nucleotides in length. In some embodiments, the antisense strand is 24 nucleotides in length. In some embodiments, the antisense strand is 25 nucleotides in length. In some embodiments, the antisense strand is 26 nucleotides in length. In some embodiments, the antisense strand is 27 nucleotides in length. In some embodiments, the antisense strand is 28 nucleotides in length. In some embodiments, the antisense strand is 29 nucleotides in length. In some embodiments, the antisense strand is 30 nucleotides in length. In some embodiments, the antisense strand is 31 nucleotides in length. In some embodiments, the antisense strand is 32 nucleotides in length. In some embodiments, the antisense strand is 33 nucleotides in length. In some embodiments, the antisense strand is 34 nucleotides in length. In some embodiments, the antisense strand is 35 nucleotides in length.

[0246] In some embodiments of any one of the foregoing aspects, the sense strand is 13 nucleotides in length. In certain embodiments, the sense strand is 14 nucleotides in length. In certain embodiments, the sense strand is 15 nucleotides in length. In certain embodiments, the sense strand is 16 nucleotides in length. In certain embodiments, the sense strand is 17 nucleotides in length. In certain embodiments, the sense strand is 18 nucleotides in length. In certain embodiments, the sense strand is 19 nucleotides in length. In some embodiments, the sense strand is 20 nucleotides in length. In some embodiments, the sense strand is 21 nucleotides in length. In some embodiments, the sense strand is 22 nucleotides in length. In some embodiments, the sense strand is 23 nucleotides in length. In some embodiments, the sense strand is 24 nucleotides in length. In some embodiments, the sense strand is 25 nucleotides in length. In some embodiments, the sense strand is 26 nucleotides in length. In some embodiments, the sense strand is 27 nucleotides in length. In some embodiments, the

sense strand is 28 nucleotides in length. In some embodiments, the sense strand is 29 nucleotides in length. In some embodiments, the sense strand is 30 nucleotides in length. In some embodiments, the sense strand is 31 nucleotides in length. In some embodiments, the sense strand is 32 nucleotides in length. In some embodiments, the sense strand is 33 nucleotides in length. In some embodiments, the sense strand is 34 nucleotides in length. In some embodiments, the sense strand is 35 nucleotides in length.

[0247] In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 14 nucleotides in length.

[0248] In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 15 nucleotides in length.

[0249] In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 16 nucleotides in length.

[0250] In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 17 nucleotides in length.

[0251] In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 18 nucleotides in length.

[0252] In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 14 nucleotides in length.

[0253] In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 15 nucleotides in length.

[0254] In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 16 nucleotides in length.

[0255] In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 17 nucleotides in length.

[0256] In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 18 nucleotides in length.

[0257] In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 19 nucleotides in length.

[0258] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 14 nucleotides in length.

[0259] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 15 nucleotides in length.

[0260] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 16 nucleotides in length.

[0261] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 17 nucleotides in length.

[0262] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 18 nucleotides in length.

[0263] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 19 nucleotides in length.

[0264] In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 20 nucleotides in length.

[0265] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 14 nucleotides in length.

[0266] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 15 nucleotides in length.

[0267] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 16 nucleotides in length.

[0268] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 17 nucleotides in length.

[0269] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 18 nucleotides in length.

[0270] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 19 nucleotides in length.

[0271] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 20 nucleotides in length.

[0272] In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 21 nucleotides in length.

[0273] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 14 nucleotides in length.

[0274] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 15 nucleotides in length.

[0275] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 16 nucleotides in length.

[0276] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 17 nucleotides in length.

[0277] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 18 nucleotides in length.

[0278] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 19 nucleotides in length.

[0279] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 20 nucleotides in length.

[0280] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 21 nucleotides in length.

[0281] In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 22 nucleotides in length.

[0282] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 14 nucleotides in length.

[0283] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 15 nucleotides in length.

[0284] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 16 nucleotides in length.

[0285] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 17 nucleotides in length.

[0286] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 18 nucleotides in length.

[0287] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 19 nucleotides in length.

[0288] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 20 nucleotides in length.

[0289] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 21 nucleotides in length.

[0290] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 22 nucleotides in length.

[0291] In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 23 nucleotides in length.

[0292] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 14 nucleotides in length.

[0293] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 15 nucleotides in length.

[0294] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 16 nucleotides in length.

[0295] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 17 nucleotides in length.

[0296] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 18 nucleotides in length.

[0297] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 19 nucleotides in length.

[0298] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 20 nucleotides in length.

[0299] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 21 nucleotides in length.

[0300] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 22 nucleotides in length.

[0301] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 23 nucleotides in length.

[0302] In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 24 nucleotides in length.

[0303] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 14 nucleotides in length.

[0304] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 15 nucleotides in length.

[0305] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 16 nucleotides in length.

[0306] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 17 nucleotides in length.

[0307] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 18 nucleotides in length.

[0308] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 19 nucleotides in length.

[0309] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 20 nucleotides in length.

[0310] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 21 nucleotides in length.

[0311] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 22 nucleotides in length.

[0312] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 23 nucleotides in length.

[0313] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 24 nucleotides in length.

[0314] In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 25 nucleotides in length.

[0315] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 14 nucleotides in length.

[0316] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 15 nucleotides in length.

[0317] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 16 nucleotides in length.

[0318] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 17 nucleotides in length.

[0319] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 18 nucleotides in length.

[0320] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 19 nucleotides in length.

[0321] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 20 nucleotides in length.

[0322] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 21 nucleotides in length.

[0323] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 22 nucleotides in length.

[0324] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 23 nucleotides in length.

[0325] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 24 nucleotides in length.

[0326] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 25 nucleotides in length.

[0327] In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 26 nucleotides in length.

[0328] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 14 nucleotides in length.

[0329] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 15 nucleotides in length.

[0330] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 16 nucleotides in length.

[0331] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 17 nucleotides in length.

[0332] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 18 nucleotides in length.

[0333] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 19 nucleotides in length.

[0334] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 20 nucleotides in length.

[0335] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 21 nucleotides in length.

[0336] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 22 nucleotides in length.

[0337] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 23 nucleotides in length.

[0338] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 24 nucleotides in length.

[0339] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 25 nucleotides in length.

[0340] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 26 nucleotides in length.

[0341] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 27 nucleotides in length.

[0342] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 14 nucleotides in length.

[0343] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 15 nucleotides in length.

[0344] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 16 nucleotides in length.

[0345] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 17 nucleotides in length.

[0346] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 18 nucleotides in length.

[0347] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 19 nucleotides in length.

[0348] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 20 nucleotides in length.

[0349] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 21 nucleotides in length.

[0350] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 22 nucleotides in length.

[0351] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 23 nucleotides in length.

[0352] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 24 nucleotides in length.

[0353] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 25 nucleotides in length.

[0354] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 26 nucleotides in length.

[0355] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 27 nucleotides in length.

[0356] In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 28 nucleotides in length.

[0357] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 14 nucleotides in length.

[0358] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 15 nucleotides in length.

[0359] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 16 nucleotides in length.

[0360] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 17 nucleotides in length.

[0361] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 18 nucleotides in length.

[0362] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 19 nucleotides in length.

[0363] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 20 nucleotides in length.

[0364] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 21 nucleotides in length.

[0365] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 22 nucleotides in length.

[0366] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 23 nucleotides in length.

[0367] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 24 nucleotides in length.

[0368] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 25 nucleotides in length.

[0369] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 26 nucleotides in length.

[0370] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 27 nucleotides in length.

[0371] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 28 nucleotides in length.

[0372] In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 29 nucleotides in length.

[0373] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 14 nucleotides in length.

[0374] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 15 nucleotides in length.

[0375] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 16 nucleotides in length.

[0376] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 17 nucleotides in length.

[0377] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 18 nucleotides in length.

[0378] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 19 nucleotides in length.

[0379] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 20 nucleotides in length.

[0380] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 21 nucleotides in length.

[0381] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 22 nucleotides in length.

[0382] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 23 nucleotides in length.

[0383] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 24 nucleotides in length.

[0384] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 25 nucleotides in length.

[0385] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 26 nucleotides in length.

[0386] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 27 nucleotides in length.

[0387] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 28 nucleotides in length.

[0388] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 29 nucleotides in length.

[0389] In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 30 nucleotides in length.

[0390] In certain embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 15 nucleotides in length or 16 nucleotides in length.

[0391] In certain embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 15 nucleotides in length or 16 nucleotides in length.

[0392] In certain embodiments, the antisense strand is 20 nucleotides in length or 21 nucleotides in length and the sense strand is 15 nucleotides in length.

[0393] In certain embodiments, the antisense strand is 20 nucleotides in length or 21 nucleotides in length and the sense strand is 16 nucleotides in length.

[0394] In certain embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 15 nucleotides in length.

[0395] In certain embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 16 nucleotides in length.

[0396] In certain embodiments, the dsRNA comprises a double-stranded region of 14 base pairs to 35 base pairs. In certain embodiments, the dsRNA comprises a double-stranded region of 14 base pairs. In certain embodiments, the dsRNA comprises a double-stranded region of 15 base pairs. In certain embodiments, the dsRNA comprises a double-stranded region of 16 base pairs. In certain embodiments, the dsRNA comprises a double-stranded region of 18 base pairs. In certain embodiments, the dsRNA comprises a double-stranded region of 20 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 21 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 22 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 23 base pairs. In some

embodiments, the dsRNA comprises a double-stranded region of 24 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 25 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 26 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 27 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 28 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 29 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 30 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 31 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 32 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 33 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 34 base pairs. In some embodiments, the dsRNA comprises a double-stranded region of 35 base pairs.

[0397] In certain embodiments, the dsRNA comprises a blunt-end.

[0398] In certain embodiments, the dsRNA comprises at least one single stranded nucleotide overhang. In certain embodiments, the dsRNA comprises between a 2-nucleotide to 5-nucleotide single stranded nucleotide overhang.

[0399] In certain embodiments, the dsRNA comprises naturally occurring nucleotides.

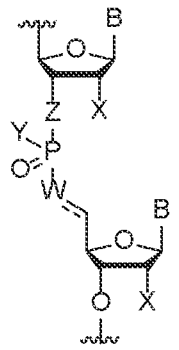
[0400] In certain embodiments, the dsRNA comprises at least one modified nucleotide.

[0401] In certain embodiments, the modified nucleotide comprises a 2'-O-methyl modified nucleotide, a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.

[0402] In certain embodiments, the dsRNA comprises at least one modified internucleotide linkage.

[0403] In certain embodiments, the modified internucleotide linkage comprises a phosphorothioate internucleotide linkage. In certain embodiments, the branched RNA compound comprises 4-16 phosphorothioate internucleotide linkages. In certain embodiments, the branched RNA compound comprises 8-13 phosphorothioate internucleotide linkages.

[0404] In certain embodiments, the dsRNA comprises at least one modified internucleotide linkage of Formula I:



(I),

wherein:

B is a base pairing moiety;

W is selected from the group consisting of O, OCH_2, OCH, CH_2, and CH;

X is selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

Y is selected from the group consisting of O^-, OH, OR, NH^-, NH_2, S^-, and SH;

Z is selected from the group consisting of O and CH_2;

R is a protecting group; and

=== is an optional double bond.

[0405] In certain embodiments, when W is CH, === is a double bond.

[0406] In certain embodiments, when W is selected from the group consisting of O, OCH_2, OCH, CH_2, === is a single bond.

[0407] In certain embodiments, the dsRNA comprises at least 70% chemically modified nucleotides (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% chemically modified nucleotides). In certain embodiments, the dsRNA is fully chemically modified. In certain embodiments, the dsRNA comprises at least 60% 2'-O-methyl nucleotide modifications (e.g., 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% 2'-O-methyl modifications).

[0408] In certain embodiments, the antisense strand comprises at least 70% chemically modified nucleotides (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% chemically modified nucleotides).

[0409] In certain embodiments, the antisense strand is fully chemically modified.

[0410] In certain embodiments, the antisense strand comprises at least 55% 2'-O-methyl nucleotide modifications (e.g., 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% 2'-O-methyl modifications). In certain embodiments, the antisense strand comprises about 70% to 90% 2'-O-methyl nucleotide modifications. In certain embodiments, the antisense strand comprises from about 85% to about 90% 2'-O-methyl modifications (e.g., about 85%, 86%, 87%, 88%, 89%, or 90% 2'-O-methyl modifications).

[0411] In certain embodiments, the antisense strand comprises about 75% to 85% 2'-O-methyl nucleotide modifications (e.g., about 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, or 85% 2'-O-methyl modifications). In certain embodiments, the antisense strand comprises from about 76% to about 80% 2'-O-methyl modifications (e.g., about 76%, 77%, 78%, 79%, or 80% 2'-O-methyl modifications).

[0412] In certain embodiments, the sense strand comprises at least 70% chemically modified nucleotides (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% chemically modified nucleotides). In certain embodiments, the sense strand is fully chemically modified. In certain embodiments, the sense strand comprises at least 55% 2'-O-methyl nucleotide modifications (e.g., 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% 2'-O-methyl modifications). In certain embodiments, the sense strand comprises 100% 2'-O-methyl nucleotide modifications.

[0413] In certain embodiments, the sense strand comprises one or more nucleotide mismatches between the antisense strand and the sense strand. In certain embodiments, the one or more nucleotide mismatches are present at positions 2, 6, and 12 from the 5' end of sense strand. In certain embodiments, the nucleotide mismatches are present at positions 2, 6, and 12 from the 5' end of the sense strand.

[0414] In certain embodiments, the antisense strand comprises a 5' phosphate, a 5'-alkyl phosphonate, a 5' alkylene phosphonate, a 5' alkenyl phosphonate, or a mixture thereof.

[0415] In certain embodiments, the antisense strand comprises a 5' vinyl phosphonate.

[0416] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises alternating 2'-methoxy-ribonucleotides and 2'-fluoro-ribonucleotides; (3) the nucleotides at positions 2 and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides; (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises alternating 2'-methoxy-ribonucleotides and 2'-fluoro-ribonucleotides; and (7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0417] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 70% 2'-O-methyl modifications (e.g., from about 75% to about 80% or from about 85% to about 90% 2'-O-methyl modifications); (3) the nucleotide at position 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides; (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises at least 65% 2'-O-methyl modifications (e.g., from about 65% to about 75% or from about 75% to about 80% 2'-O-methyl modifications); and (7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0418] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 85% 2'-O-methyl modifications; (3) the nucleotides at positions 2 and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides; (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises 100% 2'-O-methyl modifications; and (7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0419] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 75% 2'-O-methyl modifications; (3) the nucleotides at positions 4, 5, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides; (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises 100% 2'-O-methyl modifications; and (7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0420] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 85% 2'-O-methyl modifications (e.g., from about 85% to about 90% 2'-O-methyl modifications); (3) the nucleotides at positions 2 and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides (e.g., the nucleotides at positions 2 and 14 from the 5' end of the antisense strand may be 2'-fluoro nucleotides); (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises at least 75% 2'-O-methyl modifications (e.g., from about 75% to about 80% 2'-O-methyl modifications); (7) the nucleotides at positions 7, 10, and 11 from the 3' end of the sense strand are not 2'-methoxy-ribonucleotides (e.g., the nucleotides at positions 7, 10, and 11 from the 3' end of the sense strand are 2'-fluoro nucleotides); and (8) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0421] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of

SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 75% 2'-O-methyl modifications (e.g., from about 75% to about 80% 2'-O-methyl modifications); (3) the nucleotides at positions 2, 4, 5, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides (e.g., the nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand may be 2'-fluoro nucleotides); (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises 100% 2'-O-methyl modifications; and (7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0422] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 75% 2'-O-methyl modifications e.g., from about 75% to about 80% 2'-O-methyl modifications); (3) the nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides (e.g., the nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand may be 2'-fluoro nucleotides); (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand; (6) the sense strand comprises at least 65% 2'-O-methyl modifications (e.g., from about 65% to about 75% 2'-O-methyl modifications); (7) the nucleotides at positions 7, 9, 10, and 11 from the 3' end of the sense strand are not 2'-methoxy-ribonucleotides; and (8) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0423] In certain embodiments, the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein: (1) the antisense strand has a nucleic acid sequence that is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; (2) the antisense strand comprises at least 75% 2'-O-methyl modifications; (3) the nucleotides at positions 2, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides; (4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages; (5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises at least 80% 2'-O-methyl modifications; (7) the nucleotides at positions 7, 10, and 11 from the 3' end of the sense strand are not 2'-methoxy-ribonucleotides; and (8) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0424] In certain embodiments, a functional moiety is linked to the 5' end and/or 3' end of the antisense strand. In certain embodiments, a functional moiety is linked to the 5' end and/or 3' end of the sense strand. In certain embodiments, a functional moiety is linked to the 3' end of the sense strand.

[0425] In certain embodiments, the functional moiety comprises a hydrophobic moiety.

[0426] In certain embodiments, the hydrophobic moiety is selected from the group consisting of fatty acids, steroids, secosteroids, lipids, gangliosides, nucleoside analogs, endocannabinoids, vitamins, and a mixture thereof.

[0427] In certain embodiments, the steroid selected from the group consisting of cholesterol and Lithocholic acid (LCA).

[0428] In certain embodiments, the fatty acid selected from the group consisting of Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA) and Docosanoic acid (DCA).

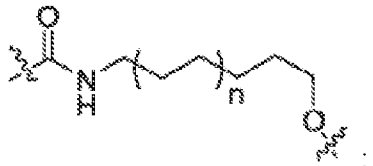
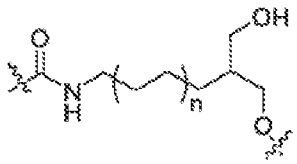
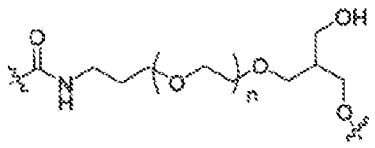
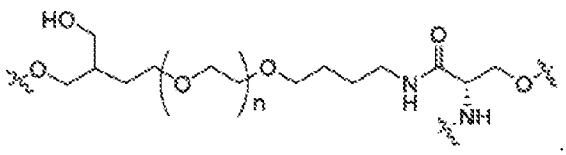
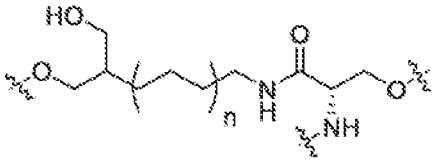
[0429] In certain embodiments, the vitamin selected from the group consisting of choline, vitamin A, vitamin E, derivatives thereof, and metabolites thereof.

[0430] In certain embodiments, the vitamin is selected from the group consisting of retinoic acid and alpha-tocopheryl succinate.

[0431] In certain embodiments, the functional moiety is linked to the antisense strand and/or sense strand by a linker.

[0432] In certain embodiments, the linker comprises a divalent or trivalent linker.

[0433] In certain embodiments, the divalent or trivalent linker is selected from the group consisting of:

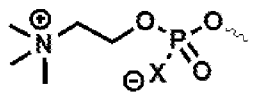

;

;

;


; and ,

wherein n is 1, 2, 3, 4, or 5.

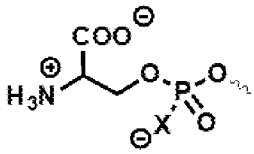
[0434] In certain embodiments, the linker comprises an ethylene glycol chain, an alkyl chain, a peptide, RNA, DNA, a phosphodiester, a phosphorothioate, a phosphoramidate, an amide, a carbamate, or a combination thereof.

[0435] In certain embodiments, when the linker is a trivalent linker, the linker further links a phosphodiester or phosphodiester derivative.

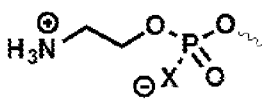
[0436] In certain embodiments, the phosphodiester or phosphodiester derivative is selected from the group consisting of:


;

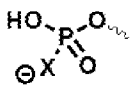
(Zc1);


;

(Zc2);


; and

(Zc3)

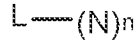

;

(Zc4)

wherein X is O, S or BH_3.

[0437] In certain embodiments, the nucleotides at positions 1 and 2 from the 3' end of sense strand, and the nucleotides at positions 1 and 2 from the 5' end of antisense strand, are connected to adjacent ribonucleotides via phosphorothioate linkages.

[0438] In one aspect, the disclosure provides a compound of formula (I):



(I)

wherein:

L comprises an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, or combinations thereof, optionally wherein formula (I) further comprises one or more branch point B, and one or more spacer S, wherein:

B is independently for each occurrence a polyvalent organic species or derivative thereof;

S comprises independently for each occurrence an ethylene glycol chain, an alkyl chain, a peptide, RNA, DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, or combinations thereof;

n is 2, 3, 4, 5, 6, 7 or 8; and

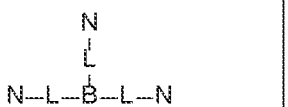
N is a double stranded nucleic acid, such as a dsRNA molecule of any of the above aspects or embodiments of the disclosure. In certain embodiments, each N is from 15 to 40 bases in length.

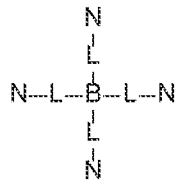
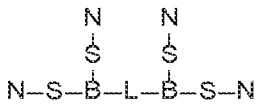
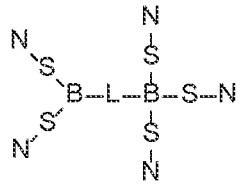
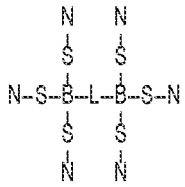
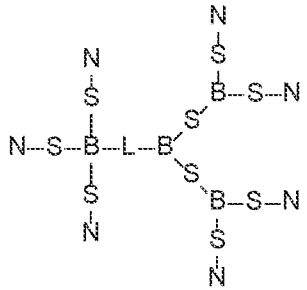
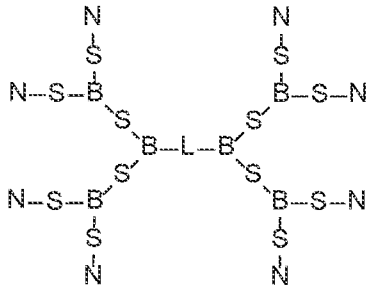
In certain embodiments, each N comprises a sense strand and an antisense strand; wherein:

the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; and

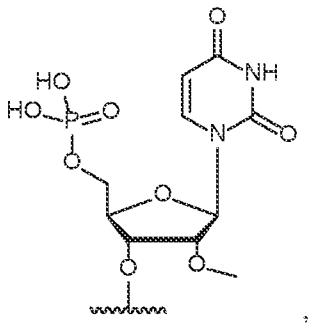
the sense strand and antisense strand each independently comprise one or more chemical modifications.

[0439] In certain embodiments, the compound comprises a structure selected from formulas (I-1)-(I-9):

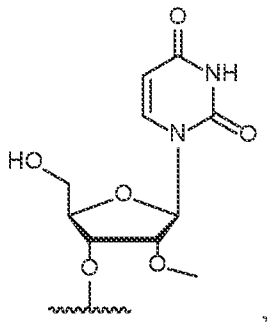
N—L—N	N—S—L—S—N	

(I-1)	(I-2)	(I-3)
		
(I-4)	(I-5)	(I-6)
		
(I-7)	(I-8)	(I-9)

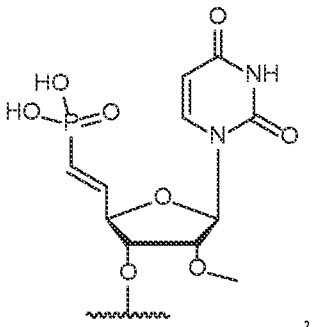
[0440] In certain embodiments, the antisense strand comprises a 5' terminal group R selected from the group consisting of:



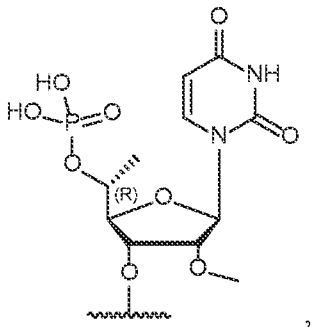
R^1,



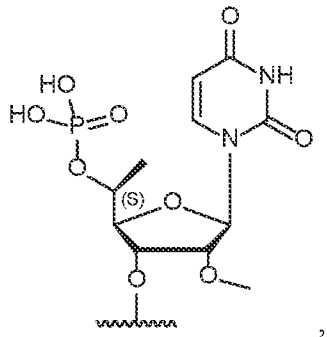
R^2,



R^3,

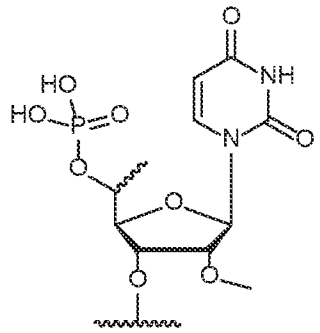


R^4,



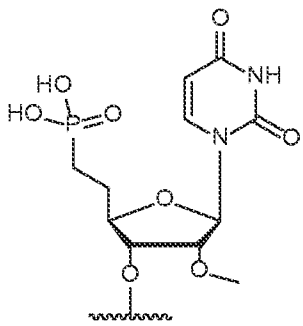
,

R5



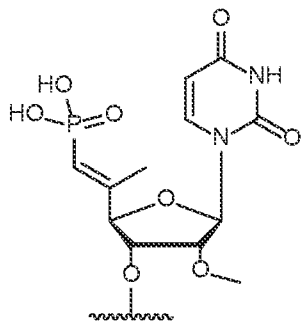
,

R6



, and

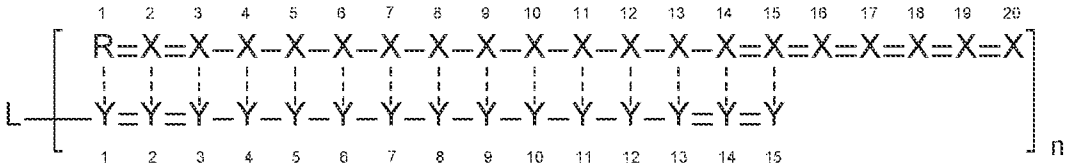
R7



.

R8

[0441] In certain embodiments, the compound comprises the structure of formula (II):



(II)

wherein:

X, for each occurrence, independently, is selected from adenosine, guanosine, uridine, cytidine, and chemically-modified derivatives thereof;

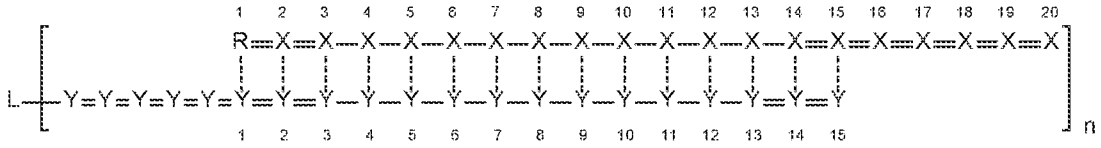
Y, for each occurrence, independently, is selected from adenosine, guanosine, uridine, cytidine, and chemically-modified derivatives thereof;

- represents a phosphodiester internucleoside linkage;

= represents a phosphorothioate internucleoside linkage; and

---- represents, individually for each occurrence, a base-pairing interaction or a mismatch.

[0442] In certain embodiments, the compound comprises the structure of formula (IV):



(IV)

wherein:

X, for each occurrence, independently, is selected from adenosine, guanosine, uridine, cytidine, and chemically-modified derivatives thereof;

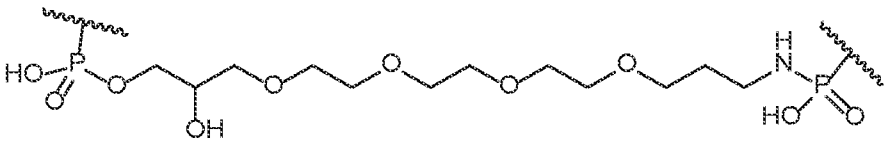
Y, for each occurrence, independently, is selected from adenosine, guanosine, uridine, cytidine, and chemically-modified derivatives thereof;

- represents a phosphodiester internucleoside linkage;

= represents a phosphorothioate internucleoside linkage; and

--- represents, individually for each occurrence, a base-pairing interaction or a mismatch.

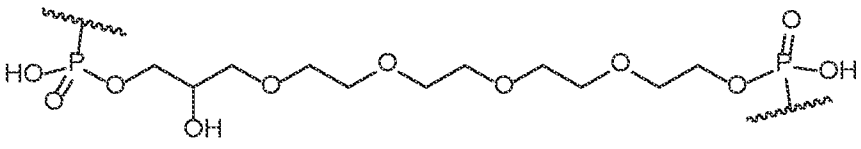
[0443] In certain embodiments, L is structure L1:



(L1).

[0444] In certain embodiments, R is R^3 and n is 2.

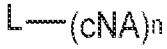
[0445] In certain embodiments, L is structure L2:



(L2).

[0446] In certain embodiments, R is R^3 and n is 2.

[0447] In one aspect, the disclosure provides a delivery system for therapeutic nucleic acids having the structure of Formula (VI):



(VI)

wherein:

L comprises an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, or combinations thereof, optionally wherein formula (VI) further comprises one or more branch point B, and one or more spacer S, wherein

B comprises independently for each occurrence a polyvalent organic species or derivative thereof;

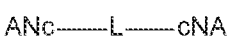
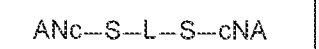
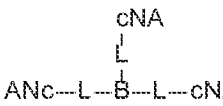
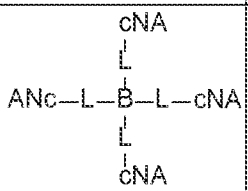
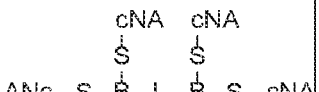
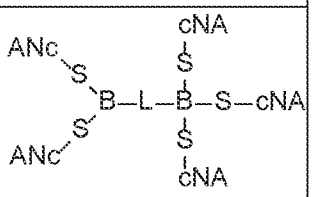
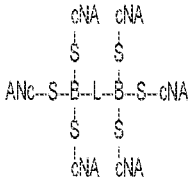
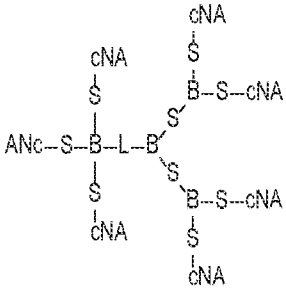
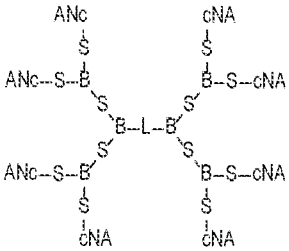
S comprises independently for each occurrence an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, or combinations thereof;

each cNA, independently, is a carrier nucleic acid comprising one or more chemical modifications;

each cNA, independently, comprises at least 15 contiguous nucleotides of a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; and

n is 2, 3, 4, 5, 6, 7 or 8.

[0448] In certain embodiments, the delivery system comprises a structure selected from formulas (VI-1)-(VI-9):

		
(VI-1)	(VI -2)	(VI -3)
		
(VI-4)	(VI -5)	(VI -6)
		

(VI -7)	(VI-8)	(VI-9)

[0449] In certain embodiments, each cNA independently comprises chemically-modified nucleotides.

[0450] In certain embodiments, delivery system further comprises n therapeutic nucleic acids (NA), wherein each NA is hybridized to at least one cNA.

[0451] In certain embodiments, each NA independently comprises at least 14 contiguous nucleotides (e.g., at least 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or more contiguous nucleotides).

[0452] In certain embodiments, each NA independently comprises 14-35 contiguous nucleotides. In some embodiments, each NA independently comprises 14 contiguous nucleotides. In some embodiments, each NA independently comprises 15 contiguous nucleotides. In some embodiments, each NA independently comprises 16 contiguous nucleotides. In some embodiments, each NA independently comprises 17 contiguous nucleotides. In some embodiments, each NA independently comprises 18 contiguous nucleotides. In some embodiments, each NA independently comprises 19 contiguous nucleotides. In some embodiments, each NA independently comprises 20 contiguous nucleotides. In some embodiments, each NA independently comprises 21 contiguous nucleotides. In some embodiments, each NA independently comprises 22 contiguous nucleotides. In some embodiments, each NA independently comprises 23 contiguous nucleotides. In some embodiments, each NA independently comprises 24 contiguous nucleotides. In some embodiments, each NA independently comprises 25 contiguous nucleotides. In some embodiments, each NA independently comprises 26 contiguous nucleotides. In some embodiments, each NA independently comprises 27 contiguous nucleotides. In some embodiments, each NA independently comprises 28 contiguous nucleotides. In some embodiments, each NA independently comprises 29 contiguous nucleotides. In some embodiments, each NA independently comprises 30 contiguous nucleotides. In some embodiments, each NA independently comprises 31 contiguous nucleotides. In some embodiments, each NA independently comprises 32 contiguous nucleotides. In some embodiments, each NA independently comprises 33 contiguous nucleotides. In some embodiments, each NA independently comprises 34 contiguous nucleotides. In some embodiments, each NA independently comprises 35 contiguous nucleotides.

[0453] In certain embodiments, each NA comprises an unpaired overhang of at least 2 nucleotides.

[0454] In certain embodiments, the nucleotides of the overhang are connected via phosphorothioate linkages.

[0455] In certain embodiments, each NA, independently, is selected from the group consisting of DNAs, siRNAs, antagomiRs, miRNAs, gapmers, mixmers, and guide RNAs.

[0456] In certain embodiments, each NA is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

[0457] In one aspect, the disclosure provides a pharmaceutical composition for inhibiting the expression of *MAPT* gene in an organism, comprising a compound recited above or a system recited above, and a pharmaceutically acceptable carrier.

[0458] In certain embodiments, the compound or system inhibits the expression of the *MAPT* gene by at least 50%. In certain embodiments, the compound or system inhibits the expression of the *MAPT* gene by at least 80%.

[0459] In one aspect, the disclosure provides a method for inhibiting expression of *MAPT* gene in a cell, the method comprising: (a) introducing into the cell a compound recited above or a system recited above; and (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of the *MAPT* gene, thereby inhibiting expression of the *MAPT* gene in the cell.

[0460] In one aspect, the disclosure provides a method of treating or managing a neurodegenerative disease comprising administering to a patient in need of such treatment or management a therapeutically effective amount of a compound recited above or a system recited above.

[0461] In certain embodiments, the dsRNA is administered to the brain of the patient.

[0462] In certain embodiments, the dsRNA is administered by intracerebroventricular (ICV) injection, intrastriatal (IS) injection, intravenous (IV) injection, subcutaneous (SQ) injection, or a combination thereof.

[0463] 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.

[0464] In certain embodiments, the dsRNA inhibits the expression of said *MAPT* gene by at least 50%. In certain embodiments, the dsRNA inhibits the expression of said *MAPT* gene by at least 80%.

Brief Description of the Drawings

[0465] The foregoing and other features and advantages of the present disclosure will be more fully understood from the following detailed description of illustrative embodiments taken in conjunction with the accompanying drawings. The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0466] **FIG. 1A-1D** depicts a screen of siRNAs targeting sequences of human *MAPT* mRNA in SH-SY5Y human neuroblastoma cells. FIG. 1A, Screen of twelve sequences identifying MAPT 1971, MAPT 2051 and MAPT 2012 as novel targeting regions; FIG. 1B-1D, 8-point does response curves obtained with MAPT 1971 (B), MAPT 2051 (C) and MAPT 2012 (D) siRNA.

[0467] **FIG. 2A-2D** depicts a screen of siRNAs targeting sequences of human and mouse *MAPT* mRNA in SH-SY5Y human neuroblastoma cells. FIG. 2A, Screen of twelve sequences identifying MAPT 2034, MAPT 2007 and MAPT 2005 as novel targeting regions; FIG. 1B-1D, 8-point does response curves obtained with MAPT 2034 (B), MAPT 2007 (C) and MAPT 2005 (D) siRNA.

[0468] **FIG. 3** depicts siRNA chemical scaffolds evaluated for MAPT.

[0469] **FIG. 4A-4F** depicts screens of 48 sequences targeting MAPT with 6 different chemical scaffolds applied. Hit sequences are shown in yellow. *, small amount of duplex; **, not fully protected; red arrow: caused cell death. FIG. 4A, P3 blunt scaffold; FIG. 4B, P3 blunt plus mismatches at positions 10 and 11 on sense strand scaffold; FIG. 4C, P3 asymmetric scaffold; FIG. 4D, P3 asymmetric plus ribose sense strand scaffold; FIG. 4E, OMe rich asymmetric scaffold; FIG. 4F, OMe rich asymmetric plus ribose sense strand scaffold.

[0470] **FIG. 5A-5C** depicts a concentration response for active MAPT sequences (selection). FIG. 5A, MAPT 357, FIG. 5B, MAPT 2257; FIG. 5C, MAPT 2378.

[0471] **FIG. 6** depicts a screen of siRNAs targeting sequences of human *MAPT* mRNA in SH-SY5Y human neuroblastoma cells.

[0472] **FIG. 7A-7B** depict two screens of siRNAs targeting sequences of human *MAPT* mRNA in SH-SY5Y human neuroblastoma cells (FIG. 7A) and mouse *MAPT* mRNA in N2A mouse neuroblastoma cells (FIG. 7B).

[0473] **FIG. 8** depicts a dose response for select MAPT target sequences in a P5 chemical modification pattern.

[0474] **FIG. 9** depicts a dose response for select MAPT target sequences in a P3 chemical modification pattern.

[0475] **FIG. 10** depicts a further screen of siRNAs targeting various MAPT mRNA target sequences across the ORF and 3' UTR. The screen was performed in SH-SY5Y human neuroblastoma cells. Each siRNA was used at a concentration of 1.5 μM and incubated for 72 hours with the cells before quantifying relative mRNA expression.

[0476] **FIG. 11** depicts further screens of siRNAs targeting various MAPT mRNA target sequences across the ORF. Targets are found in both human and mouse MAPT mRNA. The screen was performed in SH-SY5Y human neuroblastoma cells. Each siRNA was used at a concentration of 1.5 μM and incubated for 72 hours with the cells before quantifying relative mRNA expression.

[0477] **FIG. 12A-FIG. 12B** depict normalized MAPT mRNA (FIG. 12A) and protein (FIG. 12B) expression levels in several mouse brain regions 1 month after intracerebroventricular (ICV) injection. A 10 nmol dose in a 10 μl injection volume of siRNAs targeting MAPT target sites designated MAPT 2005, MAPT 3309, and MAPT 3292 were used. Tau protein levels were normalized to the protein vinculin and gapdh.

Detailed Description

[0478] Novel *MAPT* target sequences are provided. Also provided are novel RNA molecules, such as siRNAs and branched RNA compounds containing the same, that target the *MAPT* mRNA, such as one or more target sequences of the disclosure.

[0479] Unless otherwise specified, nomenclature used in connection with cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well-known and commonly used

in the art. Unless otherwise specified, the methods and techniques provided herein are performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclature used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, delivery, and treatment of patients.

[0480] Unless otherwise defined herein, scientific and technical terms used herein have the meanings that are commonly understood by those of ordinary skill in the art. In the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The use of "or" means "and/or" unless stated otherwise. The use of the term "including," as well as other forms, such as "includes" and "included," is not limiting.

[0481] So that the disclosure may be more readily understood, certain terms are first defined.

[0482] The term "nucleoside" refers to a molecule having a purine or pyrimidine base covalently linked to a ribose or deoxyribose sugar. Exemplary nucleosides include adenosine, guanosine, cytidine, uridine and thymidine. Additional exemplary nucleosides include inosine, 1-methyl inosine, pseudouridine, 5,6-dihydrouridine, ribothymidine, 2N-methylguanosine and N2,N2-dimethylguanosine (also referred to as "rare" nucleosides). The term "nucleotide" refers to a nucleoside having one or more phosphate groups joined in ester linkages to the sugar moiety. Exemplary nucleotides include nucleoside monophosphates, diphosphates and triphosphates. The terms "polynucleotide" and "nucleic acid molecule" are used interchangeably herein and refer to a polymer of nucleotides joined together by a phosphodiester or phosphorothioate linkage between 5' and 3' carbon atoms.

[0483] The term "RNA" or "RNA molecule" or "ribonucleic acid molecule" refers to a polymer of ribonucleotides (e.g., 2, 3, 4, 5, 10, 15, 20, 25, 30, or more ribonucleotides). The term "DNA" or "DNA molecule" or "deoxyribonucleic acid molecule" refers to a polymer

of deoxyribonucleotides. DNA and RNA can be synthesized naturally (e.g., by DNA replication or transcription of DNA, respectively). RNA can be post-transcriptionally modified. DNA and RNA can also be chemically synthesized. DNA and RNA can be single-stranded (i.e., ssRNA and ssDNA, respectively) or multi-stranded (e.g., double stranded, i.e., dsRNA and dsDNA, respectively). "mRNA" or "messenger RNA" is single-stranded RNA that specifies the amino acid sequence of one or more polypeptide chains. This information is translated during protein synthesis when ribosomes bind to the mRNA.

[0484] As used herein, the term "small interfering RNA" ("siRNA") (also referred to in the art as "short interfering RNAs") refers to an RNA (or RNA analog) comprising between about 10-50 nucleotides (or nucleotide analogs), which is capable of directing or mediating RNA interference. In certain embodiments, a siRNA comprises between about 15-30 nucleotides or nucleotide analogs, or between about 16-25 nucleotides (or nucleotide analogs), or between about 18-23 nucleotides (or nucleotide analogs), or between about 19-22 nucleotides (or nucleotide analogs) (e.g., 19, 20, 21 or 22 nucleotides or nucleotide analogs). The term "short" siRNA refers to a siRNA comprising about 21 nucleotides (or nucleotide analogs), for example, 19, 20, 21 or 22 nucleotides. The term "long" siRNA refers to a siRNA comprising about 24-25 nucleotides, for example, 23, 24, 25 or 26 nucleotides. Short siRNAs may, in some instances, include fewer than 19 nucleotides, e.g., 16, 17 or 18 nucleotides, provided that the shorter siRNA retains the ability to mediate RNAi. Likewise, long siRNAs may, in some instances, include more than 26 nucleotides, provided that the longer siRNA retains the ability to mediate RNAi absent further processing, e.g., enzymatic processing, to a short siRNA.

[0485] The term "nucleotide analog" or "altered nucleotide" or "modified nucleotide" refers to a non-standard nucleotide, including non-naturally occurring ribonucleotides or deoxyribonucleotides. Exemplary nucleotide analogs are modified at any position so as to alter certain chemical properties of the nucleotide yet retain the ability of the nucleotide analog to perform its intended function. Examples of positions of the nucleotide, which may be derivatized include: the 5 position, e.g., 5-(2-amino)propyl uridine, 5-bromo uridine, 5-propyne uridine, 5-propenyl uridine, etc.; the 6 position, e.g., 6-(2-amino)propyl uridine; and the 8-position for adenosine and/or guanosines, e.g., 8-bromo guanosine, 8-chloro guanosine, 8-fluoroguanosine, etc. Nucleotide analogs also include deaza nucleotides, e.g., 7-deaza-adenosine; O- and N-modified (e.g., alkylated, e.g., N6-methyl adenosine, or as otherwise

known in the art) nucleotides; and other heterocyclically modified nucleotide analogs, such as those described in Herdewijn, Antisense Nucleic Acid Drug Dev., 2000 Aug. 10(4):297-310.

[0486] Nucleotide analogs may also comprise modifications to the sugar portion of the nucleotides. For example, the 2' OH-group may be replaced by a group selected from H, OR, R, F, Cl, Br, I, SH, SR, NH_2, NHR, NR_2, or COOR, wherein R is substituted or unsubstituted C_1-C_6 alkyl, alkenyl, alkynyl, aryl, etc. Other possible modifications include those described in U.S. Pat. Nos. 5,858,988, and 6,291,438.

[0487] The phosphate group of the nucleotide may also be modified, e.g., by substituting one or more of the oxygens of the phosphate group with sulfur (e.g., phosphorothioates), or by making other substitutions, which allow the nucleotide to perform its intended function, such as described in, for example, Eckstein, Antisense Nucleic Acid Drug Dev. 2000 Apr. 10(2):117-21, Rusckowski et al. Antisense Nucleic Acid Drug Dev. 2000 Oct. 10(5):333-45, Stein, Antisense Nucleic Acid Drug Dev. 2001 Oct. 11(5): 317-25, Vorobjev et al. Antisense Nucleic Acid Drug Dev. 2001 Apr. 11(2):77-85, and U.S. Pat. No. 5,684,143. Certain of the above-referenced modifications (e.g., phosphate group modifications) decrease the rate of hydrolysis of, for example, polynucleotides comprising said analogs *in vivo* or *in vitro*.

[0488] The term "oligonucleotide" refers to a short polymer of nucleotides and/or nucleotide analogs.

[0489] The term "RNA analog" refers to a polynucleotide (e.g., a chemically synthesized polynucleotide) having at least one altered or modified nucleotide as compared to a corresponding unaltered or unmodified RNA, but retaining the same or similar nature or function as the corresponding unaltered or unmodified RNA. As discussed above, the oligonucleotides may be linked with linkages, which result in a lower rate of hydrolysis of the RNA analog as compared to an RNA molecule with phosphodiester linkages. For example, the nucleotides of the analog may comprise methylenediol, ethylene diol, oxymethylthio, oxyethylthio, oxycarbonyloxy, phosphorodiamidate, phosphoroamidate, and/or phosphorothioate linkages. Some RNA analogues include sugar- and/or backbone-modified ribonucleotides and/or deoxyribonucleotides. Such alterations or modifications can further include addition of non-nucleotide material, such as to the end(s) of the RNA or internally (at one or more nucleotides of the RNA). An RNA analog need only be sufficiently similar to natural RNA that it has the ability to mediate RNA interference.

[0490] As used herein, the term "RNA interference" ("RNAi") refers to a selective intracellular degradation of RNA. RNAi occurs in cells naturally to remove foreign RNAs (e.g., viral RNAs). Natural RNAi proceeds via fragments cleaved from free dsRNA, which direct the degradative mechanism to other similar RNA sequences. Alternatively, RNAi can be initiated by the hand of man, for example, to silence the expression of target genes.

[0491] An RNAi agent, e.g., an RNA silencing agent, having a strand, which is "sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi)" means that the strand has a sequence sufficient to trigger the destruction of the target mRNA by the RNAi machinery or process.

[0492] As used herein, the term "isolated RNA" (e.g., "isolated siRNA" or "isolated siRNA precursor") refers to RNA molecules, which are substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

[0493] As used herein, the term "RNA silencing" refers to a group of sequence-specific regulatory mechanisms (e.g. RNA interference (RNAi), transcriptional gene silencing (TGS), post-transcriptional gene silencing (PTGS), quelling, co-suppression, and translational repression) mediated by RNA molecules, which result in the inhibition or "silencing" of the expression of a corresponding protein-coding gene. RNA silencing has been observed in many types of organisms, including plants, animals, and fungi.

[0494] The term "discriminatory RNA silencing" refers to the ability of an RNA molecule to substantially inhibit the expression of a "first" or "target" polynucleotide sequence while not substantially inhibiting the expression of a "second" or "non-target" polynucleotide sequence," e.g., when both polynucleotide sequences are present in the same cell. In certain embodiments, the target polynucleotide sequence corresponds to a target gene, while the non-target polynucleotide sequence corresponds to a non-target gene. In other embodiments, the target polynucleotide sequence corresponds to a target allele, while the non-target polynucleotide sequence corresponds to a non-target allele. In certain embodiments, the target polynucleotide sequence is the DNA sequence encoding the regulatory region (e.g. promoter or enhancer elements) of a target gene. In other embodiments, the target polynucleotide sequence is a target mRNA encoded by a target gene.

[0495] The term "*in vitro*" has its art recognized meaning, e.g., involving purified reagents or extracts, e.g., cell extracts. The term "*in vivo*" also has its art recognized meaning,

e.g., involving living cells, e.g., immortalized cells, primary cells, cell lines, and/or cells in an organism.

[0496] As used herein, the term "transgene" refers to any nucleic acid molecule, which is inserted by artifice into a cell, and becomes part of the genome of the organism that develops from the cell. Such a transgene may include a gene that is partly or entirely heterologous (i.e., foreign) to the transgenic organism, or may represent a gene homologous to an endogenous gene of the organism. The term "transgene" also means a nucleic acid molecule that includes one or more selected nucleic acid sequences, e.g., DNAs, that encode one or more engineered RNA precursors, to be expressed in a transgenic organism, e.g., animal, which is partly or entirely heterologous, i.e., foreign, to the transgenic animal, or homologous to an endogenous gene of the transgenic animal, but which is designed to be inserted into the animal's genome at a location which differs from that of the natural gene. A transgene includes one or more promoters and any other DNA, such as introns, necessary for expression of the selected nucleic acid sequence, all operably linked to the selected sequence, and may include an enhancer sequence.

[0497] A gene "involved" in a disease or disorder includes a gene, the normal or aberrant expression or function of which effects or causes the disease or disorder or at least one symptom of said disease or disorder.

[0498] The term "gain-of-function mutation" as used herein, refers to any mutation in a gene in which the protein encoded by said gene (i.e., the mutant protein) acquires a function not normally associated with the protein (i.e., the wild type protein) and causes or contributes to a disease or disorder. The gain-of-function mutation can be a deletion, addition, or substitution of a nucleotide or nucleotides in the gene, which gives rise to the change in the function of the encoded protein. In one embodiment, the gain-of-function mutation changes the function of the mutant protein or causes interactions with other proteins. In another embodiment, the gain-of-function mutation causes a decrease in or removal of normal wild-type protein, for example, by interaction of the altered, mutant protein with said normal, wild-type protein.

[0499] As used herein, the term "target gene" is a gene whose expression is to be substantially inhibited or "silenced." This silencing can be achieved by RNA silencing, e.g., by cleaving the mRNA of the target gene or translational repression of the target gene. The term "non-target gene" is a gene whose expression is not to be substantially silenced. In one

embodiment, the polynucleotide sequences of the target and non-target gene (e.g. mRNA encoded by the target and non-target genes) can differ by one or more nucleotides. In another embodiment, the target and non-target genes can differ by one or more polymorphisms (e.g., Single Nucleotide Polymorphisms or SNPs). In another embodiment, the target and non-target genes can share less than 100% sequence identity. In another embodiment, the non-target gene may be a homologue (e.g. an orthologue or paralogue) of the target gene.

[0500] A "target allele" is an allele (e.g., a SNP allele) whose expression is to be selectively inhibited or "silenced." This silencing can be achieved by RNA silencing, e.g., by cleaving the mRNA of the target gene or target allele by a siRNA. The term "non-target allele" is an allele whose expression is not to be substantially silenced. In certain embodiments, the target and non-target alleles can correspond to the same target gene. In other embodiments, the target allele corresponds to, or is associated with, a target gene, and the non-target allele corresponds to, or is associated with, a non-target gene. In one embodiment, the polynucleotide sequences of the target and non-target alleles can differ by one or more nucleotides. In another embodiment, the target and non-target alleles can differ by one or more allelic polymorphisms (e.g., one or more SNPs). In another embodiment, the target and non-target alleles can share less than 100% sequence identity.

[0501] The term "polymorphism" as used herein, refers to a variation (e.g., one or more deletions, insertions, or substitutions) in a gene sequence that is identified or detected when the same gene sequence from different sources or subjects (but from the same organism) are compared. For example, a polymorphism can be identified when the same gene sequence from different subjects are compared. Identification of such polymorphisms is routine in the art, the methodologies being similar to those used to detect, for example, breast cancer point mutations. Identification can be made, for example, from DNA extracted from a subject's lymphocytes, followed by amplification of polymorphic regions using specific primers to said polymorphic region. Alternatively, the polymorphism can be identified when two alleles of the same gene are compared. In certain embodiments, the polymorphism is a single nucleotide polymorphism (SNP).

[0502] A variation in sequence between two alleles of the same gene within an organism is referred to herein as an "allelic polymorphism." In certain embodiments, the allelic polymorphism corresponds to a SNP allele. For example, the allelic polymorphism may comprise a single nucleotide variation between the two alleles of a SNP. The polymorphism can be at a nucleotide within a coding region but, due to the degeneracy of the genetic code, no

change in amino acid sequence is encoded. Alternatively, polymorphic sequences can encode a different amino acid at a particular position, but the change in the amino acid does not affect protein function. Polymorphic regions can also be found in non-encoding regions of the gene. In exemplary embodiments, the polymorphism is found in a coding region of the gene or in an untranslated region (e.g., a 5' UTR or 3' UTR) of the gene.

[0503] As used herein, the term "allelic frequency" is a measure (e.g., proportion or percentage) of the relative frequency of an allele (e.g., a SNP allele) at a single locus in a population of individuals. For example, where a population of individuals carry n loci of a particular chromosomal locus (and the gene occupying the locus) in each of their somatic cells, then the allelic frequency of an allele is the fraction or percentage of loci that the allele occupies within the population. In certain embodiments, the allelic frequency of an allele (e.g., an SNP allele) is at least 10% (e.g., at least 15%, 20%, 25%, 30%, 35%, 40% or more) in a sample population.

[0504] As used herein, the term "sample population" refers to a population of individuals comprising a statistically significant number of individuals. For example, the sample population may comprise 50, 75, 100, 200, 500, 1000 or more individuals. In certain embodiments, the sample population may comprise individuals, which share at least on common disease phenotype (e.g., a gain-of-function disorder) or mutation (e.g., a gain-of-function mutation).

[0505] As used herein, the term "heterozygosity" refers to the fraction of individuals within a population that are heterozygous (e.g., contain two or more different alleles) at a particular locus (e.g., at a SNP). Heterozygosity may be calculated for a sample population using methods that are well known to those skilled in the art.

[0506] The term "polyglutamine domain," as used herein, refers to a segment or domain of a protein that consist of consecutive glutamine residues linked to peptide bonds. In one embodiment, the consecutive region includes at least 5 glutamine residues.

[0507] 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 interaction with microtubules, leading to microtubule dysfunction and impaired axonal transport, and tau fibrillization.

[0508] As described herein, the term tauopathy refers to a family of neurodegenerative diseases characterized by the aggregation of tau protein into neurofibrillary or gliofibrillary tangles (NFTs) in the human brain. The tangles are formed by hyperphosphorylation of tau protein. Hyperphorphorylation causes tau protein to dissociate from microtubules and to form insoluble aggregates. The aggregates may also be referred to as paired helical filaments. Examples of tauopathies are Alzheimer's disease, primary age-related tauopathy (PART), which is a neurofibrillary tangle-predominant senile dementia with neurofibrillary tangles similar to AD, but without plaques, chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), Lytico-bodig disease (Parkinson-dementia complex of Guam), ganglioglioma and gangliocytoma, meningioangiomatosis, postencephalitic parkinsonism, subacute sclerosing panencephalitis (SSPE), lead encephalopathy, tuberous sclerosis, pantothenate kinase-associated neurodegeneration, and lipofuscinosis, Pick's disease, corticobasal degeneration. Further, patients with Huntington's disease present aggregated tau inclusions within various structures of the brain. Tauopathies can also overlap with synucleinopathies, such as Parkinson's disease, due to potential interactions between synuclein and tau proteins.

[0509] The term "expanded polyglutamine domain" or "expanded polyglutamine segment," as used herein, refers to a segment or domain of a protein that includes at least 35 consecutive glutamine residues linked by peptide bonds. Such expanded segments are found in subjects afflicted with a polyglutamine disorder, as described herein, whether or not the subject manifests symptoms.

[0510] The term "trinucleotide repeat" or "trinucleotide repeat region" as used herein, refers to a segment of a nucleic acid sequence that consists of consecutive repeats of a particular trinucleotide sequence. In one embodiment, the trinucleotide repeat includes at least 5 consecutive trinucleotide sequences. Exemplary trinucleotide sequences include, but are not limited to, CAG, CGG, GCC, GAA, CTG and/or CGG.

[0511] The term "trinucleotide repeat diseases" as used herein, refers to any disease or disorder characterized by an expanded trinucleotide repeat region located within a gene, the expanded trinucleotide repeat region being causative of the disease or disorder. Examples of trinucleotide repeat diseases include, but are not limited to Huntington's disease (HD), spino-cerebellar ataxia type 12 spino-cerebellar ataxia type 8, fragile X syndrome, fragile XE mental retardation, Friedreich's ataxia and myotonic dystrophy. Exemplary trinucleotide repeat diseases for treatment according to the present disclosure are those characterized or caused by an expanded trinucleotide repeat region at the 5' end of the coding region of a gene, the gene encoding a mutant protein, which causes or is causative of the disease or disorder. Certain trinucleotide diseases, for example, fragile X syndrome, where the mutation is not associated with a coding region, may not be suitable for treatment according to the methodologies of the present disclosure, as there is no suitable mRNA to be targeted by RNAi. By contrast, disease such as Friedreich's ataxia may be suitable for treatment according to the methodologies of the disclosuredisclosure because, although the causative mutation is not within a coding region (i.e., lies within an intron), the mutation may be within, for example, an mRNA precursor (e.g., a pre-spliced mRNA precursor).

[0512] The phrase "examining the function of a gene in a cell or organism" refers to examining or studying the expression, activity, function or phenotype arising therefrom.

[0513] As used herein, the term "RNA silencing agent" refers to an RNA, which is capable of inhibiting or "silencing" the expression of a target gene. In certain embodiments, the RNA silencing agent is capable of preventing complete processing (e.g., the full translation and/or expression) of a mRNA molecule through a post-transcriptional silencing mechanism. RNA silencing agents include small (<50 b.p.), noncoding RNA molecules, for example RNA duplexes comprising paired strands, as well as precursor RNAs from which such small non-coding RNAs can be generated. Exemplary RNA silencing agents include siRNAs, miRNAs, siRNA-like duplexes, antisense oligonucleotides, GAPMER molecules, and dual-function oligonucleotides, as well as precursors thereof. In one embodiment, the RNA silencing agent

is capable of inducing RNA interference. In another embodiment, the RNA silencing agent is capable of mediating translational repression.

[0514] As used herein, the term "rare nucleotide" refers to a naturally occurring nucleotide that occurs infrequently, including naturally occurring deoxyribonucleotides or ribonucleotides that occur infrequently, e.g., a naturally occurring ribonucleotide that is not guanosine, adenosine, cytosine, or uridine. Examples of rare nucleotides include, but are not limited to, inosine, 1-methyl inosine, pseudouridine, 5,6-dihydrouridine, ribothymidine, 2N-methylguanosine and 2,2N,N-dimethylguanosine.

[0515] The term "engineered," as in an engineered RNA precursor, or an engineered nucleic acid molecule, indicates that the precursor or molecule is not found in nature, in that all or a portion of the nucleic acid sequence of the precursor or molecule is created or selected by a human. Once created or selected, the sequence can be replicated, translated, transcribed, or otherwise processed by mechanisms within a cell. Thus, an RNA precursor produced within a cell from a transgene that includes an engineered nucleic acid molecule is an engineered RNA precursor.

[0516] As used herein, the term "microRNA" ("miRNA"), also known in the art as "small temporal RNAs" ("stRNAs"), refers to a small (10-50 nucleotide) RNA, which are genetically encoded (e.g., by viral, mammalian, or plant genomes) and are capable of directing or mediating RNA silencing. An "miRNA disorder" shall refer to a disease or disorder characterized by an aberrant expression or activity of a miRNA.

[0517] As used herein, the term "dual functional oligonucleotide" refers to a RNA silencing agent having the formula T-L-μ, wherein T is an mRNA targeting moiety, L is a linking moiety, and μ is a miRNA recruiting moiety. As used herein, the terms "mRNA targeting moiety," "targeting moiety," "mRNA targeting portion" or "targeting portion" refer to a domain, portion or region of the dual functional oligonucleotide having sufficient size and sufficient complementarity to a portion or region of an mRNA chosen or targeted for silencing (i.e., the moiety has a sequence sufficient to capture the target mRNA).

[0518] As used herein, the term "linking moiety" or "linking portion" refers to a domain, portion or region of the RNA-silencing agent which covalently joins or links the mRNA.

[0519] As used herein, the term "antisense strand" of an RNA silencing agent, e.g., an siRNA or RNA silencing agent, refers to a strand that is substantially complementary to a

section of about 10-50 nucleotides, e.g., about 15-30, 16-25, 18-23 or 19-22 nucleotides of the mRNA of the gene targeted for silencing. The antisense strand or first strand has sequence sufficiently complementary to the desired target mRNA sequence to direct target-specific silencing, e.g., complementarity sufficient to trigger the destruction of the desired target mRNA by the RNAi machinery or process (RNAi interference) or complementarity sufficient to trigger translational repression of the desired target mRNA.

[0520] The term "sense strand" or "second strand" of an RNA silencing agent, e.g., an siRNA or RNA silencing agent, refers to a strand that is complementary to the antisense strand or first strand. Antisense and sense strands can also be referred to as first or second strands, the first or second strand having complementarity to the target sequence and the respective second or first strand having complementarity to said first or second strand. miRNA duplex intermediates or siRNA-like duplexes include a miRNA strand having sufficient complementarity to a section of about 10-50 nucleotides of the mRNA of the gene targeted for silencing and a miRNA* strand having sufficient complementarity to form a duplex with the miRNA strand.

[0521] As used herein, the term "guide strand" refers to a strand of an RNA silencing agent, e.g., an antisense strand of an siRNA duplex or siRNA sequence, that enters into the RISC complex and directs cleavage of the target mRNA.

[0522] As used herein, the term "asymmetry," as in the asymmetry of the duplex region of an RNA silencing agent (e.g., the stem of an shRNA), refers to an inequality of bond strength or base pairing strength between the termini of the RNA silencing agent (e.g., between terminal nucleotides on a first strand or stem portion and terminal nucleotides on an opposing second strand or stem portion), such that the 5' end of one strand of the duplex is more frequently in a transient unpaired, e.g., single-stranded, state than the 5' end of the complementary strand. This structural difference determines that one strand of the duplex is preferentially incorporated into a RISC complex. The strand whose 5' end is less tightly paired to the complementary strand will preferentially be incorporated into RISC and mediate RNAi.

[0523] As used herein, the term "bond strength" or "base pair strength" refers to the strength of the interaction between pairs of nucleotides (or nucleotide analogs) on opposing strands of an oligonucleotide duplex (e.g., an siRNA duplex), due primarily to H-bonding, van der Waals interactions, and the like, between said nucleotides (or nucleotide analogs).

[0524] As used herein, the "5' end," as in the 5' end of an antisense strand, refers to the 5' terminal nucleotides, e.g., between one and about 5 nucleotides at the 5' terminus of the antisense strand. As used herein, the "3' end," as in the 3' end of a sense strand, refers to the region, e.g., a region of between one and about 5 nucleotides, that is complementary to the nucleotides of the 5' end of the complementary antisense strand.

[0525] As used herein the term "destabilizing nucleotide" refers to a first nucleotide or nucleotide analog capable of forming a base pair with second nucleotide or nucleotide analog such that the base pair is of lower bond strength than a conventional base pair (i.e., Watson-Crick base pair). In certain embodiments, the destabilizing nucleotide is capable of forming a mismatch base pair with the second nucleotide. In other embodiments, the destabilizing nucleotide is capable of forming a wobble base pair with the second nucleotide. In yet other embodiments, the destabilizing nucleotide is capable of forming an ambiguous base pair with the second nucleotide.

[0526] As used herein, the term "base pair" refers to the interaction between pairs of nucleotides (or nucleotide analogs) on opposing strands of an oligonucleotide duplex (e.g., a duplex formed by a strand of a RNA silencing agent and a target mRNA sequence), due primarily to H-bonding, van der Waals interactions, and the like between said nucleotides (or nucleotide analogs). As used herein, the term "bond strength" or "base pair strength" refers to the strength of the base pair.

[0527] As used herein, the term "mismatched base pair" refers to a base pair consisting of non-complementary or non-Watson-Crick base pairs, for example, not normal complementary G:C, A:T or A:U base pairs. As used herein the term "ambiguous base pair" (also known as a non-discriminatory base pair) refers to a base pair formed by a universal nucleotide.

[0528] As used herein, term "universal nucleotide" (also known as a "neutral nucleotide") include those nucleotides (e.g. certain destabilizing nucleotides) having a base (a "universal base" or "neutral base") that does not significantly discriminate between bases on a complementary polynucleotide when forming a base pair. Universal nucleotides are predominantly hydrophobic molecules that can pack efficiently into antiparallel duplex nucleic acids (e.g., double-stranded DNA or RNA) due to stacking interactions. The base portion of universal nucleotides typically comprise a nitrogen-containing aromatic heterocyclic moiety.

[0529] As used herein, the terms "sufficient complementarity" or "sufficient degree of complementarity" mean that the RNA silencing agent has a sequence (e.g. in the antisense strand, mRNA targeting moiety or miRNA recruiting moiety), which is sufficient to bind the desired target RNA, respectively, and to trigger the RNA silencing of the target mRNA.

[0530] As used herein, the term "translational repression" refers to a selective inhibition of mRNA translation. Natural translational repression proceeds via miRNAs cleaved from shRNA precursors. Both RNAi and translational repression are mediated by RISC. Both RNAi and translational repression occur naturally or can be initiated by the hand of man, for example, to silence the expression of target genes.

[0531] Various methodologies of the instant disclosure include a step that involves comparing a value, level, feature, characteristic, property, etc. to a "suitable control," referred to interchangeably herein as an "appropriate control." A "suitable control" or "appropriate control" is any control or standard familiar to one of ordinary skill in the art useful for comparison purposes. In one embodiment, a "suitable control" or "appropriate control" is a value, level, feature, characteristic, property, etc. determined prior to performing an RNAi methodology, as described herein. For example, a transcription rate, mRNA level, translation rate, protein level, biological activity, cellular characteristic or property, genotype, phenotype, etc. can be determined prior to introducing an RNA silencing agent of the disclosure into a cell or organism. In another embodiment, a "suitable control" or "appropriate control" is a value, level, feature, characteristic, property, etc. determined in a cell or organism, e.g., a control or normal cell or organism, exhibiting, for example, normal traits. In yet another embodiment, a "suitable control" or "appropriate control" is a predefined value, level, feature, characteristic, property, etc.

[0532] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and example are illustrative only and not intended to be limiting.

[0533] Various aspects of the disclosure are described in further detail in the following subsections.

I. Novel Target Sequences

[0534] In certain exemplary embodiments, RNA silencing agents of the disclosuredisclosure are capable of targeting a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295, as recited in **Table 4** -6. In certain exemplary embodiments, RNA silencing agents of the disclosuredisclosure are capable of targeting one or more of a *MAPT* nucleic acid sequence selected from the group consisting of SEQ ID NOs: 14-33, 299, and 302, as recited in **Tables 7-8**.

[0535] Genomic sequence for each target sequence can be found in, for example, the publicly available database maintained by the NCBI.

II. siRNA Design

[0536] In some embodiments, siRNAs are designed as follows. First, a portion of the target gene (e.g., the *MAPT* gene), e.g., one or more of the target sequences set forth in **Tables 4-6** is selected. Cleavage of mRNA at these sites should eliminate translation of corresponding protein. Antisense strands were designed based on the target sequence and sense strands were designed to be complementary to the antisense strand. Hybridization of the antisense and sense strands forms the siRNA duplex. The antisense strand includes about 19 to 25 nucleotides, e.g., 19, 20, 21, 22, 23, 24 or 25 nucleotides. In other embodiments, the antisense strand includes 20, 21, 22 or 23 nucleotides. The sense strand includes about 14 to 25 nucleotides, e.g., 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides. In other embodiments, the sense strand is 15 nucleotides. In other embodiments, the sense strand is 18 nucleotides. In other embodiments, the sense strand is 20 nucleotides. The skilled artisan will appreciate, however, that siRNAs having a length of less than 19 nucleotides or greater than 25 nucleotides can also function to mediate RNAi. Accordingly, siRNAs of such length are also within the scope of the instant disclosure, provided that they retain the ability to mediate RNAi. Longer RNAi agents have been demonstrated to elicit an interferon or PKR response in certain mammalian cells, which may be undesirable. In certain embodiments, the RNAi agents of the disclosuredisclosure do not elicit a PKR response (i.e., are of a sufficiently short length). However, longer RNAi agents may be useful, for example, in cell types incapable of generating

a PKR response or in situations where the PKR response has been down-regulated or dampened by alternative means.

[0537] The sense strand sequence can be designed such that the target sequence is essentially in the middle of the strand. Moving the target sequence to an off-center position can, in some instances, reduce efficiency of cleavage by the siRNA. Such compositions, i.e., less efficient compositions, may be desirable for use if off-silencing of the wild-type mRNA is detected.

[0538] The antisense strand can be the same length as the sense strand and includes complementary nucleotides. In one embodiment, the strands are fully complementary, i.e., the strands are blunt-ended when aligned or annealed. In another embodiment, the strands align or anneal such that 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-nucleotide overhangs are generated, i.e., the 3' end of the sense strand extends 1, 2, 3, 4, 5, 6, 7, or 8 nucleotides further than the 5' end of the antisense strand and/or the 3' end of the antisense strand extends 1, 2, 3, 4, 5, 6, 7, or 8 nucleotides further than the 5' end of the sense strand. Overhangs can comprise (or consist of) nucleotides corresponding to the target gene sequence (or complement thereof). Alternatively, overhangs can comprise (or consist of) deoxyribonucleotides, for example dTs, or nucleotide analogs, or other suitable non-nucleotide material.

[0539] To facilitate entry of the antisense strand into RISC (and thus increase or improve the efficiency of target cleavage and silencing), the base pair strength between the 5' end of the sense strand and 3' end of the antisense strand can be altered, e.g., lessened or reduced, as described in detail in U.S. Patent Nos. 7,459,547, 7,772,203 and 7,732,593, entitled "Methods and Compositions for Controlling Efficacy of RNA Silencing" (filed Jun. 2, 2003) and U.S. Patent Nos. 8,309,704, 7,750,144, 8,304,530, 8,329,892 and 8,309,705, entitled "Methods and Compositions for Enhancing the Efficacy and Specificity of RNAi" (filed Jun. 2, 2003), the contents of which are incorporated in their entirety by this reference. In one embodiment of these aspects of the disclosure, the base-pair strength is less due to fewer G:C base pairs between the 5' end of the first or antisense strand and the 3' end of the second or sense strand than between the 3' end of the first or antisense strand and the 5' end of the second or sense strand. In another embodiment, the base pair strength is less due to at least one mismatched base pair between the 5' end of the first or antisense strand and the 3' end of the second or sense strand. In certain exemplary embodiments, the mismatched base pair is selected from the group consisting of G:A, C:A, C:U, G:G, A:A, C:C and U:U. In another embodiment, the base pair strength is less due to at least one wobble base pair, e.g., G:U,

between the 5' end of the first or antisense strand and the 3' end of the second or sense strand. In another embodiment, the base pair strength is less due to at least one base pair comprising a rare nucleotide, e.g., inosine (I). In certain exemplary embodiments, the base pair is selected from the group consisting of an I:A, I:U and I:C. In yet another embodiment, the base pair strength is less due to at least one base pair comprising a modified nucleotide. In certain exemplary embodiments, the modified nucleotide is selected from the group consisting of 2-amino-G, 2-amino-A, 2,6-diamino-G, and 2,6-diamino-A.

[0540] The design of siRNAs suitable for targeting the *MAPT* target sequences set forth in **Tables 4-6** is described in detail below. siRNAs can be designed according to the above exemplary teachings for any other target sequences found in the *MAPT* gene. Moreover, the technology is applicable to targeting any other target sequences, e.g., non-disease-causing target sequences.

[0541] To validate the effectiveness by which siRNAs destroy mRNAs (e.g., *MAPT* mRNA), the siRNA can be incubated with cDNA (e.g., *MAPT* cDNA) in a *Drosophila*-based *in vitro* mRNA expression system. Radiolabeled with ^{32}P, newly synthesized mRNAs (e.g., *MAPT* mRNA) are detected autoradiographically on an agarose gel. The presence of cleaved mRNA indicates mRNA nuclease activity. Suitable controls include omission of siRNA. Alternatively, control siRNAs are selected having the same nucleotide composition as the selected siRNA, but without significant sequence complementarity to the appropriate target gene. Such negative controls can be designed by randomly scrambling the nucleotide sequence of the selected siRNA; a homology search can be performed to ensure that the negative control lacks homology to any other gene in the appropriate genome. In addition, negative control siRNAs can be designed by introducing one or more base mismatches into the sequence. Sites of siRNA-mRNA complementation are selected which result in optimal mRNA specificity and maximal mRNA cleavage.

III. RNAi Agents

[0542] The present disclosuredisclosure includes RNAi molecules, such as siRNA molecules designed, for example, as described above. The siRNA molecules of the disclosuredisclosure can be chemically synthesized, or can be transcribed *in vitro* from a DNA template, or *in vivo* from e.g., shRNA, or by using recombinant human DICER enzyme, to

cleave *in vitro* transcribed dsRNA templates into pools of 20-, 21- or 23-bp duplex RNA mediating RNAi. The siRNA molecules can be designed using any method known in the art.

[0543] In one aspect, instead of the RNAi agent being an interfering ribonucleic acid, e.g., an siRNA or shRNA as described above, the RNAi agent can encode an interfering ribonucleic acid, e.g., an shRNA, as described above. In other words, the RNAi agent can be a transcriptional template of the interfering ribonucleic acid. Thus, RNAi agents of the present disclosuredisclosure can also include small hairpin RNAs (shRNAs), and expression constructs engineered to express shRNAs. Transcription of shRNAs is initiated at a polymerase III (pol III) promoter, and is thought to be terminated at position 2 of a 4-5-thymine transcription termination site. Upon expression, shRNAs are thought to fold into a stem-loop structure with 3' UU-overhangs; subsequently, the ends of these shRNAs are processed, converting the shRNAs into siRNA-like molecules of about 21-23 nucleotides (Brummelkamp et al., 2002; Lee et al., 2002, *Supra*; Miyagishi et al., 2002; Paddison et al., 2002, *supra*; Paul et al., 2002, *supra*; Sui et al., 2002 *supra*; Yu et al., 2002, *supra*. More information about shRNA design and use can be found on the internet at the following addresses: katandin.cshl.org:9331/RNAi/docs/BseRI-BamHI_Strategy.pdf and katandin.cshl.org:9331/RNAi/docs/Web_version_of_PCR_strategy1.pdf).

[0544] Expression constructs of the present disclosuredisclosure include any construct suitable for use in the appropriate expression system and include, but are not limited to, retroviral vectors, linear expression cassettes, plasmids and viral or virally-derived vectors, as known in the art. Such expression constructs can include one or more inducible promoters, RNA Pol III promoter systems, such as U6 snRNA promoters or H1 RNA polymerase III promoters, or other promoters known in the art. The constructs can include one or both strands of the siRNA. Expression constructs expressing both strands can also include loop structures linking both strands, or each strand can be separately transcribed from separate promoters within the same construct. Each strand can also be transcribed from a separate expression construct. (Tuschl, T., 2002, *Supra*).

[0545] Synthetic siRNAs can be delivered into cells by methods known in the art, including cationic liposome transfection and electroporation. To obtain longer term suppression of the target genes (e.g., *MAPT* genes) and to facilitate delivery under certain circumstances, one or more siRNA can be expressed within cells from recombinant DNA constructs. Such methods for expressing siRNA duplexes within cells from recombinant DNA constructs to allow longer-term target gene suppression in cells are known in the art, including

mammalian Pol III promoter systems (e.g., H1 or U6/snRNA promoter systems (Tuschl, T., 2002, *supra*) capable of expressing functional double-stranded siRNAs; (Bagella et al., 1998; Lee et al., 2002, *supra*; Miyagishi et al., 2002, *supra*; Paul et al., 2002, *supra*; Yu et al., 2002, *supra*; Sui et al., 2002, *supra*). Transcriptional termination by RNA Pol III occurs at runs of four consecutive T residues in the DNA template, providing a mechanism to end the siRNA transcript at a specific sequence. The siRNA is complementary to the sequence of the target gene in 5'-3' and 3'-5' orientations, and the two strands of the siRNA can be expressed in the same construct or in separate constructs. Hairpin siRNAs, driven by H1 or U6 snRNA promoter and expressed in cells, can inhibit target gene expression (Bagella et al., 1998; Lee et al., 2002, *supra*; Miyagishi et al., 2002, *supra*; Paul et al., 2002, *supra*; Yu et al., 2002), *supra*; Sui et al., 2002, *supra*). Constructs containing siRNA sequence under the control of T7 promoter also make functional siRNAs when co-transfected into the cells with a vector expressing T7 RNA polymerase (Jacque et al., 2002, *supra*). A single construct may contain multiple sequences coding for siRNAs, such as multiple regions of the gene encoding *MAPT*, targeting the same gene or multiple genes, and can be driven, for example, by separate PolIII promoter sites.

[0546] Animal cells express a range of noncoding RNAs of approximately 22 nucleotides termed micro RNA (miRNAs), which can regulate gene expression at the post transcriptional or translational level during animal development. One common feature of miRNAs is that they are all excised from an approximately 70 nucleotide precursor RNA stem-loop, probably by Dicer, an RNase III-type enzyme, or a homolog thereof. By substituting the stem sequences of the miRNA precursor with sequence complementary to the target mRNA, a vector construct that expresses the engineered precursor can be used to produce siRNAs to initiate RNAi against specific mRNA targets in mammalian cells (Zeng et al., 2002, *supra*). When expressed by DNA vectors containing polymerase III promoters, micro-RNA designed hairpins can silence gene expression (McManus et al., 2002, *supra*). MicroRNAs targeting polymorphisms may also be useful for blocking translation of mutant proteins, in the absence of siRNA-mediated gene-silencing. Such applications may be useful in situations, for example, where a designed siRNA caused off-target silencing of wild type protein.

[0547] Viral-mediated delivery mechanisms can also be used to induce specific silencing of targeted genes through expression of siRNA, for example, by generating recombinant adenoviruses harboring siRNA under RNA Pol II promoter transcription control (Xia et al., 2002, *supra*). Infection of HeLa cells by these recombinant adenoviruses allows

for diminished endogenous target gene expression. Injection of the recombinant adenovirus vectors into transgenic mice expressing the target genes of the siRNA results in *in vivo* reduction of target gene expression. *Id.* In an animal model, whole-embryo electroporation can efficiently deliver synthetic siRNA into post-implantation mouse embryos (Calegari et al., 2002). In adult mice, efficient delivery of siRNA can be accomplished by "high-pressure" delivery technique, a rapid injection (within 5 seconds) of a large volume of siRNA containing solution into animal via the tail vein (Liu et al., 1999, *supra*; McCaffrey et al., 2002, *supra*; Lewis et al., 2002. Nanoparticles and liposomes can also be used to deliver siRNA into animals. In certain exemplary embodiments, recombinant adeno-associated viruses (rAAVs) and their associated vectors can be used to deliver one or more siRNAs into cells, e.g., neural cells (e.g., brain cells) (US Patent Applications 2014/0296486, 2010/0186103, 2008/0269149, 2006/0078542 and 2005/0220766).

[0548] The nucleic acid compositions of the disclosure include both unmodified siRNAs and modified siRNAs, such as crosslinked siRNA derivatives or derivatives having non-nucleotide moieties linked, for example to their 3' or 5' ends. Modifying siRNA derivatives in this way may improve cellular uptake or enhance cellular targeting activities of the resulting siRNA derivative, as compared to the corresponding siRNA, and are useful for tracing the siRNA derivative in the cell, or improving the stability of the siRNA derivative compared to the corresponding siRNA.

[0549] Engineered RNA precursors, introduced into cells or whole organisms as described herein, will lead to the production of a desired siRNA molecule. Such an siRNA molecule will then associate with endogenous protein components of the RNAi pathway to bind to and target a specific mRNA sequence for cleavage and destruction. In this fashion, the mRNA, which will be targeted by the siRNA generated from the engineered RNA precursor, and will be depleted from the cell or organism, leading to a decrease in the concentration of the protein encoded by that mRNA in the cell or organism. The RNA precursors are typically nucleic acid molecules that individually encode either one strand of a dsRNA or encode the entire nucleotide sequence of an RNA hairpin loop structure.

[0550] The nucleic acid compositions of the disclosure can be unconjugated or can be conjugated to another moiety, such as a nanoparticle, to enhance a property of the compositions, e.g., a pharmacokinetic parameter such as absorption, efficacy, bioavailability and/or half-life. The conjugation can be accomplished by methods known in the art, e.g., using the methods of Lambert et al., Drug Deliv. Rev.: 47(1), 99-112 (2001) (describes nucleic acids

loaded to polyalkylcyanoacrylate (PACA) nanoparticles); Fattal et al., J. Control Release 53(1-3):137-43 (1998) (describes nucleic acids bound to nanoparticles); Schwab et al., Ann. Oncol. 5 Suppl. 4:55-8 (1994) (describes nucleic acids linked to intercalating agents, hydrophobic groups, polycations or PACA nanoparticles); and Godard et al., Eur. J. Biochem. 232(2):404-10 (1995) (describes nucleic acids linked to nanoparticles).

[0551] The nucleic acid molecules of the present disclosure can also be labeled using any method known in the art. For instance, the nucleic acid compositions can be labeled with a fluorophore, e.g., Cy3, fluorescein, or rhodamine. The labeling can be carried out using a kit, e.g., the SILENCER™ siRNA labeling kit (Ambion). Additionally, the siRNA can be radiolabeled, e.g., using ^{3}H, ^{32}P or another appropriate isotope.

[0552] Moreover, because RNAi is believed to progress via at least one single-stranded RNA intermediate, the skilled artisan will appreciate that ss-siRNAs (e.g., the antisense strand of a ds-siRNA) can also be designed (e.g., for chemical synthesis), generated (e.g., enzymatically generated), or expressed (e.g., from a vector or plasmid) as described herein and utilized according to the claimed methodologies. Moreover, in invertebrates, RNAi can be triggered effectively by long dsRNAs (e.g., dsRNAs about 100-1000 nucleotides in length, such as about 200-500, for example, about 250, 300, 350, 400 or 450 nucleotides in length) acting as effectors of RNAi. (Brondani et al., Proc Natl Acad Sci USA. 2001 Dec. 4; 98(25):14428-33. Epub 2001 Nov. 27.)

IV. Anti-MAPT RNA Silencing Agents

[0553] In certain embodiments, the present disclosure provides novel anti-MAPT RNA silencing agents (e.g., siRNA, shRNA, and antisense oligonucleotides), methods of making said RNA silencing agents, and methods (e.g., research and/or therapeutic methods) for using said improved RNA silencing agents (or portions thereof) for RNA silencing of MAPT protein. The RNA silencing agents comprise an antisense strand (or portions thereof), wherein the antisense strand has sufficient complementary to a target MAPT mRNA to mediate an RNA-mediated silencing mechanism (e.g. RNAi).

[0554] In certain embodiments, siRNA compounds are provided having one or any combination of the following properties: (1) fully chemically-stabilized (i.e., no unmodified 2'-OH residues); (2) asymmetry; (3) 11-20 base pair duplexes; (4) greater than 50% 2'-methoxy modifications, such as 70%-100% 2'-methoxy modifications, although an alternating

pattern of chemically-modified nucleotides (e.g., 2'-fluoro and 2'-methoxy modifications), are also contemplated; and (5) single-stranded, fully phosphorothioated tails of 5-8 bases. In certain embodiments, the number of phosphorothioate modifications is varied from 4 to 16 total. In certain embodiments, the number of phosphorothioate modifications is varied from 8 to 13 total.

[0555] In certain embodiments, the siRNA compounds described herein can be conjugated to a variety of targeting agents, including, but not limited to, cholesterol, docosahexaenoic acid (DHA), phenyltropanes, cortisol, vitamin A, vitamin D, N-acetylgalactosamine (GalNac), and gangliosides. The cholesterol-modified version showed 5-10 fold improvement in efficacy *in vitro* versus previously used chemical stabilization patterns (e.g., wherein all purine but not pyrimidines are modified) in wide range of cell types (e.g., HeLa, neurons, hepatocytes, trophoblasts).

[0556] Certain compounds of the disclosure having the structural properties described above and herein may be referred to as "hsiRNA-ASP" (hydrophobically-modified, small interfering RNA, featuring an advanced stabilization pattern). In addition, this hsiRNA-ASP pattern showed a dramatically improved distribution through the brain, spinal cord, delivery to liver, placenta, kidney, spleen and several other tissues, making them accessible for therapeutic intervention.

[0557] The compounds of the disclosure can be described in the following aspects and embodiments.

[0558] In a first aspect, provided herein is a double stranded RNA (dsRNA) comprising an antisense strand and a sense strand, each strand comprising at least 14 contiguous nucleotides, with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises alternating 2'-methoxy-ribonucleotides and 2'-fluoro-ribonucleotides;

(3) the nucleotides at positions 2 and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises alternating 2'-methoxy-ribonucleotides and 2'-fluoro-

ribonucleotides; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0559] In a second aspect, provided herein is a dsRNA comprising an antisense strand and a sense strand, each strand comprising at least 14 contiguous nucleotides, with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 70% 2'-O-methyl modifications;

(3) the nucleotide at position 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises at least 70% 2'-O-methyl modifications; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0560] In a third aspect, provided herein is a dsRNA comprising an antisense strand and a sense strand, each strand comprising at least 14 contiguous nucleotides, with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 85% 2'-O-methyl modifications;

(3) the nucleotides at positions 2 and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises 100% 2'-O-methyl modifications; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0561] In a fourth aspect, provided herein is a dsRNA comprising an antisense strand and a sense strand, each strand comprising at least 14 contiguous nucleotides, with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 75% 2'-O-methyl modifications;

(3) the nucleotides at positions 4, 5, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises 100% 2'-O-methyl modifications; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0562] In a fifth aspect, provided herein is a dsRNA comprising an antisense strand and a sense strand, each strand comprising at least 14 contiguous nucleotides, with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 75% 2'-O-methyl modifications;

(3) the nucleotides at positions 2, 4, 5, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises 100% 2'-O-methyl modifications; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0563] In a sixth aspect, provided herein is a dsRNA comprising an antisense strand and a sense strand, each strand comprising at least 14 contiguous nucleotides, with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 75% 2'-O-methyl modifications;

(3) the nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are

connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises at least 70% 2'-O-methyl modifications;

(7) the nucleotides at positions 7, 9, 10, and 11 from the 3' end of the sense strand are not 2'-methoxy-ribonucleotides; and

(8) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

[0564] In a seventh aspect, provided herein is a dsRNA comprising an antisense strand and a sense strand, each strand comprising at least 14 contiguous nucleotides, with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 75% 2'-O-methyl modifications;

(3) the nucleotides at positions 2, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises at least 80% 2'-O-methyl modifications;

(7) the nucleotides at positions 7, 10, and 11 from the 3' end of the sense strand are not 2'-methoxy-ribonucleotides; and

(8) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

a) Design of Anti-MAPT siRNA Molecules

[0565] An siRNA molecule of the application is a duplex made of a sense strand and complementary antisense strand, the antisense strand having sufficient complementary to a *MAPT* mRNA to mediate RNAi. In certain embodiments, the siRNA molecule has a length from about 10-50 or more nucleotides, i.e., each strand comprises 10-50 nucleotides (or nucleotide analogs). In other embodiments, the siRNA molecule has a length from about 15-30, e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in each strand, wherein one of the strands is sufficiently complementary to a target region. In certain embodiments, the strands are aligned such that there are at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 bases at the end of the strands, which do not align (i.e., for which no complementary bases

occur in the opposing strand), such that an overhang of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 residues occurs at one or both ends of the duplex when strands are annealed.

[0566] Usually, siRNAs can be designed by using any method known in the art, for instance, by using the following protocol:

[0567] 1. The siRNA should be specific for a target sequence, e.g., a target sequence set forth in the Examples. The first strand should be complementary to the target sequence, and the other strand is substantially complementary to the first strand. (See Examples for exemplary sense and antisense strands.) Exemplary target sequences are selected from any region of the target gene that leads to potent gene silencing. Regions of the target gene include, but are not limited to, the 5' untranslated region (5'-UTR) of a target gene, the 3' untranslated region (3'-UTR) of a target gene, an exon of a target gene, or an intron of a target gene. Cleavage of mRNA at these sites should eliminate translation of corresponding MAPT protein. Target sequences from other regions of the *MAPT* gene are also suitable for targeting. A sense strand is designed based on the target sequence.

[0568] 2. The sense strand of the siRNA is designed based on the sequence of the selected target site. In certain embodiments, the sense strand includes about 15 to 25 nucleotides, e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides. In certain embodiments, the sense strand includes 15, 16, 17, 18, 19, or 20 nucleotides. In certain embodiments, the sense strand is 15 nucleotides in length. In certain embodiments, the sense strand is 18 nucleotides in length. In certain embodiments, the sense strand is 20 nucleotides in length. The skilled artisan will appreciate, however, that siRNAs having a length of less than 15 nucleotides or greater than 25 nucleotides can also function to mediate RNAi. Accordingly, siRNAs of such length are also within the scope of the instant disclosure, provided that they retain the ability to mediate RNAi. Longer RNA silencing agents have been demonstrated to elicit an interferon or Protein Kinase R (PKR) response in certain mammalian cells which may be undesirable. In certain embodiments, the RNA silencing agents of the disclosure do not elicit a PKR response (i.e., are of a sufficiently short length). However, longer RNA silencing agents may be useful, for example, in cell types incapable of generating a PKR response or in situations where the PKR response has been down-regulated or dampened by alternative means.

[0569] The siRNA molecules of the disclosure have sufficient complementarity with the target sequence such that the siRNA can mediate RNAi. In general, siRNA containing nucleotide sequences sufficiently complementary to a target sequence portion of the target gene

to effect RISC-mediated cleavage of the target gene are contemplated. Accordingly, in a certain embodiment, the antisense strand of the siRNA is designed to have a sequence sufficiently complementary to a portion of the target. For example, the antisense strand may have 100% complementarity to the target site. However, 100% complementarity is not required. Greater than 80% identity, e.g., 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or even 100% complementarity, between the antisense strand and the target RNA sequence is contemplated. The present application has the advantage of being able to tolerate certain sequence variations to enhance efficiency and specificity of RNAi. In one embodiment, the antisense strand has 4, 3, 2, 1, or 0 mismatched nucleotide(s) with a target region, such as a target region that differs by at least one base pair between a wild-type and mutant allele, e.g., a target region comprising the gain-of-function mutation, and the other strand is identical or substantially identical to the first strand. Moreover, siRNA sequences with small insertions or deletions of 1 or 2 nucleotides may also be effective for mediating RNAi. Alternatively, siRNA sequences with nucleotide analog substitutions or insertions can be effective for inhibition.

[0570] Sequence identity may be determined by sequence comparison and alignment algorithms known in the art. To determine the percent identity of two nucleic acid sequences (or of two amino acid sequences), the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the first sequence or second sequence for optimal alignment). The nucleotides (or amino acid residues) at corresponding nucleotide (or amino acid) positions are then compared. When a position in the first sequence is occupied by the same residue as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % homology = number of identical positions / total number of positions x 100), optionally penalizing the score for the number of gaps introduced and/or length of gaps introduced.

[0571] The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In one embodiment, the alignment generated over a certain portion of the sequence aligned having sufficient identity but not over portions having low degree of identity (i.e., a local alignment). A non-limiting example of a local alignment algorithm utilized for the comparison of sequences is the algorithm of Karlin and Altschul (1990) Proc. Natl. Acad. Sci. USA 87:2264-68, modified as in Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873-77. Such an algorithm is

incorporated into the BLAST programs (version 2.0) of Altschul, et al. (1990) J. Mol. Biol. 215:403-10.

[0572] In another embodiment, the alignment is optimized by introducing appropriate gaps and the percent identity is determined over the length of the aligned sequences (i.e., a gapped alignment). To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) Nucleic Acids Res. 25(17):3389-3402. In another embodiment, the alignment is optimized by introducing appropriate gaps and percent identity is determined over the entire length of the sequences aligned (i.e., a global alignment). A non-limiting example of a mathematical algorithm utilized for the global comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

[0573] 3. The antisense or guide strand of the siRNA is routinely the same length as the sense strand and includes complementary nucleotides. In one embodiment, the guide and sense strands are fully complementary, i.e., the strands are blunt-ended when aligned or annealed. In another embodiment, the strands of the siRNA can be paired in such a way as to have a 3' overhang of 1 to 7 (e.g., 2, 3, 4, 5, 6 or 7), or 1 to 4, e.g., 2, 3 or 4 nucleotides. Overhangs can comprise (or consist of) nucleotides corresponding to the target gene sequence (or complement thereof). Alternatively, overhangs can comprise (or consist of) deoxyribonucleotides, for example dTs, or nucleotide analogs, or other suitable non-nucleotide material. Thus, in another embodiment, the nucleic acid molecules may have a 3' overhang of 2 nucleotides, such as TT. The overhanging nucleotides may be either RNA or DNA. As noted above, it is desirable to choose a target region wherein the mutant:wild type mismatch is a purine:purine mismatch.

[0574] 4. Using any method known in the art, compare the potential targets to the appropriate genome database (human, mouse, rat, etc.) and eliminate from consideration any target sequences with significant homology to other coding sequences. One such method for such sequence homology searches is known as BLAST, which is available at National Center for Biotechnology Information website.

[0575] 5. Select one or more sequences that meet your criteria for evaluation.

[0576] Further general information about the design and use of siRNA may be found in "The siRNA User Guide," available at The Max-Plank-Institut fur Biophysikalische Chemie website.

[0577] Alternatively, the siRNA may be defined functionally as a nucleotide sequence (or oligonucleotide sequence) that is capable of hybridizing with the target sequence (e.g., 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50 °C or 70 °C hybridization for 12-16 hours; followed by washing). Additional hybridization conditions include hybridization at 70 °C in 1xSSC or 50 °C in 1xSSC, 50% formamide followed by washing at 70 °C in 0.3xSSC or hybridization at 70 °C in 4xSSC or 50 °C in 4xSSC, 50% formamide followed by washing at 67 °C in 1xSSC. The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10 °C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C)=2(# of A+T bases)+4(# of G+C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C)=81.5+16.6(log 10[Na+])+0.41(% G+C)-(600/N), where N is the number of bases in the hybrid, and [Na+] is the concentration of sodium ions in the hybridization buffer ([Na^+] for 1xSSC=0.165 M). Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E. F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F. M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

[0578] Negative control siRNAs should have the same nucleotide composition as the selected siRNA, but without significant sequence complementarity to the appropriate genome. Such negative controls may be designed by randomly scrambling the nucleotide sequence of the selected siRNA. A homology search can be performed to ensure that the negative control lacks homology to any other gene in the appropriate genome. In addition, negative control siRNAs can be designed by introducing one or more base mismatches into the sequence.

[0579] 6. To validate the effectiveness by which siRNAs destroy target mRNAs (e.g., wild-type or mutant *MAPT* mRNA), the siRNA may be incubated with target cDNA (e.g., *MAPT* cDNA) in a *Drosophila*-based *in vitro* mRNA expression system. Radiolabeled with ^{32}P, newly synthesized target mRNAs (e.g., *MAPT* mRNA) are detected autoradiographically on an agarose gel. The presence of cleaved target mRNA indicates mRNA nuclease activity. Suitable controls include omission of siRNA and use of non-target cDNA. Alternatively,

control siRNAs are selected having the same nucleotide composition as the selected siRNA, but without significant sequence complementarity to the appropriate target gene. Such negative controls can be designed by randomly scrambling the nucleotide sequence of the selected siRNA. A homology search can be performed to ensure that the negative control lacks homology to any other gene in the appropriate genome. In addition, negative control siRNAs can be designed by introducing one or more base mismatches into the sequence.

[0580] Anti-MAPT siRNAs may be designed to target any of the target sequences described supra. Said siRNAs comprise an antisense strand, which is sufficiently complementary with the target sequence to mediate silencing of the target sequence. In certain embodiments, the RNA silencing agent is a siRNA.

[0581] In certain embodiments, the siRNA comprises a sense strand comprising a sequence set forth in **Table 7** and **Table 8**, and an antisense strand comprising a sequence set forth in **Table 7** and **Table 8**.

[0582] Sites of siRNA-mRNA complementation are selected, which result in optimal mRNA specificity and maximal mRNA cleavage.

b) siRNA-Like Molecules

[0583] siRNA-like molecules of the disclosure have a sequence (i.e., have a strand having a sequence) that is "sufficiently complementary" to a target sequence of an *MAPT* mRNA to direct gene silencing either by RNAi or translational repression. siRNA-like molecules are designed in the same way as siRNA molecules, but the degree of sequence identity between the sense strand and target RNA approximates that observed between a miRNA and its target. In general, as the degree of sequence identity between a miRNA sequence and the corresponding target gene sequence is decreased, the tendency to mediate post-transcriptional gene silencing by translational repression rather than RNAi is increased. Therefore, in an alternative embodiment, where post-transcriptional gene silencing by translational repression of the target gene is desired, the miRNA sequence has partial complementarity with the target gene sequence. In certain embodiments, the miRNA sequence has partial complementarity with one or more short sequences (complementarity sites) dispersed within the target mRNA (e.g. within the 3'-UTR of the target mRNA) (Hutvagner and Zamore, Science, 2002; Zeng et al., Mol. Cell, 2002; Zeng et al., RNA, 2003; Doench et

al., Genes & Dev., 2003). Since the mechanism of translational repression is cooperative, multiple complementarity sites (e.g., 2, 3, 4, 5, or 6) may be targeted in certain embodiments.

[0584] The capacity of a siRNA-like duplex to mediate RNAi or translational repression may be predicted by the distribution of non-identical nucleotides between the target gene sequence and the nucleotide sequence of the silencing agent at the site of complementarity. In one embodiment, where gene silencing by translational repression is desired, at least one non-identical nucleotide is present in the central portion of the complementarity site so that duplex formed by the miRNA guide strand and the target mRNA contains a central "bulge" (Doench J G et al., Genes & Dev., 2003). In another embodiment 2, 3, 4, 5, or 6 contiguous or non-contiguous non-identical nucleotides are introduced. The non-identical nucleotide may be selected such that it forms a wobble base pair (e.g., G:U) or a mismatched base pair (G:A, C:A, C:U, G:G, A:A, C:C, U:U). In a further embodiment, the "bulge" is centered at nucleotide positions 12 and 13 from the 5' end of the miRNA molecule.

c) Short Hairpin RNA (shRNA) Molecules

[0585] In certain featured embodiments, the instant disclosure provides shRNAs capable of mediating RNA silencing of an *MAPT* target sequence with enhanced selectivity. In contrast to siRNAs, shRNAs mimic the natural precursors of micro RNAs (miRNAs) and enter at the top of the gene silencing pathway. For this reason, shRNAs are believed to mediate gene silencing more efficiently by being fed through the entire natural gene silencing pathway.

[0586] miRNAs are noncoding RNAs of approximately 22 nucleotides, which can regulate gene expression at the post transcriptional or translational level during plant and animal development. One common feature of miRNAs is that they are all excised from an approximately 70 nucleotide precursor RNA stem-loop termed pre-miRNA, probably by Dicer, an RNase III-type enzyme, or a homolog thereof. Naturally-occurring miRNA precursors (pre-miRNA) have a single strand that forms a duplex stem including two portions that are generally complementary, and a loop, that connects the two portions of the stem. In typical pre-miRNAs, the stem includes one or more bulges, e.g., extra nucleotides that create a single nucleotide "loop" in one portion of the stem, and/or one or more unpaired nucleotides that create a gap in the hybridization of the two portions of the stem to each other. Short hairpin RNAs, or engineered RNA precursors, of the present application are artificial constructs based on these naturally occurring pre-miRNAs, but which are engineered to deliver desired RNA silencing

agents (e.g., siRNAs of the disclosure). By substituting the stem sequences of the pre-miRNA with sequence complementary to the target mRNA, a shRNA is formed. The shRNA is processed by the entire gene silencing pathway of the cell, thereby efficiently mediating RNAi.

[0587] The requisite elements of a shRNA molecule include a first portion and a second portion, having sufficient complementarity to anneal or hybridize to form a duplex or double-stranded stem portion. The two portions need not be fully or perfectly complementary. The first and second "stem" portions are connected by a portion having a sequence that has insufficient sequence complementarity to anneal or hybridize to other portions of the shRNA. This latter portion is referred to as a "loop" portion in the shRNA molecule. The shRNA molecules are processed to generate siRNAs. shRNAs can also include one or more bulges, i.e., extra nucleotides that create a small nucleotide "loop" in a portion of the stem, for example a one-, two- or three-nucleotide loop. The stem portions can be the same length, or one portion can include an overhang of, for example, 1-5 nucleotides. The overhanging nucleotides can include, for example, uracils (Us), e.g., all Us. Such Us are notably encoded by thymidines (Ts) in the shRNA-encoding DNA which signal the termination of transcription.

[0588] In shRNAs (or engineered precursor RNAs) of the instant disclosure, one portion of the duplex stem is a nucleic acid sequence that is complementary (or anti-sense) to the *MAPT* target sequence. In certain embodiments, one strand of the stem portion of the shRNA is sufficiently complementary (e.g., antisense) to a target RNA (e.g., mRNA) sequence to mediate degradation or cleavage of said target RNA via RNA interference (RNAi). Thus, engineered RNA precursors include a duplex stem with two portions and a loop connecting the two stem portions. The antisense portion can be on the 5' or 3' end of the stem. The stem portions of a shRNA are about 15 to about 50 nucleotides in length. In certain embodiments, the two stem portions are about 18 or 19 to about 21, 22, 23, 24, 25, 30, 35, 37, 38, 39, or 40 or more nucleotides in length. In certain embodiments, the length of the stem portions should be 21 nucleotides or greater. When used in mammalian cells, the length of the stem portions should be less than about 30 nucleotides to avoid provoking non-specific responses like the interferon pathway. In non-mammalian cells, the stem can be longer than 30 nucleotides. In fact, the stem can include much larger sections complementary to the target mRNA (up to, and including the entire mRNA). In fact, a stem portion can include much larger sections complementary to the target mRNA (up to, and including the entire mRNA).

[0589] The two portions of the duplex stem must be sufficiently complementary to hybridize to form the duplex stem. Thus, the two portions can be, but need not be, fully or

perfectly complementary. In addition, the two stem portions can be the same length, or one portion can include an overhang of 1, 2, 3, or 4 nucleotides. The overhanging nucleotides can include, for example, uracils (Us), e.g., all Us. The loop in the shRNAs or engineered RNA precursors may differ from natural pre-miRNA sequences by modifying the loop sequence to increase or decrease the number of paired nucleotides, or replacing all or part of the loop sequence with a tetraloop or other loop sequences. Thus, the loop in the shRNAs or engineered RNA precursors can be 2, 3, 4, 5, 6, 7, 8, 9, or more, e.g., 15 or 20, or more nucleotides in length.

[0590] The loop in the shRNAs or engineered RNA precursors may differ from natural pre-miRNA sequences by modifying the loop sequence to increase or decrease the number of paired nucleotides, or replacing all or part of the loop sequence with a tetraloop or other loop sequences. Thus, the loop portion in the shRNA can be about 2 to about 20 nucleotides in length, i.e., about 2, 3, 4, 5, 6, 7, 8, 9, or more, e.g., 15 or 20, or more nucleotides in length. In certain embodiments, a loop consists of or comprises a "tetraloop" sequence. Exemplary tetraloop sequences include, but are not limited to, the sequences GNRA, where N is any nucleotide and R is a purine nucleotide, GGGG, and UUUU.

[0591] In certain embodiments, shRNAs of the present application include the sequences of a desired siRNA molecule described *supra*. In other embodiments, the sequence of the antisense portion of a shRNA can be designed essentially as described above or generally by selecting an 18, 19, 20, 21 nucleotide, or longer, sequence from within the target RNA (e.g., *MAPT* mRNA), for example, from a region 100 to 200 or 300 nucleotides upstream or downstream of the start of translation. In general, the sequence can be selected from any portion of the target RNA (e.g., mRNA) including the 5' UTR (untranslated region), coding sequence, or 3' UTR. This sequence can optionally follow immediately after a region of the target gene containing two adjacent AA nucleotides. The last two nucleotides of the nucleotide sequence can be selected to be UU. This 21 or so nucleotide sequence is used to create one portion of a duplex stem in the shRNA. This sequence can replace a stem portion of a wild-type pre-miRNA sequence, e.g., enzymatically, or is included in a complete sequence that is synthesized. For example, one can synthesize DNA oligonucleotides that encode the entire stem-loop engineered RNA precursor, or that encode just the portion to be inserted into the duplex stem of the precursor, and using restriction enzymes to build the engineered RNA precursor construct, e.g., from a wild-type pre-miRNA.

[0592] Engineered RNA precursors include, in the duplex stem, the 21-22 or so nucleotide sequences of the siRNA or siRNA-like duplex desired to be produced *in vivo*. Thus, the stem portion of the engineered RNA precursor includes at least 18 or 19 nucleotide pairs corresponding to the sequence of an exonic portion of the gene whose expression is to be reduced or inhibited. The two 3' nucleotides flanking this region of the stem are chosen so as to maximize the production of the siRNA from the engineered RNA precursor and to maximize the efficacy of the resulting siRNA in targeting the corresponding mRNA for translational repression or destruction by RNAi *in vivo* and *in vitro*.

[0593] In certain embodiments, shRNAs of the disclosure include miRNA sequences, optionally end-modified miRNA sequences, to enhance entry into RISC. The miRNA sequence can be similar or identical to that of any naturally occurring miRNA (see e.g. The miRNA Registry; Griffiths-Jones S, Nuc. Acids Res., 2004). Over one thousand natural miRNAs have been identified to date and together they are thought to comprise about 1% of all predicted genes in the genome. Many natural miRNAs are clustered together in the introns of pre-mRNAs and can be identified *in silico* using homology-based searches (Pasquinelli et al., 2000; Lagos-Quintana et al., 2001; Lau et al., 2001; Lee and Ambros, 2001) or computer algorithms (e.g. MiRScan, MiRSeeker) that predict the capability of a candidate miRNA gene to form the stem loop structure of a pri-mRNA (Grad et al., Mol. Cell., 2003; Lim et al., Genes Dev., 2003; Lim et al., Science, 2003; Lai E C et al., Genome Bio., 2003). An online registry provides a searchable database of all published miRNA sequences (The miRNA Registry at the Sanger Institute website; Griffiths-Jones S, Nuc. Acids Res., 2004). Exemplary, natural miRNAs include lin-4, let-7, miR-10, mirR-15, miR-16, miR-168, miR-175, miR-196 and their homologs, as well as other natural miRNAs from humans and certain model organisms including *Drosophila melanogaster*, *Caenorhabditis elegans*, zebrafish, *Arabidopsis thalania*, Mus musculus, and *Rattus norvegicus* as described in International PCT Publication No. WO 03/029459.

[0594] Naturally-occurring miRNAs are expressed by endogenous genes *in vivo* and are processed from a hairpin or stem-loop precursor (pre-miRNA or pri-miRNAs) by Dicer or other RNAses (Lagos-Quintana et al., Science, 2001; Lau et al., Science, 2001; Lee and Ambros, Science, 2001; Lagos-Quintana et al., Curr. Biol., 2002; Mourelatos et al., Genes Dev., 2002; Reinhart et al., Science, 2002; Ambros et al., Curr. Biol., 2003; Brennecke et al., 2003; Lagos-Quintana et al., RNA, 2003; Lim et al., Genes Dev., 2003; Lim et al., Science, 2003). miRNAs can exist transiently *in vivo* as a double-stranded duplex, but only one strand

is taken up by the RISC complex to direct gene silencing. Certain miRNAs, e.g., plant miRNAs, have perfect or near-perfect complementarity to their target mRNAs and, hence, direct cleavage of the target mRNAs. Other miRNAs have less than perfect complementarity to their target mRNAs and, hence, direct translational repression of the target mRNAs. The degree of complementarity between a miRNA and its target mRNA is believed to determine its mechanism of action. For example, perfect or near-perfect complementarity between a miRNA and its target mRNA is predictive of a cleavage mechanism (Yekta et al., Science, 2004), whereas less than perfect complementarity is predictive of a translational repression mechanism. In certain embodiments, the miRNA sequence is that of a naturally-occurring miRNA sequence, the aberrant expression or activity of which is correlated with a miRNA disorder.

d) Dual Functional Oligonucleotide Tethers

[0595] In other embodiments, the RNA silencing agents of the present disclosure include dual functional oligonucleotide tethers useful for the intercellular recruitment of a miRNA. Animal cells express a range of miRNAs, noncoding RNAs of approximately 22 nucleotides which can regulate gene expression at the post transcriptional or translational level. By binding a miRNA bound to RISC and recruiting it to a target mRNA, a dual functional oligonucleotide tether can repress the expression of genes involved e.g., in the arteriosclerotic process. The use of oligonucleotide tethers offers several advantages over existing techniques to repress the expression of a particular gene. First, the methods described herein allow an endogenous molecule (often present in abundance), a miRNA, to mediate RNA silencing. Accordingly, the methods described herein obviate the need to introduce foreign molecules (e.g., siRNAs) to mediate RNA silencing. Second, the RNA-silencing agents and the linking moiety (e.g., oligonucleotides such as the 2'-O-methyl oligonucleotide), can be made stable and resistant to nuclease activity. As a result, the tethers of the present disclosure can be designed for direct delivery, obviating the need for indirect delivery (e.g. viral) of a precursor molecule or plasmid designed to make the desired agent within the cell. Third, tethers and their respective moieties, can be designed to conform to specific mRNA sites and specific miRNAs. The designs can be cell and gene product specific. Fourth, the methods disclosed herein leave the mRNA intact, allowing one skilled in the art to block protein synthesis in short pulses using the cell's own machinery. As a result, these methods of RNA silencing are highly regulatable.

[0596] The dual functional oligonucleotide tethers ("tethers") of the disclosure are designed such that they recruit miRNAs (e.g., endogenous cellular miRNAs) to a target mRNA so as to induce the modulation of a gene of interest. In certain embodiments, the tethers have the formula T-L-μ, wherein T is an mRNA targeting moiety, L is a linking moiety, and μ is a miRNA recruiting moiety. Any one or more moiety may be double stranded. In certain embodiments, each moiety is single stranded.

[0597] Moieties within the tethers can be arranged or linked (in the 5' to 3' direction) as depicted in the formula T-L-μ (i.e., the 3' end of the targeting moiety linked to the 5' end of the linking moiety and the 3' end of the linking moiety linked to the 5' end of the miRNA recruiting moiety). Alternatively, the moieties can be arranged or linked in the tether as follows: μ-T-L (i.e., the 3' end of the miRNA recruiting moiety linked to the 5' end of the linking moiety and the 3' end of the linking moiety linked to the 5' end of the targeting moiety).

[0598] The mRNA targeting moiety, as described above, is capable of capturing a specific target mRNA. According to the disclosure, expression of the target mRNA is undesirable, and, thus, translational repression of the mRNA is desired. The mRNA targeting moiety should be of sufficient size to effectively bind the target mRNA. The length of the targeting moiety will vary greatly, depending, in part, on the length of the target mRNA and the degree of complementarity between the target mRNA and the targeting moiety. In various embodiments, the targeting moiety is less than about 200, 100, 50, 30, 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, or 5 nucleotides in length. In a certain embodiment, the targeting moiety is about 15 to about 25 nucleotides in length.

[0599] The miRNA recruiting moiety, as described above, is capable of associating with a miRNA. According to the present application, the miRNA may be any miRNA capable of repressing the target mRNA. Mammals are reported to have over 250 endogenous miRNAs (Lagos-Quintana et al. (2002) Current Biol. 12:735-739; Lagos-Quintana et al. (2001) Science 294:858-862; and Lim et al. (2003) Science 299:1540). In various embodiments, the miRNA may be any art-recognized miRNA.

[0600] The linking moiety is any agent capable of linking the targeting moieties such that the activity of the targeting moieties is maintained. Linking moieties can be oligonucleotide moieties comprising a sufficient number of nucleotides, such that the targeting agents can sufficiently interact with their respective targets. Linking moieties have little or no sequence homology with cellular mRNA or miRNA sequences. Exemplary linking moieties

include one or more 2'-O-methylnucleotides, e.g., 2'-β-methyladenosine, 2'-O-methylthymidine, 2'-O-methylguanosine or 2'-O-methyluridine.

e) Gene Silencing Oligonucleotides

[0601] In certain exemplary embodiments, gene expression (i.e., *MAPT* gene expression) can be modulated using oligonucleotide-based compounds comprising two or more single stranded antisense oligonucleotides that are linked through their 5'-ends that allow the presence of two or more accessible 3'-ends to effectively inhibit or decrease *MAPT* gene expression. Such linked oligonucleotides are also known as Gene Silencing Oligonucleotides (GSOs). (See, e.g., US 8,431,544 assigned to Idera Pharmaceuticals, Inc., incorporated herein by reference in its entirety for all purposes.)

[0602] The linkage at the 5' ends of the GSOs is independent of the other oligonucleotide linkages and may be directly via 5', 3' or 2'hydroxyl groups, or indirectly, via a non-nucleotide linker or a nucleoside, utilizing either the 2' or 3' hydroxyl positions of the nucleoside. Linkages may also utilize a functionalized sugar or nucleobase of a 5' terminal nucleotide.

[0603] GSOs can comprise two identical or different sequences conjugated at their 5'-5' ends via a phosphodiester, phosphorothioate or non-nucleoside linker. Such compounds may comprise 15 to 27 nucleotides that are complementary to specific portions of mRNA targets of interest for antisense down regulation of a gene product. GSOs that comprise identical sequences can bind to a specific mRNA via Watson-Crick hydrogen bonding interactions and inhibit protein expression. GSOs that comprise different sequences are able to bind to two or more different regions of one or more mRNA target and inhibit protein expression. Such compounds are comprised of heteronucleotide sequences complementary to target mRNA and form stable duplex structures through Watson-Crick hydrogen bonding. Under certain conditions, GSOs containing two free 3'-ends (5'-5'-attached antisense) can be more potent inhibitors of gene expression than those containing a single free 3'-end or no free 3'-end.

[0604] In some embodiments, the non-nucleotide linker is glycerol or a glycerol homolog of the formula $HO--(CH_2)_o--CH(OH)--(CH_2)_p--OH$, wherein o and p independently are integers from 1 to about 6, from 1 to about 4 or from 1 to about 3. In some other embodiments, the non-nucleotide linker is a derivative of 1,3-diamino-2-hydroxypropane.

Some such derivatives have the formula HO--(CH_2)m--C(O)NH--CH_2--CH(OH)--CH_2--NHC(O)--(CH_2)$_m$--OH, wherein m is an integer from 0 to about 10, from 0 to about 6, from 2 to about 6 or from 2 to about 4.

[0605] Some non-nucleotide linkers permit attachment of more than two GSO components. For example, the non-nucleotide linker glycerol has three hydroxyl groups to which GSO components may be covalently attached. Some oligonucleotide-based compounds of the disclosure, therefore, comprise two or more oligonucleotides linked to a nucleotide or a non-nucleotide linker. Such oligonucleotides according to the disclosure are referred to as being "branched."

[0606] In certain embodiments, GSOs are at least 14 nucleotides in length. In certain exemplary embodiments, GSOs are 15 to 40 nucleotides long or 20 to 30 nucleotides in length. Thus, the component oligonucleotides of GSOs can independently be 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 nucleotides in length.

[0607] These oligonucleotides can be prepared by the art recognized methods, such as phosphoramidate or H-phosphonate chemistry, which can be carried out manually or by an automated synthesizer. These oligonucleotides may also be modified in a number of ways without compromising their ability to hybridize to mRNA. Such modifications may include at least one internucleotide linkage of the oligonucleotide being an alkylphosphonate, phosphorothioate, phosphorodithioate, methylphosphonate, phosphate ester, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate hydroxyl, acetamidate, carboxymethyl ester, or a combination of these and other internucleotide linkages between the 5' end of one nucleotide and the 3' end of another nucleotide, in which the 5' nucleotide phosphodiester linkage has been replaced with any number of chemical groups.

V. Modified Anti-MAPT RNA Silencing Agents

[0608] In certain aspects of the disclosure, an RNA silencing agent (or any portion thereof) of the present application, as described supra, may be modified, such that the activity of the agent is further improved. For example, the RNA silencing agents described in Section II supra, may be modified with any of the modifications described infra. The modifications can, in part, serve to further enhance target discrimination, to enhance stability of the agent (e.g., to prevent degradation), to promote cellular uptake, to enhance the target efficiency, to

improve efficacy in binding (e.g., to the targets), to improve patient tolerance to the agent, and/or to reduce toxicity.

1) Modifications to Enhance Target Discrimination

[0609] In certain embodiments, the RNA silencing agents of the present application may be substituted with a destabilizing nucleotide to enhance single nucleotide target discrimination (see U.S. application Ser. No. 11/698,689, filed Jan. 25, 2007 and U.S. Provisional Application No. 60/762,225 filed Jan. 25, 2006, both of which are incorporated herein by reference). Such a modification may be sufficient to abolish the specificity of the RNA silencing agent for a non-target mRNA (e.g. wild-type mRNA), without appreciably affecting the specificity of the RNA silencing agent for a target mRNA (e.g. gain-of-function mutant mRNA).

[0610] In certain embodiments, the RNA silencing agents of the present application are modified by the introduction of at least one universal nucleotide in the antisense strand thereof. Universal nucleotides comprise base portions that are capable of base pairing indiscriminately with any of the four conventional nucleotide bases (e.g. A, G, C, U). A universal nucleotide is contemplated because it has relatively minor effect on the stability of the RNA duplex or the duplex formed by the guide strand of the RNA silencing agent and the target mRNA. Exemplary universal nucleotides include those having an inosine base portion or an inosine analog base portion selected from the group consisting of deoxyinosine (e.g. 2'-deoxyinosine), 7-deaza-2'-deoxyinosine, 2'-aza-2'-deoxyinosine, PNA-inosine, morpholino-inosine, LNA-inosine, phosphoramidate-inosine, 2'-O-methoxyethyl-inosine, and 2'-OMe-inosine. In certain embodiments, the universal nucleotide is an inosine residue or a naturally occurring analog thereof.

[0611] In certain embodiments, the RNA silencing agents of the disclosure are modified by the introduction of at least one destabilizing nucleotide within 5 nucleotides from a specificity-determining nucleotide (i.e., the nucleotide which recognizes the disease-related polymorphism). For example, the destabilizing nucleotide may be introduced at a position that is within 5, 4, 3, 2, or 1 nucleotide(s) from a specificity-determining nucleotide. In exemplary embodiments, the destabilizing nucleotide is introduced at a position which is 3 nucleotides from the specificity-determining nucleotide (i.e., such that there are 2 stabilizing nucleotides between the destablilizing nucleotide and the specificity-determining nucleotide). In RNA

silencing agents having two strands or strand portions (e.g. siRNAs and shRNAs), the destabilizing nucleotide may be introduced in the strand or strand portion that does not contain the specificity-determining nucleotide. In certain embodiments, the destabilizing nucleotide is introduced in the same strand or strand portion that contains the specificity-determining nucleotide.

2) Modifications to Enhance Efficacy and Specificity

[0612] In certain embodiments, the RNA silencing agents of the disclosure may be altered to facilitate enhanced efficacy and specificity in mediating RNAi according to asymmetry design rules (see U.S. Patent Nos. 8,309,704, 7,750,144, 8,304,530, 8,329,892 and 8,309,705). Such alterations facilitate entry of the antisense strand of the siRNA (e.g., a siRNA designed using the methods of the present application or an siRNA produced from a shRNA) into RISC in favor of the sense strand, such that the antisense strand preferentially guides cleavage or translational repression of a target mRNA, and thus increasing or improving the efficiency of target cleavage and silencing. In certain embodiments, the asymmetry of an RNA silencing agent is enhanced by lessening the base pair strength between the antisense strand 5' end (AS 5') and the sense strand 3' end (S 3') of the RNA silencing agent relative to the bond strength or base pair strength between the antisense strand 3' end (AS 3') and the sense strand 5' end (S '5) of said RNA silencing agent.

[0613] In one embodiment, the asymmetry of an RNA silencing agent of the present application may be enhanced such that there are fewer G:C base pairs between the 5' end of the first or antisense strand and the 3' end of the sense strand portion than between the 3' end of the first or antisense strand and the 5' end of the sense strand portion. In another embodiment, the asymmetry of an RNA silencing agent of the disclosure may be enhanced such that there is at least one mismatched base pair between the 5' end of the first or antisense strand and the 3' end of the sense strand portion. In certain embodiments, the mismatched base pair is selected from the group consisting of G:A, C:A, C:U, G:G, A:A, C:C and U:U. In another embodiment, the asymmetry of an RNA silencing agent of the disclosure may be enhanced such that there is at least one wobble base pair, e.g., G:U, between the 5' end of the first or antisense strand and the 3' end of the sense strand portion. In another embodiment, the asymmetry of an RNA silencing agent of the disclosure may be enhanced such that there is at least one base pair comprising a rare nucleotide, e.g., inosine (I). In certain embodiments, the base pair is selected from the

group consisting of an I:A, I:U and I:C. In yet another embodiment, the asymmetry of an RNA silencing agent of the disclosure may be enhanced such that there is at least one base pair comprising a modified nucleotide. In certain embodiments, the modified nucleotide is selected from the group consisting of 2-amino-G, 2-amino-A, 2,6-diamino-G, and 2,6-diamino-A.

3) RNA Silencing Agents with Enhanced Stability

[0614] The RNA silencing agents of the present application can be modified to improve stability in serum or in growth medium for cell cultures. In order to enhance the stability, the 3'-residues may be stabilized against degradation, e.g., they may be selected such that they consist of purine nucleotides, such as adenosine or guanosine nucleotides. Alternatively, substitution of pyrimidine nucleotides by modified analogues, e.g., substitution of uridine by 2'-deoxythymidine is tolerated and does not affect the efficiency of RNA interference.

[0615] In a one aspect, the present application features RNA silencing agents that include first and second strands wherein the second strand and/or first strand is modified by the substitution of internal nucleotides with modified nucleotides, such that in vivo stability is enhanced as compared to a corresponding unmodified RNA silencing agent. As defined herein, an "internal" nucleotide is one occurring at any position other than the 5' end or 3' end of nucleic acid molecule, polynucleotide or oligonucleotide. An internal nucleotide can be within a single-stranded molecule or within a strand of a duplex or double-stranded molecule. In one embodiment, the sense strand and/or antisense strand is modified by the substitution of at least one internal nucleotide. In another embodiment, the sense strand and/or antisense strand is modified by the substitution of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more internal nucleotides. In another embodiment, the sense strand and/or antisense strand is modified by the substitution of at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of the internal nucleotides. In yet another embodiment, the sense strand and/or antisense strand is modified by the substitution of all of the internal nucleotides.

[0616] In one aspect, the present application features RNA silencing agents that are at least 80% chemically modified. In certain embodiments, the RNA silencing agents may be fully chemically modified, i.e., 100% of the nucleotides are chemically modified. In another aspect, the present application features RNA silencing agents comprising 2'-OH ribose groups

that are at least 80% chemically modified. In certain embodiments, the RNA silencing agents comprise 2'-OH ribose groups that are about 80%, 85%, 90%, 95%, or 100% chemically modified.

[0617] In certain embodiments, the RNA silencing agents may contain at least one modified nucleotide analogue. The nucleotide analogues may be located at positions where the target-specific silencing activity, e.g., the RNAi mediating activity or translational repression activity is not substantially affected, e.g., in a region at the 5'-end and/or the 3'-end of the siRNA molecule. Moreover, the ends may be stabilized by incorporating modified nucleotide analogues.

[0618] Exemplary nucleotide analogues include sugar- and/or backbone-modified ribonucleotides (i.e., include modifications to the phosphate-sugar backbone). For example, the phosphodiester linkages of natural RNA may be modified to include at least one of a nitrogen or sulfur heteroatom. In exemplary backbone-modified ribonucleotides, the phosphoester group connecting to adjacent ribonucleotides is replaced by a modified group, e.g., of phosphothioate group. In exemplary sugar-modified ribonucleotides, the 2' OH-group is replaced by a group selected from H, OR, R, halo, SH, SR, NH_2, NHR, NR_2 or ON, wherein R is C_1-C_6 alkyl, alkenyl or alkynyl and halo is F, Cl, Br or I.

[0619] In certain embodiments, the modifications are 2'-fluoro, 2'-amino and/or 2'-thio modifications. Modifications include 2'-fluoro-cytidine, 2'-fluoro-uridine, 2'-fluoro-adenosine, 2'-fluoro-guanosine, 2'-amino-cytidine, 2'-amino-uridine, 2'-amino-adenosine, 2'-amino-guanosine, 2,6-diaminopurine, 4-thio-uridine, and/or 5-amino-allyl-uridine. In a certain embodiment, the 2'-fluoro ribonucleotides are every uridine and cytidine. Additional exemplary modifications include 5-bromo-uridine, 5-iodo-uridine, 5-methyl-cytidine, ribo-thymidine, 2-aminopurine, 2'-amino-butyryl-pyrene-uridine, 5-fluoro-cytidine, and 5-fluoro-uridine. 2'-deoxy-nucleotides and 2'-Ome nucleotides can also be used within modified RNA-silencing agents moities of the instant disclosure. Additional modified residues include, deoxy-abasic, inosine, N3-methyl-uridine, N6,N6-dimethyl-adenosine, pseudouridine, purine ribonucleoside and ribavirin. In a certain embodiment, the 2' moiety is a methyl group such that the linking moiety is a 2'-O-methyl oligonucleotide.

[0620] In a certain embodiment, the RNA silencing agent of the present application comprises Locked Nucleic Acids (LNAs). LNAs comprise sugar-modified nucleotides that resist nuclease activities (are highly stable) and possess single nucleotide discrimination for

mRNA (Elmen et al., Nucleic Acids Res., (2005), 33(1): 439-447; Braasch et al. (2003) Biochemistry 42:7967-7975, Petersen et al. (2003) Trends Biotechnol 21:74-81). These molecules have 2'-O,4'-C-ethylene-bridged nucleic acids, with possible modifications such as 2'-deoxy-2''-fluorouridine. Moreover, LNAs increase the specificity of oligonucleotides by constraining the sugar moiety into the 3'-endo conformation, thereby pre-organizing the nucleotide for base pairing and increasing the melting temperature of the oligonucleotide by as much as 10 °C per base.

[0621] In another exemplary embodiment, the RNA silencing agent of the present application comprises Peptide Nucleic Acids (PNAs). PNAs comprise modified nucleotides in which the sugar-phosphate portion of the nucleotide is replaced with a neutral 2-amino ethylglycine moiety capable of forming a polyamide backbone ,which is highly resistant to nuclease digestion and imparts improved binding specificity to the molecule (Nielsen, et al., Science, (2001), 254: 1497-1500).

[0622] Also contemplated are nucleobase-modified ribonucleotides, i.e., ribonucleotides, containing at least one non-naturally occurring nucleobase instead of a naturally occurring nucleobase. Bases may be modified to block the activity of adenosine deaminase. Exemplary modified nucleobases include, but are not limited to, uridine and/or cytidine modified at the 5-position, e.g., 5-(2-amino)propyl uridine, 5-bromo uridine; adenosine and/or guanosines modified at the 8 position, e.g., 8-bromo guanosine; deaza nucleotides, e.g., 7-deaza-adenosine; O- and N-alkylated nucleotides, e.g., N6-methyl adenosine are suitable. It should be noted that the above modifications may be combined.

[0623] In other embodiments, cross-linking can be employed to alter the pharmacokinetics of the RNA silencing agent, for example, to increase half-life in the body. Thus, the present application includes RNA silencing agents having two complementary strands of nucleic acid, wherein the two strands are crosslinked. The present application also includes RNA silencing agents which are conjugated or unconjugated (e.g., at its 3' terminus) to another moiety (e.g. a non-nucleic acid moiety such as a peptide), an organic compound (e.g., a dye), or the like). Modifying siRNA derivatives in this way may improve cellular uptake or enhance cellular targeting activities of the resulting siRNA derivative as compared to the corresponding siRNA, are useful for tracing the siRNA derivative in the cell, or improve the stability of the siRNA derivative compared to the corresponding siRNA.

[0624] Other exemplary modifications include: (a) 2' modification, e.g., provision of a 2' OMe moiety on a U in a sense or antisense strand, but especially on a sense strand, or provision of a 2' OMe moiety in a 3' overhang, e.g., at the 3' terminus (3' terminus means at the 3' atom of the molecule or at the most 3' moiety, e.g., the most 3' P or 2' position, as indicated by the context); (b) modification of the backbone, e.g., with the replacement of an 0 with an S, in the phosphate backbone, e.g., the provision of a phosphorothioate modification, on the U or the A or both, especially on an antisense strand; e.g., with the replacement of a O with an S; (c) replacement of the U with a C5 amino linker; (d) replacement of an A with a G (sequence changes can be located on the sense strand and not the antisense strand in certain embodiments); and (d) modification at the 2', 6', 7', or 8' position. Exemplary embodiments are those in which one or more of these modifications are present on the sense but not the antisense strand, or embodiments where the antisense strand has fewer of such modifications. Yet other exemplary modifications include the use of a methylated P in a 3' overhang, e.g., at the 3' terminus; combination of a 2' modification, e.g., provision of a 2' O Me moiety and modification of the backbone, e.g., with the replacement of a O with an S, e.g., the provision of a phosphorothioate modification, or the use of a methylated P, in a 3' overhang, e.g., at the 3' terminus; modification with a 3' alkyl; modification with an abasic pyrrolidone in a 3' overhang, e.g., at the 3' terminus; modification with naproxen, ibuprofen, or other moieties which inhibit degradation at the 3' terminus.

Heavily modified RNA silencing agents

[0625] In certain embodiments, the RNA silencing agent comprises at least 80% chemically modified nucleotides. In certain embodiments, the RNA silencing agent is fully chemically modified, i.e., 100% of the nucleotides are chemically modified.

[0626] In certain embodiments, the RNA silencing agent is 2'-O-methyl rich, i.e., comprises greater than 50% 2'-O-methyl content. In certain embodiments, the RNA silencing agent comprises at least about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% 2'-O-methyl nucleotide content. In certain embodiments, the RNA silencing agent comprises at least about 70% 2'-O-methyl nucleotide modifications. In certain embodiments, the RNA silencing agent comprises between about 70% and about 90% 2'-O-methyl nucleotide modifications. In certain embodiments, the RNA silencing agent is a dsRNA comprising an antisense strand and sense strand. In certain embodiments, the antisense strand comprises at

least about 70% 2'-O-methyl nucleotide modifications. In certain embodiments, the antisense strand comprises between about 70% and about 90% 2'-O-methyl nucleotide modifications. In certain embodiments, the sense strand comprises at least about 70% 2'-O-methyl nucleotide modifications. In certain embodiments, the sense strand comprises between about 70% and about 90% 2'-O-methyl nucleotide modifications. In certain embodiments, the sense strand comprises between 100% 2'-O-methyl nucleotide modifications.

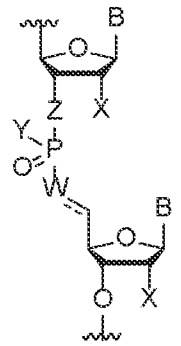
[0627] 2'-O-methyl rich RNA silencing agents and specific chemical modification patterns are further described in U.S.S.N. 16/550,076 (filed August 23, 2019) and U.S.S.N. 62/891,185 (filed August 23, 2019), each of which is incorporated herein by reference.

Internucleotide linkage modifications

[0628] In certain embodiments, at least one internucleotide linkage, intersubunit linkage, or nucleotide backbone is modified in the RNA silencing agent. In certain embodiments, all of the internucleotide linkages in the RNA silencing agent are modified. In certain embodiments, the modified internucleotide linkage comprises a phosphorothioate internucleotide linkage. In certain embodiments, the RNA silencing agent comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 phosphorothioate internucleotide linkages. In certain embodiments, the RNA silencing agent comprises 4-16 phosphorothioate internucleotide linkages. In certain embodiments, the RNA silencing agent comprises 8-13 phosphorothioate internucleotide linkages. In certain embodiments, the RNA silencing agent is a dsRNA comprising an antisense strand and a sense strand, each comprising a 5' end and a 3' end. In certain embodiments, the nucleotides at positions 1 and 2 from the 5' end of sense strand are connected to adjacent ribonucleotides via phosphorothioate internucleotide linkages. In certain embodiments, the nucleotides at positions 1 and 2 from the 3' end of sense strand are connected to adjacent ribonucleotides via phosphorothioate internucleotide linkages. In certain embodiments, the nucleotides at positions 1 and 2 from the 5' end of antisense strand are connected to adjacent ribonucleotides via phosphorothioate internucleotide linkages. In certain embodiments, the nucleotides at positions 1-2 to 1-8 from the 3' end of antisense strand are connected to adjacent ribonucleotides via phosphorothioate internucleotide linkages. In certain embodiments, the nucleotides at positions 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, or 1-8 from the 3' end of antisense strand are connected to adjacent ribonucleotides via phosphorothioate internucleotide linkages. In certain embodiments, the nucleotides at

positions 1-2 to 1-7 from the 3' end of antisense strand are connected to adjacent ribonucleotides via phosphorothioate internucleotide linkages.

[0629] In one aspect, the disclosure provides a modified oligonucleotide, said oligonucleotide having a 5' end, a 3' end, that is complementary to a target, wherein the oligonucleotide comprises a sense and antisense strand, and at least one modified intersubunit linkage of Formula (I):



(I);

wherein:

B is a base pairing moiety;

W is selected from the group consisting of O, OCH_2, OCH, CH_2, and CH;

X is selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

Y is selected from the group consisting of O^-, OH, OR, NH^-, NH_2, S^-, and SH;

Z is selected from the group consisting of O and CH_2;

R is a protecting group; and

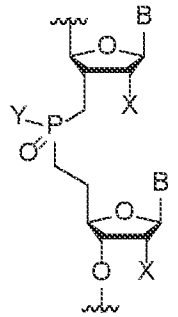
=== is an optional double bond.

[0630]In an embodiment of Formula (I), when W is CH, === is a double bond.

[0631] In an embodiment of Formula (I), when W selected from the group consisting of O, OCH_2, OCH, CH_2, === is a single bond.

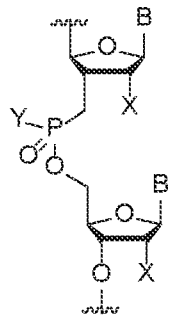
[0632]In an embodiment of Formula (I), when Y is O^-, either Z or W is not O.

[0633] In an embodiment of Formula (I), Z is CH_2 and W is CH_2. In another embodiment, the modified intersubunit linkage of Formula (I) is a modified intersubunit linkage of Formula (II):



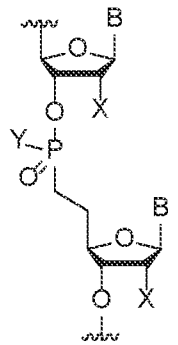
(II).

[0634] In an embodiment of Formula (I), Z is CH_2 and W is O. In another embodiment, wherein the modified intersubunit linkage of Formula (I) is a modified intersubunit linkage of Formula (III):



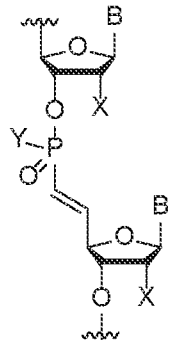
(III).

[0635] In an embodiment of Formula (I), Z is O and W is CH_2. In another embodiment, the modified intersubunit linkage of Formula (I) is a modified intersubunit linkage of Formula (IV):



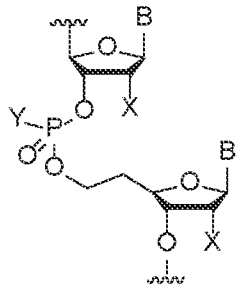
(IV).

[0636] In an embodiment of Formula (I), Z is O and W is CH. In another embodiment, the modified intersubunit linkage of Formula (I) is a modified intersubunit linkage of Formula V:



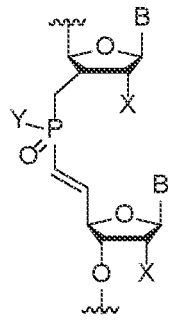
(V).

[0637] In an embodiment of Formula (I), Z is O and W is OCH_2. In another embodiment, the modified intersubunit linkage of Formula (I) is a modified intersubunit linkage of Formula VI:



(VI).

[0638] In an embodiment of Formula (I), Z is CH_2 and W is CH. In another embodiment, the modified intersubunit linkage of Formula (I) is a modified intersubunit linkage of Formula VII:



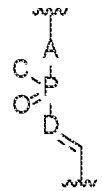
(VII).

[0639] In an embodiment of Formula (I), the base pairing moiety B is selected from the group consisting of adenine, guanine, cytosine, and uracil.

[0640] In an embodiment, the modified oligonucleotide is incorporated into siRNA, said modified siRNA having a 5' end, a 3' end, that is complementary to a target, wherein the

siRNA comprises a sense and antisense strand, and at least one modified intersubunit linkage of any one or more of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (V), Formula (VI), or Formula (VII).

[0641] In an embodiment, the modified oligonucleotide is incorporated into siRNA, said modified siRNA having a 5' end, a 3' end, that is complementary to a target and comprises a sense and antisense strand, wherein the siRNA comprises at least one modified intersubunit linkage is of Formula VIII:



(VIII);

wherein:

D is selected from the group consisting of O, OCH_2, OCH, CH2, and CH;

C is selected from the group consisting of O^-, OH, OR^1, NH^-, NH_2, S^-, and SH;

A is selected from the group consisting of O and CH_2;

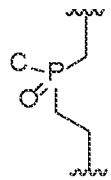
R^1 is a protecting group;

⎓ is an optional double bond; and

the intersubunit is bridging two optionally modified nucleosides.

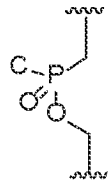
[0642] In an embodiment, when C is O^-, either A or D is not O.

[0643] In an embodiment, D is CH_2. In another embodiment, the modified intersubunit linkage of Formula VIII is a modified intersubunit linkage of Formula (IX):



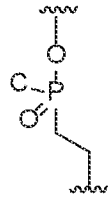
(IX).

[0644] In an embodiment, D is O. In another embodiment, the modified intersubunit linkage of Formula VIII is a modified intersubunit linkage of Formula (X):



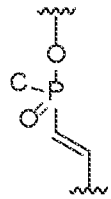
(X).

[0645] In an embodiment, D is CH_2. In another embodiment, the modified intersubunit linkage of Formula (VIII) is a modified intersubunit linkage of Formula (XI):



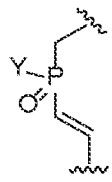
(XI).

[0646] In an embodiment, D is CH. In another embodiment, the modified intersubunit linkage of Formula VIII is a modified intersubunit linkage of Formula (XII):



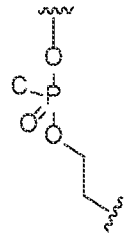
(XII).

[0647] In another embodiment, the modified intersubunit linkage of Formula (VII) is a modified intersubunit linkage of Formula (XIV):



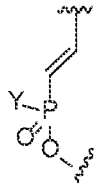
(XIV).

[0648] In an embodiment, D is OCH_2. In another embodiment, the modified intersubunit linkage of Formula (VII) is a modified intersubunit linkage of Formula (XIII):



(XIII).

[0649] In another embodiment, the modified intersubunit linkage of Formula (VII) is a modified intersubunit linkage of Formula (XXa):



(XXa).

[0650] In an embodiment of the modified siRNA linkage, each optionally modified nucleoside is independently, at each occurrence, selected from the group consisting of adenosine, guanosine, cytidine, and uridine.

[0651] In certain exemplary embodiments of Formula (I), W is O. In another embodiment, W is CH_2. In yet another embodiment, W is CH.

[0652] In certain exemplary embodiments of Formula (I), X is OH. In another embodiment, X is OCH_3. In yet another embodiment, X is halo.

[0653] In a certain embodiment of Formula (I), the modified siRNA does not comprise a 2'-fluoro substituent.

[0654] In an embodiment of Formula (I), Y is O^-. In another embodiment, Y is OH. In yet another embodiment, Y is OR. In still another embodiment, Y is NH^-. In an embodiment, Y is NH_2. In another embodiment, Y is S^-. In yet another embodiment, Y is SH.

[0655] In an embodiment of Formula (I), Z is O. In another embodiment, Z is CH_2.

[0656] In an embodiment, the modified intersubunit linkage is inserted on position 1-2 of the antisense strand. In another embodiment, the modified intersubunit linkage is inserted on position 6-7 of the antisense strand. In yet another embodiment, the modified intersubunit linkage is inserted on position 10-11 of the antisense strand. In still another embodiment, the modified intersubunit linkage is inserted on position 19-20 of the antisense strand. In an

embodiment, the modified intersubunit linkage is inserted on positions 5-6 and 18-19 of the antisense strand.

[0657] In an exemplary embodiment of the modified siRNA linkage of Formula (VIII), C is O^-. In another embodiment, C is OH. In yet another embodiment, C is OR^1. In still another embodiment, C is NH^-. In an embodiment, C is NH_2. In another embodiment, C is S^-. In yet another embodiment, C is SH.

[0658] In an exemplary embodiment of the modified siRNA linkage of Formula (VIII), A is O. In another embodiment, A is CH_2. In yet another embodiment, C is OR^1. In still another embodiment, C is NH^-. In an embodiment, C is NH_2. In another embodiment, C is S^-. In yet another embodiment, C is SH.

[0659] In a certain embodiment of the modified siRNA linkage of Formula (VIII), the optionally modified nucleoside is adenosine. In another embodiment of the modified siRNA linkage of Formula (VIII), the optionally modified nucleoside is guanosine. In another embodiment of the modified siRNA linkage of Formula (VIII), the optionally modified nucleoside is cytidine. In another embodiment of the modified siRNA linkage of Formula (VIII), the optionally modified nucleoside is uridine.

[0660] In an embodiment of the modified siRNA linkage, wherein the linkage is inserted on position 1-2 of the antisense strand. In another embodiment, the linkage is inserted on position 6-7 of the antisense strand. In yet another embodiment, the linkage is inserted on position 10-11 of the antisense strand. In still another embodiment, the linkage is inserted on position 19-20 of the antisense strand. In an embodiment, the linkage is inserted on positions 5-6 and 18-19 of the antisense strand.

[0661] In certain embodiments of Formula (I), the base pairing moiety B is adenine. In certain embodiments of Formula (I), the base pairing moiety B is guanine. In certain embodiments of Formula (I), the base pairing moiety B is cytosine. In certain embodiments of Formula (I), the base pairing moiety B is uracil.

[0662] In an embodiment of Formula (I), W is O. In an embodiment of Formula (I), W is CH_2. In an embodiment of Formula (I), W is CH.

[0663] In an embodiment of Formula (I), X is OH. In an embodiment of Formula (I), X is OCH_3. In an embodiment of Formula (I), X is halo.

[0664] In an exemplary embodiment of Formula (I), the modified oligonucleotide does not comprise a 2'-fluoro substituent.

[0665] In an embodiment of Formula (I), Y is O^-. In an embodiment of Formula (I), Y is OH. In an embodiment of Formula (I), Y is OR. In an embodiment of Formula (I), Y is NH^-. In an embodiment of Formula (I), Y is NH_2. In an embodiment of Formula (I), Y is S^-. In an embodiment of Formula (I), Y is SH.

[0666] In an embodiment of Formula (I), Z is O. In an embodiment of Formula (I), Z is CH_2.

[0667] In an embodiment of the Formula (I), the linkage is inserted on position 1-2 of the antisense strand. In another embodiment of Formula (I), the linkage is inserted on position 6-7 of the antisense strand. In yet another embodiment of Formula (I), the linkage is inserted on position 10-11 of the antisense strand. In still another embodiment of Formula (I), the linkage is inserted on position 19-20 of the antisense strand. In an embodiment of Formula (I), the linkage is inserted on positions 5-6 and 18-19 of the antisense strand.

[0668] Modified intersubunit linkages are further described in U.S.S.N. 62/824,136 (filed March 26, 2019), U.S.S.N. 62/826,454 (filed March 29, 2019), and U.S.S.N. 62/864,792 (filed June 21, 2019), each of which is incorporated herein by reference.

4) Conjugated Functional Moieties

[0669] In other embodiments, RNA silencing agents may be modified with one or more functional moieties. A functional moiety is a molecule that confers one or more additional activities to the RNA silencing agent. In certain embodiments, the functional moieties enhance cellular uptake by target cells (e.g., neuronal cells). Thus, the disclosure includes RNA silencing agents which are conjugated or unconjugated (e.g., at its 5' and/or 3' terminus) to another moiety (e.g. a non-nucleic acid moiety such as a peptide), an organic compound (e.g., a dye), or the like. The conjugation can be accomplished by methods known in the art, e.g., using the methods of Lambert et al., Drug Deliv. Rev.: 47(1), 99-112 (2001) (describes nucleic acids loaded to polyalkylcyanoacrylate (PACA) nanoparticles); Fattal et al., J. Control Release 53(1-3):137-43 (1998) (describes nucleic acids bound to nanoparticles); Schwab et al., Ann. Oncol. 5 Suppl. 4:55-8 (1994) (describes nucleic acids linked to intercalating agents, hydrophobic groups, polycations or PACA nanoparticles); and Godard et al., Eur. J. Biochem. 232(2):404-10 (1995) (describes nucleic acids linked to nanoparticles).

[0670] In a certain embodiment, the functional moiety is a hydrophobic moiety. In a certain embodiment, the hydrophobic moiety is selected from the group consisting of fatty acids, steroids, secosteroids, lipids, gangliosides and nucleoside analogs, endocannabinoids, and vitamins. In a certain embodiment, the steroid selected from the group consisting of cholesterol and Lithocholic acid (LCA). In a certain embodiment, the fatty acid selected from the group consisting of Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA) and Docosanoic acid (DCA). In a certain embodiment, the vitamin selected from the group consisting of choline, vitamin A, vitamin E, derivatives thereof, and metabolites thereof. In a certain embodiment, the vitamin is selected from the group consisting of retinoic acid and alpha-tocopheryl succinate.

[0671] In a certain embodiment, an RNA silencing agent of disclosure is conjugated to a lipophilic moiety. In one embodiment, the lipophilic moiety is a ligand that includes a cationic group. In another embodiment, the lipophilic moiety is attached to one or both strands of an siRNA. In an exemplary embodiment, the lipophilic moiety is attached to one end of the sense strand of the siRNA. In another exemplary embodiment, the lipophilic moiety is attached to the 3' end of the sense strand. In certain embodiments, the lipophilic moiety is selected from the group consisting of cholesterol, vitamin E, vitamin K, vitamin A, folic acid, a cationic dye (e.g., Cy3). In an exemplary embodiment, the lipophilic moiety is cholesterol. Other lipophilic moieties include 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.

[0672] In certain embodiments, the functional moieties may comprise one or more ligands tethered to an RNA silencing agent to improve stability, hybridization thermodynamics with a target nucleic acid, targeting to a particular tissue or cell-type, or cell permeability, e.g., by an endocytosis-dependent or -independent mechanism. Ligands and associated modifications can also increase sequence specificity and consequently decrease off-site targeting. A tethered ligand can include one or more modified bases or sugars that can function as intercalators. These can be located in an internal region, such as in a bulge of RNA silencing agent/target duplex. The intercalator can be an aromatic, e.g., a polycyclic aromatic or heterocyclic aromatic compound. A polycyclic intercalator can have stacking capabilities, and can include systems with 2, 3, or 4 fused rings. The universal bases described herein can be

included on a ligand. In one embodiment, the ligand can include a cleaving group that contributes to target gene inhibition by cleavage of the target nucleic acid. The cleaving group can be, for example, a bleomycin (e.g., bleomycin-A5, bleomycin-A2, or bleomycin-B2), pyrene, phenanthroline (e.g., O-phenanthroline), a polyamine, a tripeptide (e.g., lys-tyr-lys tripeptide), or a metal ion chelating group. The metal ion chelating group can include, e.g., an Lu(III) or EU(III) macrocyclic complex, a Zn(II) 2,9-dimethylphenanthroline derivative, a Cu(II) terpyridine, or acridine, which can promote the selective cleavage of target RNA at the site of the bulge by free metal ions, such as Lu(III). In some embodiments, a peptide ligand can be tethered to a RNA silencing agent to promote cleavage of the target RNA, e.g., at the bulge region. For example, 1,8-dimethyl-1,3,6,8,10,13-hexaazacyclotetradecane (cyclam) can be conjugated to a peptide (e.g., by an amino acid derivative) to promote target RNA cleavage. A tethered ligand can be an aminoglycoside ligand, which can cause an RNA silencing agent to have improved hybridization properties or improved sequence specificity. Exemplary aminoglycosides include glycosylated polylysine, galactosylated polylysine, neomycin B, tobramycin, kanamycin A, and acridine conjugates of aminoglycosides, such as Neo-N-acridine, Neo-S-acridine, Neo-C-acridine, Tobra-N-acridine, and KanaA-N-acridine. Use of an acridine analog can increase sequence specificity. For example, neomycin B has a high affinity for RNA as compared to DNA, but low sequence-specificity. An acridine analog, neo-5-acridine, has an increased affinity for the HIV Rev-response element (RRE). In some embodiments, the guanidine analog (the guanidinoglycoside) of an aminoglycoside ligand is tethered to an RNA silencing agent. In a guanidinoglycoside, the amine group on the amino acid is exchanged for a guanidine group. Attachment of a guanidine analog can enhance cell permeability of an RNA silencing agent. A tethered ligand can be a poly-arginine peptide, peptoid or peptidomimetic, which can enhance the cellular uptake of an oligonucleotide agent.

[0673] Exemplary ligands are coupled, either directly or indirectly, via an intervening tether, to a ligand-conjugated carrier. In certain embodiments, the coupling is through a covalent bond. In certain embodiments, the ligand is attached to the carrier via an intervening tether. In certain embodiments, a ligand alters the distribution, targeting or lifetime of an RNA silencing agent into which it is incorporated. In certain embodiments, a ligand provides an enhanced 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.

[0674] Exemplary ligands can improve transport, hybridization, and specificity properties and may also improve nuclease resistance of the resultant natural or modified RNA silencing agent, or a polymeric molecule comprising any combination of monomers described herein and/or natural or modified ribonucleotides. Ligands in general can include therapeutic modifiers, e.g., for enhancing uptake; diagnostic compounds or reporter groups e.g., for monitoring distribution; cross-linking agents; nuclease-resistance conferring moieties; and natural or unusual nucleobases. General examples include lipophiles, lipids, steroids (e.g., uvaol, hecigenin, diosgenin), terpenes (e.g., triterpenes, e.g., sarsasapogenin, Friedelin, epifriedelanol derivatized lithocholic acid), vitamins (e.g., folic acid, vitamin A, biotin, pyridoxal), carbohydrates, proteins, protein binding agents, integrin targeting molecules, polycationics, peptides, polyamines, and peptide mimics. Ligands can include a naturally occurring substance, (e.g., human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); amino acid, or a lipid. The ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, e.g., a synthetic polyamino acid. Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. 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.

[0675] Ligands can also include targeting groups, e.g., 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. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine (GalNAc) or derivatives thereof, N-acetyl-glucosamine, multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, biotin, or an RGD peptide or RGD peptide mimetic. Other examples of ligands include dyes, intercalating agents (e.g. acridines and substituted acridines), cross-

linkers (e.g. psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine, phenanthroline, pyrenes), lys-tyr-lys tripeptide, aminoglycosides, guanidium aminoglycodies, artificial endonucleases (e.g. EDTA), lipophilic molecules, e.g, cholesterol (and thio analogs thereof), cholic acid, cholanic acid, lithocholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, glycerol (e.g., esters (e.g., mono, bis, or tris fatty acid esters, e.g., C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} fatty acids) and ethers thereof, e.g., C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, or C_{20} alkyl; e.g., 1,3-bis-O(hexadecyl)glycerol, 1,3-bis-O(octaadecyl)glycerol), geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, stearic acid (e.g., glyceryl distearate), oleic 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, naproxen, vitamin E, folic acid), synthetic ribonucleases (e.g., imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu^{3+} complexes of tetraazamacrocycles), dinitrophenyl, HRP or AP. In certain embodiments, the ligand is GalNAc or a derivative thereof.

[0676] Ligands can be proteins, e.g., glycoproteins, or peptides, e.g., molecules having a specific affinity for a co-ligand, or antibodies e.g., an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, or bone cell. Ligands may also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, or multivalent fucose. The ligand can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an activator of NF-kB.

[0677] The ligand can be a substance, e.g., a drug, which can increase the uptake of the RNA silencing 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. The drug can be, for example, taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin. The ligand can increase the uptake of the RNA silencing agent into the cell by activating an inflammatory response, for example. Exemplary ligands that would have such an effect include tumor necrosis factor alpha

(TNF□), interleukin-1 beta, or gamma interferon. In one aspect, the ligand is a lipid or lipid-based molecule. Such a lipid or lipid-based molecule can bind a serum protein, e.g., human serum albumin (HSA). An HSA binding ligand allows for distribution of the conjugate to a target tissue, e.g., a non-kidney target tissue of the body. For example, the target tissue can be the liver, including parenchymal cells of the liver. Other molecules that can bind HSA can also be used as ligands. For example, neproxin or aspirin can be used. A lipid or lipid-based ligand can (a) increase resistance to degradation of the conjugate, (b) increase targeting or transport into a target cell or cell membrane, and/or (c) can be used to adjust binding to a serum protein, e.g., HSA. A lipid based ligand can be used to modulate, e.g., control the binding of the conjugate to a target tissue. For example, a lipid or lipid-based ligand that binds to HSA more strongly will be less likely to be targeted to the kidney and therefore less likely to be cleared from the body. A lipid or lipid-based ligand that binds to HSA less strongly can be used to target the conjugate to the kidney. In a certain embodiment, the lipid based ligand binds HSA. A lipid-based ligand can bind HSA with a sufficient affinity such that the conjugate will be distributed to a non-kidney tissue. However, it is contemplated that the affinity not be so strong that the HSA-ligand binding cannot be reversed. In another embodiment, the lipid based ligand binds HSA weakly or not at all, such that the conjugate will be distributed to the kidney. Other moieties that target to kidney cells can also be used in place of or in addition to the lipid based ligand.

[0678] In another aspect, the ligand is a moiety, e.g., a vitamin, which is taken up by a target cell, e.g., a proliferating cell. These can be useful for treating disorders characterized by unwanted cell proliferation, e.g., of the malignant or non-malignant type, e.g., cancer cells. Exemplary vitamins include vitamin A, E, and K. Other exemplary vitamins include are B vitamin, e.g., folic acid, B12, riboflavin, biotin, pyridoxal or other vitamins or nutrients taken up by cancer cells. Also included are HSA and low density lipoprotein (LDL).

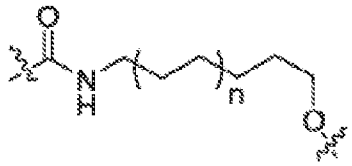
[0679] In another aspect, the ligand is a cell-permeation agent, such as a helical cell-permeation agent. In certain embodiments, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopedia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. The helical agent can be an alpha-helical agent, which may have a lipophilic and a lipophobic phase.

[0680] The ligand can be a peptide or peptidomimetic. A peptidomimetic (also referred to herein as an oligopeptidomimetic) is a molecule capable of folding into a defined

three-dimensional structure similar to a natural peptide. The attachment of peptide and peptidomimetics to oligonucleotide agents can affect pharmacokinetic distribution of the RNA silencing agent, such as by enhancing cellular recognition and absorption. The peptide or peptidomimetic moiety can be about 5-50 amino acids long, e.g., about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long. A peptide or peptidomimetic can be, for example, a cell permeation peptide, cationic peptide, amphipathic peptide, or hydrophobic peptide (e.g., consisting primarily of Tyr, Trp or Phe). The peptide moiety can be a dendrimer peptide, constrained peptide or crosslinked peptide. The peptide moiety can be an L-peptide or D-peptide. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). A peptide or peptidomimetic can be encoded by a random sequence of DNA, such as a peptide identified from a phage-display library, or one-bead-one-compound (OBOC) combinatorial library (Lam et al., Nature 354:82-84, 1991). In exemplary embodiments, the peptide or peptidomimetic tethered to an RNA silencing agent via an incorporated monomer unit is a cell targeting peptide such as an arginine-glycine-aspartic acid (RGD)-peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.

[0681] In certain embodiments, the functional moiety is linked to the 5' end and/or 3' end of the RNA silencing agent of the disclosure. In certain embodiments, the functional moiety is linked to the 5' end and/or 3' end of an antisense strand of the RNA silencing agent of the disclosure. In certain embodiments, the functional moiety is linked to the 5' end and/or 3' end of a sense strand of the RNA silencing agent of the disclosure. In certain embodiments, the functional moiety is linked to the 3' end of a sense strand of the RNA silencing agent of the disclosure.

[0682] In certain embodiments, the functional moiety is linked to the RNA silencing agent by a linker. In certain embodiments, the functional moiety is linked to the antisense strand and/or sense strand by a linker. In certain embodiments, the functional moiety is linked to the 3' end of a sense strand by a linker. In certain embodiments, the linker comprises a divalent or trivalent linker. In certain embodiments, the linker comprises an ethylene glycol chain, an alkyl chain, a peptide, RNA, DNA, a phosphodiester, a phosphorothioate, a phosphoramidate, an amide, a carbamate, or a combination thereof. In certain embodiments, the divalent or trivalent linker is selected from: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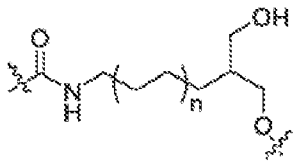
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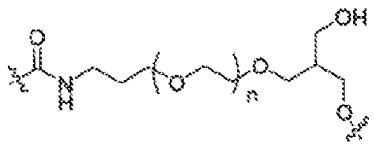
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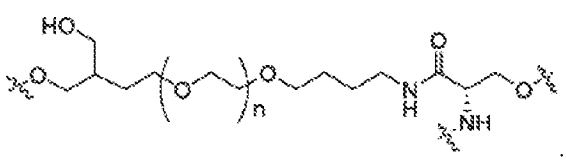
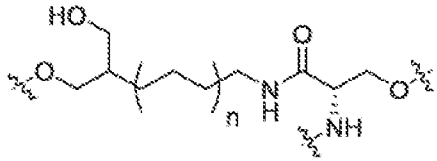
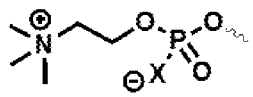


; or wherein n is 1, 2, 3, 4, or 5.

[0683] In certain embodiments, the linker further comprises a phosphodiester or phosphodiester derivative. In certain embodiments, the phosphodiester or phosphodiester derivative is selected from the group consisting of: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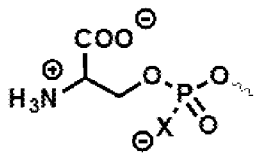
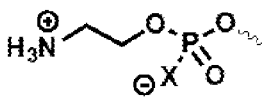
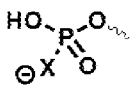
(Zc1);


;

(Zc2);


; and

(Zc3)


;

(Zc4)

wherein X is O, S or BH_3.

[0684] The various functional moieties of the disclosure and means to conjugate them to RNA silencing agents are described in further detail in WO2017/030973A1 and WO2018/031933A2, incorporated herein by reference.

VI. Branched Oligonucleotides

[0685] Two or more RNA silencing agents as disclosed *supra*, for example oligonucleotide constructs such as anti-MAPT siRNAs, may be connected to one another by one or more moieties independently selected from a linker, a spacer and a branching point, to form a branched oligonucleotide RNA silencing agent. In certain embodiments, the branched oligonucleotide RNA silencing agent consists of two siRNAs to form a di-branched siRNA ("di-siRNA") scaffolding for delivering two siRNAs. In representative embodiments, the nucleic acids of the branched oligonucleotide each comprise an antisense strand (or portions thereof), wherein the antisense strand has sufficient complementarity to a target mRNA (e.g., *MAPT* mRNA) to mediate an RNA-mediated silencing mechanism (e.g. RNAi).

[0686] In exemplary embodiments, the branched oligonucleotides may have two to eight RNA silencing agents attached through a linker. The linker may be hydrophobic. In an embodiment, branched oligonucleotides of the present application have two to three oligonucleotides. In an embodiment, the oligonucleotides independently have substantial chemical stabilization (e.g., at least 40% of the constituent bases are chemically-modified). In an exemplary embodiment, the oligonucleotides have full chemical stabilization (i.e., all the constituent bases are chemically-modified). In some embodiments, branched oligonucleotides comprise one or more single-stranded phosphorothioated tails, each independently having two to twenty nucleotides. In a non-limiting embodiment, each single-stranded tail has two to ten nucleotides.

[0687] In certain embodiments, branched oligonucleotides are characterized by three properties: (1) a branched structure, (2) full metabolic stabilization, and (3) the presence of a single-stranded tail comprising phosphorothioate linkers. In certain embodiments, branched oligonucleotides have 2 or 3 branches. It is believed that the increased overall size of the branched structures promotes increased uptake. Also, without being bound by a particular theory of activity, multiple adjacent branches (e.g., 2 or 3) are believed to allow each branch to act cooperatively and thus dramatically enhance rates of internalization, trafficking and release.

[0688] Branched oligonucleotides are provided in various structurally diverse embodiments. In some embodiments nucleic acids attached at the branching points are single stranded or double stranded and consist of miRNA inhibitors, gapmers, mixmers, SSOs, PMOs, or PNAs. These single strands can be attached at their 3' or 5' end. Combinations of siRNA and single stranded oligonucleotides could also be used for dual function. In another embodiment, short nucleic acids complementary to the gapmers, mixmers, miRNA inhibitors,

SSOs, PMOs, and PNAs are used to carry these active single-stranded nucleic acids and enhance distribution and cellular internalization. The short duplex region has a low melting temperature (Tm ~37 °C) for fast dissociation upon internalization of the branched structure into the cell.

[0689] The Di-siRNA branched oligonucleotides may comprise chemically diverse conjugates, such as the functional moieties described above. Conjugated bioactive ligands may be used to enhance cellular specificity and to promote membrane association, internalization, and serum protein binding. Examples of bioactive moieties to be used for conjugation include DHA, GalNAc, and cholesterol. These moieties can be attached to Di-siRNA either through the connecting linker or spacer, or added via an additional linker or spacer attached to another free siRNA end.

[0690] The presence of a branched structure improves the level of tissue retention in the brain more than 100-fold compared to non-branched compounds of identical chemical composition, suggesting a new mechanism of cellular retention and distribution. Branched oligonucleotides have unexpectedly uniform distribution throughout the spinal cord and brain. Moreover, branched oligonucleotides exhibit unexpectedly efficient systemic delivery to a variety of tissues, and very high levels of tissue accumulation.

[0691] Branched oligonucleotides comprise a variety of therapeutic nucleic acids, including siRNAs, ASOs, miRNAs, miRNA inhibitors, splice switching, PMOs, PNAs. In some embodiments, branched oligonucleotides further comprise conjugated hydrophobic moieties and exhibit unprecedented silencing and efficacy *in vitro* and *in vivo*.

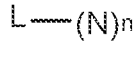
Linkers

[0692] In an embodiment of the branched oligonucleotide, each linker is independently selected from an ethylene glycol chain, an alkyl chain, a peptide, RNA, DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, and combinations thereof; wherein any carbon or oxygen atom of the linker is optionally replaced with a nitrogen atom, bears a hydroxyl substituent, or bears an oxo substituent. In one embodiment, each linker is an ethylene glycol chain. In another embodiment, each linker is an alkyl chain. In another embodiment, each linker is a peptide. In another embodiment, each linker is RNA. In another embodiment, each linker is DNA. In another embodiment, each linker is a phosphate. In another embodiment, each linker is a phosphonate. In another embodiment, each linker is a

phosphoramidate. In another embodiment, each linker is an ester. In another embodiment, each linker is an amide. In another embodiment, each linker is a triazole.

VII. Compound of Formula (I)

[0693] In another aspect, provided herein is a branched oligonucleotide compound of formula (I):



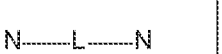
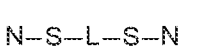
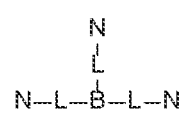
(I)

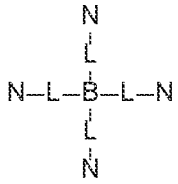
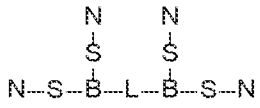
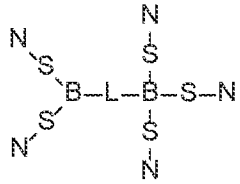
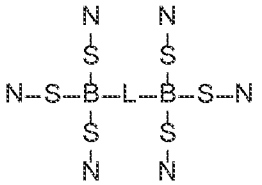
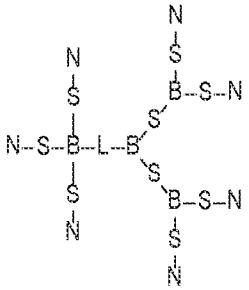
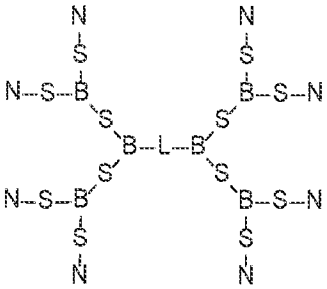
wherein L is selected from an ethylene glycol chain, an alkyl chain, a peptide, RNA, DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, and combinations thereof, wherein formula (I) optionally further comprises one or more branch point B, and one or more spacer S; wherein B is independently for each occurrence a polyvalent organic species or derivative thereof; S is independently for each occurrence selected from an ethylene glycol chain, an alkyl chain, a peptide, RNA, DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, and combinations thereof.

[0694] Moiety N is an RNA duplex comprising a sense strand and an antisense strand; and n is 2, 3, 4, 5, 6, 7 or 8. In an embodiment, the antisense strand of N comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295, as recited in **Tables 4-6**. In further embodiments, N includes strands that are capable of targeting one or more of a *MAPT* nucleic acid sequence selected from the group consisting of SEQ ID NOs: 14-33, 299, and 302, as recited in **Tables 7-8**. The sense strand and antisense strand may each independently comprise one or more chemical modifications.

[0695] In an embodiment, the compound of formula (I) has a structure selected from formulas (I-1)-(I-9) of **Table 1**.

Table 1

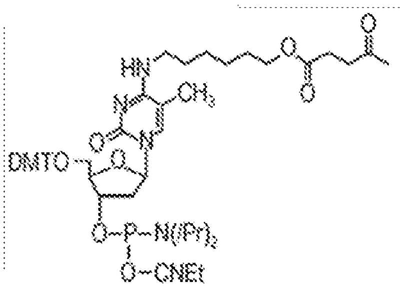
(I-1)	(I-2)	(I-3)
		
(I-4)	(I-5)	(I-6)
		
(I-7)	(I-8)	(I-9)

[0696] In one embodiment, the compound of formula (I) is formula (I-1). In another embodiment, the compound of formula (I) is formula (I-2). In another embodiment, the compound of formula (I) is formula (I-3). In another embodiment, the compound of formula (I) is formula (I-4). In another embodiment, the compound of formula (I) is formula (I-5). In another embodiment, the compound of formula (I) is formula (I-6). In another embodiment, the compound of formula (I) is formula (I-7). In another embodiment, the compound of formula (I) is formula (I-8). In another embodiment, the compound of formula (I) is formula (I-9).

[0697] In an embodiment of the compound of formula (I), each linker is independently selected from an ethylene glycol chain, an alkyl chain, a peptide, RNA, DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, and combinations thereof; wherein any carbon or oxygen atom of the linker is optionally replaced with a nitrogen atom, bears a hydroxyl substituent, or bears an oxo substituent. In one embodiment of the compound of formula (I), each linker is an ethylene glycol chain. In another embodiment, each linker is an alkyl chain. In another embodiment of the compound of formula (I), each linker is a peptide. In another embodiment of the compound of formula (I), each linker is RNA. In another embodiment of the compound of formula (I), each linker is DNA. In another embodiment of the compound of formula (I), each linker is a phosphate. In another embodiment, each linker is a phosphonate. In another embodiment of the compound of formula (I), each linker is a phosphoramidate. In another embodiment of the compound of formula (I),

each linker is an ester. In another embodiment of the compound of formula (I), each linker is an amide. In another embodiment of the compound of formula (I), each linker is a triazole.

[0698] In one embodiment of the compound of formula (I), B is a polyvalent organic species. In another embodiment of the compound of formula (I), B is a derivative of a polyvalent organic species. In one embodiment of the compound of formula (I), B is a triol or tetrol derivative. In another embodiment, B is a tri- or tetra-carboxylic acid derivative. In another embodiment, B is an amine derivative. In another embodiment, B is a tri- or tetra-amine derivative. In another embodiment, B is an amino acid derivative. In another embodiment of the compound of formula (I), B is selected from the formulas of: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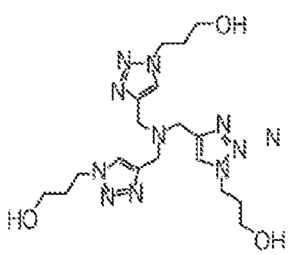
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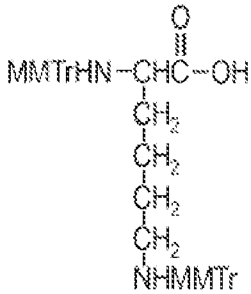
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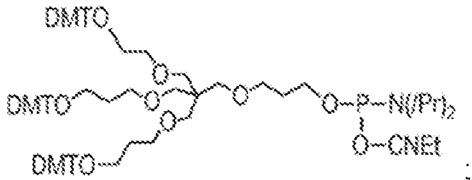
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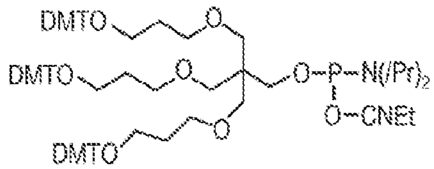
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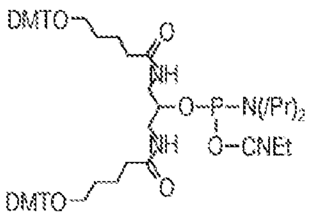
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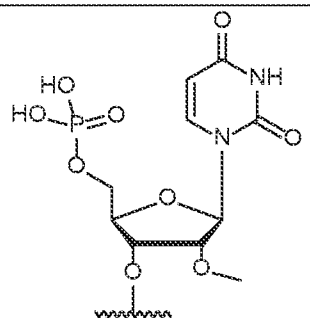
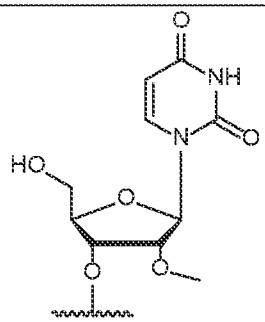
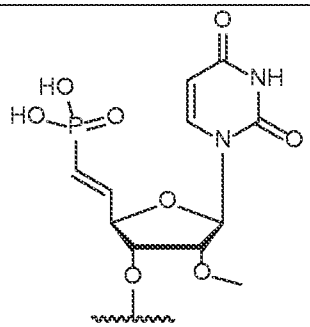
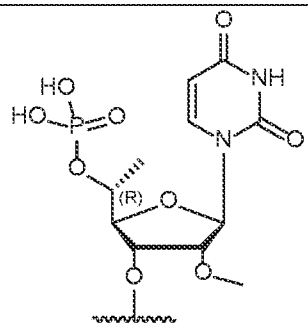
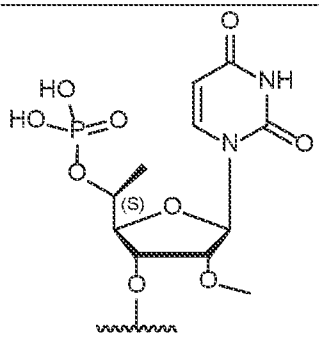
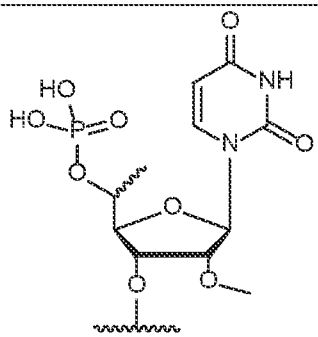
[0699] Polyvalent organic species are moieties comprising carbon and three or more valencies (i.e., points of attachment with moieties such as S, L or N, as defined above). Non-limiting examples of polyvalent organic species include triols (e.g., glycerol, phloroglucinol, and the like), tetrols (e.g., ribose, pentaerythritol, 1,2,3,5-tetrahydroxybenzene, and the like), tri-carboxylic acids (e.g., citric acid, 1,3,5-cyclohexanetricarboxylic acid, trimesic acid, and the like), tetra-carboxylic acids (e.g., ethylenediaminetetraacetic acid, pyromellitic acid, and the like), tertiary amines (e.g., tripropargylamine, triethanolamine, and the like), triamines (e.g., diethylenetriamine and the like), tetramines, and species comprising a combination of

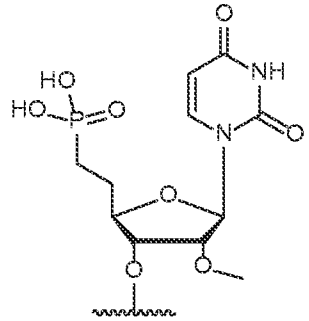
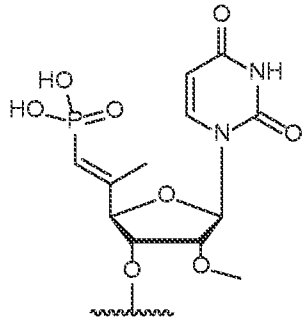
hydroxyl, thiol, amino, and/or carboxyl moieties (e.g., amino acids such as lysine, serine, cysteine, and the like).

[0700] In an embodiment of the compound of formula (I), each nucleic acid comprises one or more chemically-modified nucleotides. In an embodiment of the compound of formula (I), each nucleic acid consists of chemically-modified nucleotides. In certain embodiments of the compound of formula (I), >95%, >90%, >85%, >80%, >75%, >70%, >65%, >60%, >55% or >50% of each nucleic acid comprises chemically-modified nucleotides.

[0701] In an embodiment, each antisense strand independently comprises a 5' terminal group R selected from the groups of **Table 2**.

Table 2

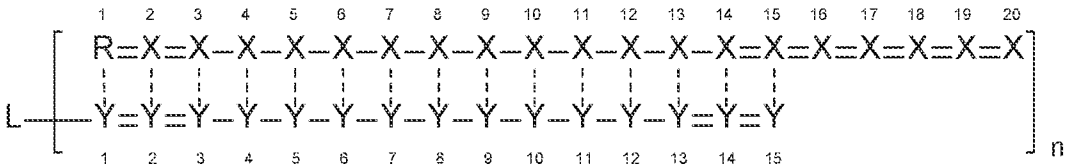
	
R^1	R^2
	
R^3	R^4
	
R^5	R^6

	
R^7	R^8

[0702] In one embodiment, R is R_1. In another embodiment, R is R_2. In another embodiment, R is R_3. In another embodiment, R is R_4. In another embodiment, R is R_5. In another embodiment, R is R_6. In another embodiment, R is R_7. In another embodiment, R is R_8.

Structure of Formula (II)

[0703] In an embodiment, the compound of formula (I) has the structure of formula (II):



(II)

wherein X, for each occurrence, independently, is selected from adenosine, guanosine, uridine, cytidine, and chemically-modified derivatives thereof; Y, for each occurrence, independently, is selected from adenosine, guanosine, uridine, cytidine, and chemically-modified derivatives thereof; - represents a phosphodiester internucleoside linkage; = represents a phosphorothioate internucleoside linkage; and --- represents, individually for each occurrence, a base-pairing interaction or a mismatch.

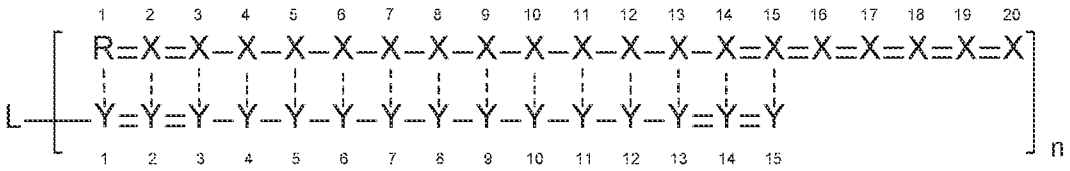
[0704] In certain embodiments, the structure of formula (II) does not contain mismatches. In one embodiment, the structure of formula (II) contains 1 mismatch. In another embodiment, the compound of formula (II) contains 2 mismatches. In another embodiment, the compound of formula (II) contains 3 mismatches. In another embodiment, the compound of

formula (II) contains 4 mismatches. In an embodiment, each nucleic acid consists of chemically-modified nucleotides.

[0705] In certain embodiments, >95%, >90%, >85%, >80%, >75%, >70%, >65%, >60%, >55% or >50% of X's of the structure of formula (II) are chemically-modified nucleotides. In other embodiments, >95%, >90%, >85%, >80%, >75%, >70%, >65%, >60%, >55% or >50% of X's of the structure of formula (II) are chemically-modified nucleotides.

Structure of Formula (III)

[0706] In an embodiment, the compound of formula (I) has the structure of formula (III):



(III)

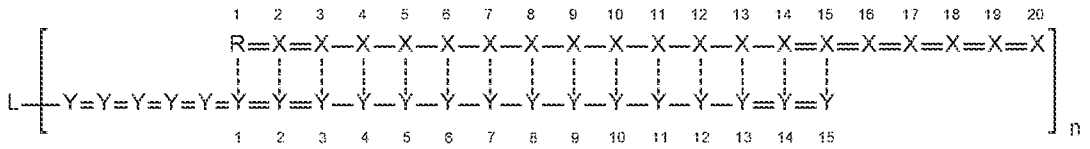
[0707] wherein X, for each occurrence, independently, is a nucleotide comprising a 2'-deoxy-2'-fluoro modification; X, for each occurrence, independently, is a nucleotide comprising a 2'-O-methyl modification; Y, for each occurrence, independently, is a nucleotide comprising a 2'-deoxy-2'-fluoro modification; and Y, for each occurrence, independently, is a nucleotide comprising a 2'-O-methyl modification.

[0708] In an embodiment, X is chosen from the group consisting of 2'-deoxy-2'-fluoro modified adenosine, guanosine, uridine or cytidine. In an embodiment, X is chosen from the group consisting of 2'-O-methyl modified adenosine, guanosine, uridine or cytidine. In an embodiment, Y is chosen from the group consisting of 2'-deoxy-2'-fluoro modified adenosine, guanosine, uridine or cytidine. In an embodiment, Y is chosen from the group consisting of 2'-O-methyl modified adenosine, guanosine, uridine or cytidine.

[0709] In certain embodiments, the structure of formula (III) does not contain mismatches. In one embodiment, the structure of formula (III) contains 1 mismatch. In another embodiment, the compound of formula (III) contains 2 mismatches. In another embodiment, the compound of formula (III) contains 3 mismatches. In another embodiment, the compound of formula (III) contains 4 mismatches.

Structure of Formula (IV)

[0710] In an embodiment, the compound of formula (I) has the structure of formula (IV):



(IV)

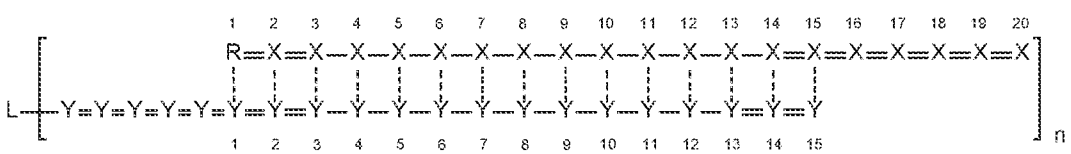
wherein X, for each occurrence, independently, is selected from adenosine, guanosine, uridine, cytidine, and chemically-modified derivatives thereof; Y, for each occurrence, independently, is selected from adenosine, guanosine, uridine, cytidine, and chemically-modified derivatives thereof; - represents a phosphodiester internucleoside linkage; = represents a phosphorothioate internucleoside linkage; and --- represents, individually for each occurrence, a base-pairing interaction or a mismatch.

[0711] In certain embodiments, the structure of formula (IV) does not contain mismatches. In one embodiment, the structure of formula (IV) contains 1 mismatch. In another embodiment, the compound of formula (IV) contains 2 mismatches. In another embodiment, the compound of formula (IV) contains 3 mismatches. In another embodiment, the compound of formula (IV) contains 4 mismatches. In an embodiment, each nucleic acid consists of chemically-modified nucleotides.

[0712] In certain embodiments, >95%, >90%, >85%, >80%, >75%, >70%, >65%, >60%, >55% or >50% of X's of the structure of formula (IV) are chemically-modified nucleotides. In other embodiments, >95%, >90%, >85%, >80%, >75%, >70%, >65%, >60%, >55% or >50% of X's of the structure of formula (IV) are chemically-modified nucleotides.

Structure of Formula (V)

[0713] In an embodiment, the compound of formula (I) has the structure of formula (V):



(V)

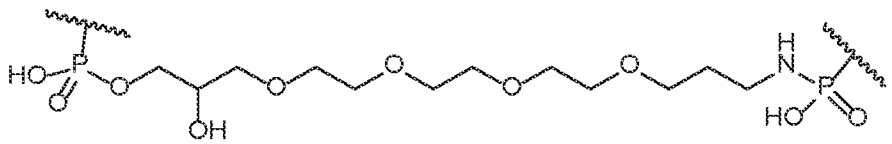
wherein X, for each occurrence, independently, is a nucleotide comprising a 2'-deoxy-2'-fluoro modification; X, for each occurrence, independently, is a nucleotide comprising a 2'-O-methyl modification; Y, for each occurrence, independently, is a nucleotide comprising a 2'-deoxy-2'-fluoro modification; and Y, for each occurrence, independently, is a nucleotide comprising a 2'-O-methyl modification.

[0714] In certain embodiments, X is chosen from the group consisting of 2'-deoxy-2'-fluoro modified adenosine, guanosine, uridine or cytidine. In an embodiment, X is chosen from the group consisting of 2'-O-methyl modified adenosine, guanosine, uridine or cytidine. In an embodiment, Y is chosen from the group consisting of 2'-deoxy-2'-fluoro modified adenosine, guanosine, uridine or cytidine. In an embodiment, Y is chosen from the group consisting of 2'-O-methyl modified adenosine, guanosine, uridine or cytidine.

[0715] In certain embodiments, the structure of formula (V) does not contain mismatches. In one embodiment, the structure of formula (V) contains 1 mismatch. In another embodiment, the compound of formula (V) contains 2 mismatches. In another embodiment, the compound of formula (V) contains 3 mismatches. In another embodiment, the compound of formula (V) contains 4 mismatches.

Variable Linkers

[0716] In an embodiment of the compound of formula (I), L has the structure of L1:

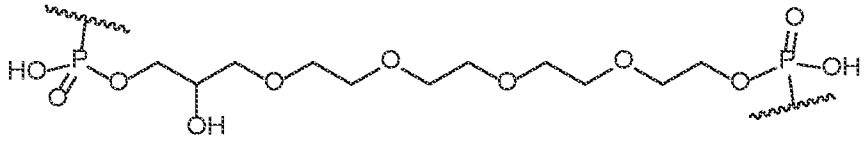


(L1)

In an embodiment of L1, R is R^3 and n is 2.

[0717] In an embodiment of the structure of formula (II), L has the structure of L1. In an embodiment of the structure of formula (III), L has the structure of L1. In an embodiment of the structure of formula (IV), L has the structure of L1. In an embodiment of the structure of formula (V), L has the structure of L1. In an embodiment of the structure of formula (VI), L has the structure of L1. In an embodiment of the structure of formula (VI), L has the structure of L1.

[0718] In an embodiment of the compound of formula (I), L has the structure of L2:



(L2)

[0719] In an embodiment of L2, R is R3 and n is 2. In an embodiment of the structure of formula (II), L has the structure of L2. In an embodiment of the structure of formula (III), L has the structure of L2. In an embodiment of the structure of formula (IV), L has the structure of L2. In an embodiment of the structure of formula (V), L has the structure of L2. In an embodiment of the structure of formula (VI), L has the structure of L2. In an embodiment of the structure of formula (VI), L has the structure of L2.

Delivery System

[0720] In a third aspect, provided herein is a delivery system for therapeutic nucleic acids having the structure of formula (VI):

$$L\text{—}(cNA)_n$$

(VI)

[0721] wherein L is selected from an ethylene glycol chain, an alkyl chain, a peptide, RNA, DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, and combinations thereof, wherein formula (VI) optionally further comprises one or more branch point B, and one or more spacer S; wherein B is independently for each occurrence a polyvalent organic species or derivative thereof; S is independently for each occurrence selected from an ethylene glycol chain, an alkyl chain, a peptide, RNA, DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, and combinations thereof; each cNA, independently, is a carrier nucleic acid comprising one or more chemical modifications; and n is 2, 3, 4, 5, 6, 7 or 8.

[0722] In one embodiment of the delivery system, L is an ethylene glycol chain. In another embodiment of the delivery system, L is an alkyl chain. In another embodiment of the delivery system, L is a peptide. In another embodiment of the delivery system, L is RNA. In another embodiment of the delivery system, L is DNA. In another embodiment of the delivery system, L is a phosphate. In another embodiment of the delivery system, L is a phosphonate. In another embodiment of the delivery system, L is a phosphoramidate. In another embodiment of the delivery system, L is an ester. In another embodiment of the delivery system, L is an amide. In another embodiment of the delivery system, L is a triazole.

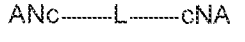
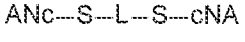
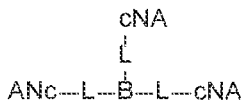
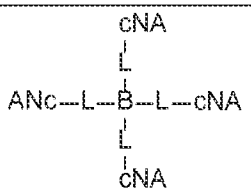
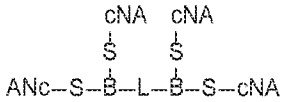
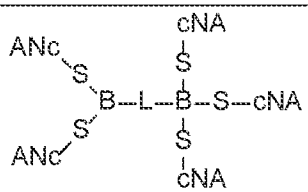
[0723] In one embodiment of the delivery system, S is an ethylene glycol chain. In another embodiment, S is an alkyl chain. In another embodiment of the delivery system, S is a peptide. In another embodiment, S is RNA. In another embodiment of the delivery system, S is DNA. In another embodiment of the delivery system, S is a phosphate. In another embodiment of the delivery system, S is a phosphonate. In another embodiment of the delivery system, S is a phosphoramidate. In another embodiment of the delivery system, S is an ester. In another embodiment, S is an amide. In another embodiment, S is a triazole.

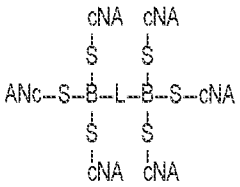
[0724] In one embodiment of the delivery system, n is 2. In another embodiment of the delivery system, n is 3. In another embodiment of the delivery system, n is 4. In another embodiment of the delivery system, n is 5. In another embodiment of the delivery system, n is 6. In another embodiment of the delivery system, n is 7. In another embodiment of the delivery system, n is 8.

[0725] In certain embodiments, each cNA comprises >95%, >90%, >85%, >80%, >75%, >70%, >65%, >60%, >55% or >50% chemically-modified nucleotides.

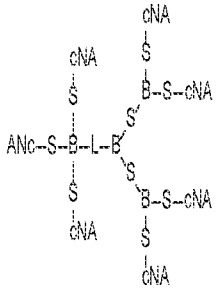
[0726] In an embodiment, the compound of formula (VI) has a structure selected from formulas (VI-1)-(VI-9) of **Table 3**:

Table 3

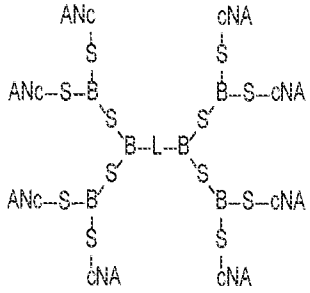
 (VI-1)	 (VI-2)	 (VI-3)
 (VI-4)	 (VI-5)	 (VI-6)



(VI-7)



(VI-8)



(VI-9)

[0727] In an embodiment, the compound of formula (VI) is the structure of formula (VI-1). In an embodiment, the compound of formula (VI) is the structure of formula (VI-2). In an embodiment, the compound of formula (VI) is the structure of formula (VI-3). In an embodiment, the compound of formula (VI) is the structure of formula (VI-4). In an embodiment, the compound of formula (VI) is the structure of formula (VI-5). In an embodiment, the compound of formula (VI) is the structure of formula (VI-6). In an embodiment, the compound of formula (VI) is the structure of formula (VI-7). In an embodiment, the compound of formula (VI) is the structure of formula (VI-8). In an embodiment, the compound of formula (VI) is the structure of formula (VI-9).

[0728] In an embodiment, the compound of formulas (VI) (including, e.g., formulas (VI-1)-(VI-9), each cNA independently comprises at least 15 contiguous nucleotides. In an embodiment, each cNA independently consists of chemically-modified nucleotides.

[0729] In an embodiment, the delivery system further comprises n therapeutic nucleic acids (NA), wherein each NA comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295, as recited in **Table 4-6**. In further embodiments, NA includes strands that are capable of targeting one or more of a *MAPT* nucleic acid sequence selected from the group consisting of SEQ ID NOs: 14-33, 299, and 302, as recited in **Tables 6-8**.

[0730] Also, each NA is hybridized to at least one cNA. In one embodiment, the delivery system is comprised of 2 NAs. In another embodiment, the delivery system is comprised of 3 NAs. In another embodiment, the delivery system is comprised of 4 NAs. In another embodiment, the delivery system is comprised of 5 NAs. In another embodiment, the delivery system is comprised of 6 NAs. In another embodiment, the delivery system is comprised of 7 NAs. In another embodiment, the delivery system is comprised of 8 NAs.

[0731] In an embodiment, each NA independently comprises at least 15 contiguous nucleotides. In an embodiment, each NA independently comprises 15-25 contiguous nucleotides. In an embodiment, each NA independently comprises 15 contiguous nucleotides. In an embodiment, each NA independently comprises 16 contiguous nucleotides. In another embodiment, each NA independently comprises 17 contiguous nucleotides. In another embodiment, each NA independently comprises 18 contiguous nucleotides. In another embodiment, each NA independently comprises 19 contiguous nucleotides. In another embodiment, each NA independently comprises 20 contiguous nucleotides. In an embodiment, each NA independently comprises 21 contiguous nucleotides. In an embodiment, each NA independently comprises 22 contiguous nucleotides. In an embodiment, each NA independently comprises 23 contiguous nucleotides. In an embodiment, each NA independently comprises 24 contiguous nucleotides. In an embodiment, each NA independently comprises 25 contiguous nucleotides.

[0732] In an embodiment, each NA comprises an unpaired overhang of at least 2 nucleotides. In another embodiment, each NA comprises an unpaired overhang of at least 3 nucleotides. In another embodiment, each NA comprises an unpaired overhang of at least 4 nucleotides. In another embodiment, each NA comprises an unpaired overhang of at least 5 nucleotides. In another embodiment, each NA comprises an unpaired overhang of at least 6 nucleotides. In an embodiment, the nucleotides of the overhang are connected via phosphorothioate linkages.

[0733] In an embodiment, each NA, independently, is selected from the group consisting of: DNAs, siRNAs, antagomiRs, miRNAs, gapmers, mixmers, or guide RNAs. In one embodiment, each NA, independently, is a DNA. In another embodiment, each NA, independently, is a siRNA. In another embodiment, each NA, independently, is an antagomiR. In another embodiment, each NA, independently, is a miRNA. In another embodiment, each NA, independently, is a gapmer. In another embodiment, each NA, independently, is a mixmer. In another embodiment, each NA, independently, is a guide RNA. In an embodiment, each NA is the same. In an embodiment, each NA is not the same.

[0734] In an embodiment, the delivery system further comprising n therapeutic nucleic acids (NA) has a structure selected from formulas (I), (II), (III), (IV), (V), (VI), and embodiments thereof described herein. In one embodiment, the delivery system has a structure selected from formulas (I), (II), (III), (IV), (V), (VI), and embodiments thereof described herein further comprising 2 therapeutic nucleic acids (NA). In another embodiment, the delivery

system has a structure selected from formulas (I), (II), (III), (IV), (V), (VI), and embodiments thereof described herein further comprising 3 therapeutic nucleic acids (NA). In one embodiment, the delivery system has a structure selected from formulas (I), (II), (III), (IV), (V), (VI), and embodiments thereof described herein further comprising 4 therapeutic nucleic acids (NA). In one embodiment, the delivery system has a structure selected from formulas (I), (II), (III), (IV), (V), (VI), and embodiments thereof described herein further comprising 5 therapeutic nucleic acids (NA). In one embodiment, the delivery system has a structure selected from formulas (I), (II), (III), (IV), (V), (VI), and embodiments thereof described herein further comprising 6 therapeutic nucleic acids (NA). In one embodiment, the delivery system has a structure selected from formulas (I), (II), (III), (IV), (V), (VI), and embodiments thereof described herein further comprising 7 therapeutic nucleic acids (NA). In one embodiment, the delivery system has a structure selected from formulas (I), (II), (III), (IV), (V), (VI), and embodiments thereof described herein further comprising 8 therapeutic nucleic acids (NA).

[0735] In one embodiment, the delivery system has a structure selected from formulas (I), (II), (III), (IV), (V), (VI), further comprising a linker of structure L1 or L2 wherein R is R^3 and n is 2. In another embodiment, the delivery system has a structure selected from formulas (I), (II), (III), (IV), (V), (VI), further comprising a linker of structure L1 wherein R is R^3 and n is 2. In another embodiment, the delivery system has a structure selected from formulas (I), (II), (III), (IV), (V), (VI), further comprising a linker of structure L2 wherein R is R^3 and n is 2.

[0736] In an embodiment of the delivery system, the target of delivery is selected from the group consisting of: brain, liver, skin, kidney, spleen, pancreas, colon, fat, lung, muscle, and thymus. In one embodiment, the target of delivery is the brain. In another embodiment, the target of delivery is the striatum of the brain. In another embodiment, the target of delivery is the cortex of the brain. In another embodiment, the target of delivery is the striatum of the brain. In one embodiment, the target of delivery is the liver. In one embodiment, the target of delivery is the skin. In one embodiment, the target of delivery is the kidney. In one embodiment, the target of delivery is the spleen. In one embodiment, the target of delivery is the pancreas. In one embodiment, the target of delivery is the colon. In one embodiment, the target of delivery is the fat. In one embodiment, the target of delivery is the lung. In one embodiment, the target of delivery is the muscle. In one embodiment, the target of delivery is the thymus. In one embodiment, the target of delivery is the spinal cord.

[0737] In certain embodiments, compounds of the disclosure are characterized by the following properties: (1) two or more branched oligonucleotides, e.g., wherein there is a non-equal number of 3' and 5' ends; (2) substantially chemically stabilized, e.g., wherein more than 40%, optimally 100%, of oligonucleotides are chemically modified (e.g., no RNA and optionally no DNA); and (3) phoshorothioated single oligonucleotides containing at least 3, phosphorothioated bonds. In certain embodiments, the phoshorothioated single oligonucleotides contain 4-20 phosphorothioated bonds.

[0738] It is to be understood that the methods described in this disclosure are not limited to particular methods and experimental conditions disclosed herein; as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0739] Furthermore, the experiments described herein, unless otherwise indicated, use conventional molecular and cellular biological and immunological techniques within the skill of the art. Such techniques are well known to the skilled worker, and are explained fully in the literature. See, e.g., Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY (1987-2008), including all supplements, Molecular Cloning: A Laboratory Manual (Fourth Edition) by MR Green and J. Sambrook and Harlow et al., Antibodies: A Laboratory Manual, Chapter 14, Cold Spring Harbor Laboratory, Cold Spring Harbor (2013, 2nd edition).

[0740] Branched oligonucleotides, including synthesis and methods of use, are described in greater detail in WO2017/132669, incorporated herein by reference.

Methods of Introducing Nucleic Acids, Vectors and Host Cells

[0741] RNA silencing agents of the disclosure may be directly introduced into the cell (e.g., a neural cell) (i.e., intracellularly); or introduced extracellularly into a cavity, interstitial space, into the circulation of an organism, introduced orally, or may be introduced by bathing a cell or organism in a solution containing the nucleic acid. Vascular or extravascular circulation, the blood or lymph system, and the cerebrospinal fluid are sites where the nucleic acid may be introduced.

[0742] The RNA silencing agents of the disclosure can be introduced using nucleic acid delivery methods known in art including injection of a solution containing the nucleic acid, bombardment by particles covered by the nucleic acid, soaking the cell or organism in a

solution of the nucleic acid, or electroporation of cell membranes in the presence of the nucleic acid. Other methods known in the art for introducing nucleic acids to cells may be used, such as lipid-mediated carrier transport, chemical-mediated transport, and cationic liposome transfection such as calcium phosphate, and the like. The nucleic acid may be introduced along with other components that perform one or more of the following activities: enhance nucleic acid uptake by the cell or other-wise increase inhibition of the target gene.

[0743] Physical methods of introducing nucleic acids include injection of a solution containing the RNA, bombardment by particles covered by the RNA, soaking the cell or organism in a solution of the RNA, or electroporation of cell membranes in the presence of the RNA. A viral construct packaged into a viral particle would accomplish both efficient introduction of an expression construct into the cell and transcription of RNA encoded by the expression construct. Other methods known in the art for introducing nucleic acids to cells may be used, such as lipid-mediated carrier transport, chemical-mediated transport, such as calcium phosphate, and the like. Thus, the RNA may be introduced along with components that perform one or more of the following activities: enhance RNA uptake by the cell, inhibit annealing of single strands, stabilize the single strands, or other-wise increase inhibition of the target gene.

[0744] RNA may be directly introduced into the cell (i.e., intracellularly); or introduced extracellularly into a cavity, interstitial space, into the circulation of an organism, introduced orally, or may be introduced by bathing a cell or organism in a solution containing the RNA. Vascular or extravascular circulation, the blood or lymph system, and the cerebrospinal fluid are sites where the RNA may be introduced.

[0745] The cell having the target gene may be from the germ line or somatic, totipotent or pluripotent, dividing or non-dividing, parenchyma or epithelium, immortalized or transformed, or the like. The cell may be a stem cell or a differentiated cell. Cell types that are differentiated include adipocytes, fibroblasts, myocytes, cardiomyocytes, endothelium, neurons, glia, blood cells, megakaryocytes, lymphocytes, macrophages, neutrophils, eosinophils, basophils, mast cells, leukocytes, granulocytes, keratinocytes, chondrocytes, osteoblasts, osteoclasts, hepatocytes, and cells of the endocrine or exocrine glands.

[0746] Depending on the particular target gene and the dose of double stranded RNA material delivered, this process may provide partial or complete loss of function for the target gene. A reduction or loss of gene expression in at least 50%, 60%, 70%, 80%, 90%, 95% or

99% or more of targeted cells is exemplary. Inhibition of gene expression refers to the absence (or observable decrease) in the level of protein and/or mRNA product from a target gene. Specificity refers to the ability to inhibit the target gene without manifest effects on other genes of the cell. The consequences of inhibition can be confirmed by examination of the outward properties of the cell or organism (as presented below in the examples) or by biochemical techniques such as RNA solution hybridization, nuclease protection, Northern hybridization, reverse transcription, gene expression monitoring with a microarray, antibody binding, Enzyme Linked ImmunoSorbent Assay (ELISA), Western blotting, RadioImmunoAssay (RIA), other immunoassays, and Fluorescence Activated Cell Sorting (FACS).

[0747] For RNA-mediated inhibition in a cell line or whole organism, gene expression is conveniently assayed by use of a reporter or drug resistance gene whose protein product is easily assayed. Such reporter genes include acetohydroxyacid synthase (AHAS), alkaline phosphatase (AP), beta galactosidase (LacZ), beta glucoronidase (GUS), chloramphenicol acetyltransferase (CAT), green fluorescent protein (GFP), horseradish peroxidase (HRP), luciferase (Luc), nopaline synthase (NOS), octopine synthase (OCS), and derivatives thereof. Multiple selectable markers are available that confer resistance to ampicillin, bleomycin, chloramphenicol, gentarnycin, hygromycin, kanamycin, lincomycin, methotrexate, phosphinothricin, puromycin, and tetracyclin. Depending on the assay, quantitation of the amount of gene expression allows one to determine a degree of inhibition which is greater than 10%, 33%, 50%, 90%, 95% or 99% as compared to a cell not treated according to the present disclosure. Lower doses of injected material and longer times after administration of RNAi agent may result in inhibition in a smaller fraction of cells (e.g., at least 10%, 20%, 50%, 75%, 90%, or 95% of targeted cells). Quantization of gene expression in a cell may show similar amounts of inhibition at the level of accumulation of target mRNA or translation of target protein. As an example, the efficiency of inhibition may be determined by assessing the amount of gene product in the cell; mRNA may be detected with a hybridization probe having a nucleotide sequence outside the region used for the inhibitory double-stranded RNA, or translated polypeptide may be detected with an antibody raised against the polypeptide sequence of that region.

[0748] The RNA may be introduced in an amount which allows delivery of at least one copy per cell. Higher doses (e.g., at least 5, 10, 100, 500 or 1000 copies per cell) of material may yield more effective inhibition; lower doses may also be useful for specific applications.

[0749] In an exemplary aspect, the efficacy of an RNAi agent of the disclosure (e.g., an siRNA targeting an *MAPT* target sequence) is tested for its ability to specifically degrade mutant mRNA (e.g., *MAPT* mRNA and/or the production of MAPT protein) in cells, such as cells in the central nervous system. In certain embodiments, cells in the central nervous system include, but are not limited to, neurons (e.g., striatal or cortical neuronal clonal lines and/or primary neurons), glial cells, and astrocytes. Also suitable for cell-based validation assays are other readily transfectable cells, for example, HeLa cells or COS cells. Cells are transfected with human wild type or mutant cDNAs (e.g., human wild type or mutant *MAPT* cDNA). Standard siRNA, modified siRNA or vectors able to produce siRNA from U-looped mRNA are co-transfected. Selective reduction in target mRNA (e.g., *MAPT* mRNA) and/or target protein (e.g., MAPT protein) is measured. Reduction of target mRNA or protein can be compared to levels of target mRNA or protein in the absence of an RNAi agent or in the presence of an RNAi agent that does not target *MAPT* mRNA. Exogenously-introduced mRNA or protein (or endogenous mRNA or protein) can be assayed for comparison purposes. When utilizing neuronal cells, which are known to be somewhat resistant to standard transfection techniques, it may be desirable to introduce RNAi agents (e.g., siRNAs) by passive uptake.

Recombinant Adeno-Associated Viruses and Vectors

[0750] In certain exemplary embodiments, recombinant adeno-associated viruses (rAAVs) and their associated vectors can be used to deliver one or more siRNAs into cells, e.g., neural cells (e.g., brain cells). AAV is able to infect many different cell types, although the infection efficiency varies based upon serotype, which is determined by the sequence of the capsid protein. Several native AAV serotypes have been identified, with serotypes 1-9 being the most commonly used for recombinant AAV. AAV-2 is the most well-studied and published serotype. The AAV-DJ system includes serotypes AAV-DJ and AAV-DJ/8. These serotypes were created through DNA shuffling of multiple AAV serotypes to produce AAV with hybrid capsids that have improved transduction efficiencies *in vitro* (AAV-DJ) and *in vivo* (AAV-DJ/8) in a variety of cells and tissues.

[0751] In certain embodiments, widespread central nervous system (CNS) delivery can be achieved by intravascular delivery of recombinant adeno-associated virus 7 (rAAV7), RAAV9 and rAAV10, or other suitable rAAVs (Zhang et al. (2011) *Mol. Ther.* 19(8):1440-8.

doi: 10.1038/mt.2011.98. Epub 2011 May 24). rAAVs and their associated vectors are well-known in the art and are described in US Patent Applications 2014/0296486, 2010/0186103, 2008/0269149, 2006/0078542 and 2005/0220766, each of which is incorporated herein by reference in its entirety for all purposes.

[0752] rAAVs may be delivered to a subject in compositions according to any appropriate methods known in the art. An rAAV can be suspended in a physiologically compatible carrier (i.e., in a composition), and may be administered to a subject, i.e., a host animal, such as a human, mouse, rat, cat, dog, sheep, rabbit, horse, cow, goat, pig, guinea pig, hamster, chicken, turkey, a non-human primate (e.g., Macaque) or the like. In certain embodiments, a host animal is a non-human host animal.

[0753] Delivery of one or more rAAVs to a mammalian subject may be performed, for example, by intramuscular injection or by administration into the bloodstream of the mammalian subject. Administration into the bloodstream may be by injection into a vein, an artery, or any other vascular conduit. In certain embodiments, one or more rAAVs are administered into the bloodstream by way of isolated limb perfusion, a technique well known in the surgical arts, the method essentially enabling the artisan to isolate a limb from the systemic circulation prior to administration of the rAAV virions. A variant of the isolated limb perfusion technique, described in U.S. Pat. No. 6,177,403, can also be employed by the skilled artisan to administer virions into the vasculature of an isolated limb to potentially enhance transduction into muscle cells or tissue. Moreover, in certain instances, it may be desirable to deliver virions to the central nervous system (CNS) of a subject. By "CNS" is meant all cells and tissue of the brain and spinal cord of a vertebrate. Thus, the term includes, but is not limited to, neuronal cells, glial cells, astrocytes, cerebrospinal fluid (CSF), interstitial spaces, bone, cartilage and the like. Recombinant AAVs may be delivered directly to the CNS or brain by injection into, e.g., the ventricular region, as well as to the striatum (e.g., the caudate nucleus or putamen of the striatum), spinal cord and neuromuscular junction, or cerebellar lobule, with a needle, catheter or related device, using neurosurgical techniques known in the art, such as by stereotactic injection (see, e.g., Stein et al., J Virol 73:3424-3429, 1999; Davidson et al., PNAS 97:3428-3432, 2000; Davidson et al., Nat. Genet. 3:219-223, 1993; and Alisky and Davidson, Hum. Gene Ther. 11:2315-2329, 2000).

[0754] The compositions of the disclosure may comprise an rAAV alone, or in combination with one or more other viruses (e.g., a second rAAV encoding having one or more

different transgenes). In certain embodiments, a composition comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more different rAAVs each having one or more different transgenes.

[0755] An effective amount of an rAAV is an amount sufficient to target infect an animal, target a desired tissue. In some embodiments, an effective amount of an rAAV is an amount sufficient to produce a stable somatic transgenic animal model. The effective amount will depend primarily on factors such as the species, age, weight, health of the subject, and the tissue to be targeted, and may thus vary among animal and tissue. For example, an effective amount of one or more rAAVs is generally in the range of from about 1 ml to about 100 ml of solution containing from about 10^9 to 10^{16} genome copies. In some cases, a dosage between about 10^{11} to 10^{12} rAAV genome copies is appropriate. In certain embodiments, 10^{12} rAAV genome copies is effective to target heart, liver, and pancreas tissues. In some cases, stable transgenic animals are produced by multiple doses of an rAAV.

[0756] In some embodiments, rAAV compositions are formulated to reduce aggregation of AAV particles in the composition, particularly where high rAAV concentrations are present (e.g., about 10^{13} genome copies/mL or more). Methods for reducing aggregation of rAAVs are well known in the art and, include, for example, addition of surfactants, pH adjustment, salt concentration adjustment, etc. (See, e.g., Wright et al. (2005) Molecular Therapy 12:171-178, the contents of which are incorporated herein by reference.)

[0757] "Recombinant AAV (rAAV) vectors" comprise, at a minimum, a transgene and its regulatory sequences, and 5' and 3' AAV inverted terminal repeats (ITRs). It is this recombinant AAV vector which is packaged into a capsid protein and delivered to a selected target cell. In some embodiments, the transgene is a nucleic acid sequence, heterologous to the vector sequences, which encodes a polypeptide, protein, functional RNA molecule (e.g., siRNA) or other gene product, of interest. The nucleic acid coding sequence is operatively linked to regulatory components in a manner which permits transgene transcription, translation, and/or expression in a cell of a target tissue.

[0758] The AAV sequences of the vector typically comprise the cis-acting 5' and 3' inverted terminal repeat (ITR) sequences (See, e.g., B. J. Carter, in "Handbook of Parvoviruses", ed., P. Tijsser, CRC Press, pp. 155 168 (1990)). The ITR sequences are usually about 145 basepairs in length. In certain embodiments, substantially the entire sequences encoding the ITRs are used in the molecule, although some degree of minor modification of these sequences is permissible. The ability to modify these ITR sequences is within the skill

of the art. (See, e.g., texts such as Sambrook et al, "Molecular Cloning. A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory, New York (1989); and K. Fisher et al., J Virol., 70:520 532 (1996)). An example of such a molecule employed in the present disclosure is a "cis-acting" plasmid containing the transgene, in which the selected transgene sequence and associated regulatory elements are flanked by the 5' and 3' AAV ITR sequences. The AAV ITR sequences may be obtained from any known AAV, including mammalian AAV types described further herein.

VIII. Methods of Treatment

[0759] In one aspect, the present disclosure provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) developing insoluble aggregates in the brain comprising tau protein. In one embodiment, the disease or disorder is such that MAPT levels in the central nervous system (CNS) have been found to be predictive of neurodegeneration progression. In another embodiment, the disease or disorder is a proteopathy characterized by the aggregation of misfolded proteins. In a certain embodiment, the disease or disorder one in which reduction of MAPT in the CNS reduces clinical manifestations seen in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, or Huntington's disease.

[0760] "Treatment," or "treating," as used herein, is defined as the application or administration of a therapeutic agent (e.g., a RNA agent or vector or transgene encoding same) to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient, who has the disease or disorder, a symptom of disease or disorder or a predisposition toward a disease or disorder, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disease or disorder, the symptoms of the disease or disorder, or the predisposition toward disease.

[0761] In one aspect, the disclosure provides a method for preventing in a subject, a disease or disorder as described above, by administering to the subject a therapeutic agent (e.g., an RNAi agent or vector or transgene encoding same). Subjects at risk for the disease can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the disease or disorder, such that the disease or disorder is prevented or, alternatively, delayed in its progression.

[0762] Another aspect of the disclosure pertains to methods treating subjects therapeutically, i.e., alter onset of symptoms of the disease or disorder. In an exemplary embodiment, the modulatory method of the disclosure involves contacting a CNS cell expressing *MAPT* with a therapeutic agent (e.g., a RNAi agent or vector or transgene encoding same) that is specific for a target sequence within the gene (e.g., *MAPT* target sequences of **Tables 4-6**), such that sequence specific interference with the gene is achieved. These methods can be performed *in vitro* (e.g., by culturing the cell with the agent) or, alternatively, *in vivo* (e.g., by administering the agent to a subject).

IX. Pharmaceutical Compositions and Methods of Administration

[0763] The disclosure pertains to uses of the above-described agents for prophylactic and/or therapeutic treatments as described *infra*. Accordingly, the modulators (e.g., RNAi agents) of the present disclosure can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, antibody, or modulatory compound and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0764] A pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, intraperitoneal, intramuscular, oral (e.g., inhalation), transdermal (topical), and transmucosal administration. In certain exemplary embodiments, the pharmaceutical composition of the disclosure is adminsitered intravenously and is capable of crossing the blood brain barrier to enter the central nervous system. In certain exemplary embodiments, a pharmaceutical composition of the disclosure is delivered to the cerebrospinal fluid (CSF) by a route of administration that includes, but is not limited to, intrastriatal (IS) administration, intracerebroventricular (ICV) administration and intrathecal (IT) administration (e.g., via a pump, an infusion or the like).

[0765] The nucleic acid molecules of the disclosure can be inserted into expression constructs, e.g., viral vectors, retroviral vectors, expression cassettes, or plasmid viral vectors, e.g., using methods known in the art, including but not limited to those described in Xia et al., (2002), *Supra*. Expression constructs can be delivered to a subject by, for example, inhalation, orally, intravenous injection, local administration (see U.S. Pat. No. 5,328,470) or by stereotactic injection (see e.g., Chen et al. (1994), Proc. Natl. Acad. Sci. USA, 91, 3054-3057). The pharmaceutical preparation of the delivery vector can include the vector in an acceptable diluent, or can comprise a slow release matrix in which the delivery vehicle is imbedded. Alternatively, where the complete delivery vector can be produced intact from recombinant cells, e.g., retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

[0766] The nucleic acid molecules of the disclosure can also include small hairpin RNAs (shRNAs), and expression constructs engineered to express shRNAs. Transcription of shRNAs is initiated at a polymerase III (pol III) promoter, and is thought to be terminated at position 2 of a 4-5-thymine transcription termination site. Upon expression, shRNAs are thought to fold into a stem-loop structure with 3' UU-overhangs; subsequently, the ends of these shRNAs are processed, converting the shRNAs into siRNA-like molecules of about 21 nucleotides. Brummelkamp et al. (2002), Science, 296, 550-553; Lee et al, (2002). *supra*; Miyagishi and Taira (2002), Nature Biotechnol., 20, 497-500; Paddison et al. (2002), *supra*; Paul (2002), *supra*; Sui (2002) *supra*; Yu et al. (2002), *supra*.

[0767] The expression constructs may be any construct suitable for use in the appropriate expression system and include, but are not limited to retroviral vectors, linear expression cassettes, plasmids and viral or virally-derived vectors, as known in the art. Such expression constructs may include one or more inducible promoters, RNA Pol III promoter systems such as U6 snRNA promoters or H1 RNA polymerase III promoters, or other promoters known in the art. The constructs can include one or both strands of the siRNA. Expression constructs expressing both strands can also include loop structures linking both strands, or each strand can be separately transcribed from separate promoters within the same construct. Each strand can also be transcribed from a separate expression construct, Tuschl (2002), *Supra*.

[0768] In certain embodiments, a composition that includes a compound of the disclosure can be delivered to the nervous system of a subject by a variety of routes. Exemplary routes include intrathecal, parenchymal (e.g., in the brain), nasal, and ocular delivery. The

composition can also be delivered systemically, e.g., by intravenous, subcutaneous or intramuscular injection. One route of delivery is directly to the brain, e.g., into the ventricles or the hypothalamus of the brain, or into the lateral or dorsal areas of the brain. The compounds for neural cell delivery can be incorporated into pharmaceutical compositions suitable for administration.

[0769] For example, compositions can include one or more species of a compound of the disclosure and a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present disclosure may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic, intranasal, transdermal), oral or parenteral. Parenteral administration includes intravenous drip, subcutaneous, intraperitoneal or intramuscular injection, intrathecal, or intraventricular (e.g., intracerebroventricular) administration. In certain exemplary embodiments, a compound of the disclosure is delivered across the Blood-Brain-Barrier (BBB) suing a variety of suitable compositions and methods described herein.

[0770] The route of delivery can be dependent on the disorder of the patient. For example, a subject diagnosed with a neurodegenerative disease can be administered an anti-*MAPT* compoun of the disclosure directly into the brain (e.g., into the globus pallidus or the corpus striatum of the basal ganglia, and near the medium spiny neurons of the corpus striatum). In addition to a compound of the disclosure, a patient can be administered a second therapy, e.g., a palliative therapy and/or disease-specific therapy. The secondary therapy can be, for example, symptomatic (e.g., for alleviating symptoms), neuroprotective (e.g., for slowing or halting disease progression), or restorative (e.g., for reversing the disease process). Other therapies can include psychotherapy, physiotherapy, speech therapy, communicative and memory aids, social support services, and dietary advice.

[0771] A compound of the disclosure can be delivered to neural cells of the brain. In certain embodiments, the compounds of the disclosure may be delivered to the brain without direct adminsitration to the central nervous sysytem, i.e., the compounds may be delivered intravenously and cross the blood brain barrier to enter ther brain. Delivery methods that do not require passage of the composition across the blood-brain barrier can be utilized. For example, a pharmaceutical composition containing a compound of the disclosure can be delivered to the patient by injection directly into the area containing the disease-affected cells. For example, the pharmaceutical composition can be delivered by injection directly into the brain. The injection can be by stereotactic injection into a particular region of the brain (e.g.,

the substantia nigra, cortex, hippocampus, striatum, or globus pallidus). The compound can be delivered into multiple regions of the central nervous system (e.g., into multiple regions of the brain, and/or into the spinal cord). The compound can be delivered into diffuse regions of the brain (e.g., diffuse delivery to the cortex of the brain).

[0772] In one embodiment, the compound can be delivered by way of a cannula or other delivery device having one end implanted in a tissue, e.g., the brain, e.g., the substantia nigra, cortex, hippocampus, striatum or globus pallidus of the brain. The cannula can be connected to a reservoir containing the compound. The flow or delivery can be mediated by a pump, e.g., an osmotic pump or minipump, such as an Alzet pump (Durect, Cupertino, CA). In one embodiment, a pump and reservoir are implanted in an area distant from the tissue, e.g., in the abdomen, and delivery is effected by a conduit leading from the pump or reservoir to the site of release. Devices for delivery to the brain are described, for example, in U.S. Pat. Nos. 6,093,180, and 5,814,014.

[0773] It will be readily apparent to those skilled in the art that other suitable modifications and adaptations of the methods described herein may be made using suitable equivalents without departing from the scope of the embodiments disclosed herein. Having now described certain embodiments in detail, the same will be more clearly understood by reference to the following example, which is included for purposes of illustration only and is not intended to be limiting.

EXAMPLES

Example 1. *In vitro* identification of *MAPT* targeting sequences

[0774] The *MAPT* gene was used as a target for mRNA knockdown. A panel of siRNAs targeting several different sequences of the human and mouse *MAPT* mRNA was developed and screened in SH-SY5Y human neuroblastoma cells A549 *in vitro* and compared to untreated control cells. SiRNAs were designed to target the open reading frame (ORF) and 3' untranslated region (3'UTR). The siRNAs were each tested at a concentration of 1.5 μM and the mRNA was evaluated with the QuantiGene gene expression assay (ThermoFisher, Waltham, MA) at the 72 hours timepoint. **FIG. 1** reports the results of the screen against human *MAPT* mRNA and **FIG. 2** reports the results of the screen of human and mouse targeting siRNAs in SH-SY5Y human neuroblastoma cells.

[0775] **Table 4** and **Table 6** below recites the human *MAPT* target sequences that demonstrated reduced *MAPT* mRNA expression relative to % untreated control. **Table 5** below recites the cross-species and mouse *MAPT* target sequences that demonstrated reduced *MAPT* mRNA expression relative to % untreated control. The cross-species targets are found in both the human and mouse *MAPT* mRNA and may be useful in comparative *in vivo* studies. Overall, of the panel of siRNA target sites tested, 13 were identified that yielded potent and efficacious silencing of *MAPT* mRNA relative to % untreated control (**Tables 4-6**). **Table 7** and **Table 8** below recites the antisense and sense strands of the 12 siRNAs that resulted in potent and efficacious silencing of *MAPT* mRNA. The active chemical scaffolds of the compounds recited in **Table 8** are shown in **Table 9**. The antisense strands contain a 5' uracil to enhance loading into RISC. In certain instances, the corresponding complementary adenosine in the MAPT target is not present, leading to a 5' mismatch between the antisense strand and target. As shown in the data of **FIG. 1, FIG. 2**, and **FIG. 4**, this did not negatively impact silencing efficacy. Furthermore, several of the antisense strands contain a 3' end mismatch with the MAPT target to further enhance RISC loading, which also did not negatively impact silencing efficacy. **Table 8** below recites additional antisense and sense strands, wherein the sense strands are either asymmetric, or blunt type. **FIG. 4** summarizes the results obtained for each of the siRNA's evaluated with six different scaffolds (see **FIG. 3** for a graphic depiction of the various chemical scaffold): P3 blunt scaffold (FIG. 4A), P3 blunt plus mismatches at positions 10 and 11 on the sense strand scaffold (FIG. 4B), P3 asymmetric scaffold (FIG. 4C), P3 asymmetric plus ribose sense strand scaffold (FIG. 4D), OMe rich asymmetric scaffold (FIG. 4E) and OMe rich asymmetric plus ribose sense strand scaffold (FIG. 4F). FIG. 5A-5C depict the concentrations responses for the MAPT 357, MAPT 2257 and MAPT 2378 sequences with the indicated chemical modifications. **Table 10** lists *MAPT* mRNA sequences recited in additional embodiments. **Table 11** lists *MAPT* targets identified by *in silico* screening that are candidates for development of novel siRNAs.

Table 4 – Human *MAPT* mRNA targets sequences

Sequence ID	**45mer Gene Region**
MAPT_1971	GTGACCTCCAAGTGTGGCTCATTAGGCAACATCCATCATAAACCA (SEQ ID NO: 1)
MAPT_2012	ACCAGGAGGTGGCCAGGTGGAAGTAAAATCTGAGAAGCTTGACTT (SEQ ID NO: 2)
MAPT_2051	TGACTTCAAGGACAGAGTCCAGTCGAAGATTGGGTCCCTGGACAA (SEQ ID NO: 3)

Table 5 – Cross-species and mouse *MAPT* mRNA targets sequences.

Sequence ID	**45mer_Gene_Region**
MAPT_2005	ATCATAAACCAGGAGGTGGCCAGGTGGAAGTAAAATCTGAGAAGC (SEQ ID NO: 4)
MAPT_2007	CATAAACCAGGAGGTGGCCAGGTGGAAGTAAAATCTGAGAAGCTT (SEQ ID NO: 5)
MAPT_2034	GTAAAATCTGAGAAGCTTGACTTCAAGGACAGAGTCCAGTCGAAG (SEQ ID NO: 6)

Table 6 –MAPT mRNA sequences – additional embodiments

Sequence ID	**45mer Gene Region**
MAPT_357	AGTTCGAAGTGATGGAAGATCACGCTGGGACGTACGGGTTGGGGG (SEQ ID NO: 7)
MAPT_2257	TGTGCAAATAGTCTACAAACCAGTTGACCTGAGCAAGGTGACCTC (SEQ ID NO: 8)
MAPT_2378	TTCAAGGACAGAGTCCAGTCGAAGATTGGGTCCCTGGACAATATC (SEQ ID NO: 9)
MAPT_2417	AATATCACCCACGTCCCTGGCGGAGGAAATAAAAAGATTGAAACC (SEQ ID NO: 10)
MAPT_2666	TGATCAGGCCCCTGGGGCGGTCAATAATTGTGGAGAGGAGAGAAT (SEQ ID NO: 11)
MAPT_4518	CTGTTGAGTTGTAGTTGGATTTGTCTGTTTATGCTTGGATTCACC (SEQ ID NO: 12)
MAPT_6750	GTATTGTGTGTTTTAACAAATGATTTACACTGACTGTTGCTGTAA (SEQ ID NO: 13)

Table 7 – *MAPT* antisense and sense strand siRNA sequences used in screens of FIG. 1 and FIG. 2.

Sequence ID	**Antisense Sequence (5'-3')**	**Sense Sequence (5'-3')**
MAPT_1971	UGGAUGUUGCCUAAUGAGCC (SEQ ID NO: 34)	AUUAGGCAACAUCCA (SEQ ID NO: 14)
MAPT_2012	UCUCAGAUUUUACUUCCACC SEQ ID NO: 35)	AAGUAAAAUCUGAGA (SEQ ID NO: 15)
MAPT_2051	UCCCAAUCUUCGACUGGACU (SEQ ID NO: 36)	AGUCGAAGAUUGGGA (SEQ ID NO: 16)
MAPT_2005	UUUUACUUCCACCUGGCCACC (SEQ ID NO: 37)	CAGGUGGAAGUAAAA (SEQ ID NO: 17)
MAPT_2007	UAUUUUACUUCCACCUGGCC (SEQ ID NO: 38)	GGUGGAAGUAAAAUA (SEQ ID NO: 18)
MAPT_2034	UCUCUGUCCUUGAAGUCAAG	CUUCAAGGACAGAGA

	(SEQ ID NO: 39)	(SEQ OID NO: 19)

Table 8 – *MAPT* antisense and sense strand siRNA sequences used in screens of FIG. 4.

Sequence ID	**Antisense Sequence** (5'-3')	**Sense Sequence (Asymmetric)** (5'-3')	**Sense Sequence (Blunt)** (5'-3')
MAPT_357	UUACGUCCCAGCGUGAUCUU (SEQ ID NO: 40)	CACGCUGGGACGUAA (SEQ ID NO: 20)	AAGAUCACGCUGGGACGUAA (SEQ ID NO: 21)
MAPT_2257	UGCUCAGGUCAACUGGUUUG (SEQ ID NO: 41)	CAGUUGACCUGAGCA (SEQ ID NO: 22)	CAAACCAGUUGACCUGAGCA (SEQ ID NO: 23)
MAPT_2378*	UGGGACCCAAUCUUCGACUG (SEQ ID NO: 42)	GAAGAUUGGGUCCCA (SEQ ID NO: 24)	CAGUCGAAGAUUGGGUCCCA (SEQ ID NO: 25)
MAPT_2417	UUUUUAUUUCCUCCGCCAGG (SEQ ID NO: 43)	CGGAGGAAAUAAAAA (SEQ ID NO: 26)	CCUGGCGGAGGAAAUAAAAA (SEQ ID NO: 27)
MAPT_2666	UUCCACAAUUAUUGACCGCC (SEQ ID NO: 44)	UCAAUAAUUGUGGAA (SEQ ID NO: 28)	GGCGGUCAAUAAUUGUGGAA (SEQ ID NO: 29)
MAPT_4518	UGCAUAAACAGACAAAUCCA (SEQ ID NO: 45)	UUGUCUGUUUAUGCA (SEQ ID NO: 30)	UGGAUUUGUCUGUUUAUGCA (SEQ ID NO: 31)
MAPT_6750	UGUCAGUGUAAAUCAUUUGU (SEQ ID NO: 46)	UGAUUUACACUGACA (SEQ ID NO: 32)	ACAAAUGAUUUACACUGACA (SEQ ID NO: 33)

* miRNA hit

Table 9 – Active chemical scaffolds of the antisense and sense sequences of Table 8.

Sequence ID	**Active Chemical Scaffolds**
MAPT_357	P3 Blunt, P3 Asymmetric; P3 Asymmetric + Ribose and OMe Rich Asymmetric + Ribose formulations contained small amounts of duplex
MAPT_2257	P3 Blunt, P3 Asymmetric, P3 Asymmetric + Ribose
MAPT_2378	P3 Blunt, P3 Blunt + Mismatches, P3 Asymmetric, P3 Asymmetric + Ribose; P3 Asymmetric + Ribose formulation contained small amount of duplex
MAPT_2417	P3 Asymmetric
MAPT_2666	P3 Asymmetric
MAPT_4518	P3 Asymmetric + Ribose
MAPT_6750	P3 Asymmetric

Table 10 - MAPT mRNA sequences – additional embodiments

Sequence ID	Location	45mer Gene Region	Target Sequence
MAPT 120	5UTR	GAGGGTGACACGGACGCTGGCCTGAAAGAAT CTCCCCTGCAGACC (SEQ ID NO: 47)	GCUGGCCUGAAAGAAUC UCC (SEQ ID NO: 104)
MAPT 206	5UTR	TGATGCTAAGAGCACTCCAACAGCGGAAGATG TGACAGCACCCTT (SEQ ID NO: 48)	UCCAACAGCGGAAGAUG UGA (SEQ ID NO: 105)
MAPT 221	5UTR	TCCAACAGCGGAAGATGTGACAGCACCCTTAG TGGATGAGGGAGC (SEQ ID NO: 49)	UGUGACAGCACCCUUAG UGG (SEQ ID NO: 106)
MAPT 892	ORF	AAGGGCAGGATGCCCCCCTGGAGTTCACGTTT CACGTGGAAATCA (SEQ ID NO: 50)	CCCUGGAGUUCACGUUUC AC (SEQ ID NO: 107)
MAPT 963	ORF	CACTCGGAGGAGCATTTGGGAAGGGCTGCATT TCCAGGGGCCCCT (SEQ ID NO: 51)	UUGGGAAGGGCUGCAUU UCC (SEQ ID NO: 108)
MAPT 1111	ORF	AGCCCGTCAGCCGGGTCCCTCAACTCAAAGCT CGCATGGTCAGTA (SEQ ID NO: 52)	UCCCUCAACUCAAAGCUC GC (SEQ ID NO: 109)
MAPT 1178	ORF	CGATGACAAAAAAGCCAAGACATCCACACGTT CCTCTGCTAAAAC (SEQ ID NO: 53)	CAAGACAUCCACACGUUC CU (SEQ ID NO: 110)
MAPT 1820	ORF	GCACCAGCCGGGAGGCGGGAAGGTGCAGATA ATTAATAAGAAGCT (SEQ ID NO: 54)	CGGGAAGGUGCAGAUAA UUA (SEQ ID NO: 111)
MAPT 1971	ORF	GTGACCTCCAAGTGTGGCTCATTAGGCAACAT CCATCATAAACCA (SEQ ID NO: 1)	GGCUCAUUAGGCAACAU CCA (SEQ ID NO: 112)
MAPT 2051	ORF	TGACTTCAAGGACAGAGTCCAGTCGAAGATTG GGTCCCTGGACAA (SEQ ID NO: 3)	AGUCCAGUCGAAGAUUG GGU (SEQ ID NO: 113)
MAPT 2253	ORF	TCCTCCACCGGCAGCATCGACATGGTAGACTC GCCCCAGCTCGCC (SEQ ID NO: 55)	AUCGACAUGGUAGACUC GCC (SEQ ID NO: 114)
MAPT 2012	ORF	ACCAGGAGGTGGCCAGGTGGAAGTAAAATCT GAGAAGCTTGACTT (SEQ ID NO: 2)	GGUGGAAGUAAAAUCUG AGA (SEQ ID NO: 115)
MAPT 1911	ORF	AAACACGTCCCGGGAGGCGGCAGTGTGCAAAT AGTCTACAAACCA (SEQ ID NO: 56)	GGCGGCAGUGUGCAAAU AGU (SEQ ID NO: 116)
MAPT 2034	ORF	GTAAAATCTGAGAAGCTTGACTTCAAGGACAG AGTCCAGTCGAAG (SEQ ID NO: 6)	CUUGACUUCAAGGACAG AGU (SEQ ID NO: 117)
MAPT 1848	ORF	ATAATTAATAAGAAGCTGGATCTTAGCAACGT CCAGTCCAAGTGT (SEQ ID NO: 57)	CUGGAUCUUAGCAACGU CCA (SEQ ID NO: 118)
MAPT 1914	ORF	CACGTCCCGGGAGGCGGCAGTGTGCAAATAGT CTACAAACCAGTT (SEQ ID NO: 58)	GGCAGUGUGCAAAUAGU CUA (SEQ ID NO:119)
MAPT 1832	ORF	AGGCGGGAAGGTGCAGATAATTAATAAGAAG CTGGATCTTAGCAA (SEQ ID NO: 59)	GAUAAUUAAUAAGAAGC UGG (SEQ ID NO: 120)
MAPT 1838	ORF	GAAGGTGCAGATAATTAATAAGAAGCTGGATC TTAGCAACGTCCA (SEQ ID NO: 60)	UAAUAAGAAGCUGGAUC UUA (SEQ ID NO: 121)
MAPT 2005	ORF	ATCATAAACCAGGAGGTGGCCAGGTGGAAGT AAAATCTGAGAAGC (SEQ ID NO: 4)	GUGGCCAGGUGGAAGUA AAA (SEQ ID NO: 122)
MAPT 1887	ORF	AAGTGTGGCTCAAAGGATAATATCAAACACGT CCCGGGAGGCGGC (SEQ ID NO: 61)	GAUAAUAUCAAACACGU CCC (SEQ ID NO: 123)
MAPT 2007	ORF	CATAAACCAGGAGGTGGCCAGGTGGAAGTAA AATCTGAGAAGCTT (SEQ ID NO: 5)	GGCCAGGUGGAAGUAAA AUC (SEQ ID NO: 124)
MAPT 1833	ORF	GGCGGGAAGGTGCAGATAATTAATAAGAAGC TGGATCTTAGCAAC (SEQ ID NO: 62)	AUAAUUAAUAAGAAGCU GGA (SEQ ID NO: 125)
MAPT 1955	ORF	AGTTGACCTGAGCAAGGTGACCTCCAAGTGTG GCTCATTAGGCAA (SEQ ID NO: 63)	GGUGACCUCCAAGUGUG GCU (SEQ ID NO: 126)
MAPT 357	ORF	AGTTCGAAGTGATGGAAGATCACGCTGGGACG TACGGGTTGGGGG (SEQ ID NO: 7)	AAGAUCACGCUGGGACG UAC (SEQ ID NO: 127)
MAPT 522	ORF	AAACCTCTGATGCTAAGAGCACTCCAACAGCG GAAGATGTGACAG (SEQ ID NO: 64)	AGAGCACUCCAACAGCGG AA (SEQ ID NO: 128)
MAPT 626	ORF	ATCCCAGAAGGAACCACAGCTGAAGAAGCAG GCATTGGAGACACC (SEQ ID NO: 65)	ACAGCUGAAGAAGCAGG CAU (SEQ ID NO: 129)
MAPT 896	ORF	CTGCTCAAGCACCAGCTTCTAGGAGACCTGCA CCAGGAGGGGCCG (SEQ ID NO: 66)	CUUCUAGGAGACCUGCAC CA (SEQ ID NO: 130)

MAPT 1231	ORF	CCTGGAGTTCACGTTTCACGTGGAAATCACAC CCAACGTGCAGAA (SEQ ID NO: 67)	UCACGUGGAAAUCACACC CA (SEQ ID NO: 131)
MAPT 1385	ORF	GACCTTCCAGAGCCCTCTGAAAAGCAGCCTGC TGCTGCTCCGCGG (SEQ ID NO: 68)	UCUGAAAAGCAGCCUGC UGC (SEQ ID NO: 132)
MAPT 1484	ORF	AAAGACGGGACTGGAAGCGATGACAAAAAAG CCAAGACATCCACA (SEQ ID NO: 69)	AGCGAUGACAAAAAAGC CAA (SEQ ID NO: 133)
MAPT 1574	ORF	AAACACCCCACTCCTGGTAGCTCAGACCCTCT GATCCAACCCTCC (SEQ ID NO: 70)	GGUAGCUCAGACCCUCUG AU (SEQ ID NO: 134)
MAPT 1670	ORF	GTCACTTCCCGAACTGGCAGTTCTGGAGCAAA GGAGATGAAACTC (SEQ ID NO: 71)	GGCAGUUCUGGAGCAAA GGA (SEQ ID NO: 135)
MAPT 1835	ORF	CCCAGCTCTGCGACTAAGCAAGTCCAGAGAAG ACCACCCCCTGCA (SEQ ID NO: 72)	AAGCAAGUCCAGAGAAG ACC (SEQ ID NO: 136)
MAPT 2115	ORF	CCAAGATCGGCTCCACTGAGAACCTGAAGCAC CAGCCGGGAGGCG (SEQ ID NO: 73)	CUGAGAACCUGAAGCACC AG (SEQ ID NO: 137)
MAPT 2191	ORF	TCTTAGCAACGTCCAGTCCAAGTGTGGCTCAA AGGATAATATCAA (SEQ ID NO: 74)	GUCCAAGUGUGGCUCAA AGG (SEQ ID NO: 138)
MAPT 2257	ORF	TGTGCAAATAGTCTACAAACCAGTTGACCTGA GCAAGGTGACCTC (SEQ ID NO: 8)	CAAACCAGUUGACCUGA GCA (SEQ ID NO: 139)
MAPT 2314	ORF	ATTAGGCAACATCCATCATAAACCAGGAGGTG GCCAGGTGGAAGT (SEQ ID NO: 75)	UCAUAAACCAGGAGGUG GCC (SEQ ID NO: 140)
MAPT 2378	ORF	TTCAAGGACAGAGTCCAGTCGAAGATTGGGTC CCTGGACAATATC (SEQ ID NO: 9)	CAGUCGAAGAUUGGGUC CCU (SEQ ID NO: 141)
MAPT 2417	ORF	AATATCACCCACGTCCCTGGCGGAGGAAATAA AAAGATTGAAACC (SEQ ID NO: 10)	CCUGGCGGAGGAAAUAA AAA (SEQ ID NO: 142)
MAPT 2428	ORF	CGTCCCTGGCGGAGGAAATAAAAAGATTGAA ACCCACAAGCTGAC (SEQ ID NO: 76)	AAAUAAAAAGAUUGAAA CCC (SEQ ID NO: 143)
MAPT 2443	ORF	AAATAAAAAGATTGAAACCCACAAGCTGACCT TCCGCGAGAACGC (SEQ ID NO: 77)	AACCCACAAGCUGACCUU CC (SEQ ID NO: 144)
MAPT 2666	ORF_ 3UTR	TGATCAGGCCCCTGGGGCGGTCAATAATTGTG GAGAGGAGAGAAT (SEQ ID NO: 11)	GGCGGUCAAUAAUUGUG GAG (SEQ ID NO: 145)
MAPT 2758	3UTR	GCCCCCAGCTGCTCCTCGCAGTTCGGTTAATTG GTTAATCACTTA (SEQ ID NO: 78)	UCGCAGUUCGGUUAAUU GGU (SEQ ID NO: 146)
MAPT 2819	3UTR	CGGCTTTGGCTCGGGACTTCAAAATCAGTGAT GGGAGTAAGAGCA (SEQ ID NO: 79)	ACUUCAAAAUCAGUGAU GGG (SEQ ID NO: 147)
MAPT 2871	3UTR	TCTTTCCAAATTGATGGGTGGGCTAGTAATAA AATATTTAAAAAA (SEQ ID NO: 80)	GGGUGGGCUAGUAAUAA AAU (SEQ ID NO: 148)
MAPT 2873	3UTR	TTTCCAAATTGATGGGTGGGCTAGTAATAAAA TATTTAAAAAAAA (SEQ ID NO: 81)	GUGGGCUAGUAAUAAAA UAU (SEQ ID NO: 149)
MAPT 3101	3UTR	AGCAACAAAGGATTTGAAACTTGGTGTGTTCG TGGAGCCACAGGC (SEQ ID NO: 82)	GAAACUUGGUGUGUUCG UGG (SEQ ID NO: 150)
MAPT 3411	3UTR	GCAGCCTGTGGGAGAAGGGACAGCGGGTAAA AAGAGAAGGCAAGC (SEQ ID NO: 83)	AGGGACAGCGGGUAAAA AGA (SEQ ID NO: 151)
MAPT 3607	3UTR	TCTGAAGGTTGGAACTGCTGCCATGATTTTGG CCACTTTGCAGAC (SEQ ID NO: 84)	UGCUGCCAUGAUUUUGG CCA (SEQ ID NO: 152)
MAPT 3666	3UTR	CTAACCAGTTCTCTTTGTAAGGACTTGTGCCTC TTGGGAGACGTC (SEQ ID NO: 85)	UGUAAGGACUUGUGCCU CUU (SEQ ID NO: 153)
MAPT 3967	3UTR	GAAATTAAGGGAAGGCAAAGTCCAGGCACAA GAGTGGGACCCCAG (SEQ ID NO: 86)	CAAAGUCCAGGCACAAG AGU (SEQ ID NO: 154)
MAPT 4055	3UTR	CGAATCTCATGATCTGATTCGGTTCCCTGTCTC CTCCTCCCGTCA (SEQ ID NO: 87)	GAUUCGGUUCCCUGUCUC CU (SEQ ID NO: 155)
MAPT 4447	3UTR	GCCATGCTGTCTGTTCTGCTGGAGCAGCTGAA CATATACATAGAT (SEQ ID NO: 88)	CUGCUGGAGCAGCUGAA CAU (SEQ ID NO: 156)
MAPT 4518	3UTR	CTGTTGAGTTGTAGTTGGATTTGTCTGTTTATG CTTGGATTCACC (SEQ ID NO: 12)	UGGAUUUGUCUGUUUAU GCU (SEQ ID NO: 157)
MAPT 4710	3UTR	CTGGGGCCTCCCAAGTTTTGAAAGGCTTTCCTC AGCACCTGGGAC (SEQ ID NO: 89)	UUUUGAAAGGCUUUCCU CAG (SEQ ID NO: 158)
MAPT 4808	3UTR	CCTGAAGCACAGGATTAGGACTGAAGCGATGA TGTCCCCTTCCCT (SEQ ID NO: 90)	UAGGACUGAAGCGAUGA UGU (SEQ ID NO: 159)

MAPT 5126	3UTR	CCTGCGACCACAGCAGGGATTGGGATGAATTG CCTGTCCTGGATC (SEQ ID NO: 91)	GGGAUUGGGAUGAAUUG CCU (SEQ ID NO: 160)
MAPT 5208	3UTR	GACTTGACAAGTCAGGAGACACTGTTCCCAAA GCCTTGACCAGAG (SEQ ID NO: 92)	GAGACACUGUUCCCAAA GCC (SEQ ID NO: 161)
MAPT 5350	3UTR	CTCAGGCCCAATTCTGCCACTTCTGGTTTGGGT ACAGTTAAAGGC (SEQ ID NO: 93)	GCCACUUCUGGUUUGGG UAC (SEQ ID NO: 162)
MAPT 5441	3UTR	TGGCAGCTTCGTGTGCAGCTAGAGCTTTACCT GAAAGGAAGTCTC (SEQ ID NO: 94)	CAGCUAGAGCUUUACCU GAA (SEQ ID NO: 163)
MAPT 5640	3UTR	TGCATTTCTTCACGCACCTCGGTTCCTCTTCCT GAAGTTCTTGTG (SEQ ID NO: 95)	ACCUCGGUUCCUCUUCCU GA (SEQ ID NO: 164)
MAPT 5745	3UTR	GGGCAGGCTCTTGGGGCCAGCCTAAGATCATG GTTTAGGGTGATC (SEQ ID NO: 96)	GCCAGCCUAAGAUCAUG GUU (SEQ ID NO: 165)
MAPT 5934	3UTR	TATGCCGGCTCCTTCAAGCTGCTGACTCACTTT ATCAATAGTTCC (SEQ ID NO: 97)	AAGCUGCUGACUCACUU UAU (SEQ ID NO: 166)
MAPT 5984	3UTR	AATTGACTTCAGTGGTGAGACTGTATCCTGTTT GCTATTGCTTGT (SEQ ID NO: 98)	UGAGACUGUAUCCUGUU UGC (SEQ ID NO: 167)
MAPT 6170	3UTR	GTTAGAGGCCCTTGGGGTTTCTCTTTTCCACTG ACAGGCTTTCCC (SEQ ID NO: 99)	GGUUUCUCUUUUCCACU GAC (SEQ ID NO: 168)
MAPT 6290	3UTR	CTGCCCTCTTTCAGGGGTCCTAAGCCCACAATC ATGCCTCCCTAA (SEQ ID NO: 100)	GGUCCUAAGCCCACAAUC AU (SEQ ID NO: 169)
MAPT 6482	3UTR	CGAGGGCAGAGGTGATCACCTGCGTGTCCCAT CTACAGACCTGCA (SEQ ID NO: 101)	UCACCUGCGUGUCCCAUC UA (SEQ ID NO: 170)
MAPT 6541	3UTR	CTGATTTCTCTTCAGCTTTGAAAAGGGTTACCC TGGGCACTGGCC (SEQ ID NO: 102)	CUUUGAAAAGGGUUACC CUG (SEQ ID NO: 171)
MAPT 6699	3UTR	GGACATGAAATCATCTTAGCTTAGCTTTCTGTC TGTGAATGTCTA (SEQ ID NO: 103)	UUAGCUUAGCUUUCUGU CUG (SEQ ID NO: 172)
MAPT 6750	3UTR	GTATTGTGTGTTTTAACAAATGATTTACACTGA CTGTTGCTGTAA (SEQ ID NO: 13)	ACAAAUGAUUUACACUG ACU (SEQ ID NO: 173)
MAPT 6784	3UTR	Not included	GAAUUUGGAAAUAAAGU UAU (SEQ ID NO: 174)

Table 10 - *continued* - MAPT anti-sense and sense sequences – additional embodiments

Sequence ID	**Antisense Sequence**	**Sense Sequence (20 nucleotide)**	**P3_Asymmetric_Target_mRNA_Expression (% relative to control)**	**P5_Asymmetric_Target_mRNA_Expression (% relative to control)**
MAPT_120	UGAGAUUCUUUCAGGCCAGC (SEQ ID NO: 233)	CCUGAAAGAAUCUCA (SEQ ID NO: 175)		98
MAPT_206	UCACAUCUUCCGCUGUUGGA (SEQ ID NO: 234)	CAGCGGAAGAUGUGA (SEQ ID NO: 176)		90
MAPT_221	UCACUAAGGGUGCUGUCACA (SEQ ID NO: 235)	CAGCACCCUUAGUGA (SEQ ID NO: 177)		87
MAPT_892	UUGAAACGUGAACUCCAGGG (SEQ ID NO: 236)	GAGUUCACGUUUCAA (SEQ ID NO: 178)		111

MAPT_963	UGAAAUGCAGCCCU UCCCAA (SEQ ID NO: 237)	AAGGGCUGCAUUUCA (SEQ ID NO: 179)		103
MAPT_1111	UCGAGCUUUGAGUU GAGGGA (SEQ ID NO: 238)	CAACUCAAAGCUCGA (SEQ ID NO: 180)		95.
MAPT_1178	UGGAACGUGUGGAU GUCUUG (SEQ ID NO: 239)	CAUCCACACGUUCCA (SEQ ID NO: 181)		104
MAPT_1820	UAAUUAUCUGCACC UUCCCG (SEQ ID NO: 240)	AGGUGCAGAUAAUUA (SEQ ID NO: 182)		98
MAPT_1971	UGGAUGUUGCCUAA UGAGCC (SEQ ID NO: 34)	AUUAGGCAACAUCCA (SEQ ID NO: 14)		51
MAPT_2051	UCCCAAUCUUCGAC UGGACU (SEQ ID NO: 36)	AGUCGAAGAUUGGGA (SEQ ID NO: 16)		61
MAPT_2253	UGCGAGUCUACCAU GUCGAU (SEQ ID NO: 241)	CAUGGUAGACUCGCA (SEQ ID NO: 183)		87
MAPT_2012	UCUCAGAUUUUACU UCCACC (SEQ ID NO: 35)	AAGUAAAAUCUGAGA (SEQ ID NO: 15)		26
MAPT_1911	UCUAUUUGCACACU GCCGCC (SEQ ID NO: 242)	CAGUGUGCAAAUAGA (SEQ ID NO: 184)		72
MAPT_2034	UCUCUGUCCUUGAA GUCAAG (SEQ ID NO: 39)	CUUCAAGGACAGAGA (SEQ ID NO: 19)		56
MAPT_1848	UGGACGUUGCUAAG AUCCAG (SEQ ID NO: 243)	UCUUAGCAACGUCCA (SEQ ID NO: 185)		74
MAPT_1914	UAGACUAUUUGCAC ACUGCC (SEQ ID NO: 244)	UGUGCAAAUAGUCUA (SEQ ID NO: 186)		96
MAPT_1832	UCAGCUUCUUAUUA AUUAUC (SEQ ID NO: 245)	UUAAUAAGAAGCUGA (SEQ ID NO: 187)		103
MAPT_1838	UAAGAUCCAGCUUC UUAUUA (SEQ ID NO: 246)	AGAAGCUGGAUCUUA (SEQ ID NO: 188)		120
MAPT_2005	UUUUACUUCCACCU GGCCAC (SEQ ID NO: 37)	CAGGUGGAAGUAAAA (SEQ ID NO: 17)		98
MAPT_1887	UGGACGUGUUUGAU AUUAUC (SEQ ID NO: 247)	UAUCAAACACGUCCA (SEQ ID NO: 189)		155

MAPT_2007	UAUUUUACUUCCACCUGGCC (SEQ ID NO: 38)	GGUGGAAGUAAAAUA (SEQ ID NO: 18)		35
MAPT_1833	UCCAGCUUCUUAUUAAUUAU (SEQ ID NO: 248)	UAAUAAGAAGCUGGA (SEQ ID NO: 190)		77
MAPT_2005	UUUUACUUCCACCUGGCCAC (SEQ ID NO: 37)	CAGGUGGAAGUAAAA (SEQ ID NO: 17)		42
MAPT_1955	UGCCACACUUGGAGGUCACC (SEQ ID NO: 249)	CCUCCAAGUGUGGCA (SEQ ID NO: 191)		79
MAPT_357	UUACGUCCCAGCGUGAUCUU (SEQ ID NO: 40)	AAGAUCACGCUGGGACGUAA (SEQ ID NO: 21)	30	
MAPT_522	UUCCGCUGUUGGAGUGCUCU (SEQ ID NO: 250)	AGAGCACUCCAACAGCGGAA (SEQ ID NO: 192)	69	
MAPT_626	UUGCCUGCUUCUUCAGCUGU (SEQ ID NO: 251)	ACAGCUGAAGAAGCAGGCAA (SEQ ID NO: 193)	85	
MAPT_896	UGGUGCAGGUCUCCUAGAAG (SEQ ID NO: 252)	CUUCUAGGAGACCUGCACCA (SEQ ID NO: 194)	81	
MAPT_1231	UGGGUGUGAUUUCCACGUGA (SEQ ID NO: 253)	UCACGUGGAAAUCACACCCA (SEQ ID NO: 195)	77	
MAPT_1385	UCAGCAGGCUGCUUUUCAGA (SEQ ID NO: 254)	UCUGAAAAGCAGCCUGCUGA (SEQ ID NO: 196)	82	
MAPT_1484	UUGGCUUUUUUGUCAUCGCU (SEQ ID NO: 255)	AGCGAUGACAAAAAAGCCAA (SEQ ID NO: 197)	74	
MAPT_1574	UUCAGAGGGUCUGAGCUACC (SEQ ID NO: 256)	GGUAGCUCAGACCCUCUGAA (SEQ ID NO: 198)	69	
MAPT_1670	UCCUUUGCUCCAGAACUGCC (SEQ ID NO: 257)	GGCAGUUCUGGAGCAAAGGA (SEQ ID NO: 199)	93	
MAPT_1835	UGUCUUCUCUGGACUUGCUU (SEQ ID NO: 258)	AAGCAAGUCCAGAGAAGACA (SEQ ID NO: 200)	ND	
MAPT_2115	UUGGUGCUUCAGGUUCUCAG (SEQ ID NO: 259)	CUGAGAACCUGAAGCACCAA (SEQ ID NO: 201)	69	
MAPT_2191	UCUUUGAGCCACACUUGGAC (SEQ ID NO: 260)	GUCCAAGUGUGGCUCAAAGA (SEQ ID NO: 202)	75	

MAPT_2257	UGCUCAGGUCAACUGGUUUG (SEQ ID NO: 41)	CAAACCAGUUGACCUGAGCA (SEQ ID NO: 23)	19	
MAPT_2314	UGCCACCUCCUGGUUUAUGA (SEQ ID NO: 261)	UCAUAAACCAGGAGGUGGCA (SEQ ID NO: 203)	48	
MAPT_2378	UGGGACCCAAUCUUCGACUG (SEQ ID NO: 42)	CAGUCGAAGAUUGGGUCCCA (SEQ ID NO: 25)	29	
MAPT_2417	UUUUUAUUUCCUCCGCCAGG (SEQ ID NO: 43)	CCUGGCGGAGGAAAUAAAAA (SEQ ID NO: 27)	31	
MAPT_2428	UGGUUUCAAUCUUUUUAUUU (SEQ ID NO:262)	AAAUAAAAAGAUUGAAACCA (SEQ ID NO: 204)	62	
MAPT_2443	UGAAGGUCAGCUUGUGGGUU (SEQ ID NO: 263)	AACCCACAAGCUGACCUUCA (SEQ ID NO: 205)	68	
MAPT_2666	UUCCACAAUUAUUGACCGCC (SEQ ID NO: 44)	GGCGGUCAAUAAUUGUGGAA (SEQ ID NO: 29)	39	
MAPT_2758	UCCAAUUAACCGAACUGCGA (SEQ ID NO: 264)	UCGCAGUUCGGUUAAUUGGA (SEQ ID NO: 206)	72	
MAPT_2819	UCCAUCACUGAUUUUGAAGU (SEQ ID NO: 265)	ACUUCAAAAUCAGUGAUGGA (SEQ ID NO: 207)	56	
MAPT_2871	UUUUUAUUACUAGCCCACCC (SEQ ID NO: 266)	GGGUGGGCUAGUAAUAAAAA (SEQ ID NO: 208)	81	
MAPT_2873	UUAUUUUAUUACUAGCCCAC (SEQ ID NO: 267)	GUGGGCUAGUAAUAAAAUAA (SEQ ID NO: 209)	50	
MAPT_3101	UCACGAACACACCAAGUUUC (SEQ ID NO: 268)	GAAACUUGGUGUGUUCGUGA (SEQ ID NO: 210)	60	
MAPT_3411	UCUUUUUACCCGCUGUCCCU (SEQ ID NO: 269)	AGGGACAGCGGGUAAAAAGA (SEQ ID NO: 211)	75	
MAPT_3607	UGGCCAAAAUCAUGGCAGCA (SEQ ID NO: 270)	UGCUGCCAUGAUUUUGGCCA (SEQ ID NO: 212)	82	
MAPT_3666	UAGAGGCACAAGUCCUUACA (SEQ ID NO: 271)	UGUAAGGACUUGUGCCUCUA (SEQ ID NO: 213)	58	
MAPT_3967	UCUCUUGUGCCUGGACUUUG (SEQ ID NO: 272)	CAAAGUCCAGGCACAAGAGA (SEQ ID NO: 214)	73	

MAPT_4055	UGGAGACAGGGAACCGAAUC (SEQ ID NO: 273)	GAUUCGGUUCCCUGUCUCCA (SEQ ID NO: 215)	61	
MAPT_4447	UUGUUCAGCUGCUCCAGCAG (SEQ ID NO: 274)	CUGCUGGAGCAGCUGAACAA (SEQ ID NO: 216)	57	
MAPT_4518	UGCAUAAACAGACAAAUCCA (SEQ ID NO: 45)	UGGAUUUGUCUGUUUAUGCA (SEQ ID NO: 31)	54	
MAPT_4710	UUGAGGAAAGCCUUUCAAAA (SEQ ID NO: 275)	UUUUGAAAGGCUUUCCUCAA (SEQ ID NO: 217)	74	
MAPT_4808	UCAUCAUCGCUUCAGUCCUA (SEQ ID NO: 276)	UAGGACUGAAGCGAUGAUGA (SEQ ID NO: 218)	53	
MAPT_5126	UGGCAAUUCAUCCCAAUCCC (SEQ ID NO: 277)	GGGAUUGGGAUGAAUUGCCA (SEQ ID NO: 219)	71	
MAPT_5208	UGCUUUGGGAACAGUGUCUC (SEQ ID NO: 278)	GAGACACUGUUCCCAAAGCA (SEQ ID NO: 220)	53	
MAPT_5350	UUACCCAAACCAGAAGUGGC (SEQ ID NO: 279)	GCCACUUCUGGUUUGGGUAA (SEQ ID NO: 221)	68	
MAPT_5441	UUCAGGUAAAGCUCUAGCUG (SEQ ID NO: 280)	CAGCUAGAGCUUUACCUGAA (SEQ ID NO: 222)	83	
MAPT_5640	UCAGGAAGAGGAACCGAGGU (SEQ ID NO: 281)	ACCUCGGUUCCUCUUCCUGA (SEQ ID NO: 223)	83	
MAPT_5745	UACCAUGAUCUUAGGCUGGC (SEQ ID NO: 282)	GCCAGCCUAAGAUCAUGGUA (SEQ ID NO: 224)	73	
MAPT_5934	UUAAAGUGAGUCAGCAGCUU (SEQ ID NO: 283)	AAGCUGCUGACUCACUUUAA (SEQ ID NO: 225)	55	
MAPT_5984	UCAAACAGGAUACAGUCUCA (SEQ ID NO: 284)	UGAGACUGUAUCCUGUUUGA (SEQ ID NO: 226)	49	
MAPT_6170	UUCAGUGGAAAAGAGAAACC (SEQ ID NO: 285)	GGUUUCUCUUUUCCACUGAA (SEQ ID NO: 227)	55	
MAPT_6290	UUGAUUGUGGGCUUAGGACC (SEQ ID NO: 286)	GGUCCUAAGCCCACAAUCAA (SEQ ID NO: 228)	71	
MAPT_6482	UAGAUGGGACACGCAGGUGA (SEQ ID NO: 287)	UCACCUGCGUGUCCCAUCUA (SEQ ID NO: 229)	74	

MAPT_6541	UAGGGUAACCCUUUUCAAAG (SEQ ID NO: 288)	CUUUGAAAAGGGUUACCCUA (SEQ ID NO: 230)	52	
MAPT_6699	UAGACAGAAAGCUAAGCUAA (SEQ ID NO: 289)	UUAGCUUAGCUUUCUGUCUA (SEQ ID NO: 231)	51	
MAPT_6750	UGUCAGUGUAAAUCAUUUGU (SEQ ID NO: 46)	ACAAAUGAUUUACACUGACA (SEQ ID NO: 33)	37	
MAPT_6784	UUAACUUUAUUUCCAAAUUC (SEQ ID NO: 290)	GAAUUUGGAAAUAAAGUUAA (SEQ ID NO: 232)	74	

Table 11 - MAPT targets identified by *in silico* screening

Sequence ID	**Location**	**45mer_Gene_Region**	**Target Sequence**
MAPT_21	5UTR	GAGCCCCGCCAGGAGTTCGAAGTGATGGAAGATCACGCTGGGACG (SEQ ID NO:)	UUCGAAGUGAUGGAAGAUCA (SEQ ID NO:)
MAPT_42	5UTR	GTGATGGAAGATCACGCTGGGACGTACGGGTTGGGGGACAGGAAA (SEQ ID NO:)	GCUGGGACGUACGGGUUGGG (SEQ ID NO:)
MAPT_44	5UTR	GATGGAAGATCACGCTGGGACGTACGGGTTGGGGGACAGGAAAGA (SEQ ID NO:)	UGGGACGUACGGGUUGGGGG (SEQ ID NO:)
MAPT_58	5UTR	CTGGGACGTACGGGTTGGGGGACAGGAAAGATCAGGGGGGCTACA (SEQ ID NO:)	UGGGGGACAGGAAAGAUCAG (SEQ ID NO:)
MAPT_60	5UTR	GGGACGTACGGGTTGGGGGACAGGAAAGATCAGGGGGGCTACACC (SEQ ID NO:)	GGGGACAGGAAAGAUCAGGG (SEQ ID NO:)
MAPT_75	5UTR	GGGGACAGGAAAGATCAGGGGGGCTACACCATGCACCAAGACCAA (SEQ ID NO:)	CAGGGGGGCUACACCAUGCA (SEQ ID NO:)
MAPT_84	5UTR	AAAGATCAGGGGGGCTACACCATGCACCAAGACCAAGAGGGTGAC (SEQ ID NO:)	UACACCAUGCACCAAGACCA (SEQ ID NO:)
MAPT_85	5UTR	AAGATCAGGGGGGCTACACCATGCACCAAGACCAAGAGGGTGACA (SEQ ID NO:)	ACACCAUGCACCAAGACCAA (SEQ ID NO:)
MAPT_105	5UTR	ATGCACCAAGACCAAGAGGGTGACACGGACGCTGGCCTGAAAGAA (SEQ ID NO:)	GAGGGUGACACGGACGCUGG (SEQ ID NO:)
MAPT_108	5UTR	CACCAAGACCAAGAGGGTGACACGGACGCTGGCCTGAAAGAATCT (SEQ ID NO:)	GGUGACACGGACGCUGGCCU (SEQ ID NO:)

MAPT_120	5UTR	GAGGGTGACACGGACGCTGGCCTGAAAGAATCTCCCCTGCAGACC (SEQ ID NO:)	GCUGGCCUGAAAGAAUCUCC (SEQ ID NO:)
MAPT_124	5UTR	GTGACACGGACGCTGGCCTGAAAGAATCTCCCCTGCAGACCCCCA (SEQ ID NO:)	GCCUGAAAGAAUCUCCCCUG (SEQ ID NO:)
MAPT_147	5UTR	GAATCTCCCCTGCAGACCCCCACTGAGGACGGATCTGAGGAACCG (SEQ ID NO:)	ACCCCCACUGAGGACGGAUC (SEQ ID NO:)
MAPT_175	5UTR	ACGGATCTGAGGAACCGGGCTCTGAAACCTCTGATGCTAAGAGCA (SEQ ID NO:)	CGGGCUCUGAAACCUCUGAU (SEQ ID NO:)
MAPT_176	5UTR	CGGATCTGAGGAACCGGGCTCTGAAACCTCTGATGCTAAGAGCAC (SEQ ID NO:)	GGGCUCUGAAACCUCUGAUG (SEQ ID NO:)
MAPT_177	5UTR	GGATCTGAGGAACCGGGCTCTGAAACCTCTGATGCTAAGAGCACT (SEQ ID NO:)	GGCUCUGAAACCUCUGAUGC (SEQ ID NO:)
MAPT_192	5UTR	GGCTCTGAAACCTCTGATGCTAAGAGCACTCCAACAGCGGAAGAT (SEQ ID NO:)	GAUGCUAAGAGCACUCCAAC (SEQ ID NO:)
MAPT_192	5UTR	GGCTCTGAAACCTCTGATGCTAAGAGCACTCCAACAGCGGAAGAT (SEQ ID NO:)	GAUGCUAAGAGCACUCCAAC (SEQ ID NO:)
MAPT_198	5UTR	GAAACCTCTGATGCTAAGAGCACTCCAACAGCGGAAGATGTGACA (SEQ ID NO:)	AAGAGCACUCCAACAGCGGA (SEQ ID NO:)
MAPT_206	5UTR	TGATGCTAAGAGCACTCCAACAGCGGAAGATGTGACAGCACCCTT (SEQ ID NO:)	UCCAACAGCGGAAGAUGUGA (SEQ ID NO:)
MAPT_214	5UTR	AGAGCACTCCAACAGCGGAAGATGTGACAGCACCCTTAGTGGATG (SEQ ID NO:)	CGGAAGAUGUGACAGCACCC (SEQ ID NO:)
MAPT_219	5UTR	ACTCCAACAGCGGAAGATGTGACAGCACCCTTAGTGGATGAGGGA (SEQ ID NO:)	GAUGUGACAGCACCCUUAGU (SEQ ID NO:)
MAPT_221	5UTR	TCCAACAGCGGAAGATGTGACAGCACCCTTAGTGGATGAGGGAGC (SEQ ID NO:)	UGUGACAGCACCCUUAGUGG (SEQ ID NO:)
MAPT_252	5UTR	GTGGATGAGGGAGCTCCCGGCAAGCAGGCTGCCGCGCAGCCCCAC (SEQ ID NO:)	CCCGGCAAGCAGGCUGCCGC (SEQ ID NO:)
MAPT_290	5UTR	GCCCCACACGGAGATCCCAGAAGGAACCACAGCTGAAGAAGCAGG (SEQ ID NO:)	CCCAGAAGGAACCACAGCUG (SEQ ID NO:)
MAPT_299	5UTR	GGAGATCCCAGAAGGAACCACAGCTGAAGAAGCAGGCATTGGAGA (SEQ ID NO:)	AACCACAGCUGAAGAAGCAG (SEQ ID NO:)

MAPT_315	5UTR_ORF	ACCACAGCTGAAGAAGCAGGCATTGGAGACACCCCCAGCCTGGAA (SEQ ID NO:)	GCAGGCAUUGGAGACACCCC (SEQ ID NO:)
MAPT_359	ORF	AGACGAAGCTGCTGGTCACGTGACCCAAGAGCCTGAAAGTGGTAA (SEQ ID NO:)	UCACGUGACCCAAGAGCCUG (SEQ ID NO:)
MAPT_370	ORF	CTGGTCACGTGACCCAAGAGCCTGAAAGTGGTAAGGTGGTCCAGG (SEQ ID NO:)	AAGAGCCUGAAAGUGGUAAG (SEQ ID NO:)
MAPT_376	ORF	ACGTGACCCAAGAGCCTGAAAGTGGTAAGGTGGTCCAGGAAGGCT (SEQ ID NO:)	CUGAAAGUGGUAAGGUGGUC (SEQ ID NO:)
MAPT_378	ORF	GTGACCCAAGAGCCTGAAAGTGGTAAGGTGGTCCAGGAAGGCTTC (SEQ ID NO:)	GAAAGUGGUAAGGUGGUCCA (SEQ ID NO:)
MAPT_390	ORF	CCTGAAAGTGGTAAGGTGGTCCAGGAAGGCTTCCTCCGAGAGCCA (SEQ ID NO:)	GUGGUCCAGGAAGGCUUCCU (SEQ ID NO:)
MAPT_391	ORF	CTGAAAGTGGTAAGGTGGTCCAGGAAGGCTTCCTCCGAGAGCCAG (SEQ ID NO:)	UGGUCCAGGAAGGCUUCCUC (SEQ ID NO:)
MAPT_406	ORF	TGGTCCAGGAAGGCTTCCTCCGAGAGCCAGGCCCCCCAGGTCTGA (SEQ ID NO:)	UCCUCCGAGAGCCAGGCCCC (SEQ ID NO:)
MAPT_450	ORF	AGCCACCAGCTCATGTCCGGCATGCCTGGGGCTCCCCTCCTGCCT (SEQ ID NO:)	UCCGGCAUGCCUGGGGCUCC (SEQ ID NO:)
MAPT_633	ORF	GGGGGCAAAGAGAGGCCGGGGAGCAAGGAGGAGGTGGATGAAGAC (SEQ ID NO:)	CCGGGGAGCAAGGAGGAGGU (SEQ ID NO:)
MAPT_636	ORF	GGCAAAGAGAGGCCGGGGAGCAAGGAGGAGGTGGATGAAGACCGC (SEQ ID NO:)	GGGAGCAAGGAGGAGGUGGA (SEQ ID NO:)
MAPT_663	ORF	GAGGTGGATGAAGACCGCGACGTCGATGAGTCCTCCCCCCAAGAC (SEQ ID NO:)	CGCGACGUCGAUGAGUCCUC (SEQ ID NO:)
MAPT_666	ORF	GTGGATGAAGACCGCGACGTCGATGAGTCCTCCCCCCAAGACTCC (SEQ ID NO:)	GACGUCGAUGAGUCCUCCCC (SEQ ID NO:)
MAPT_759	ORF	GCCGCCAGAGAAGCCACCAGCATCCCAGGCTTCCCAGCGGAGGGT (SEQ ID NO:)	ACCAGCAUCCCAGGCUUCCC (SEQ ID NO:)
MAPT_786	ORF	GGCTTCCCAGCGGAGGGTGCCATCCCCCTCCCTGTGGATTTCCTC (SEQ ID NO:)	GGUGCCAUCCCCCUCCCUGU (SEQ ID NO:)
MAPT_798	ORF	GAGGGTGCCATCCCCCTCCCTGTGGATTTCCTCTCCAAAGTTTCC (SEQ ID NO:)	CUCCCUGUGGAUUUCCUCUC (SEQ ID NO:)

MAPT_810	ORF	CCCCTCCCTGTGGATTTCCTCTCCAAAGTTTCCACAGAGATCCCA (SEQ ID NO:)	UUCCUCUCCAAAGUUUCCAC (SEQ ID NO:)
MAPT_872	ORF	GCCCAGTGTAGGGCGGGCCAAAGGGCAGGATGCCCCCCTGGAGTT (SEQ ID NO:)	GGCCAAAGGGCAGGAUGCCC (SEQ ID NO:)
MAPT_877	ORF	GTGTAGGGCGGGCCAAAGGGCAGGATGCCCCCCTGGAGTTCACGT (SEQ ID NO:)	AAGGGCAGGAUGCCCCCCUG (SEQ ID NO:)
MAPT_890	ORF	CAAAGGGCAGGATGCCCCCCTGGAGTTCACGTTTCACGTGGAAAT (SEQ ID NO:)	CCCCCUGGAGUUCACGUUUC (SEQ ID NO:)
MAPT_892	ORF	AAGGGCAGGATGCCCCCCTGGAGTTCACGTTTCACGTGGAAATCA (SEQ ID NO:)	CCCUGGAGUUCACGUUUCAC (SEQ ID NO:)
MAPT_912	ORF	GAGTTCACGTTTCACGTGGAAATCACACCCAACGTGCAGAAGGAG (SEQ ID NO:)	GUGGAAAUCACACCCAACGU (SEQ ID NO:)
MAPT_914	ORF	GTTCACGTTTCACGTGGAAATCACACCCAACGTGCAGAAGGAGCA (SEQ ID NO:)	GGAAAUCACACCCAACGUGC (SEQ ID NO:)
MAPT_955	ORF	AGCAGGCGCACTCGGAGGAGCATTTGGGAAGGGCTGCATTTCCAG (SEQ ID NO:)	AGGAGCAUUUGGGAAGGGCU (SEQ ID NO:)
MAPT_963	ORF	CACTCGGAGGAGCATTTGGGAAGGGCTGCATTTCCAGGGGCCCCT (SEQ ID NO:)	UUGGGAAGGGCUGCAUUUCC (SEQ ID NO:)
MAPT_1006	ORF	CTGGAGAGGGGCCAGAGGCCCGGGGCCCCTCTTTGGGAGAGGACA (SEQ ID NO:)	AGGCCCGGGGCCCCUCUUUG (SEQ ID NO:)
MAPT_1029	ORF	GGCCCCTCTTTGGGAGAGGACACAAAAGAGGCTGACCTTCCAGAG (SEQ ID NO:)	GAGGACACAAAAGAGGCUGA (SEQ ID NO:)
MAPT_1044	ORF	GAGGACACAAAAGAGGCTGACCTTCCAGAGCCCTCTGAAAAGCAG (SEQ ID NO:)	GCUGACCUUCCAGAGCCCUC (SEQ ID NO:)
MAPT_1095	ORF	GCTGCTCCGCGGGGGAAGCCCGTCAGCCGGGTCCCTCAACTCAAA (SEQ ID NO:)	AAGCCCGUCAGCCGGGUCCC (SEQ ID NO:)
MAPT_1111	ORF	AGCCCGTCAGCCGGGTCCCTCAACTCAAAGCTCGCATGGTCAGTA (SEQ ID NO:)	UCCCUCAACUCAAAGCUCGC (SEQ ID NO:)
MAPT_1114	ORF	CCGTCAGCCGGGTCCCTCAACTCAAAGCTCGCATGGTCAGTAAAA (SEQ ID NO:)	CUCAACUCAAAGCUCGCAUG (SEQ ID NO:)
MAPT_1137	ORF	AAAGCTCGCATGGTCAGTAAAAGCAAAGACGGGACTGGAAGCGAT (SEQ ID NO:)	AGUAAAAGCAAAGACGGGAC (SEQ ID NO:)

MAPT_1146	ORF	ATGGTCAGTAAAAGCAAAGACGGGACTGGAAGCGATGACAAAAAA (SEQ ID NO:)	AAAGACGGGACUGGAAGCGA (SEQ ID NO:)
MAPT_1150	ORF	TCAGTAAAAGCAAAGACGGGACTGGAAGCGATGACAAAAAAGCCA (SEQ ID NO:)	ACGGGACUGGAAGCGAUGAC (SEQ ID NO:)
MAPT_1151	ORF	CAGTAAAAGCAAAGACGGGACTGGAAGCGATGACAAAAAAGCCAA (SEQ ID NO:)	CGGGACUGGAAGCGAUGACA (SEQ ID NO:)
MAPT_1155	ORF	AAAAGCAAAGACGGGACTGGAAGCGATGACAAAAAAGCCAAGACA (SEQ ID NO:)	ACUGGAAGCGAUGACAAAAA (SEQ ID NO:)
MAPT_1159	ORF	GCAAAGACGGGACTGGAAGCGATGACAAAAAAGCCAAGACATCCA (SEQ ID NO:)	GAAGCGAUGACAAAAAAGCC (SEQ ID NO:)
MAPT_1161	ORF	AAAGACGGGACTGGAAGCGATGACAAAAAAGCCAAGACATCCACA (SEQ ID NO:)	AGCGAUGACAAAAAAGCCAA (SEQ ID NO:)
MAPT_1176	ORF	AGCGATGACAAAAAAGCCAAGACATCCACACGTTCCTCTGCTAAA (SEQ ID NO:)	GCCAAGACAUCCACACGUUC (SEQ ID NO:)
MAPT_1177	ORF	GCGATGACAAAAAAGCCAAGACATCCACACGTTCCTCTGCTAAAA (SEQ ID NO:)	CCAAGACAUCCACACGUUCC (SEQ ID NO:)
MAPT_1178	ORF	CGATGACAAAAAAGCCAAGACATCCACACGTTCCTCTGCTAAAAC (SEQ ID NO:)	CAAGACAUCCACACGUUCCU (SEQ ID NO:)
MAPT_1179	ORF	GATGACAAAAAAGCCAAGACATCCACACGTTCCTCTGCTAAAACC (SEQ ID NO:)	AAGACAUCCACACGUUCCUC (SEQ ID NO:)
MAPT_1181	ORF	TGACAAAAAAGCCAAGACATCCACACGTTCCTCTGCTAAAACCTT (SEQ ID NO:)	GACAUCCACACGUUCCUCUG (SEQ ID NO:)
MAPT_1186	ORF	AAAAAGCCAAGACATCCACACGTTCCTCTGCTAAAACCTTGAAAA (SEQ ID NO:)	CCACACGUUCCUCUGCUAAA (SEQ ID NO:)
MAPT_1193	ORF	CAAGACATCCACACGTTCCTCTGCTAAAACCTTGAAAAATAGGCC (SEQ ID NO:)	UUCCUCUGCUAAAACCUUGA (SEQ ID NO:)
MAPT_1194	ORF	AAGACATCCACACGTTCCTCTGCTAAAACCTTGAAAAATAGGCCT (SEQ ID NO:)	UCCUCUGCUAAAACCUUGAA (SEQ ID NO:)
MAPT_1200	ORF	TCCACACGTTCCTCTGCTAAAACCTTGAAAAATAGGCCTTGCCTT (SEQ ID NO:)	GCUAAAACCUUGAAAAAUAG (SEQ ID NO:)
MAPT_1207	ORF	GTTCCTCTGCTAAAACCTTGAAAAATAGGCCTTGCCTTAGCCCCA (SEQ ID NO:)	CCUUGAAAAAUAGGCCUUGC (SEQ ID NO:)

MAPT_1208	ORF	TTCCTCTGCTAAAACCTTGAAAAATAGGCCTTGCCTTAGCCCCAA (SEQ ID NO:)	CUUGAAAAAUAGGCCUUGCC (SEQ ID NO:)
MAPT_1209	ORF	TCCTCTGCTAAAACCTTGAAAAATAGGCCTTGCCTTAGCCCCAAA (SEQ ID NO:)	UUGAAAAAUAGGCCUUGCCU (SEQ ID NO:)
MAPT_1248	ORF	CCCAAACACCCCACTCCTGGTAGCTCAGACCCTCTGATCCAACCC (SEQ ID NO:)	CCUGGUAGCUCAGACCCUCU (SEQ ID NO:)
MAPT_1291	ORF	CCTCCAGCCCTGCTGTGTGCCCAGAGCCACCTTCCTCTCCTAAAT (SEQ ID NO:)	UGUGCCCAGAGCCACCUUCC (SEQ ID NO:)
MAPT_1292	ORF	CTCCAGCCCTGCTGTGTGCCCAGAGCCACCTTCCTCTCCTAAATA (SEQ ID NO:)	GUGCCCAGAGCCACCUUCCU (SEQ ID NO:)
MAPT_1298	ORF	CCCTGCTGTGTGCCCAGAGCCACCTTCCTCTCCTAAATACGTCTC (SEQ ID NO:)	AGAGCCACCUUCCUCUCCUA (SEQ ID NO:)
MAPT_1307	ORF	GTGCCCAGAGCCACCTTCCTCTCCTAAATACGTCTCTTCTGTCAC (SEQ ID NO:)	UUCCUCUCCUAAAUACGUCU (SEQ ID NO:)
MAPT_1308	ORF	TGCCCAGAGCCACCTTCCTCTCCTAAATACGTCTCTTCTGTCACT (SEQ ID NO:)	UCCUCUCCUAAAUACGUCUC (SEQ ID NO:)
MAPT_1309	ORF	GCCCAGAGCCACCTTCCTCTCCTAAATACGTCTCTTCTGTCACTT (SEQ ID NO:)	CCUCUCCUAAAUACGUCUCU (SEQ ID NO:)
MAPT_1310	ORF	CCCAGAGCCACCTTCCTCTCCTAAATACGTCTCTTCTGTCACTTC (SEQ ID NO:)	CUCUCCUAAAUACGUCUCUU (SEQ ID NO:)
MAPT_1313	ORF	AGAGCCACCTTCCTCTCCTAAATACGTCTCTTCTGTCACTTCCCG (SEQ ID NO:)	UCCUAAAUACGUCUCUUCUG (SEQ ID NO:)
MAPT_1329	ORF	CCTAAATACGTCTCTTCTGTCACTTCCCGAACTGGCAGTTCTGGA (SEQ ID NO:)	UCUGUCACUUCCCGAACUGG (SEQ ID NO:)
MAPT_1339	ORF	TCTCTTCTGTCACTTCCCGAACTGGCAGTTCTGGAGCAAAGGAGA (SEQ ID NO:)	CCCGAACUGGCAGUUCUGGA (SEQ ID NO:)
MAPT_1344	ORF	TCTGTCACTTCCCGAACTGGCAGTTCTGGAGCAAAGGAGATGAAA (SEQ ID NO:)	ACUGGCAGUUCUGGAGCAAA (SEQ ID NO:)
MAPT_1364	ORF	CAGTTCTGGAGCAAAGGAGATGAAACTCAAGGGGGCTGATGGTAA (SEQ ID NO:)	GGAGAUGAAACUCAAGGGGG (SEQ ID NO:)
MAPT_1367	ORF	TTCTGGAGCAAAGGAGATGAAACTCAAGGGGGCTGATGGTAAAAC (SEQ ID NO:)	GAUGAAACUCAAGGGGGCUG (SEQ ID NO:)

MAPT_1444	ORF	CAGGCCAGAAGGGCCAGGCCAACGCCACCAGGATTCCAGCAAAAA (SEQ ID NO:)	AGGCCAACGCCACCAGGAUU (SEQ ID NO:)
MAPT_1460	ORF	GGCCAACGCCACCAGGATTCCAGCAAAAACCCCGCCCCGCTCCAAA (SEQ ID NO:)	GAUUCCAGCAAAAACCCCGC (SEQ ID NO:)
MAPT_1464	ORF	AACGCCACCAGGATTCCAGCAAAAACCCCGCCCGCTCCAAAGACA (SEQ ID NO:)	CCAGCAAAAACCCCGCCCGC (SEQ ID NO:)
MAPT_1482	ORF	GCAAAAACCCCGCCCGCTCCAAAGACACCACCCAGCTCTGCGACT (SEQ ID NO:)	GCUCCAAAGACACCACCCAG (SEQ ID NO:)
MAPT_1487	ORF	AACCCCGCCCGCTCCAAAGACACCACCCAGCTCTGCGACTAAGCA (SEQ ID NO:)	AAAGACACCACCCAGCUCUG (SEQ ID NO:)
MAPT_1502	ORF	AAAGACACCACCCAGCTCTGCGACTAAGCAAGTCCAGAGAAGACC (SEQ ID NO:)	CUCUGCGACUAAGCAAGUCC (SEQ ID NO:)
MAPT_1503	ORF	AAGACACCACCCAGCTCTGCGACTAAGCAAGTCCAGAGAAGACCA (SEQ ID NO:)	UCUGCGACUAAGCAAGUCCA (SEQ ID NO:)
MAPT_1519	ORF	CTGCGACTAAGCAAGTCCAGAGAAGACCACCCCCTGCAGGGCCCA (SEQ ID NO:)	UCCAGAGAAGACCACCCCCU (SEQ ID NO:)
MAPT_1535	ORF	CCAGAGAAGACCACCCCCTGCAGGGCCCAGATCTGAGAGAGGTGA (SEQ ID NO:)	CCCUGCAGGGCCCAGAUCUG (SEQ ID NO:)
MAPT_1565	ORF	ATCTGAGAGAGGTGAACCTCCAAAATCAGGGGATCGCAGCGGCTA (SEQ ID NO:)	ACCUCCAAAAUCAGGGGAUC (SEQ ID NO:)
MAPT_1664	ORF	TCCAACCCCACCCACCCGGGAGCCCAAGAAGGTGGCAGTGGTCCG (SEQ ID NO:)	CCGGGAGCCCAAGAAGGUGG (SEQ ID NO:)
MAPT_1700	ORF	AGTGGTCCGTACTCCACCCAAGTCGCCGTCTTCCGCCAAGAGCCG (SEQ ID NO:)	ACCCAAGUCGCCGUCUUCCG (SEQ ID NO:)
MAPT_1730	ORF	TTCCGCCAAGAGCCGCCTGCAGACAGCCCCCGTGCCCATGCCAGA (SEQ ID NO:)	CCUGCAGACAGCCCCCGUGC (SEQ ID NO:)
MAPT_1745	ORF	CCTGCAGACAGCCCCCGTGCCCATGCCAGACCTGAAGAATGTCAA (SEQ ID NO:)	CGUGCCCAUGCCAGACCUGA (SEQ ID NO:)
MAPT_1746	ORF	CTGCAGACAGCCCCCGTGCCCATGCCAGACCTGAAGAATGTCAAG (SEQ ID NO:)	GUGCCCAUGCCAGACCUGAA (SEQ ID NO:)
MAPT_1751	ORF	GACAGCCCCCGTGCCCATGCCAGACCTGAAGAATGTCAAGTCCAA (SEQ ID NO:)	CAUGCCAGACCUGAAGAAUG (SEQ ID NO:)

MAPT_1754	ORF	AGCCCCCGTGCCCATGCCAGACCTGAAGAATGTCAAGTCCAAGAT (SEQ ID NO:)	GCCAGACCUGAAGAAUGUCA (SEQ ID NO:)
MAPT_1760	ORF	CGTGCCCATGCCAGACCTGAAGAATGTCAAGTCCAAGATCGGCTC (SEQ ID NO:)	CCUGAAGAAUGUCAAGUCCA (SEQ ID NO:)
MAPT_1772	ORF	AGACCTGAAGAATGTCAAGTCCAAGATCGGCTCCACTGAGAACCT (SEQ ID NO:)	CAAGUCCAAGAUCGGCUCCA (SEQ ID NO:)
MAPT_1811	ORF	GAACCTGAAGCACCAGCCGGGAGGCGGGAAGGTGCAGATAATTAA (SEQ ID NO:)	GCCGGGAGGCGGGAAGGUGC (SEQ ID NO:)
MAPT_1813	ORF	ACCTGAAGCACCAGCCGGGAGGCGGGAAGGTGCAGATAATTAATA (SEQ ID NO:)	CGGGAGGCGGGAAGGUGCAG (SEQ ID NO:)
MAPT_1818	ORF	AAGCACCAGCCGGGAGGCGGGAAGGTGCAGATAATTAATAAGAAG (SEQ ID NO:)	GGCGGGAAGGUGCAGAUAAU (SEQ ID NO:)
MAPT_1819	ORF	AGCACCAGCCGGGAGGCGGGAAGGTGCAGATAATTAATAAGAAGC (SEQ ID NO:)	GCGGGAAGGUGCAGAUAAUU (SEQ ID NO:)
MAPT_1820	ORF	GCACCAGCCGGGAGGCGGGAAGGTGCAGATAATTAATAAGAAGCT (SEQ ID NO:)	CGGGAAGGUGCAGAUAAUUA (SEQ ID NO:)
MAPT_1825	ORF	AGCCGGGAGGCGGGAAGGTGCAGATAATTAATAAGAAGCTGGATC (SEQ ID NO:)	AGGUGCAGAUAAUUAAUAAG (SEQ ID NO:)
MAPT_1828	ORF	CGGGAGGCGGGAAGGTGCAGATAATTAATAAGAAGCTGGATCTTA (SEQ ID NO:)	UGCAGAUAAUUAAUAAGAAG (SEQ ID NO:)
MAPT_1829	ORF	GGGAGGCGGGAAGGTGCAGATAATTAATAAGAAGCTGGATCTTAG (SEQ ID NO:)	GCAGAUAAUUAAUAAGAAGC (SEQ ID NO:)
MAPT_1832	ORF	AGGCGGGAAGGTGCAGATAATTAATAAGAAGCTGGATCTTAGCAA (SEQ ID NO:)	GAUAAUUAAUAAGAAGCUGG (SEQ ID NO:)
MAPT_1833	ORF	GGCGGGAAGGTGCAGATAATTAATAAGAAGCTGGATCTTAGCAAC (SEQ ID NO:)	AUAAUUAAUAAGAAGCUGGA (SEQ ID NO:)
MAPT_1838	ORF	GAAGGTGCAGATAATTAATAAGAAGCTGGATCTTAGCAACGTCCA (SEQ ID NO:)	UAAUAAGAAGCUGGAUCUUA (SEQ ID NO:)
MAPT_1848	ORF	ATAATTAATAAGAAGCTGGATCTTAGCAACGTCCAGTCCAAGTGT (SEQ ID NO:)	CUGGAUCUUAGCAACGUCCA (SEQ ID NO:)
MAPT_1854	ORF	AATAAGAAGCTGGATCTTAGCAACGTCCAGTCCAAGTGTGGCTCA (SEQ ID NO:)	CUUAGCAACGUCCAGUCCAA (SEQ ID NO:)

MAPT_1861	ORF	AGCTGGATCTTAGCAACGTCCAGTCCAAGTGTGGCTCAAAGGATA (SEQ ID NO:)	ACGUCCAGUCCAAGUGUGGC (SEQ ID NO:)
MAPT_1866	ORF	GATCTTAGCAACGTCCAGTCCAAGTGTGGCTCAAAGGATAATATC (SEQ ID NO:)	CAGUCCAAGUGUGGCUCAAA (SEQ ID NO:)
MAPT_1875	ORF	AACGTCCAGTCCAAGTGTGGCTCAAAGGATAATATCAAACACGTC (SEQ ID NO:)	UGUGGCUCAAAGGAUAAUAU (SEQ ID NO:)
MAPT_1887	ORF	AAGTGTGGCTCAAAGGATAATATCAAACACGTCCCGGGAGGCGGC (SEQ ID NO:)	GAUAAUAUCAAACACGUCCC (SEQ ID NO:)
MAPT_1903	ORF	ATAATATCAAACACGTCCCGGGAGGCGGCAGTGTGCAAATAGTCT (SEQ ID NO:)	UCCCGGGAGGCGGCAGUGUG (SEQ ID NO:)
MAPT_1904	ORF	TAATATCAAACACGTCCCGGGAGGCGGCAGTGTGCAAATAGTCTA (SEQ ID NO:)	CCCGGGAGGCGGCAGUGUGC (SEQ ID NO:)
MAPT_1906	ORF	ATATCAAACACGTCCCGGGAGGCGGCAGTGTGCAAATAGTCTACA (SEQ ID NO:)	CGGGAGGCGGCAGUGUGCAA (SEQ ID NO:)
MAPT_1911	ORF	AAACACGTCCCGGGAGGCGGCAGTGTGCAAATAGTCTACAAACCA (SEQ ID NO:)	GGCGGCAGUGUGCAAAUAGU (SEQ ID NO:)
MAPT_1914	ORF	CACGTCCCGGGAGGCGGCAGTGTGCAAATAGTCTACAAACCAGTT (SEQ ID NO:)	GGCAGUGUGCAAAUAGUCUA (SEQ ID NO:)
MAPT_1915	ORF	ACGTCCCGGGAGGCGGCAGTGTGCAAATAGTCTACAAACCAGTTG (SEQ ID NO:)	GCAGUGUGCAAAUAGUCUAC (SEQ ID NO:)
MAPT_1919	ORF	CCCGGGAGGCGGCAGTGTGCAAATAGTCTACAAACCAGTTGACCT (SEQ ID NO:)	UGUGCAAAUAGUCUACAAAC (SEQ ID NO:)
MAPT_1926	ORF	GGCGGCAGTGTGCAAATAGTCTACAAACCAGTTGACCTGAGCAAG (SEQ ID NO:)	AUAGUCUACAAACCAGUUGA (SEQ ID NO:)
MAPT_1933	ORF	GTGTGCAAATAGTCTACAAACCAGTTGACCTGAGCAAGGTGACCT (SEQ ID NO:)	ACAAACCAGUUGACCUGAGC (SEQ ID NO:)
MAPT_1942	ORF	TAGTCTACAAACCAGTTGACCTGAGCAAGGTGACCTCCAAGTGTG (SEQ ID NO:)	UUGACCUGAGCAAGGUGACC (SEQ ID NO:)
MAPT_1947	ORF	TACAAACCAGTTGACCTGAGCAAGGTGACCTCCAAGTGTGGCTCA (SEQ ID NO:)	CUGAGCAAGGUGACCUCCAA (SEQ ID NO:)
MAPT_1955	ORF	AGTTGACCTGAGCAAGGTGACCTCCAAGTGTGGCTCATTAGGCAA (SEQ ID NO:)	GGUGACCUCCAAGUGUGGCU (SEQ ID NO:)

MAPT_1962	ORF	CTGAGCAAGGTGACCTCCAAGTGTGGCTCATTAGGCAACATCCAT (SEQ ID NO:)	UCCAAGUGUGGCUCAUUAGG (SEQ ID NO:)
MAPT_1968	ORF	AAGGTGACCTCCAAGTGTGGCTCATTAGGCAACATCCATCATAAA (SEQ ID NO:)	UGUGGCUCAUUAGGCAACAU (SEQ ID NO:)
MAPT_1970	ORF	GGTGACCTCCAAGTGTGGCTCATTAGGCAACATCCATCATAAACC (SEQ ID NO:)	UGGCUCAUUAGGCAACAUCC (SEQ ID NO:)
MAPT_1971	ORF	GTGACCTCCAAGTGTGGCTCATTAGGCAACATCCATCATAAACCA (SEQ ID NO:)	GGCUCAUUAGGCAACAUCCA (SEQ ID NO:)
MAPT_1973	ORF	GACCTCCAAGTGTGGCTCATTAGGCAACATCCATCATAAACCAGG (SEQ ID NO:)	CUCAUUAGGCAACAUCCAUC (SEQ ID NO:)
MAPT_1977	ORF	TCCAAGTGTGGCTCATTAGGCAACATCCATCATAAACCAGGAGGT (SEQ ID NO:)	UUAGGCAACAUCCAUCAUAA (SEQ ID NO:)
MAPT_1978	ORF	CCAAGTGTGGCTCATTAGGCAACATCCATCATAAACCAGGAGGTG (SEQ ID NO:)	UAGGCAACAUCCAUCAUAAA (SEQ ID NO:)
MAPT_1989	ORF	TCATTAGGCAACATCCATCATAAACCAGGAGGTGGCCAGGTGGAA (SEQ ID NO:)	CAUCAUAAACCAGGAGGUGG (SEQ ID NO:)
MAPT_2004	ORF	CATCATAAACCAGGAGGTGGCCAGGTGGAAGTAAAATCTGAGAAG (SEQ ID NO:)	GGUGGCCAGGUGGAAGUAAA (SEQ ID NO:)
MAPT_2005	ORF	ATCATAAACCAGGAGGTGGCCAGGTGGAAGTAAAATCTGAGAAGC (SEQ ID NO:)	GUGGCCAGGUGGAAGUAAAA (SEQ ID NO:)
MAPT_2007	ORF	CATAAACCAGGAGGTGGCCAGGTGGAAGTAAAATCTGAGAAGCTT (SEQ ID NO:)	GGCCAGGUGGAAGUAAAAUC (SEQ ID NO:)
MAPT_2009	ORF	TAAACCAGGAGGTGGCCAGGTGGAAGTAAAATCTGAGAAGCTTGA (SEQ ID NO:)	CCAGGUGGAAGUAAAAUCUG (SEQ ID NO:)
MAPT_2011	ORF	AACCAGGAGGTGGCCAGGTGGAAGTAAAATCTGAGAAGCTTGACT (SEQ ID NO:)	AGGUGGAAGUAAAAUCUGAG (SEQ ID NO:)
MAPT_2012	ORF	ACCAGGAGGTGGCCAGGTGGAAGTAAAATCTGAGAAGCTTGACTT (SEQ ID NO:)	GGUGGAAGUAAAAUCUGAGA (SEQ ID NO:)
MAPT_2018	ORF	AGGTGGCCAGGTGGAAGTAAAATCTGAGAAGCTTGACTTCAAGGA (SEQ ID NO:)	AGUAAAAUCUGAGAAGCUUG (SEQ ID NO:)
MAPT_2020	ORF	GTGGCCAGGTGGAAGTAAAATCTGAGAAGCTTGACTTCAAGGACA (SEQ ID NO:)	UAAAAUCUGAGAAGCUUGAC (SEQ ID NO:)

MAPT_2027	ORF	GGTGGAAGTAAAATCTGAGAAGCTTGACTTCAAGGACAGAGTCCA (SEQ ID NO:)	UGAGAAGCUUGACUUCAAGG (SEQ ID NO:)
MAPT_2034	ORF	GTAAAATCTGAGAAGCTTGACTTCAAGGACAGAGTCCAGTCGAAG (SEQ ID NO:)	CUUGACUUCAAGGACAGAGU (SEQ ID NO:)
MAPT_2037	ORF	AAATCTGAGAAGCTTGACTTCAAGGACAGAGTCCAGTCGAAGATT (SEQ ID NO:)	GACUUCAAGGACAGAGUCCA (SEQ ID NO:)
MAPT_2038	ORF	AATCTGAGAAGCTTGACTTCAAGGACAGAGTCCAGTCGAAGATTG (SEQ ID NO:)	ACUUCAAGGACAGAGUCCAG (SEQ ID NO:)
MAPT_2050	ORF	TTGACTTCAAGGACAGAGTCCAGTCGAAGATTGGGTCCCTGGACA (SEQ ID NO:)	GAGUCCAGUCGAAGAUUGGG (SEQ ID NO:)
MAPT_2051	ORF	TGACTTCAAGGACAGAGTCCAGTCGAAGATTGGGTCCCTGGACAA (SEQ ID NO:)	AGUCCAGUCGAAGAUUGGGU (SEQ ID NO:)
MAPT_2053	ORF	ACTTCAAGGACAGAGTCCAGTCGAAGATTGGGTCCCTGGACAATA (SEQ ID NO:)	UCCAGUCGAAGAUUGGGUCC (SEQ ID NO:)
MAPT_2058	ORF	AAGGACAGAGTCCAGTCGAAGATTGGGTCCCTGGACAATATCACC (SEQ ID NO:)	UCGAAGAUUGGGUCCCUGGA (SEQ ID NO:)
MAPT_2067	ORF	GTCCAGTCGAAGATTGGGTCCCTGGACAATATCACCCACGTCCCT (SEQ ID NO:)	GGGUCCCUGGACAAUAUCAC (SEQ ID NO:)
MAPT_2068	ORF	TCCAGTCGAAGATTGGGTCCCTGGACAATATCACCCACGTCCCTG (SEQ ID NO:)	GGUCCCUGGACAAUAUCACC (SEQ ID NO:)
MAPT_2076	ORF	AAGATTGGGTCCCTGGACAATATCACCCACGTCCCTGGCGGAGGA (SEQ ID NO:)	GACAAUAUCACCCACGUCCC (SEQ ID NO:)
MAPT_2083	ORF	GGTCCCTGGACAATATCACCCACGTCCCTGGCGGAGGAAATAAAA (SEQ ID NO:)	UCACCCACGUCCCUGGCGGA (SEQ ID NO:)
MAPT_2096	ORF	TATCACCCACGTCCCTGGCGGAGGAAATAAAAAGATTGAAACCCA (SEQ ID NO:)	UGGCGGAGGAAAUAAAAAGA (SEQ ID NO:)
MAPT_2098	ORF	TCACCCACGTCCCTGGCGGAGGAAATAAAAAGATTGAAACCCACA (SEQ ID NO:)	GCGGAGGAAAUAAAAAGAUU (SEQ ID NO:)
MAPT_2099	ORF	CACCCACGTCCCTGGCGGAGGAAATAAAAAGATTGAAACCCACAA (SEQ ID NO:)	CGGAGGAAAUAAAAAGAUUG (SEQ ID NO:)
MAPT_2106	ORF	GTCCCTGGCGGAGGAAATAAAAAGATTGAAACCCACAAGCTGACC (SEQ ID NO:)	AAUAAAAAGAUUGAAACCCA (SEQ ID NO:)

MAPT_2122	ORF	ATAAAAAGATTGAAACCCACAAGCTGACCTTCCGCGAGAACGCCA (SEQ ID NO:)	CCCACAAGCUGACCUUCCGC (SEQ ID NO:)
MAPT_2151	ORF	TTCCGCGAGAACGCCAAAGCCAAGACAGACCACGGGGCGGAGATC (SEQ ID NO:)	AAAGCCAAGACAGACCACGG (SEQ ID NO:)
MAPT_2175	ORF	ACAGACCACGGGGCGGAGATCGTGTACAAGTCGCCAGTGGTGTCT (SEQ ID NO:)	GAGAUCGUGUACAAGUCGCC (SEQ ID NO:)
MAPT_2182	ORF	ACGGGGCGGAGATCGTGTACAAGTCGCCAGTGGTGTCTGGGGACA (SEQ ID NO:)	UGUACAAGUCGCCAGUGGUG (SEQ ID NO:)
MAPT_2189	ORF	GGAGATCGTGTACAAGTCGCCAGTGGTGTCTGGGGACACGTCTCC (SEQ ID NO:)	GUCGCCAGUGGUGUCUGGGG (SEQ ID NO:)
MAPT_2198	ORF	GTACAAGTCGCCAGTGGTGTCTGGGGACACGTCTCCACGGCATCT (SEQ ID NO:)	GGUGUCUGGGGACACGUCUC (SEQ ID NO:)
MAPT_2205	ORF	TCGCCAGTGGTGTCTGGGGACACGTCTCCACGGCATCTCAGCAAT (SEQ ID NO:)	GGGGACACGUCUCCACGGCA (SEQ ID NO:)
MAPT_2207	ORF	GCCAGTGGTGTCTGGGGACACGTCTCCACGGCATCTCAGCAATGT (SEQ ID NO:)	GGACACGUCUCCACGGCAUC (SEQ ID NO:)
MAPT_2239	ORF	ATCTCAGCAATGTCTCCTCCACCGGCAGCATCGACATGGTAGACT (SEQ ID NO:)	CCUCCACCGGCAGCAUCGAC (SEQ ID NO:)
MAPT_2244	ORF	AGCAATGTCTCCTCCACCGGCAGCATCGACATGGTAGACTCGCCC (SEQ ID NO:)	ACCGGCAGCAUCGACAUGGU (SEQ ID NO:)
MAPT_2253	ORF	TCCTCCACCGGCAGCATCGACATGGTAGACTCGCCCCAGCTCGCC (SEQ ID NO:)	AUCGACAUGGUAGACUCGCC (SEQ ID NO:)
MAPT_2282	ORF	CTCGCCCCAGCTCGCCACGCTAGCTGACGAGGTGTCTGCCTCCCT (SEQ ID NO:)	CACGCUAGCUGACGAGGUGU (SEQ ID NO:)

[0776] A second *in vitro* screen was performed to identify additional siRNAs effective in silencing *MAPT* mRNA. The screen was performed as described above. The results of the screen are depicted in **FIG. 6**. The tested siRNAs were of the P3 Asymmetric design, as depicted in **FIG. 6**. The results of the second screen identified several additional siRNAs capable of effectively silencing *MAPT* mRNA, including several that reduce *MAPT* mRNA levels to less than 40%. The MAPT gene and mRNA target sequences, and panel of siRNAs used in the second screen are recited below in **Table 12** and **Table 13**.

Table 12. MAPT gene and mRNA target sequences used in the screen of FIG. 6.

ID	45mer_Gene_Region	Target Sequence
MAPT_347	CCCCGCCAGGAGTTCGAAGTGATGGAAGATCACGCTGGGACGTAC	GAAGUGAUGGAAGAUCACGC
MAPT_349	CCGCCAGGAGTTCGAAGTGATGGAAGATCACGCTGGGACGTACGG	AGUGAUGGAAGAUCACGCUG
MAPT_351	GCCAGGAGTTCGAAGTGATGGAAGATCACGCTGGGACGTACGGGT	UGAUGGAAGAUCACGCUGGG
MAPT_353	CAGGAGTTCGAAGTGATGGAAGATCACGCTGGGACGTACGGGTTG	AUGGAAGAUCACGCUGGGAC
MAPT_2247	GAGGCGGCAGTGTGCAAATAGTCTACAAACCAGTTGACCTGAGCA	AAAUAGUCUACAAACCAGUU
MAPT_2249	GGCGGCAGTGTGCAAATAGTCTACAAACCAGTTGACCTGAGCAAG	AUAGUCUACAAACCAGUUGA
MAPT_2251	CGGCAGTGTGCAAATAGTCTACAAACCAGTTGACCTGAGCAAGGT	AGUCUACAAACCAGUUGACC
MAPT_2253	GCAGTGTGCAAATAGTCTACAAACCAGTTGACCTGAGCAAGGTGA	UCUACAAACCAGUUGACCUG
MAPT_2255	AGTGTGCAAATAGTCTACAAACCAGTTGACCTGAGCAAGGTGACC	UACAAACCAGUUGACCUGAG
MAPT_2259	TGCAAATAGTCTACAAACCAGTTGACCTGAGCAAGGTGACCTCCA	AACCAGUUGACCUGAGCAAG
MAPT_2261	CAAATAGTCTACAAACCAGTTGACCTGAGCAAGGTGACCTCCAAG	CCAGUUGACCUGAGCAAGGU
MAPT_2263	AATAGTCTACAAACCAGTTGACCTGAGCAAGGTGACCTCCAAGTG	AGUUGACCUGAGCAAGGUGA
MAPT_2265	TAGTCTACAAACCAGTTGACCTGAGCAAGGTGACCTCCAAGTGTG	UUGACCUGAGCAAGGUGACC
MAPT_2368	GAAGCTTGACTTCAAGGACAGAGTCCAGTCGAAGATTGGGTCCCT	GGACAGAGUCCAGUCGAAGA
MAPT_2370	AGCTTGACTTCAAGGACAGAGTCCAGTCGAAGATTGGGTCCCTGG	ACAGAGUCCAGUCGAAGAUU
MAPT_2372	CTTGACTTCAAGGACAGAGTCCAGTCGAAGATTGGGTCCCTGGAC	AGAGUCCAGUCGAAGAUUGG
MAPT_2374	TGACTTCAAGGACAGAGTCCAGTCGAAGATTGGGTCCCTGGACAA	AGUCCAGUCGAAGAUUGGGU
MAPT_2376	ACTTCAAGGACAGAGTCCAGTCGAAGATTGGGTCCCTGGACAATA	UCCAGUCGAAGAUUGGGUCC
MAPT_2384	GACAGAGTCCAGTCGAAGATTGGGTCCCTGGACAATATCACCCAC	AAGAUUGGGUCCCUGGACAA
MAPT_2386	CAGAGTCCAGTCGAAGATTGGGTCCCTGGACAATATCACCCACGT	GAUUGGGUCCCUGGACAAUA
MAPT_2388	GAGTCCAGTCGAAGATTGGGTCCCTGGACAATATCACCCACGTCC	UUGGGUCCCUGGACAAUAUC
MAPT_2415	ACAATATCACCCACGTCCCTGGCGGAGGAAATAAAAAGATTGAAA	UCCCUGGCGGAGGAAAUAAA
MAPT_2419	TATCACCCACGTCCCTGGCGGAGGAAATAAAAAGATTGAAACCCA	UGGCGGAGGAAAUAAAAAGA
MAPT_2421	TCACCCACGTCCCTGGCGGAGGAAATAAAAAGATTGAAACCCACA	GCGGAGGAAAUAAAAAGAUU
MAPT_2423	ACCCACGTCCCTGGCGGAGGAAATAAAAAGATTGAAACCCACAAG	GGAGGAAAUAAAAAGAUUGA
MAPT_2425	CCACGTCCCTGGCGGAGGAAATAAAAAGATTGAAACCCACAAGCT	AGGAAAUAAAAAGAUUGAAA
MAPT_2427	ACGTCCCTGGCGGAGGAAATAAAAAGATTGAAACCCACAAGCTGA	GAAAUAAAAAGAUUGAAACC
MAPT_2668	ATCAGGCCCCTGGGGCGGTCAATAATTGTGGAGAGGAGAGAATGA	CGGUCAAUAAUUGUGGAGAG
MAPT_2670	CAGGCCCCTGGGGCGGTCAATAATTGTGGAGAGGAGAGAATGAGA	GUCAAUAAUUGUGGAGAGGA
MAPT_2672	GGCCCCTGGGGCGGTCAATAATTGTGGAGAGGAGAGAATGAGAGA	CAAUAAUUGUGGAGAGGAGA
MAPT_2674	CCCCTGGGGCGGTCAATAATTGTGGAGAGGAGAGAATGAGAGAGT	AUAAUUGUGGAGAGGAGAGA
MAPT_2676	CCTGGGGCGGTCAATAATTGTGGAGAGGAGAGAATGAGAGAGTGT	AAUUGUGGAGAGGAGAGAAU
MAPT_4508	CATCTGCACCCTGTTGAGTTGTAGTTGGATTTGTCTGTTTATGCT	GAGUUGUAGUUGGAUUUGUC
MAPT_4510	TCTGCACCCTGTTGAGTTGTAGTTGGATTTGTCTGTTTATGCTTG	GUUGUAGUUGGAUUUGUCUG
MAPT_4512	TGCACCCTGTTGAGTTGTAGTTGGATTTGTCTGTTTATGCTTGGA	UGUAGUUGGAUUUGUCUGUU
MAPT_4514	CACCCTGTTGAGTTGTAGTTGGATTTGTCTGTTTATGCTTGGATT	UAGUUGGAUUUGUCUGUUUA
MAPT_4516	CCCTGTTGAGTTGTAGTTGGATTTGTCTGTTTATGCTTGGATTCA	GUUGGAUUUGUCUGUUUAUG
MAPT_4520	GTTGAGTTGTAGTTGGATTTGTCTGTTTATGCTTGGATTCACCAG	GAUUUGUCUGUUUAUGCUUG
MAPT_4522	TGAGTTGTAGTTGGATTTGTCTGTTTATGCTTGGATTCACCAGAG	UUUGUCUGUUUAUGCUUGGA
MAPT_4524	AGTTGTAGTTGGATTTGTCTGTTTATGCTTGGATTCACCAGAGTG	UGUCUGUUUAUGCUUGGAUU
MAPT_4526	TTGTAGTTGGATTTGTCTGTTTATGCTTGGATTCACCAGAGTGAC	UCUGUUUAUGCUUGGAUUCA
MAPT_4528	GTAGTTGGATTTGTCTGTTTATGCTTGGATTCACCAGAGTGACTA	UGUUUAUGCUUGGAUUCACC
MAPT_6740	TCTATATAGTGTATTGTGTGTTTTAACAAATGATTTACACTGACT	GUGUGUUUUAACAAAUGAUU
MAPT_6742	TATATAGTGTATTGTGTGTTTTAACAAATGATTTACACTGACTGT	GUGUUUUAACAAAUGAUUUA
MAPT_6744	TATAGTGTATTGTGTGTTTTAACAAATGATTTACACTGACTGTTG	GUUUUAACAAAUGAUUUACA
MAPT_6746	TAGTGTATTGTGTGTTTTAACAAATGATTTACACTGACTGTTGCT	UUUAACAAAUGAUUUACACU
MAPT_6748	GTGTATTGTGTGTTTTAACAAATGATTTACACTGACTGTTGCTGT	UAACAAAUGAUUUACACUGA
MAPT_6752	ATTGTGTGTTTTAACAAATGATTTACACTGACTGTTGCTGTAAAA	AAAUGAUUUACACUGACUGU
MAPT_6754	TGTGTGTTTTAACAAATGATTTACACTGACTGTTGCTGTAAAAGT	AUGAUUUACACUGACUGUUG
MAPT_6756	TGTGTTTTAACAAATGATTTACACTGACTGTTGCTGTAAAAGTGA	GAUUUACACUGACUGUUGCU
MAPT_6758	TGTTTTAACAAATGATTTACACTGACTGTTGCTGTAAAAGTGAAT	UUUACACUGACUGUUGCUGU
MAPT_6760	TTTTAACAAATGATTTACACTGACTGTTGCTGTAAAAGTGAATTT	UACACUGACUGUUGCUGUAA

Table 13. *MAPT* antisense and sense strand siRNA sequences used in screens of FIG. 6.

ID	AS modified	S modified
MAPT 347	P(mU)#(fC)#(mG)(fU)(fG)(fA)(mU)(fC)(mU)(fU)(mC)(fC)(mA)#(fU)#(mC)#(fA)#(mC)#(mU)#(mU)#(fC)	(mG)#(mA)#(fU)(mG)(fG)(mA)(fA)(mG)(fA)(mU)(mC)(mA)(fC)#(mG)#(mA)-TegChol
MAPT 349	P(mU)#(fA)#(mG)(fC)(fG)(fU)(mG)(fA)(mU)(fC)(mU)(fU)(mC)#(fC)#(mA)#(fU)#(mC)#(mA)#(mC)#(fU)	(mU)#(mG)#(fG)(mA)(fA)(mG)(fA)(mU)(fC)(mA)(mC)(mG)(fC)#(mU)#(mA)-TegChol
MAPT 351	P(mU)#(fC)#(mC)(fA)(fG)(fC)(mG)(fU)(mG)(fA)(mU)(fC)(mU)#(fU)#(mC)#(fC)#(mA)#(mU)#(mC)#(fA)	(mG)#(mA)#(fA)(mG)(fA)(mU)(fC)(mA)(fC)(mG)(mC)(mU)(fG)#(mG)#(mA)-TegChol

MAPT 353	P(mU)#(fU)#(mC)(fC)(fC)(fA)(mG)(fC)(mG)(fU)(mG)(fA)(mU)#(fC)#(mU)#(fU)#(mC)#(mC)#(mA)#(fU)	(mA)#(mG)#(fA)(mU)(fC)(mA)(fC)(mG)(fC)(mU)(mG)(mG)(fG)#(mA)#(mA)-TegChol
MAPT 2247	P(mU)#(fA)#(mC)(fU)(fG)(fG)(mU)(fU)(mU)(fG)(mU)(fA)(mG)#(fA)#(mC)#(fU)#(mA)#(mU)#(mU)#(fU)	(mG)#(mU)#(fC)(mU)(fA)(mC)(fA)(mA)(fA)(mC)(mC)(mA)(fG)#(mU)#(mA)-TegChol
MAPT 2249	P(mU)#(fC)#(mA)(fA)(fC)(fU)(mG)(fG)(mU)(fU)(mU)(fG)(mU)#(fA)#(mG)#(fA)#(mC)#(mU)#(mA)#(fU)	(mC)#(mU)#(fA)(mC)(fA)(mA)(fA)(mC)(fC)(mA)(mG)(mU)(fU)#(mG)#(mA)-TegChol
MAPT 2251	P(mU)#(fG)#(mU)(fC)(fA)(fA)(mC)(fU)(mG)(fG)(mU)(fU)(mU)#(fG)#(mU)#(fA)#(mG)#(mA)#(mC)#(fU)	(mA)#(mC)#(fA)(mA)(fA)(mC)(fC)(mA)(fG)(mU)(mU)(mG)(fA)#(mC)#(mA)-TegChol
MAPT 2253	P(mU)#(fA)#(mG)(fG)(fU)(fC)(mA)(fA)(mC)(fU)(mG)(fG)(mU)#(fU)#(mU)#(fG)#(mU)#(mA)#(mG)#(fA)	(mA)#(mA)#(fA)(mC)(fC)(mA)(fG)(mU)(fU)(mG)(mA)(mC)(fC)#(mU)#(mA)-TegChol
MAPT 2255	P(mU)#(fU)#(mC)(fA)(fG)(fG)(mU)(fC)(mA)(fA)(mC)(fU)(mG)#(fG)#(mU)#(fU)#(mU)#(mG)#(mU)#(fA)	(mA)#(mC)#(fC)(mA)(fG)(mU)(fU)(mG)(fA)(mC)(mC)(mU)(fG)#(mA)#(mA)-TegChol
MAPT 2259	P(mU)#(fU)#(mU)(fG)(fC)(fU)(mC)(fA)(mG)(fG)(mU)(fC)(mA)#(fA)#(mC)#(fU)#(mG)#(mG)#(mU)#(fU)	(mG)#(mU)#(fU)(mG)(fA)(mC)(fC)(mU)(fG)(mA)(mG)(mC)(fA)#(mA)#(mA)-TegChol
MAPT 2261	P(mU)#(fC)#(mC)(fU)(fU)(fG)(mC)(fU)(mC)(fA)(mG)(fG)(mU)#(fC)#(mA)#(fA)#(mC)#(mU)#(mG)#(fG)	(mU)#(mG)#(fA)(mC)(fC)(mU)(fG)(mA)(fG)(mC)(mA)(mA)(fG)#(mG)#(mA)-TegChol
MAPT 2263	P(mU)#(fC)#(mA)(fC)(fC)(fU)(mU)(fG)(mC)(fU)(mC)(fA)(mG)#(fG)#(mU)#(fC)#(mA)#(mA)#(mC)#(fU)	(mA)#(mC)#(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mA)(mG)(mG)(fU)#(mG)#(mA)-TegChol
MAPT 2265	P(mU)#(fG)#(mU)(fC)(fA)(fC)(mC)(fU)(mU)(fG)(mC)(fU)(mC)#(fA)#(mG)#(fG)#(mU)#(mC)#(mA)#(fA)	(mC)#(mU)#(fG)(mA)(fG)(mC)(fA)(mA)(fG)(mG)(mU)(mG)(fA)#(mC)#(mA)-TegChol
MAPT 2368	P(mU)#(fC)#(mU)(fU)(fC)(fG)(mA)(fC)(mU)(fG)(mG)(fA)(mC)#(fU)#(mC)#(fU)#(mG)#(mU)#(mC)#(fC)	(mG)#(mA)#(fG)(mU)(fC)(mC)(fA)(mG)(fU)(mC)(mG)(mA)(fA)#(mG)#(mA)-TegChol
MAPT 2370	P(mU)#(fA)#(mU)(fC)(fU)(fU)(mC)(fG)(mA)(fC)(mU)(fG)(mG)#(fA)#(mC)#(fU)#(mC)#(mU)#(mG)#(fU)	(mG)#(mU)#(fC)(mC)(fA)(mG)(fU)(mC)(fG)(mA)(mA)(mG)(fA)#(mU)#(mA)-TegChol
MAPT 2372	P(mU)#(fC)#(mA)(fA)(fU)(fC)(mU)(fU)(mC)(fG)(mA)(fC)(mU)#(fG)#(mG)#(fA)#(mC)#(mU)#(mC)#(fU)	(mC)#(mC)#(fA)(mG)(fU)(mC)(fG)(mA)(fA)(mG)(mA)(mU)(fU)#(mG)#(mA)-TegChol
MAPT 2374	P(mU)#(fC)#(mC)(fC)(fA)(fA)(mU)(fC)(mU)(fU)(mC)(fG)(mA)#(fC)#(mU)#(fG)#(mG)#(mA)#(mC)#(fU)	(mA)#(mG)#(fU)(mC)(fG)(mA)(fA)(mG)(fA)(mU)(mU)(mG)(fG)#(mG)#(mA)-TegChol
MAPT 2376	P(mU)#(fG)#(mA)(fC)(fC)(fC)(mA)(fA)(mU)(fC)(mU)(fU)(mC)#(fG)#(mA)#(fC)#(mU)#(mG)#(mG)#(fA)	(mU)#(mC)#(fG)(mA)(fA)(mG)(fA)(mU)(fU)(mG)(mG)(mG)(fU)#(mC)#(mA)-TegChol
MAPT 2384	P(mU)#(fU)#(mG)(fU)(fC)(fC)(mA)(fG)(mG)(fG)(mA)(fC)(mC)#(fC)#(mA)#(fA)#(mU)#(mC)#(mU)#(fU)	(mU)#(mG)#(fG)(mG)(fU)(mC)(fC)(mC)(fU)(mG)(mG)(mA)(fC)#(mA)#(mA)-TegChol
MAPT 2386	P(mU)#(fA)#(mU)(fU)(fG)(fU)(mC)(fC)(mA)(fG)(mG)(fG)(mA)#(fC)#(mC)#(fC)#(mA)#(mA)#(mU)#(fC)	(mG)#(mG)#(fU)(mC)(fC)(mC)(fU)(mG)(fG)(mA)(mC)(mA)(fA)#(mU)#(mA)-TegChol
MAPT 2388	P(mU)#(fA)#(mU)(fA)(fU)(fU)(mG)(fU)(mC)(fC)(mA)(fG)(mG)#(fG)#(mA)#(fC)#(mC)#(mC)#(mA)#(fA)	(mU)#(mC)#(fC)(mC)(fU)(mG)(fG)(mA)(fC)(mA)(mA)(mU)(fA)#(mU)#(mA)-TegChol
MAPT 2415	P(mU)#(fU)#(mU)(fA)(fU)(fU)(mU)(fC)(mC)(fU)(mC)(fC)(mG)#(fC)#(mC)#(fA)#(mG)#(mG)#(mG)#(fA)	(mG)#(mG)#(fC)(mG)(fG)(mA)(fG)(mG)(fA)(mA)(mA)(mU)(fA)#(mA)#(mA)-TegChol
MAPT 2419	P(mU)#(fC)#(mU)(fU)(fU)(fU)(mU)(fA)(mU)(fU)(mU)(fC)(mC)#(fU)#(mC)#(fC)#(mG)#(mC)#(mC)#(fA)	(mG)#(mA)#(fG)(mG)(fA)(mA)(fA)(mU)(fA)(mA)(mA)(mA)(fA)#(mG)#(mA)-TegChol
MAPT 2421	P(mU)#(fA)#(mU)(fC)(fU)(fU)(mU)(fU)(mU)(fA)(mU)(fU)(mU)#(fC)#(mC)#(fU)#(mC)#(mC)#(mG)#(fC)	(mG)#(mG)#(fA)(mA)(fA)(mU)(fA)(mA)(fA)(mA)(mA)(mG)(fA)#(mU)#(mA)-TegChol
MAPT 2423	P(mU)#(fC)#(mA)(fA)(fU)(fC)(mU)(fU)(mU)(fU)(mU)(fA)(mU)#(fU)#(mU)#(fC)#(mC)#(mU)#(mC)#(fC)	(mA)#(mA)#(fA)(mU)(fA)(mA)(fA)(mA)(fA)(mG)(mA)(mU)(fU)#(mG)#(mA)-TegChol
MAPT 2425	P(mU)#(fU)#(mU)(fC)(fA)(fA)(mU)(fC)(mU)(fU)(mU)(fU)(mU)#(fA)#(mU)#(fU)#(mU)#(mC)#(mC)#(fU)	(mA)#(mU)#(fA)(mA)(fA)(mA)(fA)(mG)(fA)(mU)(mU)(mG)(fA)#(mA)#(mA)-TegChol
MAPT 2427	P(mU)#(fG)#(mU)(fU)(fU)(fC)(mA)(fA)(mU)(fC)(mU)(fU)(mU)#(fU)#(mU)#(fA)#(mU)#(mU)#(mU)#(fC)	(mA)#(mA)#(fA)(mA)(fA)(mG)(fA)(mU)(fU)(mG)(mA)(mA)(fA)#(mC)#(mA)-TegChol
MAPT 2668	P(mU)#(fU)#(mC)(fU)(fC)(fC)(mA)(fC)(mA)(fA)(mU)(fU)(mA)#(fU)#(mU)#(fG)#(mA)#(mC)#(mC)#(fG)	(mA)#(mA)#(fU)(mA)(fA)(mU)(fU)(mG)(fU)(mG)(mG)(mA)(fG)#(mA)#(mA)-TegChol
MAPT 2670	P(mU)#(fC)#(mC)(fU)(fC)(fU)(mC)(fC)(mA)(fC)(mA)(fA)(mU)#(fU)#(mA)#(fU)#(mU)#(mG)#(mA)#(fC)	(mU)#(mA)#(fA)(mU)(fU)(mG)(fU)(mG)(fG)(mA)(mG)(mA)(fG)#(mG)#(mA)-TegChol
MAPT 2672	P(mU)#(fC)#(mU)(fC)(fC)(fU)(mC)(fU)(mC)(fC)(mA)(fC)(mA)#(fA)#(mU)#(fU)#(mA)#(mU)#(mU)#(fG)	(mA)#(mU)#(fU)(mG)(fU)(mG)(fG)(mA)(fG)(mA)(mG)(mG)(fA)#(mG)#(mA)-TegChol
MAPT 2674	P(mU)#(fC)#(mU)(fC)(fU)(fC)(mC)(fU)(mC)(fU)(mC)(fC)(mA)#(fC)#(mA)#(fA)#(mU)#(mU)#(mA)#(fU)	(mU)#(mG)#(fU)(mG)(fG)(mA)(fG)(mA)(fG)(mG)(mA)(mG)(fA)#(mG)#(mA)-TegChol
MAPT 2676	P(mU)#(fU)#(mU)(fC)(fU)(fC)(mU)(fC)(mC)(fU)(mC)(fU)(mC)#(fC)#(mA)#(fC)#(mA)#(mA)#(mU)#(fU)	(mU)#(mG)#(fG)(mA)(fG)(mA)(fG)(mG)(fA)(mG)(mA)(mG)(fA)#(mA)#(mA)-TegChol
MAPT 4508	P(mU)#(fA)#(mC)(fA)(fA)(fA)(mU)(fC)(mC)(fA)(mA)(fC)(mU)#(fA)#(mC)#(fA)#(mA)#(mC)#(mU)#(fC)	(mG)#(mU)#(fA)(mG)(fU)(mU)(fG)(mG)(fA)(mU)(mU)(mU)(fG)#(mU)#(mA)-TegChol
MAPT 4510	P(mU)#(fA)#(mG)(fA)(fC)(fA)(mA)(fA)(mU)(fC)(mC)(fA)(mA)#(fC)#(mU)#(fA)#(mC)#(mA)#(mA)#(fC)	(mA)#(mG)#(fU)(mU)(fG)(mG)(fA)(mU)(fU)(mU)(mG)(mU)(fC)#(mU)#(mA)-TegChol
MAPT 4512	P(mU)#(fA)#(mC)(fA)(fG)(fA)(mC)(fA)(mA)(fA)(mU)(fC)(mC)#(fA)#(mA)#(fC)#(mU)#(mA)#(mC)#(fA)	(mU)#(mU)#(fG)(mG)(fA)(mU)(fU)(mU)(fG)(mU)(mC)(mU)(fG)#(mU)#(mA)-TegChol
MAPT 4514	P(mU)#(fA)#(mA)(fA)(fC)(fA)(mG)(fA)(mC)(fA)(mA)(fA)(mU)#(fC)#(mC)#(fA)#(mA)#(mC)#(mU)#(fA)	(mG)#(mG)#(fA)(mU)(fU)(mU)(fG)(mU)(fC)(mU)(mG)(mU)(fU)#(mU)#(mA)-TegChol
MAPT 4516	P(mU)#(fA)#(mU)(fA)(fA)(fA)(mC)(fA)(mG)(fA)(mC)(fA)(mA)#(fA)#(mU)#(fC)#(mC)#(mA)#(mA)#(fC)	(mA)#(mU)#(fU)(mU)(fG)(mU)(fC)(mU)(fG)(mU)(mU)(mU)(fA)#(mU)#(mA)-TegChol
MAPT 4520	P(mU)#(fA)#(mA)(fG)(fC)(fA)(mU)(fA)(mA)(fA)(mC)(fA)(mG)#(fA)#(mC)#(fA)#(mA)#(mA)#(mU)#(fC)	(mG)#(mU)#(fC)(mU)(fG)(mU)(fU)(mU)(fA)(mU)(mG)(mC)(fU)#(mU)#(mA)-TegChol
MAPT 4522	P(mU)#(fC)#(mC)(fA)(fA)(fG)(mC)(fA)(mU)(fA)(mA)(fA)(mC)#(fA)#(mG)#(fA)#(mC)#(mA)#(mA)#(fA)	(mC)#(mU)#(fG)(mU)(fU)(mU)(fA)(mU)(fG)(mC)(mU)(mU)(fG)#(mG)#(mA)-TegChol

MAPT 4524	P(mU)#(fA)#(mU)(fC)(fC)(fA)(mA)(fG)(mC)(fA)(mU)(fA)(mA)#(fA)#(mC)#(fA)#(mG)#(mA)#(mC)#(fA)	(mG)#(mU)#(fU)(mU)(fA)(mU)(fG)(mC)(fU)(mU)(mG)(mG)(fA)#(mU)#(mA)-TegChol
MAPT 4526	P(mU)#(fG)#(mA)(fA)(fU)(fC)(mC)(fA)(mA)(fG)(mC)(fA)(mU)#(fA)#(mA)#(fA)#(mC)#(mA)#(mG)#(fA)	(mU)#(mU)#(fA)(mU)(fG)(mC)(fU)(mU)(fG)(mG)(mA)(mU)(fU)#(mC)#(mA)-TegChol
MAPT 4528	P(mU)#(fG)#(mU)(fG)(fA)(fA)(mU)(fC)(mC)(fA)(mA)(fG)(mC)#(fA)#(mU)#(fA)#(mA)#(mA)#(mC)#(fA)	(mA)#(mU)#(fG)(mC)(fU)(mU)(fG)(mG)(fA)(mU)(mU)(mC)(fA)#(mC)#(mA)-TegChol
MAPT 6740	P(mU)#(fA)#(mU)(fC)(fA)(fU)(mU)(fU)(mG)(fU)(mU)(fA)(mA)#(fA)#(mA)#(fC)#(mA)#(mC)#(mA)#(fC)	(mU)#(mU)#(fU)(mU)(fA)(mA)(fC)(mA)(fA)(mA)(mU)(mG)(fA)#(mU)#(mA)-TegChol
MAPT 6742	P(mU)#(fA)#(mA)(fA)(fU)(fC)(mA)(fU)(mU)(fU)(mG)(fU)(mU)#(fA)#(mA)#(fA)#(mA)#(mC)#(mA)#(fC)	(mU)#(mU)#(fA)(mA)(fC)(mA)(fA)(mA)(fU)(mG)(mA)(mU)(fU)#(mU)#(mA)-TegChol
MAPT 6744	P(mU)#(fG)#(mU)(fA)(fA)(fA)(mU)(fC)(mA)(fU)(mU)(fU)(mG)#(fU)#(mU)#(fA)#(mA)#(mA)#(mA)#(fC)	(mA)#(mA)#(fC)(mA)(fA)(mA)(fU)(mG)(fA)(mU)(mU)(mU)(fA)#(mC)#(mA)-TegChol
MAPT 6746	P(mU)#(fG)#(mU)(fG)(fU)(fA)(mA)(fA)(mU)(fC)(mA)(fU)(mU)#(fU)#(mG)#(fU)#(mU)#(mA)#(mA)#(fA)	(mC)#(mA)#(fA)(mA)(fU)(mG)(fA)(mU)(fU)(mU)(mA)(mC)(fA)#(mC)#(mA)-TegChol
MAPT 6748	P(mU)#(fC)#(mA)(fG)(fU)(fG)(mU)(fA)(mA)(fA)(mU)(fC)(mA)#(fU)#(mU)#(fU)#(mG)#(mU)#(mU)#(fA)	(mA)#(mA)#(fU)(mG)(fA)(mU)(fU)(mU)(fA)(mC)(mA)(mC)(fU)#(mG)#(mA)-TegChol
MAPT 6752	P(mU)#(fC)#(mA)(fG)(fU)(fC)(mA)(fG)(mU)(fG)(mU)(fA)(mA)#(fA)#(mU)#(fC)#(mA)#(mU)#(mU)#(fU)	(mA)#(mU)#(fU)(mU)(fA)(mC)(fA)(mC)(fU)(mG)(mA)(mC)(fU)#(mG)#(mA)-TegChol
MAPT 6754	P(mU)#(fA)#(mA)(fC)(fA)(fG)(mU)(fC)(mA)(fG)(mU)(fG)(mU)#(fA)#(mA)#(fA)#(mU)#(mC)#(mA)#(fU)	(mU)#(mU)#(fA)(mC)(fA)(mC)(fU)(mG)(fA)(mC)(mU)(mG)(fU)#(mU)#(mA)-TegChol
MAPT 6756	P(mU)#(fG)#(mC)(fA)(fA)(fC)(mA)(fG)(mU)(fC)(mA)(fG)(mU)#(fG)#(mU)#(fA)#(mA)#(mA)#(mU)#(fC)	(mA)#(mC)#(fA)(mC)(fU)(mG)(fA)(mC)(fU)(mG)(mU)(mU)(fG)#(mC)#(mA)-TegChol
MAPT 6758	P(mU)#(fC)#(mA)(fG)(fC)(fA)(mA)(fC)(mA)(fG)(mU)(fC)(mA)#(fG)#(mU)#(fG)#(mU)#(mA)#(mA)#(fA)	(mA)#(mC)#(fU)(mG)(fA)(mC)(fU)(mG)(fU)(mU)(mG)(mC)(fU)#(mG)#(mA)-TegChol
MAPT 6760	P(mU)#(fU)#(mA)(fC)(fA)(fG)(mC)(fA)(mA)(fC)(mA)(fG)(mU)#(fC)#(mA)#(fG)#(mU)#(mG)#(mU)#(fA)	(mU)#(mG)#(fA)(mC)(fU)(mG)(fU)(mU)(fG)(mC)(mU)(mG)(fU)#(mA)#(mA)-TegChol

[0777] A third *in vitro* screen was performed to identify additional 3'UTR-trageting siRNAs effective in silencing *MAPT* mRNA. The screen was performed as described above for the human SHSY cells. The mouse neuroblastoma cell line, N2A, was also used in the screen. The results of the screen are depicted in **FIG. 7A** and **FIG. 7B**. The tested siRNAs were of the P5 Asymmetric design with a 21-nucelotide antisense strand and 16-nuceltoide sense strand, as depicted in **FIG. 7A**. The results of the third screen identified several additional siRNAs capable of effectively silencing *MAPT* mRNA. Several hits were further tested to generate dose response curves, as shown in **FIG. 8**. To demonstrate the efficacy of siRNAs with alternative chemical modification patterns, an additional dose response curve was performed with a P3 Asymmetric pattern. The results of this dose response curve are shown in **FIG. 9**. The MAPT gene and mRNA target sequences, and panel of siRNAs used in the third screen are recited below in **Table 14** and **Table 15**.

Table 14. MAPT gene and mRNA target sequences used in the screen of FIGS. 7-9.

ID	Targeting region	Sequence
MAPT_3291	TCCTTCAAGCTGCTGACTCACTTTATCAATAGTTCCATTTAAATT (SEQ ID NO: 291)	ACUCACUUUAUCAAUAGUUC (SEQ ID NO: 298)
MAPT_3292	CCTTCAAGCTGCTGACTCACTTTATCAATAGTTCCATTTAAATTG (SEQ ID NO: 292)	CUCACUUUAUCAAUAGUUCC (SEQ ID NO: 299)

MAPT_3299	GCTGCTGACTCACTTTATCAATAGTTCCATTTAAATTGACTTCAG (SEQ ID NO: 293)	UAUCAAUAGUUCCAUUUAAA (SEQ ID NO: 300)
MAPT_3306	ACTCACTTTATCAATAGTTCCATTTAAATTGACTTCAGTGGTGAG (SEQ ID NO: 294)	AGUUCCAUUUAAAUUGACUU (SEQ ID NO: 301)
MAPT_3309	CACTTTATCAATAGTTCCATTTAAATTGACTTCAGTGGTGAGACT (SEQ ID NO: 295)	UCCAUUUAAAUUGACUUCAG (SEQ ID NO: 302)
MAPT_3986	GGACTATTTCTGGCACTTGCAAGTCCCATGATTTCTTCGGTAATT (SEQ ID NO: 296)	CUUGCAAGUCCCAUGAUUUC (SEQ ID NO: 303)
MAPT_4089	CTATATAGTGTATTGTGTGTTTTAACAAATGATTTACACTGACTG (SEQ ID NO: 297)	UGUGUUUUAACAAAUGAUUU (SEQ ID NO: 304)

Table 15. *MAPT* antisense and sense strand siRNA sequences used in screens of FIGS. 7-9.

ID	AS modified	S modified
MAPT_3291	P(mU)#(fA)#(mA)(mC)(mU)(fA)(mU)(mU)(mG)(mA)(mU)(mA)(mA)(fA)#(mG)#(fU)#(mG)#(mA)#(mG)#(fU)#(mU)	(mA)#(mC)#(mU)(mU)(mU)(fA)(fU)(fC)(mA)(fA)(mU)(mA)(mG)(mU)#(mU)#(mA)-TegChol
MAPT_3292	P(mU)#(fG)#(mA)(mA)(mC)(fU)(mA)(mU)(mU)(mG)(mA)(mU)(mA)(fA)#(mA)#(fG)#(mU)#(mG)#(mA)#(fG)#(mU)	(mC)#(mU)#(mU)(mU)(mA)(fU)(fC)(fA)(mA)(fU)(mA)(mG)(mU)(mU)#(mC)#(mA)-TegChol
MAPT_3299	P(mU)#(fU)#(mU)(mA)(mA)(fA)(mU)(mG)(mG)(mA)(mA)(mC)(mU)(fA)#(mU)#(fU)#(mG)#(mA)#(mU)#(fA)#(mU)	(mA)#(mA)#(mU)(mA)(mG)(fU)(fU)(fC)(mC)(fA)(mU)(mU)(mU)(mA)#(mA)#(mA)-TegChol
MAPT_3306	P(mU)#(fA)#(mG)(mU)(mC)(fA)(mA)(mU)(mU)(mU)(mA)(mA)(mA)(fU)#(mG)#(fG)#(mA)#(mA)#(mC)#(fU)#(mU)	(mC)#(mC)#(mA)(mU)(mU)(fU)(fA)(fA)(mA)(fU)(mU)(mG)(mA)(mC)#(mU)#(mA)-TegChol
MAPT_3309	P(mU)#(fU)#(mG)(mA)(mA)(fG)(mU)(mC)(mA)(mA)(mU)(mU)(mU)(fA)#(mA)#(fA)#(mU)#(mG)#(mG)#(fA)#(mU)	(mU)#(mU)#(mU)(mA)(mA)(fA)(fU)(fU)(mG)(fA)(mC)(mU)(mU)(mC)#(mA)#(mA)-TegChol
MAPT_3986	P(mU)#(fA)#(mA)(mA)(mU)(fC)(mA)(mU)(mG)(mG)(mG)(mA)(mC)(fU)#(mU)#(fG)#(mC)#(mA)#(mA)#(fG)#(mU)	(mC)#(mA)#(mA)(mG)(mU)(fC)(fC)(fC)(mA)(fU)(mG)(mA)(mU)(mU)#(mU)#(mA)-TegChol
MAPT_4089	P(mU)#(fA)#(mA)(mU)(mC)(fA)(mU)(mU)(mU)(mG)(mU)(mU)(mA)(fA)#(mA)#(fA)#(mC)#(mA)#(mC)#(fA)#(mU)	(mU)#(mU)#(mU)(mU)(mA)(fA)(fC)(fA)(mA)(fA)(mU)(mG)(mA)(mU)#(mU)#(mA)-TegChol

[0778] A further screen of siRNAs targeting various MAPT mRNA target sequences across the ORF and 3' UTR was conducted with siRNAs in the a P3 Asymmetric pattern shown in FIG. 4. The screen was performed in SH-SY5Y human neuroblastoma cells. Each siRNA was used at a concentration of 1.5 μM and incubated for 72 hours with the cells before quantifying relative mRNA expression (**FIG. 10**). An additional screen was performed with siRNAs targeting various MAPT mRNA target sequences across the ORF. Targets are found in both human and mouse MAPT mRNA. The screen was performed in SH-SY5Y human neuroblastoma cells. Each siRNA was used at a concentration of 1.5 μM and incubated for 72 hours with the cells before quantifying relative mRNA expression (**FIG. 11**). The data shows that there are numerous MAPT target areas useful for robust silencing of MAPT mRNA expression.

Example 2. *In vivo* silencing of *MAPT* in the mouse brain

[0779] Based on the results here and the screens performed in Example 1, the MAPT target sites designated MAPT 2005, MAPT 3309, and MAPT 3292 were selected for further study in the mouse brain. Mice were given a 10 nmol dose of the siRNA in a 10 µl volume, administered via an intracerebroventricular (ICV) route. No treatment control mice were used for comparison (5 mice per group). After a one-month incubation period, mice were sacrificed and MAPT mRNA (**FIG. 12A**) and Tau protein (**FIG. 12B**) levels were determined. The mRNA levels were determined with the QuantiGene gene expression assay (ThermoFisher, Waltham, MA) and protein expression was determined with the Protein Simple western blot system. Tau protein levels were normalized to the protein vinculin and gapdh. The following siRNA chemical modification pattern was employed for this *in vivo* study:

Antisense strand, from 5' to 3' (21-nucleotides in length):

VP(mX)#(fX)#(mX)(fX)(fX)(fX)(mX)(fX)(mX)(fX)(mX)(fX)(mX)(fX)#(mX)#(fX)#(mX)#(mX)#(mX)#(fX)#(mX)

Sense strand, from 5' to 3' (16-nucleotides in length):

(mX)#(mX)#(mX)(fX)(mX)(fX)(mX)(fX)(mX)(fX)(mX)(mX)(mX)(fX)#(mX)#(mX)

"m" corresponds to a 2'-O-methyl modification; "f" corresponds to a 2'-fluoro modification; "X" corresponds to any nucleotide of A, U, G, or C; "#" corresponds to a phosphorothioate internucleotide linkage; and "VP" corresponds to a 5' vinylphosphonate modification.

[0780] The siRNA targeting the sites designated MAPT 2005, MAPT 3309, and MAPT 3292 lead to potent silencing in several mouse central nervous system regions tested, including the frontal cortex, medial cortex, hippocampus, thalamus, striatum, cerebellum, and spinal cord. Both mRNA and protein levels reached about 50% compared to the no treatment control. The siRNA antisense and sense strand sequences, with chemical modiciation patterns, are depicted below.

MAPT 2005 Antisense strand, from 5' to 3' (21-nucleotides in length):

VP(mU)#(fU)#(mU)(fU)(fA)(fC)(mU)(fU)(mC)(fC)(mA)(fC)(mC)(fU)#(mG)#(fG)#(mC)#(mC)#(mA)#(fC)#(mU)

MAPT 2005 Sense strand, from 5' to 3' (16-nucleotides in length):

(mC)#(mC)#(mA)(fG)(mG)(fU)(mG)(fG)(mA)(fA)(mG)(mU)(mA)(fA)#(mA)#(mA)

MAPT 3292 Antisense strand, from 5' to 3' (21-nucleotides in length):

VP(mU)#(fG)#(mA)(fA)(fC)(fU)(mA)(fU)(mU)(fG)(mA)(fU)(mA)(fA)#(mA)#(fG)#(mU)#(mG)#(mA)#(fG)#(mU)

MAPT 3292 Sense strand, from 5' to 3' (16-nucleotides in length):

(mC)#(mU)#(mU)(fU)(mA)(fU)(mC)(fA)(mA)(fU)(mA)(mG)(mU)(fU)#(mC)#(mA)

MAPT 3309 Antisense strand, from 5' to 3' (21-nucleotides in length):

VP(mU)#(fU)#(mG)(fA)(fA)(fG)(mU)(fC)(mA)(fA)(mU)(fU)(mU)(fA)#(mA)#(fA)#(mU)#(mG)#(mG)#(fA)#(mU)

MAPT 3309 Sense strand, from 5' to 3' (16-nucleotides in length):

(mU)#(mU)#(mU)(fA)(mA)(fA)(mU)(fU)(mG)(fA)(mC)(mU)(mU)(fC)#(mA)#(mA)

Incorporation by Reference

[0781] The contents of all cited references (including literature references, patents, patent applications, and websites) that maybe cited throughout this application are hereby expressly incorporated by reference in their entirety for any purpose, as are the references cited therein. The disclosure will employ, unless otherwise indicated, conventional techniques of immunology, molecular biology and cell biology, which are well known in the art.

[0782] The present disclosure also incorporates by reference in their entirety techniques well known in the field of molecular biology and drug delivery. These techniques include, but are not limited to, techniques described in the following publications:

Atwell et al. J. Mol. Biol. 1997, 270: 26-35;

Ausubel et al. (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley &Sons, NY (1993);

Ausubel, F.M. et al. eds., SHORT PROTOCOLS IN MOLECULAR BIOLOGY (4th Ed. 1999) John Wiley & Sons, NY. (ISBN 0-471-32938-X);

CONTROLLED DRUG BIOAVAILABILITY, DRUG PRODUCT DESIGN AND PERFORMANCE, Smolen and Ball (eds.), Wiley, New York (1984);

Giege, R. and Ducruix, A. Barrett, CRYSTALLIZATION OF NUCLEIC ACIDS AND PROTEINS, a Practical Approach, 2nd ea., pp. 20 1-16, Oxford University Press, New York, New York, (1999);

Goodson, in MEDICAL APPLICATIONS OF CONTROLLED RELEASE, vol. 2, pp. 115-138 (1984);

Hammerling, et al., in: MONOCLONAL ANTIBODIES AND T-CELL HYBRIDOMAS 563-681 (Elsevier, N.Y., 1981;

Harlow et al., ANTIBODIES: A LABORATORY MANUAL, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988);

Kabat et al., SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST (National Institutes of Health, Bethesda, Md. (1987) and (1991);

Kabat, E.A., *et al.* (1991) SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242;

Kontermann and Dubel eds., ANTIBODY ENGINEERING (2001) Springer-Verlag. New York. 790 pp. (ISBN 3-540-41354-5).

Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990);

Lu and Weiner eds., CLONING AND EXPRESSION VECTORS FOR GENE FUNCTION ANALYSIS (2001) BioTechniques Press. Westborough, MA. 298 pp. (ISBN 1-881299-21-X).

MEDICAL APPLICATIONS OF CONTROLLED RELEASE, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974);

Old, R.W. & S.B. Primrose, PRINCIPLES OF GENE MANIPULATION: AN INTRODUCTION TO GENETIC ENGINEERING (3d Ed. 1985) Blackwell Scientific Publications, Boston. Studies in Microbiology; V.2:409 pp. (ISBN 0-632-01318-4).

Sambrook, J. et al. eds., MOLECULAR CLONING: A LABORATORY MANUAL (2d Ed. 1989) Cold Spring Harbor Laboratory Press, NY. Vols. 1-3. (ISBN 0-87969-309-6).

SUSTAINED AND CONTROLLED RELEASE DRUG DELIVERY SYSTEMS, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978

Winnacker, E.L. FROM GENES TO CLONES: INTRODUCTION TO GENE TECHNOLOGY (1987) VCH Publishers, NY (translated by Horst Ibelgaufts). 634 pp. (ISBN 0-89573-614-4).

Equivalents

[0783] The disclosure may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting of the disclosure. Scope of the disclosure is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are therefore intended to be embraced herein.

Claims

What is claimed:

1. A double stranded (dsRNA) molecule comprising a sense strand and an antisense strand,

wherein the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

2. The dsRNA of claim 1, wherein the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 14-33, 299, and 302.

3. The dsRNA of claim 1, comprising complementarity to at least 10, 11, 12 or 13 contiguous nucleotides of the *MAPT* nucleic acid sequence of SEQ ID NOs: 1-13, 292, and 295.

4. The dsRNA of claim 1 or 3, comprising no more than 3 mismatches with the *MAPT* nucleic acid sequence of SEQ ID NOs: 1-13, 292, and 295.

5. The dsRNA of claim 1, comprising full complementarity to the *MAPT* nucleic acid sequence of SEQ ID NOs: 1-13, 292, and 295.

6. The dsRNA of any one of claims 1-5, wherein the antisense strand comprises about 15 nucleotides to 25 nucleotides in length.

7. The dsRNA of any one of claims 1-6, wherein the sense strand comprises about 15 nucleotides to 25 nucleotides in length.

8. The dsRNA of any one of claims 1-7, wherein the antisense strand is 20 nucleotides in length.

9. The dsRNA of any one of claims 1-7, wherein the antisense strand is 21 nucleotides in length.

10. The dsRNA of any one of claims 1-7, wherein the antisense strand is 22 nucleotides in length.

11. The dsRNA of any one of claims 1-10, wherein the sense strand is 15 nucleotides in length.

12. The dsRNA of any one of claims 1-10, wherein the sense strand is 16 nucleotides in length.

13. The dsRNA of any one of claims 1-10, wherein the sense strand is 18 nucleotides in length.

14. The dsRNA of any one of claims 1-10, wherein the sense strand is 20 nucleotides in length.

15. The dsRNA of any one of claims 1-14, comprising a double-stranded region of 15 base pairs to 20 base pairs.

16. The dsRNA of any one of claims 1-15, comprising a double-stranded region of 15 base pairs.

17. The dsRNA of any one of claims 1-15, comprising a double-stranded region of 16 base pairs.

18. The dsRNA of any one of claims 1-15, comprising a double-stranded region of 18 base pairs.

19. The dsRNA of any one of claims 1-15, comprising a double-stranded region of 20 base pairs.

20. The dsRNA of any one of claims 1-19, wherein said dsRNA comprises a blunt-end.

21. The dsRNA of any one of claims 1-20, wherein said dsRNA comprises at least one single stranded nucleotide overhang.

22. The dsRNA of claim 21, wherein said dsRNA comprises about a 2-nucleotide to 5-nucleotide single stranded nucleotide overhang.

23. The dsRNA of claim 21, wherein said dsRNA comprises 2-nucleotide single stranded nucleotide overhang.

24. The dsRNA of claim 21, wherein said dsRNA comprises 5-nucleotide single stranded nucleotide overhang.

25. The dsRNA of any one of claims 1-24, wherein said dsRNA comprises naturally occurring nucleotides.

26. The dsRNA of any one of claims 1-24, wherein said dsRNA comprises at least one modified nucleotide.

27. The dsRNA of claim 26, wherein said modified nucleotide comprises a 2'-O-methyl modified nucleotide, a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, or a mixture thereof.

28. The dsRNA of any one of claims 1-27, wherein said dsRNA comprises at least one modified internucleotide linkage.

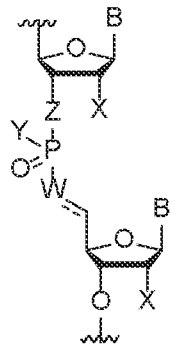
29. The dsRNA of claim 28, wherein said modified internucleotide linkage comprises a phosphorothioate internucleotide linkage.

30. The dsRNA of any one of claims 1-29, comprising 4-16 phosphorothioate internucleotide linkages.

31. The dsRNA of any one of claims 1-29, comprising 8-13 phosphorothioate

internucleotide linkages.

32. The dsRNA of any one of claims 1-28, wherein said dsRNA comprises at least one modified internucleotide linkage of Formula I:



(I);

wherein:

B is a base pairing moiety;

W is selected from the group consisting of O, OCH_2, OCH, CH_2, and CH;

X is selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

Y is selected from the group consisting of O^-, OH, OR, NH^-, NH_2, S^-, and SH;

Z is selected from the group consisting of O and CH_2;

R is a protecting group; and

=== is an optional double bond.

33. The dsRNA of any one of claims 1-32, wherein said dsRNA comprises at least 80% chemically modified nucleotides.

34. The dsRNA of any one of claims 1-33, wherein said dsRNA is fully chemically modified.

35. The dsRNA of any one of claims 1-33, wherein said dsRNA comprises at least 70% 2'-O-methyl nucleotide modifications.

36. The dsRNA of any one of claims 1-33, wherein the antisense strand comprises at least 70% 2'-O-methyl nucleotide modifications.

37. The dsRNA of claim 36, wherein the antisense strand comprises about 70% to 90% 2'-O-methyl nucleotide modifications.

38. The dsRNA of any one of claims 1-33, wherein the sense strand comprises at least 65% 2'-O-methyl nucleotide modifications.

39. The dsRNA of claim 38, wherein the sense strand comprises 100% 2'-O-methyl nucleotide modifications.

40. The dsRNA of any one of claims 1-39, wherein the sense strand comprises one or more nucleotide mismatches between the antisense strand and the sense strand.

41. The dsRNA of claim 40, wherein the one or more nucleotide mismatches are present at positions 2, 6, and 12 from the 5' end of sense strand.

42. The dsRNA of claim 40, wherein the nucleotide mismatches are present at positions 2, 6, and 12 from the 5' end of the sense strand.

43. The dsRNA of any one of claims 1-42, wherein the antisense strand comprises a 5' phosphate, a 5'-alkyl phosphonate, a 5' alkylene phosphonate, or a 5' alkenyl phosphonate.

44. The dsRNA of claim 43, wherein the antisense strand comprises a 5' vinyl phosphonate.

45. The dsRNA of claim 1, said dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises alternating 2'-methoxy-ribonucleotides and 2'-fluoro-ribonucleotides;

(3) the nucleotides at positions 2 and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises alternating 2'-methoxy-ribonucleotides and 2'-fluoro-ribonucleotides; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

46. The dsRNA of claim 1, said dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 70% 2'-O-methyl modifications;

(3) the nucleotide at position 14 from the 5' end of the antisense strand is not a 2'-methoxy-ribonucleotide;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises at least 70% 2'-O-methyl modifications; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

47. The dsRNA of claim 1, said dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 85% 2'-O-methyl modifications;

(3) the nucleotides at positions 2 and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises 100% 2'-O-methyl modifications; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

48. The dsRNA of claim 1, said dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 75% 2'-O-methyl modifications;

(3) the nucleotides at positions 4, 5, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises 100% 2'-O-methyl modifications; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

49. The dsRNA of claim 1, said dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 75% 2'-O-methyl modifications;

(3) the nucleotides at positions 2, 4, 5, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises 100% 2'-O-methyl modifications; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

50. The dsRNA of claim 1, said dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 75% 2'-O-methyl modifications;

(3) the nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand

are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises at least 65% 2'-O-methyl modifications;

(7) the nucleotides at positions 7, 9, 10, and 11 from the 3' end of the sense strand are not 2'-methoxy-ribonucleotides; and

(8) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

51. The dsRNA of claim 1, said dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 75% 2'-O-methyl modifications;

(3) the nucleotides at positions 2, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises at least 75% 2'-O-methyl modifications;

(7) the nucleotides at positions 7, 10, and 11 from the 3' end of the sense strand are not 2'-methoxy-ribonucleotides; and

(8) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

52. The dsRNA of any one of claims 1-51, wherein a functional moiety is linked to the 5' end and/or 3' end of the antisense strand.

53. The dsRNA of any one of claims 1-51, wherein a functional moiety is linked to the 5' end and/or 3' end of the sense strand.

54. The dsRNA of any one of claims 1-51, wherein a functional moiety is linked to the 3' end of the sense strand.

55. The dsRNA of any one of claims 52-54, wherein the functional moiety comprises a hydrophobic moiety.

56. The dsRNA of claim 55, wherein the hydrophobic moiety is selected from the group consisting of fatty acids, steroids, secosteroids, lipids, gangliosides, nucleoside analogs, endocannabinoids, vitamins, and a mixture thereof.

57. The dsRNA of claim 56, wherein the steroid is selected from the group consisting of cholesterol and Lithocholic acid (LCA).

58. The dsRNA of claim 56, wherein the fatty acid selected from the group consisting of Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA) and Docosanoic acid (DCA).

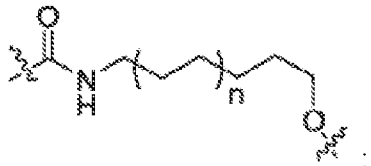
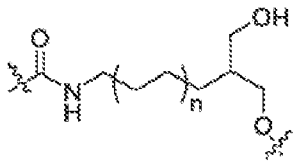
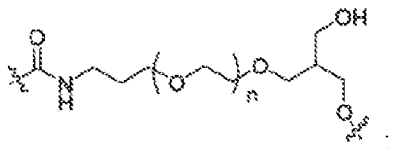
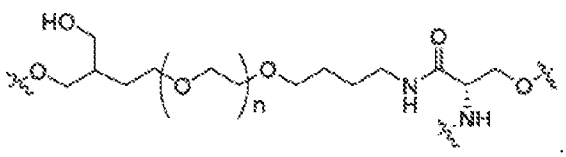
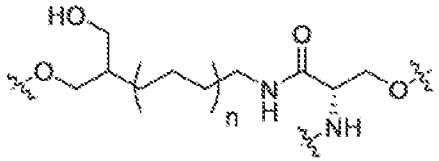
59. The dsRNA of claim 56, wherein the vitamin is selected from the group consisting of choline, vitamin A, vitamin E, derivatives thereof, and metabolites thereof.

60. The dsRNA of claim 59, wherein the vitamin is selected from the group consisting of retinoic acid and alpha-tocopheryl succinate.

61. The dsRNA of any one of claims 54-60, wherein the functional moiety is linked to the antisense strand and/or sense strand by a linker.

62. The dsRNA of claim 61, wherein the linker comprises a divalent or trivalent linker.

63. The dsRNA of claim 62, wherein the divalent or trivalent linker is selected from the group consisting of:

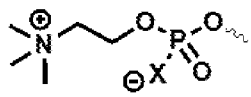

;

;

;


; and ,

wherein n is 1, 2, 3, 4, or 5.

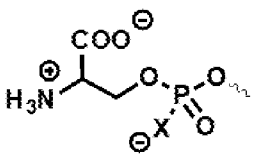
64. The dsRNA of claim 61 or 62, wherein the linker comprises an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphodiester, a phosphorothioate, a phosphoramidate, an amide, a carbamate, or a combination thereof.

65. The dsRNA of claim 62 or 63, wherein when the linker is a trivalent linker, the linker further links a phosphodiester or phosphodiester derivative.

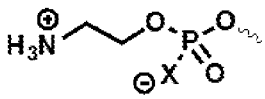
66. The dsRNA of claim 65, wherein the phosphodiester or phosphodiester derivative is selected from the group consisting of:


;

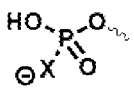
(Zc1);


;

(Zc2);


; and

(Zc3)


;

(Zc4)

wherein X is O, S or BH_3.

67. The dsRNA of any one of claims 1-66, wherein the nucleotides at positions 1 and 2 from the 3' end of sense strand, and the nucleotides at positions 1 and 2 from the 5' end of antisense strand, are connected to adjacent ribonucleotides via phosphorothioate linkages.

68. A pharmaceutical composition for inhibiting the expression of tau protein (*MAPT*) gene in an organism, comprising the dsRNA of any one of claims 1-67 and a pharmaceutically acceptable carrier.

69. The pharmaceutical composition of claim 68, wherein the dsRNA inhibits the expression of said *MAPT* gene by at least 50%.

70. The pharmaceutical composition of claim 68, wherein the dsRNA inhibits the expression of said *MAPT* gene by at least 80%.

71. A method for inhibiting expression of *MAPT* gene in a cell, the method comprising:

(a) introducing into the cell a double-stranded ribonucleic acid (dsRNA) of any one of claims 1-67; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of the *MAPT* gene, thereby inhibiting expression of the *MAPT* gene in the cell.

72. A method of treating or managing a neurodegenerative disease comprising administering to a patient in need of such treatment or management a therapeutically effective amount of said dsRNA of any one of claims 1-67.

73. The method of claim 72, wherein said dsRNA is administered to the brain of the patient.

74. The method of claim 72, wherein said dsRNA is administered by intracerebroventricular (ICV) injection, intrastriatal (IS) injection, intravenous (IV) injection, subcutaneous (SQ) injection or a combination thereof.

75. The method of claim 72, wherein 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.

76. The method of any one of claims 71-75, wherein the dsRNA inhibits the expression of said *MAPT* gene by at least 50%.

77. The method of any one of claims 71-75, wherein the dsRNA inhibits the expression of said *MAPT* gene by at least 80%.

78 A vector comprising a regulatory sequence operably linked to a nucleotide sequence that encodes a dsRNA molecule substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NOs: 1-13, 292, and 295.

79. The vector of claim 78, wherein said RNA molecule inhibits the expression of said *MAPT* gene by at least 30%

80. The vector of claim 78, wherein said RNA molecule inhibits the expression of said *MAPT* gene by at least 50%.

81. The vector of claim 78, wherein said RNA molecule inhibits the expression of said *MAPT* gene by at least 80%.

82. The vector of claim 78, wherein the dsRNA comprises a sense strand and an antisense strand, wherein the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of SEQ ID NOs: 1-13, 292, and 295.

83. A cell comprising the vector of any one of claims 78-82.

84. A recombinant adeno-associated virus (rAAV) comprising the vector of any one of claims 78-82 and an AAV capsid.

85. A branched RNA compound comprising two or more of the dsRNA molecules of any one of claims 1-67 covalently bound to one another.

86. The branched RNA compound of claim 85, wherein the dsRNA molecules are covalently bound to one another by way of a linker, spacer, or branching point.

87. A branched RNA compound comprising:

two or more RNA molecules comprising 15 to 35 nucleotides in length, and

a sequence substantially complementary to a *MAPT* mRNA,

wherein the two RNA molecules are connected to one another by one or more moieties independently selected from a linker, a spacer and a branching point.

88. The branched RNA compound of claim 87, comprising a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

89. The branched RNA compound of claim 87, comprising a sequence substantially complementary to one or more of a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 14-33, 299, and 302.

90. The branched RNA compound of any one of claims 87-89, wherein said RNA molecule comprises one or both of ssRNA and dsRNA.

91. The branched RNA compound of any one of claims 87-89, wherein said RNA molecule comprises an antisense oligonucleotide.

92. The branched RNA compound of any one of claims 87-91, wherein each RNA molecule comprises 15 to 25 nucleotides in length.

93. The branched RNA compound of any one of claims 87-89, wherein each RNA molecule comprises a dsRNA comprising a sense strand and an antisense strand, wherein each antisense strand independently comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

94. The branched RNA compound of claim 93, comprising complementarity to at least 10, 11, 12 or 13 contiguous nucleotides of a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

95. The branched RNA compound of claim 93, wherein each RNA molecule comprises no more than 3 mismatches with a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

96. The branched RNA compound of claim 93, comprising full complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

97. The branched RNA compound of any one of claims 93-96, wherein the antisense strand comprises a portion having the nucleic acid sequence of any one of SEQ ID NOs: 34-46.

98. The branched RNA compound of any one of claims 93-97, wherein the antisense strand and/or sense strand comprises about 15 nucleotides to 25 nucleotides in length.

99. The branched RNA compound of any one of claims 93-98, wherein the antisense strand is 20 nucleotides in length.

100. The branched RNA compound of any one of claims 93-98, wherein the antisense strand is 21 nucleotides in length.

101. The branched RNA compound of any one of claims 93-98, wherein the antisense strand is 22 nucleotides in length.

102. The branched RNA compound of any one of claims 93-101, wherein the sense strand is 15 nucleotides in length.

103. The branched RNA compound of any one of claims 93-101, wherein the sense strand is 16 nucleotides in length.

104. The branched RNA compound of any one of claims 93-101, wherein the sense strand is 18 nucleotides in length.

105. The branched RNA compound of any one of claims 93-101, wherein the sense strand is 20 nucleotides in length.

106. The branched RNA compound of any one of claims 90-105, wherein the dsRNA comprises a double-stranded region of 15 base pairs to 20 base pairs.

107. The branched RNA compound of any one of claims 90-106, wherein the dsRNA comprises a double-stranded region of 15 base pairs.

108. The branched RNA compound of any one of claims 90-106, wherein the dsRNA comprises a double-stranded region of 16 base pairs.

109. The branched RNA compound of any one of claims 90-106, wherein the dsRNA comprises a double-stranded region of 18 base pairs.

110. The branched RNA compound of any one of claims 90-106, wherein the dsRNA comprises a double-stranded region of 20 base pairs.

111. The branched RNA compound of any one of claims 90-110, wherein the dsRNA comprises a blunt-end.

112. The branched RNA compound of any one of claims 90-110, wherein the dsRNA comprises at least one single stranded nucleotide overhang.

113. The branched RNA compound of any one of claims 90-112, wherein the dsRNA comprises between a 2-nucleotide to 5-nucleotide single stranded nucleotide overhang.

14. The branched RNA compound of any one of claims 90-113, wherein the dsRNA comprises naturally occurring nucleotides.

115. The branched RNA compound of any one of claims 90-114, wherein the dsRNA comprises at least one modified nucleotide.

116. The branched RNA compound of claim 115, wherein said modified nucleotide comprises a 2'-O-methyl modified nucleotide, a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.

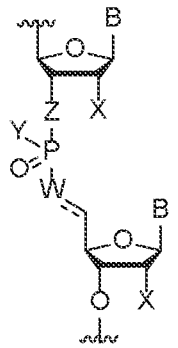
117. The branched RNA compound of any one of claims 90-116, wherein the dsRNA comprises at least one modified internucleotide linkage.

118. The branched RNA compound of claim 117, wherein said modified internucleotide linkage comprises a phosphorothioate internucleotide linkage.

119. The branched RNA compound of any one of claims 90-118, comprising 4-16 phosphorothioate internucleotide linkages.

120. The branched RNA compound of any one of claims 90-118, comprising 8-13 phosphorothioate internucleotide linkages.

121. The branched RNA compound of any one of claims 90-117, wherein said dsRNA comprises at least one modified internucleotide linkage of Formula I:



(I);

wherein:

B is a base pairing moiety;

W is selected from the group consisting of O, OCH_2, OCH, CH_2, and CH;

X is selected from the group consisting of halo, hydroxy, and C_{1-6} alkoxy;

Y is selected from the group consisting of O^-, OH, OR, NH^-, NH_2, S^-, and SH;

Z is selected from the group consisting of O and CH_2;

R is a protecting group; and

=== is an optional double bond.

122. The branched RNA compound of any one of claims 90-121, wherein said dsRNA comprises at least 75% chemically modified nucleotides.

123. The branched RNA compound of any one of claims 90-122, wherein said dsRNA is fully chemically modified.

124. The branched RNA compound of any one of claims 90-123, wherein said dsRNA comprises at least 70% 2'-O-methyl nucleotide modifications.

125. The branched RNA compound of any one of claims 90-124, wherein the antisense strand comprises at least 70% 2'-O-methyl nucleotide modifications.

126. The branched RNA compound of claim 125, wherein the antisense strand comprises about 70% to 90% 2'-O-methyl nucleotide modifications.

127. The branched RNA compound of any one of claims 91-124, wherein the sense strand comprises at least 65% 2'-O-methyl nucleotide modifications.

128. The branched RNA compound of claim 127, wherein the sense strand comprises 100% 2'-O-methyl nucleotide modifications.

129. The branched RNA compound of any one of claims 93-128, wherein the sense strand comprises one or more nucleotide mismatches between the antisense strand and the sense strand.

130. The branched RNA compound of claim 129, wherein the one or more nucleotide mismatches are present at positions 2, 6, and 12 from the 5' end of sense strand.

131. The branched RNA compound of claim 129, wherein the nucleotide mismatches are present at positions 2, 6, and 12 from the 5' end of the sense strand.

132. The branched RNA compound of any one of claims 93-131, wherein the antisense strand comprises a 5' phosphate, a 5'-alkyl phosphonate, a 5' alkylene phosphonate, a 5' alkenyl phosphonate, or a mixture thereof.

133. The branched RNA compound of claim 132, wherein the antisense strand comprises a 5' vinyl phosphonate.

134. The branched RNA compound of claim 90, wherein the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises alternating 2'-methoxy-ribonucleotides and 2'-fluoro-ribonucleotides;

(3) the nucleotides at positions 2 and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises alternating 2'-methoxy-ribonucleotides and 2'-fluoro-ribonucleotides; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

135. The branched RNA compound of claim 90, wherein the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 70% 2'-O-methyl modifications;

(3) the nucleotide at position 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are

connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises at least 70% 2'-O-methyl modifications; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

136. The branched RNA compound of claim 90, wherein the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 85% 2'-O-methyl modifications;

(3) the nucleotides at positions 2 and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises 100% 2'-O-methyl modifications; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

137. The branched RNA compound of claim 90, wherein the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 75% 2'-O-methyl modifications;

(3) the nucleotides at positions 4, 5, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises 100% 2'-O-methyl modifications; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

138. The branched RNA compound of claim 90, wherein the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 75% 2'-O-methyl modifications;

(3) the nucleotides at positions 2, 4, 5, 6, and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises 100% 2'-O-methyl modifications; and

(7) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

139. The branched RNA compound of claim 90, wherein the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 75% 2'-O-methyl modifications;

(3) the nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises at least 65% 2'-O-methyl modifications;

(7) the nucleotides at positions 7, 9, 10, and 11 from the 3' end of the sense strand are not 2'-methoxy-ribonucleotides; and

(8) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

140. The branched RNA compound of claim 90, wherein the dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

(2) the antisense strand comprises at least 75% 2'-O-methyl modifications;

(3) the nucleotides at positions 2and 14 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(4) the nucleotides at positions 1-2 to 1-7 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(5) a portion of the antisense strand is complementary to a portion of the sense strand;

(6) the sense strand comprises at least 75% 2'-O-methyl modifications;

(7) the nucleotides at positions 7, 10, and 11 from the 3' end of the sense strand are not 2'-methoxy-ribonucleotides; and

(8) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

141. The branched RNA compound of any one of claims 93-140, wherein a functional moiety is linked to the 5' end and/or 3' end of the antisense strand.

142. The branched RNA compound of any one of claims 93-140, wherein a functional moiety is linked to the 5' end and/or 3' end of the sense strand.

143. The branched RNA compound of any one of claims 93-140, wherein a functional moiety is linked to the 3' end of the sense strand.

144. The branched RNA compound of any one of claims 141-143, wherein the functional moiety comprises a hydrophobic moiety.

145. The branched RNA compound of claim 144, wherein the hydrophobic moiety is selected from the group consisting of fatty acids, steroids, secosteroids, lipids, gangliosides, nucleoside analogs, endocannabinoids, vitamins, and a mixture thereof.

146. The branched RNA compound of claim 145, wherein the steroid is selected from the group consisting of cholesterol and Lithocholic acid (LCA).

147. The branched RNA compound of claim 145, wherein the fatty acid is selected from the group consisting of Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA) and Docosanoic acid (DCA).

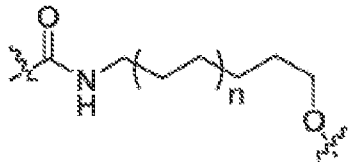
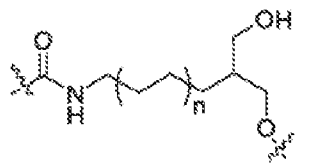
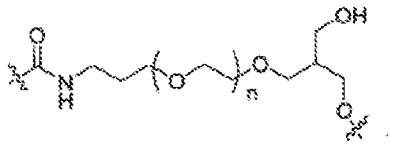
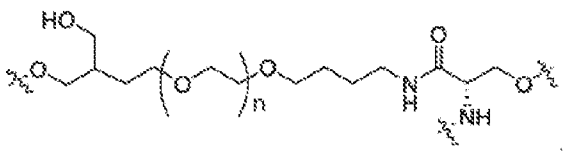
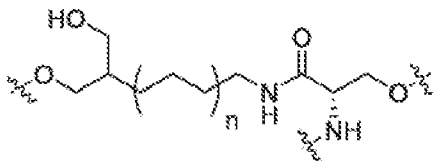
148. The branched RNA compound of claim 145, wherein the vitamin is selected from the group consisting of choline, vitamin A, vitamin E, derivatives thereof, and metabolites thereof.

149. The branched RNA compound of claim 145, wherein the vitamin is selected from the group consisting of retinoic acid and alpha-tocopheryl succinate.

150. The branched RNA compound of any one of claims 141-149, wherein the functional moiety is linked to the antisense strand and/or sense strand by a linker.

151. The branched RNA compound of claim 150, wherein the linker comprises a divalent or trivalent linker.

152. The branched RNA compound of claim 151, wherein the divalent or trivalent linker is selected from the group consisting of:


;

;

;


; and ,

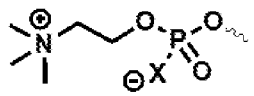
wherein n is 1, 2, 3, 4, or 5.

153. The branched RNA compound of claim 150 or 151, wherein the linker comprises an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphodiester, a phosphorothioate, a phosphoramidate, an amide, a carbamate, or a combination thereof.

154. The branched RNA compound of claim 150, wherein when the linker is a trivalent linker, the linker further links a phosphodiester or phosphodiester derivative.

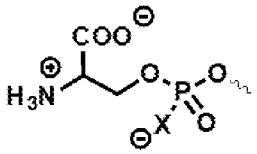
155. The branched RNA compound of claim 154, wherein the phosphodiester or

phosphodiester derivative is selected from the group consisting of:



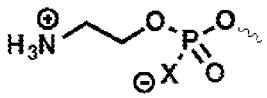
;

(Zc1);



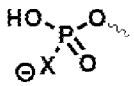
;

(Zc2);



; and

(Zc3)



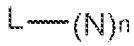
;

(Zc4)

wherein X is O, S or BH_3.

156. The branched RNA compound of any one of claims 93-155, wherein the nucleotides at positions 1 and 2 from the 3' end of sense strand, and the nucleotides at positions 1 and 2 from the 5' end of antisense strand, are connected to adjacent ribonucleotides via phosphorothioate linkages.

157. A compound of formula (I):



(I)

wherein:

L comprises an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, or combinations thereof, wherein formula (I) optionally further comprises one or more branch point B, and one or more spacer S, wherein

B is independently for each occurrence a polyvalent organic species or derivative thereof;

S comprises independently for each occurrence an ethylene glycol chain, an alkyl chain, a peptide, RNA, DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, or combinations thereof; and

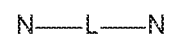
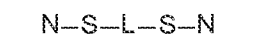
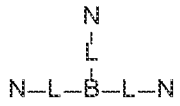
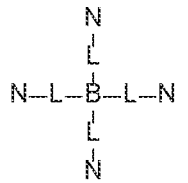
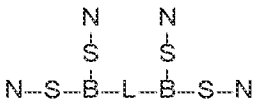
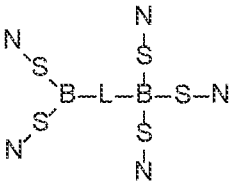
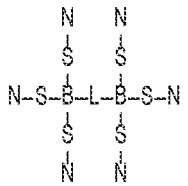
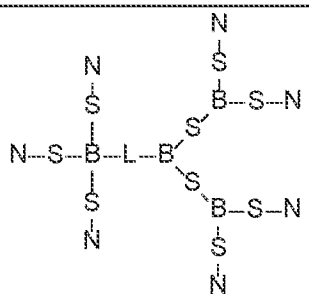
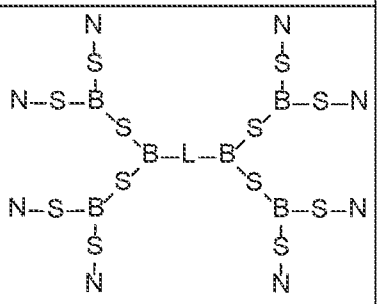
N is a double stranded nucleic acid comprising 15 to 35 bases in length comprising a sense strand and an antisense strand; wherein

the antisense strand comprises a sequence substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295;

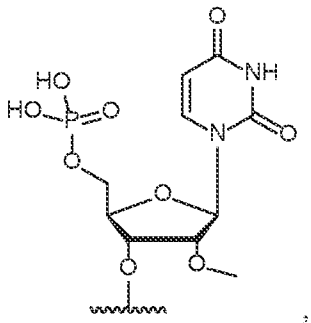
the sense strand and antisense strand each independently comprise one or more chemical modifications; and

n is 2, 3, 4, 5, 6, 7 or 8.

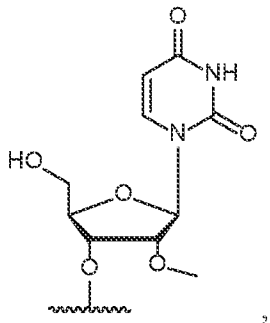
158. The compound of claim 157, having a structure selected from formulas (I-1)-(I-9):

		
(I-1)	(I-2)	(I-3)
		
(I-4)	(I-5)	(I-6)
		
(I-7)	(I-8)	(I-9)

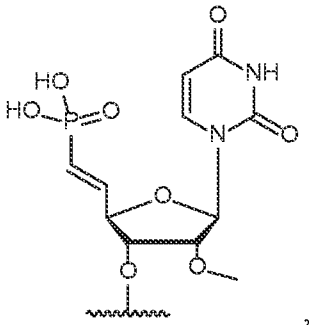
159. The compound of claim 157, wherein the antisense strand comprises a 5' terminal group R selected from the group consisting of:



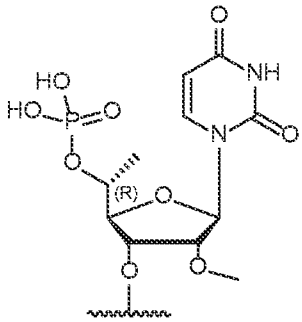
, R^1



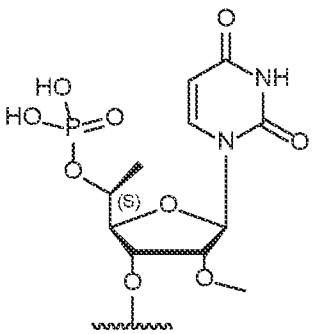
, R^2



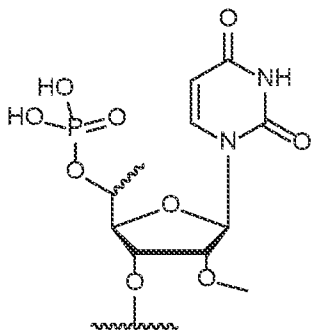
, R^3



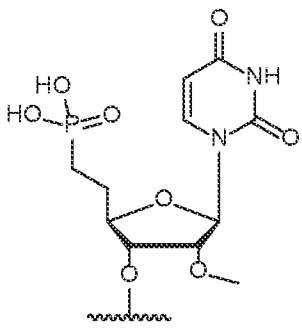
, R^4



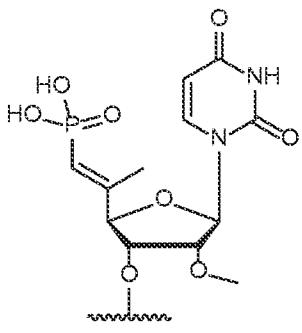
, R^5



, R^6

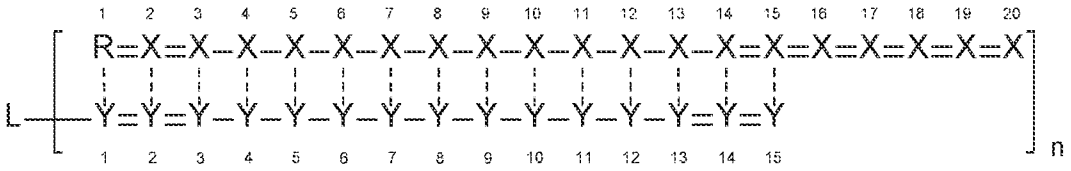


, and R^7



. R^8

160. The compound of claim 157, having the structure of formula (II):



(II)

wherein:

X, for each occurrence, independently, is selected from adenosine, guanosine, uridine, cytidine, and chemically-modified derivatives thereof;

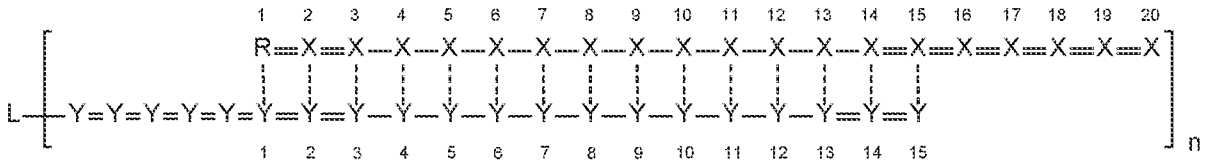
Y, for each occurrence, independently, is selected from adenosine, guanosine, uridine, cytidine, and chemically-modified derivatives thereof;

- represents a phosphodiester internucleoside linkage;

= represents a phosphorothioate internucleoside linkage; and

--- represents, individually for each occurrence, a base-pairing interaction or a mismatch.

161. The compound of claim 157, having the structure of formula (IV):



(IV)

wherein:

X, for each occurrence, independently, is selected from adenosine, guanosine, uridine, cytidine, and chemically-modified derivatives thereof;

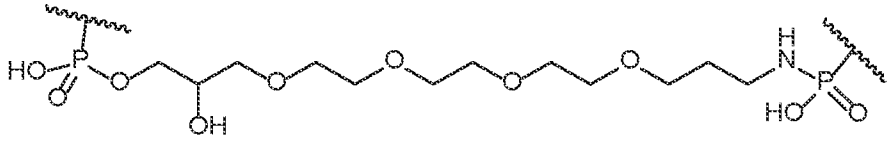
Y, for each occurrence, independently, is selected from adenosine, guanosine, uridine, cytidine, and chemically-modified derivatives thereof;

- represents a phosphodiester internucleoside linkage;

= represents a phosphorothioate internucleoside linkage; and

--- represents, individually for each occurrence, a base-pairing interaction or a mismatch.

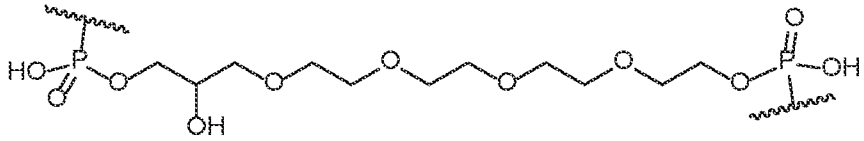
162. The compound of any one of claims 157-161, wherein L is structure L1:



(L1).

163. The compound of claim 164, wherein R is R^3 and n is 2.

164. The compound of any one of claims 157-161, wherein L is structure L2:



(L2).

165. The compound of claim 164, wherein R is R^3 and n is 2.

166. A delivery system for therapeutic nucleic acids having the structure of Formula (VI):

$$L\text{—}(cNA)_n$$

(VI)

wherein:

L comprises an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, or combinations thereof, wherein formula (VI) optionally further comprises one or more branch point B, and one or more spacer S, wherein:

B comprises independently for each occurrence a polyvalent organic species or derivative thereof;

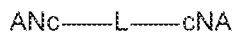
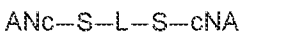
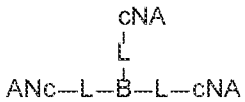
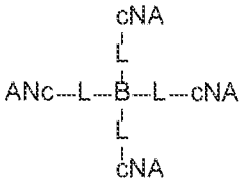
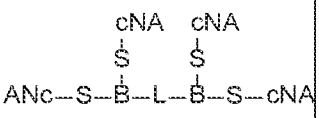
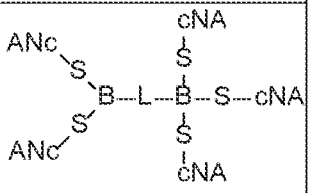
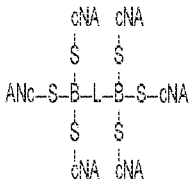
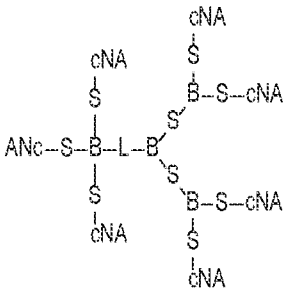
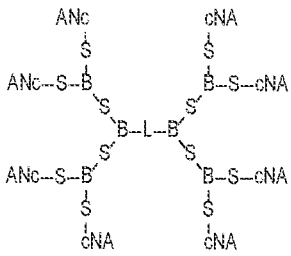
S comprises independently for each occurrence an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphate, a phosphonate, a phosphoramidate, an ester, an amide, a triazole, or combinations thereof;

each cNA, independently, is a carrier nucleic acid comprising one or more chemical modifications;

each cNA, independently, comprises at least 15 contiguous nucleotides of a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295; and

n is 2, 3, 4, 5, 6, 7 or 8.

167. The delivery system of claim 166, having a structure selected from formulas (VI-1)-(VI-9):

		
(VI-1)	(VI -2)	(VI -3)
		
(VI-4)	(VI -5)	(VI -6)
		
(VI -7)	(VI-8)	(VI-9)

168. The delivery system of claim 166, wherein each cNA independently comprises chemically-modified nucleotides.

169. The delivery system of claim 166, further comprising n therapeutic nucleic acids (NA), wherein each NA is hybridized to at least one cNA.

170. The delivery system of claim 169, wherein each NA independently comprises at least 16 contiguous nucleotides.

171. The delivery system of claim 170, wherein each NA independently comprises 16-20 contiguous nucleotides.

172. The delivery system of claim 169, wherein each NA comprises an unpaired overhang of at least 2 nucleotides.

173. The delivery system of claim 172, wherein the nucleotides of the overhang are connected via phosphorothioate linkages.

174. The delivery system of claim 169, wherein each NA, independently, is selected from the group consisting of DNAs, siRNAs, antagomiRs, miRNAs, gapmers, mixmers, and guide RNAs.

175. The delivery system of claim 169, wherein each NA is substantially complementary to a *MAPT* nucleic acid sequence of any one of SEQ ID NOs: 1-13, 292, and 295.

176. A pharmaceutical composition for inhibiting the expression of *MAPT* gene in an organism, comprising a compound of any one of claims 85-165 or a system of any of claims 166-75, and a pharmaceutically acceptable carrier.

177. The pharmaceutical composition of claim 176, wherein the compound or system inhibits the expression of the *MAPT* gene by at least 50%.

178. The pharmaceutical composition of claim 176, wherein the compound or system inhibits the expression of the *MAPT* gene by at least 80%.

179. A method for inhibiting expression of *MAPT* gene in a cell, the method comprising:

(a) introducing into the cell a compound of any one of claims 85-162 or a system of any of claims 166-175; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of the *MAPT* gene, thereby inhibiting expression of the *MAPT* gene in the cell.

180. A method of treating or managing a neurodegenerative disease comprising administering to a patient in need of such treatment or management a therapeutically effective amount of a compound of any one of claims 85-165 or a system of any of claims 166-175.

181. The method of claim 180, wherein said dsRNA is administered to the brain of the patient.

182. The method of claim 180, wherein said dsRNA is administered by intracerebroventricular (ICV) injection, intrastriatal (IS) injection, intravenous (IV) injection, subcutaneous (SQ) injection, or a combination thereof.

183. The method of claim 180, wherein 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.

184. The method of any one of claims 179-183, wherein the dsRNA inhibits the expression of said *MAPT* gene by at least 50%.

185. The method of any one of claims 179-183, wherein the dsRNA inhibits the expression of said *MAPT* gene by at least 80%.

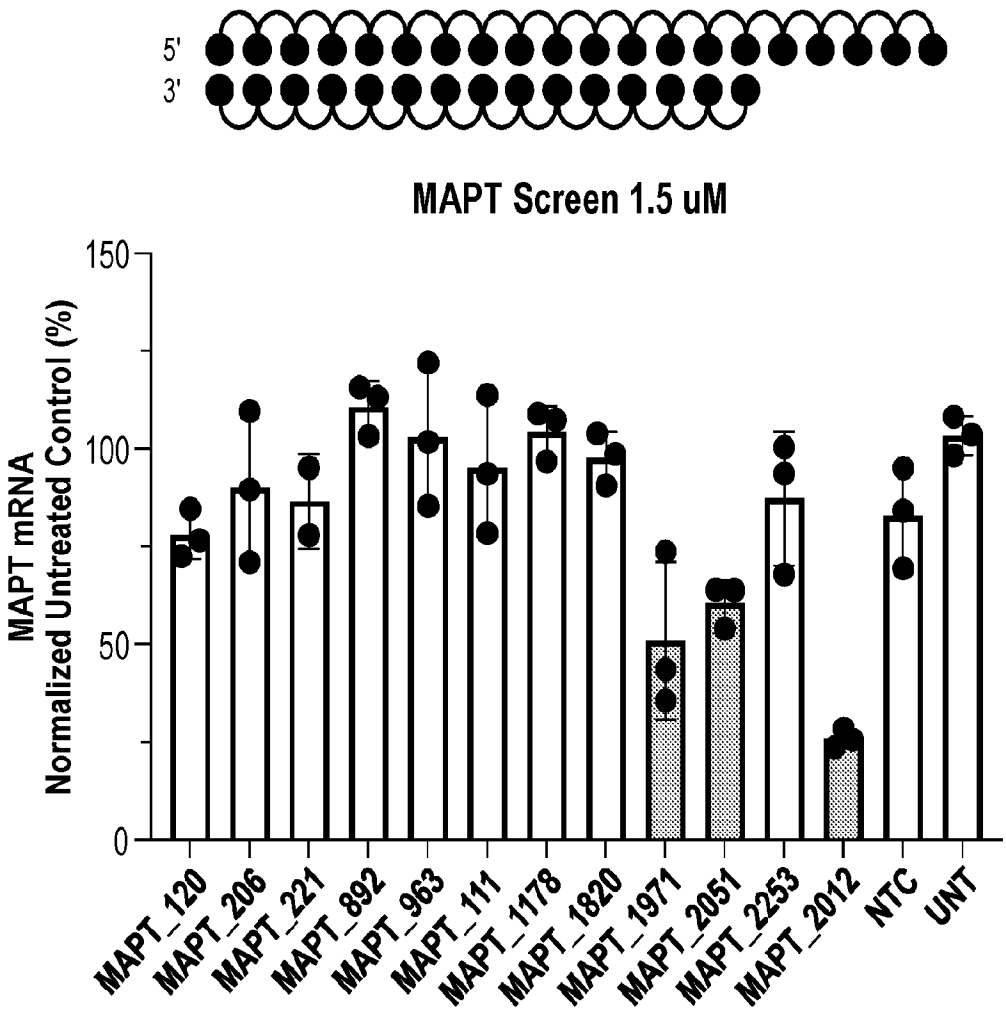

5'
3'
MAPT Screen 1.5 uM
MAPT mRNA
Normalized Untreated Control (%)
150
100
50
0
MAPT_120
MAPT_206
MAPT_221
MAPT_892
MAPT_963
MAPT_111
MAPT_1178
MAPT_1820
MAPT_1971
MAPT_2051
MAPT_2253
MAPT_2012
NTC
UNT

Fig. 1A

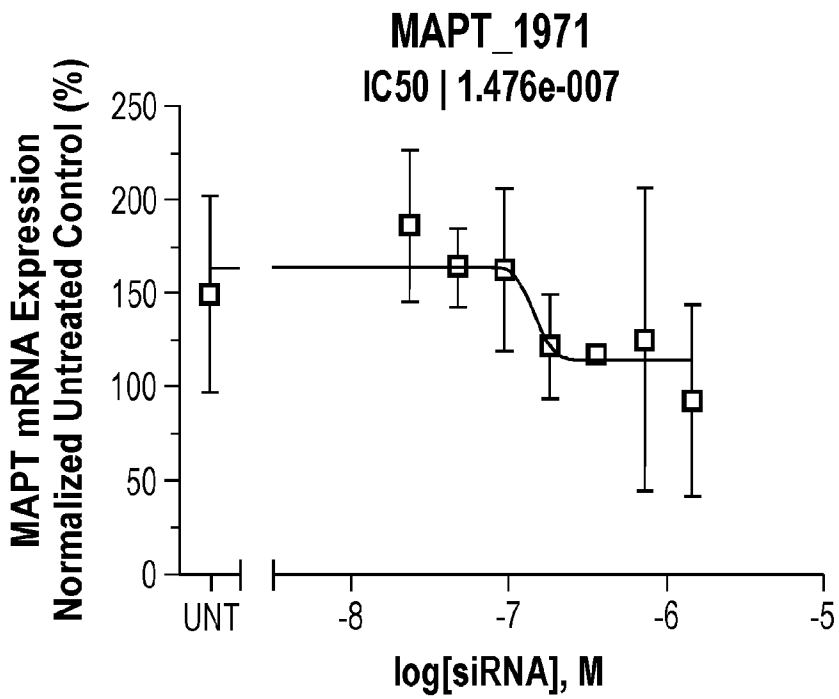

MAPT_1971
IC50 | 1.476e-007
MAPT mRNA Expression
Normalized Untreated Control (%)
250
200
150
100
50
0
UNT
-8
-7
-6
-5
log[siRNA], M

Fig. 1B

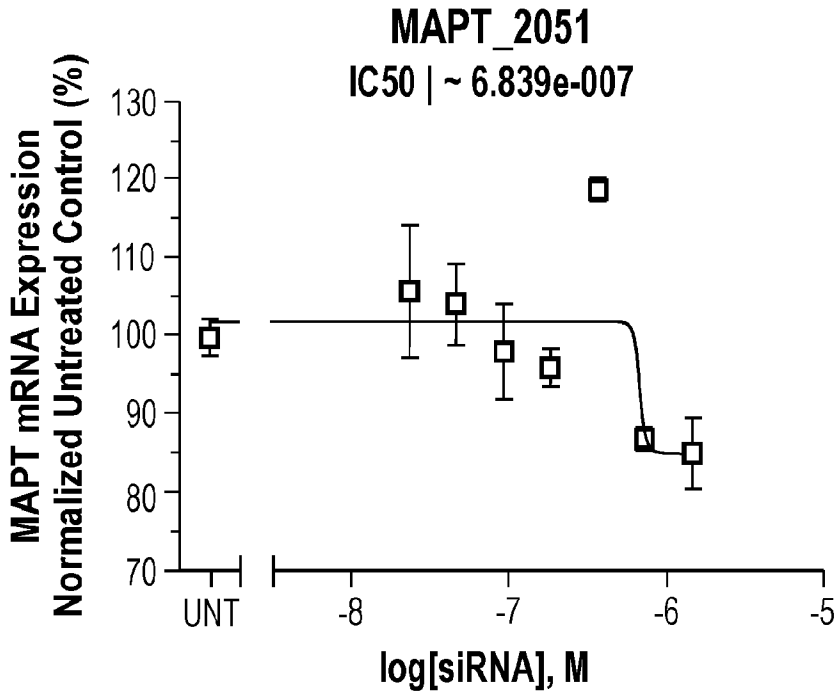

MAPT_2051
IC50 | ~ 6.839e-007
MAPT mRNA Expression
Normalized Untreated Control (%)
130
120
110
100
90
80
70
UNT
-8
-7
-6
-5
log[siRNA], M

Fig. 1C

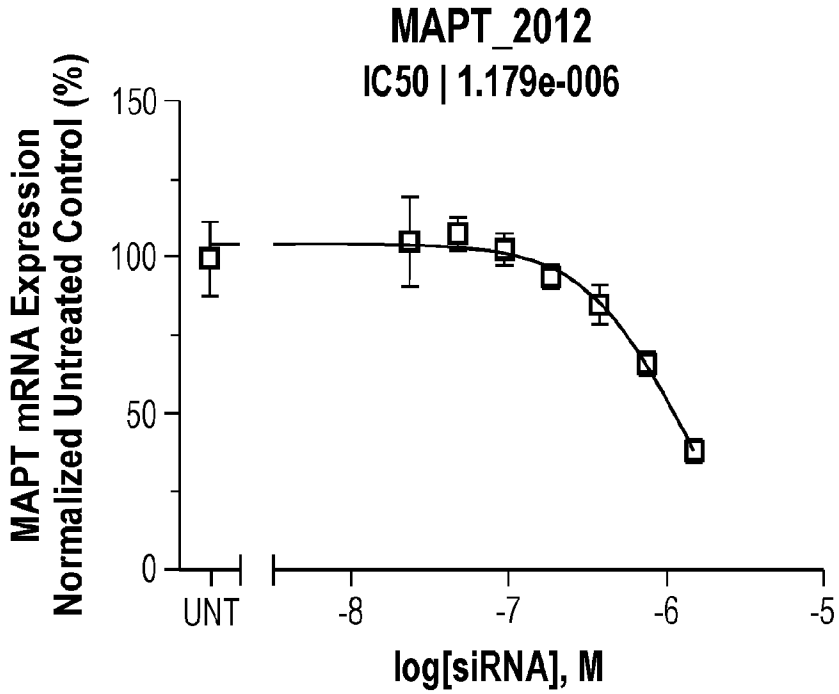

MAPT_2012
IC50 | 1.179e-006
MAPT mRNA Expression
Normalized Untreated Control (%)
150
100
50
0
UNT
-8
-7
-6
-5
log[siRNA], M

Fig. 1D

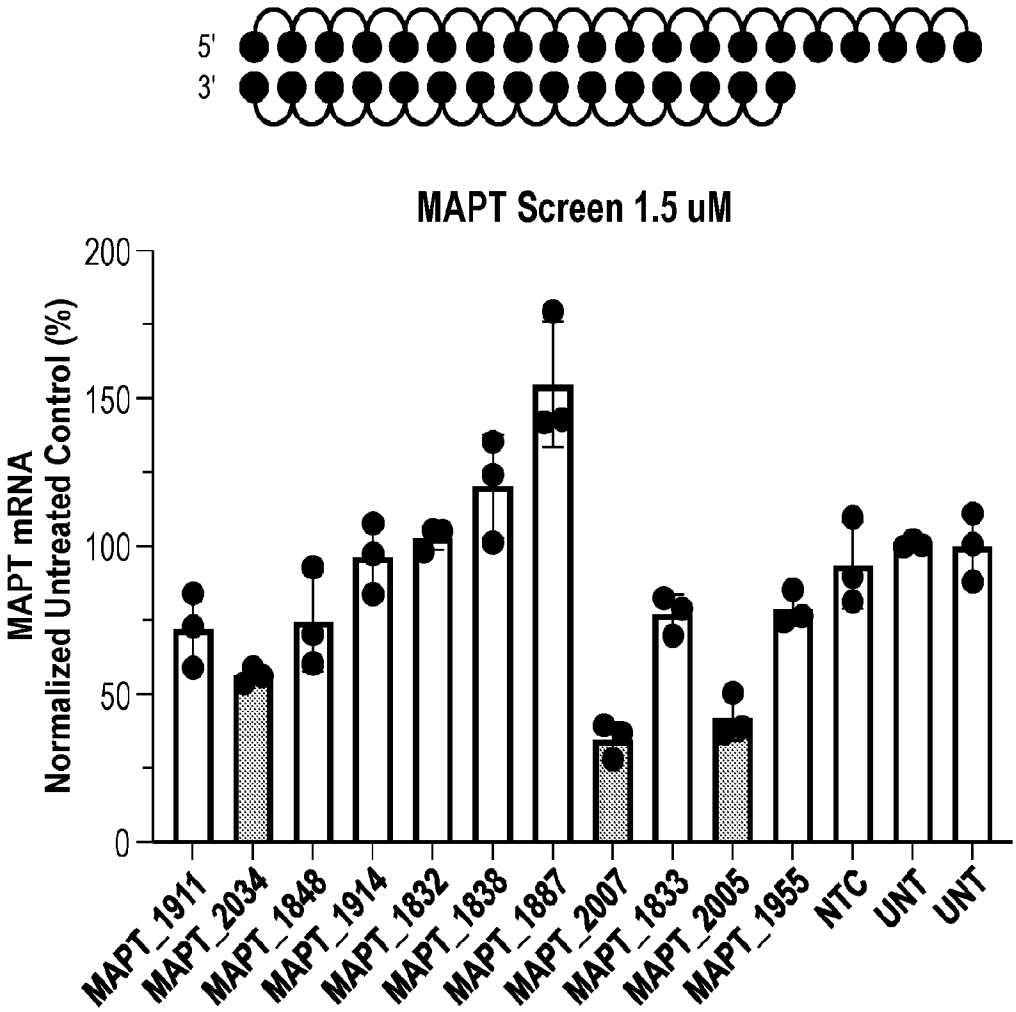

5'
3'
MAPT Screen 1.5 uM
MAPT mRNA
Normalized Untreated Control (%)
200
150
100
50
0
MAPT_1911
MAPT_2034
MAPT_1848
MAPT_1914
MAPT_1832
MAPT_1838
MAPT_1887
MAPT_2007
MAPT_1833
MAPT_2005
MAPT_1955
NTC
UNT
UNT

Fig. 2A

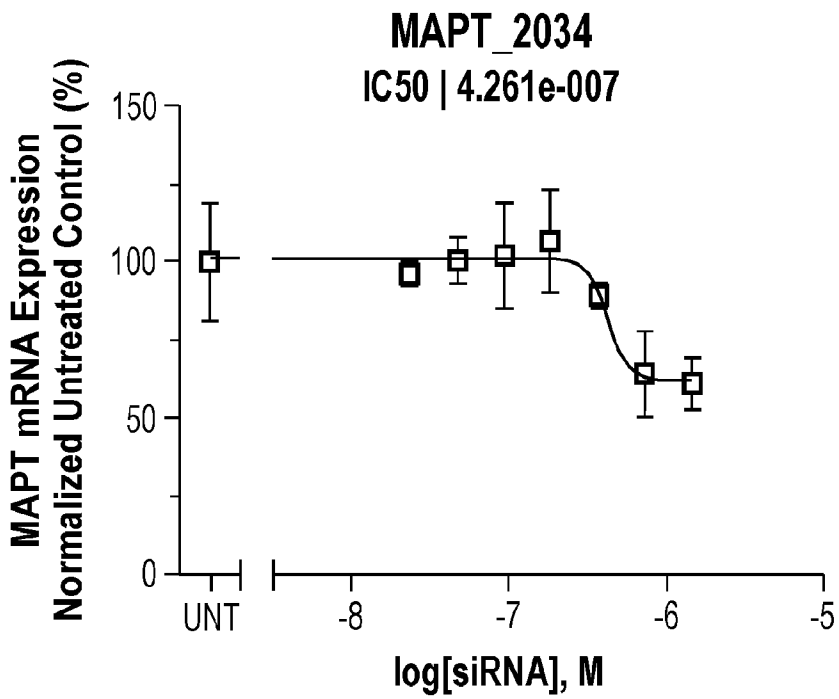

MAPT_2034
IC50 | 4.261e-007
MAPT mRNA Expression
Normalized Untreated Control (%)
150
100
50
0
UNT
-8
-7
-6
-5
log[siRNA], M

Fig. 2B

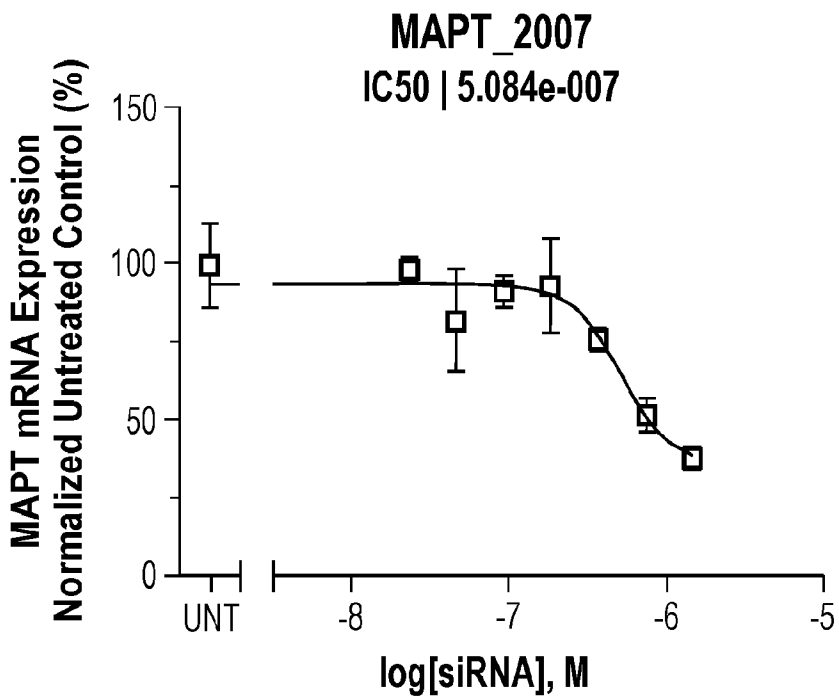

MAPT_2007
IC50 | 5.084e-007
MAPT mRNA Expression
Normalized Untreated Control (%)
150
100
50
0
UNT
-8
-7
-6
-5
log[siRNA], M

Fig. 2C

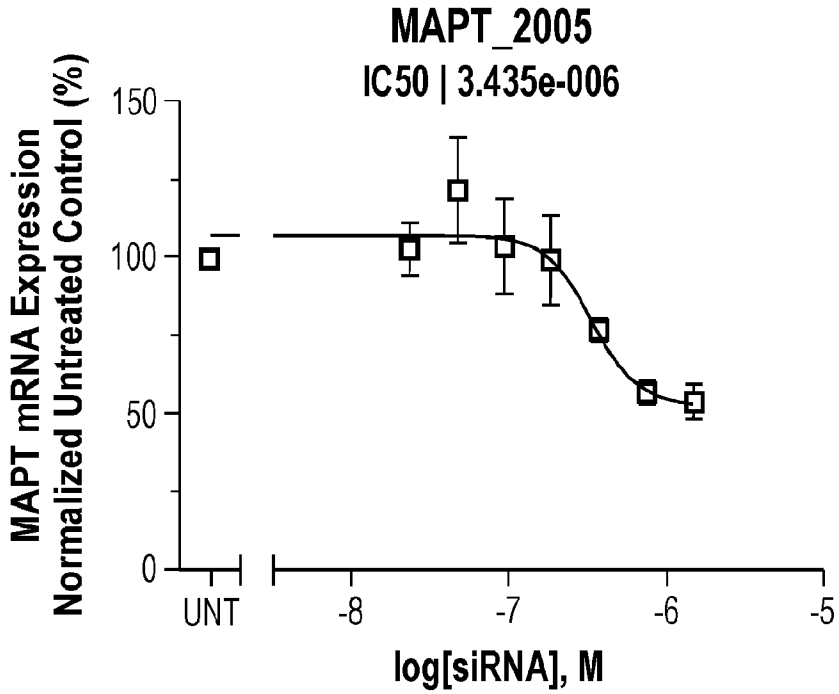

MAPT_2005
IC50 | 3.435e-006
MAPT mRNA Expression
Normalized Untreated Control (%)
150
100
50
0
UNT
-8
-7
-6
-5
log[siRNA], M

Fig. 2D

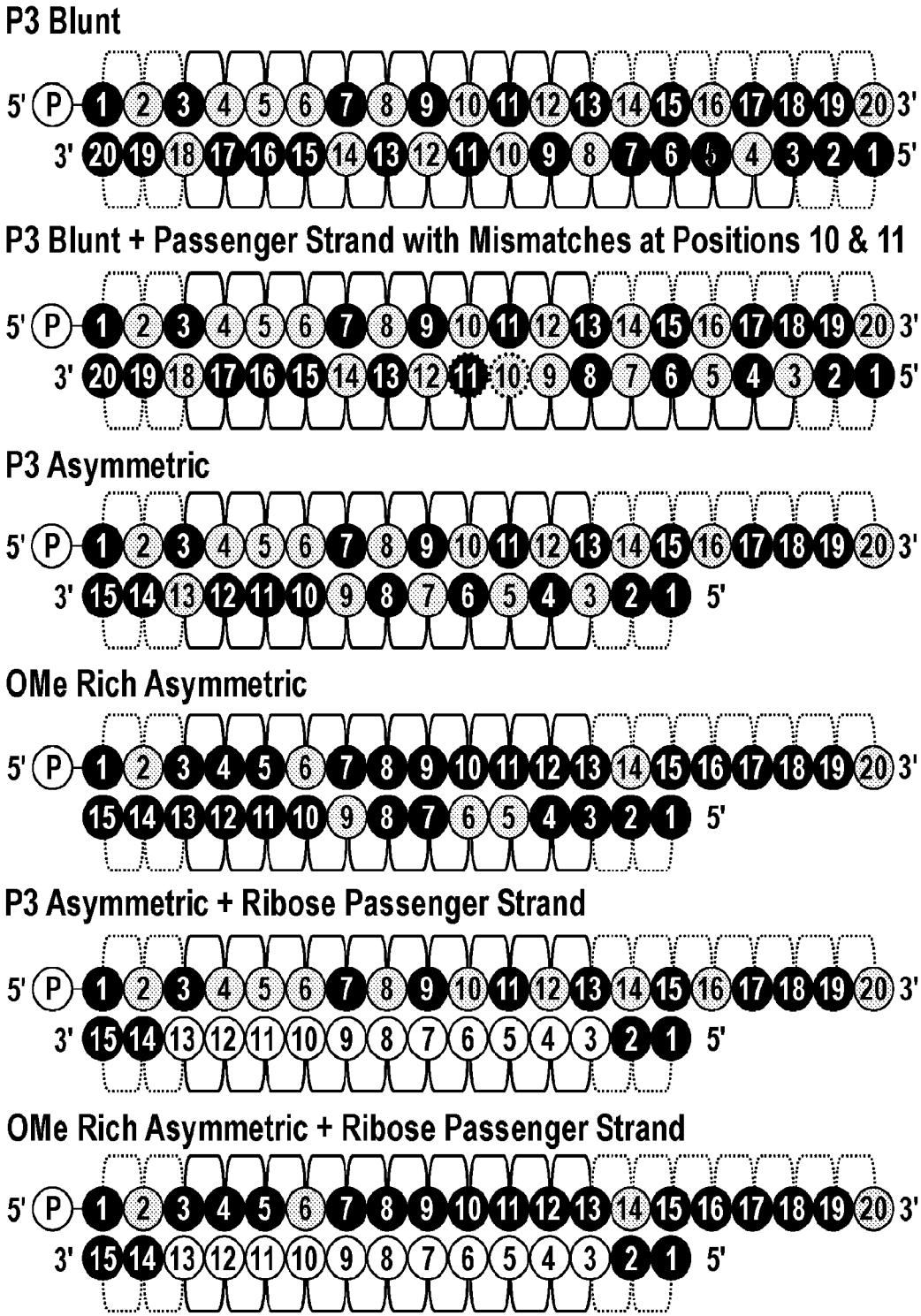

P3 Blunt
5' P 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 3'
3' 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 5'
P3 Blunt + Passenger Strand with Mismatches at Positions 10 & 11
5' P 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 3'
3' 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 5'
P3 Asymmetric
5' P 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 3'
3' 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 5'
OMe Rich Asymmetric
5' P 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 3'
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 5'
P3 Asymmetric + Ribose Passenger Strand
5' P 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 3'
3' 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 5'
OMe Rich Asymmetric + Ribose Passenger Strand
5' P 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 3'
3' 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 5'
P 5' phosphate
2'-O-methyl RNA
2'-fluoro RNA
2'-hydroxyl RNA
base mismatch
phosphorothioate
phosphodiester

Fig. 3

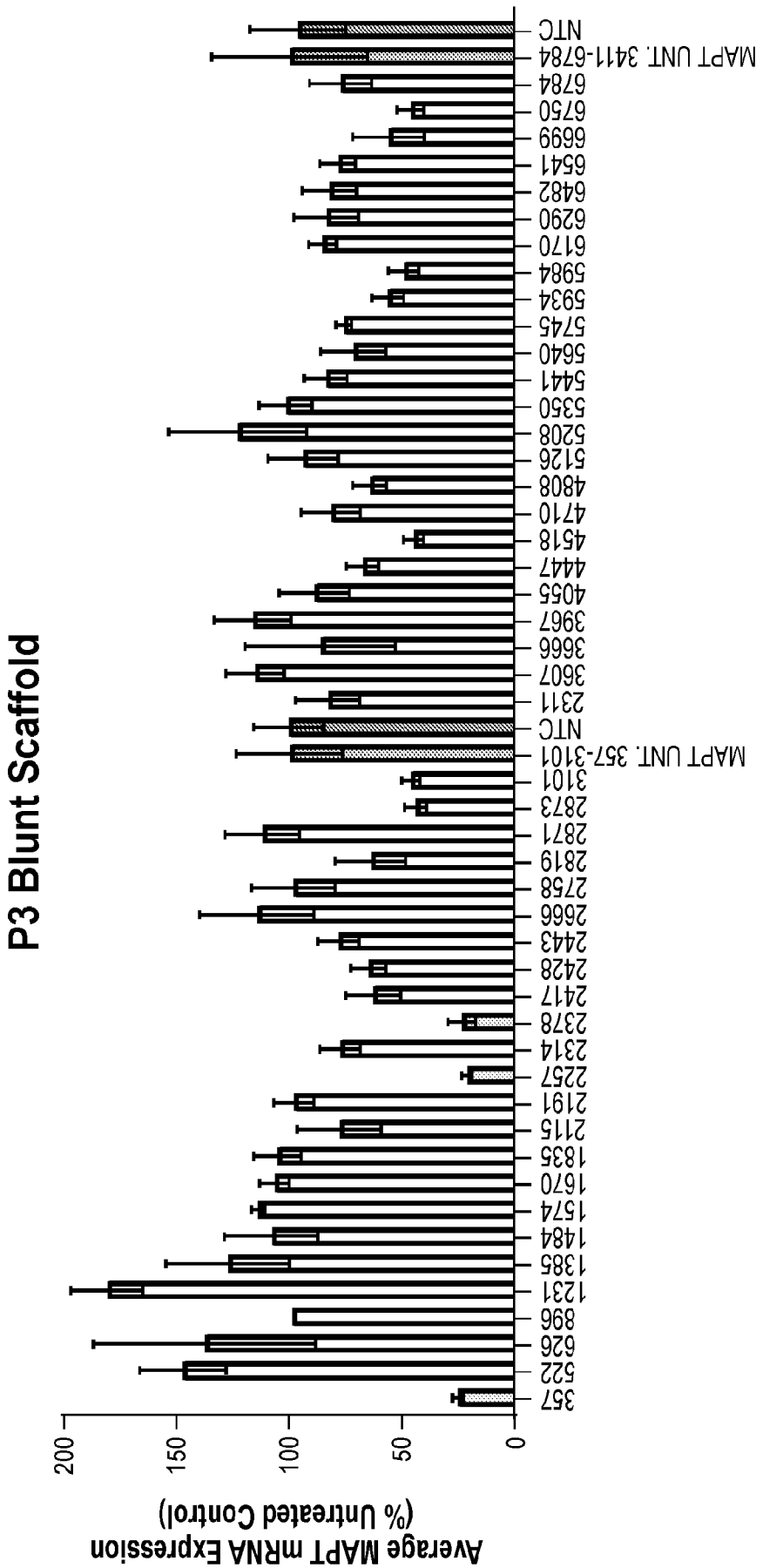

P3 Blunt Scaffold
Average MAPT mRNA Expression
(% Untreated Control)
0
50
100
150
200
357
522
626
896
1231
1385
1484
1574
1670
1835
2115
2191
2257
2314
2378
2417
2428
2443
2666
2758
2819
2871
2873
3101
MAPT UNT. 357-3101
NTC
2311
3607
3666
3967
4055
4447
4518
4710
4808
5126
5208
5350
5441
5640
5745
5934
5984
6170
6290
6482
6541
6699
6750
6784
MAPT UNT. 3411-6784
NTC

Fig. 4A

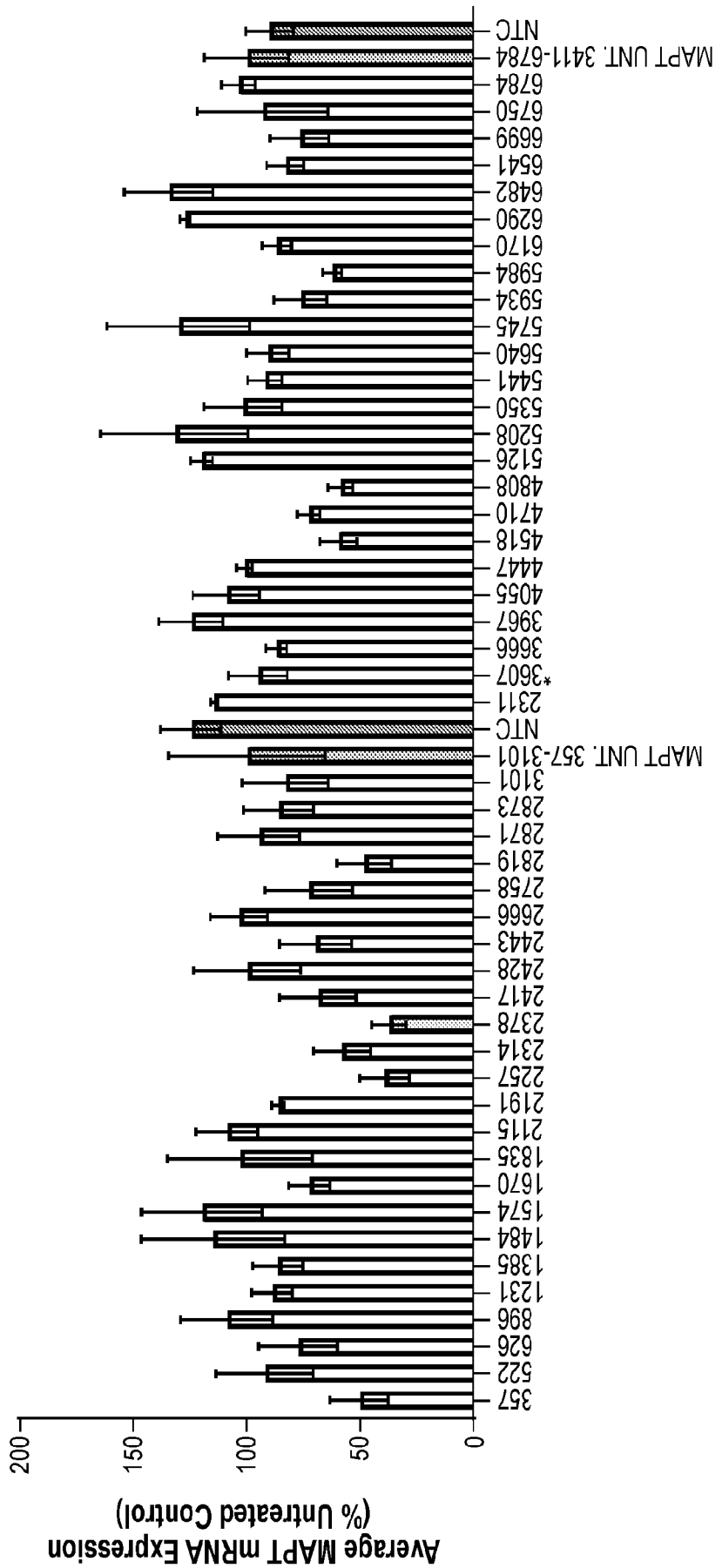

P3 Blunt + Mismatches at Positions 10 and 11 on Sense Strand Scaffold
Average MAPT mRNA Expression
(% Untreated Control)
0
50
100
150
200
357
522
626
896
1231
1385
1484
1574
1670
1835
2115
2191
2257
2314
2378
2417
2428
2443
2666
2758
2819
2871
2873
3101
MAPT UNT. 357-3101
NTC
2311
*3607
3666
3967
4055
4447
4518
4710
4808
5126
5208
5350
5441
5640
5745
5934
5984
6170
6290
6482
6541
6699
6750
6784
MAPT UNT. 3411-6784
NTC

Fig. 4B

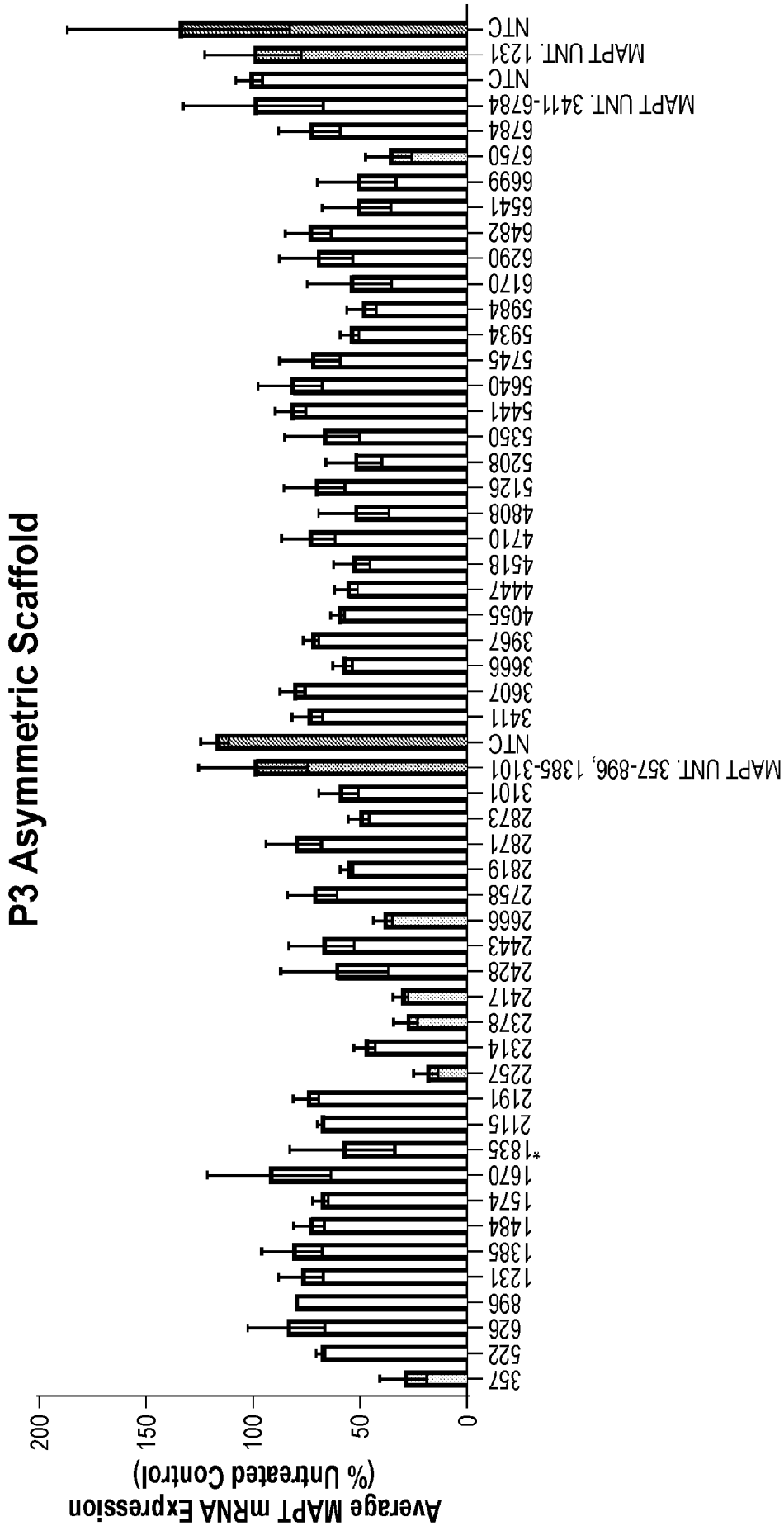

P3 Asymmetric Scaffold
Average MAPT mRNA Expression
(% Untreated Control)
0
50
100
150
200
357
522
626
896
1231
1385
1484
1574
1670
*1835
2115
2191
2257
2314
2378
2417
2428
2443
2666
2758
2819
2871
2873
3101
MAPT UNT. 357-896, 1385-3101
NTC
3411
3607
3666
3967
4055
4447
4518
4710
4808
5126
5208
5350
5441
5640
5745
5934
5984
6170
6290
6482
6541
6699
6750
6784
MAPT UNT. 3411-6784
NTC
MAPT UNT. 1231
NTC

Fig. 4C

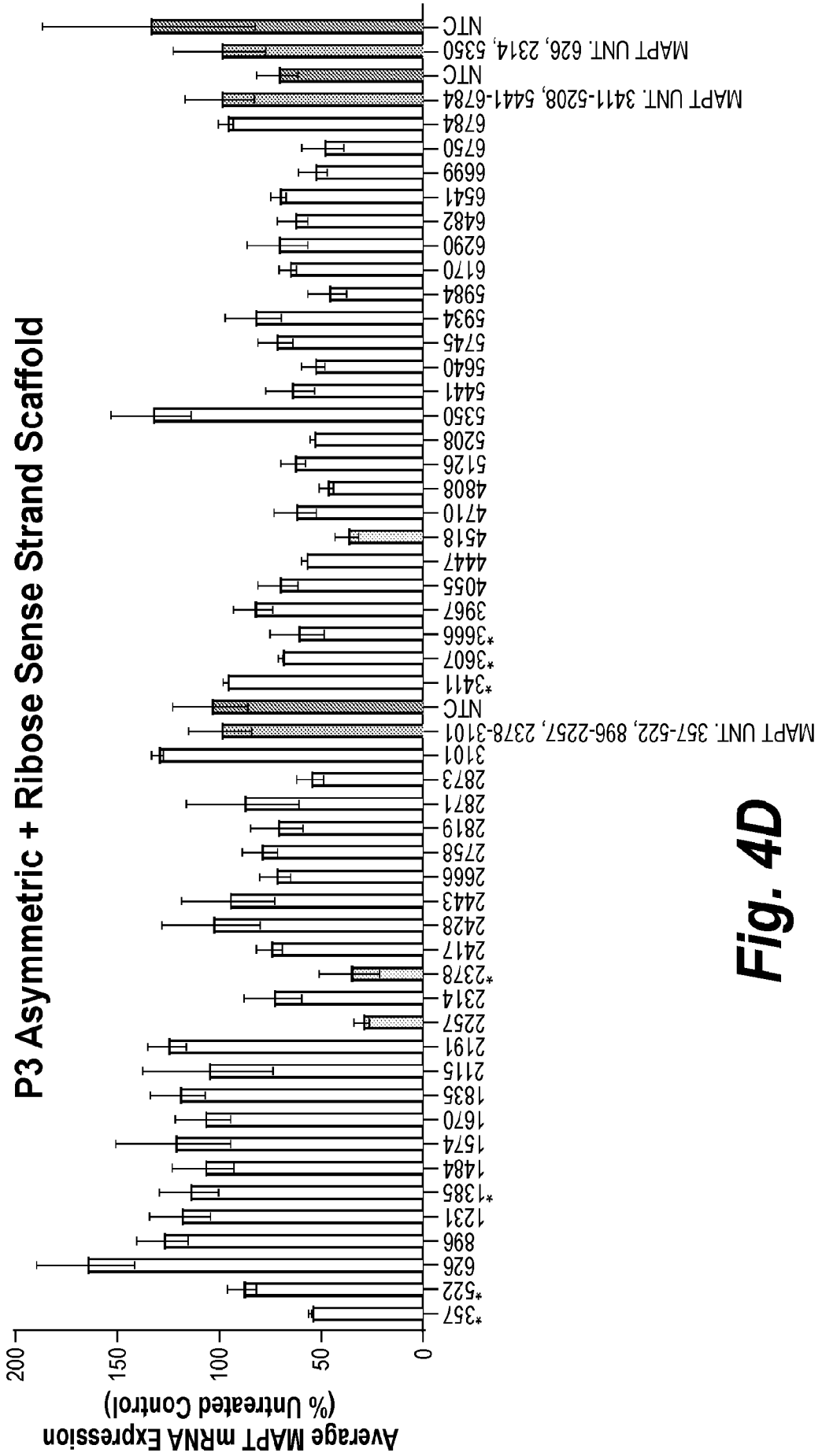

P3 Asymmetric + Ribose Sense Strand Scaffold
Average MAPT mRNA Expression
(% Untreated Control)
0
50
100
150
200
*357
*522
626
896
1231
*1385
1484
1574
1670
1835
2115
2191
2257
2314
*2378
2417
2428
2443
2666
2758
2819
2871
2873
3101
MAPT UNT. 357-522, 896-2257, 2378-3101
NTC
*3411
*3607
*3666
3967
4055
4447
4518
4710
4808
5126
5208
5350
5441
5640
5745
5934
5984
6170
6290
6482
6541
6699
6750
6784
MAPT UNT. 3411-5208, 5441-6784
NTC
MAPT UNT. 626, 2314, 5350
NTC

Fig. 4D

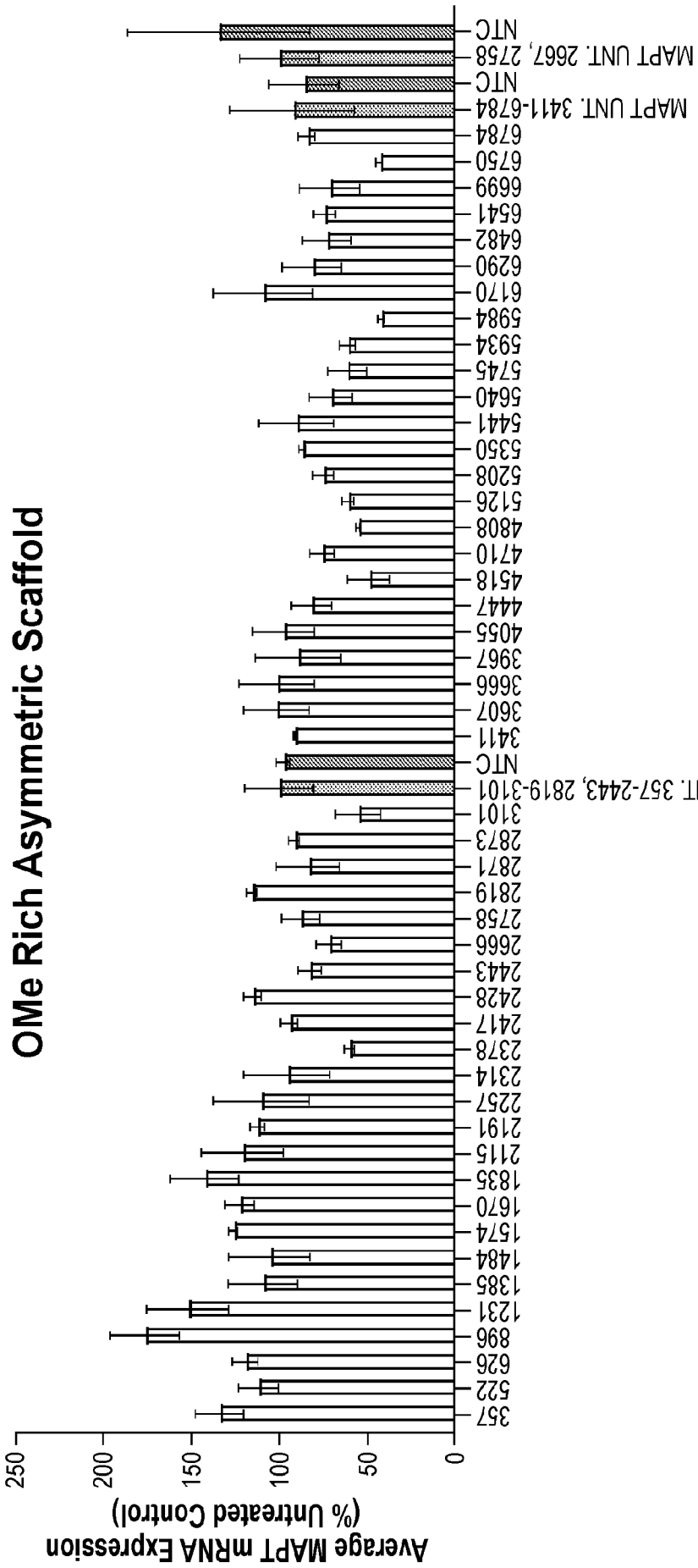

OMe Rich Asymmetric Scaffold
Average MAPT mRNA Expression
(% Untreated Control)
0
50
100
150
200
250
357
522
626
896
1231
1385
1484
1574
1670
1835
2115
2191
2257
2314
2378
2417
2428
2443
2666
2758
2819
2871
2873
3101
MAPT UNT. 357-2443, 2819-3101
NTC
3411
3607
3666
3967
4055
4447
4518
4710
4808
5126
5208
5350
5441
5640
5745
5934
5984
6170
6290
6482
6541
6699
6750
6784
MAPT UNT. 3411-6784
NTC
MAPT UNT. 2667, 2758
NTC

Fig. 4E

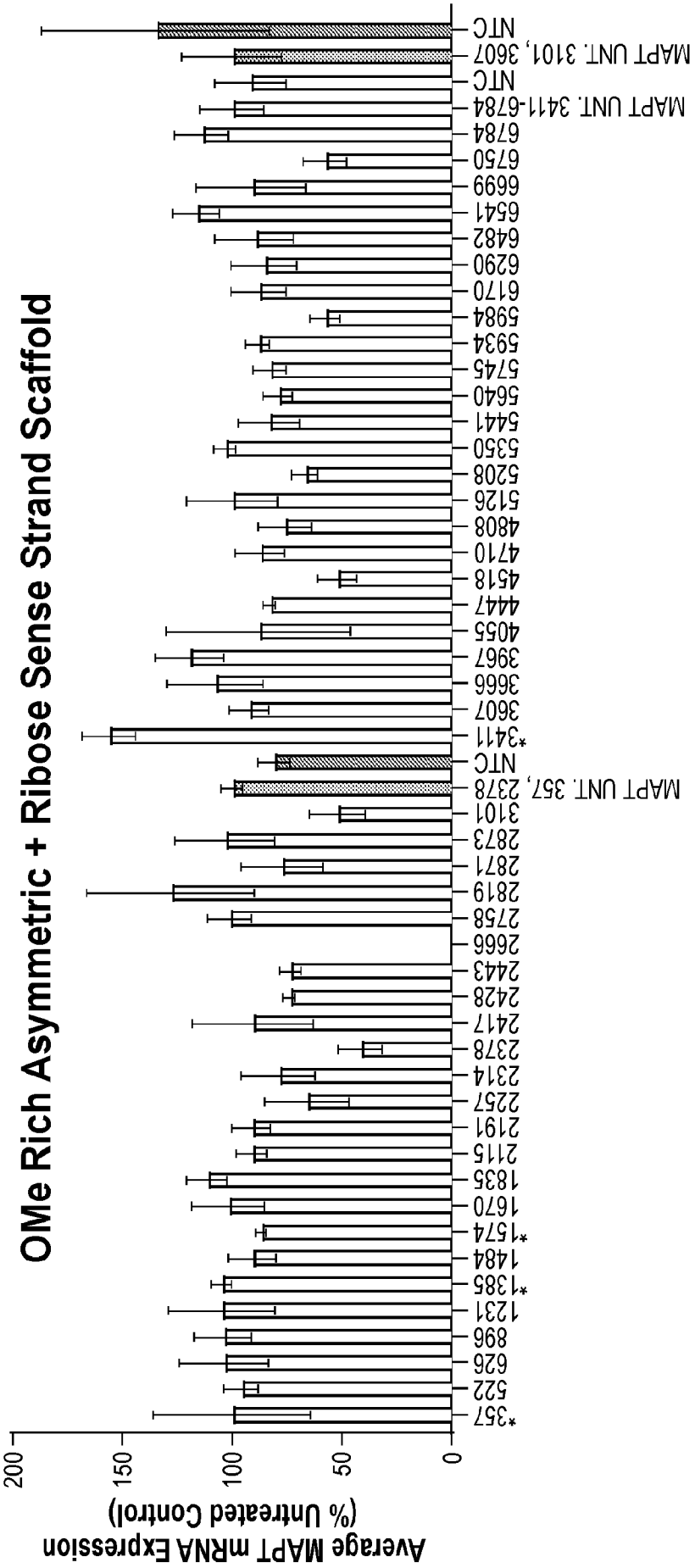

OMe Rich Asymmetric + Ribose Sense Strand Scaffold
Average MAPT mRNA Expression
(% Untreated Control)
0
50
100
150
200
NTC
MAPT UNT. 3101, 3607
NTC
MAPT UNT. 3411-6784
6784
6750
6699
6541
6482
6290
6170
5984
5934
5745
5640
5441
5350
5208
5126
4808
4710
4518
4447
4055
3967
3666
3607
*3411
NTC
MAPT UNT. 357, 2378
3101
2873
2871
2819
2758
2666
2443
2428
2417
2378
2314
2257
2191
2115
1835
1670
*1574
1484
*1385
1231
896
626
522
*357

Fig. 4F

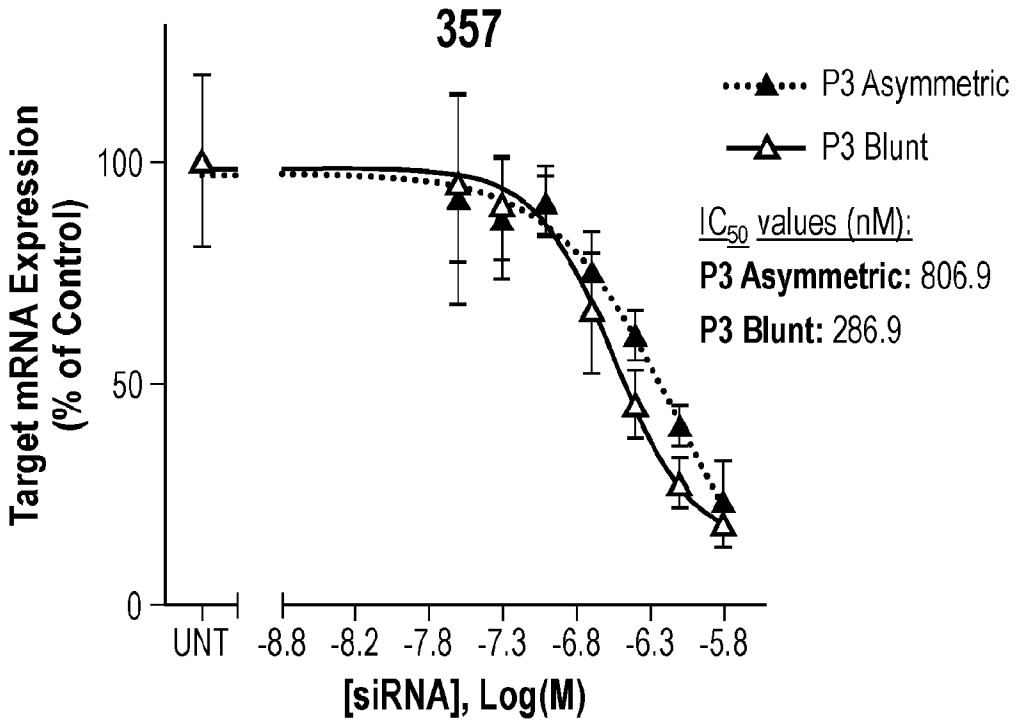

357
Target mRNA Expression (% of Control)
100
50
0
UNT
-8.8
-8.2
-7.8
-7.3
-6.8
-6.3
-5.8
[siRNA], Log(M)
P3 Asymmetric
P3 Blunt
IC50 values (nM):
P3 Asymmetric: 806.9
P3 Blunt: 286.9

Fig. 5A

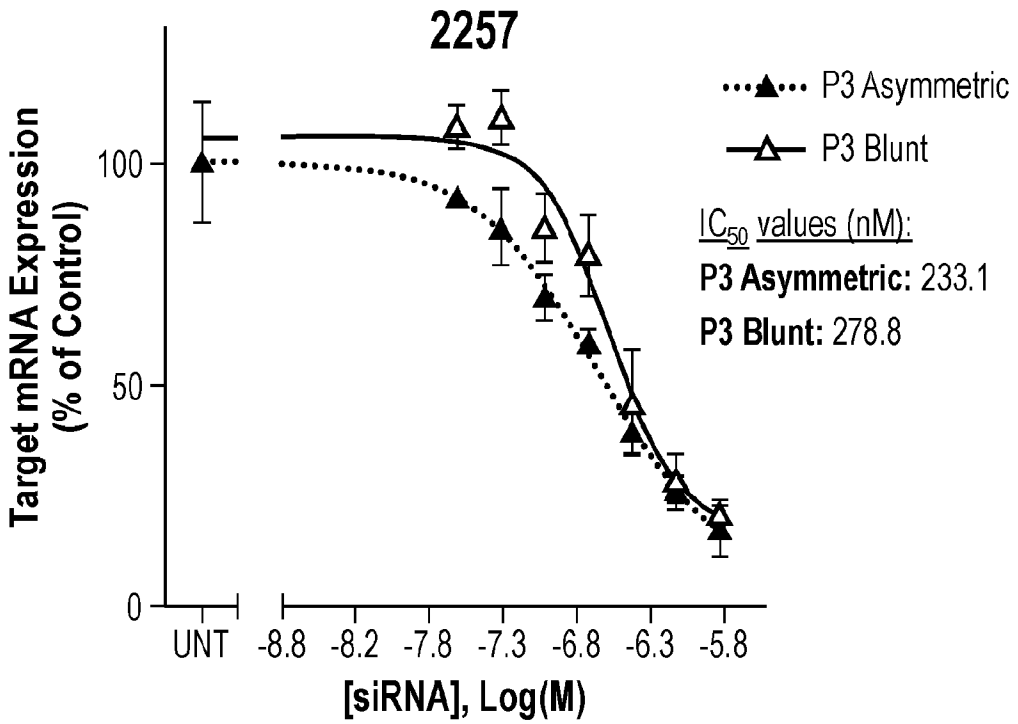

2257
Target mRNA Expression (% of Control)
100
50
0
UNT
-8.8
-8.2
-7.8
-7.3
-6.8
-6.3
-5.8
[siRNA], Log(M)
P3 Asymmetric
P3 Blunt
IC50 values (nM):
P3 Asymmetric: 233.1
P3 Blunt: 278.8

Fig. 5B

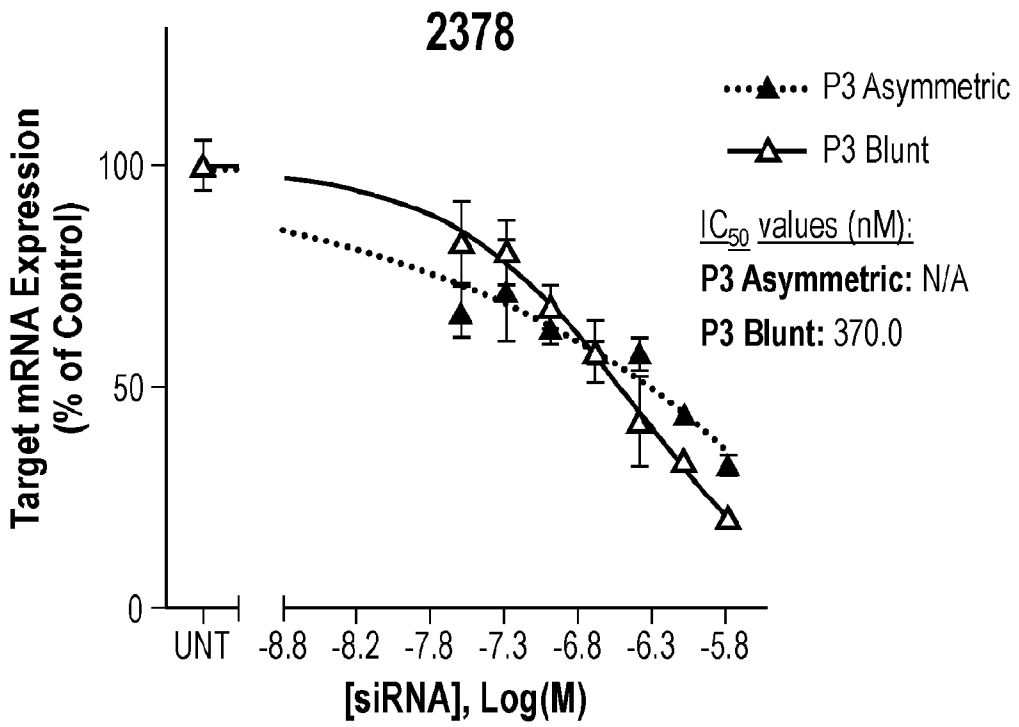

2378
P3 Asymmetric
P3 Blunt
IC50 values (nM):
P3 Asymmetric: N/A
P3 Blunt: 370.0
Target mRNA Expression (% of Control)
100
50
0
UNT
-8.8
-8.2
-7.8
-7.3
-6.8
-6.3
-5.8
[siRNA], Log(M)

Fig. 5C

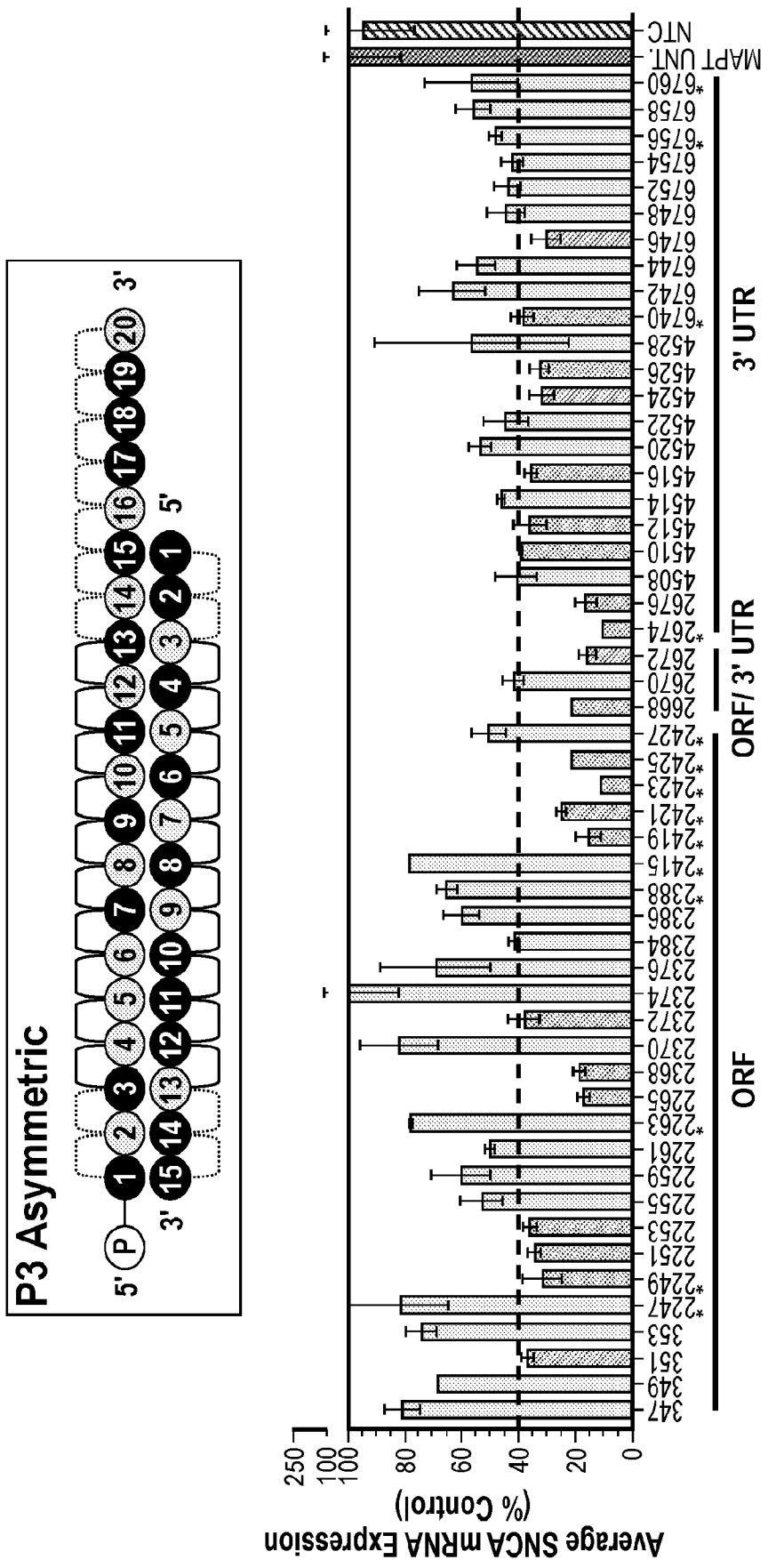

P3 Asymmetric
5'
P
3'
3'
5'
Average SNCA mRNA Expression
(% Control)
250
100
100
80
60
40
20
0
NTC
MAPT UNT.
347
349
351
353
*2247
2249
2251
2253
2255
2259
2261
*2263
2265
2368
2370
2372
2374
2376
2384
2386
*2388
*2415
*2419
*2421
*2423
*2425
*2427
2668
2670
2672
*2674
2676
4508
4510
4512
4514
4516
4520
4522
4524
4526
4528
*6740
6742
6744
6746
6748
6752
6754
*6756
6758
*6760
ORF
ORF/ 3' UTR
3' UTR

Fig. 6

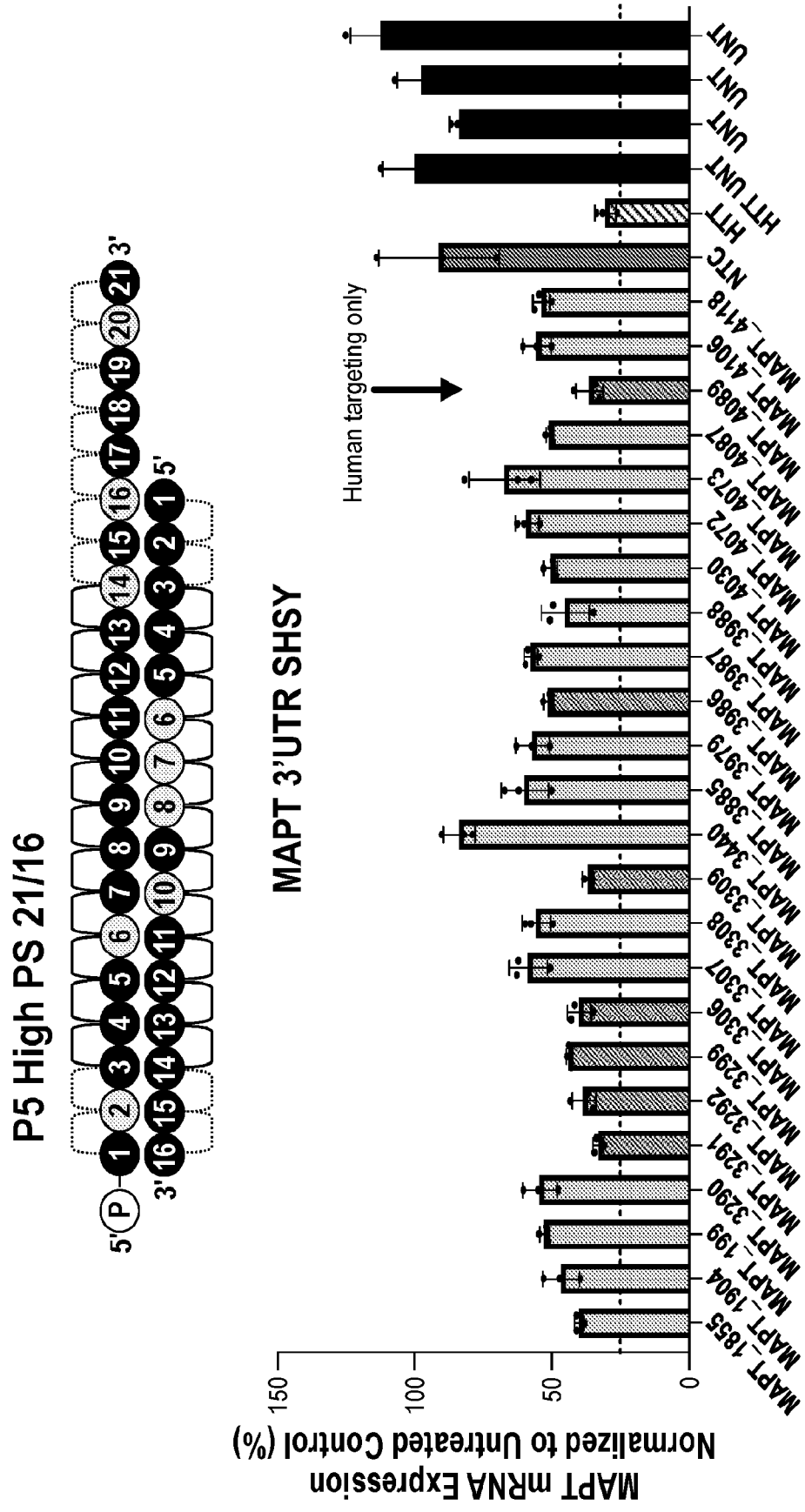

P5 High PS 21/16
5'
P
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
3'
3'
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
5'
MAPT 3'UTR SHSY
Human targeting only
MAPT mRNA Expression
Normalized to Untreated Control (%)
150
100
50
0
MAPT_1853
MAPT_1904
MAPT_199
MAPT_3290
MAPT_3291
MAPT_3292
MAPT_3299
MAPT_3306
MAPT_3307
MAPT_3308
MAPT_3309
MAPT_3440
MAPT_3865
MAPT_3979
MAPT_3986
MAPT_3987
MAPT_3988
MAPT_4030
MAPT_4072
MAPT_4073
MAPT_4087
MAPT_4089
MAPT_4106
MAPT_4118
NTC
HTT
HTT UNT
UNT
UNT
UNT
UNT

Fig. 7A

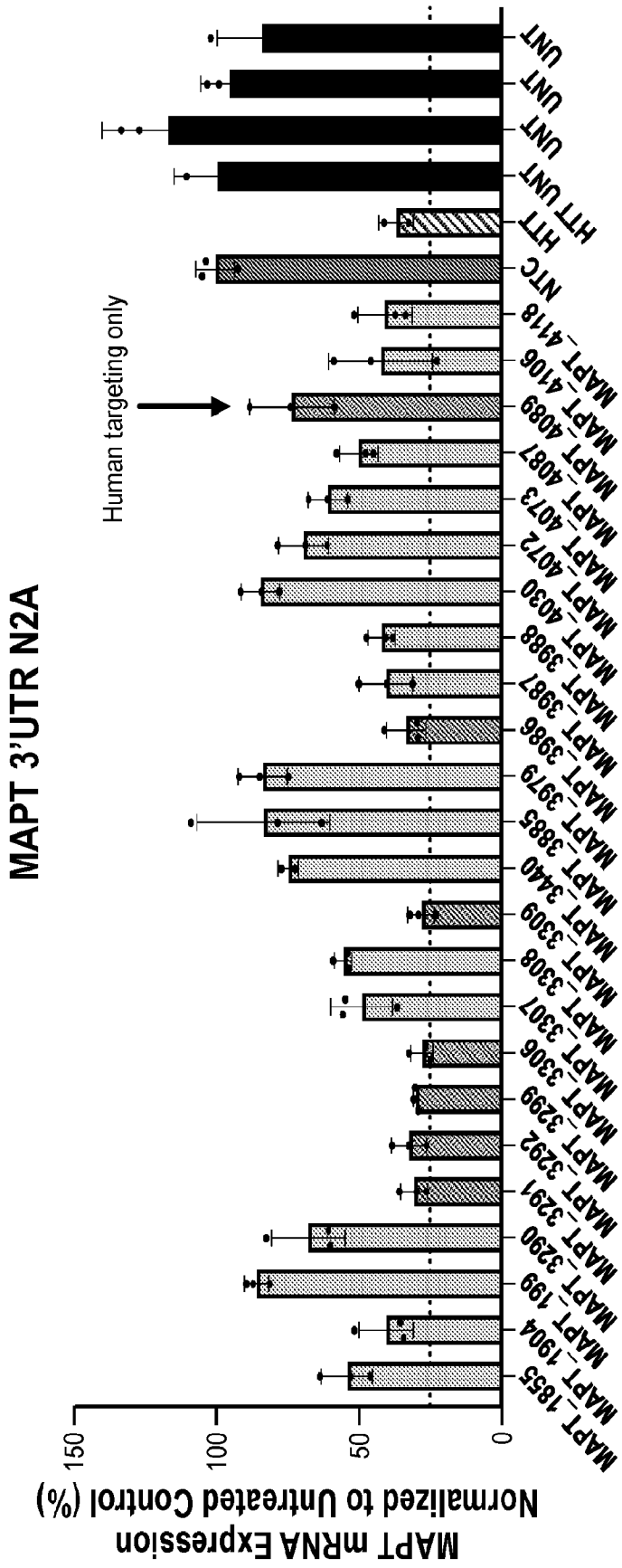

MAPT 3'UTR N2A
MAPT mRNA Expression
Normalized to Untreated Control (%)
150
100
50
0
Human targeting only
UNT
UNT
UNT
UNT
HTT
HTT UNT
NTC
MAPT_4118
MAPT_4106
MAPT_4089
MAPT_4087
MAPT_4073
MAPT_4072
MAPT_4030
MAPT_3988
MAPT_3987
MAPT_3986
MAPT_3979
MAPT_3865
MAPT_3440
MAPT_3309
MAPT_3308
MAPT_3307
MAPT_3306
MAPT_3299
MAPT_3292
MAPT_3291
MAPT_3290
MAPT_199
MAPT_1904
MAPT_1855

Fig. 7B

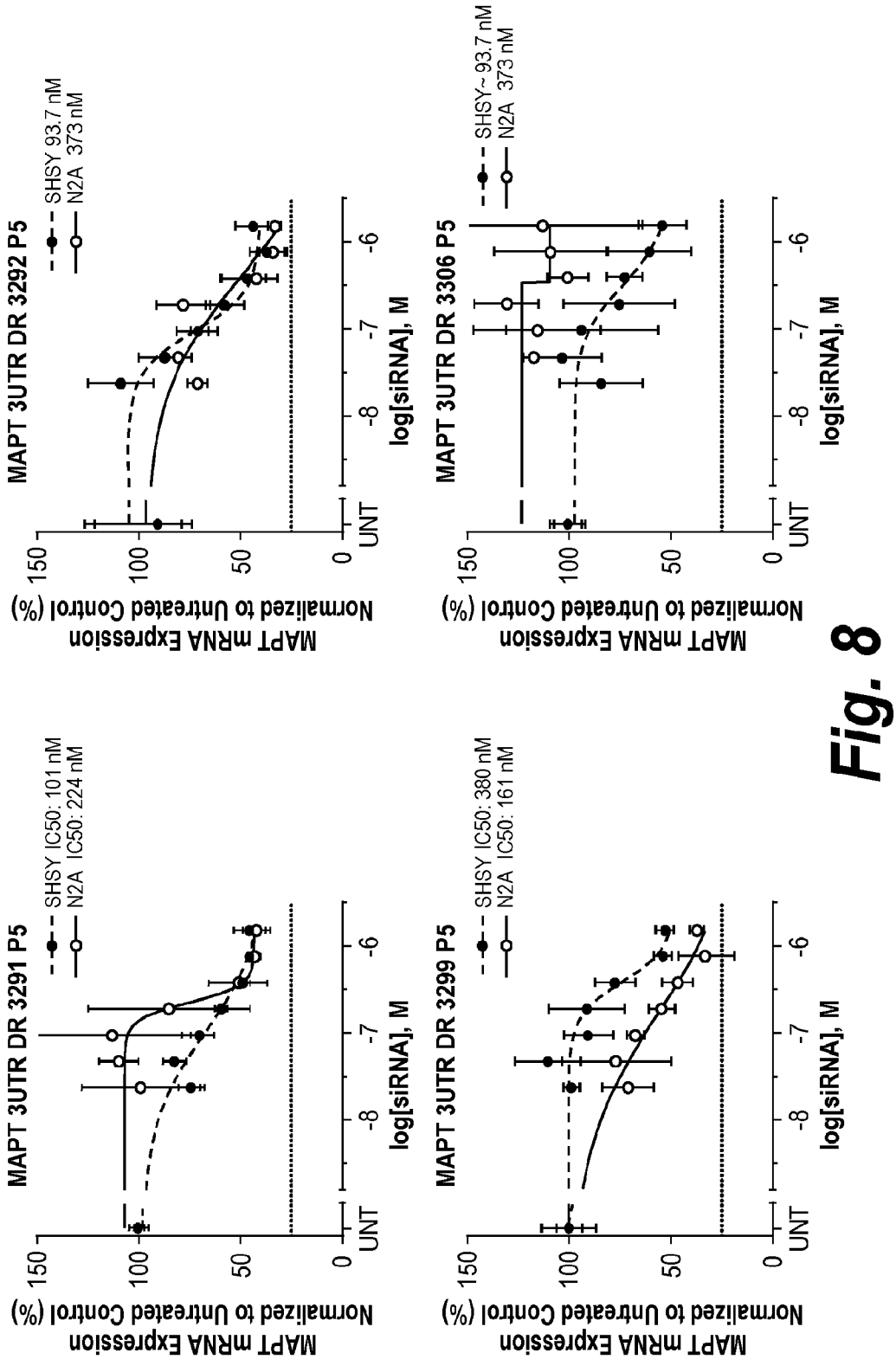

MAPT 3UTR DR 3292 P5
SHSY 93.7 nM
N2A 373 nM
MAPT mRNA Expression
Normalized to Untreated Control (%)
150
100
50
0
UNT
-8
-7
-6
log[siRNA], M
MAPT 3UTR DR 3306 P5
SHSY~ 93.7 nM
N2A 373 nM
MAPT 3UTR DR 3291 P5
SHSY IC50: 101 nM
N2A IC50: 224 nM
MAPT 3UTR DR 3299 P5
SHSY IC50: 380 nM
N2A IC50: 161 nM

Fig. 8

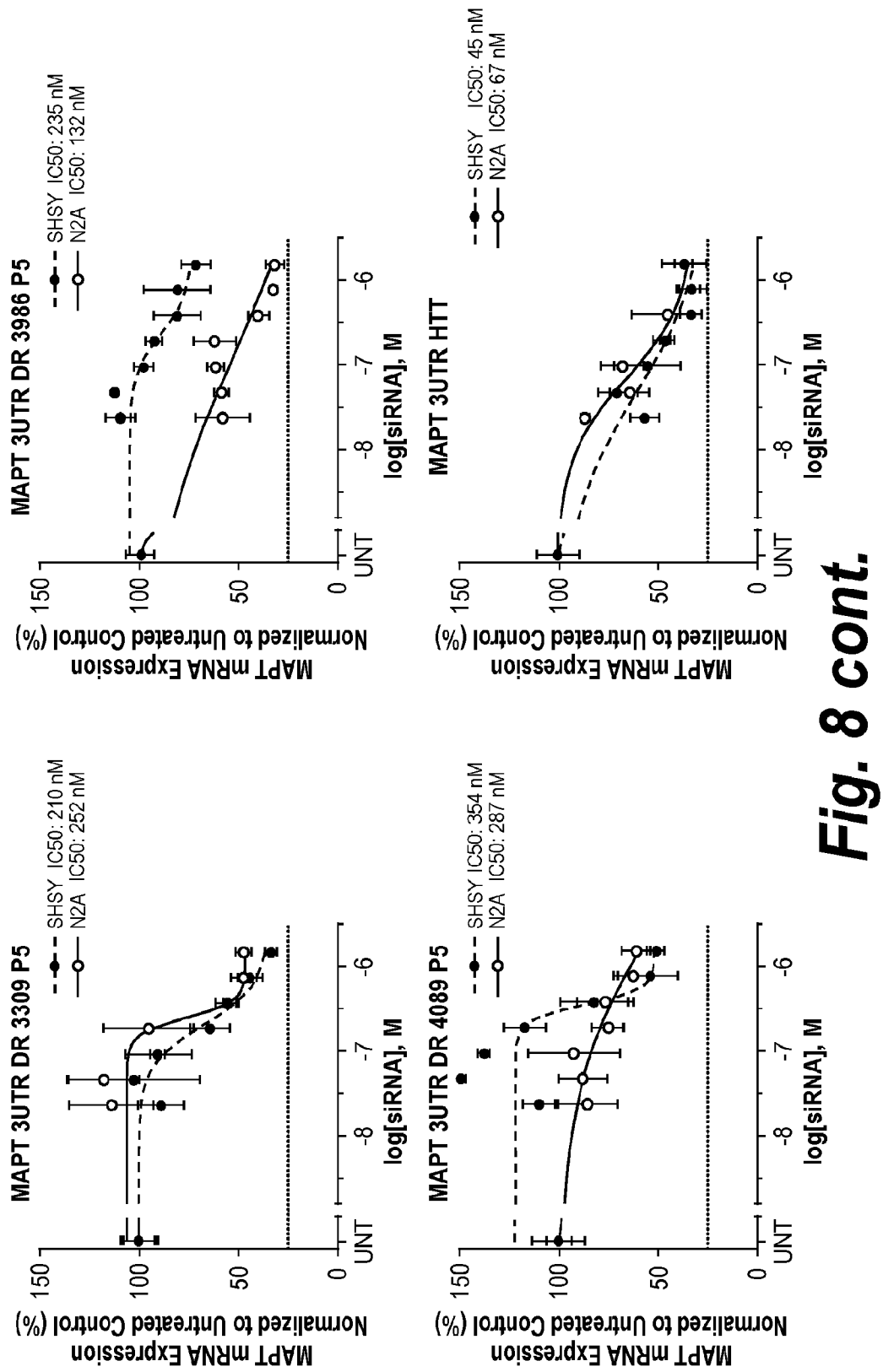

MAPT 3UTR DR 3986 P5
SHSY IC50: 235 nM
N2A IC50: 132 nM
MAPT 3UTR HTT
SHSY IC50: 45 nM
N2A IC50: 67 nM
MAPT 3UTR DR 3309 P5
SHSY IC50: 210 nM
N2A IC50: 252 nM
MAPT 3UTR DR 4089 P5
SHSY IC50: 354 nM
N2A IC50: 287 nM
MAPT mRNA Expression
Normalized to Untreated Control (%)
log[siRNA], M
UNT
150
100
50
0
-6
-7
-8

Fig. 8 cont.

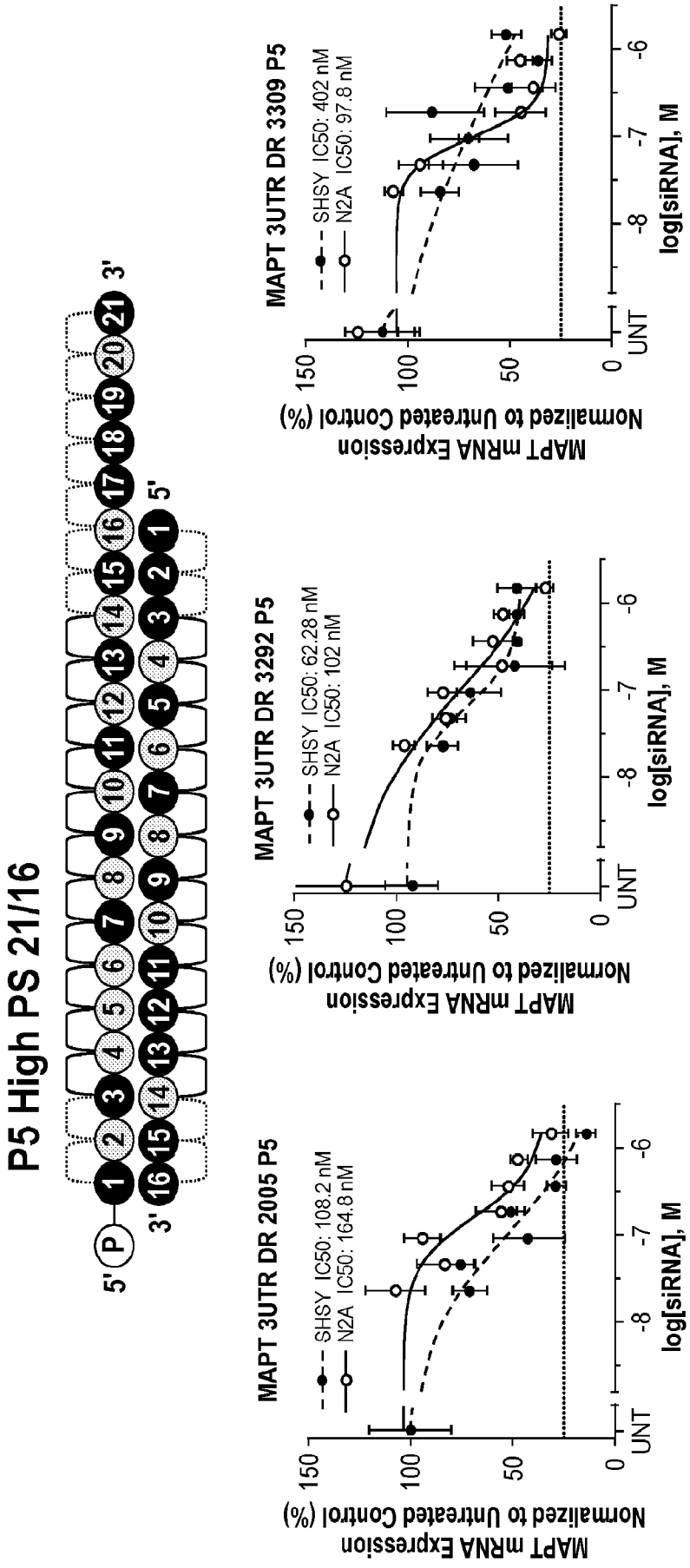

P5 High PS 21/16
5'
P
3'
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
3'
5'
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1
21
MAPT 3UTR DR 2005 P5
SHSY IC50: 108.2 nM
N2A IC50: 164.8 nM
MAPT mRNA Expression
Normalized to Untreated Control (%)
150
100
50
0
UNT
-8
-7
-6
log[siRNA], M
MAPT 3UTR DR 3292 P5
SHSY IC50: 62.28 nM
N2A IC50: 102 nM
MAPT mRNA Expression
Normalized to Untreated Control (%)
150
100
50
0
UNT
-8
-7
-6
log[siRNA], M
MAPT 3UTR DR 3309 P5
SHSY IC50: 402 nM
N2A IC50: 97.8 nM
MAPT mRNA Expression
Normalized to Untreated Control (%)
150
100
50
0
UNT
-8
-7
-6
log[siRNA], M

Fig. 9

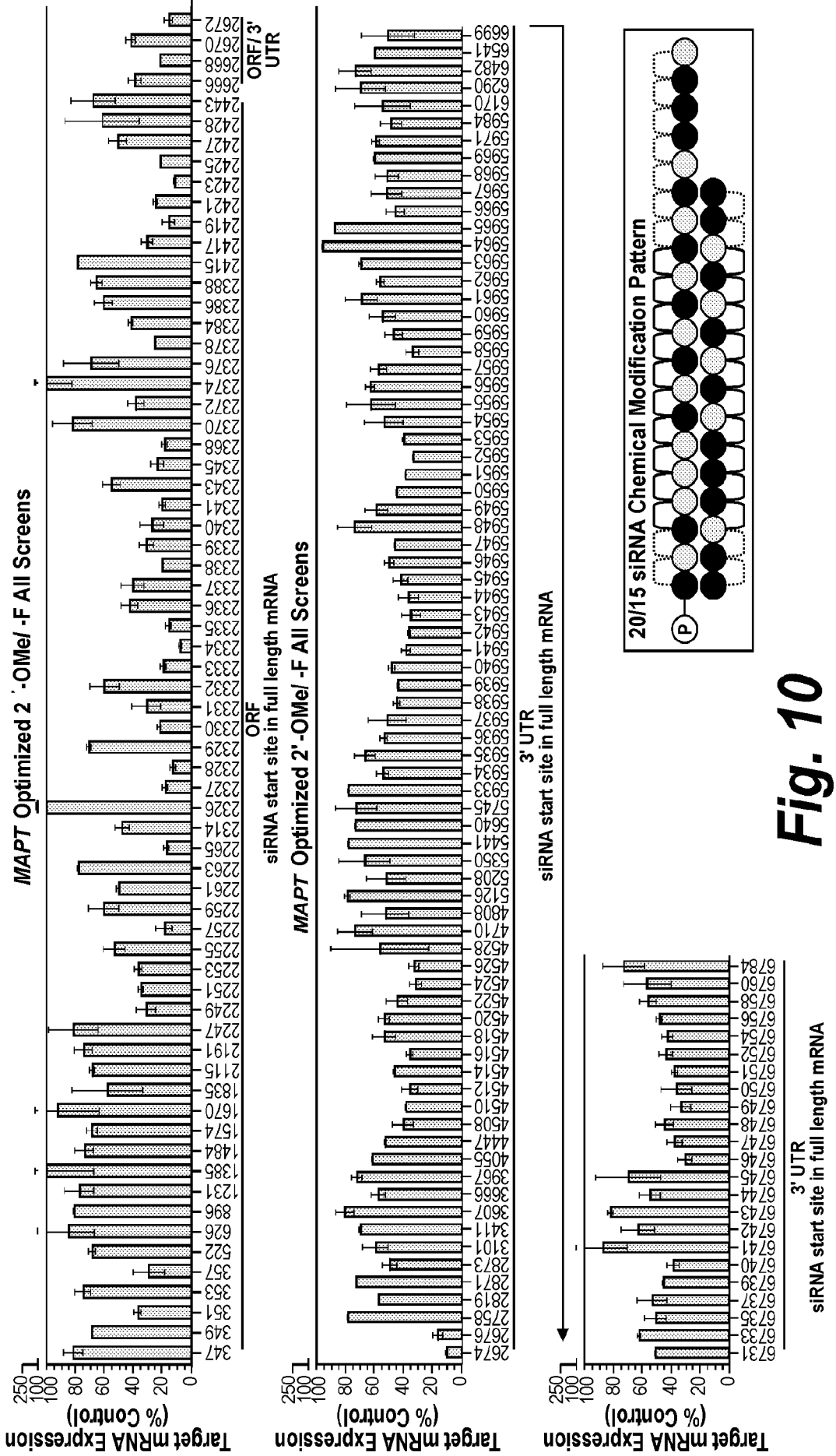
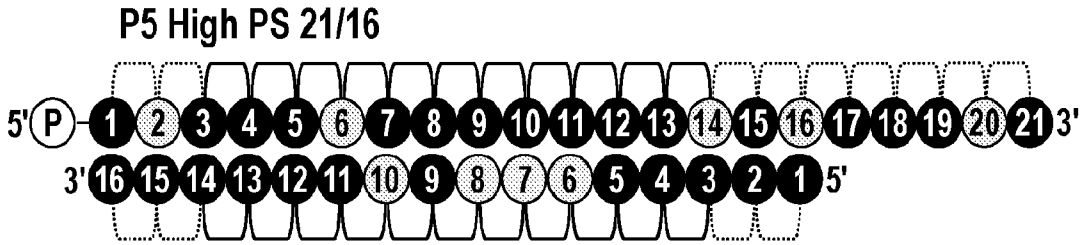
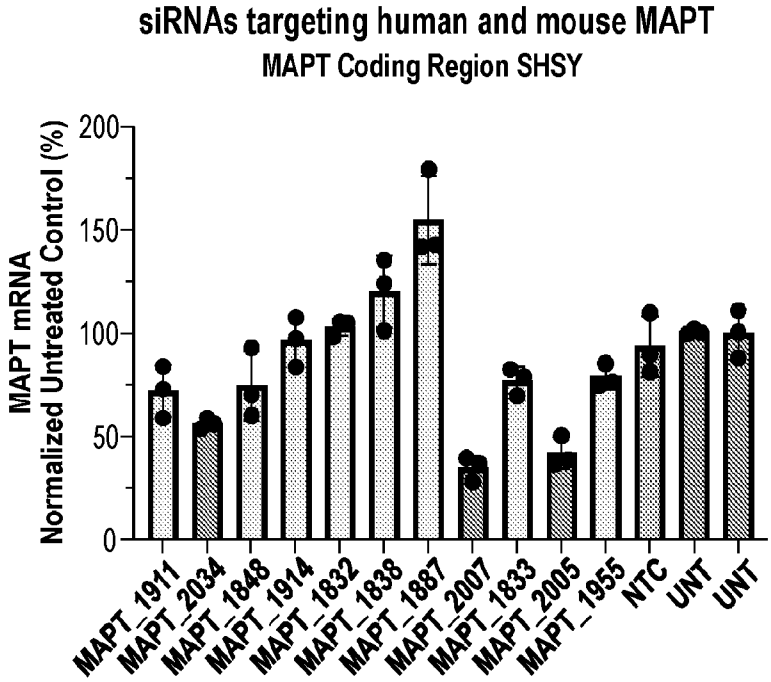

MAPT Optimized 2 '-OMe/ -F All Screens
Target mRNA Expression (% Control)
siRNA start site in full length mRNA
ORF
ORF/ 3' UTR
MAPT Optimized 2'-OMe/ -F All Screens
3' UTR
20/15 siRNA Chemical Modification Pattern
P

Fig. 10


P5 High PS 21/16
5'
P
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
3'
3'
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1
5'


siRNAs targeting human and mouse MAPT
MAPT Coding Region SHSY
MAPT mRNA
Normalized Untreated Control (%)
200
150
100
50
0
MAPT_1911
MAPT_2034
MAPT_1848
MAPT_1914
MAPT_1832
MAPT_1838
MAPT_1887
MAPT_2007
MAPT_1833
MAPT_2005
MAPT_1955
NTC
UNT
UNT

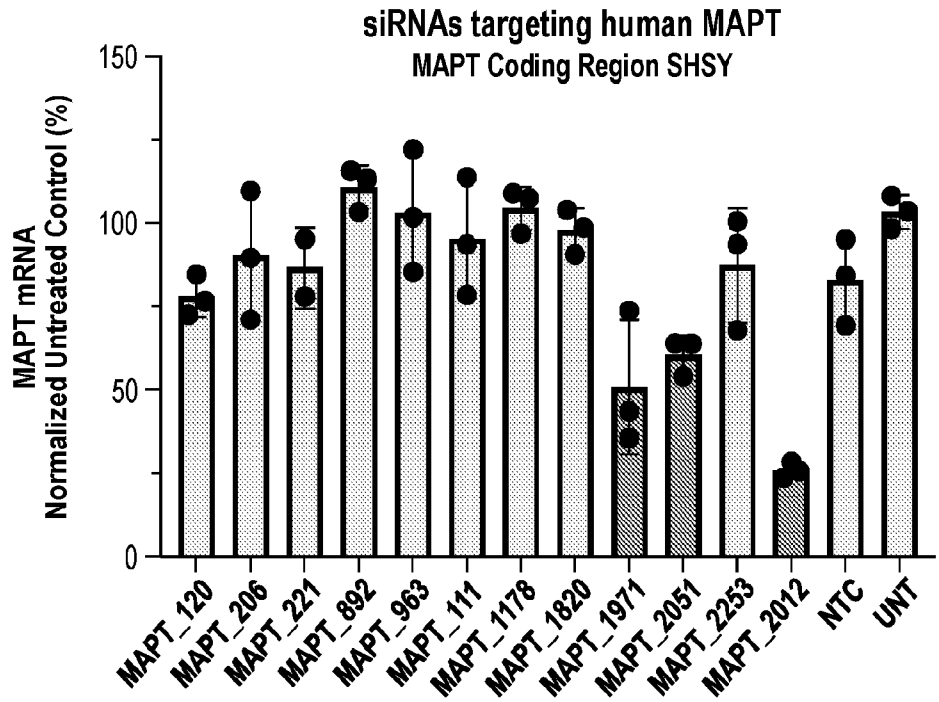

siRNAs targeting human MAPT
MAPT Coding Region SHSY
MAPT mRNA
Normalized Untreated Control (%)
150
100
50
0
MAPT_120
MAPT_206
MAPT_221
MAPT_892
MAPT_963
MAPT_111
MAPT_1178
MAPT_1820
MAPT_1971
MAPT_2051
MAPT_2253
MAPT_2012
NTC
UNT

Fig. 11

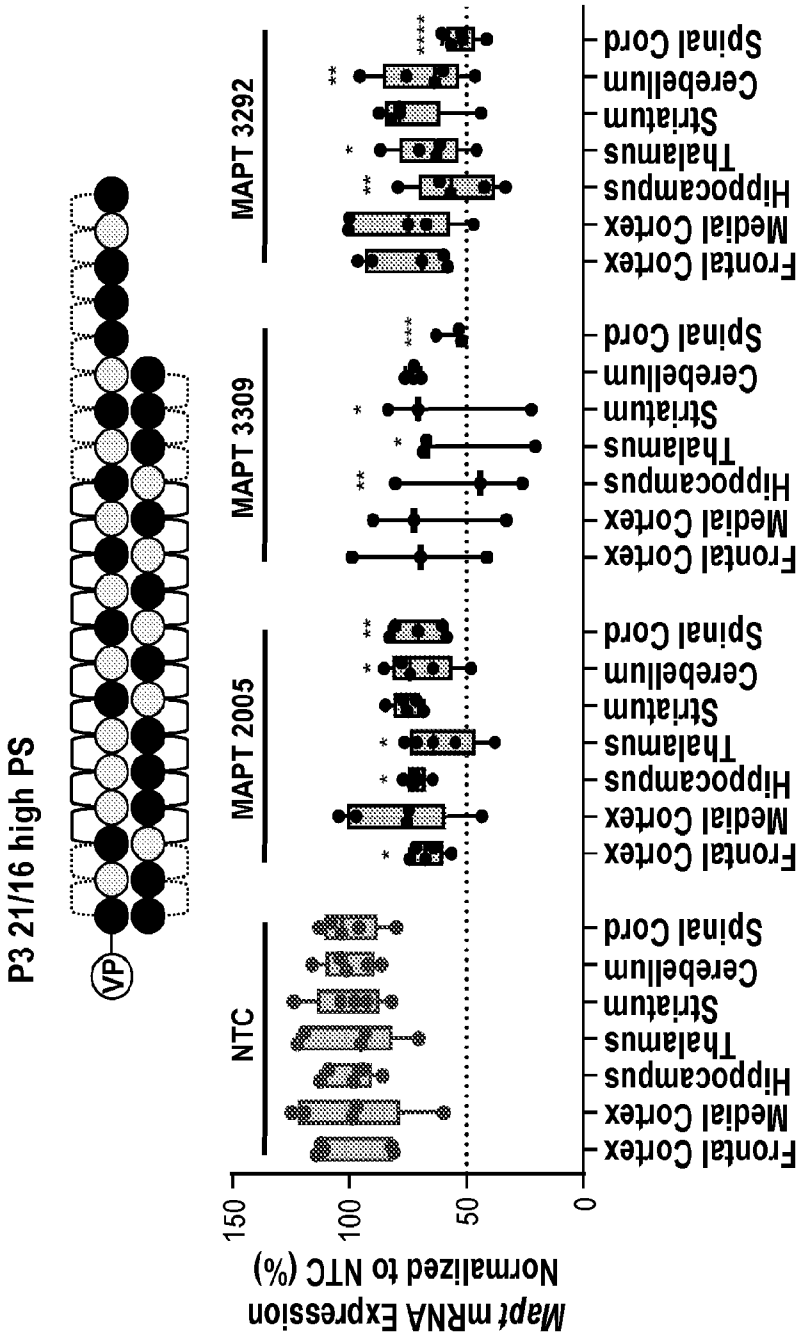

P3 21/16 high PS
VP
Maptmrna Expression
Normalized to NTC (%)
150
100
50
0
NTC
MAPT 2005
MAPT 3309
MAPT 3292
Frontal Cortex
Medial Cortex
Hippocampus
Thalamus
Striatum
Cerebellum
Spinal Cord

Fig. 12A

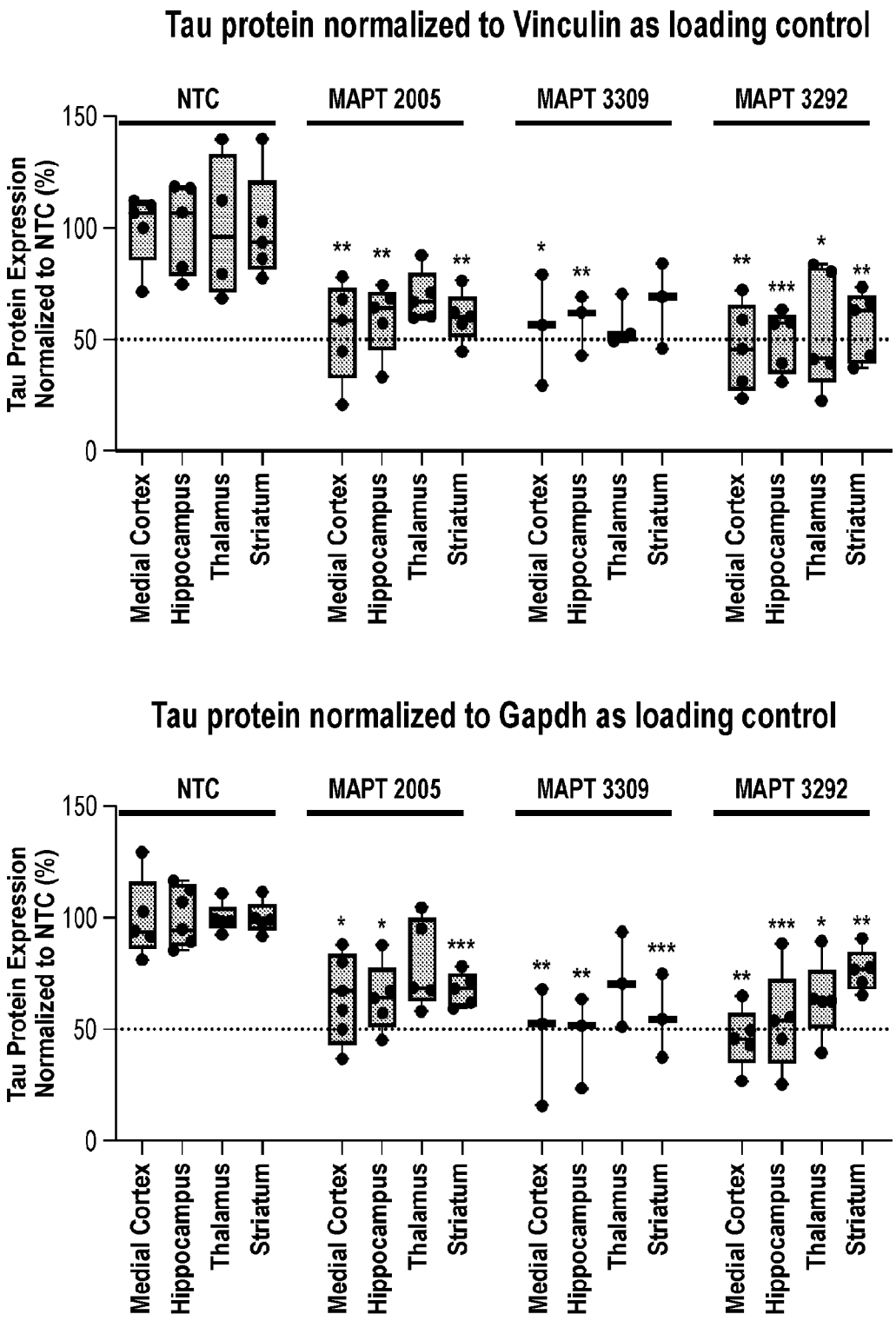

Tau protein normalized to Vinculin as loading control
NTC
MAPT 2005
MAPT 3309
MAPT 3292
Tau Protein Expression Normalized to NTC (%)
150
100
50
0
Medial Cortex
Hippocampus
Thalamus
Striatum
Tau protein normalized to Gapdh as loading control
NTC
MAPT 2005
MAPT 3309
MAPT 3292
Tau Protein Expression Normalized to NTC (%)
150
100
50
0
Medial Cortex
Hippocampus
Thalamus
Striatum

Fig. 12B